ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2021 September 26; 13(9): 381-525

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

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NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Ramdas G Pai, Dimitrios Tousoulis, Marco Matteo Ciccone

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

PUBLICATION DATE
September 26, 2021

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World Journal of Cardiology

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World J Cardiol 2021 September 26; 13(9): 381-398

DOI: 10.4330/wjc.v13.i9.381

ISSN 1949-8462 (online)

REVIEW

Quantifying tissue perfusion after peripheral endovascular procedures: Novel tissue perfusion endpoints to improve outcomes

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Author contributions: All authors equally contributed to this paper with conception and design of the review, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: All the authors are aware of the content of the manuscript and have no conflict of interest.

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Abstract

Peripheral artery disease (PAD) is a flow-limiting condition caused by narrowing of the peripheral arteries typically due to atherosclerosis. It affects almost 200 million people globally with patients either being asymptomatic or presenting with claudication or critical or acute limb ischemia. PAD-affected patients display increased mortality rates, rendering their management critical. Endovascular interventions have proven crucial in PAD treatment and decreasing mortality and have significantly increased over the past years. However, for the functional assessment of the outcomes of revascularization procedures for the treatment of PAD, the same tests that have been used over the past decades are still being employed. Those only allow an indirect evaluation, while an objective quantification of limb perfusion is not feasible. Standard intraarterial angiography only demonstrates post-intervention vessel patency, hence is unable to accurately estimate actual limb perfusion and is incapable of quantifying treatment outcome. Therefore, there is a significant necessity for real-time objectively measurable procedural outcomes of limb perfusion that will allow vascular experts to intraop-

Manuscript source: Invited manuscript

Specialty type: Radiology, nuclear medicine and medical imaging

Country/Territory of origin: Greece

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 7, 2021
Peer-review started: March 7, 2021
First decision: May 6, 2021
Revised: May 11, 2021
Accepted: July 26, 2021
Article in press: July 26, 2021
Published online: September 26, 2021

P-Reviewer: Taydas O
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Wu RR

eratively quantify and assess outcomes, thus optimizing treatment, obviating misinterpretation, and providing significantly improved clinical results. The purpose of this review is to familiarize readers with the currently available perfusion-assessment methods and to evaluate possible prospects.

Key Words: Peripheral arterial disease; Critical limb ischemia; Endovascular treatment; Peripheral angioplasty; Tissue perfusion; Quantification

Core Tip: Endovascular interventions have been proven critical in the treatment and management of peripheral artery disease-affected patients, by decreasing mortality and improving quality of life. However, currently available methods only allow an indirect evaluation of the functional assessment of treatment outcomes, while an objective quantification of limb perfusion is not feasible. This review aims to familiarize readers with currently available perfusion-assessment techniques that will allow vascular experts to intraoperatively quantify and evaluate outcomes, hence optimizing treatment, obviating misinterpretation, and providing significantly improved clinical results.

Citation: Arkoudis NA, Katsanos K, Inchingolo R, Paraskevopoulos I, Mariappan M, Spiliopoulos S. Quantifying tissue perfusion after peripheral endovascular procedures: Novel tissue perfusion endpoints to improve outcomes. *World J Cardiol* 2021; 13(9): 381-398
URL: https://www.wjgnet.com/1949-8462/full/v13/i9/381.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i9.381

INTRODUCTION

Peripheral artery disease (PAD) is caused by narrowing of the peripheral arteries typically due to atherosclerosis, which instigates restriction of blood flow to the distal extremities. Risk factors for developing atherosclerosis include smoking, diabetes mellitus, obesity (body mass index > 30), increasing age, hypertension, high cholesterol levels, raised homocysteine levels, and family history of cardiovascular disease[1,2].

PAD affects almost 200 million people globally[3] with patients either being asymptomatic or presenting with claudication, critical limb ischemia (CLI), or acute limb ischemia (ALI)[4,5]. It has been shown that PAD-affected patients have an increased risk of coronary artery disease (CAD) mortality, cardiovascular mortality, and all-cause mortality[6]. Additionally, when compared to patients with symptomatic CAD, patients presenting with CLI can demonstrate higher mortality rates[7]. Diabetes mellitus is another recognized risk factor for CLI correlated with increased lower-limb major amputation and mortality rates. A recent large retrospective analysis of the 2002–2015 National Inpatient Sample database demonstrated a significant increase in hospitalization for CLI for subjects with diabetes in the United States but a decreased in-hospital mortality over time, correlated with revascularization[8]. As a result, PAD management is critical to improve patients' long-term survival and decrease mortality, with management varying depending on symptoms and severity of the disease. Aggressive risk factor modification is vital to improve cardiovascular risk. Lifestyle changes, pharmacotherapy, exercise therapy, endovascular, and/or surgical intervention are further available treatment options[9]. Notably, endovascular interventions for PAD treatment have significantly increased in recent years, significantly outnumbering surgical procedures[8,10]. Amongst other factors, this could be due to the high technical success, low complication rates, and shorter hospitalization stays observed with endovascular treatments but also because many PAD patients either do not have surgical options or are deemed unfit for surgery[11-13].

Over the past few years, several beneficial devices have been introduced in everyday clinical practice to improve outcomes of endovascular procedures used for the management of PAD. Yet, for the functional assessment of these outcomes, the same tests that have been used in the past decades [*e.g.*, intraprocedural morphological

assessment with digital subtraction angiography (DSA), ankle-brachial index (ABI), pressure measurements across the treated lesion] are still being employed. Nonetheless, these methods only allow an indirect evaluation of the outcomes of revascularization procedures for the treatment of PAD, while an objective quantification of limb perfusion is not feasible. For example, since angiography only demonstrates post-intervention vessel patency, it is unable to accurately estimate actual limb perfusion and hence is incapable of quantifying treatment outcome. Therefore, for the appropriate assessment of endovascular procedures in the management of PAD, there is a significant necessity for objectively measurable procedural outcomes of limb perfusion.

The purpose of this review is to familiarize readers with currently available perfusion-assessment methods and to evaluate possible prospects in quantifying and optimizing endovascular outcomes in the treatment of lower limb arterial ischemia.

STANDARD ARTERIAL PRESSURE MEASUREMENTS

Systolic blood pressure (SBP) measurements throughout the vascular tree offer valuable information in PAD diagnosis.

The ABI is a readily available, fast, inexpensive examination[14] that calculates the ratio produced by dividing the SBP measured at the ankle with the higher SBP measured at either arm. Ankle pressure and ABI should be calculated with the patient lying flat in the supine position after a 5 to 10-min rest[15]. Values most considered as indicative of PAD are those ≤ 0.90. More importantly, in patients with signs of ischemia, an ABI < 0.90 is considered diagnostic for PAD with sensitivity and specificity reaching 95% and 100% accordingly[16]. Furthermore, an ABI < 0.50 has been linked to more severe CAD and increased mortality[17]. On the other hand, values between 1.0 and 1.4 are considered normal, while values > 1.4 are attributed to non-compressible arteries and are therefore considered non-diagnostic[15,18]. As heavily calcified, non-compressible vessels are very common in patients with diabetes mellitus and chronic kidney disease; ankle pressures and ABI values are often untrustworthy and rendered non-diagnostic in such patients because they can be falsely increased[18,19].

Toe-brachial index - Toe systolic pressure

Great toe pressures and measurements of the toe-brachial index (TBI) can prove superior to non-diagnostic, high-value ABIs in these patient groups demonstrating severely calcified vessels, because the digital arteries are typically spared, thus being able to more accurately determine vascular disease[19,20]. A TBI ≤ 0.70 is abnormal and considered diagnostic of PAD[21], and a TBI < 0.11 is related to ischemic rest pain [22]. However, since toe pressure evaluation between studies demonstrates variable diagnostic accuracy, there has not yet been a widely accepted TBI or toe pressure threshold that can confirm the diagnosis of CLI[23].

Limitations

The ABI may not prove useful in the setting of severely calcified, non-compressible vessels. Moreover, false-negative ABI measurement can occur in up to 17% of diabetic patients and 24% of hemodialysis patients[24,25]. Nonetheless, there are several additional significant limitations to the employment of arterial pressure measurements. Amongst other considerations, some of the technical factors that should be thought through when calculating the ABI include correct cuff placement (2 cm above the medial malleolus)[26], use of the appropriate pressure cuff size (width should be at least 40% of the limb circumference)[27,28], use of a suitable Doppler probe (8-10 MHz), and correct probe-to-skin surface angle (45-60°)[15]. Additionally, the potential risk of thrombosis does not allow segmental pressure measurements over formerly placed stents or bypass grafts. Moreover, the utilization of arterial pressure measurements can be limited in patients with CLI since placing the cuff over an affected limb will often prove intolerable and painful. Nevertheless, in the presence of open wounds and ulcers, cuff placement may also pose the risk of contamination, rendering ankle or toe pressure measurements inapplicable depending on wound/ulcer location. In the same setting, arterial pressure measurements will not be applicable in cases of prior amputation.

Reed *et al*[29] showed that a post interventional ABI increase of ≥ 0.23 can augment wound healing and potentially reduce the necessity for a subsequent angioplasty, while a post endovascular revascularization TBI increase of ≥ 0.21 is correlated with

reduced major adverse limb events and with improved wound healing. Also, Decrinis *et al*[30] found that a post-angioplasty ABI increase of 0.10 and 0.15 can predict no residual > 50% stenosis, with sensitivities of 79% and 67% and specificities of 92% and 100%, respectively. However, other studies show that ABI correlates poorly with Rutherford classification and the angiographic vessel runoff and that it may not adequately predict wound healing[31,32].

Notably, the ABI can only imply the approximate site of stenosis or occlusion, but it cannot determine its exact location since it could also reflect changes elsewhere in the arterial tree[33]. Due to this fact it cannot accurately differentiate graft failure from PAD progression, hence rendering its accuracy in predicting revascularization failure poor. Considering the above, ABI alone is not a dependable method of post-revascularization follow-up. Lastly, arterial pressure measurements such as ABI and TBI can only assess tibial or toe pressure, respectively, but are not able to quantify oxygenation and tissue perfusion. Hence, they only indirectly evaluate treatment outcomes.

Overall, post-procedural foot perfusion outcomes cannot be accurately quantified using ABI, as the existing data does not consider ABI a sufficient predictor of post-procedural results and relegate it a poor predictor of wound healing.

LASER DOPPLER SKIN PERFUSION PRESSURE MEASUREMENTS AND TRANSCUTANEOUS OXYGEN MONITORING

The first attempt to non-invasively assess post-revascularization limb perfusion was made using laser Doppler skin perfusion pressure (SPP) measurements and transcutaneous oxygen ($TcPO_2$) monitoring.

Laser doppler skin perfusion pressure measurements

Laser Doppler measurement of SPP is a non-invasive technique that (by using a laser Doppler sensor) detects the movement of red blood cells (RBCs) following the slow release of the pressure occlusion cuff. In this way, SPP measurements calculate the capillary opening pressure and provide an indirect estimation of the microcirculatory flow status within the artery at skin level[34]. SPP is advantageous in that it is not altered by vascular calcifications[35]. Notably, SPP values > 30 mmHg after successful endovascular treatment with balloon angioplasty and/or stenting have been correlated with improved wound healing in a retrospective study of 113 consecutive CLI patients, with a sensitivity and a specificity of 81.4% and 69.2%, respectively[34]. On the other hand, if SPP values are < 30 mmHg, wound healing is doubtful[36]. More recently, in a large sub-analysis of 156 CLI patients included in a prospective multicenter registry, postprocedural SPP was significantly correlated with amputation-free survival, major adverse limb events, and wound healing at 1-year follow-up. Additionally, the authors reported that ABI did not correlate with clinical outcomes[37].

Transcutaneous oxygen monitoring

Transcutaneous oxygen ($TcPO_2$) is a non-invasive test measuring oxygen concentration in the subcutaneous tissue 1 to 2 mm below the skin that can be performed at the bedside and does not use ionizing radiation. First, a conductive gel is applied over the area under examination, and subsequently, an electrode that can sense oxygen is placed on the affected limb. The electrodes heat the area beneath the skin, dilating the capillaries and allowing oxygen to readily flow to the skin, thus providing an optimal reading. The test serves as an indicator of oxygen and nutrients reaching the tissues through microcirculation[38], and since these are carried to tissues through the arteries, it can indirectly measure blood flow. Therefore, it can provide direct information about the endpoint of limb perfusion, which is tissue oxygenation. Normal $TcPO_2$ values are between 50-70 mmHg.

Over the past years, several authors have investigated the role of $TcPO_2$ in PAD patients, and sufficient data support its use both for PAD screening and post-revascularization success evaluation. Patients with CLI (ABI < 0.4) will almost always have $TcPO_2$ values < 30 mmHg[39]. Moreover, it is a highly accurate and particularly valuable test in predicting wound/ulcer and amputation healing[40]. Specifically, values over 30 mmHg have been correlated with improved wound healing rates[41, 42], while values < 30 mmHg have been associated with a reduced chance of wound healing[43,44]. Likewise, Andrews *et al*[45] found that a cut-off $TcPO_2$ value of 38 mmHg had a sensitivity and specificity of 71% in predicting wound healing or failure.

When compared to the ABI, Pardo *et al*[38] found that an increase in $TcPO_2$ measurements following endovascular procedures has more specificity and sensitivity compared to ABI, and hence may be a better alternative in the evaluation of angioplasty results.

In the setting of open wounds or prior amputations, where arterial pressure measurements are not applicable, $TcPO_2$ and SPP measurements can be adequate alternatives. Additionally, since arterial pressure measurements cannot accurately identify the exact arterial disease location, these local perfusion tests may prove advantageous in angiosome-based revascularization[46,47].

Limitations

Despite published evidence suggesting the clinical utility of SPP and $TcPO_2$, these techniques are not widely available and present several limitations. $TcPO_2$ is only a skin perfusion marker, whose measurements are performed in a small area. $TcPO_2$ results can be affected by numerous physiological, methodological, and technical issues. Perfusion assessment measures should be attained in a warm room to avoid cold-induced vessel constriction that could alter $TcPO_2$ and SPP values[39]. Similarly, in patients exhibiting abnormal involuntary movements, reliable measurements will also not be feasible[48]. Other factors such as site selection, electrode equilibration, patient age, patient positioning, patient status before examination, pain, smoking and caffeine consumption, skin temperature changes, sympathetic tone, tissue edema, hyperkeratosis, cellulitis, and local skin integrity[35,39] may affect the accuracy of measurements, hence decreasing overall reliability. In addition, bony prominences, larger veins, or varicose veins should be avoided during cuff placement for SPP measurements, since they may produce artifacts[48].

Also, $TcPO_2$ can calculate the partial pressure of oxygen adjacently to the wound but cannot determine actual measurements within the wound itself[49]. In the same manner, since measurements are relatively localized, values may not accurately represent total limb ischemia[39].

MATTERS THAT NEED TO BE ADDRESSED

The above-mentioned non-invasive techniques that are being employed in the assessment of limb perfusion estimate different perfusion characteristics, and each one of them has its advantages and disadvantages. For instance, ABI/TBI measures arterial pressures and hence cannot quantify tissue oxygenation and cannot provide sufficient information regarding wound healing and patient outcome. $TcPO_2$ measures oxygen tension, while SPP measures capillary opening pressure. Although the latter methods are more reliable predictors of outcomes and offer a quantifiable outcome indicative of tissue perfusion, accurate tissue perfusion values cannot be obtained. Moreover, despite optimistic initial results, data regarding the role of SPP and $TcPO_2$ in guiding or predicting endovascular treatment outcomes in PAD patients remain limited, and large prospective controlled studies are awaited.

NON-INVASIVE IMAGING STUDIES

Examples of non-invasive imaging studies include duplex ultrasound (DUS), computed tomography (CT) angiography (CTA), and magnetic resonance imaging angiography (MRA). DUS uses two modes of ultrasound, the B-mode that assesses vessel structure, and Doppler that evaluates blood flow velocity and direction. CTA/MRA provide information regarding the vessel's anatomic relationship with other organs and provide information regarding vessel structure and morphology of stenosis. As a result, these methods can only measure lower extremity blood flow, and thus, are only surrogate tissue perfusion markers. Techniques that enable more accurate quantification of tissue perfusion include perfusion CT and arterial spin labeling (ASL) and blood oxygen level-dependent (BOLD) magnetic resonance imaging (MRI). However, these techniques are not employed regularly in the clinical evaluation of PAD.

CT perfusion

CT perfusion (CTP) has been readily employed in cerebral imaging, with its most well-known application being the non-invasive diagnosis of cerebral infarction/ischemia

[50]. Similarly, Hur *et al*[51] demonstrated that CTP could be used to measure blood flow in lower limbs and also in the diagnosis of PAD by providing quantitative information regarding foot perfusion, while in the same study, color-coded perfusion map readings correlated well with both clinical and angiographic findings in PAD patients undergoing revascularization. Additionally, Sah *et al*[51] showed that CTP is feasible in PAD assessment and demonstrated a positive correlation between CTP blood flow, blood volume, and lesion length, and an inverse correlation between blood volume and ABI, suggesting that CTP may serve as a non-invasive technique, supplementing the diagnostic workup of PAD[52]. CTP examinations can be performed by contemporary CT scanners, as a supplement to CTA. Although CTP has the potential to quantify perfusion and monitor treatment response, it is a costly examination that necessitates the use of iodinated contrast and exposes patients to radiation.

Arterial spin labeling MRI

Arterial spin labeling (ASL) MRI is a non-invasive and non-ionizing perfusion measurement technique that allows measurements at the tissue level by exploiting the ability of MRI to magnetically label inflowing arterial blood before it enters the tissue under investigation (below the imaging slab)[53]. T1 signal differences between control and tag images are proportionate to blood flow and are used to produce perfusion maps[54]. With this technique, blood serves as an endogenous tracer, obviating the need for contrast agents.

Although initially developed and used to measure brain perfusion[55], ASL has found several clinical applications since. Notably, it is a reproducible, radiation-free technique that can successfully quantify peak exercise blood flow in calf muscles in patients experiencing claudication[56].

Limitations of ASL include low signal-to-noise ratio, relatively long scan acquisition times, patient movement artifacts, and errors owing to potentially slow blood flow, often seen in PAD/CLI patients.

Blood oxygen level–dependent MRI

BOLD MRI has been used for many years in functional MRI (fMRI) of the brain. This technique exploits the ability of fMRI to detect changes in the concentration of oxygenated and deoxygenated hemoglobin (Hb) due to a fundamental difference in their paramagnetic properties (deoxy Hb is paramagnetic while oxyHb is not). As a result, it uses the Hb saturation state as an endogenous tracer, hence also eliminating the need for contrast agents. Heavily T2* weighted sequences are used to detect such changes[57]. Even though BOLD imaging has been mostly used in fMRI to detect which parts of the brain demonstrate most activity, Bajwa *et al*[58] evaluated BOLD MRI as a clinical tool for the measurements of calf muscle perfusion in CLI patients. This study demonstrated statistically significant interuser and interscan reproducibility and found a significant correlation between MRI measurements and tissue vascularity found in muscle biopsy samples obtained in the scanned region.

Limitations of BOLD imaging include erroneous measurements potentially related to slow blood flow (as mentioned with ASL) often seen in PAD patients and susceptibility of T2* sequences to artifacts. However, when compared to ASL MRI, BOLD MRI seems to have a higher signal-to-noise ratio, faster acquisition times, and reduced motion artifacts[58].

Nonetheless, for the purposes of this review, the most important limitation of ASL and BOLD imaging is the fact that although they can be used to quantify post-procedural perfusion outcomes, they are impractical when physicians require real-time feedback during endovascular interventions.

INTRA-OPERATIVE TWO-DIMENSIONAL PERFUSION ANGIOGRAPHY

Neuro-interventional procedures associated with acute stroke treatment have effectively employed two-dimensional perfusion angiography (2D-PA) by using flat detector technology[59]. This application has improved acute stroke patient management by allowing cerebral blood volume (CBV) assessment and by predicting final infarct volume.

When applied in peripheral vessels, standard DSA is used, with a rate of three frames per second. The images that are attained are reconstructed with a post-processing software that calculates the changes in density per pixel before and after the endovascular intervention, and the results are then viewed on a dedicated workstation[60]. In a study conducted by Jens *et al*[60], the DSA data obtained during

this technique were used to produce a time–density curve, which represented foot perfusion concerning time. Successful endovascular interventions performed on below the knee arteries in this study showcased improved perfusion curves, hence making functional imaging in CLI patients a more feasible goal. Moreover, another study conducted by Kagadis *et al*[61], using a custom-made, 2D perfusion DSA algorithm (Figure 1) demonstrated a post angioplasty mean transit time decrease that indicated increased tissue perfusion following successful revascularization. However, this study was limited mainly by the very small number of patients investigated.

Overall, advantages of 2DPA include the fact that it does not require additional radiation exposure or additional contrast administration[62] and that it can be used instantly, while the procedure is being conducted to evaluate the interventional results [60]. This will allow physicians to make more informative and objective decisions on whether the undertaken treatment is sufficient or further improvements are required [62], while it could also aid in determining a meaningful, functional revascularization endpoint, beyond the anatomical endpoint assessed with standard intraprocedural DSA (less than 30% residual stenosis)[60]. However, acquisition of the appropriate software is required while obtained images are very susceptible to patient/limb movement-induced artifacts[60-62]. The fact that such perfusion software is currently incorporated in new Angiography systems (Siemens, Toshiba, Phillips) indicates that there is a recognized need to overcome standard anatomical imaging and progress to the era of real-time, functional, quantifiable imaging.

Nonetheless, additional studies are necessary to further validate this technique and determine its role in PAD/CLI-related interventions by comparing it to other available methods and correlating it with clinical outcomes.

IMPLANTABLE DEVICES - O_2 MICRO-SENSORS

Implantable devices such as O_2 micro biosensors may be advantageous because they can measure oxygen concentrations in tissues instead of vascular oxygenation. They can calculate tissue oxygenation in multiple areas and can potentially be utilized in monitoring tissues at risk, wounds, and reconstructive surgery. These phosphorescence devices are as small as 0.5 mm × 0.5 mm × 5 mm and can be integrated within the area/tissue of interest *via* a 16G or 18G needle[63]. Once positioned, these biocompatible hydrogel sensors remain in the body permanently, surpassing the foreign body response[64]. Subsequently, a reader is fixed on the skin above the microdevice, and then a LED source emits light into the skin above the sensor. Local tissue O_2 levels will then be calculated by an external photodetector in the reader and can be continuously tracked. The first-in-man prospective, single-arm, observational study included 10 patients with CLI (four micro-oxygen sensors injected in the foot of each patient). The study demonstrated that injectable micro-oxygen sensors could effectively and safely calculate tissue O2 concentrations in CLI patients during their endovascular intervention and post-operatively for 28 days[63]. Moreover, a statistically significant postoperative increase in the concentration of oxygen was noted. Nonetheless, additional and larger studies are required to confirm the utility and applications of these devices.

MICROWAVE RADIOMETRY THERMOMETRY

Microwave radiometry (MWR) is a non-invasive technique allowing accurate temperature measurements of internal tissues. Based on the principle that radiation intensity is proportional to tissue temperature, this method detects internal tissue temperatures at microwave frequencies by using contrasting dielectric qualities of different tissues[65]. This technique uses an antenna containing a microwave and an infrared sensor, which is applied at a 90 angle over the tissue surface being examined, for an approximate duration of 8-10 s. To obtain measurements, the microwave emissions are converted into temperature by using a data processing unit and suitable software.

Tissue temperature measurements have previously been applied in the diagnosis of numerous entities[66] including the characterization of neoplastic tissue or inflammation of atherosclerotic plaques[67-69]. Guidelines for diabetic foot management suggest that pedal perfusion is evaluated by the combination of ABI, TBI, Doppler arterial waveforms, and $TcPO_2$[70,71]. However, detecting the concomitant presence of vascular disease in diabetic foot ulcers remains a difficult and challenging task.

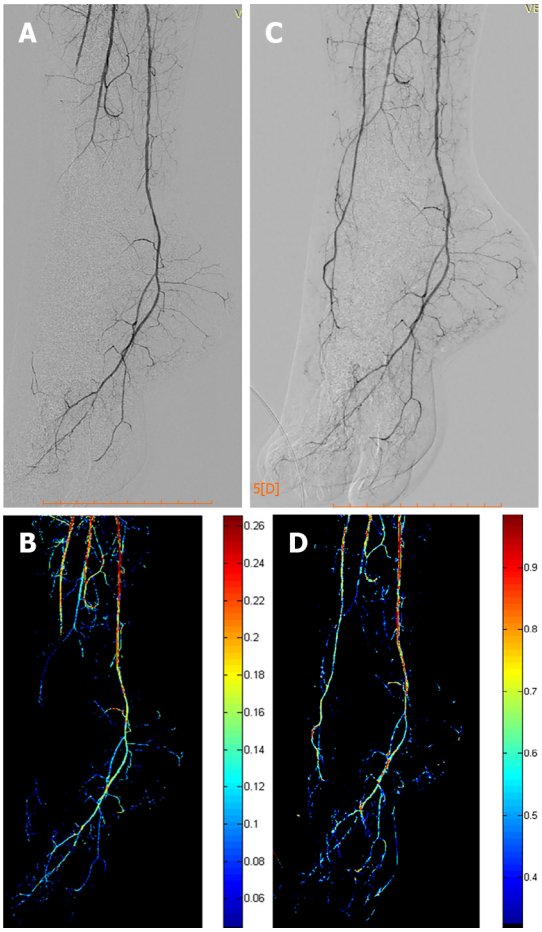

Figure 1 Two-dimensional perfusion digital subtraction angiography algorithm. A and B: Pre-procedural digital subtraction angiography (DSA) depicting a chronic total occlusion of the distal anterior tibial and pedal arteries with the respective perfusion blood volume (PBV) map; C and D: Post-procedural DSA after balloon angioplasty of the occlusion and corresponding post-procedural PBV map.

Spiliopoulos *et al*[72] conducted a study to investigate the ability of MWR thermometry to non-invasively differentiate CLI in patients with diabetic foot ulcers. This multicenter study including 80 patients demonstrated that the temperatures measured near ulcers were significantly lower in patients with CLI (either with or without diabetes) than in non-ischemic controls. Importantly, it showed that a cut-off temperature less than 31.8 °C was diagnostic of CLI with a sensitivity and specificity of 100.0% and 88.37%, respectively.

The above findings indicate that MWR thermometry could be employed in the differentiation of arterial ischemia in patients with diabetic foot ulcers. This thermometric technology is currently being studied for the quantifiable assessment of post revascularization foot perfusion to predict successful wound healing and initial data are awaited. Limitations of this modality include the fact that it needs to be performed in standard room temperatures and that in cases of overlying infection/inflammation, false-negative results may be obtained.

PERIPHERAL FRACTIONAL FLOW RESERVE

Fractional flow reserve (FFR) is an invasive method frequently employed in coronary artery revascularization to calculate pressure variations across a stenotic lesion[73,74]. It is a pressure ratio produced by dividing the mean pressure distal to the lesion with that proximal to the lesion. The cutoff FFR value is 0.80, with an FFR above 0.80 indicating non-significant stenosis and an FFR below 0.80 indicating a significant lesion[75]. Measurements are obtained *via* a small sensor/ transducer on the tip of the angiographic wire during pharmacologically induced hyperemia, which is achieved by injecting vasodilating agents. FFR allows the determination of whether certain stenosis is oxygen depriving, hence rendering it a valuable indicator of the stenosis's functional severity and the necessity for coronary intervention[73].

Notably, according to a meta-analysis from Christou *et al*[76], the concordance of FFR when compared with non-invasive imaging conveyed a sensitivity and specificity of 76%, concluding that FFR results usually agree with non-invasive imaging studies, although their correlation can be deficient.

The use of FFR in PAD (peripheral FFR-pFFR) uses the same principles as the FFR in CAD. It has been recently employed in the evaluation of the physiological implications of iliac and superficial femoral artery stenosis[77,78] and also in CLI patients with severe below-the-knee arterial disease[79]. Hioki *et al*[77] found a significant association between pFFR and post-exercise ABI and noted a substantial pFFR improvement after endovascular procedures, while Banerjee *et al*[80] demonstrated an important correlation between walking impairment, pFFR, and rest and exercise ABI. Potential applications of pFFR include its intraoperative evaluation after apparently successful revascularization. Although FFR has been thoroughly investigated in CAD and is considered to be a valuable tool (particularly in the management of intermediate lesions), the use of pFFR has been limited, with available evidence-based data being sparse, and clinical efficacy remaining questionable warranting further investigation.

An advantage of FFR is that it is unaffected by heart rate and SBP changes and that it considers collateral flow[73]. The latter means that it could potentially render morphologically severe stenosis functionally insignificant. Moreover, FFR allows for simultaneous intraprocedural diagnosis and treatment with angioplasty and stenting. Importantly, FFR can have significant value in vessels with multiple stenotic lesions [81]. The pFFR can be obtained by 2D perfusion DSA and therefore implemented in real-time decision-making during peripheral angioplasty procedures. Nevertheless, its drawbacks include its invasive, time-consuming nature and the requirement for drug administration (vasodilating agents), which could cause important side effects[82].

INDOCYANINE GREEN FLUORESCENCE ANGIOGRAPHY

Indocyanine green (ICG) fluorescence angiography was initially used in retinal vessel imaging[83] and subsequently in the evaluation of tissue perfusion in various medical fields[84,85]. Following intravenous injection of the fluorescent ICG dye, the latter is activated by the use of near-infrared laser (approximately 780 nm)[84]. This procedure produces fluorescence that is subsequently detected and measured.

There is currently an insufficient number of studies that have applied this method in PAD patients. ICG fluorescence angiography perfusion measurements have been shown to predict the possibility of amputation healing[86] and have the potential to detect PAD patients with lower limb arterial occlusions who have developed extensive collaterals[87]. Additionally, it may permit real-time evaluation of flow in peripheral bypass and endovascular procedures[88]. In a retrospective study of 11 patients (13 peripheral bypass grafts), Yamamoto *et al*[89] performed quantitative near-infrared fluorescence angiography (NIR) using the fluorescence ICG to visualize blood perfusion and predict the patency of peripheral arterial bypass graft patency by measuring their fluorescence luminance intensities. Time-intensity curves of ICG opacification through the graft (Q graft) and distal host artery (Q distal) were assessed. Interestingly, increased Δ(Qgraft − Qdistal) and integral(Qgraft − Qdistal) quantitatively analyzed using NIR could predict anastomotic stenosis.

Igari *et al*[90] enabled peripheral blood circulation assessment during DSA in a retrospective study of ICG intraarterial DSA in 16 patients, (22 limbs) with PAD. The authors concluded that ICG evaluation during DSA might be used to assess peripheral blood flow during endovascular procedures.

ICG fluorescence angiography has the limitation of only being able to evaluate tissues up to 3 mm beneath the surface of the skin, hence only allowing microcirculation evaluation in the aforementioned regions. As a result, this technique may demonstrate inadequate efficacy in early PAD patients, because in this patient category microcirculation perfusion alterations will initially occur in deeper muscular tissue than at the skin, as seen in advanced CLI patients[84].

NEAR-INFRARED SPECTROSCOPY

Near-infrared spectroscopy (NIRS) is a non-invasive method that employs near-infrared light to determine tissue oxygenation. It comprises a light source emitting near-infrared wavelengths and a detector that measures the reflected light after the

latter has been absorbed and scattered by illuminated tissue being examined. According to the device being used, NIRS can illuminate tissue at depths between 1-3 cm. Variations in wavelength absorption reflect the concentration of oxygenated and deoxygenated hemoglobin, thus providing information regarding tissue oxygen saturation and, as a result, tissue perfusion (Figure 2)[91].

NIRS applications vary widely, including several utilizations in the field of medicine[92]. Amongst these, it has also been investigated in PAD where it appears to have the ability to be used as a complementary method in its diagnosis and evaluation of severity[93]. Importantly, studies from Mesquita *et al*[94] and Kagaya *et al*[95] revealed significantly lower tissue oxygen saturation values in PAD patients when compared to healthy patients, while a comparative study from Boezeman *et al*[96] found that using NIRS to monitor foot oxygenation (tissue oxygen saturation; StO_2 in muscle tissue) in 14 CLI patients being subjected to EVT is a safe and feasible technique that can detect and record hemodynamic changes.

Limitations of NIRS include overlying infection/inflammation and the strong possibility of erroneous measurements when examining tissues with an abundance of overlaying fat[97]. Moreover, NIRS measurement results can be sensitive to oxygen delivery and extraction[98].

Nonetheless, additional studies are necessary to further clarify the role of NIRS in PAD, its intraprocedural applications, and its potential in predicting wound healing.

LASER-BASED IMAGING

Laser doppler imaging

Laser doppler imaging (LDI) is a non-invasive, non-ionizing, bedside-performed technique measuring blood cell speed and concentration. Similar to other methods, it also employs laser light, but in this instance, it is reflected and scattered by flowing blood cells, and then detected and converted into an electrical signal[99]. Subsequently, a color-coded perfusion image can be generated that may allow for a more accurate evaluation of the angiosome(s) associated with the disease[99]. Applied from a distance, LDI evaluates a larger area of skin by implementing a scanning motion that includes the whole leg[100]. Laser wavelength, scanning speed, and distance between scanner and area under examination can alter tissue penetration and hence should be unchanged to permit reproducibility of measurements and reliability in their comparison[101].

LDI has already found several clinical applications, including rheumatologic disorders, burn and dermal inflammation assessment, and assessment of wound healing and cutaneous ulceration[101]. The prospect of wound healing and cutaneous ulcer evaluation could prove valuable in PAD patients. Moreover, in the setting of PAD, quantifiable real-time increases in microcirculatory perfusion following EVT have been reported[102]. As a result, when using LDI, the operator can obtain real-time quantitative data regarding changes in target angiosome perfusion during the endovascular procedure, while it also has the potential to be proven valuable in the perioperative assessment.

Disadvantages of this technique include the low-depth penetration of laser light, the fact that measurements can be altered by temperature and vasoactive substance consumption, and the fact that measurements can be inconstant, rendering their serial comparison problematic[84].

Laser speckle contrast imaging

Laser speckle contrast imaging (LSCI) is a fast, inexpensive, and relatively simple imaging technique with the ability to produce 2D perfusion maps of large areas under investigation[103]. A typical LSCI comprises a laser light emitter and its diffuser, a camera with its lens, and appropriate processing software. When the tissue under investigation is illuminated with coherent laser light, it serves as a scattering medium and the backscatter produced causes a random interference pattern, which is called a speckle. This technique is based on the variations of backscattered light caused by the interaction of light with flowing RBCs[104]. LSCI is similar to laser Doppler in many ways, but it is still unclear if it measures flow or velocity[104]. Although originally used to measure retinal blood flow, LSCI has been employed in cerebral and skin perfusion assessment[105] and can generally be used in perfusion assessment of various tissues with many additional clinical applications (*e.g.*, burn wound assessment and rheumatological disorders, to name a few)[104]. Moreover, LSCI has been shown useful in assessing diabetic foot ulcers owning to local ischemia[106],

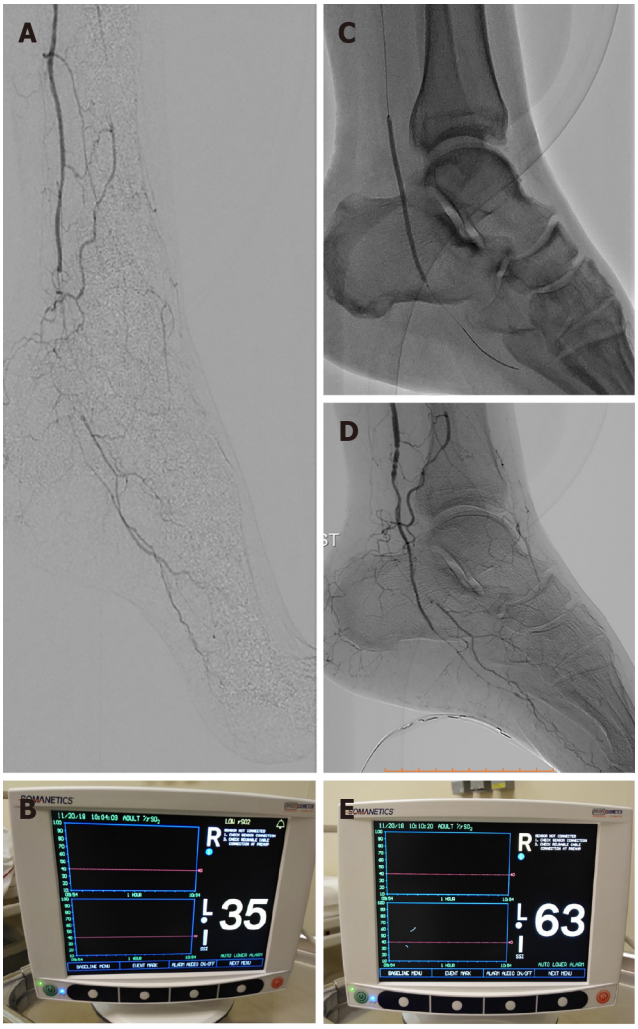

Figure 2 A case of 68-year-old male patient with insulin-dependent diabetes mellitus and advanced Rutherford-Becker class 6 gangrene of the left foot. A and B: Digital subtraction angiography depicting a total occlusion of the distal posterior tibial artery and very low percentage value (35%) of regional hemoglobin oxygen saturation according to real-time near-infrared spectroscopy (NIRS) assessment of foot perfusion; C and D: Balloon angioplasty and final angiographic result demonstrating revascularization of the target occlusion. Note the NIRS electrode attached to the plantar surface of the treated foot; E: Immediately after revascularization, the percentage value of regional hemoglobin oxygen saturation was increased to 63%, demonstrating an 80% increase in foot tissue perfusion.

while - along with $TcPO_2$ – it has also proven beneficial in the diagnosis of severe foot ischemia[107].

LSCI allows microvascular blood flow assessment owning to its high spatial resolution, while it has an added advantage of not necessitating direct contact with the tissue being examined to measure blood flow[105,107]. LSCI is mainly limited by its susceptibility to motion artifacts either due to patient breathing or movement[108]. As a result, addressing this issue is crucial in order to increase the usage of this technique in PAD/CLI patient management, where involuntary limb movements are often present.

Diffuse contrast speckle analysis

Diffuse contrast speckle analysis (DSCA) is a new non-invasive, non-ionizing optical modality that combines LSCI and diffuse correlation spectroscopy (DCS) in order to measure deep tissue blood flow by exploiting the sensitivity of the speckle contrast signal to RBCs movement[109]. DCS can probe deep tissue blood flow by monitoring light intensity fluctuations of the reflected diffuse speckle from tissue and can offer continuous blood flow monitoring, while LSCI (which has been analyzed above) is more suitable for shallow depths[109]. As a result, DSCA employs the deep tissue probing applications of DCS and the simple instrumentation and analysis of LSCI. The difference between DCS and DSCA is that with DSCA a specific region is imaged using a charge-couple device camera so that speckle contrast can be attained for a specific exposure time[110].

DSCA has found several applications in many fields since its development. Clinical applications include cerebral blood flow assessment[111], peripheral vascular health assessment for the evaluation of burns[112], and monitoring of foot tissue blood perfusion in diabetic patients with non-healing wound lesions undergoing vascular interventions[113].

Similar to other optical modalities, this technique has a limited depth penetration and, just as previously mentioned with LSCI, is susceptible to motion artifacts[111].

EMERGING DEVICES

Based on these latter technologies, novel perfusion devices have been available in the market, and others are currently under development. Recently, a real-time tissue perfusion device (PEDRA™ Xauron™ Perfusion System) has received Food and Drug Administration Breakthrough Device Designation for intraprocedural use during CLI treatment. It is a portable laser-based tissue monitoring system currently undergoing its first-in-man study. It provides real-time intraprocedural feedback on whether microcirculation has been improved post-intervention. As blood flows through the skin, the RBCs scatter the laser light, the amount of which is reflected on the monitor, hence quantifying perfusion. Data achieved with this system are claimed to be highly reproducible, however, further research on its clinical utility is required.

Additionally, the HyperView monitor (HyperMed Imaging; Memphis, TN, United States), which enables hyperspectral imaging for superficial tissue oximetry by measuring oxyhemoglobin, deoxyhemoglobin, and oxyhemoglobin saturation in superficial limb tissue, has recently received CE-Mark.

CONCLUSION

Current research validates the prospect of real-time, intraoperative, perfusion-guided revascularization techniques that will allow vascular experts to intraoperatively quantify and assess outcomes optimizing treatment. Such modalities have the potential to obviate misinterpretation of treatment outcomes and provide significantly improved clinical results. Also, novel four-dimensional angiography systems are expected to introduce state-of-the-art fusion imaging and real-time foot perfusion monitoring in everyday clinical practice soon. This will enable the use of novel tissue perfusion endpoints that could improve outcomes of endovascular treatment of arterial ischemia.

Therefore, the development of real-time tissue perfusion imaging and monitoring modalities that allow objective measurements and accurate quantification should be further investigated and validated by large, randomized trials.

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 September 26; 13(9): 399-415

DOI: 10.4330/wjc.v13.i9.399

ISSN 1949-8462 (online)

REVIEW

Exercise-mediated adaptations in vascular function and structure: Beneficial effects in coronary artery disease

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Author contributions: Sakellariou X and Papafaklis M contributed to the conception and design of the research; Sakellariou X and Domouzoglou E drafted the manuscript; Papafaklis M, Katsouras C, Michalis L, and Naka K critically revised the manuscript for important intellectual content; all authors approved the final version of the manuscript.

Conflict-of-interest statement: The authors declare no conflict of interests for this article

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Abstract

Exercise exerts direct effects on the vasculature *via* the impact of hemodynamic forces on the endothelium, thereby leading to functional and structural adaptations that lower cardiovascular risk. The patterns of blood flow and endothelial shear stress during exercise lead to atheroprotective hemodynamic stimuli on the endothelium and contribute to adaptations in vascular function and structure. The structural adaptations observed in arterial lumen dimensions after prolonged exercise supplant the need for acute functional vasodilatation in case of an increase in endothelial shear stress due to repeated exercise bouts. In contrast, wall thickness is affected by rather systemic factors, such as transmural pressure modulated during exercise by generalized changes in blood pressure. Several mechanisms have been proposed to explain the exercise-induced benefits in patients with coronary artery disease (CAD). They include decreased progression of coronary plaques in CAD, recruitment of collaterals, enhanced blood rheological properties, improvement of vascular smooth muscle cell and endothelial function, and coronary blood flow. This review describes how exercise *via* alterations in hemodynamic factors influences vascular function and structure which contributes to cardiovascular risk reduction, and highlights which mechanisms are involved in the positive effects of exercise on CAD.

Key Words: Exercise; Endothelium; Flow-mediated dilation; Endothelial shear stress; Coronary artery disease; Hemodynamics

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: Greece

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 25, 2021
Peer-review started: March 25, 2021
First decision: May 13, 2021
Revised: May 30, 2021
Accepted: July 21, 2021
Article in press: July 21, 2021
Published online: September 26, 2021

P-Reviewer: Chen SM
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Wang LYT

Core Tip: Exercise has beneficial effects on the function and structure of the vasculature, thereby leading to a reduction of the cardiovascular risk. Hemodynamic forces, in particular endothelial shear stress, play a critical role in modulating the endothelial cell phenotype towards atherogenesis or atheroprotection. Exercise improves clinical outcomes in patients with coronary artery disease (CAD). We herein discuss the alterations induced by exercise on vascular function and structure, and the mechanisms involved in the benefits of exercise regarding patients with CAD.

Citation: Sakellariou XM, Papafaklis MI, Domouzoglou EM, Katsouras CS, Michalis LK, Naka KK. Exercise-mediated adaptations in vascular function and structure: Beneficial effects in coronary artery disease. *World J Cardiol* 2021; 13(9): 399-415
URL: https://www.wjgnet.com/1949-8462/full/v13/i9/399.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i9.399

INTRODUCTION

Cardiovascular disease is the main cause of morbidity and mortality in western societies. Although traditional risk factors (hypertension, dyslipidemia, diabetes mellitus, smoking) have a systemic atherogenic effect on the entire vasculature, local hemodynamic factors determine the distribution of atherosclerotic lesions. Endothelial shear stress (ESS), the frictional force acting on the endothelium as the result of blood flow, represents a continuous stimulus eliciting structural and functional effects on the endothelium and plays a critical role in the development of atherosclerosis. Atherosclerotic lesions develop preferentially at areas with disturbed local hemodynamic factors, mainly in regions with low ESS, such as the inner curvature of coronary arteries or in the outer waist of a coronary bifurcation and downstream from a luminal obstruction where ESS is oscillatory. In contrast, arterial regions with physiologic/increased local flow and ESS are thought to be protected from atherosclerosis[1-3].

Multiple studies suggest that exercise decreases the risk of coronary artery disease (CAD) with the positive impact on both primary and secondary prevention being greater than 30%[4,5]. Exercise-based cardiac rehabilitation has been associated with reduced both all-cause and cardiac mortality as well as hospital admissions[6,7]. Exercise also decreases the risk of cardiovascular events and, in patients with CAD, increases exercise capacity, decreases myocardial ischemia, and delays the onset or inhibits angina pectoris[8,9].

The effects of exercise on traditional risk factors do not fully explain the tremendous impact of exercise on cardiovascular risk: differences in known traditional and novel risk factors explain approximately 60% of exercise-mediated cardiovascular disease risk reduction and only 35% of the heart disease risk reduction[10]. Exercise exerts direct effects on the vasculature through the impact of ESS on the endothelium, which leads to functional and structural adaptations that decrease atherosclerotic risk[9,11]. In addition, exercise-induced changes in flow-mediated dilation (FMD), an index of vascular function, do not correlate well with changes in traditional cardiovascular risk factors[12]. Therefore, it is possible that the cardioprotective effect of exercise is, at least in part, independent of changes in traditional risk factors and is mediated by functional and structural adaptations.

The purpose of this review is to describe how exercise *via* alterations in hemodynamic factors influences vascular function and structure contributing to cardiovascular risk reduction, and to highlight which mechanisms are involved in the positive effects of exercise on CAD.

EXERCISE AND MECHANISMS OF ACTION: ROLE OF HEMODYNAMIC FACTORS

Exercise-induced hemodynamic alterations have been reported to play a major role in cardiovascular disease risk reduction, leading to direct effects on the vasculature that

are atheroprotective. These vascular adaptations concern mainly the endothelium and the cross-talk between the endothelium and smooth muscle cells (Figure 1)[11,13,14].

The normal endothelial phenotype is of utmost importance in artery health, and thus, changes in endothelial cell phenotype are related to the development and progression of atherosclerosis. Endothelial dysfunction precedes and is present during the evolution of atherosclerosis, indicating that a proatherogenic endothelial phenotype plays an important role in both the initiation and progression of atherosclerosis[13,15,16]. Furthermore, latest evidence suggests that physical activity exerts beneficial effects by maintaining a normal phenotype of arterial endothelial cells[17-19].

Exercise has beneficial effects in the primary and secondary prevention of CAD, which are closely related to changes in the endothelial cell phenotype[17,20,21]. Exercise augments nitric oxide (NO) bioavailability through a variety of mechanisms; data from cell-culture and animal experiments suggest that NO bioavailability can be affected by many different alterations in the following steps of the NO pathway. Exercise acts as a stimulus for the endothelium to (1) increase the availability of L-arginine (the precursor molecule for NO); (2) promote NO synthase (NOS) activity and expression; and (3) augment the production of extracellular superoxide dismutase, which prevents premature breakdown of NO. These effects likely contribute to amplified exercise capacity and, ultimately, cardiovascular protection. Cardiovascular risk factors, as well as established atherosclerotic disease, are associated with profound impairment of the NO pathway and systems, which may lead to limitations in exercise capacity. Exercise in populations with coronary artery disease can increase NO bioavailability and contribute to secondary prevention[17,22,23]. In addition, the beneficial effects of exercise on preventing atherosclerosis progression and the improvement of endothelial function and phenotype are associated with decreased expression of adhesion molecules as well as inflammatory cell infiltration[24].

The beneficial effects of physical activity on vascular health result from exercise-induced changes in hemodynamic factors. Exercise produces increases in blood flow to the heart and active skeletal muscle, generating shear forces that have been suggested to differentiate gene expression in endothelial and vascular smooth muscle cells[13,25]. Increases in mean ESS positively modify the expression of atheroprotective genes; the beneficial effect of exercise also extends to arteries that do not directly present increased mean ESS during exercise (Figure 1)[14,26]. Accumulating data suggest that elevated ESS is a signal for increased endothelial NOS, decreased endothelin-1 and decreased vascular cell adhesion molecule 1 (VCAM-1) expression. Several intracellular signaling mechanisms have been identified, including G proteins, calcium, and proto-oncogene tyrosine-protein kinase Src (c-Src)[27-30]. Investigation of gene expression patterns of cultured endothelium exposed to different flow waveforms has shown that mean ESS significantly influences the expression of approximately 3000 genes[31]. Data from *in vivo* models provide a correlation between increases in mean ESS and antiatherogenic effects. Chronic increases in blood flow are associated with upregulation of endothelial NOS mRNA, protein and activity, as well as with decreased endothelin-1 bioavailability[13]. Furthermore, during chronic exercise training, improvement of endothelial and mitochondrial function is found to be mediated by adenosine monophosphate-activated protein kinase alpha-2 (AMPKα 2) in studies with *AMPKα2* knockout mice[32-34].

Elevated blood flow during exercise is also related to increases in pulse pressure leading to an increase in cyclic strain across the vasculature. However, data obtained from cell culture demonstrated controversial results regarding the effect of cyclic strain. Although some studies reported that cyclic strain produced an antiatherogenic endothelial cell phenotype, other experiments suggested that cyclic strain had the opposite effect leading to a proatherogenic phenotype in cultured endothelial cells[35-38]. A more recent experiment using a whole vessel preparation reported that the decrease of cyclic strain stimulus leads to lower levels of phosphorylation of the endothelial NOS while it increases the production of reactive oxygen species[39].

EFFECTS OF EXERCISE ON VASCULAR FUNCTION AND STRUCTURE

Exercise and vascular function

Exercise has well-documented positive effects on endothelium-dependent vasodilator capacity, and ESS plays a major role in transducing these changes since enhancement in endothelial function is induced by increased endothelium-derived NOS shear-related protein expression[17]. Many studies have been conducted to investigate not

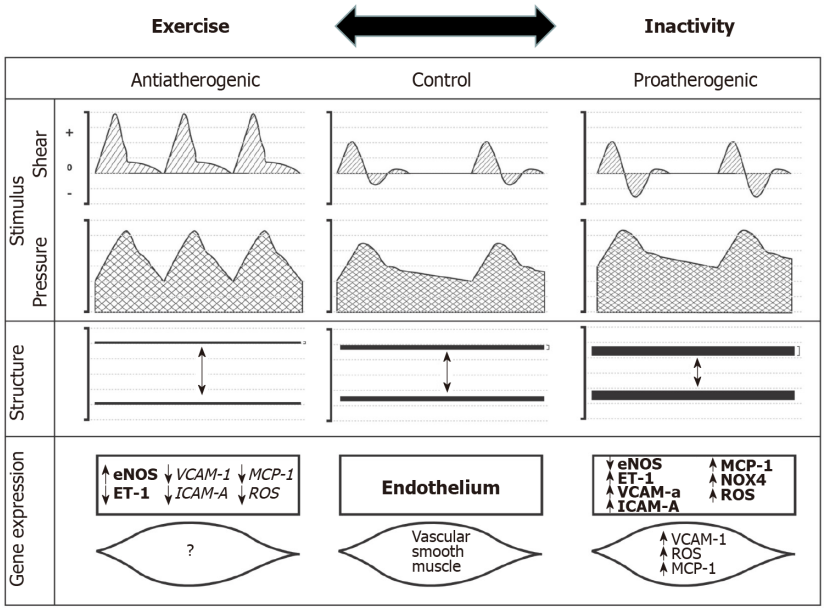

Figure 1 Schematic and hypothetical representation of how hemodynamics during exercise may impact vascular phenotype. The middle panel (Control) represents an artery being exposed to a "typical" hemodynamic stimulus [*i.e.* shear stress pattern (upper signal) and blood pressure (lower signal)]. No abnormalities are observed in artery structure [*i.e.* diameter (arrow) or wall thickness (bracket) or gene expression in the endothelial or smooth muscle cells. The left panel represents hemodynamic stimuli that may be associated with antiatherogenic effects, which include a predominant antegrade shear pattern and cyclic, intermittent elevations in arterial blood pressure (or pulse pressure). These hemodynamic stimuli are related to outward remodeling and a smaller arterial wall thickness, while some observed (in TextTitleface) antiatherogenic genes have been shown to be upregulated, and proatherogenic genes are hypothesized (in italics) to be downregulated under these conditions. On the right panel, proatherogenic shear (dominant retrograde shear component) and pressure (chronic elevation in systolic and diastolic pressure) hemodynamic stimuli are presented. These stimuli are believed to contribute to inward remodeling, thickening of the artery wall and increased expression of proatherogenic genes and downregulation of genes involved on the NO pathway. Adapted from Newcomer *et al*[14] with permission from the American Physiological Society. Citation: Newcomer SC, Thijssen DH, Green DJ. Effects of exercise on endothelium and endothelium/smooth muscle cross talk: role of exercise-induced hemodynamics. *J Appl Physiol (1985)* 2011; 111: 311-320. Copyright ©The American Physiological Society (APS).

only the impact of different patterns of exercise-related ESS on NO-mediated endothelial function, but also the manipulation of the shear stress stimulus during exercise. The modality by which vascular response to exercise training can be influenced in hypertensive individuals has been studied by the SEFRET study, while in spontaneous hypertensive mice the lack of a positive effect of high intensity exercise on endothelial function was found to be related to NO availability imbalance[40,41]. Kim *et al*[42] enrolled middle-aged marathoners with exercise-induced hypertension and reported increased angiotensin II with a reduction in NO levels. These findings may explain the deterioration of arteries vasodilator capacity and elevated blood pressure during exercise in this group of long-distance runners, as well as the therapeutic effect of angiotensin II inhibitors in patients with exercise-induced hypertension. Experimental data also support the hypothesis that physical exercise combined with the administration of renin-angiotensin-aldosterone system blockers could have beneficial effects in order to prevent hypertensive cardiac alterations (*e.g.*, left ventricular hypertrophy)[43].

Exercise effect on the vasculature has also been investigated in respect to other conditions, considering a load of high fat meal in healthy subjects, or in a different study considering glucose ingestion in adults with pre-diabetes. Both studies concluded *via* FMD measurements that exercise produces beneficial effects by attenuating the susceptibility to oxidative damage[44,45]. In patients with type 2 diabetes, acute (2 h after exercise) improvement of endothelial function was observed by FMD measurements after a bout of seven 1-minute cycling intervals using leg resistance exercises, while without leg resistance the beneficial effects were observed at 1 h post exercise[46]. No long-term study on patients with diabetes is available yet.

The acute impact of different exercise modalities, and as a consequence different patterns of blood velocity and flow on the upper limb vasculature function, has also been investigated. FMD, a largely NO-mediated vasodilator response, has been simultaneously studied in both brachial arteries of healthy young men before and after 30-min interventions consisting of bilateral forearm heating, recumbent leg cycling, and bilateral handgrip exercise. During each intervention, a cuff was inflated on 1 arm to unilaterally manipulate the shear rate stimulus. These studies revealed a significant

difference in the pattern of ESS between the 3 interventions. Post-intervention FMD was significantly increased compared with pre-intervention in response to each intervention[47,48]. Beneficial effects have also been reported in women[49]. Taken these results into account, we speculate that increases in anterograde blood flow and ESS lead to enhanced endothelial function.

Observations that predominantly lower limb exercise induces upper limb vascular adaptation have indicated that a generalized or systemic impact of exercise on endothelial function occurs in vascular beds other than those where the exercise stimulus is focused[50-52]. Therefore, exercise induces both localized improvements in vascular function in the active regions through repetitive increases in ESS and systemic vascular adaptations in case of large muscle group exercise.

Based on the above studies one can speculate that different patterns of blood flow and ESS during exercise lead to different hemodynamic and ESS stimuli to which the endothelium is exposed and as a consequence to different vascular adaptations, including the production and bioavailability of NO (Figure 1)[14].

Flow-mediated dilation in response to reactive hyperemia is, surprisingly, manifested only after blood flow drops back to baseline levels. It remains a puzzle whether this discrepancy (*i.e.* dissociation of flow and diameter) could be explained by a reduction in transmural pressure produced by high flow. Dedicated studies have shown that blood pressure and transmural pressure fall after cuff release at the time of peak hyperemic flow. Flow interruption 20 s after cuff release (during high flow but no dilation) leads to an immediate increase in artery diameter. These observations suggest that flow-dependent dilation may be offset by a flow-induced fall in local arterial pressure, and thus, in transmural pressure. This observation indicates that the combination of systemic pressure and local ESS may determine the ultimate vasoactive arterial response following acute exercise[53]. The critical role of these parameters is further confirmed by showing that during a single handgrip exercise, the response (measured by FMD 15 minutes after exercise) was blunted by the addition of an inflated pneumatic cuff to the exercising arm, clearly by abruptly influencing the local ESS[54]. Finally, improvement of the endothelial function was the conclusion of a recent systematic review meta-analysis, where the overall effect of exercise training on the endothelial function in heart failure patients was assessed by FMD in a total of 16 studies[55].

Adaptations that occur in human vasculature following acute exercise, as mentioned above, are useful to understand the impact of repeated episodic exposure to exercise. Previous studies conducted in healthy, asymptomatic subjects have reported that there was no adaptation in endothelial function following exercise and, interestingly, this observation was independent of whether exercise involved localized or large muscle systemic exercise[4]. Therefore, it may be difficult to enhance normal endothelial function in healthy subjects. However, there is evidence suggesting that a moderate-to-higher load (intensity, frequency, duration) of exercise may be necessary for improving endothelial function in healthy asymptomatic humans[56]. Campbell *et al*[57] examined the impact of long-term aerobic exercise during advancing age. They highlighted the importance of remaining active throughout a lifetime, since enhancement of endothelial vascular function is apparent only in athletic older persons, and not in otherwise healthy sedentary individuals following only a period of exercise training. Despite this beneficial effect, it is not clear which exercise load is most appropriate since exercise of high intensity may also cause oxidative stress[58, 59]. Qiu *et al*[60] revealed that chronic aerobic and combined aerobic and resistance exercise training programs improved endothelial function even in patients with type 2 diabetes, whose endothelium is characterized by impaired nitric oxide bioavailability following exercise training. Limited data are available regarding the endothelial function of coronary microcirculation, which suggest that coronary microvascular vasodilator response is enhanced following high-intensity exercise in humans[23]. Finally, we should consider that exercise may induce a transient increase in vascular function in healthy humans, which also influences conduit coronary arteries. FMD may be initially enhanced, but subsequently declined to pre-training levels, as exercise induces changes in arterial structure[52,61,62].

Exercise and vascular structure

Remodeling of luminal dimension: Exercise induces adaptations in the cross-sectional size of arteries, and athletes are characterized by augmented peak vasodilator capacity, which is associated with luminal expansion of resistance arteries[63,64]. Peak vasodilator capacity is significantly greater in the dominant limb of athletes compared to both their non-dominant limb and non-athletic control subjects[65,66]. These data suggest that resistance artery luminal adaptation is apparent in athletes and can occur

as a result of localized and intrinsic vascular stimuli. However, there are some studies in which lower limb exercise induced enhanced peak vasodilator capacity of the upper limb, thereby suggesting a generalized effect of exercise on arterial lumen adaptations [67].

As far as structural adaptations of resistance vessels in the normal heart are concerned, exercise increases arteriolar densities and diameters as suggested by experimental studies in animals[68]. An increase of total cross-sectional area of arterioles in the diameter range of 20-120 μm has been reported, with a higher increase in arterioles of 20-40 μm than in arterioles of 40-120 μm[69]. The impact of aerobic training on the growth of the capillaries of the coronary circulation is also well established. Capillary proliferation is a fundamental response to exercise but is accompanied by concurrent transformation of capillaries into arterioles[70]. Although some experimental studies suggested that exercise causes an increase in myocardial capillary density in prepubescent rats, it seems to have no effect on capillary density in postpubescent ones[71,72]. Exercise-induced angiogenesis may temporarily exceed the increase in left ventricular mass, but with prolonged exercise, angiogenesis matches the left ventricular hypertrophic response[69].

Various methodological approaches suggest that exercise induces growth of epicardial arteries which is in proportion to exercise-induced cardiac hypertrophy (left ventricular mass)[73-75]. Angiographic studies suggest that exercise significantly induces enhanced coronary artery dilating capacity in more active subjects, whereas there is no difference at rest between runners and control subjects[76,77]. For this reason, it is important to elicit dilator responses in order to uncover differences between athletes and control subjects; of note, basal arterial tone in athletes may be enhanced because of alpha-adrenergic and NOS inhibition-induced vasoconstriction, as well as increased resting plasma norepinephrine concentration[78]. Finally, transthoracic echocardiographic assessment has shown similar results since coronary flow reserve, an index of conduit artery vasodilator capacity, is greater in humans undergoing regular exercise[79].

Remodeling of arterial wall: Arterial wall thickness may have implications for cardiovascular risk since common carotid and femoral artery intima-media thickness have been found to be independent predictors of future clinical cardiovascular adverse events[80,81]. Furthermore, arterial wall remodeling may differentiate vascular functional responses since a larger wall-to-lumen ratio is correlated with greater responses to vasoactive stimuli[82].

Studies on the exercise-mediated responses of brachial, carotid, and superficial femoral arteries have shown that arterial wall thickness may be influenced by systemic factors, such as arterial pressure in contrast to shear-mediated impacts on arterial lumen size, which are more localized[64]. A decreased wall thickness is observed in all arteries (carotid, brachial and superficial femoral) of able-bodied athletes compared with control subjects. In contrast to the effects on lumen diameter, a decreased wall thickness was found in both limbs and was not related to exercise type[64,83]. Another study examined bilateral brachial artery wall thickness across an 8-wk period of bilateral handgrip training. ESS was attenuated by cuff inflation around one forearm, but brachial artery pressure responses during exercise were not affected. Handgrip exercise had no effect on baseline brachial artery diameter, blood flow, or shear rate, but significantly decreased brachial artery wall thickness after 6 and 8 wk (similar in cuffed and non-cuffed arm) and wall-to-lumen ratio after 8 wk (also similar in cuffed and non-cuffed arm)[84].

These findings suggest that in contrast to exercise-induced adaptations of arterial luminal dimensions, which are modified by more local mechanisms and mainly by ESS, wall thickness is affected by rather systemic factors, such as transmural pressure, which is modulated during exercise as a result of generalized changes in blood pressure. The interest in wall remodeling has been due to its use as an index of pre-clinical atherosclerosis and estimation of cardiovascular risk. Regarding the time period required for these adaptations, studies have reported that the effects of exercise on atherosclerosis of the carotid artery may require intensive or prolonged exercise, whereas aerobic exercise decreases femoral, popliteal, and brachial artery intima-media thickness in a relatively shorter period[85]. Therefore, a decrease in arterial wall thickness in athletes and healthy young subjects should not necessarily be considered synonymous with a decrease in cardiovascular risk, but as a physiological impact on wall remodeling with yet unknown long-term health implications (Figure 1)[14,86].

EXERCISE AND CORONARY ARTERY DISEASE

Exercise is well known to have a major role in both primary and secondary prevention of CAD, while regular physical activity of 150 min/wk reduces the risk of numerous chronic diseases and decreases cardiovascular mortality[4,9,10,22,87]. In patients with symptomatic CAD, exercise augments physical performance and raises the angina threshold. Endurance exercise has also been shown to attenuate the extent of ischemic ST-segment depression during exercise and decrease perfusion defects on scintigraphy, indicating a possible enhancement in myocardial perfusion[88,89]. The great benefits of exercise are also demonstrated by the fact that physical exercise in selected patients with CAD leads to higher event-free survival and exercise capacity at lower costs compared with percutaneous coronary angioplasty, reflecting the impact of exercise on the whole arterial tree and not only a single location[90].

Several mechanisms have been proposed to explain the exercise-induced benefits in patients with CAD. These include decreased progression (or regression) of coronary plaques/lesions in CAD, recruitment of collaterals, enhanced blood rheological properties, and improvement of endothelial function and coronary blood flow, as well as enhancement of vascular smooth muscle cell function[22,23,91].

Decreased progression or regression of atherosclerotic lesions

Early investigations indicated that the extent of myocardial perfusion was associated with the magnitude of coronary stenosis depicted by angiography. There is evidence that exercise induces enlargement of conduit coronary arteries in normal subjects, and reduces the development or even causes regression of atherosclerotic lesions in coronary arteries in animal CAD models[74,76,77]. Many studies have been conducted to document the regression or decreased progression of atherosclerotic lesions[92,93].

Experimental studies provided controversial results regarding the effect of exercise on reducing the development of coronary artery atherosclerosis or decreasing lesion progression. However, more recent experiments suggest that although exercise has cardio-protective effects and reduces the risk for cardiovascular disease, it may not inhibit progression or reverse coronary artery disease according to angiographic measures of lesion area[91,94,95]. In addition, Kim *et al*[96] studied veteran marathon runners and reported increased prevalence of coronary artery plaques among those with exercise-induced hypertension, thereby suggesting that exercise-induced hypertension could be a novel risk factor for coronary artery plaque formation.

Several randomized trials in humans evaluated angiographically the impact of exercise and investigated whether exercise has a direct effect on the extent of CAD[97-99]. However, findings derived from these studies need to be carefully interpreted since exercise is only one component of lifestyle and medical interventions.

In the Stanford Coronary Risk Intervention Project, the main angiographic outcome was the rate of change in the minimal diameter of diseased segment. Multifactor risk reduction slowed down the progression of CAD; the rate of narrowing of coronary lesion was 47% less than for subjects in the usual-care group[98]. Studies on the impact of exercise and low-fat diet on coronary morphology and myocardial perfusion found that despite the progression of CAD, patients participating in physical exercise and low-fat diet were characterized by lower stress-induced myocardial ischemia and improvement of myocardial perfusion[100]. In the long-term, when patients were reevaluated 6 years later, in the intervention group, the progression of coronary stenoses had a significantly slower rate than in the control group, and that effect was mediated by chronic physical exercise[97].

The Lifestyle Heart Trial demonstrated that lifestyle changes may induce regression of coronary artery atherosclerosis after only 1 year according to the average percentage diameter stenosis, whereas in the control group there was progression of coronary lesions[101]. After 5 years, these lifestyle changes continued to have impacts on CAD in the experimental group, since further regression of coronary lesions was documented, whereas progression of coronary atherosclerosis continued in the control group[99]. In addition, it appears that physical inactivity is considered as a significant atherosclerotic risk factor and accelerates atherosclerosis development[102]. Additionally, there have also been reports on the potential of different levels of regular–leisure time–exercise to enhance cardio-respiratory fitness and retard progression of (or reverse) CAD. Patients in the exercise intervention group have exhibited an increase in oxygen uptake and in peak exercise while a decrease in the respective parameters was observed in the control group. Decreased progression or regression of CAD lesions was observed, only when CAD patients could sustain a high level of leisure time physical activity for 1 year[103]. Nytrøen *et al*[104] investigated the effect of high-intensity interval training on cardiac allograft vasculopathy in heart

transplant recipients. They demonstrated that 1 year of exercise training resulted in significantly lower atheroma volume (assessed by intravascular ultrasound) compared with the control group. A recent review provides recommendations to physicians regarding high-intensity interval training (*i.e.* short bouts of high-intensity submaximal exercise interspersed with rest periods) which has become very popular among patients following cardiac rehabilitation programs[105]. In addition, low-volume high-intensity interval training (typically involving less than 15 minutes of high-intensity exercise per session) is a time and energy efficient way of exercise and leads to similar or even greater cardiorespiratory fitness and cardiac function enhancement when compared to traditional ways of aerobic exercise[106].

Exercise may have a greater impact on CAD progression or regression following treatment with percutaneous coronary intervention (PCI) and stent implantation. Diameter restenosis after PCI was significantly higher in untrained compared with trained patients. In addition, myocardial perfusion of patients with angiographic restenosis was enhanced only in the exercise group[107]. Studies in a porcine PCI model suggest that exercise significantly decreases the extent of neointimal hyperplasia lesion and restenosis[108]. A recent meta-analysis demonstrated that rehabilitation exercise programs (including cycle ergometer, jogging, climbing, swimming and treadmill) reduced the incidence of coronary artery restenosis following PCI in patients with CAD[109]. A possible explanation for this beneficial impact of exercise is that coronary hemodynamics are altered by interventional procedures and exercise bouts generate more beneficial "mechanical" signals in the walls of these arteries[91].

Atherosclerotic lesion composition

Experimental studies have shown that moderate physical exercise reduces the bulk of coronary lesions and spontaneous atherosclerotic plaque rupture leading to prolonged survival[110]. Exercise alters the extracellular matrix composition of the neointima in animal PCI models and decreases neointimal proliferation, which may have a significant impact on preventing restenosis following coronary angioplasty[108]. Differences in the intima/media ratio were observed after exercise, as well as higher collagen and elastin contents of atherosclerotic plaques were detected in exercise groups. Lower macrophage concentration in the atherosclerotic plaques has also been found in the exercise group. Furthermore, a significant decrease in MMP-9/TIMP-1 (matrix metalloproteinases to tissue inhibitor of matrix metalloproteinases) ratio, which has an important role in the atherosclerotic plaque vulnerability, has been reported after exercise[111]. The latest studies support the idea that physical exercise may convert a vulnerable thin-cap atheroma to a more stable lesion, less prone to rupture, which can reduce cardiac mortality[91].

Collaterals recruitment

Studies in animals suggest that exercise stimulates coronary collateral development [112-114]. Endothelial progenitor cells are considered to initiate neovascularization in response to ischemia after myocardial infarction; a significant increase of endothelial progenitor cell proliferation and function has been observed in mice both with and without myocardial infarction in the exercise group[111,115]. However, there are some contradictory data that report no development of coronary collaterals in dogs with normal coronary arteries[116,117]. The effect of physical exercise on collateral vessel growth in humans is also disputable. Patients with ischemic heart disease and left ventricular systolic dysfunction who have been randomized to exercise and control groups demonstrated that there is enhanced perfusion and contractile response to dobutamine, which were correlated with an increase in coronary collateralization in the exercise group[118]. Zbinden *et al*[119] demonstrated that a 3-month endurance exercise training program enhanced coronary collateral supply to normal vessels, as well as to previously stenotic arteries with percutaneous intervention in patients referred for diagnostic coronary angiography due to chest pain or positive treadmill exercise test. However, there are many angiographic studies conducted at rest in patients with CAD that did not confirm this hypothesis[120,121]. A randomized trial including patients with CAD did not show any significant effect of exercise on collateral formation after 1 year, although progression of CAD was significantly slowed in the intervention group[122].

Blood rheological properties

Abnormalities of blood rheological properties are an independent risk factor for cardiovascular disease, and may contribute to athero-thrombogenesis. However, there

are limited literature data about the effect of exercise on blood rheological properties. Recent studies suggest that blood becomes more dilute because of expansion of blood volume as a result of exercise training. It has been reported that this hypervolemia and blood dilutional effect may contribute to enhanced cardiac stroke volume during exercise[123]. Blood rheology may be enhanced after regular physical exercise since different experimental approaches, including regular exercise, demonstrate a decrease of blood viscosity[124]. However, blood rheology may also remain unaffected in patients with CAD and heart failure[125]. Further studies are necessary to determine the possible association between exercise and blood rheological profiles, especially since the improvement of blood viscosity remains an interesting therapeutic option for symptoms relief in patients with CAD; enhanced fluidity may facilitate oxygen delivery to the exercising muscles because of a reduced resistance to blood flow within the microcirculation.

Enhancement of endothelial function and coronary blood flow

None of the above-mentioned mechanisms fully explain the beneficial effect of exercise on cardiovascular mortality and myocardial perfusion, as well as the major role that exercise has gained in cardiac rehabilitation. During the last two decades, endothelial dysfunction has been correlated with major risk factors for CAD, and identified even before coronary stenoses are visible. Endothelial dysfunction is considered a significant predictor of coronary adverse events and has a great role in myocardial ischemia. Coronary endothelial function depends on NO bioavailability, the balance of which is disrupted in CAD. The impairment of NO production, in addition with an increase in oxidative stress, induces the loss of endothelial cells by apoptosis and the deterioration of endothelial function, leading to paradoxical vasoconstriction and myocardial ischemia[18,22,126]. Exercise attenuates paradoxical vasoconstriction in patients with CAD and leads to improvement of endothelial function as it restores the disrupted NO balance.

Patients with CAD are characterized by functional alteration of circulating progenitor cells, which maintain the integrity of the vasculature. Exercise restores the regenerative capacity of circulating progenitor cells in cardiovascular disease and prevents further impairment of vessels vasomotion. A recent meta-analysis demonstrated increased levels of endothelial progenitor cells into the peripheral blood of patients with cardiovascular disease following exercise training protocols[127]. As a consequence, exercise enhances vasodilator capacity in different vascular beds and improves myocardial perfusion in the absence of changes in baseline coronary artery diameter[18,126,128].

Exercise in patients with CAD may enhance coronary endothelial function. To investigate this hypothesis, patients with coronary endothelial dysfunction (according to abnormal acetylcholine-induced vasoconstriction) were randomized to an exercise or a control group. Coronary vasoconstriction in response to acetylcholine was significantly attenuated and adenosine-induced flow-dependent vasodilation was improved after physical exercise, which indicates that exercise had beneficial impacts on the endothelium of epicardial conduit vessels[23]. In addition, exercise induces increases in coronary blood flow reserve, as assessed by adenosine infusion, indicating augmentation in vasodilator capacity of resistance coronary vessels. A recent meta-analysis studied the long-term effects of aerobic exercise in patients with coronary artery disease, suggesting a significant enhancement of vascular vasomotor function and coronary flow velocity reserve[129]. Patients with CAD following a 6-month aerobic exercise training program had higher peak response to acetylcholine when they performed high-frequency exercise compared with low frequency cardiac rehabilitation programs[130]. In addition, a 2-wk twice daily aquatic endurance plus calisthenics exercise training program in patients with a recent myocardial infarction or revascularization intervention improved both aerobic exercise capacity and vascular endothelial function[131]. Kollet *et al*[132] conducted a randomized pilot study and enrolled post-myocardial infarction patients undergoing PCI who performed a 30-min moderate-intensity aerobic training program. This group of patients demonstrated enhanced endothelial function as determined by improved FMD of the brachial artery after each exercise period. On the contrary, prolonged sitting leads to significant deterioration of vascular function in the lower limbs. However, this deleterious effect on FMD may be reversed by "sitting interruption" strategies including simple resistance and aerobic activities[133]. All these observations suggest that exercise reduces stress-induced myocardial ischemia and improves endothelium-dependent coronary vasodilation in patients with CAD[23]. Patients with newly diagnosed CAD and improved FMD after 6 mo of optimized therapy for reducing cardiovascular risk factors had a lower rate of adverse cardiac events (10% *vs* 26%, $P < 0.01$) during 3 years

of follow-up, while persistent impairment of endothelial vasomotor function was an independent predictor of adverse outcomes[134].

Exercise does not quickly restore endothelial function to normal levels; restoration of normal endothelial function may require more extended exercise[23]. Improvement of vascular endothelial function of conduit and resistance coronary vessels may occur shortly after the beginning of exercise in patients with CAD; however, augmentation of the capillary bed needs a period of few weeks and collateral formation and regression of coronary lesions requires a much more extended exercise period[22].

The vasodilator response of epicardial arteries to nitroglycerine-induced endothelium-independent coronary vasodilation is not significantly affected following exercise. However, there is evidence that epicardial coronary arteries of highly trained middle-aged endurance runners demonstrate greater dilating capacity to nitroglycerin compared with inactive individuals. Thus, it is possible that high intensity endurance training over a long period may be necessary to enhance endothelium-independent dilation capacity of coronary vessels in patients with CAD[76].

In the majority of cases, the positive impact of exercise is limited to the function of the endothelium, whereas smooth muscle function stays unaltered. However, some studies report that enhancement of smooth muscle function is possible to occur but in more severe disease. Thus, one can speculate that there is a stepwise process of dysfunction and amelioration which begins with the endothelium and migrates to the remaining layers of the vessel wall[135].

CONCLUSION

Cardiovascular disease is closely related to local hemodynamic factors. Exercise has direct effects on the vasculature *via* the impact of ESS on the endothelium, leading to decreased atherosclerotic risk. Exercise contributes to maintaining a normal phenotype of arterial endothelial cells which is the result of changes in hemodynamic factors, ultimately leading to beneficial effects. Different patterns of blood flow and ESS exert variable stimuli on the endothelium and result in improved NO bioavailability and adaptations in vascular function and structure. Regarding arterial structure, wall thickness may also be influenced by systemic factors. In patients with CAD, exercise has multiple beneficial effects beyond endothelial function since it contributes to the conversion of vulnerable atherosclerotic plaques to a more stable phenotype, may enhance the recruitment of collaterals, and improves the blood rheological properties. These effects translate to reduced cardiac mortality indicating the value of exercise in cardiac rehabilitation programs. Further research is required to investigate and clarify the molecular mechanisms underlying the structural and vascular adaptations. Finally, it is a great challenge to study the different vascular adaptations which are induced by each type of exercise as well as which training program is most effective for each population group.

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 September 26; 13(9): 416-437

DOI: 10.4330/wjc.v13.i9.416

ISSN 1949-8462 (online)

REVIEW

Stent visualization methods to guide percutaneous coronary interventions and assess long-term patency

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Author contributions: Ghafari C and Carlier S equally contributed to this work; all authors have read and approve the final manuscript.

Conflict-of-interest statement: The authors have no any conflicts of interest.

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: Belgium

Peer-review report's scientific

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Abstract

Evaluation of acute percutaneous coronary intervention (PCI) results and long-term follow-up remains challenging with ongoing stent designs. Several imaging tools have been developed to assess native vessel atherosclerosis and stent expansion, improving overall PCI results and reducing adverse cardiac events. Quantitative coronary analysis has played a crucial role in quantifying the extent of coronary artery disease and stent results. Digital stent enhancement methods have been well validated and improved stent strut visualization. Intravascular imaging remains the gold standard in PCI guidance but adds costs and time to the procedure. With a recent shift towards non-invasive imaging assessment and coronary computed tomography angiography imaging have shown promising results. We hereby review novel stent visualization techniques used to guide PCI and assess stent patency in the modern PCI era.

Key Words: Percutaneous coronary intervention; Stent visualization; Stent underexpansion; Quantitative coronary analysis; Digital stent enhancement; Intravascular ultrasound; Optical coherence tomography; Coronary computed tomography angiography

Core Tip: Evaluation of acute and long-term percutaneous coronary intervention (PCI) results remains challenging. We hereby review current available tools for guiding and assessing PCI results.

Citation: Ghafari C, Carlier S. Stent visualization methods to guide percutaneous coronary interventions and assess long-term patency. *World J Cardiol* 2021; 13(9): 416-437

URL: https://www.wjgnet.com/1949-8462/full/v13/i9/416.htm

DOI: https://dx.doi.org/10.4330/wjc.v13.i9.416

quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 25, 2021
Peer-review started: March 25, 2021
First decision: May 13, 2021
Revised: May 24, 2021
Accepted: July 22, 2021
Article in press: July 22, 2021
Published online: September 26, 2021

P-Reviewer: Kashiwagi M
S-Editor: Ma YJ
L-Editor: A
P-Editor: Wang LYT

INTRODUCTION

Atherosclerosis is a slow-progressing multifocal immunoinflammatory disease of medium and large-sized arteries[1]. Exposure to established risk factors triggers an oxidative response leading to the formation of fatty streaks within the vessel wall. Phagocytosis of these lipid rich proteins by macrophages induces cell apoptosis leading to cellular debris which, along with necrotic endothelial and smooth muscle cells, form the principal constituent of the lipid-rich plaque core. The deposit of calcium and phosphate-rich hydroxyapatite crystals occurs as a macrophage-mediated response to oxidation and endothelial dysfunction[2]. Coronary artery disease (CAD) secondary to atherosclerosis remains the most common cause of death across the globe, imposing a major health and economic burden on nations[3,4]. Despite major technological and therapeutic advances, the prevalence of CAD is expected to continue to rise secondary to an increase in the aging population[5]. Coronary artery angiography (CAG), despite being invasive, remains the gold standard technique to assess significant coronary artery disease and to guide percutaneous coronary intervention (PCI). PCI reduces major cardiac events in acute coronary syndrome events[6] and improves the quality of life in chronic coronary syndrome[7]. The first human cardiac catheterization dates back to 1929 when Dr. Forssmann[8] auto-measured the pressure in his cardiac chambers using a urinary catheter. Cournand *et al*[9] and Nossaman *et al*[10] later developed right heart catheterization with a standard diagnostic tool, and in 1956, along with Dr. Forssmann[8], were awarded the Nobel Prize in Medicine for their work. Dr. Seldinger[11] developed his safe percutaneous catheterization technique in 1953 followed by Dr. Sones[12] who performed the first selective coronary angiogram in 1958. In 1964 the first peripheral angioplasty was performed by Drs. Dotter and Judkins[13]. Since then, PCI has undergone a rapid technological evolution, beginning with Turina *et al*[14] in 1979 who developed the initial coronary balloon angioplasty, later referred to as plain old balloon angioplasty (POBA). POBA was the first step for modern coronary intervention and was limited by the risk of acute thrombosis (3%-8%)[15,16] and early vessel recoil (5%-10%), along with a high rate of restenosis (33%)[17-22]. Nevertheless, POBA paved the way to the first coronary stents that were implanted in 1986 by Sigwart *et al*[23]. Although the recent ISCHEMIA trial did not show evidence of a reduced risk of ischemic cardiovascular events or death for an initial invasive strategy as compared with optimal medical treatment among patients with stable angina and moderate or severe ischemia[7], only 4% of contemporary real-world patients would be eligible for the trial[24]. Using coronary physiology guidance, PCI also decreases cardiac death and myocardial infarction in chronic coronary symptoms[25]. Several trials (BENESTENT, STRESS, CAVEAT) have laid the cornerstone upon which angiographic guidelines have been proposed, and coronary stent implantation after PCI has been shown to improve short- and long-term clinical outcomes[26-28]. However, a coronary stent should meet numerous design criteria in order to fulfill its function, including the fact that the stent platform must be radio-opaque enough to provide the required visibility for correct placement and proper expansion in order to ensure successful stent deployment[29,30]. In addition, a stent must have a narrow profile when collapsed for easy deliverability[31,32]. Strut thickness has been a key element of stent design, with thinner struts associated with greater deliverability. Several studies have also shown a lower rate of restenosis associated with thinner stent' struts[31,33,34]. Consequently, a move towards thinner struts stents has been made, with current stent strut thickness being between 60-100 μm. Initial stents were made of nitinol and were self-expandable. These were later replaced by balloon expandable stents.

Atherosclerosis is an intimal focal disease-causing connective tissue proliferation and lipid accumulation. In order to preserve their lumen, atherosclerotic vessels dilate in a remodeling response and only after reaching the capacity of this response does stenosis occur. These facts imply that an accurate assessment of coronary artery stenosis and reference diameter is of major importance. Lesion severity evaluation by visual estimation remains subjective and has been shown to be inadequate secondary to a high degree of intra-observer and inter-observer variability[35]. In fact, the lumen in eccentric plaques alters in shape and size, and the reference segment (deemed as normal) may be either narrowed or dilated. For decades, PCI guidance and results have been evaluated by visual assessment, nevertheless, angiography alone does not provide sufficient information in several scenarios presenting a major risk factors of stent thrombosis, such as stent fracture, stent malapposition or stent overlap[29,36,37]. To study PCI efficacy and results, several carefully acquired coronary angiographic films need to be interpreted in detail pre- and post-intervention, as well as at follow-up. Alternative imaging techniques have been developed to overcome these

limitations. We hereby review the coronary stent visualization methods currently used for the assessment of PCI results.

QUANTITATIVE CORONARY ANALYSIS

Since visual assessment of lumen diameter and stenosis is scarcely sensitive, quantitative coronary analysis (QCA) was first described for a theoretical objective evaluation of coronary artery stenosis and lumen diameter in clinical settings. Since then, the field has grown substantially, with several methods and algorithms being developed since the late 1970s[38]. The European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions Task Force on the Evaluation of Coronary Stents in Europe recommended a mandatory assessment by offline QCA core lab analysis in case of comparative studies[39], and QCA was endorsed by the Academic Research Consortium 2[40]. QCA relies on coronary angiography in order to obtain objective parameters and can also be used to assess immediate and long-term PCI results[38]. It is based on the use of dedicated software allowing the precise determination of specific parameters in an operator-independent manner and can serve either a clinical purpose (on-line during a procedure) or a research one (off-line)[41]. With ongoing research, X-ray imaging has significantly progressed, leading to many available computer-integrated applications that allow the quantification of coronary stenosis leading to QCA validation and incorporation in various systems[42]. Multiple validated software are currently available on the market, among which the most widely used are CAAS II (PIE Medical, Maastricht, The Netherlands) and QAngio XA (Medis, Leiden, The Netherlands)[43-45].

QCA requires an optical magnification of the angiographic image. A digital cineangiogram is generated on an image processor after image acquisition. Using an integrated software and analysis system, digital quantification of selected frames can be easily performed with or without magnification. After digitalization, and prior to computer analysis, the images are stored in a specifically designed image processing system.

The real challenge of QCA is the selection of the coronary angiography sequence with a minimal foreshortening and minimal overlap with nearby structures after intracoronary nitroglycerine administration in order to reduce any vasospasm. In addition, the accuracy and reliability of the analysis is improved by increasing the distinction between the contrast-filled coronary artery and the background (best achieved while the patient is in deep inspiration). A frame including a completely contrast-filled catheter is first selected and a central line is hand-drawn along the tip of catheter. Once the image has been acquired and processed, boundary delineation within the area of interest is performed by the computer. QCA usually focuses on one or more coronary segments and is generally carried out in the case of an ambiguous coronary lesion. The area of interest can be identified automatically by the computer software or manually. The operator indicates the window of interest, an approximation of the borders or points along the vessel's central line[46,47]. The software automatically recognizes its margins and performs calibration. In order to derive quantitative information from the analysis, a calibration converts measured pixels to *in vivo* millimeters by using the contrast-filled known catheter diameter as a reference standard or using an automatic calibration obtained from recent systems[48]. By assuming a homogeneous distribution of contrast within the vessel lumen, the errors within the edge definition are minimized in eccentric lesions by densitometry[38]. Then, an appropriate frame that includes the segment of interest is selected during end-diastole when coronaries are least subjected to myocardial contractions. Similar to the calibration procedure, a central line is drawn in order for the software to generate automatic contours. The frames are then automatically transferred to a digital lossless compression file that generates a series of diameters and parameters along the vessel line expressed in millimeters and percentages. This also allows an automatic reconstruction of the vessel lumen and interpolates the diseased segment to the proximal and distal references considered disease-free using an algorithm based on the calculation of mean diameter values at different points along the segment of interest (Figure 1). Edge definition, although more important than quantification, is harder to accomplish[48]. The difference in luminal cross-sectional area can then be compared between normal and diseased segments in addition to the assessment of PCI results. The analysis can also be performed after stent implantation in order to compare several parameters pre- and post-stent implantation. Hence, QCA permits the evaluation of the minimal lumen diameter (MLD, the smallest diameter within the

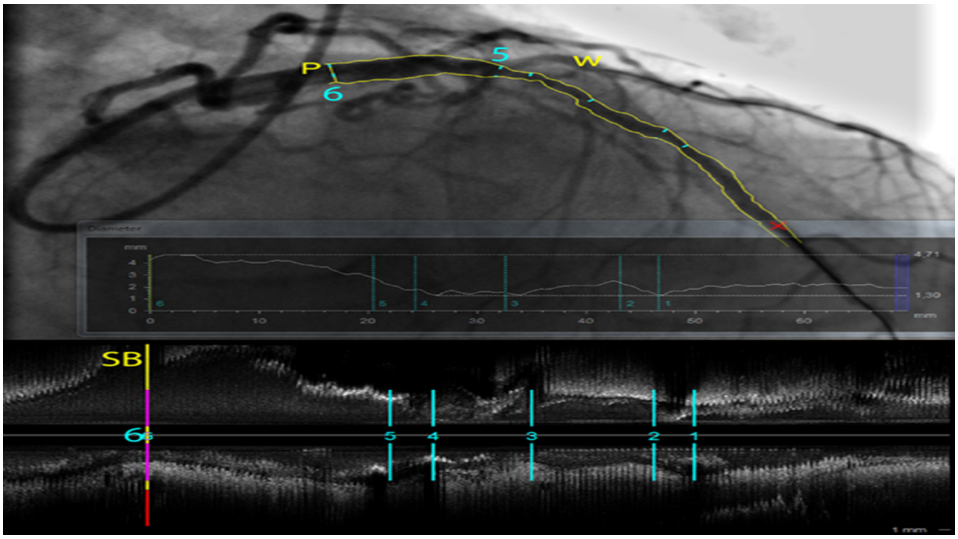

Figure 1 Quantitative coronary analysis analysis (CAAS software, Pie Medical Imaging) of a long stenosis in a left anterior descending artery. The vessel borders are automatically detected and diameters are plotted along the vessel centerline. Different measurements (1-6) are shown on a co-registered intravascular ultrasound (IVUS) pull-back longitudinal view at the bottom. At P (6), the ostium free of disease of a large side branch (first diagonal artery) is better characterized in the 3D volume data from the IVUS pull-back than on the overlapping structures of the angiogram. (W) shows a wire in the second diagonal branch, illustrating the inherent limitations in the interpretation of a coronary angiography that is only a 2D shadow projection of a complex 3D coronary tree filled with contrast that requires multiple views in different projections.

segment studied), the reference vessel diameter (RVD, averaged diameter of the coronary assumed disease-free), the diameter stenosis percentage, the lesion length (LL, measured by two points where the margins change direction), the acute gain (post-procedural MLD-pre-procedural MLD), and late loss (post-procedural MLD-follow-up MLD for example at 6 mo). On-line digital systems and off-line computer processing systems have become widely available. These systems facilitate the accurate clinical analysis of vessel diameter, percent stenosis, stent deployment, and other endovascular interventions. One of the major coronary angiography drawbacks is its two-dimensional luminogram of a three-dimensional structure, as well as vessel overlap and foreshortening during acquisition. Furthermore, QCA is influenced by the frame selection, vessel movement, end-diastolic phase and calibration[49,50].

THREE-DIMENSIONAL QCA

Currently, 2-dimensional QCA remains the most commonly used and validated technique despite its drawbacks. However, as more complex lesions are treated more frequently, 3-dimensional QCA analysis software is a valuable tool. Three-dimensional QCA is based on standard 2-dimensional angiography images obtained in two views at least 30 degrees apart and with as much minimal vessel overlap. Several 3D QCA programs are currently available, among which, the most commonly employed and validated are CAAS 5 (Pie medical Imaging, Maastricht, The Netherlands) and CardiOp-B (Paieon Medical Ltd. Park Afek, Israel)[51-53]. Although these applications defer in their respective calibration methods, nevertheless they allow a better understanding and visualization of coronary anatomy and help the operator find the optimal working angle[54,55]. Three-dimensional QCA software also allows the assessment of bifurcating lesions and helps choose the appropriate treatment strategy [56].

Although 3-dimensional QCA programs are readily available and have already been validated[55,57,58], they fail to improve accuracy by resolving the problem of vessel foreshortening. Several comparative studies between 2-dimensional and 3-dimensional QCA have led to mixed results with regards to the accuracy of this technology[55,57,59-61].

Visual assessment of coronary lesions tends to underestimate < 50% stenoses and to overestimate those > 50%[62,63], while QCA tends more to overestimate lesions < 50% than those between 50% and 75% and underestimate stenoses > 75%[41,64]. QCA may be easily and rapidly employed in everyday clinical practice to objectively, precisely and independently assess coronary lesion severity. Hence, QCA may direct treatment

of a stenosis if a functional assessment is not available. Additionally, QCA instantly assesses objective parameters, such as RVD and lesion length, allowing for a more precise choice of treatment material as well as PCI result assessment. QCA has also played a pivotal role in clinical research through its reproducibility and independence. It has become a fundamental core laboratory tool for the off-line assessment of devices and/or the progression of atherosclerosis following pharmacological therapies[65].

Although QCA has been around for more than 30 years now, it still presents multiple limitations. Nevertheless, it remains an easy-to-use tool, both when used in clinical research and as a complementary tool in practice alongside angiography.

DIGITAL STENT ENHANCEMENT

Stent positioning and deployment is carried out under angiography guidance and hence relies on the radiopaque nature of the material used for visualization. Long-term safety concerns of implanted coronary stents have led to increased research on the improvement of stent technology. It has been stipulated that thinner struts are associated with a better outcome in drug-eluting stents (DES). The ISAR STEREO trials have identified thicker struts thickness to be an independent predictor of in-stent restenosis[33,34,66]. Furthermore, the use of thinner-strut stents has been associated with a significant reduction in myocardial infarction[67]. In addition, inadequate stent deployment and underexpansion has been shown to be a major factor for stent thrombosis associated with a high death rate and non-fatal myocardial infarction[29,68]. With recent advancements in stent design technology, DES has become the standard-of-care for patients with acute and chronic coronary syndromes. The first DES consisted of a stainless-steel backbone rendering them radiopaque with good visibility on angiography. However, given the inverse relationship between strut thickness and fibrous hyperplasia, newer second-generation DES have switched to cobalt chromium or platinum chromium, along with a trend towards thinner struts decreasing stent radiopacity, all while preserving radial strength. Although the incidence of stent thrombosis has decreased during the first year after implantation as compared to BMS, its rate remains high[69]. Stent architecture assessment is also important in order to assess PCI results and complications. With the trend toward the use of lower X-ray power during procedures at 7.5 frames per second, and despite the use of radiopaque materials in stent construction, the visualization of stents remains challenging and insufficient for stent expansion assessment. Stent visibility is further altered with stent motion within the sequence as well as in larger patients due to X-ray scattering.

Since the early 2000s, a new image processing technique called digital stent enhancement (DSE) has been developed, specifically tailored for stent visualization. In order to produce an enhanced image of an implanted stent, DSE uses a motion-corrected X-ray image sequence making it reliable during the normal workflow during coronary angioplasties[70]. Due to the ease of use of this technique, several manufacturers have become interested in developing and validating new systems.

Although they cannot bring direct information regarding stent apposition onto the vessel wall, DSE systems can provide relevant images for assessing deployment irregularities, lesion treatment, and potentially measuring stent expansion[71]. Several case reports and case series have validated the use of the different DSE systems in different clinical settings. Additionally, a decrease in late loss and binary restenosis, along with a lower incidence of target lesion revascularization at 6 and 12 mo respectively, were found in patients where DSE was used as compared to patients treated without DSE[72].

StentBoost Subtract System® (Philips Healthcare, Best, The Netherlands) is currently the most used technique and is extensively validated[73-77]. StentBoost Subtract System has also been shown to have high enough specificity as compared to intravascular imaging[73,78]. StentViz (GE Healthcare, Milwaukee, WI, United States), StentOptimizer (Paieon, Rosh Haayin, Israel) and ClearStent (Siemens Healthcare, Munich, Germany) have also been studied and validated[79-81]. Nevertheless, these systems all depend on the X-ray angiographic system vendor. StentEnhancer (Pie Medical, Maastricht, The Netherlands) is a recently added DSE with the advantage of being vendor independent.

DSE improves the fluoroscopic image quality by reducing the influence of background noise. It consists of a short X-ray sequence where the stent is moving with each heartbeat and during breathing. This is based on the fact that over a whole sequence, the sum of the images of the stent is displayed with a much higher contrast

to noise ratio. Hence, the DSE algorithm "tracks" the stent motion along the sequence and automatically integrates the value of the stent' pixels along their trajectories. As a result, the overall sum of the pixels is displayed in an enhanced still-image.

After stent deployment, the stent delivery balloon is kept in place deflated and cineacquisition of the stented segment is performed without contrast injection. Stent-motion is detected using the two balloon radiopaque markers[70,82]. Forty-five frames are acquired and automatically transferred to a workstation where software corrects for motion-compensated temporal averaging[83,84]. Immediately after, an enhanced image of the stent is displayed with an improved resolution and a superior signal-to-noise ratio (Figure 2). These steps may be repeated with a post-dilation balloon. A modified DSE technique, aimed at visualizing the stent in relation to the vessel, is also available. This differs from the abovementioned technique by the contrast injection [84]. The resulting image can be used for stent expansion assessment, visually and quantitatively, much like during QCA analysis[85-87]. Its ease-of-use and availability, along with the high-quality stent images delivered, have led to DSE being an important alternative or complement to stent visualization techniques during PCI. DSE systems are rapid, cost-effective, do not require contrast injection and can be used during complex PCI cases, such as ostial or bifurcating lesions[74,88]. However, an increase in radiation exposure has been reported, but this had no significant impact on patient radiation dose[89].

INTRAVASCULAR IMAGING

Coronary angiography only provides a planar, 2-dimensional evaluation of the contrast-filled coronary lumen and fails to evaluate the atherosclerotic plaque located within the arterial wall, hence often underestimating the degree of intraluminal stenosis[35]. The addition of quantitative digital assessment (QCA and DSE) improves the overall coronary assessment but still presents pitfalls. In fact, extensive coronary disease with positive remodeling may appear "normal", leading to a false feeling of reassurance. This is especially apparent with patients presenting with extensive disease on computed tomography angiography but found to have minimal disease on angiography. In order to bypass these limitations, the idea of intravascular imaging emerged in 1971, thanks to Bom *et al*[90] in Rotterdam, and Yock *et al*[91] later recorded the first greyscale transluminal ultrasound images of human arteries. Since then, major breakthroughs have been achieved including intravascular ultrasound (IVUS) radiofrequency tissue characterization and optical coherence tomography (OCT). Intravascular imaging has the advantage of capturing plaques from close proximity. These techniques have been a valuable tool in everyday practice shedding light on whether the plaque is at risk of progression, vessel diameter size, acute PCI results and reasons behind target lesion failure and revascularization.

IVUS

IVUS imaging relies on the properties of ultrasound waves which are produced by the oscillatory movement of a transducer[92]. A piezoelectric crystal inside a transducer, attached to a catheter, produces high frequency sound waves which penetrate tissue, reflect off vascular structures and return to the transducer, which then transmits the information to a dedicated system for processing. These catheters are 3.2 to 3.5 French in size and compatible with 5 French guiding catheters over 0.014 in guidewires.

The first ultrasound imaging catheters, designed by Bom and colleagues, were used for cardiac chamber and valve assessment. It was not until 1988 that the first intracoronary images were recorded[93]. Since then, IVUS has been extensively used and developed, and has been the cornerstone of major interventional trials, from the bare metal stents era to the newer bio-absorbable stents (BVS). In addition, IVUS has allowed a better understanding of CAD progression, vessel reaction to PCI, as well as long- and short-term vessel remodeling after stent implantation.

In order to increase radial resolution, IVUS catheters use higher frequencies than non-invasive echocardiography, typically between 20 and 60 MHz. Resolution increases with increased frequency, however penetration decreases. Currently, 2 types of IVUS catheter designs exist on the market: a solid-state, phased array one and a rotational, mechanical one. Solid-state catheters (Volcano, Philips Healthcare, Best, The Netherlands) consist of multiple transducer elements mounted circumferentially at the tip of the catheter. The phased-array transducers are activated in groups in a rotational

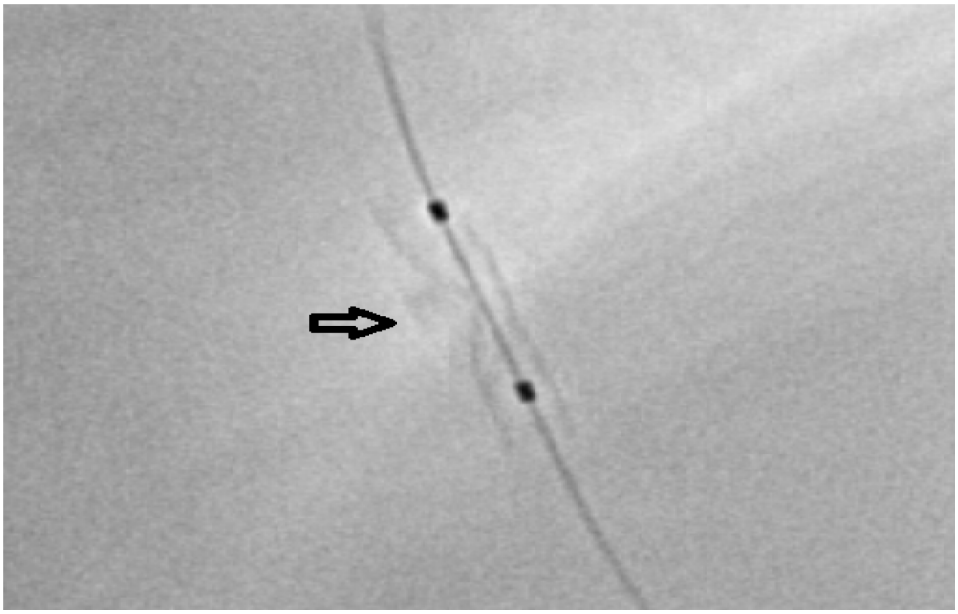

Figure 2 Digital stent enhancement image using StentBoost Subtract System (Philips Healthcare, Best, The Netherlands) showing stent underexpansion. The two balloon markers are visible (two black dots). The calcifications responsible for the underexpansion are clearly visible (arrow).

manner. The collected information is then transferred to a computer system which computes a cross sectional image of the vessel. Volcano catheters also offer kind of virtual histology, (VH-IVUS). The advantage of a solid-state system is its prepackaged ease of setup along with the lack of guidewire artefacts. This is because the catheter is advanced on the wire itself, meaning that there are no non-uniform rotational distortion (NURD) artefacts, which usually result from mechanical binding, as in this case there is no friction on the catheter. On the other hand, solid-state catheters have a low resolution, running at 20 MHz, and a blind spot all around the imaging ring, with a need for masking this "ring down" zone by digital subtraction before acquiring images. Rotational systems (Boston Scientific, Santa Clara, CA, United States; Terumo Corporation, Tokyo, Japan; Philips Healthcare, Best, The Netherlands; Acist Medical Systems Inc., Eden Prairie, MN, United States) use a single transducer element at the tip of the catheter rotated by an external motor drive attached to the catheter. Similar to solid-state systems, a cross sectional image is displayed after gathering echoes while the catheter rotates. Rotational systems have the advantage of having a significantly higher axial resolution with transducers up to 60 MHz with a large bandwidth. Nevertheless, rotational system setup is somewhat more cumbersome with the need to flush the catheter. They use a short monorail with, consequently, an artefact of the wire running along the imaging crystal. However, this offers a more stable automated pull-back of the imaging tip inside a sheath for length measurements of vessel structures. In order to perform imaging, the catheter is advanced beyond the area of interest over a 0.014 in. guidewire after a 100-200 mcg intracoronary nitroglycerin injection in order to minimize vasospasm and to have maximal vasodilation. The catheter is then pulled back in order to obtain the desired images either manually or automatically (motorized) at a standardized speed (up to 10 mm/s). Motorized pull-back has the advantage of providing longitudinal information of the area of interest in order to assess lesion length, while manual pull-back provides a more detailed and prolonged view of the area of interest. Regardless of the system used, proper identification of the three histologic vessel layers is critical for an accurate interpretation (Figure 3). The major advantage of IVUS imaging is its ability to see both intraluminal and extra-luminal elements in the vessel (coronary thrombus, edge dissection after stenting, *etc.*). It also allows for accurate and reproducible measurements of several segments of the vessel. In fact, the proximal and distal reference vessel segments can be identified and measured, along with the minimal lumen area (MLA), minimal and maximal lumen diameter, lumen eccentricity, area stenosis, cross section area (CSA), plaque area and burden, and the remodeling index can be computed. IVUS can also guide PCI, evaluate stent expansion, assess side branch compromise, determine the underlying mechanism of stent thrombosis/underexpansion and evaluate tears of the vessel from coronary dissections[94]. Although IVUS presents many advantages, several pitfalls remain. The displayed image relies on the absorption and reflection of

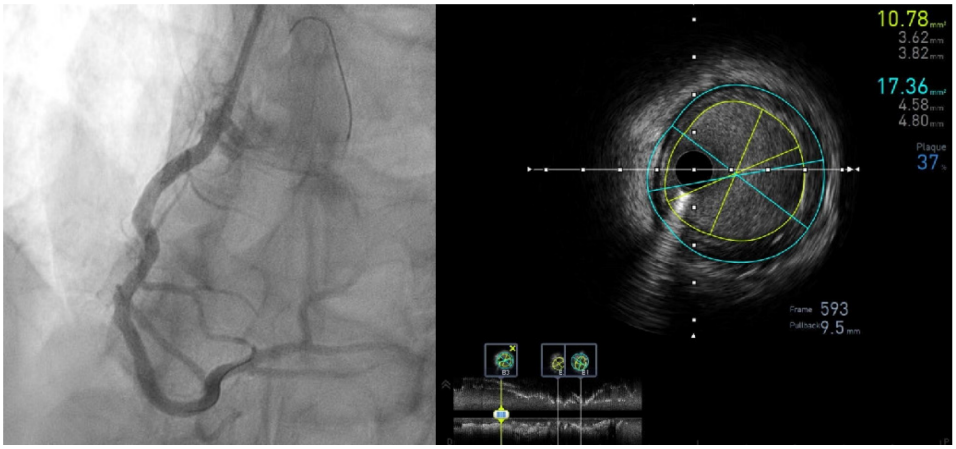

Figure 3 Intravascular ultrasound pull-back of a right coronary artery post stent implantation. Stent expansion is assessed and the minimal lumen area measured in different cross-sections (bottom longitudinal view) while the plaque burden at the distal reference (B3) is shown on the cross sectional frame 593 (lumen area 10.78 mm², vessel area 17.36 mm², plaque burden 37%).

ultrasound waves from tissues and, in the presence of calcium, which is a high reflector, all the ultrasound waves are reflected and do not penetrate beyond the underlying tissue. This reveals reverberation artefacts and shadowing behind the calcium with no possibility to analyze the extent of plaque and vessel structure behind the calcium. A wire artefact during IVUS images analysis may result in shadowing and difficulty seeing beyond the wire. Accurate analysis, especially with longitudinal measurements, can be hindered between systole and diastole secondary to the catheter movement[95]. In addition, blood speckle artefacts increase as blood flow decreases or the transducer frequency increases, hampering the ability to differentiate lumen from tissue, especially in the case of soft plaques and thrombus.

IVUS guided PCI has been shown to increase the choice of balloon and stent size by the PCI operator, increase the length of the stented segment, and increase the minimal lumen diameter and stent CSA at the end of the procedure as compared to angiography alone. Mixed results were found in multiple prospective studies during the bare metal stent era as to whether this increase improved clinical outcome[96-99]. In a meta-analysis, Parise *et al*[100] found a reduced 6-month angiographic binary restenosis with a significant reduction in revascularization rate and major adverse cardiac events in IVUS-guided PCI patients. Several retrospective and prospective studies were conducted during the DES era showing a net benefit of IVUS on overall clinical outcomes[101,102]. Several meta-analyses highlighted the net benefit of IVUS-guided PCI using DES with a significant reduction in major adverse cardiac events, myocardial infarction, target vessel revascularization, target lesion revascularization and stent thrombosis as compared to angiography guided PCI[103-105]. Recently, the 3-year follow-up of the ULTIMATE trial showed a reduction in cardiovascular death, target vessel failure and stent thrombosis in patients who underwent IVUS-guided PCI as compared to patients who underwent angiography-guided PCI alone[106,107]. With the treatment of more complex lesions, IVUS has been shown to improve mortality in left main stenting, probably due to a better stent apposition and lower rate of underexpansion[108-110], as well as in bifurcating lesions in order to predict side branch closure[111]. Moreover, IVUS is currently recommended for evaluating and guiding chronic total occlusion procedures[112,113].

VH-IVUS uses advanced backscatter signal analysis in order to try to characterize plaque composition. VH-IVUS limitations are the lack of thrombus detection and plaque characterization in the presence of calcium shadowing, and a limited resolution.

Despite the introduction of high definition IVUS catheters, the major limitation of IVUS imaging remains its limited spatial resolution, making the assessment of stent-strut tissue coverage challenging.

OCT

OCT is a light-based intravascular imaging technique that provides a high-resolution image of the tissue microstructure by using backscattering and near-infrared light

reflections from a fiber optic wire coupled with an imaging lens while simultaneously being pulled back and rotated. The first OCT clinical application on coronary arteries was reported in 1991 after the addition of transverse scanning[114]. The rapidly evolving technique was named by James Fujimoto and made way to contemporary OCT catheters that use a central light wavelength range of 1300 nm, which limits tissue penetration to 1-3 mm as compared to IVUS. With an axial resolution of 10-15 μm, OCT offers a very detailed picture of the vessel while the imaging optics of the catheter allow for a lateral resolution of 20-40 μm.

The first available OCT systems from LightLab Imaging (Westford, Massachusetts, United States) used an old OCT technology, called time-domain (TD) OCT, based on a broadband light source emitting through a fiberoptic coupler. The main disadvantage of this system was the slow speed of acquisition, which resulted in the need of total vessel flush for a long period. Newer generation OCT systems, termed Fourier-domain OCT (FD-OCT), use a fixed mirror and light is emitted by a "swept laser" source with a variable frequency. This allows for a faster frame acquisition rate (up to 100 frames/s) with only a short vessel flush duration. Continuous flush of contrast fluid is required in order to clear intraluminal blood since blood causes significant signal attenuation. The first FD-OCT was developed by St. Jude Medical (St Jude Medical, St. Paul, Minnesota; United States). It is a 2.5 Fr catheter compatible with 5 Fr guiding catheters. Currently a 2.4 Fr catheter is also available from Terumo (Terumo Corporation, Tokyo, Japan). The OCT catheter is advanced over a 0.014 inch wire to the distal vessel and an automated pull-back is then performed at a rate of up to 20-40 mm/s during short iodinated contrast injection (4 cc/s) in order to clear blood. During pull-back, a long spiral scan is created within less than 3 s in order to map the vessel and create the required frames. The emitted light splits into 2 parts: the first sample arm travels to the patient while the second reference arm travels a predefined distance. The two arms are then collected and an interferometer is used to measure the light reflected (back-scattered) from tissues in order to determine the depth of the tissue (A line). The system then processes the reflected light and computes a very high-resolution image due to the shorter wavelength of light and 3D tissue morphology.

Each image is made up of lines and pixels; the higher the lines/frames ratio is, the finer the image, and the higher the frame rate, the higher the longitudinal resolution. Artefacts associated with OCT include light attenuation from incomplete blood flushing, artefacts secondary to the guidewire, distortion of stent reflections from eccentric wire position (sunflower effect), air bubble artefacts, and stitch artefacts secondary to rapid catheter or wire movements (sew-up effect). These can be minimized through a proper positioning of the guidewire and appropriate contrast injection[115]. Even macrophage accumulation in thin-cap fibroatheroma or small intraluminal thrombi can be seen[116]. Plaque characterization can be achieved by OCT combining backscattering and attenuation measurements[117].

Currently, limited data for OCT-guided vs. angiography-guided interventions are available, while ongoing randomized clinical trials are running. A reduced rate of cardiac death and major adverse cardiac events has been reported in patients who underwent OCT-guided stenting[118], as well as larger final in-stent minimal lumen diameter[119] and a reduction in the number of stents implanted[120]. OCT-guided PCI has also been associated with better clinical outcomes in acute coronary syndrome patients[121,122]. In addition, a better stent coverage at 3 mo was found in OCT-guided PCI chronic CAD patients[123].

OCT delivers high-resolution intravascular images which are used in clinical practice, but mainly in the research field[124,125]. As compared to IVUS, OCT showed comparable stent expansions and comparative efficacy in the ILLUMIEN II and III studies respectively[126,127]. OCT was also shown to have non-inferior clinical outcomes as compared to IVUS in the OPINION[128] study. The latest European Society of Cardiology guidelines have included IVUS and OCT imaging as a class IIa recommendation[129]. Although both imaging modalities share multiple similarities, some controversy remains regarding which modality is to be used in specific cases. The need of contrast injection during OCT imaging tends to be a trigger towards IVUS use in patients with renal failure. The very high resolution of OCT images enables a more detailed evaluation at the endoluminal level and superficial plaques, and better stent implantation short- and long-term results[130]. However, OCT has lower penetration depth as compared to IVUS, which makes larger vessel visualization more challenging, in addition to the external elastic membrane-based approach for vessel sizing. IVUS images are significantly altered by the presence of calcium whereas OCT recognizes calcium plaques as well-demarcated low-intensity structures. The relatively smaller size of OCT may reduce the incidence of coronary spasm, and can identify coronary thrombosis and dissection easily. However, OCT fails to assess aorto-ostial

lesions. Several clinical studies have demonstrated the non-inferiority of OCT imaging as compared to IVUS (OPINION, ILLUMEN III)[127,131].

Co-registration of both OCT and IVUS with angiography has been developed[132] adding to the precision during PCI and reducing the risks of geographic miss[94,115]. An OCT/IVUS hybrid technology (Novasight) has been recently introduced, and further developed by Conavi Medical Inc. (Toronto, Canada), and this was reported in 2018[133]. A second hybrid system is currently under development by Terumo (Terumo, Tokyo, Japan) and is yet to be released.

Intravascular imaging has marked its place during PCI offering multiple benefits over angiography alone. Multiple meta-analyses and registries have proven its improved procedural and clinical outcome. However, intravascular usage rate remains low probably due to the increased cost, time and unfamiliarity of the operators[134]. With increasing PCI complexity, intravascular imaging adds a clinically proven indispensable benefit for successful intervention.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY

Coronary computed tomography angiography (CCTA) has recently emerged as a precise non-invasive tool for the detection and evaluation of CAD[135,136]. Computed tomography (CT) technology has advanced significantly since its first use, by Sir Godfrey Hounsfield in 1970, followed by the introduction of electron beam computed tomography by Douglas Boyd improving temporal resolution. A major breakthrough came in the 1990s with the introduction of multidetector computed tomography that has the ability of improving a 360° spatial resolution. CT images depict tissue densities and are the product of X-ray attenuation as they pass through tissue. A CT detector measures and converts the X-ray photons exiting the patient into light. This light is then transformed into an electrical signal by a photodiode and converted into a digital signal by a computer system. The image is an overall estimation of the attenuation of X-rays as they pass through tissues of different densities represented by Hounsfield units.

Currently, multidetector computed tomography scanners include 320-detector rings and two X-ray sources, allowing for the acquisition of submillimeter resolution over large volumes in milliseconds. Improvements in detector characteristics have increased the x, y and z axis spatial resolution, which allows for successful imaging of the coronary arteries while reducing radiation dose[137]. Three steps are required to successfully create a CCTA image: data acquisition, reconstruction and image display. Data acquisition involves scanning portions of the heart with each gantry rotation and requires proper patient selection, preparation, appropriate imaging protocols and contrast injection techniques. Effective heart rate control, proper timing of the scan after contrast injection and minimizing patient movement are all crucial during data acquisition. It is therefore advisable for patients known to have arrhythmias to be deferred from CCTA. CCTA has the advantage of visualizing the entire vessel, and can accurately evaluate stenoses severity and plaque morphology.

Along with CCTA already being established for the detection of CAD and confirming the ability of calcium score in providing a prognostic value in multiple large studies[137-139], it is an excellent diagnostic tool for bypass graft imaging. Moreover, CCTA has been validated and used for the assessment of coronary artery stent with recent technical refinements showing negative predictive values >90% for the exclusion of in-stent restenosis[138,140-142]. However, a blooming effect secondary to the stent struts and beam-hardening artefacts remain a challenge for proper evaluation[143,144]. This is also true for patients known to have excessive coronary calcium, as calcifications may interfere with the accurate interpretation of CCTA. Since coronary stenosis alone does not predict the risk of future cardiovascular events, the coronary artery calcium (CAC) score estimates the overall calcification burden and predicts future ischemic events without contrast use. With the introduction of bioresorbable stents (Figures 4 and 5), this set-back has been overcome[145,146]. Contrary to magnetic resonance imaging (MRI), pacemakers and defibrillators do not preclude the use of CCTA, however it should be noted that their leads may create artefacts.

CCTA has been shown to be a better predictor of obstructive CAD compared to traditional functional testing. The EVINCI study showed the superior accuracy of CCTA for the detection of CAD as compared to single photon emission CT (SPECT), position emission tomography (PET), echocardiography and cardiac MRI[147]. The prognostic value of CCTA was also demonstrated in the PROMISE and SCOT-HEART

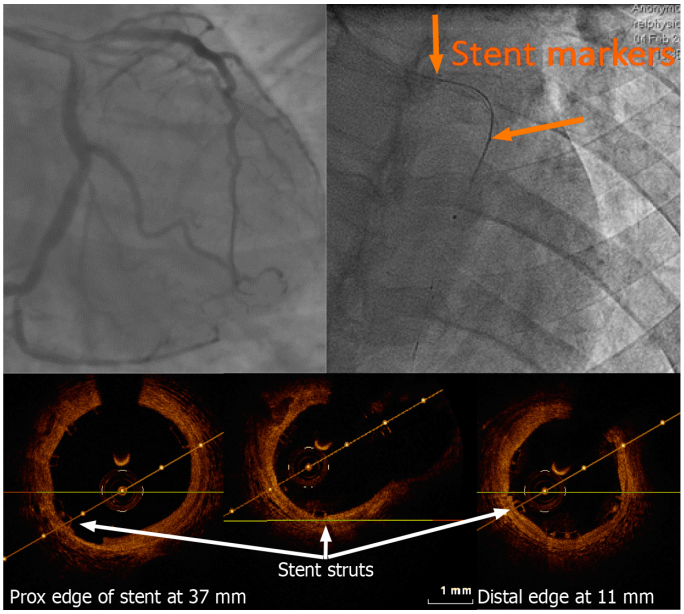

Figure 4 Left anterior descending artery optical coherence tomography pull-back post bioresorbable stent implantation carried out using a 2.7 French imaging catheter with a dedicated workstation (C7 Dragonfly and C7-XR, Lightlab Imaging [Westford, Massachusetts, United States)]. Of note, only the proximal and distal markers are visible. On optical coherence tomography (OCT), the thickness of the stent struts and its good apposition can be assessed without artefact as seen with conventional metallic struts. Stent length could be measured on the OCT pullback with a good agreement with the known stent length.

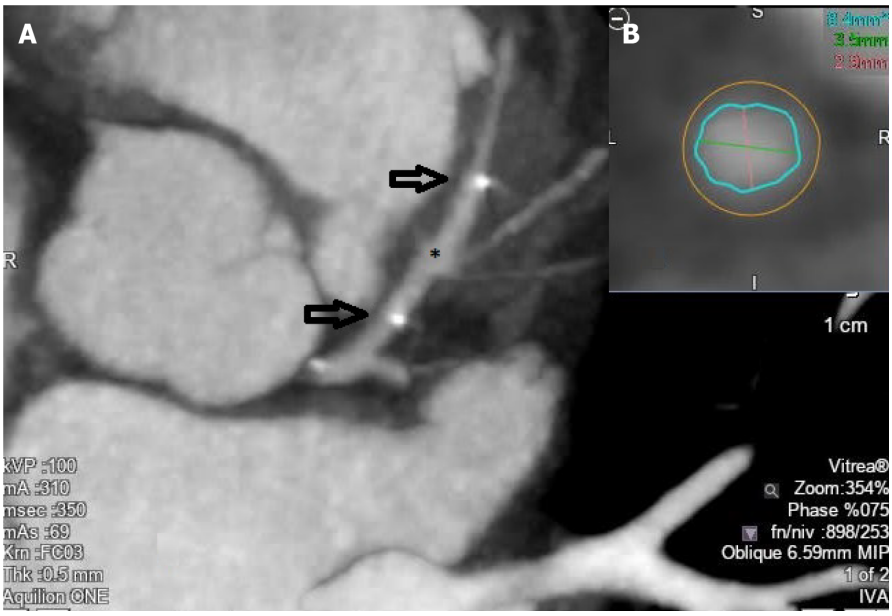

Figure 5 Coronary computed tomography angiography image of a bioresorbable stent (asterisk) implanted at the level of the proximal left anterior descending artery (A) (the two arrows represent the two radiopaque stent markers), and cross sectional cut allowing for lumen measurements (B).

studies which showed high CCTA prediction of cardiovascular events as compared to functional testing and standard care[139,148]. A meta-analysis showed a significant reduction of myocardial infarction as well as an increased incidence of coronary revascularization with no effect on all-cause mortality using CCTA in patients with chronic coronary syndrome as compared to usual care[149].

Observer variability and expertise remain a challenge for CCTA interpretation. Dedicated software programs for increasing automation and identifying high-risk plaques have been validated as well as newer technologies, including fractional flow reserve (FFR) derived from CCTA (FFR_{CT}), perivascular fat attenuation index (FAI) and wall shear stress (WSS)[136]. Advances in imaging modalities permitted a 3-

dimensional reconstruction of the coronary artery tree and a decrease in radiation exposure[150]. Myocardial perfusion by CCTA is also possible and allows for the assessment of the physiologic consequences of stenoses[136]. It has evolved as a valuable tool in guiding PCI and assessing lesion characteristics, especially in chronic total occlusion (CTO) lesions using co-registration with angiography[151]. In the acute disease setting, CCTA fails to differentiate between a thrombus and acute plaque hemorrhage.

CCTA technology still has a lot to offer in the future. It has been a useful and promising tool in the assessment and tracking of atheromatous plaques, improving understanding of early atherosclerosis.

CONCLUSION

The success of stent implantation during PCI procedures depends on proper positioning of the stent, expansion and apposition, all of which reduce the rate of major adverse cardiac events. Traditional two-dimensional angiography alone fails to fully assess the result of stent implantation. Pre-procedural measurement of the vessel diameter along with post-procedural evaluation of the strut-level and minimal lumen area and diameter improve clinical outcomes. Despite the substantial technological advances, a growing need for newer and more accurate tools for PCI guidance and assessment has emerged with the increasing number of complex procedures performed worldwide and ongoing stent technology advances.

Quantitative coronary analysis has developed substantially since its early beginnings due to its research and clinical uses both on-line and off-line. Recent 3-dimensional QCA systems have also emerged, providing more reliable assessment of lumen dimensions[152]. The ease-of-use and reproducibility of QCA analysis has made it widely available within PCI centers worldwide. However, several limitations persist and QCA measurements are lower compared with other imaging modalities [153]. Furthermore, QCA measurements are limited for diffuse lesions, as the reference diameter tends to be underestimated[50].

Digital stent enhancement imaging has been thoroughly validated for stent underexpansion. It allows for easy visualization of areas of stent underdeployment for positioning of post-dilation balloons. DSE has been reported to be associated with better angiographic and clinical outcomes[72] as well as stent fracture identification. DSE adds little additional time to the procedure, provides a better image resolution as compared to angiography with no risk of mechanical complications while using less contrast. It has been found to be particularly useful for obese patients, long lesions, in-stent restenosis and bifurcating lesions[77,86,154]. Although the accuracy and resolution of DSE is lower than intravascular imaging, measurement of stent diameters correlated well[71,73,87,153,155]. Its main drawback could be the increased radiation dose, however this does not have a significant impact on the patient[86]. DSE remains a useful and rapid tool that can be used in conjunction with intravascular imaging during PCI.

Intravascular imaging remains the gold standard during PCI and has demonstrated low complication rates. Several randomized controlled trials and observational studies have established the role of intravascular imaging-guided stent implantation during PCI with a reduction in major cardiac events and target vessel revascularization[105]. Compared to angiography, intravascular imaging-guided PCI has been shown to have a relative reduction of cardiovascular death, a lower risk of myocardial infarction, a decreased risk of target vessel revascularization and a reduction in the rate of stent thrombosis[105]. In addition, the greatest benefit of intravascular imaging guidance may be in complex lesions and stent failure patients. The non-inferiority of OCT as compared to IVUS in guiding PCI has been demonstrated in several clinical trials and meta-analyses[128,131,137,153,156]. Clear differences exist between the two technologies. OCT offers a higher resolution along with finer details, whereas IVUS has a better penetration and does not require flushing the lumen with contrast. IVUS and angiography co-registration systems have been tested and validated and provide valuable information. Furthermore, more recently, a 3-dimensional reconstruction of the coronary tree using IVUS co-registration allowed for further detailed information about vessel size, plaque size, shear stress and hemodynamic studies at every position along the vessel[152].

Thus, intracoronary imaging provides an accurate evaluation of coronary anatomy and plaque evaluation during PCI allowing for optimized stent sizing while avoiding stent malaposition, underexpansion and stent edge dissection, all in addition to an

accurate assessment of the stent result. However, its routine use in clinical practice remains low and highly variable, mainly due to the added procedure cost and time. Progress is still ongoing within the field, with further advances on the way using OCT/IVUS hybrid console systems.

With the ongoing paradigm shift towards non-invasive imaging, new reconstruction techniques have significantly improved coronary artery stent imaging by CCTA. The European Society of Cardiology recommends the use of CCTA for the evaluation of CAD for low to intermediate risk patients in the setting of chronic and acute coronary syndromes[157,158]. With its high specificity (97%), CCTA could be used to exclude in-stent restenosis[159]. The CAC score used during CCTA remains an important tool for future cardiovascular ischemic events. Artefacts secondary to the stent struts hinder the accurate evaluation of the stent lumen, however, with higher scan-detector row systems and thinner stent struts, an improved image quality can be achieved using CCTA. In addition, in the PLATFORM trial[160], the introduction of FFR_{CT} reduced the number of patients referred for invasive angiography by 61%. CMR allows the reduction of the contrast dose without compromising image quality. Both CCTA and CMR can easily and accurately assess coronary bypass grafts along with performing myocardial perfusion and a 3-dimensional reconstruction of the vessels. Furthermore, the introduction and on-going progress of newer generation bioresorbable stents have made CCTA an attractive tool for the evaluation of PCI results, as artefacts are greatly decreased[149,161].

In conclusion, invasive angiography remains the gold standard tool for the treatment of CAD and the visual guidance and evaluation of PCI results however, the conjunction and advances of several readily available alternative and complementary tools improve its sensitivity and accuracy.

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 September 26; 13(9): 438-445

DOI: 10.4330/wjc.v13.i9.438

ISSN 1949-8462 (online)

MINIREVIEWS

Interpersonal violence: Serious sequelae for heart disease in women

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Author contributions: Mazza M, Romagnoli E, Biondi-Zoccai G, and Marano G designed the study and wrote the first draft of the manuscript; Mazza M, Romagnoli E and Marano G managed the literature searches; Gonsalez del Castillo A, Chieffo D, Albano G, Biondi-Zoccai G, Galiuto L, and Sani G supervised and added important contributions to the paper; all authors have read and agreed to the published version of the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interest.

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Abstract

Experiencing various forms of violence in either childhood or adulthood has been associated with cardiovascular disease, both shortly after the event and during follow-up, particularly in women. The coronavirus disease 2019 pandemic has heightened the risk of domestic violence with serious sequelae for mental and cardiovascular health in women, possibly due to several contributing factors, ranging from lockdown, stay at home regulations, job losses, anxiety, and stress. Accordingly, it remains paramount to enforce proactive preventive strategies, at both the family and individual level, maintain a high level of attention to recognize all forms of violence or abuse, and guarantee a multidisciplinary team approach for victims of interpersonal or domestic violence in order to address physical, sexual, and emotional domains and offer a personalized care.

Key Words: Violence; Women; Depression; Cardiovascular disease; COVID-19; Personalized medicine

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

Received: December 31, 2020
Peer-review started: December 31, 2020
First decision: March 31, 2021
Revised: April 10, 2021
Accepted: July 19, 2021
Article in press: July 19, 2021
Published online: September 26, 2021

P-Reviewer: Li CY, Nashawi M
S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Ma YJ

Core Tip: Interpersonal violence has been associated with cardiovascular disease, particularly in women. The coronavirus disease 2019 pandemic has heightened the risk of domestic violence with serious sequelae for mental and cardiovascular health in women. There is a need of research aimed to better understanding the impact of intimate partner violence on cardiovascular risk in women, both shortly after the event and during follow-up. It is important to prevent violence and to guarantee a multidisciplinary team approach for patients who have experienced interpersonal violence in order to address physical, sexual, and emotional domains.

Citation: Mazza M, Marano G, Gonsalez del Castillo A, Chieffo D, Albano G, Biondi-Zoccai G, Galiuto L, Sani G, Romagnoli E. Interpersonal violence: Serious sequelae for heart disease in women. *World J Cardiol* 2021; 13(9): 438-445
URL: https://www.wjgnet.com/1949-8462/full/v13/i9/438.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i9.438

INTRODUCTION

Interpersonal violence: A public health issue

Interpersonal violence represents a serious public health issue. It is defined as physical or sexual violence, emotional abuse, and stalking, and is experienced by more than 30% of women in United States. It is globally recognized as the leading cause of homicide death for women. Psychological violence has been recognized as a traumatic event equal to other types of abuse (*e.g.*, physical or sexual violence). It causes severe consequences, not only for the victims and families involved, but also to the whole society.

It is well known that intimate partner violence has short-term and long-term effects on the physical and mental health of victims and their children[1]. Epidemiological studies have highlighted an increased risk of chronic medical conditions (including asthma, arthritis, autoimmune disorders, cancer, stroke, diabetes mellitus, hypertension, sexually transmitted infections, and traumatic brain injury) among persons who have experienced partner violence[2]. Proposed mechanisms for the link between interpersonal violence and poor health are the activation of neuroendocrine and immune system pathways (including chronic inflammation and endothelial dysfunction) or epigenetic changes (telomere shortening) occurring in the context of acute and chronic stress. Situations of chronic stress associated with partner violence may also increase detrimental behavioral coping strategies (such as smoking, substance abuse, eating habits, sedentariety, disrupted sleep, scarce adherence to therapy, and failure to follow-up with their doctors) that produce a deterioration in the state of health[1], or an exasperation of other psychological and economic factors (low socio-economic status).

It has been recently suggested that intimate partner violence might increase the risk of cardiovascular disease in women. Chandan *et al*[3] conducted a retrospective study in a cohort of 18547 women from a United Kingdom primary care registry that found that women with a history of intimate partner violence had a 31% increased risk for later cardiovascular disease (in particular a 50% increased risk for ischemic heart disease), a 51% increased risk for diabetes mellitus, and a 44% increased risk for total mortality[3]. In general, chronic diseases, including cardiovascular disease and hypertension, cancer, sexually transmitted infections, drug and alcohol abuse, smoking, diabetes, and elevated cortisol, have been ascertained at greater rates in women who have been victims of intimate partner violence[4].

Scott-Storey[5] developed a conceptual model to portray direct and indirect pathways by which severity of lifetime abuse (physical, sexual, and/or psychological) may affect women's cardiovascular risk. According to this model, there are three pathways through which lifetime abuse may increase cardiovascular disease risk among women. First, lifetime abuse as a chronic stressor contributes to creating a state of vulnerability, potentially causing significant neuroendocrine, metabolic, hemostatic, and immunologic changes within the body (for example, elevated blood pressure, a

clinically important early indicator of cardiovascular risk)[6]. It is probable that chronic upregulation of the so-called fight-or-flight hormones, chronic inflammation, or dysregulation of the hypothalamic pituitary axis may contribute to poor heart health. Second, coping strategies used by victims of abuse to deal with stress, such as smoking and overeating, represent cardiovascular risk behaviors, and tend to persist long after the experience of abuse situation has ended. Third, it has been largely demonstrated that women with histories of abuse have higher incidence of depressive disorders and depressive symptoms, and depression strictly correlates to chronically elevated levels of cortisol, catecholamines, and inflammatory markers, all of which promote the development and progression of cardiovascular disease[7]. Recently it has been highlighted that women suffering from high levels of depressive symptoms in the immediate period after leaving an abusive partner may be most at risk for persistent mental illness after the separation: this reinforces the need for early depression intervention and treatment. It has been also hypothesized that women who experience less change in their depressive symptoms over time may have higher cardiovascular risk, and therefore, may be considered a potential target group for primary and secondary prevention of cardiovascular disease[5].

Biological mechanisms underlying physical health sequelae of interpersonal violence are very poorly understood: it can be hypothesized that intimate partner violence induces a chronic inflammatory state, but further studies are needed focusing on biomarkers of inflammation and specific markers of disease in abused women, including C-reactive protein, cortisol, erythrocyte sedimentation rate, and cardiac biomarkers (troponin, creatine kinase myocardial band, brain-natriuretic-peptide)[4]. There is evidence for a link between intimate partner violence and the development of endocrine diseases, including diabetes. Additionally, interpersonal violence has been associated with lowered cortisol awakening response, flattened diurnal cortisol patterns, and higher midday cortisol. Given that cortisol is considered a biomarker of physical and psychological stress states and is involved in endocrine disease states, the effect of interpersonal violence on cortisol levels may be a promising area of future research[8].

INTERPERSONAL VIOLENCE AND RISK OF CARDIOVASCULAR DISEASE IN WOMEN

There is a bi-directional relationship between mental health disorders (including depression, anxiety, and/or cognitive dysfunction) and cardiovascular diseases. Autonomic dysfunction and inflammation may contribute to the increased cardiovascular mortality risk associated with depression, and a mutation of the ryanodine receptor sarcoplasmic reticulum calcium release channel can result in cardiac arrhythmias and seizures[9]. Complex interrelated disease mechanisms also regard specific syndromes in which pre-existing neurological or psychiatric illnesses may predispose and contribute to cardiovascular involvement (as in Takotsubo syndrome), or in which psycho-physical stress, dysregulation of the interplay between innate immune and central nervous systems, and/or pre-existing cardiovascular disease lead to secondary mental health disorders and brain damage (as in peripartum cardiomyopathy and atrial fibrillation).

Many studies have shown a mutual bond between the cardiovascular system and depression. Patients with cardiovascular disease who are also depressed have a worse outcome than those patients who are not depressed. A graded relationship can be described: the more severe the depression, the higher the subsequent risk of mortality and other cardiovascular events[10].

Depression is considered an independent risk factor for the development of cardiovascular diseases and contributes to a worse prognosis, further increasing the risk of mortality or subsequent major adverse cardiovascular events, such as nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death. After a stroke, women present poorer quality of life than men due to different risk factors among which one of the most frequent is depression[11-14]. This association between depression and cardiovascular diseases has been confirmed for both men and women, for different age groups, and in various cultures; furthermore, the strength of this link is similar to that of other risk factors, such as smoking and high cholesterol[15]. The relationship between depression and cardiovascular disease has been analyzed through etiological and prognostic studies. The possibility has been ascertained that depression exerts a direct influence on psychophysiological mechanisms, whose alterations result in the development of atherosclerosis, and thus, lead to coronary

events. Additionally, psychobiological models have identified different mechanisms of connection between depression and coronary artery disease. Other studies have shown that indirect mechanisms are based on the possibility that depression can favor cardiovascular disorders by modulating some coronary risk factors. This hypothesis has given rise to a line of research aimed at identifying various behavioral and psychosocial mediators that can explain the association between depression and coronary heart disease[11,12]. It has been also outlined that mind-body interventions, such as meditation, mindfulness and yoga can promote beneficial effects on stress reduction acting through modulation on cortisol secretion, blood pressure, heart rate variability, and immune reactions, and thus positively preserving women's cardiovascular health [15].

A growing body of research suggests that experiencing violence in either childhood or adulthood is associated with cardiovascular disease. The effects of violence may differ by life course stage. For example, violence exposure in childhood deserves a special attention, as biological mechanisms used to compensate for chronic stress exposure may be detrimental to health, leading to an early development of cardiovascular diseases. Furthermore, unhealthy habits used to cope with stress (lifestyle factors and substance use behaviors) can be formed during these early years, and could contribute to greater cardiovascular risk in childhood that may persist into adulthood. In addition, physiological development of the brain and other organ systems can be derailed under chronic exposure to stress, disrupting emerging brain architecture, as well as cognitive and behavioral functioning, and making children particularly vulnerable to the effects of violence and abuse with long-term consequences on the development of chronic disease, including cardiovascular disease [16]. Children who are exposed to threats to themselves, their family, or their community have an increased risk of subsequent myocardial infarction, stroke, ischemic heart disease, coronary heart disease, and/or death from one of these conditions. It should be noted that children from racial and ethnic minority groups or lower economic backgrounds face higher rates of such experiences, and may therefore be considered at higher risk for cardiovascular disease[17].

Long-term effects of violence exposure have been noted in relation to depression, aggression, substance use, and risk-taking behaviors. Many children and adults exposed to violence may develop post-traumatic stress disorder and depression, frequently associated with obesity, hypertension, and adverse cardiac outcomes[18]. Additionally, studies have documented an association of interpersonal violence exposure with tobacco use, alcohol use, poor dietary habits, and sedentary lifestyle, all of which potentially linked to cardiovascular health[19-21].

INCREASED CONCERNS ABOUT DOMESTIC VIOLENCE DURING THE CORONAVIRUS DISEASE 2019 PANDEMIC

The coronavirus disease 2019 (COVID-19) pandemic has produced in a few weeks a substantial disruption worldwide. In the COVID era, affectivity and sexuality are remodeled: social distancing slows down the spread of the Coronavirus but represses or changes the need for relationships. A high global prevalence of depression and anxiety during the COVID-19 pandemic has been described, with a wide variance based on the region and country, as a direct effect of physical distancing measures imposed by national governments[22].

It has been shown that physical distancing (mostly referred to as social distancing) may deteriorate physical and mental health. In particular, reduced social connection is associated with chronic physical symptoms, including cardiovascular disease, reduced nutrition, higher probability of hospital readmissions, reduced vaccine uptake, early mortality, depression with suicidal ideation, social anxiety, psychotic symptoms, and cognitive impairment[23]. In general, psychosocial risk factors such as stress, social isolation, low socioeconomic status, hostility, anger, and stress-related psychiatric disorders are known to have negative impacts on health outcomes, but their effects on ischemic heart disease, particularly in women, have not yet been fully demonstrated [24].

A heightened risk of domestic violence has been associated with the restriction of travels imposed by many governments to prevent the spread of COVID-19 and other infection-reducing measures. The reasons for this include social isolation, exposure to economic and psychological stressors, increase in negative coping mechanisms (such as alcohol or drugs misuse), and inability to access usual health and social services [25]. During quarantine due to COVID-19, home became a dangerous place for victims

of domestic violence because they are bound to stay the whole day with abusing partners and isolated from the others who could potentially give support. Present vulnerabilities can exacerbate family violence perpetration and prey victimization, and can aggravate maladaptive or dysfunctional relationships, directly impacting on cardiovascular system. It has been observed that women during quarantine report significant post-traumatic stress symptoms, and may show depression or anxiety, risk factors for the development or worsening of cardiovascular disease[26]. Currently, the pandemic has brought direct cardiac complications of infection and a potential impact on the standard acute and chronic management of cardiovascular disorders, compromising cardioprotective medications and health behavior regimens[27]. In addition, physical and social isolation can exacerbate maladaptive thought processes (such as anger, loneliness, pessimism, obsessive-compulsive behaviors, hopelessness, helplessness, and/or frustration) or extreme response to stress (such as hypervigilance or alcohol or drugs abuse) that may have consequences on population cardiovascular health[28]. Anxieties and fears related to risk of infection could result in missed cardiovascular or psychiatric medication scripts or delayed referral to psychologists or other specialists, and non-adherence or self-management of dietary, smoking, or physical activity recommendations.

Particularly in COVID, it should be mandatory to provide funding sources to provide telephone or remote counseling services to manage and prevent crisis situations[29]. As the global health community faces up to the spread of COVID-19, the ongoing epidemic wave of violence against women should be addressed.

A NEED TO IMPROVE TREATMENT AND PREVENTION OF INTERPERSONAL VIOLENCE AND CARDIOVASCULAR OUTCOMES

Cardiovascular disease is the leading cause of death in women worldwide; for women living with cardiovascular problems, the chronicity of the disease translates into substantial disability. There are sex and gender-related disparities in cardiovascular disease (including delayed onset and atypical clinical characteristics in women, non-traditional gender-specific risk factors, unconscious gender biases, underrepresentation of women in research trials, and a lack of disease awareness in racial and ethnic minorities), and significant healthcare disparities and gaps still exist in the care of female patients. For example, women are less likely to receive an early diagnosis and timely interventions for a cardiovascular disease and often have worse outcomes than men after acute coronary syndromes). Recognizing nontraditional cardiovascular disease risk factors represents an important opportunity to improve healthcare quality in women[30]. Doing so would help guarantee a multidisciplinary team approach for patients who have experienced interpersonal violence to address physical, sexual, and emotional domains of abuse and their several sequelae. Because it has been stressed that there are multiple pathways through which an experience of violence can affect cardiovascular risk, the best approach to the patients seems to be a multimodal intervention focusing concurrently on chronic stress, depressive symptoms, and cardiovascular risk behaviors[31]. Screening for psychiatric and psychological symptoms in cardiological clinical practice might necessitate increased downstream support from mental health providers, including immediate evaluation of suspected suicidality, and clinicians should be aware that treatments that improve cardiovascular function should also benefit coexisting mood disorders[32].

A routine screening with standardized instruments and trained staffs in clinical settings should be recommended, including social services and behavioral health providers. Hospitals should develop violence intervention programs in collaboration with community-based services addressing mental health and other risk factors. Specific home visitation programs should help support children and families exposed to violence. Intervention strategies should focus on traditional gender role transformation to minimize the relationship power-gap and prevent violence against women. There should be strict implementation of the legislation to penalize and possibly rehabilitate the perpetrators, and there should be widespread diffusion of digital platforms for seeking help.

It is important to disseminate as widely as possible the knowledge and tools related to prevention and to improve the empowerment of women subjected to interpersonal violence[33].

Research has a pivotal role in understanding the impact of interpersonal violence on cardiovascular risk in women, with a special focus on the mechanisms underlying biological, psychological and psychosocial underpinnings. The investigation of

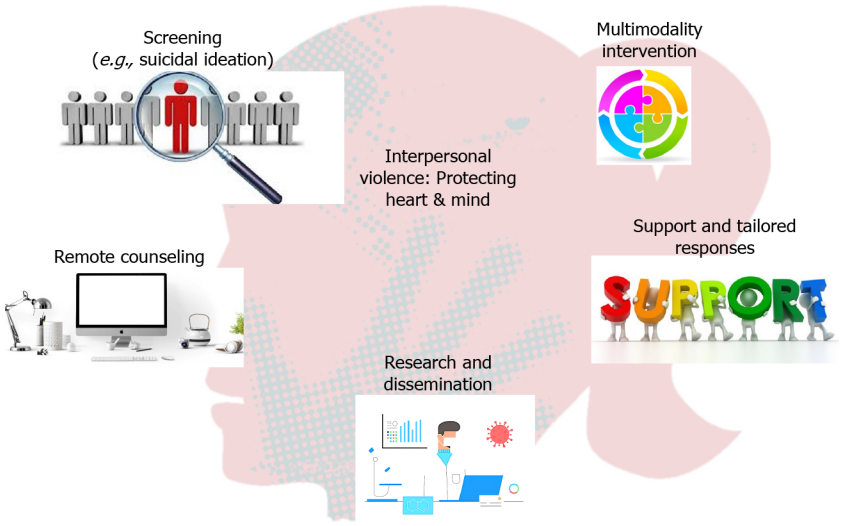

Figure 1 Recommendations to protect heart and mind of women who are victims of interpersonal violence.

potential epigenetic mechanisms by which violence exposure may contribute to heart disease by changing gene expression should not be overlooked, and other ways that the effects of violence exposure on the heart may be translated from generation to generation should be investigated[16]. Further studies designed to explore the chronicity and severity of violence exposure are needed to elucidate the relation between long-term effects of abuse and cardiovascular outcomes.

Intimate partner violence is a very complex issue, and is often difficult to identify because patients may present nonspecific sign and symptoms. Clinicians across all health care settings must be prepared to provide emotional and practical support, and to tailor personalized care to individual needs. Mental and physical health consequences related to interpersonal violence may persist long after the abusive situation has ended[34-36], and there is an urgent need to prevent long-term adverse effects and to extend periods of follow-up (Figure 1).

CONCLUSION

Prevention of violence against women of all ages, and interpersonal violence in general, is mandatory around the world. Cardiovascular disease and gender violence undoubtedly represent a key priority and a significant physical and mental health challenge facing women and clinicians today.

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 September 26; 13(9): 446-455

DOI: 10.4330/wjc.v13.i9.446

ISSN 1949-8462 (online)

MINIREVIEWS

Coronary artery aneurysm: A review

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Author contributions: All authors have contributed equally to the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: France

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Abstract

Coronary artery aneurysm (CAA) is a clinical entity defined by a focal enlargement of the coronary artery exceeding the 1.5-fold diameter of the adjacent normal segment. Atherosclerosis is the main cause in adults and Kawasaki disease in children. CAA is a silent progressive disorder incidentally detected by coronary angiography, but it may end with fatal complications such as rupture, compression of adjacent cardiopulmonary structures, thrombus formation and distal embolization. The pathophysiological mechanisms are not well understood. Atherosclerosis, proteolytic imbalance and inflammatory reaction are involved in aneurysmal formation. Data from previously published studies are scarce and controversial, thereby the management of CAA is individualized depending on clinical presentation, CAA characteristics, patient profile and physician experience. Multiple therapeutic approaches including medical treatment, covered stent angioplasty, coil insertion and surgery were described. Herein, we provide an up-to-date systematic review on the pathophysiology, complications and management of CAA.

Key Words: Coronary artery aneurysm; Complications; Atherosclerosis; Coronary artery ectasia

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 4, 2021
Peer-review started: March 4, 2021
First decision: June 7, 2021
Revised: June 9, 2021
Accepted: July 29, 2021
Article in press: July 29, 2021
Published online: September 26, 2021

P-Reviewer: Cigrovski Berkovic M, Schoenhagen P
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Ma YJ

Core Tip: Most patients with coronary artery aneurysm remain asymptomatic until the development of complications or the occurrence of obstructive coronary disease-related clinical manifestations. The underlying pathophysiology is miscellaneous. The ideal management of coronary artery aneurysm has not yet been defined, but computed tomography angiography is the recommended non-invasive test for long-term follow-up. Future prospective comparative trials targeted to define the appropriate strategy and the optimal time to intervene are required.

Citation: Matta AG, Yaacoub N, Nader V, Moussallem N, Carrie D, Roncalli J. Coronary artery aneurysm: A review. *World J Cardiol* 2021; 13(9): 446-455
URL: https://www.wjgnet.com/1949-8462/full/v13/i9/446.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i9.446

INTRODUCTION

Coronary artery aneurysm (CAA) is a rare clinical entity defined by an abnormal focal dilation of the coronary artery exceeding the 1.5-fold diameter of the adjacent normal segment, whereas coronary artery ectasia describes similar but diffuse lesions involving ≥ 50% of the coronary artery length[1]. Thus, aneurysmal coronary disease is seen as focal aneurysm (*e.g.*, Kawasaki) but also in more diffuse forms (diffuse ectasia). In general, CAAs are divided into two types: saccular when the longitudinal diameter is less than the transverse diameter; and fusiform in the opposite condition[2-4] (Figure 1). Fusiform CAAs are commonly found in the left anterior descending artery [2-4]. Aneurysmal dilation ≥ 8 mm in diameter or four times higher than reference coronary diameter characterized a giant CAA[5-7]. The incidence of true CAA varies from 0.3% to 5.3%[8,9] knowing that most recent studies reported an incidence rate below 1%[10-13]. The right coronary artery is most commonly involved followed by left anterior descending artery, circumflex and left main[8,9]. A predilection to male gender and proximal coronary segment was described[14].

CAA is usually a silent disorder incidentally detected by coronary angiography or computed tomography (CT) angiography. The wide spectrum of clinical presentations ranging from chest pain to sudden cardiac death results from the development of complications and/or the coexistence of obstructive coronary artery disease[8,15-20]. Until now, the management of CAA is individualized depending on clinical manifestations, patient conditions, CAA characteristics, physician experience and preference. A poor long-term prognosis has been attributed to the presence of CAA[21,22]. Herein, we provide an up-to-date systematic review on the pathogenesis, complications and management of CAA.

PATHOPHYSIOLOGY

The pathophysiological mechanisms of CAA are not well understood, but atherosclerosis is the main identified etiology in adults and Kawasaki disease in children[5]. Atherosclerosis is a chronic progressive transmural inflammatory disease affecting the different vascular layers from the tunica intima to the external elastic lamina, thereby contributing to a weakened vascular wall[23-27]. It is worthy to mention that stenotic coronary atherosclerosis and CAA commonly coexist. They share in common several histological patterns like hyalinization, lipid deposition, destruction of coronary layers, focal calcification and fibrosis[23-27]. All of these arteriosclerotic modifications on top of the liberation of nitric oxide, which enhances vasodilation, reduce the coronary resistance to intraluminal pressure predisposing it to dilatation and CAA formation. Kawasaki disease is an acute inflammatory syndrome that may infiltrate the arterial wall resulting in acute vasculitis and subsequent aneurysmal dilation[28]. Indeed, a high level of tumor necrosis factor-alpha, which is an inflammatory cytokine, was linked to the breakdown of elastin and the development of CAA[29]. Currently, coronavirus disease 2019 markedly increased the incidence of Kawasaki disease with cardiovascular involvement in children and young adults[30]. Other vasculitic disorders like Takayasu arteritis, polyarteritis nodosa, systemic lupus erythematosus and rheumatoid arthritis may lead to CAA[31,32].

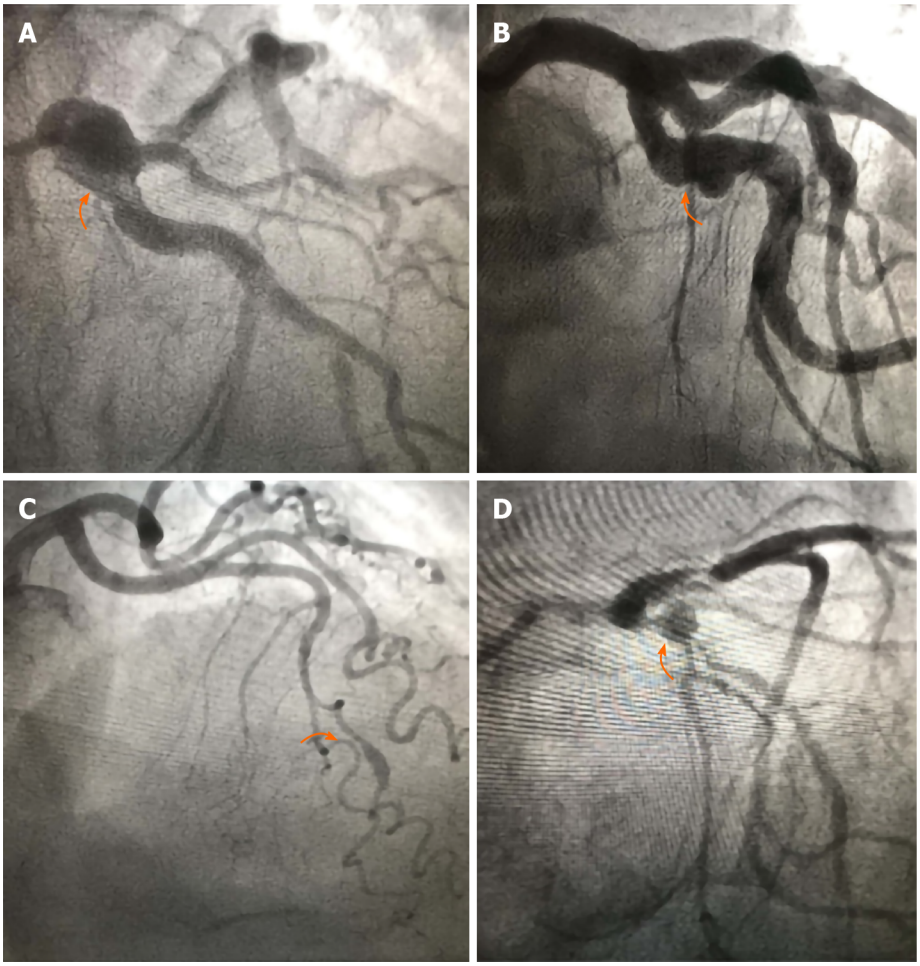

Figure 1 Coronary angiograms showing saccular aneurysm of the left main (A), saccular aneurysm of the left circumflex (B), fusiform aneurysm of the distal left anterior descending (C) and saccular aneurysm of the bifurcation left anterior descending/diagonal (D).

Otherwise, matrix-degrading enzymes play a pivotal role in the pathogenesis of CAA. A proteolytic imbalance caused by a high level of matrix metalloproteinases (MMP-2,-3,-9,-12) and a reduced level of matrix metalloproteinase inhibitors (tissue-specific inhibitors of metalloproteinases, TIMP-1,-2,-3,-4) resulting in connective tissue proteins and arterial wall matrix degradation, is reported in aneurysmal vessels[33-35]. Genetic susceptibility such as variants on chromosome 9p21.3, HLA-DR B1*13, DR16, DQ2, DQ5 and several hereditary disorders such as Marfan syndrome and Ehler-Danlos were linked to CAA[9,36]. Infectious processes that directly invade the vascular wall or provoke immune complex deposition contribute to CAA formation [37].

Lastly, CAA may complicate coronary angioplasty with stent implantation[38-40]. Aneurysmal formation was observed with bare metal stents, drug eluting stents and biodegradable stents[38-40]. Coronary dissection, oversizing, stent malapposition, high pressure balloons and local wall injury are the main mechanisms associated to stent-related CAA[41,42].

COMPLICATIONS

Most patients with CAA are asymptomatic, and the occurrence of clinical manifestations is related to a concomitant atherosclerotic coronary artery disease or to the development of complications. Local thrombosis, distal embolization, aneurysm rupture, coronary spasm and compression of adjacent structure by massive enlargement of CAA are the most observed complications[17,18,43,44] (Figure 2). The stagnation of blood flow and the reduction of shear stress in CAA contribute to thrombus formation and subsequent potential distal embolization[45]. Several published cases reported the presence of thrombus inside the aneurysm[46,47] and described myocardial wall motion abnormalities following distal embolization in

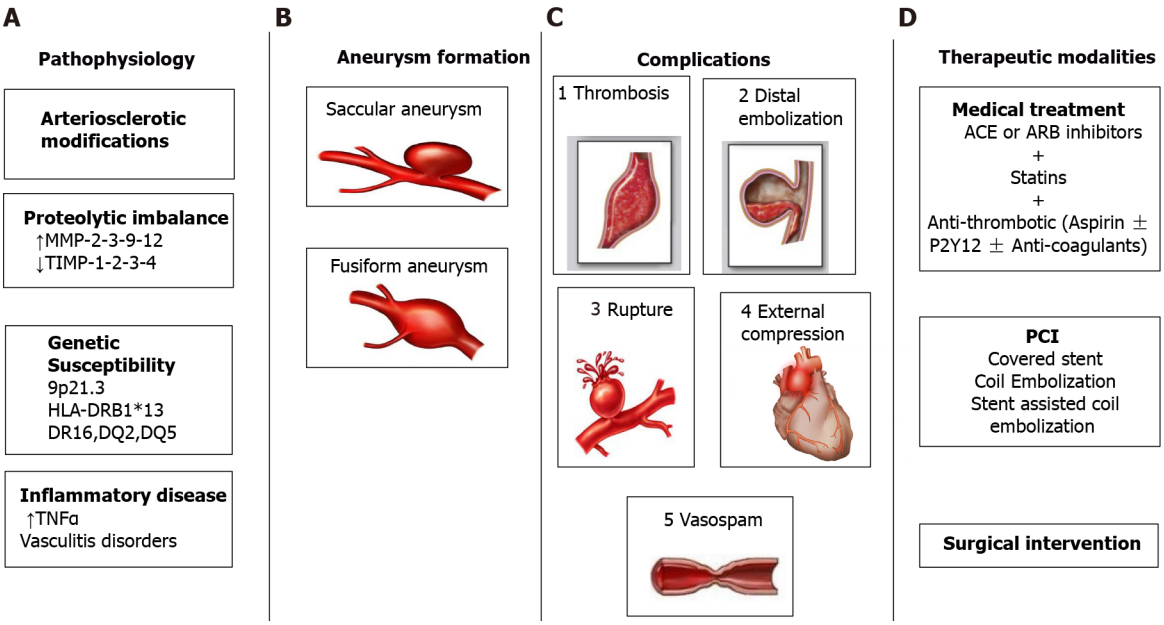

Figure 2 An illustration of the pathophysiology (A), types (B), complications (C) and therapeutic (D) modalities for coronary artery aneurysm. ACE: Angiotensin converting enzyme; ARB: Angiotensin II receptor blockers; MMP: Matrix metalloproteinases; PCI: Percutaneous coronary intervention; TIMP: Tissue-specific inhibitors of metalloproteinases; TNF: Tumor necrosis factor.

patients with CAA[48]. Theoretically, CAA does not have enough intact smooth muscle to produce significant vasoconstriction knowing that smooth muscle hypercontractility is implicated in the pathophysiological mechanism of coronary artery spasm [49]. However, Bove *et al*[50] were the first to describe a recurrent angina linked to spasm of aneurysmal coronary arteries. The rupture of CAA is rare, unpredictable and a serious life-threatening condition that results in cardiac tamponade and sudden death. Since previously published data[51-53], the incidence of rupture of CAA was dramatically decreased[54]. An excessively enlarged CAA may compress the surrounding adjacent cardiopulmonary structures like the right atrium[55], the right ventricular wall[55], the pulmonary artery and the tricuspid valve[56].

MANAGEMENT OF CAA

Until now, there are no standardized international recommendations for the management of CAA due to the lack of data from randomized clinical trials. Most of the available data are based on case series and anecdotal evidence. The management of CAA is individualized and depends on clinical presentation (silent or symptomatic), characteristics of CAA (location, size, shape, evolution, etiology), patient profile (age, comorbidities, cardiovascular risk factors) and physician experience. Different approaches including medical treatment, percutaneous coronary intervention (stent angioplasty and coil embolization) and surgical excision were priorly performed. Indeed, the optimal therapeutic strategy leading to the best outcome was not yet defined due to the absence of comparative studies. Coronary angiography is the invasive gold standard tool to assess the anatomic features of CAA, while coronary CT is the alternative non-invasive technique of choice for the follow-up[57].

Medical management

First of all, an intense control of cardiovascular risk factors is advocated in patients with CAA regardless of the presence of concomitant obstructive coronary artery disease[58]. Basing on the association between the overexpression of angiotensin-converting enzyme and aneurysm formation, it was hypothesized that angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may slow the progression of CAA[59]. Also, the use of statins in CAA patients is desirable. A beneficial role was attributed to statins by inhibiting the expression of matrix metalloproteinases, which play a crucial role in the physiological mechanism of aneurysm formation[60]. Otherwise, the proper indication of anti-thrombotic regimen for the management of CAA is a matter of debate noticing that data from previously

published studies are controversial.

Despite the risk of thrombus formation and distal embolization described above, few retrospective studies conclude that anticoagulation strategy is unbeneficial by showing a similar rate of thrombotic events in patients with and without CAA[61-63]. Contradictory results were revealed by Warisawa *et al*[21] and Baman *et al*[57] who showed greater rates of 5-year mortality and major cardiovascular adverse events (MACE) in patients with CAA. A recently published study found that prescribing oral anticoagulation led to positive outcomes in patients with coronary artery ectasia by reporting 0% of MACE in patients treated with oral anticoagulation compared to those who did not receive anti-thrombotic therapy after 49 mo of follow-up[22]. Therefore, coronary artery ectasia was identified as an independent predictor of cardiac events in patients presenting with acute coronary syndromes[22]. Myocardial infarction, MACE and death were two to four times higher in patients with coronary artery ectasia[22]. However, it is worthy to mention that prolonged anti-thrombotic therapy may provoke complications, such as bleeding. Lastly, intravenous immunoglobulin therapy in Kawasaki disease promotes CAA regression and decreases the incidence of MACE [64].

Percutaneous coronary interventions

Percutaneous coronary intervention (PCI) is a relatively new therapeutic option allowing to exclude CAA when the clinical and/or anatomical risk is high (Figure 3). Several techniques were reported in the literature, like covered stent implantation[65], coil embolization and stent-assisted coil insertion[66]. Conventionally, PCI is the preferred approach to exclude smaller CAA, while surgical approach is preferred for the larger aneurysms[67]. Several limitations like difficulty of stent delivery, occlusion of side branches and high percentage of restenosis were observed with covered stent angioplasty[68]. Bare metal stents were previously preferred over polytetrafluoroethylene covered stents due to the lower incidence of thrombosis and restenosis[69]. The last generation of covered stents, such as PK Papyrus stents, achieve a greater bending flexibility and a smaller crossing profile compared to the traditional sandwich designed stents that allow sealing of perforations and exclude aneurysms[70]. Therefore, stent-assisted coil insertion technique is favored over coil embolization in the management of wide-necked CAA because it reduces the risk of occlusion of the parent coronary vessel and rupture of CAA[66].

Previous studies investigating the outcomes of PCI performed in patients with CAA in the setting of acute myocardial infarction found a worst prognosis, thereby showing higher rates of procedural failure, mortality, no-reflow, stent thrombosis, distal embolization and target vessel revascularization[10-13,71]. Performing PCI in the setting of aneurysmal coronary arteries imposes technical challenges for physicians, such as appropriate sizing, landing zone assessment and thrombus burden. As a result, it is rare to intervene in asymptomatic patients with CAA.

Surgical interventions

Different surgical techniques have been described including aneurysmectomy with or without coronary artery bypass graft, aneurysm ligation, resection and marsupialization[72]. Indeed, the optimal surgical approach has not yet been defined. Overall, surgery is considered an alternative adequate therapeutic strategy for the management of symptomatic patients unsuitable for PCI, patients with concomitant obstructive coronary artery disease, CAA involving the large bifurcation or the left main, complicated CAA and giant CAA at high risk of rupture[72,73].

Imaging modalities for detection of CAA

A recently published study showed that CT angiography is superior to cardiac magnetic resonance imaging for detection, risk stratification and follow-up of CAA in patients with Kawasaki disease[74]. Also, CT angiography has already proven its value for the assessment of the diameter of coronary arteries in adults and patients with Kawasaki disease when compared to coronary angiography[75-78]. Indeed, the sensitivity of CT angiography for detection of CAA and related complications is remarkably high. Because radiation exposure is associated with an increase in lifetime cancer risk, especially in children, the lack of radiation exposure is the main described benefit to cardiac magnetic resonance imaging over coronary angiography and CT angiography for CAA detection[74]. Lastly, CT angiography provides accurate data concerning the coronary anatomy, calcification, luminal diameter, thrombi and aneurysmal features[79]. It represents the imaging of choice for the long-term monitoring of CAA[57].

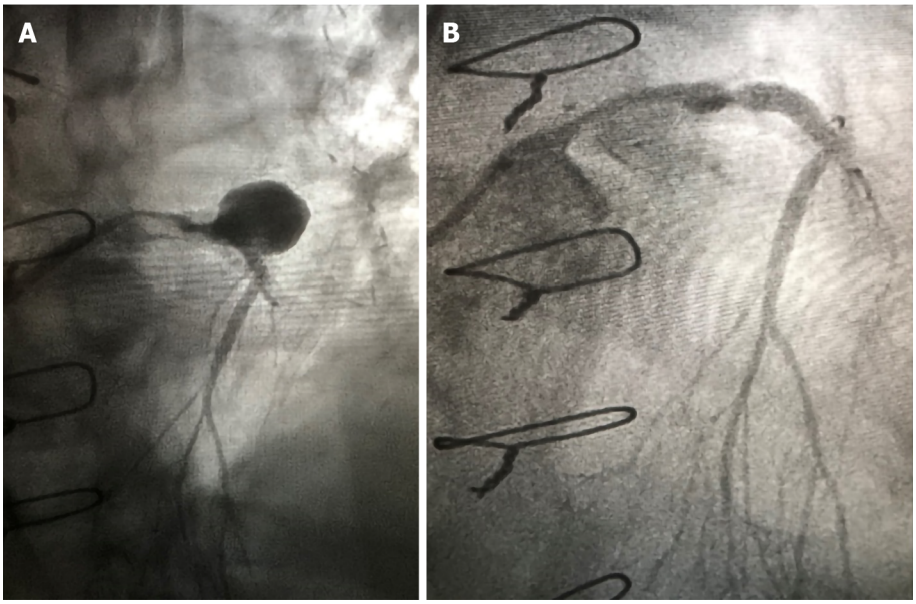

Figure 3 Coronary angiograms showing a giant coronary artery aneurysm of the proximal left anterior descending artery (A) excluded by implanting a bare metal stent with nonsignificant residual stenosis (B).

CONCLUSION

Usually, CAA is an incidental angiographic finding associated to atherosclerosis. The natural history of CAA is not well understood, but it is a progressive silent disease. Future prospective comparative trials to define the appropriate strategy and the optimal time to intervene are required in order to avoid the development of serious complications, especially in those with concomitant obstructive coronary artery disease.

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 September 26; 13(9): 456-463

DOI: 10.4330/wjc.v13.i9.456

ISSN 1949-8462 (online)

MINIREVIEWS

Coronary vasospasm: A narrative review

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Author contributions: Jewulski J and Khanal S performed literature review, and edited the manuscript; Jewulski J drafted the manuscript; Dahal K provided the image; all authors have read and approve the final manuscript.

Conflict-of-interest statement: No potential conflict of interest. No financial support.

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

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Abstract

Coronary artery vasospasm (CAVS) plays an important role in acute chest pain syndrome caused by transient and partial or complete occlusion of the coronary arteries. Pathophysiology of the disease remains incompletely understood, with autonomic and endothelial dysfunction thought to play an important role. Due to the dynamic nature of the disease, its exact prevalence is not entirely clear but is found to be more prevalent in East Asian and female population. Cigarette smoking remains a prominent risk factor, although CAVS does not follow traditional coronary artery disease risk factors. Many triggers continue to be identified, with recent findings identifying chemotherapeutics, allergens, and inflammatory mediators as playing some role in the exacerbation of CAVS. Provocative testing with direct visualization is currently the gold-standard for diagnosis, but non-invasive tests, including the use of biomarkers, are being increasingly studied to aid in the diagnosis. Treatment of the CAVS is an area of active research. Apart from risk factor modification, calcium channel blockers are currently the first line treatment, with nitrates playing an important adjunct role. High-risk patients with life-threatening complications should be considered for implantable cardioverter defibrillator (ICD), although timing criteria for escalated therapy require further investigation. The role of pharmaceuticals targeting oxidative stress remains incompletely understood.

Key Words: Coronary artery vasospasm; Vasospastic angina; Prinzmetal angina; Variant angina; Coronary artery disease

Country/Territory of origin: United States

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 19, 2021
Peer-review started: March 19, 2021
First decision: May 13, 2021
Revised: May 26, 2021
Accepted: July 23, 2021
Article in press: July 23, 2021
Published online: September 26, 2021

P-Reviewer: Ueda H
S-Editor: Ma YJ
L-Editor: A
P-Editor: Li JH

Core Tip: Coronary artery vasospasm (CAVS) represents a spectrum of transient coronary arterial occlusion which can lead to serious complications, including sudden cardiac death. CAVS, often underdiagnosed and undertreated, should be considered in symptomatic patients with nonobstructive coronary arteries. Recent studies have expanded upon the etiology, epidemiology, and treatment options for CAVS.

Citation: Jewulski J, Khanal S, Dahal K. Coronary vasospasm: A narrative review. *World J Cardiol* 2021; 13(9): 456-463
URL: https://www.wjgnet.com/1949-8462/full/v13/i9/456.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i9.456

INTRODUCTION

Coronary artery vasospasm (CAVS) was first described as a "variant" of typical angina pectoris by Dr. Myron Prinzmetal in 1959, hence launching the study of a Prinzmetal (or "variant") angina, which was subsequently termed vasospastic angina (VSA)[1]. Since then, the paradigm surrounding VSA has continued to expand. Symptoms develop upon transient partial or complete occlusion of coronary vessels resulting in a spectrum of clinical manifestations, ranging from stable angina to acute coronary syndrome (ACS), and in some cases sudden cardiac death (SCD)[1-6]. The disease process has been identified in patients both with and without coronary artery disease (CAD), affecting both epicardial and microvascular coronary arteries, and having both focal and diffuse involvement[2,4,7]. Certainly, traditional risk factors associated with CAD cannot be relied upon as predictors of CAVS, with the exception of cigarette smoking[1]. Although a prevailing precedent exists regarding the pathophysiology, diagnostics, and treatment of VSA, previous reviews have identified areas which require further study, especially in cases of refractory disease[8].

PATHOPHYSIOLOGY

A number of mechanisms have been proposed regarding the mechanism of CAVS, including impairment of parasympathetic activity, coronary vascular and microvascular endothelial dysfunction, enhanced smooth muscle vasoconstriction, chronic inflammation, and oxidative stressors[4,5,7]. Recent studies have highlighted rarer causes of CAVS resulting from excessive adrenergic stimulation in cases of catecholamine-induced cardiomyopathy in pheochromocytomas and paragangliomas [9].

EPIDEMIOLOGY

Approximately 5% to 30% of patients presenting with angina demonstrate normal or non-obstructive coronary arteries when worked up with coronary angiography, despite presenting with symptoms suggestive of acute coronary syndrome (ACS)[10-12]. Nearly half of these presentations may be attributed to CAVS[5,13], with an increased incidence amongst East Asians, especially Korean and Japanese populations [3,6,13,14]. This increased prevalence (in addition to environmental factors) has been attributed to genetic deficiency of variant aldehyde dehydrogenase 2 (ALDH2) genotype amongst these populations[15]. This correlates with increased toxic aldehyde accumulation, which may from the bases of future targeted treatment strategies in these populations[15]. Further studies demonstrate a need for exploring CAVS amongst Japanese adolescents less than 20 years old, whose clinical status matched severity of adults with refractory CAVS[16].

An increased incidence is additionally seen in women, with up to 70% of women showing ACS symptoms without CAD demonstrating findings suggestive of CAVS [17-19]. The incidence is particularly high for younger women under the age of 50 years, as well as non-white women[20,21]. For this reason, significant consideration should be given to a CAVS workup in patients from these demographics, especially

given the tendency for worse outcomes in women compared to men[21]. Women with myocardial ischemia and no obstructive coronary artery disease (MINOCA) should undergo coronary reactivity testing (CRT), which reliably identifies the presence of CAVS[17].

Consideration of CAVS requires high clinical suspicion, and should also be considered in patients with rest angina or patients with anginal symptoms despite unremarkable coronary angiography[6,18]. Patients often develop symptoms between midnight and early morning, at times awoken from sleep by symptoms[15].

ETIOLOGY

A number of triggers have been implicated in literature, with the most impactful trigger being cigarette smoking[2,18]. Other triggers include psychological stress, cold exposure, hyperventilation, alcohol consumption, stimulants (*e.g.*, cocaine)[5,22]. Given increasing legalization within the United States, marijuana consumption has been considered as a contributor to CAVS exacerbation in a number of case reports [23].

Chemotherapies are other important causes of CAVS. Studies suggest that fluoropyrimidines (including 5-fluorouracil and capecitabine) induce vascular endothelial damage which can cause ischemia secondary to coronary artery vasospasm[24]. In such cases, chemotherapy should be halted and standard therapy for CAVS initiated, which should include calcium channel blockers (CCBs) and nitrates[24]. Further research is required surrounding cardioprotective agents such as coenzyme complex, glucagon-like peptide-1 (GLP-1) analogues, degradation inhibitors [24], and uridine triacetate[25]. Other chemotherapies should be considered if feasible, otherwise a CAD workup should be considered to stratify the patient's risk for further fluoropyrimidine treatment[26].

Kounis syndrome (KS) is described as the occurrence of ACS in the setting of a mast-cell and platelet mediated hypersensitivity, anaphylactic, anaphylactoid, or allergic reaction[27,28]. One pathophysiology of KS includes CAVS, induced by inflammatory mediators[29]. Common triggers include antibiotics (especially beta-lactams[29]) and insect bites, which together account for half of reported cases[27]. Recent studies have expanded upon potential triggers, including supplements from traditional Chinese medicine (TCM)[27] and injection of cefuroxime[29].

Infectious myocarditis has been implicated in the development of CAVS in patients with otherwise non-obstructive coronary arteries. The underlying mechanism is believed to involve direct inflammatory and infectious interference with endothelial function of the coronary arteries[30]. Well documented etiologies include parasitic infections with *Treponema cruzi* (Chagas disease) and viral infections with parvovirus B19, amongst other causes[30].

DIAGNOSTICS

Studies indicate that CAVS is an underdiagnosed and underreported disease[3,6,14]. Correct diagnosis can guide appropriate treatment, which can not only improve patient's quality of life, but also reduce aforementioned serious risks associated with CAVS, including life-threatening arrhythmias and SCD[14]. Current gold standard diagnosis of CAVS utilizes pharmacological provocative testing with high-dose boluses of acetylcholine, ergonovine, or methylergonovine *via* intracoronary injection [2,3,5,13,14]. The response is then visualized as a coronary vasospasm with transient > 90% occlusion of coronary arteries[19], during coronary angiography, or *via* abnormalities of ventricular wall motion on echocardiogram[2,3]. A standard cardiac workup should initially include standard 12-lead electrocardiogram (ECG) during an attack, ambulatory cardiac monitoring, or exercise stress testing to exclude underlying CAD[18].

The Coronary Vasomotion Disorder International Study Group (COVADIS) developed diagnostic criteria for CAVS, which include: (1) Nitrate responsiveness to angina during spontaneous episodes with at least one of rest angina, marked diurnal variation in exercise tolerance, hyperventilation precipitating episodes, or calcium channel blockers (but not β-blockers) suppressing episodes; (2) Transient ischemic changes during spontaneous episodes including at least two contiguous leads with ST segment elevations ≥ 0.1 mV, ST segment depressions ≥ 0.1 mV, or new negative U waves; and (3) Coronary artery spasm visualized either spontaneously or during

provocative testing[31]. Definitive CAVS is diagnosed if the first and either second or third criteria are fulfilled, which can guide further testing[31].

Although provocative testing is favored in the diagnosis of CAVS and is generally considered safe, the procedure does carry a small chance of serious complications. Recent studies have explored the use of biomarkers *via* blood test as a possible component in the workup for CAVS. One study explored a number of biomarkers including: (1) Inflammatory markers including C-reactive proteins (CRP), cytokines, lipoprotein (a), and cystatin-C as precipitating factors; (2) Vasoconstrictors including rho-kinase, serotonin (5-hydroxytryptamine), and endothelin-1 (ET-1); and (3) Oxidative stressors including thioredoxin and nitrotyrosine[32].

Previous studies have stipulated that increased testing and sensitivity of provocative testing can enhance detection of CAVS worldwide (especially Western countries), but this must be weighed against the risks associated with such testing[14,32]. Notably, rapid administration of intracoronary nitrate following provocative testing has resulted in no reported procedure-related deaths[13]. Furthermore, recent studies have demonstrated more efficacy and safety with local administration of nitroglycerin to spasming areas through a perforated balloon rather than proximal administration of nitroglycerin, which may further reduce minor risks associated with provocative testing[33]. The impact of local nitroglycerin administration on a spasming area of coronary artery can be visualized in Figures 1 and 2.

TREATMENTS

Initial approach to patients with CAVS should include lifestyle modifications, with the most prominent impact coming from smoking cessation[2,18]. Once this initial approach has been exhausted and symptoms remain refractory, a number of pharmacological options are available to supplement lifestyle notifications, noted in Table 1. First line pharmacologic treatment should include CCBs, with non-dihydropyridine being preferred but with similar efficacy to dihydropyridine CCBs[2,5]. Patients with persistent symptoms may benefit from the addition of long-acting nitrates, which reduce the frequency of anginal symptoms[2]. Additionally, sublingual nitrates may be useful for relieving acute episodes of angina[5]. Statins and angiotensin converting enzyme (ACE) inhibitors have shown efficacy in preventing CAVS episodes, and should be considered in all patients presenting with CAVS[2,5,19]. One study analyzed the use of sarpogrelate (a serotonin receptor antagonist) in addition to high-dose statins for CAVS, but did not find significant improvement of outcomes[34]. The use of magnesium and antioxidants (such as vitamin C and E) have demonstrated efficacy in many patients[5].

Patients with refractory disease who do not respond to lifestyle changes and first line pharmacotherapy may consider alpha 1-adrenergic receptor antagonists, rho-kinase inhibitors, or nicorandil[2,5,19]. Patients with significant atherosclerosis may benefit from percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), which has shown benefit in patients with concomitant CAVS[5].

Patients who have experienced adverse outcomes of CAVS including life-threatening ventricular arrythmias or SCD may benefit from an implantable cardioverter defibrillator (ICD) in addition to medical therapy[2]. Notably, other reversible causes of SCD should be considered before escalating therapy. Although CAVS generally has a favorable prognosis, patients experiencing these adverse outcomes have worse outcomes[35]. Predictors of SCD in CAVS patients include advanced age, hypertension, hyperlipidemia, family history of sudden cardiac death, multivessel spasm, and left anterior descending (LAD) artery spasm, and should be considered for escalated therapy[35]. Recent studies have also explored the use sympathectomy, which reduced major adverse cardiac events in patients with refractory CAVS when compared to conventional treatment[36].

Beta blockers (BBs), both selective and nonselective forms (especially propranolol), should generally be avoided in patients with CAVS[2,5]. Blockage of beta-2 receptors, which prevents smooth muscle relaxation, can exacerbate anginal symptoms. The use of nebivolol, a BB with nitric oxide-releasing effects, has been compared to diltiazem for CAVS – both reduced the effects of CAVS, but diltiazem had greater reduction in symptoms at 12 wk[37]. A notable recent exception to this is drug-eluting stent-induced vasospastic angina (DES-VSA), which showed lower 2-year major cardiovascular events (MACE) with BBs compared to CCBs[38]. The use of aspirin (especially at high doses) in CAVS remains controversial, and there has been no clear demonstrated benefit of its use in patients with any degree of CAVS[2,5].

Table 1 Pharmacologic therapies for coronary artery vasospasm

Drug class	Common drugs	Usual drug dosage	Indication
CCB	Amlodipine; Diltiazem; Nifedipine-ER	10 mg qD; 240 mg qD; 30-120 mg qD	First line for CAVS[40-42]
Long-acting nitrate	Isosorbide mononitrate	60–240 mg qD (maintenance)	Symptomatic improvement in combination with first line therapy[2]
Short-acting nitrate	Sublingual nitroglycerin	0.3 mg	Acute attack[43]
Statin	Lovastatin; Fluvastatin	80 mg qD; 20-80 mg qD	All patients experiencing CAVS[15,44]
ACE inhibitor/ARB	Candesartan; Losartan	8-16 mg qD; 25–50 mg qD	All patients experiencing CAVS[45]
BB	Bisoprolol; Nebivolol	1.25–5 mg qD; 5–10 mg qD	DES-VSA[37,38]
Rho kinase inhibitors	Fasudil	240 mg qD	Refractory CAVS[46]
Antioxidants	Vitamin E	400 mg qD	Adjunct therapy[47]
Magnesium	Magnesium Chloride	20 mEq	Replenishing deficiency[5]
Potassium channel activator	Nicorandil	10–20 mg BID	If nitrates are ineffective[12]

CCB: Calcium channel blocker; ACE: Angiotensin converting enzyme; ARB: Angiotensin II receptor blocker; BB: Beta blocker; DES-VSA: Drug-eluting stent-induced vasospastic angina; CAVS: Coronary artery vasospasm; qD: Daily; BID: Twice a day.

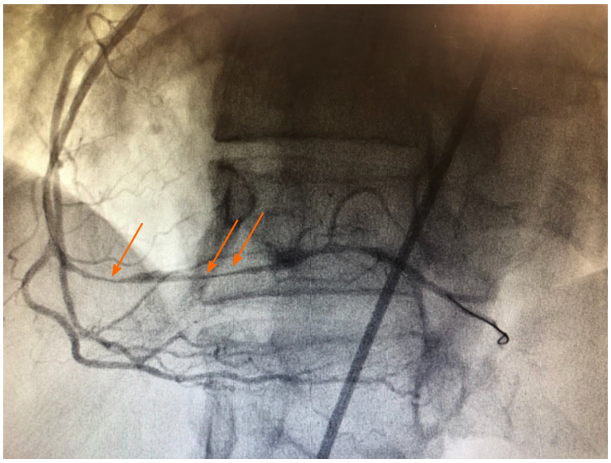

Figure 1 Coronary angiography demonstrating stenosis of the right coronary artery (arrows).

FUTURE DIRECTION

Although an understanding of CAVS continues to expand, there remains an ongoing need to better stratify the pathology. The effect of pharmacologic therapy, especially when considering generally avoided medications like BBs, should be tested in larger studies to ensure efficacy[38]. Studies have also emphasized the need to explore the use of fractional flow reserve (FFR) in the evaluation of moderate stenosis in the setting of MINOCA, nearly half of whom may have underlying CAVS[13,39]. Heart-type fatty acid-binding protein (h-FABP), myocardial performance (Tei) index, and genetic testing have been identified as potentially useful methods for tracking the development of CAVS in patients taking fluoropyrimidines[24,25]. Further studies should explore the timing of ICD implantation in high-risk patients with CAVS who would benefit from such therapy[3,35]. Future studies should consider populations in Western countries, where CAVS is generally underdiagnosed and undertreated[32].

CONCLUSION

CAVS is an important but underrecognized disease that can result in significant clinical symptoms and/or life-threatening complications. Its prevalence is decreasing

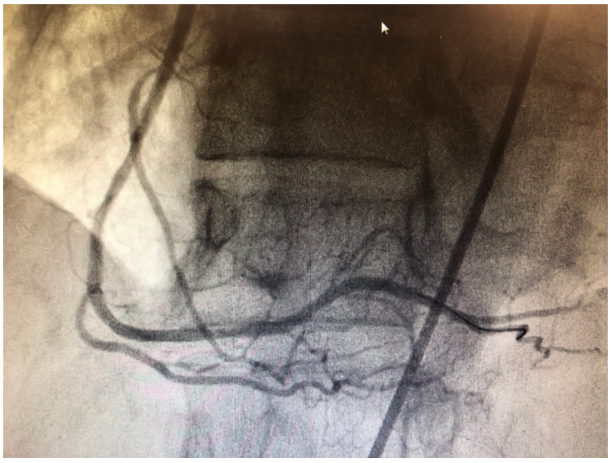

Figure 2 Coronary angiography demonstrating resolution after intracatheter injection of nitroglycerin.

due to decreasing prevalence of smoking, increasing use of the medications like calcium channel blockers, statins, and increasing use of non-invasive testing for CAD. It is important to consider CAVS in the differential of anginal chest pain in patients with non-obstructive CAD and treat it appropriately.

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 September 26; 13(9): 464-471

DOI: 10.4330/wjc.v13.i9.464

ISSN 1949-8462 (online)

MINIREVIEWS

Sodium glucose cotransporter 2 inhibitors: New horizon of the heart failure pharmacotherapy

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Author contributions: Naito R wrote the manuscript; Kasai T revised the manuscript; all authors have read and approved the final manuscript.

Conflict-of-interest statement: Authors have no conflict-of-interest relating to this work.

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: Japan

Peer-review report's scientific

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Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have gained momentum as the latest class of antidiabetic agents for improving glycemic control. Large-scale clinical trials have reported that SGLT2 inhibitors reduced cardiovascular outcomes, especially hospitalization for heart failure in patients with type 2 diabetes mellitus who have high risks of cardiovascular disease. Accumulating evidence has indicated that beneficial effects can be observed regardless of the presence or absence of type 2 diabetes mellitus. Accordingly, the Food and Drug Administration approved these agents specifically for treating patients with heart failure and a reduced ejection fraction. It has been concluded that canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin can be recommended for preventing hospitalization associated with heart failure in patients with type 2 diabetes and established cardiovascular disease or those at high cardiovascular risk. In the present review, we explore the available evidence on SGLT2 inhibitors in terms of the cardioprotective effects, potential mechanisms, and ongoing clinical trials that may further clarify the cardiovascular effects of the agents.

Key Words: Sodium glucose cotransporter 2 inhibitors; Heart failure; Clinical trials; Potential mechanisms; Diuretics

quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 21, 2021
Peer-review started: March 21, 2021
First decision: May 6, 2021
Revised: May 11, 2021
Accepted: July 23, 2021
Article in press: July 23, 2021
Published online: September 26, 2021

P-Reviewer: Al-Mohammad A
S-Editor: Ma YJ
L-Editor: A
P-Editor: Wu RR

Core Tip: Sodium glucose cotransporter 2 inhibitors are newly approved by the Food and Drug Administration as treatment choice for heart failure based on evidence from several large-scale clinical trials demonstrating reduction in cardiovascular outcomes, especially hospitalization for heart failure or cardiovascular death. The background of the approval and potential mechanisms are discussed in this review. As well, summary of available evidence from clinical trials and ongoing trials examining beneficial effects of the agents are written.

Citation: Naito R, Kasai T. Sodium glucose cotransporter 2 inhibitors: New horizon of the heart failure pharmacotherapy. *World J Cardiol* 2021; 13(9): 464-471
URL: https://www.wjgnet.com/1949-8462/full/v13/i9/464.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i9.464

INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as the latest class of antidiabetic agents for improving glycemic control. Interestingly, the EMPA-REG OUTCOME trial, which evaluated empagliflozin in patients with type 2 diabetes and cardiovascular disease, demonstrated a greater-than-expected reduction in cardiovascular death, hospitalization for heart failure, and all-cause death[1,2]. Subsequent cardiovascular outcome trials assessing other SGLT2 inhibitors reported similar results; for instance, the Canagliflozin Cardiovascular Assessment Study (CANVAS), involving 10142 type 2 diabetic patients with high cardiovascular risk, demonstrated that canagliflozin decreased the risk of the primary outcome of a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by 14%[3-5]. In the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, dapagliflozin lowered the rate of cardiovascular death or heart failure hospitalization by 17% in patients with type 2 diabetes who had or were at risk for cardiovascular disease. Those trials are summarized in Table 1. A recent meta-analysis including these clinical trials reported that SGLT2 inhibitors reduced the risk of cardiovascular death or heart failure hospitalization by 23% (HR, 0.77; 95%CI, 0.71–0.84; $P < 0.0001$), with a similar benefit in patients with and without a history of heart failure[6]. The magnitude of benefit associated with SGLT2 inhibitors varied with baseline renal function, with greater reductions in hospitalization for heart failure (P for interaction = 0.0073) observed in patients with more severe renal dysfunction at baseline. Additionally, sotagliflozin, a dual inhibitor of SGLT1 and SGLT2, has reduced the risk of cardiovascular death or heart failure events in patients with type 2 diabetes and chronic kidney disease[7] or type 2 diabetes complicated with heart failure[8] (Table 2). Despite these positive findings, the benefit of SGLT2 inhibitors on heart failure events was not primarily investigated in these studies, where study participants were patients with diabetes; accordingly, background medical therapy for heart failure might not be optimized. When investigating new heart failure pharmacotherapies, it is crucial to consider whether the therapies provide any additional benefits to established therapies. Therefore, it is uncertain whether these benefits can be generalized.

CARDIOPROTECTIVE EFFECTS IN PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION, REGARDLESS OF DIABETIC STATUS

A meta-analysis incorporating data from EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 revealed that the decrease in the composite of cardiovascular death or heart failure hospitalization did not statistically differ among patients with (HR, 0.71; 95%CI, 0.61–0.84) or without (HR, 0.79; 95%CI, 0.71–0.88) history of heart failure at baseline (P for interaction = 0.51). However, the cardioprotective effects of SGLT2 inhibitors in patients with heart failure, regardless of the presence or absence of diabetes, are uncertain. The question was answered by the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, wherein 4744

Table 1 Landmark clinical trials of sodium-glucose cotransporter 2 inhibitors

Ref.	Population (*n*)	Age, yr (mean)	Intervention	Follow-up period (median)	Patients with a history of HF	Patients with a history of CVD	Main results
EMPA-REG[1]	T2DM (7028)	63.1	Empagliflozin	3.1 yr	10.1%	100%	CV death or HF (HR, 0.66; 95%CI, 0.55–0.79) HF (HR, 0.65; 95%CI, 0.50–0.85) CV death (HR, 0.62; 95%CI, 0.49–0.77)
CANVAS[3]	T2DM (9734)	63.3	Canagliflozin	2.4 yr	14.4%	65.6%	CV death or HF (HR, 0.78; 95%CI, 0.67–0.91) HF (HR, 0.67; 95%CI, 0.52–0.87) CV death (HR, 0.87 95%CI, 0.72–1.06)
DECLARE-TIMI 58[4]	T2DM (17160)	63.9	Dapagliflozin	4.2 yr	10.0%	40.6%	CV death or HF (HR, 0.83; 95%CI, 0.73–0.95) HF (HR, 0.73; 95%CI, 0.61–0.88) CV death (HR, 0.98; 95%CI, 0.82–1.17)
VERTIS-CV[5]	T2DM (8246)	64.4	Ertugliflozin	3.5 yr (mean)	23.7%	71.4%[1]	CV death or HF (HR, 0.88; 95%CI, 0.75–1.03) HF (HR, 0.70; 95%CI, 0.54–0.90) CV death (HR, 0.92; 95%CI, 0.77–1.11)

[1]Numbers are % of patients with coronary artery disease. T2DM: Type 2 diabetes mellitus; CV: Cardiovascular; HF: Heart failure; CVD: Cardiovascular disease; HR: Hazard ratio; CI: Confidence interval.

Table 2 Summary of clinical trials of sotagliflozin

Ref.	Population (*n*)	Age, yr (median)	Follow-up period (median)	Patients with a history of HF	Patients with a history of CAD	Main results
SCORED[7]	T2DM and CKD (10584)	63	16 mo	31.0%	22.4%	CV death or HF (HR, 0.74; 95%CI, 0.63–0.88) CV death (HR, 0.90; 95%CI, 0.73–1.12)
SOLOIST-WHF [8]	T2DM and HF (1222)	70	9.2 mo	100%	58.3%	CV death or HF (HR, 0.67; 95%CI, 0.52–0.85) CV death (HR, 0.84; 95%CI, 0.58–1.22)

HF: Heart failure; CAD: Coronary artery disease (numbers indicate % of patients with coronary revascularization in the SCORED trial and % of those with ischemic heart disease in the SOLOIST-WHF trial); T2DM: Type 2 diabetes mellitus; CKD: Chronic kidney disease; CV: Cardiovascular; HF: Heart failure; HR: Hazard ratio; CI: Confidence interval.

patients with heart failure with reduced left ventricular ejection fraction (LVEF) were randomly assigned to receive either dapagliflozin or placebo, in addition to standard therapy for heart failure. Among the participants, 41.8% had diabetes mellitus. During a median follow-up of 18 months, the incidence of cardiovascular death or worsening heart failure was significantly lower in the dapagliflozin group than in the placebo (16.3% *vs* 21.2%; HR, 0.74; 95%CI, 0.65–0.85; $P < 0.001$). Subgroup analysis indicated that the benefit was observed regardless of diabetic status. The empagliflozin outcome trial in patients with chronic heart failure with reduced LVEF (EMPEROR-Reduced) followed the results, examining the potential benefit of empagliflozin in 3730 patients

with heart failure and reduced LVEF[9]. As observed in DAPA-HF, 50.2% of the study participants did not present with diabetes mellitus. The two trials are summarized in Table 3. The study participants in the EMPEROR-Reduced presented greater severity of heart failure than those in the DAPA-HF, with a mean LVEF of 27% *vs* 31% and a median N-terminal prohormone of brain natriuretic peptide (NT-proBNP) value of 1907 *vs* 1437. Furthermore, more than 70% of the patients enrolled in EMPEROR-Reduced had a LVEF less than 30%. As in the DAPA-HF, the emapagliflozin group had lower incidence of cardiovascular death or hospitalization for heart failure than the placebo (19.4% *vs* 24.7%; HR, 0.75; 95%CI, 0.65–0.86; $P < 0.001$) during the median follow-up of 16 months. Moreover, the benefit was observed regardless of the diabetes status. A meta-analysis that included DAPA-HF and EMPEROR-Reduced reported that SGLT2 inhibitors reduced both cardiovascular (HR, 0.86; 95%CI 0.76–0.98) and all-cause mortality (HR, 0.87; 95%CI, 0.77–0.98), without evident statistical heterogeneity between dapagliflozin and empagliflozin[10]. Similarly, SGLT2 inhibitors reduced the risk for the first hospitalization for heart failure (HR, 0.69; 95%CI, 0.62–0.78), the total number of heart failure hospitalizations or cardiovascular death (HR, 0.75; 95%CI, 0.68–0.84), and worsening renal function (HR, 0.62; 95%CI, 0.43–0.90). These findings were generally consistent in subgroup analyses (Table 4). Furthermore, both agents showed no excess risk of adverse events when compared with placebo, including renal adverse events, volume depletion, severe hypoglycemia, or bone fractures. Based on this evidence, the Heart Failure Association of the European Society of Cardiology has recently issued a position paper highlighting results of clinical trials on the role of SGLT2 inhibitors in patients with heart failure[11]. On May 5, 2020, the Food and Drug Administration approved dapagliflozin, specifically, to treat patients with heart failure and reduced ejection fraction. The position paper has concluded that canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin can be recommended to prevent hospitalization for heart failure in type 2 diabetic patients with established cardiovascular disease or high cardiovascular risk[11]. Dapagliflozin and empagliflozin are recommended to reduce the risk for heart failure hospitalization and cardiovascular death in symptomatic patients with heart failure with reduced LVEF already receiving guideline-directed medical therapy, regardless of diabetic status. The Canadian Cardiovascular Society and the Canadian Heart Failure Society have recommended that SGLT2 inhibitors are to be used in patients with mild or moderate heart failure who have an LVEF of 40% or less to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular death[12].

MECHANISMS LINKING SGLT2 INHIBITORS AND REDUCTIONS IN CARDIOVASCULAR EVENTS ARE UNKNOWN

Potential mechanisms

The mechanisms underlying the cardioprotective effects of SGLT2 inhibitors have not been comprehensively elucidated. SGLT2 is predominantly located in the proximal tubule of the kidney and reabsorbs glucose and sodium. Thus, SGLT2 inhibitors reduce not only glucose reabsorption but also sodium reabsorption. These inhibitors behave as diuretics presenting mechanisms such as natriuresis and enhanced diuresis, which can be attributed to an osmotic effect dependent on glycosuria, resulting in a decrease in blood pressure. Research has reported that the drug provides cardiovascular benefits by reducing plasma volume, blood pressure, arterial stiffness, and vascular resistance[2,13]. Blood pressure reduction and renal protection could be the main mechanisms contributing to favorable outcomes. Recently, basic research has suggested that SGLT2 inhibitors induce sympathetic nervous system inhibition[14]. Other studies have reported that SGLT2 inhibitors improved the circadian rhythm of sympathetic activity and reduced high fat diet-induced elevation of tyrosine hydroxylase and noradrenaline in animal models[15,16]. In agreement with this evidence, cardiovascular events that were reduced by SGLT2 inhibitors included sudden cardiac death and hospitalization for heart failure[3]. This evidence presents the hypothesis that the inhibition of sympathetic nervous activity could explain the cardiovascular benefits of SGLT2 inhibitors. Several other hypotheses beyond effects on glycemia, blood pressure lowering, and weight loss have been postulated, including improvement in myocardial energetic efficiency[17] and inhibition of sodium-hydrogen exchangers in the heart, which could prevent cardiomyocyte injury [18].

Table 3 Summary of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure and the EMPEROR-Reduced trials

Ref.	Population (*n*)	Patients with T2DM	Intervention	Follow-up period (median)	Main results
DAPA-HF[22]	HFrEF with or without T2DM (4744)	42%	Empagliflozin	18 months	CV death or HF (HR, 0.71; 95%CI, 0.65–0.85) HF (HR, 0.70; 95%CI, 0.59–0.83) CV death (HR, 0.82; 95%CI, 0.69–0.98)
EMPEROR-Reduced[9]	HFrEF (3730)	49.8%	Empagliflozin	16 months	CV death or HF (HR, 0.75; 95%CI, 0.65–0.86) HF (HR, 0.69; 95%CI, 0.59–0.81) CV death (HR, 0.92; 95%CI, 0.75–1.12)

T2DM: Type 2 diabetes mellitus; CV: Cardiovascular disease; HF: Heart failure; HR: Hazard ratio; CI: Confidence interval.

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Table 4 Subgroup analyses for the primary outcomes in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure and the EMPEROR-Reduced trials

Subgroup	HR (95%CI) of dapagliflozin compared to placebo	HR (95%CI) of empagliflozin compared to placebo
Age		
≤ 65 yr	0.78 (0.63–0.96)	0.71 (0.57–0.89)
> 65 yr	0.72 (0.60–0.85)	0.78 (0.66–0.93)
Sex		
Male	0.73 (0.63–0.85)	0.80 (0.68–0.93)
Female	0.79 (0.59–1.06)	0.59 (0.44–0.80)
T2DM		
Yes	0.75 (0.63–0.90)	0.72 (0.60–0.87)
No	0.73 (0.60–0.88)	0.78 (0.64–0.97)
eGFR < 60 mL/min/1.73 m^2		
Yes	0.72 (0.59–0.86)	0.83 (0.69–1.00)
No	0.76 (0.63–0.92)	0.67 (0.55–0.83)

T2DM: Type 2 diabetes mellitus; HR: Hazard ratio; CI: Confidence interval.

Differences between SGLT2 inhibitors and loop diuretics

Loop diuretics that act in the ascending limb of the Henle loop alleviate symptoms related to heart failure by promoting urinary sodium excretion. Despite their clinical usefulness, diuretics have failed to demonstrate prognostic effects, partly due to counter-regulatory responses through activation of the renin-angiotensin system, neurohormonal activation, and development of diuretic resistance[19]. SGLT2 inhibitors lower plasma glucose by blocking glucose reabsorption in the proximal tubule, resulting in glucose excretion into the urine. The diuretic effect of SGLT2 inhibitors was initially assumed to originate from mild osmotic diuresis owing to glycosuria. Griffin *et al*[20] recently conducted a double-blind, placebo-controlled, crossover study involving treatment with either empagliflozin of 10 mg or matched placebo for 2 wk, followed by a 2-wk washout period and crossover at 2 wk with the alternative treatment in diabetic patients with heart failure[20]. They reported that the natriuretic effect was synergistic with loop diuretics, resulting in a reduced blood and plasma volume, which did not activate the sympathetic nervous system or renin-angiotensin system. Renal dysfunction did not affect the natriuretic effect.

Table 5 Summary of ongoing heart failure outcome trials of sodium-glucose cotransporter 2 inhibitors

	PRESERVED-HF	DELIVER	DAPA ACT HF-TIMI 68	EMPEROR-Preserved	EMPULSE
NCT number	03030235	03619213	04363697	03057951	04157751
Population	HFpEF with or without T2DM	HFpEF with or without T2DM	Acute heart failure with reduced ejection fraction	HFpEF with or without T2DM	Acute Heart Failure
Sample size	320	4700	2400	5750	500
Intervention	Dapagliflozin/placebo	Dapagliflozin/placebo	Dapagliflozin/placebo	Empagliflozin/placebo	Empagliflozin/placebo
Primary endpoint	Change from baseline in NT-proBNP	Time-to-first occurrence of CV death, HF hospitalization, or urgent HF visit	CV death or worsening HF	Time-to-first event of HF hospitalization	Death, number of HF events
Status	Estimated completion; February 2021	Estimated completion; June 2021	Estimated completion; October 2022	Estimated completion; April 2021	Estimated completion; June 2021

HFpEF: Heart failure with preserved ejection fraction; T2DM: Type 2 diabetes mellitus; CV: Cardiovascular; HF: Heart failure; NT-proBNP: N-terminal pro-brain natriuretic peptide.

OPTIMAL TIME FOR ADMINISTERING THE AGENT

The EMPA-RESPONSE-AHF study is a multicenter pilot study that included 80 patients with acute heart failure receiving standard diuretic therapy, randomized to receive either empagliflozin of 10 mg or matched placebo daily for 30 d[21]. Empagliflozin did not demonstrate reduction in the primary outcomes of the visual analog scale of dyspnea, diuretic response, change in NT-proBNP, or length of hospital stay. A secondary composite outcome of in-hospital exacerbation of heart failure, re-hospitalization for heart failure, or death within 60 d reportedly occurred less frequently in the empagliflozin group (10% *vs* 13%, $P = 0.014$). The occurrence of adverse events related to renal function, blood pressure, and heart rate was comparable between the groups. Future trials investigating the benefits of SGLT2 inhibitors in patients with acute heart failure are warranted.

Another clinical question remains whether the effects of SGLT2 inhibitors are affected by the left ventricular ejection fraction. Heart failure treatments in patients with HFrEF have long been established, while evidence is scarce in patients with heart failure with preserved ejection fraction (HFpEF). Similarly, available evidence has revealed that the beneficial effects of SGLT2 inhibitors have been observed in HFrEF but not necessarily in HFpEF. Ongoing studies may provide some data on this issue. The ongoing heart failure outcome trials for SGLT2 inhibitors are summarized in Table 5.

CONCLUSION

Accumulated evidence from large-scale randomized placebo-controlled trials has demonstrated the consistent effect of SGLT2 inhibitors on the clinical course of heart failure, mainly driven by a substantial decrease in hospitalization for heart failure. These benefits were attained regardless of the presence or absence of diabetes, with agents administered once daily and requiring no up-titration; additionally, no serious adverse effects were observed. This evidence supports the role of SGLT2 inhibitors as a new standard of care for HFrEF. Further studies are needed to clarify the optimal time for administering these agents, proper candidates who most benefit from these agents, and mechanisms explaining the cardioprotective effects of SGLT2 inhibitors.

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 September 26; 13(9): 472-482

DOI: 10.4330/wjc.v13.i9.472

ISSN 1949-8462 (online)

MINIREVIEWS

Intensive lipid-lowering therapy, time to think beyond low-density lipoprotein cholesterol

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Author contributions: Alkhalil M contributed to the conceptualization, methodology and project administration; Zaman A and Alkhalil M provided the resources; Abdalwahab A and Al-atta A contributed to writing original draft and preparation; all authors finally wrote review and edited the manuscript.

Conflict-of-interest statement: The authors have no any conflicts of interest.

Manuscript source: Invited

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Abstract

Statins have been shown to be effective in reducing cardiovascular events. Their magnitude of benefits has been proportionate to the reduction in low-density lipoprotein cholesterol (LDL-c). Intensive lipid-lowering therapies using ezetimibe and more recently proprotein convertase subtilisin kexin 9 inhibitors have further improved clinical outcomes. Unselective application of these treatments is undesirable and unaffordable and, therefore, has been guided by LDL-c level. Nonetheless, the residual risk in the post-statin era is markedly heterogeneous, including thrombosis and inflammation risks. Moreover, the lipoprotein related risk is increasingly recognised to be related to other non-LDL-c markers such as Lp(a). Emerging data show that intensive lipid-lowering therapy produce larger absolute risk reduction in patients with polyvascular disease, post coronary artery bypass graft and diabetes. Notably, these clinical entities share similar phenotype of large burden of atherosclerotic plaques. Novel plaque imaging may aid decision making by identifying patients with propensity to develop lipid rich plagues at multi-vascular sites. Those patients may be suitable candidates for intensive lipid lowering treatment.

Key Words: Intensive lipid-lowering; Proprotein convertase subtilisin kexin 9 inhibitors; Ezetimibe; Plaque imaging; Low-density lipoprotein cholesterol

manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: United Kingdom

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 21, 2021
Peer-review started: March 21, 2021
First decision: May 13, 2021
Revised: May 25, 2021
Accepted: July 21, 2021
Article in press: July 21, 2021
Published online: September 26, 2021

P-Reviewer: Julius U
S-Editor: Ma YJ
L-Editor: A
P-Editor: Li JH

Core Tip: Intensive lipid-lowering therapies using ezetimibe and more recently proprotein convertase subtilisin kexin 9 inhibitors have improved clinical outcomes. Unselective application of these treatments is undesirable and unaffordable and, therefore, has been guided by low-density lipoprotein cholesterol level. Nonetheless, the residual risk in the post-statin era is markedly heterogeneous. Emerging data show that intensive lipid-lowering therapy produce larger absolute risk reduction in patients with polyvascular disease, post coronary artery bypass graft and diabetes. Notably, these clinical entities share similar phenotype of large burden of atherosclerotic plaques. Novel plaque imaging may aid decision making by identifying patients with propensity to develop lipid rich plagues at multi-vascular sites. Those patients may be suitable candidates for intensive lipid lowering treatment.

Citation: Abdalwahab A, Al-atta A, Zaman A, Alkhalil M. Intensive lipid-lowering therapy, time to think beyond low-density lipoprotein cholesterol. *World J Cardiol* 2021; 13(9): 472-482
URL: https://www.wjgnet.com/1949-8462/full/v13/i9/472.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i9.472

INTRODUCTION

Despite optimal, guideline-recommended medical therapy for secondary prevention, patients remain at increased risk of cardiovascular events. This risk, referred to as residual risk, is attributable to different processes such as lipid accumulation, inflammation, and thrombosis[1]. Estimating lipid risk has always been guided by the use of low-density lipoprotein cholesterol (LDL-c)[2]. The magnitude of LDL-c reduction was associated with proportionate decrease in cardiovascular events in response to lipid lowering treatment[3]. The Cholesterol Treatment Trialists Collaboration (CTTC) reported from 26 trials including 169138 patients that for every 1.0 mmol/L reduction in LDL-c, there was 22% reduction in cardiovascular events[3]. Importantly, these benefits were derived using HMG CoA reductase inhibitors *i.e.*, statins.

Recent development in lipid-lowering therapies, including ezetimibe and proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors have confirmed the LDL-c hypothesis[4,5]. In other words, the reduction in cardiovascular outcomes was related to LDL-c reduction and reproduced using non-statin treatments[6-8]. Therefore, the concept of lower is better should ideally be applied to all patients with vascular disease and LDL-c should be targeted using statin alongside non-statin drugs. Nonetheless, current guidelines recommend intensifying lipid-lowering therapy using ezetimibe or PCSK9 guided by LDL-c level[2]. Whilst the recommended targets for LDL-c has been lowered to reflect the reported cardiovascular benefits from recent intensive lipid-lowering trials[6-8], such an approach may deprive a subset of patients from potential benefits in response to intensive LDL-c reduction. This Review discusses the limitations of solely using LDL-c to guide intensive lipid-lowering therapy and highlights a strategy to identify patients who would benefit from adding a second lipid-lowering treatment, mainly PCSK9 inhibitor, on top of statin.

CAVEATS OF ROUTINELY USING INTENSIVE LIPID LOWERING TREATMENT

Data from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER), and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes) trials highlighted better cardiovascular outcomes in response to LDL-c reduction in patients on maximally-tolerated statin dose[6-8]. Notably, the magnitude of reduction in LDL-c did not match the decrease in clinical events[5,9]. This becomes more evident when comparing data of PCSK9 inhibitors to CTTC clinical outcomes[5,9]. When juxtaposed to the reduction in LDL-c level, there may be diminished benefits in response to very low LDL-c with lack of significant incremental benefits below a certain level of LDL-c[5,9]. This possible "plateau effect" was also highlighted on a

mechanistic level in the GLobal Assessment of Plaque reGression With a PCSK9 antibOdy as Measured by intraVascular Ultrasound (GLAGOV) trial[10]. Further reduction in LDL-c did not lead to commensurately greater plaque regression, highlighting a possible phenomenon that could be referred to as "LDL-c exhaustion". Whether longer exposure to low LDL-c may be translated into larger plaque regression using PCSK9 inhibitors is yet to be determined. A recent large meta-analysis of 34 trials highlighted that the reduction in mortality in response to intensive lipid-lowering therapy compared to less-intensive regimen was only evident at LDL-c level of 100 mg/dL[11]. The presence of a threshold is in line with the proposed concept of "LDL-c exhaustion", however, future studies are needed to identify the optimal threshold according to patients' clinical syndromes.

Importantly, residual cardiovascular risk is recognised even after achieving low LDL-c[1,12] a reflection of the multiple mechanisms underlying atherothrombotic vascular disease. Almost one in ten patients had a second vascular event within 3 years follow up despite attaining LDL-c to < 70 mg/dL[7]. Therefore, using LDL-c as the only surrogate of future adverse events has significant limitations, and there is need to characterise atherosclerotic disease processes beyond estimating future cardiovascular risk. Other disease characteristics, such as thrombosis or inflammation, maybe more prominent and tailored therapies might be more effective in reducing the residual risk.

Moreover, costs may challenge the routine use of PCSK9 inhibitors in patients with cardiovascular disease. Subjecting patients to PCSK9 inhibitors guided by the FOURIER and ODYSEEY Outcomes trials criteria would incur an increase in health care costs by $450000 and $315000 per QALY, factoring in late effect on mortality[9,13-15]. The cost would remain significant even when including patients with baseline LDL-c ≥ 100 mg/dL[9,13,14].

Overall, unselective implementation of PCSK9 inhibitors is undesirable and unaffordable given the modest effect on preventing cardiovascular events at a significant increase of health costs. Therefore, adopting a new strategy based on the characteristics of the atherosclerotic disease process may be more promising. Emerging data provide new insights into the role of certain atherosclerotic features to identify patients who sustain larger clinical benefits when using intensive lipid-lowering therapy. Such features include polyvascular disease, diabetes and post coronary artery bypass graft (CABG)

Polyvascular disease

Polyvascular disease refers to atherosclerotic involvement of two or more of arterial vascular beds[16]. Exposure to high concentrations of low-density lipoprotein, including very small, small, intermediate and large particles was associated with developing polyvascular disease in patients with peripheral arterial disease[17]. Several trials have shown the close correlation between the number of involved vascular beds with increased mortality[18,19]. Polyvascular disease is considered as one of the high risk features in initial Task Force of European Society of Cardiology (ESC)/European Atherosclerosis Society. To mitigate the risk, commencing PCSK9 in addition to statin, was recommended, albeit, to achieve LDL-c level of < 100 mg/dL, and even lower according to the new European guidelines[2,20]. Nonetheless, LDL-c remains key in titrating intensive lipid-lowering therapy in this high risk group.

The IMPROVE IT trial revealed a higher cardiovascular event rates with almost 50% increased risk in cardiovascular death in patients with polyvascular compared to monovascular disease[19]. The combination of CAD and peripheral vascular disease was associated with more than 25% incidence rate of myocardial infarction[19]. Importantly, the benefits of adding ezetimibe to statin therapy were seen regardless of the number of diseased vascular beds, although patients with polyvascular disease sustained a numerically larger absolute risk reduction in response to intensive statin therapy[19]. In pre-specified subgroup analysis of the ODYSSEY Outcomes trial, alirocumab was associated with absolute risk reduction in cardiovascular events proportional to the number of diseased vascular beds *i.e.*, 1.4% for monovascular disease, 1.9% for two beds vascular disease and 13% in three beds polyvascular disease [21]. However, in the FOURIER trial, the risk reduction associated with evolocumab was relatively modest (2.7%) in the polyvascular disease group despite having heightened residual cardiovascular risk (19.9%)[22]. The inconsistency may be related to statistical power, although other factors, such as the targeted population, definition and aetiologies of vascular disease need to be factored in when interpreting these results.

To overcome these issues, Alkhalil *et al*[23] conducted a meta-analysis of 7 studies including 94362 patients, reporting the role of intensive lipid-lowering therapy in polyvascular *vs* monovascular disease groups. They highlighted that the absolute risk reduction was more marked in patients with polyvascular disease [(6.5% (95%CI, 5.0–7.9)] compared to monovascular disease [1.8% (95%CI, 1.3–2.3)]. Notably, when the analysis was performed according to the level of baseline LDL-c, there was a differential treatment effect in response to intensive lipid-lowering therapy in patients with monovascular disease. Patients with monovascular disease and LDL-c > 100 mg/dL had absolute risk reduction of 3.2% (95%CI, 2.3–4.1) compared to 1.2% (95%CI, 0.6–1.8) in patients with monovascular disease and LDL-c ≤ 100 mg/dL. In contrast, patients with polyvascular disease had comparable treatment effects irrespective of LDL-c [5.7% (95%CI, 3.6–7.8) in patients with LDL-C >100 mg/dL and 7.2% (95%CI 5.2–9.2) in those with LDL-C ≤ 100 mg/dL)[23]. Moreover, recent data from the ODYSSEY Outcomes trial suggest that the magnitude of LDL-c reduction across the strata of evident vascular disease was comparable, yet, the reduction in clinical outcomes was more pronounced in those with polyvascular disease[21]. This was in contrast with CTTC data whereby lowering LDL-c was associated with a consistent reduction in vascular events among patients with different clinical characteristics[24]. Collectively, this may suggest that monitoring response to intensive lipid-lowering therapy can no longer be guided using LDL-c in the post statin era. A notion that was recently highlighted from the Copenhagen General Population Study.

PATIENTS WITH PRIOR CABG

Patients with previous CABG have extensive coronary artery disease and are at increased risk of adverse cardiovascular events, including mortality[25,26]. Early data showed the beneficial effect of statins in patients with previous CABG[27]. More recently, alirocumab was reported to have heterogeneity in treatment effects according to the status of previous CABG. The absolute risk reduction of major adverse events was remarkably larger [6.4%, (95%CI: 0.9 to 12.0)] in patients with CABG compared to those with no previous CABG [1.3%, (95%CI: 0.5 to 2.2)[28].

Similar outcomes were reported in the pre-specified analysis from the IMPROVE IT trial[29]. Adding ezetimibe to simvastatin was translated into 8.8% (95%CI: 3.1 to 14.6) absolute risk reduction in patients with previous CABG compared to merely 1.3% (95%CI: 0 to 2.6%) in those patients without previous CABG history[29]. Moreover, a recent meta-analysis revealed the incremental benefits of intensive lipid lowering therapy in patients post CABG[30]. Remarkably, there was a significant 14% reduction in all-cause mortality [rate ratio (RR) 0.86; (95%CI, 0.74 to 0.99)] and 25% reduction in cardiovascular mortality [RR 0.75; (95%CI, 0.65 to 0.86)] when subjecting patients post CABG to intensive lipid lowering therapy[30]. Unpublished data suggest that the mortality benefit in patients post CABG was independent of the level of baseline LDL-c. In other words, patients post CABG with LDL-c > 100 mg/dL sustained 2.5% (95%CI: 0 to 4.8%) absolute risk reduction compared to 1.2% (95%CI: -1.0 to 3.5) in patients without previous CABG.

The heightened risk in patient post CABG warrants consideration of early introduction of intensive lipid-lowering therapy, particularly since the benefits were not merely related to a composite clinical endpoint but was extended to include all-cause and cardiovascular mortality. Importantly, the level of LDL-c does not determine the efficacy of intensive lipid-lowering therapy and whether upfront and targeted approach for this group would be an alternative option in a cost-effective, sustainable platform in most health care systems needs to be explored.

PATIENTS WITH DIABETES AND METABOLIC SYNDROME

Patients with diabetes mellitus are at increased risk of future cardiovascular events[31-34]. The aggressive nature and extent of atherosclerosis burden, despite glucose normalisation, is recognised as a potential mechanism of this increased risk[31-34]. Statin is recommended in this group for primary and secondary prevention[2]. Notably, statin treatment is associated with 0.5-1.0% increase in the incidence of new-onset diabetes[24]. Similarly, certain variants in PCSK9 genes were also reported to increase the risk of diabetes. Data suggest that there is 10% increase in the risk of diabetes for each 10 mg/dL reduction in LDL-c[9,35]. Nonetheless, pharmacological inhibition of PCSK9 was not associated with an increase in the incidence of diabetes

mellitus, nor affect glycaemic control[36-38]. Moreover, in a large meta-analysis of 33 randomized trials including 163688 non-diabetic patients, PCSK9 inhibitors were not associated with new onset diabetes[39].

In the IMPROVE-IT and ODYSSEY Outcomes trials, intensive lipid-lowering therapies using ezetimibe and alirocumab, respectively, lowered LDL-c compared to placebo, irrespective of the diabetic status of patients[37,40]. Nevertheless, the absolute risk reduction using ezetimibe was 5.5% in diabetic patients, which was significantly larger compared to 0.7% in non-diabetic patients (P = 0.002 for interaction)[40]. Likewise, in response to intensive LDL-c reduction using PCSK9 inhibitors, the absolute reduction in adverse cardiovascular events in diabetic patients (2·3%, 95%CI 0·4 to 4·2) was better than in those with prediabetes (1.2%, 95%CI: 0.0 to 2.4) or normoglycaemia (1.2%, 95%CI: −0.3 to 2.7) (P = 0·0019 for interaction)[37]. Similarly, evolocumab in the FOURIER trial showed more absolute risk reduction in the primary end point in diabetic *vs* non-diabetic groups [(2.7%; 95%CI: 0.7 to 4.8) and (1.6%; 95%CI, 0.1 to 3.2)][38]. Interestingly, the reduction in atherosclerosis burden on intravascular ultrasound (IVUS) was comparable between diabetic and non-diabetic in response to PCSK9 inhibition[10].

Patients with metabolic syndrome are at increased risks of developing diabetes and cardiovascular disease[41]. It is characterised as a cluster of conditions including central obesity, insulin resistance, hypertension and dyslipidaemia. Metabolic syndrome is common and was reported in almost 60% of recruited patients in the FOURIER trial, and more importantly, was associated with 30% increase in the risk of future adverse cardiovascular events[42]. Evolocumab was associated with similar LDL-c reduction, irrespective of the status of metabolic syndrome[42]. Moreover, it reduced cardiovascular events by 17% in this subgroup HR 0.83 95%CI: 0.76 to 0.91 [42].

ELDERLY PATIENTS

Old age is a risk for adverse cardiovascular events and most individuals aged 65 or above are already at high or very high risk[43]. Elderly population are under-represented in clinical trials and the recent CTTC reported that previous statin trials included only 8% of patients > 75[44]. Moreover, side effects, co-morbidities, and interactions with other medications add more challenges to intensive lipid-lowering therapy in the elderly. Nonetheless, LDL-c reduction using statin was associated with 21% proportionate reduction in major vascular events in the elderly[44]. There was a trend towards diminishing efficacy with increased age, although this did not reach statistical significance[44].

In a pre-specified secondary analysis of the IMPROVE-IT trial, Bach *et al*[45] reported 8.7% absolute risk reduction when adding ezetimibe to simvastatin in elderly patients (> 75 years). In comparison, for patients below 65 years and between 65-74 years, their absolute risk reduction was 0.9% and 0.8%, respectively. Similar findings were reported from the ODYSSEY Outcomes trial, whereby alirocumab was associated with larger absolute risk reduction with increasing age: 2.3% at age 45; 3.8% at age 75; and 8.3% at age 85 years[46]. Interestingly, data from the FOURIER trial suggest small variations in the incidence of major vascular events according to age groups with a consistent finding that evolocumab reduced adverse events regardless of patient age [47]. Similarly, in the ODYSSEY OUTCOMES trial age did not appear to modify the beneficial effects of LDL-c lowering using PCSK9 inhibitors[7]. In contrast, the relative risk reduction associated with ezetmibe was only evident in the group of patients > 75 years (HR, 0.80; 95%CI, 0.70-0.90) while the other groups had relative risk reduction of less than 5% (P = 0.02 for interaction). Notably, the difference in LDL-c reduction was comparable across the age groups.

This apparent inconsistency in the impact of intensive lipid lowering across age in different studies should not be surprising. In fact, this phenomenon could possibly be extended to other "high risk" clinical features (Table 1). The mechanism by which lipid-lowering therapy exerts clinical benefit is by evacuating lipid from atherosclerotic plaque, rendering them more stable[5,48]. Therefore, patients with large burden of atherosclerotic plaque or more specifically lipid rich plaque are likely to benefit more from intensive lipid lowering therapy. In other words, the largest absolute risk reduction is anticipated in the highest risk group and the benefit should be proportionate to the baseline absolute risk. However, this is only true if the residual risk is homogeneous and if the applied therapy targets that specific risk[1,5,9]. However, in elderly populations the residual risk is heterogeneous, and intensive lipid

Table 1 Cardiovascular outcome of proprotein convertase subtilisin kexin 9 inhibitors *vs* Placebo in different studies and subgroups

ODYSSEY trial subgroup (*n* = 18924)	Alirocumab *vs* placebo
Patients with Polyvascular disease	
Monovascular (*n* = 17370)	Cardiovascular events: ARR 1.4% (CI 95%; 0.6%-2.3%)Mortality: 0.4% (95%CI: -0.1% to 1.0%)
2 vascular beds (*n* = 1405)	Cardiovascular events: ARR 1.9% (CI 95%; -2.4%-6.2%)Mortality: ARR 1.3% (95%CI: -1.8% to 4.3%)
3 vascular beds (*n* = 149)	Cardiovascular events: ARR 13% (CI 95%; -2%-28%)Mortality: ARR 16.2% (95%CI: 5.5% to 26.8%)
FOURIER Trial (*n* = 27564)	**Evolocumab *vs* placebo**
With PAD (*n* = 2642)	Composite of major cardiac events ARR 3.5% HR 0.79; 95%CI, 0.66-0.94; *P* = 0.0098
Without PAD (*n* = 24922)	Composite of major cardiac events ARR: 1.6% HR 0.86; 95%CI, 0.80-0.93; *P* = 0.0003
Patients with prior CABG	
ODYSSEY trial subgroup (*n* = 18924)	**Alirocumab *vs* placebo**
With Prior CABG (*n* = 1003)	Composite of major cardiac events ARR: 6.4%; 95%CI: 0.9 to 12.0
With index CABG (*n* = 1025)	Composite of major cardiac events ARR: 0.9%; 95%CI: 2.3 to 4.0
Without prior CABG (*n* = 16896)	Composite of major cardiac events ARR: 1.3%; 95%CI: 0.5 to 2.2
Patients with diabetes mellitus or metabolic syndrome	
FOURIER Trial diabetic subgroup (*n* = 27564)	**Evolocumab *vs* placebo**
With diabetes (*n* = 11031)	Composite of major cardiac events HR 0 ·83 (95%CI 0.75-0.93; *P* = 0.0008), Absolute risk reduction 2.7% (95%CI 0.7–4.8)
Without diabetes (*n* = 16533)	Composite of major cardiac events HR 0.87 (0.79-0.96; *P* = 0.0052)Absolute risk reduction 1.6% (95%CI 0.1–3.2)
FOURIER trial metabolic syndrome subgroup (*n* = 27342)	**Evolocumab *vs* placebo**
With met syndrome (*n* = 16361)	Composite of major cardiac events HR 0.83 (95%CI; 0.76-0.91)
Without met syndrome (*n* = 10981)	Composite of major cardiac events HR:0.89, CI 95% (0.79-1.01)
ODYSSEY trial subgroup (*n* = 18924)	**Alirocumab *vs* placebo**
With diabetic (*n* = 5444)	Composite of major cardiac events ARR 2.3%, 95%CI 0.4 to 4.2
Prediabetic (*n* = 8246)	Composite of major cardiac events ARR 1.2%, 95%CI: 0.0 to 2.4
Normoglycemic (*n* = 5234)	Composite of major cardiac events ARR 1.2%, 95%CI: −0.3 to 2.7
Elderly patients	
FOURIER trial (*n* = 27564) age subgroup[8]	**Evolocumab *vs* placebo**
Q1	Composite of major cardiac events HR 0.83, 95%CI 0.72-0.96
Q2	Composite of major cardiac events HR 0.88, 95%CI 0.76-1.01
Q3	Composite of major cardiac events HR 0.82, 95%CI 0.71-0.95
Q4	Composite of major cardiac events HR 0.86, 95%CI 0.74-1.00
ODYSSEY trial age subgroup (*n* = 18924)	**Alirocumab *vs* placebo**
≥ 65 yr	Composite of major cardiac events HR 0.78, 95%CI 0.68-0.91
< 65 yr	Composite of major cardiac events HR 0.89, 95%CI 0.80-1.00

lowering therapies were applied unselectively without measures of atherosclerosis disease burden. Recent developments have allowed *in-vivo* plaque imaging and lipid quantification to aid decision making in using intensive lipid lowering drug[49-51].

ROLE OF PLAQUE IMAGING TO GUIDE INTENSIVE LIPID-LOWERING TREATMENTS

The lipoprotein-related risk is heterogeneous and likely to be related to other non-LDL-c parameters. As highlighted above the use of LDL-c in the post statin era could

be challenged as the magnitude of LDL-c reduction did not reflect clinical outcomes in patients using intensive lipid lowering therapy. High-density lipoprotein (HDL-c) was highlighted as a prognostic marker with an inverse relationship with adverse outcomes in patients with cardiovascular disease[52]. Nonetheless, it failed as a therapeutic target with no effect on cardiovascular outcomes despite significant increase in HDL-c levels using niacin and cholesterol-ester transfer protein inhibitors [53-55]. Recent data suggest that the level of triglyceride and remnant cholesterol are associated with cardiovascular outcomes, independent of other risk factors, including LDL-c[56]. Moreover, VLDL-c was associated with double the hazard of myocardial infarction in the Copenhagen General Population Study which included more than 100000 individuals[57]. Targeted therapies are in development to assess whether certain lipid biomarkers, such as Lp(a), could be used as therapeutic target, in addition to LDL-c[58]. This approach is promising as certain markers such as lipoprotein (a) would identify high risk patients and, therefore, targeting this particular biomarker maybe associated with a reduction in future cardiovascular events.

Overall, the complex interaction between lipid biomarkers would render a single marker imprecise in predicting clinical outcomes. Collectively, these markers target atherosclerotic plaque progression or regression, and therefore, characterising plaque would provide a better and more comprehensive picture on future plaque, and patient risk. Invasive and non-invasive imaging tools, such as near infra-red spectroscopy and T2 mapping, would allow precise measurement and characterisation of lipid core within atherosclerotic plaque. Patients with propensity to develop lipid-rich plaque may be suitable candidate for intensive lipid-lowering drug. Remarkably, clinical entities that demonstrate large improvement in clinical outcomes shared similar profile in the atherosclerotic disease process. Patients with polyvascular disease, post CABG and diabetes are reported to have advanced and aggressive atherosclerotic disease and, therefore, intensive lipid lowering therapy had produced mortality benefits in certain cases. The use of plaque imaging may risk stratify patients and provide a platform to monitor patients response to lipid-lowering therapy. Patients with large lipid-rich plaques in multiple vascular territories or those who have poor or suboptimal response to statin, may be suitable candidates for more expensive therapies. These treatments would be rationalised according to the atherosclerotic disease characteristics and not merely based on a single marker that is unlikely to reflect patient future risk. Future randomised clinical trials are needed to assess whether the proposed approach would prove to be cost-effective. The use of atherosclerotic disease characteristics to guide decision making for intensive, yet, expensive lipid-lowering therapy is a step toward more personalised and precision medicine.

CONCLUSION

LDL-c plays an important role in the development of atherosclerotic disease as evidenced by the proportionate reduction in LDL-c improving cardiovascular outcomes with statin use. Nevertheless, the heterogeneous residual risk post statin challenges the use of LDL-c as a single maker to guide additional lipid lowering therapy. Emerging data suggest that patients with large atherosclerotic burden appear to sustain increased benefits from intensive lipid-lowering therapy. Future studies are in development to assess whether plaque imaging and phenotypic features associated with larger atherosclerotic burden would help identify patients who may benefit from additional intensive lipid lowering treatments.

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 September 26; 13(9): 483-492

DOI: 10.4330/wjc.v13.i9.483

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Study

Patients' time in therapeutic range on warfarin among atrial fibrillation patients in Warfarin Medication Therapy Adherence Clinic

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Author contributions: Mazlan-Kepli W contributed to the idea and study design; Siew-Ling L, Thien-Jian O, and Annuysia M contributed to and performed all data analyses and interpretation of results; Siew-Ling L and Thien-Jian O wrote the first manuscript; Wardati MK contributed to the interpretation of results and critically reviewed the final manuscript; All authors contributed to the review of an approved manuscript before submission.

Institutional review board statement: Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-19-839-46462).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used

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Abstract

BACKGROUND

The quality of warfarin therapy can be determined by the time in the therapeutic range (TTR) of international normalized ratio (INR). The estimated minimum TTR needed to achieve a benefit from warfarin therapy is ≥ 60%.

AIM

To determine TTR and the predictors of poor TTR among atrial fibrillation patients who receive warfarin therapy.

METHODS

A retrospective observational study was conducted at a cardiology referral center in Selangor, Malaysia. A total of 420 patients with atrial fibrillation and under follow-up at the pharmacist led Warfarin Medication Therapeutic Adherence Clinic between January 2014 and December 2018 were included. Patients' clinical data, information related to warfarin therapy, and INR readings were traced through electronic Hospital Information system. A data collection form was used for data collection. The percentage of days when INR was within range was calculated using the Rosendaal method. The poor INR control category was defined as a TTR < 60%. Predictors for poor TTR were further determined by using logistic regression.

RESULTS

anonymous clinical data that were obtained after each patient agreed to treatment. Permission to use the patient data from this facility has been obtained from the Head of Department of Cardiology, Hospital Serdang.

Conflict-of-interest statement: The authors have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: Malaysia

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

Received: March 10, 2021
Peer-review started: March 10, 2021
First decision: May 6, 2021
Revised: May 25, 2021
Accepted: July 26, 2021
Article in press: July 26, 2021
Published online: September 26, 2021

P-Reviewer: Luo W
S-Editor: Ma YJ
L-Editor: Filipodia

A total of 420 patients [54.0% male; mean age 65.7 (10.9) years] were included. The calculated mean and median TTR were 60.6% ± 20.6% and 64% (interquartile range 48%-75%), respectively. Of the included patients, 57.6% (n = 242) were in the good control category and 42.4% (n = 178) were in the poor control category. The annual calculated mean TTR between the year 2014 and 2018 ranged from 59.7% and 67.3%. A high HAS-BLED score of ≥ 3 was associated with poor TTR (adjusted odds ratio, 2.525; 95% confidence interval: 1.6-3.9, P < 0.001).

CONCLUSION

In our population, a high HAS-BLED score was associated with poor TTR. This could provide an important insight when initiating an oral anticoagulant for these patients. Patients with a high HAS-BLED score may obtain less benefit from warfarin therapy and should be considered for other available oral anticoagulants for maximum benefit.

Key Words: Atrial fibrillation; Time in therapeutic range; International normalized ratio; HAS-BLED score; Oral anticoagulants; Warfarin Medication Therapeutic Adherence Clinic

Core Tip: This is a retrospective observational study to determine time in therapeutic range (TTR) and the predictors of poor TTR among patients with atrial fibrillation under follow-up at the Warfarin Medication Therapeutic Adherence Clinic of a tertiary cardiology referral center in Selangor, Malaysia. In this study cohort, we found that high HAS-BLED score (≥ 3) was a significant predictor of poor TTR.

Citation: Lee SL, Ong TJ, Mazlan-Kepli W, Mageswaran A, Tan KH, Abd-Malek AM, Cronshaw R. Patients' time in therapeutic range on warfarin among atrial fibrillation patients in Warfarin Medication Therapy Adherence Clinic. *World J Cardiol* 2021; 13(9): 483-492
URL: https://www.wjgnet.com/1949-8462/full/v13/i9/483.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i9.483

INTRODUCTION

Atrial fibrillation (AF) is usually asymptomatic and is associated with an increased risk of major adverse cardiovascular events (MACE) and mortality in patients with coronary artery disease (CAD)[1]. The prevalence of AF in the Malaysian population is low at 0.54%, compared to the global average of 1%[2].

Warfarin is the most widely used anticoagulant in the world[3-5]. Although novel oral anticoagulants are available, warfarin remains a viable oral anticoagulant for many patients because of its availability and cost[4,6,7]. The time in therapeutic range (TTR) estimates the percentage of time a patient's international normalized ratio (INR) is within the desired treatment range or goal and is widely used as an indicator of anticoagulation control[4,9-12]. TTR is commonly used to evaluate the quality of warfarin therapy and is an essential tool for assessing the risks *vs* benefits of warfarin therapy[4,8,13,14]. A 10% increase in time spent out of TTR is associated with a 29% increase in the risk of mortality and a 10%-12% increase in the risk of an ischemic stroke and other thromboembolic events[13,15-17].

The aim of this study is to determine the percentage of time a patient's INR is within the desired treatment range and the predictors of poor TTR among patients with AF who receive warfarin therapy.

MATERIALS AND METHODS

Study design

This is a retrospective observational study that was conducted in Hospital Serdang

P-Editor: Wu RR

located in Kajang, Selangor. Hospital Serdang is a cardiology reference center that covers patients from Serdang, Bangi, Putrajaya, Kajang, Dengkil, and Puchong area in the state of Selangor, Malaysia. Ethical approval for this study was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-19-839-46462). The study was carried out in accordance with the Declaration of Helsinki.

Study setting and study population

All AF patients under Warfarin Medication Therapeutic Adherence Clinic follow-up between 2014 to 2018 were included. The electronic Hospital Information System (eHIS) was used to extract patients' demographics, comorbidities, information related to warfarin therapy, and INR readings. Baseline comorbidities were retrospectively retrieved according to available medical records in eHIS. The consecutive sampling method was used. A case report form was used for data collection. Each patient was allocated a patient identifier number that matched their patient registration number, in order to protect confidentiality. Patients were excluded if they discontinued warfarin therapy, died, or had less than three INR readings.

TTR

For patients with AF, the target INR range was between 2.0 to 3.0. TTR is defined as an estimate of the average time that a medication is dosed with optimal efficacy and safety[4]. From previous literature, the estimate of the minimum TTR needed to achieve a benefit from warfarin therapy is between 58% and 65%[18]. The percentage of days that INR was within range was calculated using the Rosendaal method[8]. Thus, based on these references, we defined the "poor" TTR category as TTR < 60% and the "good" TTR category as TTR > 60%.

Statistical analysis

This study aimed to determine to what extent the following factors are associated with poor TTR: Age, gender, ethnicity, diabetes mellitus, hypertension, previous ischemic heart disease, chronic kidney disease, peripheral vascular disease, stroke/transient ischemic attack, deep vein thrombosis/pulmonary embolism, heart failure, chronic obstructive pulmonary disease/asthma, chronic kidney disease, dyslipidaemia, chronic rheumatic heart disease, CHA2DS2-VASc score, and HAS-BLED score. A study by Peduzzi *et al*[19] on sample size for logistic regression suggests using a minimum event per variable value of ten. Since our study was interested in studying 17 risk factors, a minimum sample of 170 patients in the poor TTR category group was required. The study planned to recruit at least 400 samples in order to exceed the minimum sample size, as the prevalence of poor TTR was estimated at 38%[19].

Categorical variables were summarized using frequencies and proportions while continuous variables were summarized using mean ± standard deviation or median (inter-quartile range) values. Logistic regression analysis was used to calculate odds ratios (OR) and 95% confidence intervals (CI) to model the predictors of poor TTR. This analysis was repeated and adjusted to variables that were significant from the previous studies: Heart failure, chronic kidney disease, CHA2DS2-VASc score, and HAS-BLED score[20]. A $P < 0.05$ was considered significant. Point estimates and 95%CI are presented for all results. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20 (Armonk, NY, United States).

RESULTS

A total of 420 patients with AF were included in this study (Figure 1). Baseline characteristics are shown in Table 1. The mean age of the study population was 65.7 (10.9) years. There were slightly more male patients (54%, $n = 227$) than female patients (46%, $n = 193$). The largest ethnic population was Malay, followed by Chinese and Indian. Hypertension accounted for the highest percentage of comorbidities among patients with AF, followed by diabetes mellitus, dyslipidaemia, and ischemic heart diseases. Median CHA2DS2-VASc score was 3 (moderate risk of stroke), and median HAS-BLED score was 2 (low bleeding risk).

Time in therapeutic range

Over 5 years, the mean (standard deviation) TTR was 60.6% (20.6%) with a median of 64% (interquartile range 27%). Of the included patients, 57.6% ($n = 242$) were in the good control category, and 42.4% ($n = 178$) were in the poor control category (Table 2). The annual calculated mean TTR between the year 2014 and 2018 ranged between

Table 1 Baseline characteristics

Baseline characteristic	All patients, *n* = 420	TTR < 60%, *n* = 178	TTR ≥ 60%, *n* = 242
Age, yr			
mean ± SD	65.7 ± 10.9	65.7 ± 10.8	65.7± 10.9
Median (IQR)	67 (15)	66 (14)	67 (15)
Male	227(54.0)	99 (55.6)	128 (52.9)
Female	193 (46.0)	79 (44.4)	114 (47.1)
Ethnicity			
Malay	210 (50.0)	96 (53.9)	114 (47.1)
Chinese	179 (42.6)	64 (36.0)	115 (47.5)
Indian	26 (6.2)	16 (9.0)	10 (4.1)
Others	5 (1.2)	2 (1.1)	3 (1.2)
Comorbidities			
Diabetes mellitus	170 (40.5)	85 (47.8)	85 (35.1)
Hypertension	291 (69.3)	128 (71.9)	163 (67.4)
Ischemic heart disease	90 (21.4)	48 (27.0)	42 (17.4)
Peripheral vascular disease	8 (1.9)	2 (1.1)	6 (2.5)
Stroke/transient ischemic attack	49 (11.7)	20 (11.2)	29 (12.0)
Deep vein thrombosis/pulmonary embolism	2 (0.5)	1 (0.6)	1 (0.4)
Heart failure	27 (6.4)	12 (6.7)	15 (6.2)
Chronic obstructive pulmonary disease/asthma	22 (5.2)	8 (4.5)	14 (5.8)
Chronic kidney disease	49 (11.7)	28 (15.7)	21 (8.7)
Dyslipidaemia	125 (29.8)	47 (26.4)	78 (32.2)
Chronic rheumatic heart disease	17 (4.0)	10 (5.6)	7 (2.9)
Liver disease	0 (0.0)	0 (0.0)	0 (0.0)
CHA_2DS_2-VASc score			
Mean ± SD	2.6 ± 1.4	-	-
Median (IQR)	3 (1.0)	3 (2)	2(1)
Score 0-1	91 (21.7)	34 (19.1)	57 (23.6)
Score 2-4	297 (70.7)	125 (70.2)	172 (71.1)
Score ≥ 5	32 (7.6)	19 (10.7)	13 (5.4)
HAS-BLED score			
Median (IQR)	2 (2.0)	3 (1.0)	2 (2.0)
Low bleeding risk (score ≤ 2)	257 (61.2)	83 (46.6)	174 (71.9)
High bleeding risk (score ≥ 3)	163 (38.8)	95 (53.4)	68 (28.1)

All values are reported as *n* (%) unless otherwise noted. IQR: Interquartile range; TTR: Time in therapeutic range; SD Standard deviation.

59.7% and 67.3%. The highest percentage was in 2018, with 67.3% of days within therapeutic range in AF patients. Figure 2 shows the mean TTR for AF patients from 2014 to 2018. Patient with a high HAS-BLED (score ≥ 3) had a median TTR of 55% compared to patients with a low HAS-BLED score, who had a median TTR of 68% (Figure 3).

Predictors of poor TTR

From the multivariate analysis, a high HAS-BLED score (score ≥ 3) was significantly associated with a poor TTR (< 60%) (adjusted OR, 2.5;1.6-3.9, $P < 0.001$) compared to a

Table 2 Time in the therapeutic range of the study population

Variables	All patients, *n* = 420	TTR < 60%, *n* = 178	TTR ≥ 60%, *n* = 242
TTR			
mean ± SD	60.6 ± 20.6	41.1 ± 14.7	75.0 ± 9.6
Median (IQR)	64 (27)	44 (22)	74 (14)
Good (≥ 60%)	242 (57.6)	-	-
Poor (< 60%)	178 (42.4)	-	-

SD: Standard deviation; TTR: Time in therapeutic range.

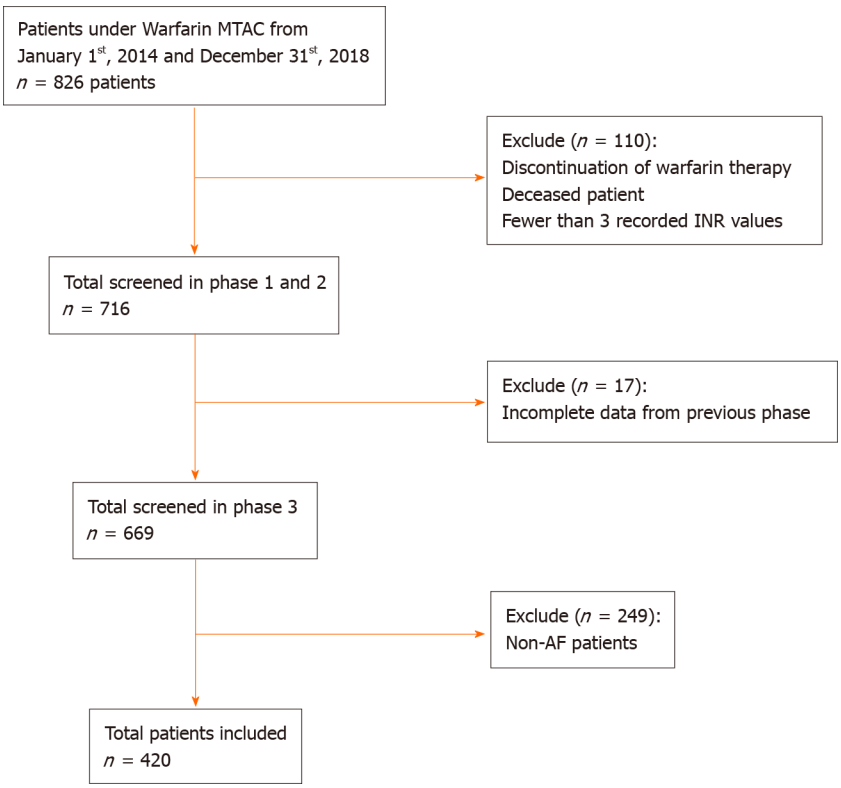

Figure 1 Flow diagram describing the selection of data for the analysis reported. AF: Atrial fibrillation; INR: International normalized ratio; MTAC: Medication Therapeutic Adherence Clinic.

low HAS-BLED score (score ≤ 2). Similarly, in the model adjusted for predictors previously described in previous reports[20] (model 2), only HAS-BLED score was found to be a significant predictor of poor TTR (adjusted OR, 2.9;1.8-4.7, $P < 0.001$) (Table 3).

DISCUSSION

This study assessed the percentage of time a patient's INR is within the desired treatment range or TTR and explored the predictors of poor TTR. Overall, the study population had a majority of men and people of Malay ethnicity. This could be explained by the Malaysian population distribution, whereby more than half of the population are of Malay ethnicity, and there are more men than women with the ratio of 107:100[21]. Our results showed similarity with other international studies, with a majority of warfarin users being male[22,23].

Hypertension had the highest prevalence, followed by diabetes mellitus, hyperlipidemia, and ischemic heart disease. The higher prevalence of cardiac-related comorbidities could be explained by Hospital Serdang's status as a cardiology center,

Table 3 Univariate and multivariate logistic regression analysis for predictors of poor time in therapeutic range < 60% among atrial fibrillation patients

Baseline characteristic	Univariate			Multivariate					
				Model 1[1]			Model 2[2]		
	OR	95%CI	*P*	aOR	95%CI	*P*	aOR	95%CI	*P*
Age	1.0	0.9-1.0	0.976						
Ethnicity									
Malay	1.0	Reference	-						
Chinese	1.3	0.2-7.7	0.800						
Indian	0.8	0.1-5.1	0.845						
Others	2.4	0.3-16.9	0.380						
Gender									
Male	1.0	Reference	-						
Female	0.9	0.6-1.3	0.580						
Comorbidities									
Diabetes mellitus	1.7	1.1-2.5	0.009	1.3	0.8-1.9	0.240			
Hypertension	1.2	0.8-1.9	0.318						
Ischemic heart disease	1.8	1.1-2.8	0.018	1.3	0.8-2.1	0.317			
Peripheral vascular disease	0.4	0.1-2.2	0.328						
Stroke/transient ischemic attack	0.9	0.5-1.7	0.814						
Deep vein Thrombosis/pulmonary embolism	1.4	0.1-21.9	0.828						
Heart failure	1.1	0.5-2.4	0.823				1.0	0.5-2.4	0.913
Chronic obstructive pulmonary disease/asthma	0.8	0.3-1.9	0.558						
Chronic kidney disease	1.9	1.1-3.6	0.028	1.2	0.6-2.3	0.585	1.2	0.7-2.4	0.514
Dyslipidaemia	0.7	0.5-1.2	0.197						
Chronic rheumatic heart disease	1.9	0.8-5.4	0.169						
CHA2DS2-VASc score	1.4	0.9-2.1	0.060				0.9	0.6-1.4	0.629
HAS-BLED Score									
Low bleeding risk (score ≤ 2)	1.0	Reference	-						
High bleeding risk (score ≥ 3)	2.9	1.9-4.4	< 0.001	2.5	1.6-3.9	< 0.001	2.9	1.8-4.7	< 0.001

[1]Model 1, adjusted to significant variables of the study populations.
[2]Model 2, adjusted to heart failure, chronic kidney disease, CHA2DS2-VASc score and HAS-BLED score. aOR: Adjusted odds ratio; CI: Confidence interval; TTR: Time in therapeutic range.

therefore catering towards patients with cardiovascular disease in the region. Additionally, these are the main risk factors for AF, which is the study population in question[24].

Interestingly, when compared to other Asian studies, the mean TTR of patients obtained in the study was 60.6%. In comparison, a study from Korea recorded a mean TTR of 49.1%[23], and a study from Singapore recorded a mean TTR of 58%[25]. Possible reasons for the higher mean TTR percentage may be due to the involvement of pharmacists in the pharmacist-led warfarin therapy. This translates to improved patient counselling, dosage adjustment, and identification of possible food-drug and drug-drug interactions.

This study found that patients with a high HAS-BLED score (≥ 3) had a lower median TTR of 55%, compared to patients with a low HAS-BLED score (score < 2) who had a higher median TTR of 68%. Previous reports have suggested that heart failure,

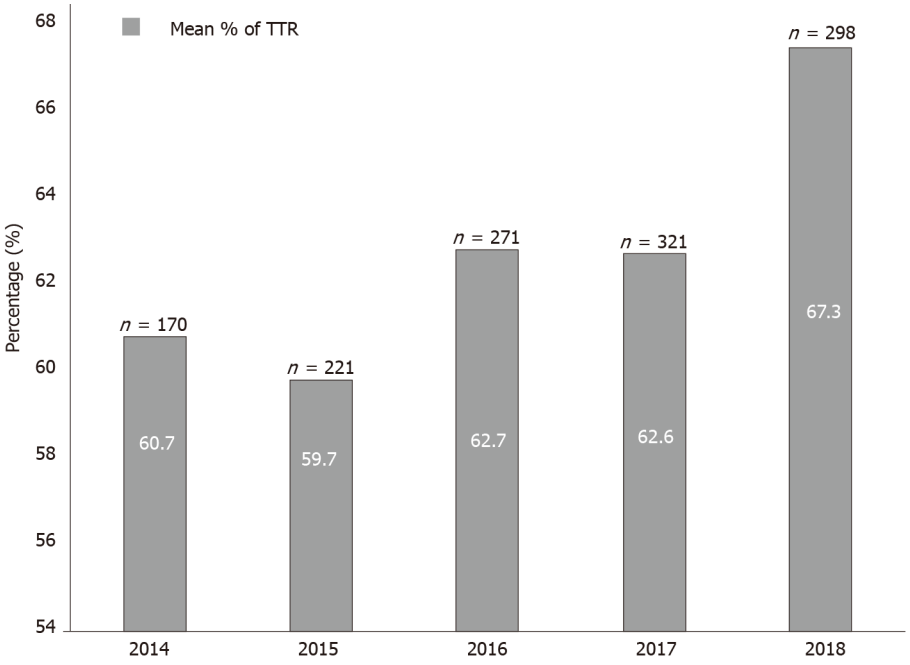

Figure 2 Mean percentage of the time in therapeutic range among atrial fibrillation patients. TTR: Time in therapeutic range.

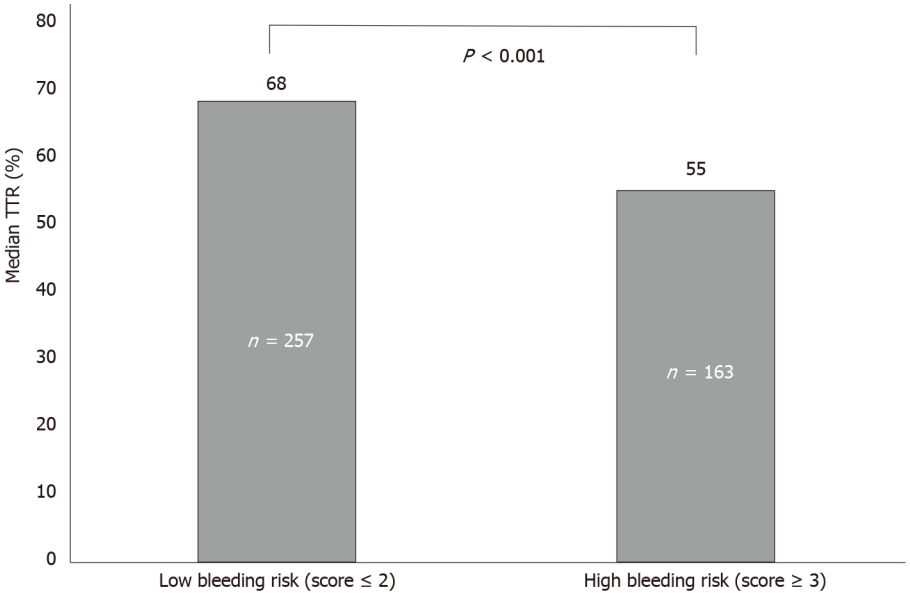

Figure 3 HAS-BLED score *vs* median time in therapeutic range (%). TTR: Time in therapeutic range.

chronic kidney disease, and CHA2DS2-VASc score in addition to high bleeding risk may also contribute to poor TTR[20]. After adjusting for these variables, we found only high HAS-BLED (score ≥ 3) was associated with poor TTR. This is supported by the study from Urbonas *et al*[15], which found median TTR was significantly lower in patients with high bleeding risk (36.4%) as compared to low-risk patients (55.6%). They suggested that the poor TTR in these patients may be due to biological variation in clotting factors[15].

Strength and limitations

Our patients' data were derived from the eHIS database, an electronic storage system of patient records, enabling straightforward access to patient records. The INR results collected in the study were obtained either through point-of-care testing (POC) or clinical laboratory INR. There may be bias in INR measurements calculated using POC compared with laboratory INR, as POC measurements tend to be higher[10], which may affect subsequent INR readings. We were unable to measure objectively patient

compliance to warfarin as a risk factor for poor TTR. Since it was a retrospective study, possible missed documentation may have occurred.

CONCLUSION

This study found the mean TTR was 60.6% in patients with AF and that a high HAS-BLED score (≥ 3) was associated with poor TTR. This could provide an important insight during the initiation of oral anticoagulant for patients with a high HAS-BLED score, who may obtain less benefit from warfarin therapy. They should therefore be considered for other available oral anticoagulants for maximum benefit.

ARTICLE HIGHLIGHTS

Research background

The time in therapeutic range (TTR) is a quality measure for anticoagulation therapy with warfarin.

Research motivation

TTR of international normalized ratio (INR) needs to be achieved with a percentage of ≥ 60% for patient to receive a maximal benefit from warfarin such as preventing stroke, major bleeding, and even death.

Research objectives

TTR and the predictors of poor TTR need to be evaluated among atrial fibrillation (AF) patients that received warfarin therapy.

Research methods

Eligible patients with AF from January 2014 to December 2018 for INR monitoring were included in this study. Demographic data, indication of warfarin therapy, INR target, and percentage of INR within range were collected using a data collection form. TTR was assessed using Rosendaal method.

Research results

In patients with AF, the mean TTR was 60.6% with the highest TTR score achieved in 2018, with a percentage of 67.3%.

Research conclusions

This study showed that high HAS-BLED score was associated to poor TTR.

Research perspectives

Patients with AF and high HAS-BLED score may have less benefit from warfarin therapy. Thus, other alternative oral anticoagulants should be considered for maximum benefit.

ACKNOWLEDGEMENTS

The authors would like to thank the Director-General of Health Malaysia for the permission to publish this paper and to those who contributed directly or indirectly in this study. Further on, the authors would also like to thank the colleagues Siaw SH, Tam AS, Mohamad RIA, Wong KY, Noor Hisham NA, So SH, Lim SY, Tee CY, and Tang MH for their contribution in data collection.

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World Journal of Cardiology

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World J Cardiol 2021 September 26; 13(9): 493-502

DOI: 10.4330/wjc.v13.i9.493

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Study

Percutaneous coronary intervention of totally occluded coronary venous bypass grafts: An exercise in futility?

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Author contributions: Savage MP, Nardone EW, Madsen BM, Fischman DL and McCarey MM contributed to the design of the research study; Savage MP, Fischman DL, Walinsky P, Ruggiero NJ, and Vishnevsky A acquired the data and conducted the procedures. Nardone EW, Madsen BM, Savage MP and Melissa McCarey performed the research. Savage MP, Nardone EW, Melissa McCarey, Fischman DL, Madsen BM, Ruggiero NJ, Walinsky P, and Vishnevsky A analyzed the data and wrote or revised the manuscript; all authors read and approve the final manuscript.

Institutional review board statement: The retrospective saphenous vein graft study was approved by the IRB at Thomas Jefferson University.

Informed consent statement: This

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Abstract

BACKGROUND

Percutaneous coronary intervention (PCI) of diseased saphenous vein grafts (SVG) continues to pose a clinical challenge. Current PCI guidelines give a class III recommendation against performing PCI on chronically occluded SVG. However, contemporary outcomes after SVG intervention have incrementally improved with distal protection devices, intracoronary vasodilators, drug-eluting stents, and prolonged dual antiplatelet therapy.

AIM

To reassess the procedural and long-term outcomes of PCI for totally occluded SVG with contemporary techniques.

METHODS

This was a retrospective observational study conducted at a single university hospital. The study population consisted of 35 consecutive patients undergoing PCI of totally occluded SVG. Post-procedure dual antiplatelet therapy was continued for a minimum of one year and aspirin was continued indefinitely. Clinical outcomes were assessed at a mean follow-up of 1221 ± 1038 d. The primary outcome was freedom from a major adverse cardiac event (MACE) defined as the occurrence of any of the following: death, myocardial infarction, stroke, repeat bypass surgery, repeat PCI, or graft reocclusion.

RESULTS
The study group included 29 men and 6 women with a mean age of 69 ± 12 years. Diabetes was present in 14 (40%) patients. All patients had Canadian Heart Classification class III or IV angina. Clinical presentation was an acute coronary syndrome in 34 (97%) patients. Mean SVG age was 12 ± 5 years. Estimated duration of occlusion was acute (< 24 h) in 34% of patients, subacute (> 24 h to 30 d) in 26%, and late (> 30 d) in 40%. PCI was initially successful in 29/35 SVG occlusions (83%). Total stent length was 52 ± 35 mm. Intraprocedural complications of distal embolization or no-reflow occurred in 6 (17%) patients. During longer term follow-up, MACE-free survival was only 30% at 3 years and 17% at 5 years.

CONCLUSION
PCI of totally occluded SVG can be performed with a high procedural success rate. However, its clinical utility remains limited by poor follow-up outcomes.

Key Words: Coronary artery bypass grafting; Coronary stents; Chronic total occlusion; Percutaneous coronary intervention; Restenosis; Saphenous vein grafts

Core Tip: Cardiovascular guidelines give a Class III recommendation against performing percutaneous coronary intervention (PCI) on chronically occluded saphenous vein grafts (SVG). Given contemporary advances in SVG intervention, the goal of this study was to reassess the outcomes of PCI for totally occluded SVG in 35 consecutive patients. PCI was initially successful in 29/35 (83%) SVG occlusions. However, at 3 years only 30% of patients survived without a major cardiac event. Although PCI of totally occluded SVG can be performed with a high procedural success rate, its clinical utility remains limited by poor follow-up outcomes.

Citation: Nardone EW, Madsen BM, McCarey MM, Fischman DL, Ruggiero NJ, Walinsky P, Vishnevsky A, Savage MP. Percutaneous coronary intervention of totally occluded coronary venous bypass grafts: An exercise in futility? *World J Cardiol* 2021; 13(9): 493-502
URL: https://www.wjgnet.com/1949-8462/full/v13/i9/493.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i9.493

INTRODUCTION

Percutaneous coronary intervention (PCI) of diseased saphenous vein grafts (SVG) continues to be a clinical challenge[1-4]. According to present cardiovascular guidelines, PCI of SVG with chronic total occlusions is discouraged and given a class III recommendation[5]. However, outcomes after SVG intervention have incrementally improved with distal protection devices, intracoronary vasodilators, drug-eluting stents, and prolonged dual antiplatelet therapy (DAPT). The goal of this study was to reassess the procedural and long-term outcomes of PCI for totally occluded SVG in contemporary practice.

MATERIALS AND METHODS

A review of medical records and coronary angiographic films was performed to identify patients with PCI performed on totally occluded SVG. This retrospective study was approved by the Institutional Review Board of the Thomas Jefferson University Hospital. All patients had a 100% occlusion of a venous bypass graft with Thrombolysis In Myocardial Infarction (TIMI) 0 or 1 flow. Patients with subtotal occlusions and TIMI 2 or 3 flow were excluded. PCI of occluded arterial bypass grafts were also excluded.

was a retrospective study which did not require written consent.

Conflict-of-interest statement: All authors have no conflicts of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at michael.savage@jefferson.edu. Consent was not obtained but the presented data are anonymized and risk of identification is low.

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: United States

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 23, 2021
Peer-review started: March 24, 2021
First decision: May 5, 2021
Revised: May 27, 2021
Accepted: July 27, 2021
Article in press: July 27, 2021
Published online: September 26, 2021

P-Reviewer: Vermeersch P
S-Editor: Ma YJ

L-Editor: A
P-Editor: Li JH

Detailed procedural information was collected on the type of anticoagulation, use of thrombectomy and distal protection device, the number of stents implanted, total stent length, and type of stent. Procedural success was defined as restored SVG patency with > TIMI 2 flow and < 20% residual stenosis. Post-discharge, all patients with successful PCI were treated with dual antiplatelet therapy (DAPT) for at least 1 year and aspirin indefinitely.

The primary outcome was freedom from a major adverse cardiac event (MACE) during a mean follow- up period of 1121 ± 1038 d. MACE was defined as the occurrence of any of the following: Death, myocardial infarction (MI), stroke, repeat bypass surgery, repeat PCI of the target vessel, or graft reocclusion. Event rates were determined by Kaplan-Meier analysis. Event free survival was also assessed as a function of the duration of SVG occlusion classified as acute (< 24 h), subacute (> 24 h to 30 days), or late (> 30 d). Duration of occlusion was estimated on the basis of the patient's history of symptom onset. Subgroup analyses were performed based on the duration of occlusion, clinical presentation, and stent type. Fisher's exact test was used to evaluate the relationship of duration of occlusion and clinical presentation with initial clinical success. Between group comparison of the survival curves was performed using the Mantel-Cox log rank test. *P* values < 0.05 were considered significant. Descriptive statistics were used to analyze baseline patient and bypass graft characteristics. Continuous variables are reported as mean ± SD.

RESULTS

Baseline characteristics of the patients are presented in Table 1. The study population consisted of 29 men and 6 women. Mean age was 69 ± 12 years. Diabetes was present in 40% of patients. Twenty patients (57%) had a history of prior MI. Mean left ventricular ejection fraction was 43% ± 12%. All patients had Canadian Heart Classification III or IV angina. Clinical presentation included ST-elevation MI (STEMI) in 6 patients (17%), non-STEMI in 14 patients (40%), unstable angina in 14 patients (40%), and stable angina in 1 patient (3%).

Bypass graft characteristics are shown in Table 2. Mean SVG age was 12.1 ± 5.1 years. The grafted native coronary artery was the left anterior descending in 9 patients (26%), left circumflex in 13 patients (37%), right coronary artery in 10 patients (29%), and multiple vessels in 3 patients (9%). Previous PCI had been performed in 10 (29%) of the SVG. The duration of graft occlusion was acute in 12 (34%), subacute in 9 (26%), and late in 14 (40%).

Procedural features and outcomes are presented in Table 3. Glycoprotein IIbIIIa inhibitors were used in 15 (43%) of cases. Thrombectomy was performed in 20 (57%). Distal protection devices were used in 9 (26%). The mean number of stents implanted was 2.1 ± 1.3 and total stent length was 52 ± 35 mm. Drug-eluting stents were used in the majority of patients.

Procedural success in restoring SVG patency was achieved in 29 of the 35 patients (83%). Of the 6 unsuccessful procedures, 2 were due to the failure to cross through the occluded graft with any guidewire; in the remaining 4 cases, successful guidewire passage to the distal native vessel was accomplished but graft patency could not be restored despite balloon angioplasty and thrombectomy. Procedural success was not correlated with either clinical presentation ($P = 0.99$) or duration of graft occlusion ($P = 0.33$). Procedural complications included distal embolization or no-reflow in 6 (17%) patients. There were no instances of coronary perforation. In-hospital MACE occurred in 3 (9%) patients including 2 deaths and one nonfatal MI.

Follow-up event free survival is shown in Figure 1. MACE free survival was 58% at 1 year, 30% at 3 years, and 17% at 5 years. Distribution of specific MACE events during follow up is shown in Table 4. Longer term outcome was not related to the initial duration of SVG occlusion (Figure 2) ($P = 0.60$) or clinical presentation ($P = 0.87$). There was no difference in MACE free survival for patients with drug-eluting stents compared to bare metal stents ($P = 0.97$).

DISCUSSION

The management of patients who develop bypass graft disease after previous coronary artery bypass grafting (CABG) surgery continue to pose a clinical challenge. For post-CABG patients with unstable or medically refractory symptoms, all revascularization options entail heightened complexity and procedural risk. Redo CABG carries an

Table 1 Patient characteristics

Characteristic	*n* = 35
Men	29 (83%)
Age (mean ± SD)	69 ± 12 yr
Hypertension	33 (94%)
Hyperlipidemia	25 (71%)
Diabetes	14 (40%)
Smoking	14 (40%)
Renal insufficiency	14 (40%)
History of CHF	6 (17%)
Prior MI	20 (57%)
Ejection fraction (mean ± SD)	43% ± 12%
Clinical presentation	
STEMI	6 (17%)
NSTEMI	14 (40%)
Unstable angina	14 (40%)
Stable angina	1 (3%)
Canadian heart class	
I, II	0
III	7 (20%)
IV	28 (80%)

CHF: Congestive heart failure; MI: Myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; SD: Standard deviation; STEMI: ST elevation myocardial infarction.

increased risk of morbidity and mortality compared to the initial operation[6,7]. The outcomes of PCI in SVG have been significantly improved by coronary stenting[8]. Nevertheless, compared to native coronary arteries, PCI of SVG continues to be associated with higher risk of both procedural and long-term adverse events[9]. Accordingly, if revascularization is indicated in the presence of SVG disease, it is generally preferable to intervene on the native coronary artery if technically feasible. On the other hand, native coronary arteries long after bypass surgery often have complex, heavily calcified chronic total occlusions (CTO) which result in a significantly augmented risk of PCI failure and major complications[10-12].

Historically, before the introduction of distal protection devices and drug-eluting stents, PCI of totally occluded SVG has been associated with low initial procedural success, a high rate of complications, and frequent follow-up adverse events[13,14]. More contemporary PCI studies of SVG in the setting of acute thrombosis and STEMI while demonstrating improved procedural success still report poor longer term clinical outcomes[15,16]. A few studies have evaluated the outcome of PCI in chronically occluded SVG in the DES era[17-20]. An early small study of 11 patients with chronically occluded SVG suggested a high procedural success rate and favorable longer term outcomes after PCI[17]. Subsequent studies of chronically occluded SVG involving 22 to 34 patients reported PCI procedural success in 68% to 79% of cases with relatively high rates of MACE during medium term follow-up[18-20].

Citing low success rates, high complication rates, and poor long-term patency, ACC/AHA/SCAI PCI guidelines have a Class III: Harm recommendation against PCI for chronic SVG occlusions[5]. However, it is important to note that these guidelines were published over a decade ago. Accordingly, the unanswered question is whether the cumulative advances in SVG intervention have translated into improved outcome for totally occluded grafts. Distal protection devices have been shown to reduce periprocedural MACE, can be deployed with high success rate, and are given a Class I recommendation in PCI guidelines[5,21-23]. Intracoronary vasodilators have been shown to be effective in treating no-reflow which is a common complication during

Table 2 Bypass graft characteristics

Characteristic	*n* (%)
SVG age (mean ± SD)	12.1 ± 5.1 yr
Prior PCI of SVG	10 (29)
Grafted native vessel	
LAD	9 (26)
LCx	13 (37)
RCA	10 (29)
Multiple	3 (9)
Duration of graft occlusion	
Acute (< 24 h)	12 (34)
Subacute (> 24 h to 30 d)	9 (26)
Late (> 30 d)	14 (40)

LAD: Left anterior descending; LCx: Left circumflex; m: mean; PCI: Percutaneous coronary intervention; SD: standard deviation; SVG: Saphenous vein graft.

SVG PCI and may have benefits if given prophylactically[24-27]. Drug-eluting stents appear to reduce restenosis in SVG early after PCI although they exhibit a catch-up phenomenon during late follow-up[28-31]. Prolonged DAPT improves outcomes following PCI in high risk patient subsets and has been suggested as a possible strategy to improve the long-term outcome after PCI of SVG[4,32,33]. In addition to these advances in SVG intervention, significant improvements in CTO outcomes have been made through continued technical and procedural innovations[34,35].

Given the aforementioned advances, the goal of the current study was to reassess the procedural and long-term outcomes of occluded SVG PCI in the context of contemporary techniques. The initial procedural success in restoring SVG patency was achieved in 83% of patients. This procedural success rate is quite favorable compared to prior reports of totally occluded SVG. On the other hand, long-term clinical outcomes remained poor even though DAPT was continued for a minimum of one year and DES were used in most patients. MACE free survival was 58% at 1 year, 30% at 3 years, and only 17% at 5 years. There was no relation between the duration of SVG occlusion prior to PCI and long-term outcome. There was also no difference in outcome with drug-eluting compared to bare metal stents. The disappointing long-term results of DES in occluded SVG is consistent with the findings of other recent studies of DES for non-occluded SVG[29-31].

Limitations of the current study should be recognized. This study was retrospective and we do not have information into why PCI of the occluded vein graft was undertaken as opposed to other treatment options. Data is not available on the number of patients who were treated by other means such as PCI of the native vessel, redo CABG, or medical therapy alone. Patients in this study who underwent PCI likely represent a small select group with totally occluded SVG. These patients were treated in the drug-eluting stent era which now spans over the past decade and a half; the study population of this report represents less than 1% of patients undergoing PCI at our institution during this time. Accordingly, the outcomes of these patients could have been affected by the selection bias of the operators.

CONCLUSION

PCI of totally occluded SVG can be performed with a relatively high rate of procedural success. However, the vast majority of patients will experience a major clinical event within a few years following the procedure. Therefore, the clinical utility of PCI for totally occluded SVG continues to be limited due to poor long-term outcome.

Table 3 Procedural features and outcomes

Feature	*n* (%)
Anticoagulation	
Heparin only	12 (34)
Bivalirudin	8 (23)
Heparin + GP IIb IIIa inhibitor	15 (43)
Thrombectomy	20 (57)
Distal protection device	9 (26)
Number of stents (mean ± SD)	2.1 ± 1.3
Total stent length (mean ± SD)	52 ± 35 mm
Stent type	
Drug-eluting	19 (55)
Bare metal	11 (31)
None	5 (14)
Procedural outcome	
Success	29 (83)
Failed	6 (17)
Procedural complications	
Distal embolization	1 (3)
No reflow	5 (15)
In-hospital MACE	
Death	2 (5.7)
Myocardial infarction	1 (2.9)
Stroke	0
Repeat PCI or CABG	0
Any MACE	3 (8.6)

CABG: Coronary artery bypass grafting; GP: Glycoprotein; m: mean; MACE: Major adverse cardiac event; SD: Standard deviation.

Table 4 Follow-up major adverse cardiac event

MACE type	*n* (%)
Death	5 (14)
Stroke	1 (3)
MI	15 (43)
Repeat bypass surgery	0
Repeat PCI	6 (17)
Graft reocclusionAny MACE	7 (20) 28 (80)

MACE: Major adverse cardiac event; MI: Myocardial infarction; PCI: Percutaneous coronary intervention.

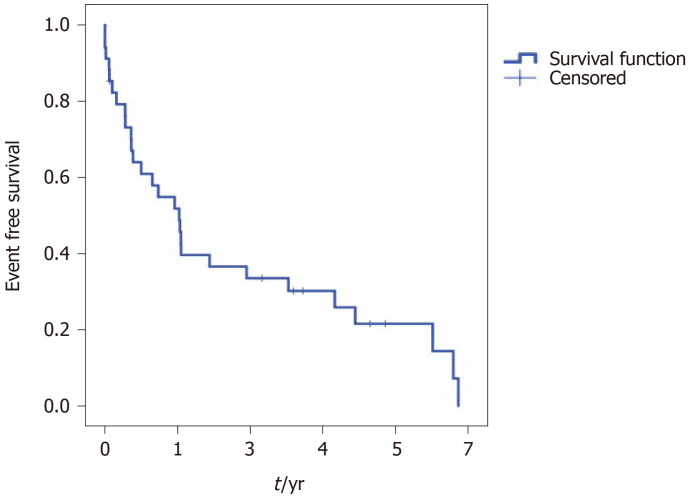

Figure 1 Major adverse cardiac event free survival after percutaneous coronary intervention of totally occluded saphenous vein grafts.

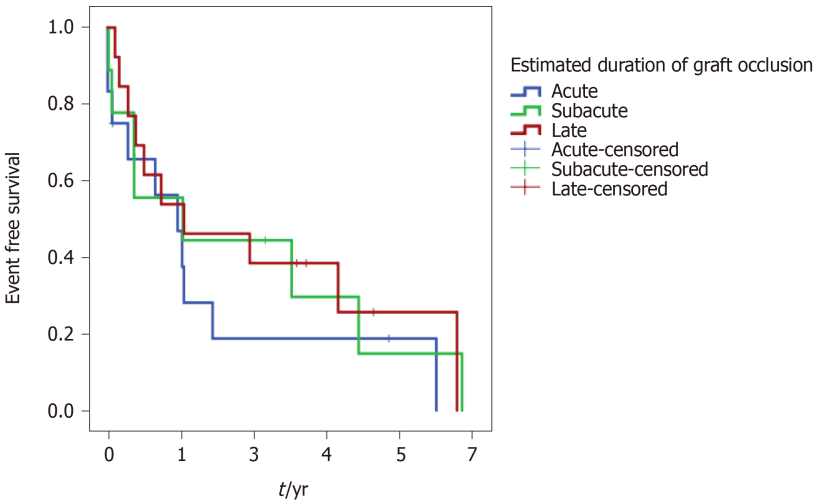

Figure 2 Duration of occlusion and major adverse cardiac event free survival.

ARTICLE HIGHLIGHTS

Research background

Percutaneous coronary intervention (PCI) of diseased saphenous vein grafts (SVG) continues to pose a clinical challenge. Given low success rates, high complication rates, and poor long term patency, current cardiovascular guidelines have a class III recommendation against PCI for chronically occluded SVG.

Research motivation

Contemporary outcomes of SVG intervention have incrementally improved with distal protection devices, intracoronary vasodilators, drug-eluting stents, and prolonged dual antiplatelet therapy. There is a paucity of studies on the outcome of PCI for totally occluded SVG using current techniques.

Research objectives

The goal of this study was to reassess the procedural and long term outcome of PCI for totally occluded SVG with contemporary techniques in the drug-eluting stent era.

Research methods

This was a retrospective observational study of 35 consecutive patients undergoing PCI of totally occluded SVG. The primary outcome was freedom from a major adverse cardiac event (MACE) defined as any of the following: Death, myocardial infarction,

stroke, repeat revascularization of the target vessel, or graft reocclusion. Mean follow-up was 1221 ± 1038 d.

Research results

The study group included 29 men and 6 women aged 69 ± 12 years. Mean SVG age was 12 ± 5 years. PCI was initially successful in 29/35 (83%) SVG occlusions. During long term follow-up, MACE-free survival was 30% at 3 years and 17% at 5 years.

Research conclusions

PCI of totally occluded SVG can be performed with a relatively high rate of procedural success. However, the vast majority of patients have a major clinical event within a few years following the procedure. Thus, the clinical utility of PCI for totally occluded SVG continues to be limited by poor long term outcomes.

Research perspectives

Although PCI of totally occluded SVG can be often initially accomplished, the long term clinical outcome remains poor. Future research is required to achieve a more sustained clinical benefit through further innovations in stent design and adjunct pharmacology.

ACKNOWLEDGEMENTS

The authors thank Scott Keith PhD, a biostatistician at the Thomas Jefferson University, for performing a statistical review.

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World J Cardiol 2021 September 26; 13(9): 503-513

DOI: 10.4330/wjc.v13.i9.503

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Prospective Study

Red blood cell distribution width in elderly hospitalized patients with cardiovascular disease

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Abstract

BACKGROUND

Red blood cell distribution width (RDW) is elevated in patients with cardiovascular disease (CVD).

AIM

To determine RDW values and impact of CV and non-CV coexisting morbidities in elderly patients hospitalized with chronic CVD.

METHODS

This prospective study included 204 consecutive elderly patients (age 77.5 [7.41] years, female 94 [46%], left ventricular ejection fraction 53.00% [37.50, 55.00]) hospitalized with chronic CVD at the Cardiology Department of Larissa University General Hospital (Larissa, Greece) from January 2019 to April 2019. Elderly patients were selected due to the high prevalence of coexisting morbidities in this patient population. Hospitalized patients with acute CVD (acute coronary syndromes, new-onset heart failure [HF], and acute pericarditis/myocarditis), primary isolated valvular heart disease, sepsis, and those with a history of blood transfusions or cancer were excluded. The evaluation of the patients within 24 h from admission included clinical examination, laboratory blood tests, and echocardiography.

RESULTS

manuscript; Giamouzis G participated, Vassilopoulos G, and Skoularigis J participated in the design and oversight of the study; Triposkiadis F participated in the design and oversight of the study and drafted the manuscript; All authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the University General Hospital of Larissa, Larissa, Greece Institutional Review Board.

Informed consent statement: The need for written informed consent was waived by the ethics committee due to the observational nature of the study.

Conflict-of-interest statement: The authors declare no conflict of interest regarding the present work

Data sharing statement: No additional data are available

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: Greece

Peer-review report's scientific

The most common cardiac morbidities were hypertension and coronary artery disease, with acutely decompensated chronic heart failure (ADCHF) and atrial fibrillation (AF) also frequently being present. The most common non-cardiac morbidities were anemia and chronic kidney disease followed by diabetes mellitus, chronic obstructive pulmonary disease, and sleep apnea. RDW was significantly elevated 15.48 (2.15); 121 (59.3%) of patients had RDW > 14.5% which represents the upper limit of normal in our institution. Factors associated with RDW in stepwise regression analysis were ADCHF (coefficient: 1.406; 95% confidence interval [CI]: 0.830-1.981; $P < 0.001$), AF (1.192; 0.673 to 1.711; $P < 0.001$), and anemia (0.806; 0.256 to 1.355; $P = 0.004$). ADCHF was the most significant factor associated with RDW. RDW was on average 1.41 higher for patients with than without ADCHF, 1.19 higher for patients with than without AF, and 0.81 higher for patients with than without anemia. When patients were grouped based on the presence or absence of anemia, ADCHF and AF, heart rate was not increased in those with anemia but was significantly increased in those with ADCHF or AF.

CONCLUSION

RDW was elevated in elderly hospitalized patients with chronic CVD. Factors associated with RDW were anemia and CV factors associated with elevated heart rate (ADCHF, AF), suggesting sympathetic overactivity.

Key Words: Red blood cell distribution width; Elderly; Cardiovascular disease; Coexisting morbidities

Core Tip: This was a prospective observational study with 204 consecutive elderly hospitalized patients seeking to evaluate the impact of cardiovascular (CV) and non-CV coexisting morbidities on red blood cell distribution width (RDW). RDW was significantly elevated and factors associated with RDW were anemia as well as CV factors associated with elevated heart rate (acutely decompensated chronic heart failure and atrial fibrillation), suggesting sympathetic overactivity.

Citation: Xanthopoulos A, Tryposkiadis K, Dimos A, Bourazana A, Zagouras A, Iakovis N, Papamichalis M, Giamouzis G, Vassilopoulos G, Skoularigis J, Triposkiadis F. Red blood cell distribution width in elderly hospitalized patients with cardiovascular disease. *World J Cardiol* 2021; 13(9): 503-513

URL: https://www.wjgnet.com/1949-8462/full/v13/i9/503.htm

DOI: https://dx.doi.org/10.4330/wjc.v13.i9.503

INTRODUCTION

Red blood cell (RBC) distribution width (RDW) is calculated as the standard deviation in RBC size divided by the mean corpuscular volume (MCV), and represents an expression of the variation in size of the RBC (anisocytosis) that make up the total population in an individual patient[1]. Emerging evidence suggests that, besides RBC abnormalities, diverse human pathologies have been frequently associated with anisocytosis. In this regard, increased RDW is associated with adverse events and mortality in many cardiovascular diseases (CVDs) such as ischemic cerebrovascular disease, peripheral artery disease, atrial fibrillation (AF), heart failure (HF), and hypertension (HTN)[2,3]. This study evaluated RDW and the impact of coexisting morbidities in elderly patients hospitalized with chronic CVD[4].

MATERIALS AND METHODS

This prospective study included 204 consecutive elderly (> 65 years) patients admitted

quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

Received: March 6, 2021
Peer-review started: March 6, 2021
First decision: March 31, 2021
Revised: June 22, 2021
Accepted: August 4, 2021
Article in press: August 4, 2021
Published online: September 26, 2021

P-Reviewer: Teragawa H, Yu L
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Ma YJ

to the Cardiology Department of Larissa University General Hospital (Larissa, Greece) from January 2019 to April 2019. Elderly patients were selected due to the high prevalence of coexisting morbidities in this patient population. Patients hospitalized for acute CVD (acute coronary syndromes [n = 49], acute *de novo* HF (n = 18), acute pericarditis/myocarditis [n = 15]), primary isolated valvular heart disease (n = 9), sepsis (n = 27), and those with a history of blood transfusions (n = 17) or cancer (n = 25) were excluded. The study complied with the Declaration of Helsinki and the study protocol was approved by the institutional ethical committee. There was no need for written informed consent as the study was observational. All authors had full access to the data, take responsibility for its integrity, contributed to the writing of the manuscript, and agree to this report as written.

Patient evaluation

The evaluation of the patients within 24 h from admission included clinical examination, laboratory blood tests, and echocardiography. Levels of hemoglobin (Hb) and RDW were measured with the use of the Siemens Advia 2120 (Siemens Healthcare Diagnostics, INC, Deerfield, IL, United States). NT-pro B-type natriuretic peptide (NT-proBNP) was measured with the use of Siemens Advia Centaur (Siemens Healthcare Diagnostics), while urea, creatinine, and electrolyte levels with Siemens Dimension (Siemens Healthcare Diagnostics). Echocardiography was performed and reviewed by two independent echocardiographers, with the use of General Electric Vivid 7 machine (GE Healthcare, Horten, Norway). The left ventricular ejection fraction (LVEF) was calculated with the use of two-dimensional echocardiography by implementing the biplane method of disks summation technique[5].

Definitions of coexisting conditions/morbidities

(1) Coronary artery disease (CAD): history of typical angina in subjects with risk factors, history of myocardial infarction, history of hospitalization for angina, history of percutaneous coronary intervention or coronary bypass grafting and accordant medical prescription list; (2) HTN: history of HTN treatment within the past 3 years; (3) Acutely decompensated chronic HF (ADCHF): deterioration of preexisting chronic HF resulting in an unplanned hospitalization; (4) AF: electrocardiographic findings of AF at admission and/or history of treatment for AF; (5) Diabetes mellitus (DM): treatment with anti-hyperglycemic agents including insulin, within the past 3 years; (6) Chronic obstructive pulmonary disease (COPD): history of dyspnea, chronic cough or sputum production, or history of recurrent lower respiratory tract infections in a patient receiving COPD treatment the past 3 years; (7) Anemia: self-reported anemia and relevant treatment within the past 3 years or hemoglobin (Hb) < 130 g/L for men and < 120 g/L for women at admission; (8) Chronic kidney disease (CKD): elevated creatinine (≥ 1.2 mg/dL) in three consecutive measurements in the past 3 years and confirmed at admission; and (9) Sleep apnea: Sleep apnea treatment with continuous positive airway pressure (CPAP) within the past 3 years.

Statistical analyses

Descriptive statistics are presented for the study population. Continuous variables exhibiting a normal distribution are summarized as the mean and standard deviation (SD), whereas continuous variables exhibiting a non-normal distribution are presented as the median and interquartile range (IQR). The distribution of each continuous variable was visually examined through histograms. Categorical variables are presented as frequencies and percentages. A linear regression model was employed to identify factors associated with the elevation of RDW. Univariate analysis was initially carried out to explore the independent association of each variable with RDW. Any such factor subsequently entered a stepwise forward selection procedure to obtain the multivariate model fitting the data best. Factors were added one-at-a-time, starting from the one indicated as the most significant in the univariate analysis, until none yielded any further improvement in the data fit. This was judged using the likelihood ratio test, a frequently used test that compares the change in deviance in nested models, with the level of significance for addition to the model set at 10%.All estimates generated from linear regression analyses were presented along with 95% confidence intervals (CIs) and P values. P values will be reported from two-sided tests at the 5% significance level. All analyses were carried out with STATA 15 (StataCorp LLC; College Station, TX, United States).

RESULTS

Patient characteristics

The characteristics of the patients enrolled in this study are presented in Table 1. Patients were elderly, and approximately half were females. Most patients suffered from HTN and CAD, with ADCHF and AF also being frequently present. The most common non-cardiac morbidities were anemia and CKD followed by DM, COPD, and sleep apnea. The RDW values of the study population appeared to be elevated (mean [SD] = 15.48 [2.15], median [IQR] = 14,9 [2.7]) compared to the upper limit of normal of our institution (14.50%). In total, 121 (59.3%) of patients had RDW > 14.5%.

Univariate regression analysis

The results obtained from the univariate linear regression analysis are presented in Table 2. The presence of ADCHF appeared to be the most important independent factor associated with the elevation of RDW, followed by the presence of AF, anemia, CKD, COPD, increased urea values, reduced LVEF, and a higher age. Other factors found to be significant at the 5% level were the presence of DM, the presence of sleep apnea, and increased C-reactive protein (CRP).

Multivariate model selection

The results obtained from the model selection procedure are presented in Table 3. ADCHF appeared to be the most important factor alone (change in deviance compared to the null model: 62.86, $P < 0.001$), and hence was contained in all sets of models considered for investigation of the best data fit. The presence of AF in the model yielded greater improvement compared to any other factor when included in the model jointly with ADCHF (change in deviance compared to model including ADCHF only: 19.33, $P < 0.001$). Thus, AF was retained in the model alongside ADCHF. Anemia provided the most significant improvement compared to any other factor when included in addition to ADCHF and AF (change in deviance compared to model including ADCHF and AF: 8.35, $P = 0.004$), and hence was retained in the model along with ADCHF and AF. No further improvement was observed when all factors excluded during the selection procedure re-entered the model, one-at-a-time, along with ADCHF, AF, and anemia ($P > 0.15$). Therefore, the best model included ADCHF, AF, and anemia.

Multivariate regression analysis

The results obtained from the multivariate linear regression analysis are presented in Table 4. ADCHF was again the most significant factor associated with RDW, with an average increase of 1.41 noted for patients with ADCHF compared with those without. Furthermore, the RDW was on average 1.19 higher for patients with AF compared to patients without AF, and on average 0.81 higher for anemic patients compared to non-anemic. It is noteworthy that when patients were grouped based on the presence or absence of anemia, ADCHF and AF, heart rate was not increased in those with anemia but was significantly increased in those with ADCHF or AF (Figure 1).

DISCUSSION

In this study that included elderly patients hospitalized with CVD, RDW was significantly elevated. ADCHF was the most significant factor associated with RDW, whereas other important factors were AF and anemia. RDW was significantly higher than the RDW of a subgroup of elderly (*i.e.* 71-85-years-old) ($n = 1479$) of a historical cohort including a total of 8089 individuals (15.48 ± 2.15 *vs* 12.6±0.8, respectively; $P < 0.0001$)[6].

An increased RDW mirrors a profound deregulation of erythrocyte homeostasis involving both impaired erythropoiesis and abnormal RBC survival and is used along with other RBC indices to help determine the causes of anemia[7]. A high RDW provides a clue for anisocytosis and/or the presence of two red cell populations, since other RBC indices (*e.g.*, MCV or mean corpuscular hemoglobin concentration [MCH]) reflect average values and may not adequately reflect RBC changes where mixed RBC populations are present (*e.g.*, dimorphic RBC populations in sideroblastic anemia or combined iron deficiency anemia (decreased MCV and MCH) and megaloblastic anemia (increased MCV).

Table 1 Baseline characteristics of the study population

Demographic/clinical	
Age (mean ± SD, yr)	77.50 ± 7.41
Female sex, *n* (%)	94 (46)
Body weight (mean ± SD, kg)	76.28 ± 14.22
Height (mean ± SD, m)	1.66 ± 0.09
Systolic blood pressure (mmHg)	135(34.8)
Diastolic blood pressure (mmHg)	79 (21)
Heart rate (beats/minute)	73.5 (19)
Left ventricular ejection fraction (%) (median, IQR)	53.00 (37.50, 55.00)
Laboratory	
RDW[1] (mean ± SD)	15.48% ± 2.15%
C-reactive protein[2] (mg/L) (median, IQR)	0.48 (0.16, 1.37)
Hemoglobin[3] (mean ± SD, g/dL)	12.25 ± 1.92
Hematocrit[3] (mean ± SD)	37.89% ± 6.04%
White blood cells[3] (K/μL)	8.31 (2.85)
Urea (mg/dL) (median, IQR)	51.70 (38.60, 70.50)
Creatinine[3] (mean ± SD, mg/dL)	1.21 (0.49)
SGOT[4] (IU/L) (median, IQR)	20.15 (16.55, 25.65)
SGPT[4] (IU/L) (median, IQR)	16.75 (11.65, 22.90)
K+[4] (mean ± SD, mmol/L)	4.20 ± 0.56
Na+[1] (mmol/L) (median, IQR)	140.00 (137.50, 142.00)
Non-cardiac conditions/morbidities, *n* (%)	
Diabetes mellitus	68 (33)
Chronic obstructive pulmonary disease	37 (18)
Chronic kidney disease	84 (41)
Sleep apnea	15 (7)
Anemia	85 (42)
Cardiac conditions/morbidities, *n* (%)	
Acutely decompensated chronic heart failure	104 (51)
Coronary artery disease	133 (65)
Hypertension	152 (75)
Atrial fibrillation	97 (47.5)
Medications (discharge), *n* (%)	
Renin-angiotensin-aldosterone system inhibitors	159 (78)
Beta-blockers	145 (71)
Diuretics	137 (67)

[1]Three values missing.
[2]Fifty-four values missing.
[3]Two values missing.
[4]Four values missing. RDW: Red blood cell distribution width; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase.

RDW has additionally been used as a prognosticator in diverse pathologies including CVD[8,9]. Many of the conditions for which an increase in RDW was

Table 2 Results obtained from univariate linear regression analysis

Factor	Coefficient	95%CI	*P* value
Age	0.072	(0.033, 0.111)	**< 0.001**
Sex (males *vs* females)	-0.520	(-1.115, 0.075)	0.09
Weight	-0.014	(-0.035, 0.007)	0.18
White blood cell count	0.081	(-0.024, 0.185)	0.13
Urea	0.022	(0.014, 0.030)	< 0.001
C-reactive protein[1]	0.085	(0.001, 0.169)	0.05
Left ventricular ejection fraction	-0.057	(-0.073, -0.038)	< 0.001
Acutely decompensated chronic heart failure	2.220	(1.708, 2.732)	< 0.001
Coronary artery disease	0.039	(-0.573, 0.650)	0.9
Hypertension	-0.519	(-1.203, 0.165)	0.14
Atrial fibrillation	1.862	(1.322, 2.402)	< 0.001
Diabetes mellitus	0.854	(0.230, 1.477)	0.01
Chronic obstructive pulmonary disease	1.569	(0.810, 2.327)	< 0.001
Anemia	1.682	(1.123, 2.242)	< 0.001
Chronic kidney disease	1.590	(1.022, 2.158)	< 0.001
Sleep apnea	1.448	(0.289, 2.606)	0.02

[1]Fifty-four values missing.

observed are associated with systemic inflammation and critical illness, but the exact pathophysiologic mechanisms underlying the association of increase in RDW with morbidity and mortality remains unclear[10]. Given that erythropoietin is a key determinant of the RDW, it has been postulated that any condition affecting erythropoietin activity (*e.g.*, inflammation, primary renal disease, HF, bone marrow failure) may potentially lead to increased RDW values[11-13]. Another consideration could be nutritional imbalance, often present in patients with chronic diseases or critical illness, expressed by micronutrient deficiencies (*e.g.*, iron, vitamin B12, or folate deficiency) that are associated with anisocytosis[14], and excess of macronutrients. On the other hand, higher RDW has been associated with the metabolic syndrome (MS) [15,16]. Proinflammatory cytokines inhibit erythropoietin-induced erythrocyte maturation, which may lead to increased RDW[16]. Macronutrient surplus causes lipotoxicity in healthy non-adipose tissues, and induces tissue damage[17]. Other physiologic determinants that are associated with RDW changes include aging, Black ethnicity, and physical exercise[6,18].

The findings of this study regarding the inflammatory nature of RDW elevation are contradictory. Inflammatory diseases[19] were both included in (*e.g.*, AF and ADCHF) and excluded from (*e.g.*, CKD, and COPD) the final model. Moreover, biomarkers of inflammation were unrelated (white blood cells) or weakly related (CRP) to RDW in univariable analysis and both were not included in the final model. The results of the studies on the relationship between RDW and inflammatory biomarkers have been conflicting. In the study of Lippi and colleagues including 3845 outpatients, when participants were grouped according to RDW quartiles, there were strong, graded increases in erythrocyte sedimentation rate and hsCRP ($P < 0.001$), both parameters being up to 3-fold higher in the fourth *vs* the first quartile[20]. In contrast, Lappe and colleagues observed a significant but meaningless correlation between RDW and high-sensitivity CRP ($r = 0.181$; $P < 0.001$) in 1489 patients with CAD[21].

Inflammatory processes are present during the development and complications of CVD. However, although there is a wealth of information about the role of inflammatory cells and pathways during acute injury and the reparative processes that are subsequently activated, little is known about the contribution of the immune system once the trajectory has been set, and chronic CVD has been established—which clinically represents the majority of patients[22]. The causative role inflammation plays in disease progression is not well defined, and the majority of clinical trials that target

Table 3 Results obtained from the model selection procedure

Explanatory factors of RDW	Change in deviance[1]	*P* value
Models including 1 factor[2]		
Age	12.84	< 0.001
Urea	26.50	< 0.001
C-reactive protein	4.01	0.05
LVEF	30.42	< 0.001
ADCHF	**62.86**	**< 0.001**
Atrial fibrillation	42.01	< 0.001
Diabetes mellitus	7.23	0.007
COPD	16.14	< 0.001
Anemia	32.69	< 0.001
CKD	28.60	< 0.001
Sleep apnea	6.04	0.01
Models including 2 factors[3]		
ADCHF + Age	0.15	0.70
ADCHF + Urea	3.03	0.08
ADCHF + C-reactive protein	0.30	0.59
ADCHF + LVEF	0.06	0.80
ADCHF + Atrial fibrillation	**19.33**	**< 0.001**
ADCHF + Diabetes mellitus	3.08	0.08
ADCHF + COPD	2.39	0.12
ADCHF + Anemia	7.74	0.005
ADCHF + CKD	0.85	0.36
ADCHF + Sleep apnea	0.34	0.56
Models including 3 factors[3]		
ADCHF + Atrial fibrillation + Age	0.08	0.78
ADCHF + Atrial fibrillation + Urea	2.10	0.15
ADCHF + Atrial fibrillation + C-reactive protein	0.54	0.46
ADCHF + Atrial fibrillation + LVEF	0.75	0.39
ADCHF + Atrial fibrillation + Diabetes mellitus	2.30	0.13
ADCHF + Atrial fibrillation + COPD	0.89	0.35
ADCHF + Atrial fibrillation + Anemia	**8.35**	**0.004**
ADCHF + Atrial fibrillation + CKD	0.73	0.39
Models including 4 factors[3]		
ADCHF + Atrial fibrillation + Anemia + Age	0.50	0.48
ADCHF + Atrial fibrillation + Anemia + Urea	1.16	0.28
ADCHF + Atrial fibrillation + Anemia + C-reactive protein	0.34	0.56
ADCHF + Atrial fibrillation + Anemia + LVEF	1.86	0.17
ADCHF + Atrial fibrillation + Anemia + Diabetes mellitus	0.92	0.34
ADCHF + Atrial fibrillation + Anemia + COPD	0.77	0.38
ADCHF + Atrial fibrillation + Anemia + CKD	0.26	0.61

[1]Largest change in deviance indicates the best model in each set (highlighted).
[2]Models were compared to the null model.
[3]Models were compared to those indicated as best in the previous set. ADCHF: Acutely decompensated chronic heart failure; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; LVEF: Left ventricular ejection fraction.

Table 4 Results obtained from multivariate linear regression analysis

Factor	Coefficient	95%CI	*P* value
Acutely decompensated chronic heart failure	1.406	(0.830, 1.981)	< 0.001
Atrial fibrillation	1.192	(0.673, 1.711)	< 0.001
Anemia	0.806	(0.256, 1.355)	0.004

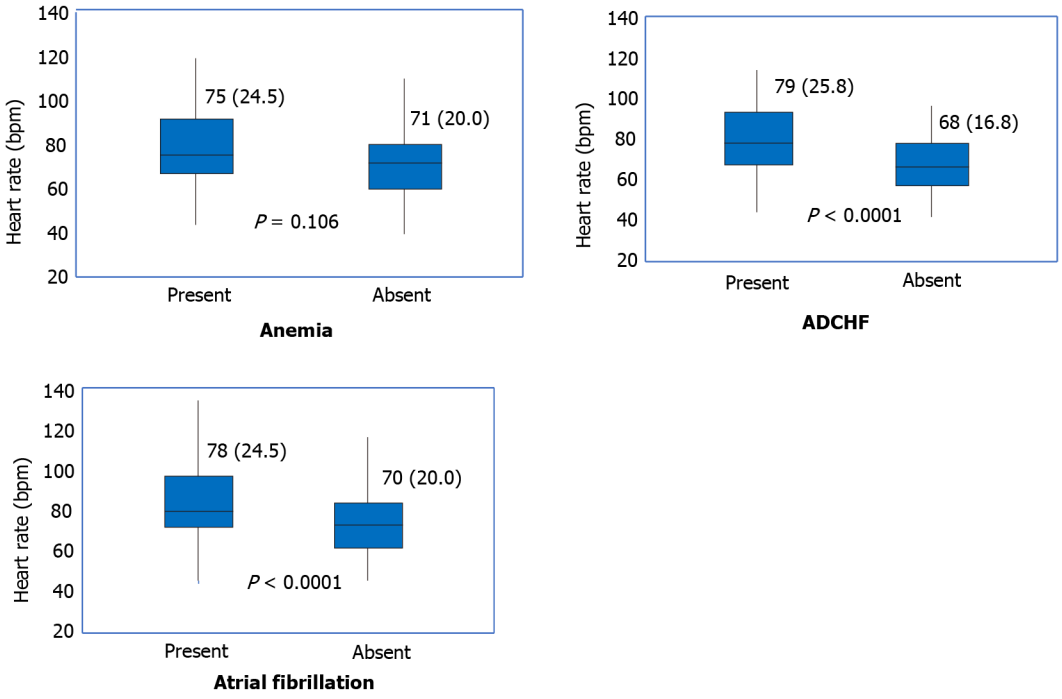

Figure 1 Heart rate in the presence or absence of anemia, acutely decompensated chronic heart failure, and atrial fibrillation. ADCHF: Acutely decompensated chronic heart failure; bpm: Beats per minute.

aspects of inflammation in patients with chronic CVD have largely been negative[23,24]. This may be partly due to the fact that the tools currently used to measure "inflammation" are insufficiently precise and do not provide information about disease site, activity, or discrimination between functionally important activation pathways[23,25].

Anisocytosis can be produced by any factor that increases erythropoiesis. In the present study, in contrast to anemia the two most important non-CV factors inducing anisocytosis, ADCHF and AF were associated with increased heart rate confirming that both are hyper-catecholaminergic states[26,27]. The nervous system emerges as a critical regulatory player of the bone marrow, the primary site of postnatal hematopoiesis and hematopoietic stem cell maintenance, both under homeostatic and pathologic settings, with essential roles in cellular anchorage and egress, stem cell differentiation, and endothelial cell permeability[28,29]. Factors involved in erythropoiesis appear to revolve around the nervous system, and catecholamines seem to be the centerpiece. Several studies support the central role of the sympathetic nervous system (SNS) in the regulation of hematopoiesis[30,31]. Norepinephrine (NE) is delivered to the bone marrow (BM) by the sympathetic nerve in a circadian (diurnal) manner[32]. A close communication exists between the SNS and the BM and dysregulation in this communication may lead to aberrant hematopoietic and immune system responses[33].

This study had several limitations. (1) The study enrolled elderly patients (≥ 65-years-old) and therefore the results should be interpreted with caution in younger populations. As previously mentioned the decision to include only elderly patients was based on the fact that these patients usually suffer from several coexisting morbidities enabling us to study their potential impact on RDW. (2) A control group was lacking to compare RDW. However, a normal range of RDW value of 14.5% representing the upper normal limit is widely accepted[1,6] and RDW was compared with an aged-matched historical control[6]; (3) The cause of anemia was not determined. Iron deficiency anemia is diagnosed in 16.6%–25% of non-hospitalized older adults, 22%–40% of institutionalized older adults, and 15%–65% of hospitalized older adults[34]. Iron deficiency and iron deficiency anemia are common problems in patients with CVD[35]. Therefore, it is reasonable to assume that the study findings were driven by iron deficiency anemia. And (4) By assessing heart rate, we achieved information predominantly on the cardiac sympathetic drive. However, differentiation of sympathetic responses means that no simple test can ever represent each and every sympathetic outflow[36]. Nevertheless, the presence of sympathetic overactivity in ADCHF and AF has been demonstrated in numerous studies.

CONCLUSION

In elderly patients hospitalized with chronic CVD, RDW was elevated and associated both with anemia and factors unrelated to anemia such as ADCHF and AF. It is of interest that ADCHF and AF shared a common characteristic, namely heart rate elevation, which is suggestive of SNS overactivity a well-known regulator of BM. Further studies are necessary to establish the relationship between RDW and SNS.

ARTICLE HIGHLIGHTS

Research background

An increased red blood cell distribution width (RDW) is associated with poor outcomes in patients with several cardiovascular diseases (CVDs).

Research motivation

Data on the pathophysiology of RDW increase in hospitalized patients with CVD are limited.

Research objectives

The current study explored the impact of CV and non-CV coexisting morbidities in elderly patients hospitalized with chronic CVD.

Research methods

This prospective observational study included 204 consecutive elderly (> 65 years) patients admitted to a tertiary university hospital of Greece. Elderly patients were selected due to the high prevalence of coexisting morbidities in this patient population.

Research results

Factors associated with RDW were anemia, acutely decompensated chronic heart failure (ADCHF), and atrial fibrillation (AF).

Research conclusions

ADCHF and AF shared a common characteristic, namely heart rate elevation, which suggests sympathetic nervous system (SNS) overactivity, a well-known regulator of bone marrow.

Research perspectives

Further studies will establish the relationship between RDW and SNS.

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 September 26; 13(9): 514-525

DOI: 10.4330/wjc.v13.i9.514

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Prospective Study

Effects of exercise training on diastolic and systolic dysfunction in patients with chronic heart failure

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Author contributions: Chaveles I, Ntalianis A, Panagopoulou N, Shamari MA, and Delis D engaged in acquisition of data (echocardiographic measurements, cardiopulmonary exercise testing, and application of exercise rehabilitation program); Chaveles I and Karatzanos E contributed to the data analysis and results interpretation; Chaveles I and Papazachou O drafted the manuscript; Papazachou O, Nanas S and Katatzanos E critically revised the manuscript; All authors gave final approval.

Institutional review board statement: The study was approved by the Administration Board and the Ethics Committee of the 'Evangelismos' Hospital (Athens, Greece) (approval number: 43/28.03.2016).

Clinical trial registration statement: The clinical trial has been

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Abstract

BACKGROUND

Chronic heart failure (CHF) is a complex syndrome characterized by a progressive reduction of the left ventricular (LV) contractility, low exercise tolerance, and increased mortality and morbidity. Diastolic dysfunction (DD) of the LV, is a keystone in the pathophysiology of CHF and plays a major role in the progression of most cardiac diseases. Also, it is well estimated that exercise training induces several beneficial effects on patients with CHF.

AIM

To evaluate the impact of a cardiac rehabilitation program on the DD and LV ejection fraction (EF) in patients with CHF.

METHODS

Thirty-two stable patients with CHF (age: 56 ± 10 years, EF: 32% ± 8%, 88% men) participated in an exercise rehabilitation program. They were randomly assigned to aerobic exercise (AER) or combined aerobic and strength training (COM), based on age and peak oxygen uptake, as stratified randomization criteria. Before and

registered with ClinicalTrials.gov (NCT04916184).

Informed consent statement: All study participants provided written consent prior to study enrollment.

Conflict-of-interest statement: The authors of this manuscript have no conflicts of interest to disclose.

Data sharing statement: There is no additional data available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

Manuscript source: Invited manuscript

Specialty type: Rehabilitation

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 3, 2021
Peer-review started: April 3, 2021
First decision: May 13, 2021
Revised: May 26, 2021
Accepted: July 23, 2021
Article in press: July 23, 2021
Published online: September 26, 2021

after the program, they underwent a symptom-limited maximal cardiopulmonary exercise testing (CPET) and serial echocardiography evaluation to evaluate peak oxygen uptake (VO_{2peak}), peak workload (W_{peak}), DD grade, right ventricular systolic pressure (RVSP), and EF.

RESULTS

The whole cohort improved VO_{2peak}, and W_{peak}, as well as DD grade ($P < 0.05$). Overall, 9 patients (28.1%) improved DD grade, while 23 (71.9%) remained at the same DD grade; this was a significant difference, considering DD grade at baseline ($P < 0.05$). In addition, the whole cohort improved RVSP and EF ($P < 0.05$). Not any between-group differences were observed in the variables assessed ($P > 0.05$).

CONCLUSION

Exercise rehabilitation improves indices of diastolic and systolic dysfunction. Exercise protocol was not observed to affect outcomes. These results need to be further investigated in larger samples.

Key Words: Chronic heart failure; Cardiovascular effects; Cardiac rehabilitation; Aerobic exercise; Strength training; Diastolic dysfunction

Core Tip: In this study, the exercise training rehabilitation (aerobic exercise with/without strength training) effects on indices of diastolic and systolic cardiac function, were evaluated in stable chronic heart failure patients. Exercise training overall induced benefits on the diastolic dysfunction grade, the ejection fraction of the left ventricle, the right ventricular systolic pressure, as well as aerobic exercise capacity.

Citation: Chaveles I, Papazachou O, Shamari MA, Delis D, Ntalianis A, Panagopoulou N, Nanas S, Karatzanos E. Effects of exercise training on diastolic and systolic dysfunction in patients with chronic heart failure. *World J Cardiol* 2021; 13(9): 514-525
URL: https://www.wjgnet.com/1949-8462/full/v13/i9/514.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i9.514

INTRODUCTION

Chronic heart failure (CHF) is a multisystem syndrome, characterized by an abnormality of the cardiac structure or function, condition, which leads to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabo-lizing tissues, despite normal filling pressures[1].

Left ventricular diastolic dysfunction plays an essential role in the pathophysiology of the CHF. The term "diastolic dysfunction" (DD) refers to abnormalities in right or/and left ventricular relaxation[2-5]. Although DD most frequently refers to the context of HF with preserved ejection fraction (EF), due to its central role in its pathophysiology, impaired diastolic function often coexists with systolic dysfunction. HF patients may not accomplish the necessary increase in diastolic relaxation to accommodate the preload increase[1]. Severity of exercise intolerance is associated with left ventricular filling pressure and so the strong relationship between diastolic abnormality and exercise limitation should be underlined[6-8]. It is in that context, that exercise training is currently being extensively evaluated for additional benefits, over the classical medication, in the treatment of DD in patients with CHF[9].

As mentioned before, in patients with CHF, the exercise capacity may be limited by the number of frequently coexisting factors such as decreased contractility, DD, chronotropic incompetence, oxygen metabolism, or skeletal muscle mass disorders. This importance of skeletal muscle dysfunction provides part of the rationale for the use of cardiac rehabilitation[10]. It is well established that exercise training improves functional capacity, quality of life, and clinical outcomes in patients with stable CHF [10,11]. Specifically, in patients with reduced EF, exercise is beneficial in total and HF-

P-Reviewer: Osailan A
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Wang LYT

related hospitalizations and relieves the symptoms of depression. Also, it decreases myocardial oxygen demands for the same level of external work performed, as demonstrated by the product of heart rate × systolic blood pressure, reducing in that way the likelihood of myocardial ischemia[12,13]. In major Cardiology Society Guidelines, exercise training is recommended in all patients with New York Heart Association functional class II to III, no matter of the EF[14-16].

Finally, aerobic regimes have been a major component of exercise rehabilitation to improve cardiorespiratory fitness and disease symptoms[16]. As skeletal muscle abnormalities are an important limitation to exercise intolerance and muscular strength impacts patients' capacities to perform daily tasks, combined regimes of aerobic exercise (AER) and strength training have been employed to induce additional benefit[17,18]. However, there have not been any data on the effects of different regimes on diastolic dysfunction.

The main aim of this study was to evaluate the impact of a cardiac exercise rehabilitation program, on the DD and the EF of the LV in patients with CHF. A secondary aim was the comparison of an aerobic and combined regimes to explore any potential difference on these indices.

MATERIALS AND METHODS

Study population and design of the study

The study population consisted of 32 consecutive CHF patients. The demographic, anthropometric, and clinical characteristics of these patients at baseline are described in Table 1. The patients were referred to our hospital's laboratory by HF outpatient clinics, screened for inclusion/exclusion criteria and consented to attend a rehabilitation program and undergo related evaluations including echocardiography assessment. They randomly assigned to AER (n = 17) or combined aerobic and strength training (COM, n = 15). Randomization process, based on age (50 years as cut-off value) and peak oxygen uptake (16 mL/kg/min as cut-off value) as stratified randomization criteria, was made by a researcher not involved in the rest of the tasks, such as exercise sessions and pre/post evaluations. Before and after the program, they underwent a symptom-limited maximal cardiopulmonary exercise testing (CPET) and serial echocardiography assessment. The researchers performed these evaluations were blinded to participants' allocation.

CHF diagnosis was based on history forms, clinical evaluation, and laboratory testing. Patients were considered for inclusion in the study in case they were on stable systolic CHF, under optimal medication for at least 3 mo and had an EF value up to 49%. Exclusion criteria were severe valvulopathy, uncontrolled arterial hypertension, severe chronic obstructive pulmonary disease, severe peripheral angiopathy, neuromuscular diseases and contraindications for CPET. The patients were mainly treated with diuretics, b-blockers, aldosterone antagonists, angiotensin-converting enzyme inhibitors or sacubitril/valsartan. There were not any changes in treatment regimen during the study.

The study was conducted in accordance with the principles of the Helsinki Declaration and approved by the Administration Board and the Ethics Committee of our Hospital. Informed consent was provided by the participants.

Exercise training program

Participants attended supervised exercise sessions at the laboratory three times per week for 12 wk in the early afternoon hours. If any sessions were missed, the duration of the program was extended so that the 36 sessions were accomplished. AER and COM protocols have been previously described in detail[19]. In short, the AER group performed 31 min of interval training (4 × 4–min at 80% VO_{2peak}–5 × 3-min at 50% VO_{2peak}) on a cycle ergometer (Ironman M3 Cycle) followed by balance and coordination exercises. The COM group performed 31 min of AER (in the same way as the AER group) followed by 14 min of strength training (2–3 sets, 10–12 repetitions, 60%-75% of 1 repetition maximum test-knee extension, knee flexion, chest press). Both regimes were of the same total duration.

Cardiopulmonary exercise testing

Participants underwent a ramp incremental CPET on an electromagnetically braked cycle ergometer (Ergoline 800; Sensor Medics, Anaheim, CA, United States), before and after completion of the program. Individualized workload increments were estimated according to the equation of Hansen *et al*[20]. Gas exchange was measured

Table 1 Demographic, anthropometric, and clinical characteristics of all chronic heart failure patients at the beginning of the study

Patients, *n*	32
Age[1], yr	56 ± 10
Gender (Males/Females)	30/2
Height[1], cm	178 ± 8
Body mass[1], kg	93 ± 25
BMI[1], kg/m^2	29 ± 6
NYHA class (I/II/III)	3/21/ 8
LVEF[1], %	32 ± 8
VO_{2peak}[1], mL/kg/min	19.4 ± 4.5
Etiology of CHF, *n*	
Ischemic/Dilated/Other cardiomyopathy	20 / 10 / 2

[1]Values are mean ± SD.

BMI: Body mass index; CHF: Chronic heart failure; LVEF: Ejection fraction of the left ventricle; NYHA: New York Heart Association; VO_{2peak}: Peak oxygen uptake.

with the patient breathing through a low resistance valve, with the nose clamped, using an ergospirometry system (Vmax229D; Sensor Medics) calibrated with a known gas mixture before each test. Respiratory indicators (breath-by-breath oxygen uptake [VO_2], carbon dioxide output [VCO_2] and ventilation [V_E]) were measured. Peripheral O_2 saturation was monitored continuously by pulse oximetry. Heart rate and rhythm were monitored by a MAX 1, 12-lead electrocardiographic system (Marquette Electronics, Milwaukee, WI, United States) and blood pressure was measured every 2 min with a mercury sphygmomanometer. All patients were verbally encouraged to exercise to intolerable leg fatigue or dyspnea. CPET variables employed in the study were VO_{2peak} and peak workload (W_{peak}). VO_{2peak} was determined as the average value of VO_2 data measured at the final 20-s period of the exercise phase, and W_{peak} as the corresponding work rate[20].

Echocardiographic measurements

Detailed echocardiography assessment was performed in all patients. A Philips E 33 Doppler analyzer equipped with tissue Doppler imaging (TDI) was used. The period between echocardiography assessment and cardiopulmonary exercise testing was less than 2 wk. Each patient was examined, according to the guidelines of the European Society of Echocardiography (2016 update[21]), in the left lateral and supine position. The EF was calculated using the modified Simpson method from apical two- and four-chambers view (2D and 4D). Analysis of pulsed Doppler mitral flow velocity was attained, and three consecutive cardiac cycles were analyzed and averaged for each patient. Transmitral inflow velocities (E, A, deceleration time of E [DTe] and E/A ratio) were assessed by pulsed-wave Doppler, with the sample volume placed between the mitral leaflet tips in the apical four-chamber view during diastole. When from the Echo–TDI the septal e' was less than 8 and the lateral e' less than 10, the Echo-Doppler transmitral flow was examined. Based on this, three grades of diastolic dysfunction (DD) are described: Grade I (impaired relaxation) is characterized by E/A ratio less than 0.8 and DTe more than 200 ms. Grade II (pseudonormal) is characterized by elevated left atrial pressures. The E/A ratio is 0.8–2 and the DTe is more than 200 ms. Grade III (restrictive pattern), is characterized by a marked decrease in left ventricular compliance (E/A ratio more than 2, DTe less than 160 ms[15]). Another grade, grade 0, refers to normal diastolic function. The E/A ratio was considered as normal if it was 0.78–1.78 and the DTe 150–200 ms. Valsalva maneuver was used to discriminate pseudo normal from true normal pattern. From the apical four-chamber view, a 10 mm^3 sample volume was placed at the septal and lateral mitral annulus, and spectral TDI was recorded, calculating septal e', lateral e' and the mean value (E'). Left atrial volume was measured at end-systole and it was normalized to body surface area (LAVI, mL/m^2). Finally, the right ventricular systolic pressure (RVSP) was calculated using the Bernoulli equation RVSP = 4(V)^2 of peak tricuspid regurgitation velocity (V).

Statistical analyses

Continuous variables were tested for normality of distribution with Shapiro-Wilk test. Within-group differences were assessed with paired sample Student *t*-test or Wilcoxon signed-rank test, based on normality of distribution. Chi-square test was employed to check for between-group differences on categorical variables. Between-group differences of ordinal variables were assessed with Mann-Whitney *U* test. McNemar-Bowker test was also used to check for differences on diastolic dysfunction grade before and after exercise intervention. Time by group interactions were assessed with factorial 2 × 2 analysis of variance. Correlations between variables were tested with Pearson or Spearman coefficient. Continuous variables were presented as mean ± SD. Level of statistical significance *P* was set at 0.05. Statistical computations were made with IBM SPSS 26 statistics.

RESULTS

The whole cohort improved indices of AER capacity, namely VO_{2peak} (from 19.4 ± 4.5 to 21.3 ± 6.0 mL/kg/min, $P = 0.03$) and W_{peak} (from 109 ± 39 to 130 ± 43 watts, $P < 0.01$).

The whole group improved DD, as assessed with grades. Before the exercise program, the number of patients categorized as grade -0, -I, -II, or -III were 1 (3.1%), 18 (56.3%), 10 (31.2%), 3 (9.4%) respectively. After the program, the respective patients were 4 (12.5%), 21 (65.6%), 6 (18.8%), 1 (3.1%). A significant difference was found between total pre- and post-values ($P = 0.01$) (Figure 1A). That was also the case when analysis was performed based on change of DD grade ($P = 0.06$) (Figure 1B). Overall, 9 patients (28.1%) improved DD grade, while 23 ones (71.9%) remained at the same DD grade; this was a significant difference, considering DD grade at baseline ($P < 0.01$) (Figure 1C). In addition, VO_{2peak}, tended to improve more in patients that also improved grade ($P = 0.09$), while W_{peak} was improved more in these patients ($P = 0.04$) (Figure 2).

The whole sample did not improve any of the other DD variables examined individually. These were E/A ratio (from 1.00 ± 0.64 to 0.88 ± 0.35, $P = 0.27$), LAVI (from 38.70 ± 13.74 to 38.44 ± 17.03 mL/m^2, $P = 0.14$), E' (from 7.74 ± 2.31 to 7.55 ± 1.85 cm/s, $P = 0.62$), E/E' ratio (from 9.15 ± 3.41 to 8.48 ± 3.45, $P = 0.15$), and DTe (from 213.34 ± 41.60 to 212.38 ± 32.99 m/s, $P = 0.59$). In addition, the whole cohort improved RVSP (from 28.92 ± 7.75 to 27.75 ± 6.46 mmHg, $P = 0.05$) and EF (from 32% ± 8% to 36% ± 8%, $P < 0.01$), after completion of the exercise rehabilitation program.

Pre- and post-values of the variables examined in relation to AER and COM groups comparison are presented in Table 2. The AER group improved DD grades ($P = 0.02$) and tended to improve LAVI ($P = 0.10$). The COM group improved RVSP ($P = 0.01$) and tended to improve grades ($P = 0.10$). Both groups improved EF ($P < 0.01$). Not any between-group differences were observed in the variables observed ($P > 0.05$).

DISCUSSION

The exercise rehabilitation effects on parameters of diastolic and systolic dysfunction were explored among CHF patients in this study. Exercise training overall beneficially affected DD stage, RVSP, EF of the left ventricle and AER capacity. Not any differences between the aerobic and combined group were observed.

HF is currently considered a pathophysiological syndrome of multifactorial origin and not just a disease. DD is a common characteristic of the HF patients[22]. Hamlin *et al*[4] showed that CHF patients present with reduced ability to augment the diastolic relaxation, accountable for the inability to accommodate the increase in estimated preload during exercise, resulting in turn in higher filling pressure. Also, HF patients have generally shorter diastolic periods, situation that lead to inability of the myocardium to relax and accept the large volume of blood[23]. The inability to perform exercise without discomfort may be one of the first symptoms experienced by patients with HF and is often the principal reason for seeking medical care[14,24]. Therefore, exercise intolerance is inextricably linked to the diagnosis of HF. Exercise training has been an important means of rehabilitation, with a class IA recommendation on the improvement of functional capacity and symptoms[16]. In line with previous studies[17,25], indices of aerobic capacity as assessed with peak oxygen uptake (VO_{2peak}) and workload (W_{peak}) were also improved in this study. A significant improvement in the DD grades was found in this study. Other diastolic indices, such as E/E', were not found to improve, which may be related to the small sample size.

Table 2 Values of the variables evaluated before and after the exercise training intervention

	Aerobic group		Combined group	
	Pre	Post	Pre	Post
VO_{2peak} (ml/kg/min)	19.0 ± 5.5	22.2 ± 7.8[a]	19.8 ± 3.1	20.3 ± 2.9
W_{peak} (watt)	111 ± 46	129 ± 48[a]	108 ± 31	131 ± 39[a]
E/A	1.15 ± 0.80	1.00 ± 0.41	0.83 ± 0.37	0.74 ± 0.20
LAVI (ml/m^2)	38.83 ± 12.75	37.23 ± 11.78	38.55 ± 15.23	39.81 ± 21.91
E′ (cm/s)	8.00 ± 2.81	7.74 ± 1.97	7.45 ± 1.61	7.33 ± 1.74
E/E′	9.09 ± 4.06	8.76 ± 4.57	9.22 ± 2.63	8.15 ± 1.51
DTe (m/s)	220.65 ± 51.59	213.00 ± 38.08	205.07 ± 25.54	211.67 ± 27.41
RVSP (mmHg)	28.56 ± 7.65	28.23 ± 6.36	29.33 ± 8.10	27.20 ± 6.74[a]
EF (%)	34 ± 8	38 ± 9[a]	29 ± 6	33 ± 6[a]
DD grade 0/I/II/III (*n*)	1/9/4/3	3/10/3/1[a]	0/9/6/0	1/11/3/0

Values are mean ± SD.

[a]$P < 0.05$, significant within-group difference.

DD: Diastolic dysfunction; DTe: Deceleration time of E wave; E': Mean value of the septal and lateral e' of TDI of the mitral annulus; E/A: Ratio of the E and A waves of the transmitral inflow; E/E': Ratio of the E wave to E' wave; EF: Ejection fraction; LAVi: Left atrial volume index; RVSP: Right ventricular systolic pressure; VO_{2peak}: Peak oxygen uptake; W_{peak}: Peak workload.

Belardinelli *et al*[26,27] showed an improvement in DD, after a 2-mo exercise training intervention in HF patients with moderate/severe systolic dysfunction. Similarly, improved LV stiffness[28] and decreased filling pressure[29] have been also reported in other HF trials as a result of exercise training. A meta-analysis of 6 studies, with 144 patients with reduced EF[30], indicated a significant reduction in the ratio E/E' with exercise training. Among them, 3 studies in patients with reduced EF, reported post intervention improvement in all DD grades[31].

The RVSP improvement observed in this study is also in line with previous findings. Mehani *et al*[32] after a 5-mo training program, showed a significant decrease of RVSP by 12.05 mmHg in a group of patients suffering from pulmonary hypertension. Maximal exercise capacity and exercise-triggered symptoms are linked to increased pulmonary capillary pressure and therefore a subsequent increase of left ventricular filling pressure. In this way, filling pressures are directly associated to the LV diastolic function. This point can explain the beneficial reflection of DD improvement on the pulmonary hypertension and the ventilatory limitation of patients with CHF.

In our study, there was not any decrease in the LAVI, an important index in determination of DD. Previous studies showed that left atrial enlargement is an independent marker of adverse outcome in both primary and secondary cardiovascular prevention [33]. Limited data, however, have been reported on the exercise training effects on LAVI in CHF, suggesting conflicting results. Edelmann *et al*[34] reported a significant decrease in LAVI in the training group, while Palau *et al*[35] reported no change in LAVI after interval training. Sandri *et al*[36] also, failed to find a significant change in LA size after 4 wk of training.

A significant improvement in the left ventricular EF (LVEF) was also found in this study. This finding is in line with a recent metanalysis[37], which included trials reporting on LVEF, LV end-diastolic and end-systolic volumes. Overall, AER training improved these parameters. Both continuous and interval regimes were able to induce similar benefits, which may be also affected by the program duration.

Finally, considering the regimes of the exercise applied in this study, overall aerobic and combined regimes improved EF, RVSP, and DD grades. Not any between-group differences were observed. Aerobic training can induce beneficial effects also on skeletal muscles, and continuous aerobic training has been found to reverse partially skeletal myopathy of the HF[38]. Interval exercise training, which was also employed in the present study, can be an effective regime, as it can apply higher exercise stimuli on skeletal muscles *via* a higher exercise intensity[39,40]. Furthermore, strength training has been shown to induce muscle hypertrophy, while the combination of resistance training with aerobic training has the potential to induces greater benefits in

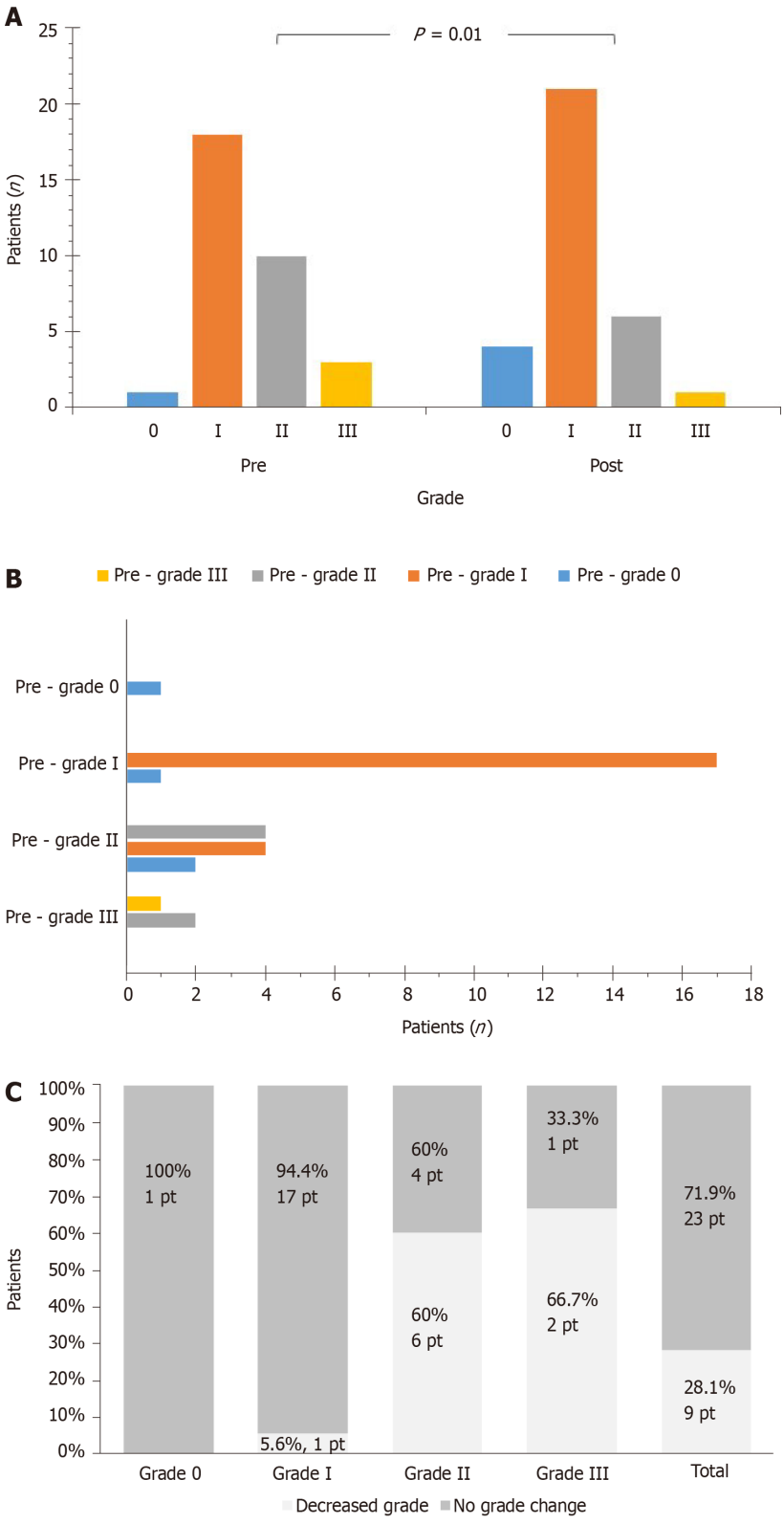

Figure 1 Changes in diastolic dysfunction grades. A: Pre- and post-number of grade-0, -I, -II, -III patients (P = 0.01, as assessed with Wilcoxon signed-rank test); B: Patients' distribution according to pre- and post-level of grade (P = -0.06, as analyzed with McNemar-Bowker test); C: Number of patients that decreased grade or remained at the same grade in relation to baseline grade (P < 0.01, as assessed with χ^2 test).

vascular endothelium[19], muscle strength and aerobic improvement of CHF patients than AER alone[17,18,41]. Interestingly, in a CHF study that employed a combined exercise protocol *vs* control, ventricular stroke volume and left ventricular diastolic indices were improved[28]. The effects of different exercise regimes on the diastolic dysfunction need to be further investigated.

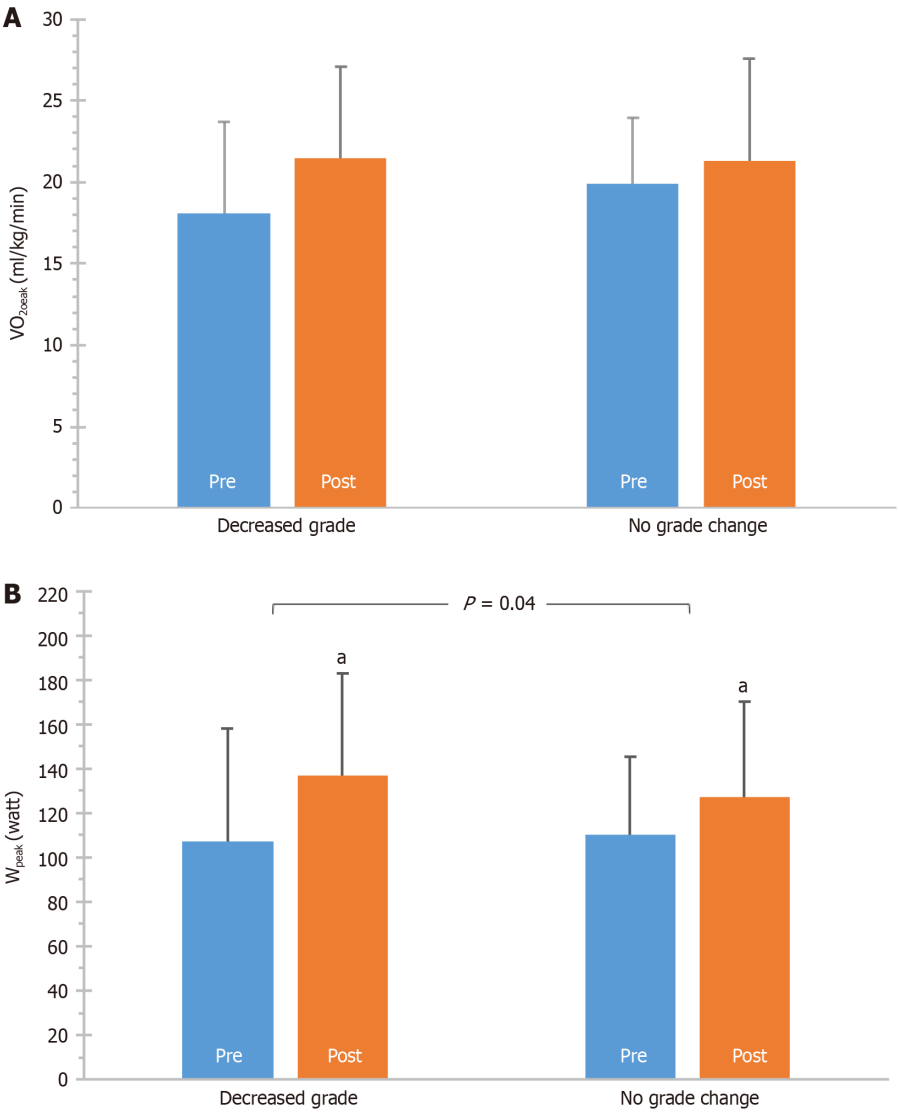

Figure 2 Values of VO_{2peak}(A) and W_{peak}(B) before and after the program for the groups of patients according to DD grade alteration *i.e.* "decreased grade" *vs* "no grade change". $^{a}P < 0.05$, significant within-group difference.

This study had some limitations. First, there is no single non-invasive measure that quantifies the LV diastolic function. Instead, a number of indices are utilized, and current recommendations use a combination of conversional and TDI parameters to determine the diastolic function of the LV[21]. In our study, there was a statistically significant improvement on the DD grades, but other parameters, such as E/A and E/E', were not found to improve. This may be related to the method used to determine the diastolic stage and the sample size. In fact, some results were underpowered to reach definite conclusion. Also, LV diastolic filling patterns as evaluated with transmitral Echo-Doppler are influenced by a variety of factors including valvular insufficiency, myocardium viscoelastic properties, ventricular compliance and loading conditions[21]. However, all patients were under constant medication during the study and all of them had mild degree of mitral regurgitation. Finally, considering that the exercise benefits on CHF have already been well documented, a control group was not employed, and patients randomized in two groups, AER and COM, to explore any potential differences on the diastolic dysfunction.

CONCLUSION

In conclusion, DD plays an essential role in the pathophysiology of the HF syndrome and interventions that improve it can be beneficial in terms of symptoms and outcome. In this study, the effects of an exercise training rehabilitation program (AER with/

without strength training), were evaluated on the indices of diastolic and systolic cardiac function, in stable CHF patients. Exercise training overall induced benefits on the DD as assessed with grades, the EF of the LV, the RVSP and the AER capacity. The exercise protocol was not observed to affect outcomes.

ARTICLE HIGHLIGHTS

Research background

Diastolic dysfunction (DD) of the left ventricular (LV) is a keystone in the pathophysiology of chronic heart failure (CHF). Exercise training in general induces several beneficial effects in CHF patients, including functional capacity, quality of life and clinical outcomes. In this study, the impact of a rehabilitation program on the DD and the ejection fraction (EF) of the LV is evaluated in patients with CHF and EF < 50%.

Research motivation

Exercise training induces several beneficial effects on CHF patients. However, the effects of exercise training on diastolic DD have not been adequately studied. This is also the case for the effects of different exercise regimes on DD.

Research objectives

The main aim of the study was to evaluate the impact of a cardiac exercise rehabilitation program, on the DD and the ejection fraction (EF) of the LV in patients with CHF. A secondary aim was the comparison of an aerobic and combined regimes to explore any potential difference on these indices.

Research methods

In this randomized clinical trial study, 32 patients with CHF were screened for inclusion/exclusion criteria and consented to attend a rehabilitation program and undergo related evaluations. They randomly assigned to aerobic exercise (AER) or combined aerobic and strength training, by a researcher not involved in the rest of the tasks. Before and after the program, they underwent a symptom-limited maximal cardiopulmonary exercise testing (CPET) and serial echocardiography assessment. The researchers performed these evaluations were blinded to participants' allocation.

Research results

Exercise training overall beneficially affected DD grade, right ventricular systolic pressure (RVSP), EF of the LV and AER capacity. No differences between the aerobic and combined group were observed.

Research conclusions

In this study, the effects of an exercise training rehabilitation program (AER with/without strength training) were evaluated on the indices of diastolic and systolic cardiac function, in stable CHF patients. Exercise training overall induced benefits on the DD as assessed with grades, the EF of the LV, the RVSP and the AER capacity. The exercise protocol was not observed to affect outcomes.

Research perspectives

Future research is warranted to further explore the effects of different exercise training regimes on diastolic dysfunction.

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