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EDITORIAL

Development of pulmonary hypertension remains a major hurdle to corrective surgery in Down syndrome

Akash Batta, Juniali Hatwal

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Abstract

Down syndrome is the most common chromosomal abnormality encountered in clinical practice with 50% of them having associated congenital heart disease (CHD). Shunt lesions account for around 75% of all CHDs in Down syndrome. Down syndrome patients, especially with large shunts are particularly predisposed to early development of severe pulmonary hypertension (PH) compared with shunt lesions in general population. This necessitates timely surgical correction which remains the only viable option to prevent long term morbidity and mortality. However, despite clear recommendations, there is wide gap between actual practice and fear of underlying PH which often leads to surgical refusals in Down syndrome even when the shunt is reversible. Another peculiarity is that Down syndrome patients can develop PH even after successful correction of shunt. It is not uncommon to come across Down syndrome patients with uncorrected shunts in adulthood with irreversible PH at which stage intracardiac repair is contraindicated and the only option available is a combined heart-lung transplant. However, despite the guidelines laid by authorities, the rates of cardiac transplant in adult Down syndrome remain dismal largely attributable to the high prevalence of intellectual disability in them. The index case presents a real-world scenario highlighting the impact of severe PH on treatment strategies and discrimination driven by the fear of worse outcomes in these patients.

Key Words: Down syndrome; Congenital heart disease; Pulmonary hypertension; Cardiac transplantation; Pulmonary vascular resistance; Surgical correction

Core Tip: Down syndrome is the most common chromosomal abnormality with roughly half of them having associated congenital heart disease (CHD). People with Down syndrome are especially predisposed to early development of severe pulmonary hypertension (PH) compared with CHDs in general population. It is not uncommon to come across Down syndrome patients with uncorrected shunts in adulthood with irreversible PH at which stage the only option available is a combined heart-lung transplant. However, despite the guidelines laid by authorities, the rates of cardiac transplant in adults with Down syndrome remain dismal largely attributable to the high prevalence of intellectual disability in them.

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INTRODUCTION

Down syndrome is the most common chromosomal abnormality encountered in clinical practice[1]. Congenital heart disease (CHD) is present in roughly half of all people with Down syndrome and remains the leading cause of mortality in this population[2]. Amongst the wide variety of CHDs seen in Down syndrome, shunt lesions in particular atrio-ventricular septal defects and ventricular septal defects are the most frequent accounting for 3/4th of all CHDs in this population[3]. People with Down syndrome especially with large shunts are particularly predisposed to early development of severe pulmonary hypertension (PH) compared with CHDs in general population (10 times higher risk)[4,5]. In patients with Down syndrome and large post-tricuspid shunts, PH is present in up to 1/3rd of them within the first year itself[6,7]. The reason for earlier development of significant PH is attributable to genetic predisposition and associated comorbidities (most notably lung developmental disorders). Another peculiarity is the development of PH even after timely corrective repair of the shunt lesions in some patients with Down syndrome[6]. Thus, screening for PH is an essential component of life-long care in Down syndrome.

Therefore, in Down syndrome early surgical repair is critical in preventing the development of PH which once established significantly increases the procedural risks and prohibits surgical repair. Development of severe and irreversible PH (Eisenmenger syndrome) due to structural changes and fibroses in pulmonary vasculature is associated with high morbidity and mortality in these patients. Guidelines recommend management of shunt lesions in Down syndrome similar to general population, however, early development of severe PH often leads to reluctance on the part of surgeon to go ahead with corrective repair. The reluctance is largely driven by the fear of adverse hemodynamic consequences of severe PH in these patients. Further, limited representation of Down syndrome patients in trials of PH reducing therapies (endothelin antagonists and prostacyclin analogues) makes choice of optimal medical therapy difficult which further contributes to poorer outcomes[8,9].

SURGICAL INTERVENTION IN DOWN SYNDROME WITH CHD

Despite, the high-risk nature of intracardiac repair in Down syndrome, there has been progress over the last few decades and now intracardiac repair is increasingly being offered to this subset of patients[10]. In general, patients with Down syndrome are much younger and have lower body weight at the time of intracardiac repair compared to general population[11]. Overall, the increased perioperative risk and high prevalence of non-cardiac developmental diseases has resulted in lack of enthusiasm amongst pediatric cardiac surgeons to take these patients up for intracardiac repair despite the evidence supporting comparable outcomes of cardiac surgery in these patients[12]. As such, presentation at a later stage with severe PH and shunt reversal is not uncommon[4,5]. At this stage given the pulmonary vascular resistance and irreversible nature of PH, intracardiac repair is contraindicated and the only option available is a combined heart-lung transplant. However, this is easier said than done with dismal rates of transplant procedures being performed in these patients. Since the first report of heart-lung transplant in Down syndrome in 1996 after a national wide anti-discrimination campaign, only a handful of Down syndrome patients have undergone cardiac transplant rendering the assessment of outcomes difficult[13,14]. A major reason for low rates of cardiac transplant in adult Down syndrome remains the high prevalence of intellectual disability in them[7]. Another major concern remains the predisposition of Down syndrome to develop oncological disorders which is further aggravated because of the immunosuppressive agents post-transplant and Epstein-Barr virus infection[15]. Nonetheless, the international society for heart-lung transplant and the committee on bioethics has made clear stance that patients with Down syndrome should be given equal right to transplant listings and that discrimination on the basis of intellectual disability or syndrome is unjustified[13,16].

The recent paper by Kong *et al*[17], appropriately reflects the current practice in regards to the management of Down syndrome with CHD. In the index paper, a 13-year-old boy having a large atrial septal defect and patent ductus arteriosus (PDA), underwent PDA closure in childhood. Despite, this he developed severe PH many years later. This in fact highlights the genetic predisposition to develop that these patients have which is not the case in shunt lesions with normal chromosomal structure. Given the high pulmonary vascular resistance, the boy was denied definitive a procedure (heart-lung transplant) at multiple hospitals possibly due to the fear of worse outcome. This is a reflection of the wide gap

between recommendations and actual clinical practice. As mentioned earlier the governing authorities should provide Down syndrome patients with equal opportunities for heart transplantation, which is in fact is hardly ever the case in real world setting[13,16,18]. The authors deserve credit for their decision to offer heart-lung transplant to the index child albeit it did not materialize on this occasion.

CONCLUSION

Down syndrome with CHD is particularly predisposed to develop severe PH early in the course. Hence, timely surgical correction is crucial to improve long term outcomes. Another oddity in these patients is the development of PH even after successful closure of the shunt lesions which highlights the predisposition to develop pulmonary remodeling and fibroses de novo. The index case highlights the same and also raises concern for the discrimination faced by this group of individuals and preferential exclusion from advanced intervention in the form of heart-lung transplantation despite the opposition to the same by the governing bodies.

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EDITORIAL

Venous Doppler flow patterns, venous congestion, heart disease and renal dysfunction: A complex liaison

Alessio Di Maria, Rossella Siligato, Marta Bondanelli, Fabio Fabbian

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Abstract

The *World Journal of Cardiology* published an article written by Kuwahara *et al* that we take the pleasure to comment on. We focused our attention on venous congestion. In intensive care settings, it is now widely accepted that venous congestion is an important clinical feature worthy of investigation. Evaluating venous Doppler profile abnormalities at multiple sites could suggest adequate treatment and monitor its efficacy. Renal dysfunction could trigger or worsen fluid overload in heart disease, and cardio-renal syndrome is a well-characterized spectrum of disorders describing the complex interactions between heart and kidney diseases. Fluid overload and venous congestion, including renal venous hypertension, are major determinants of acute and chronic renal dysfunction arising in heart disease. Organ congestion from venous hypertension could be involved in the development of organ injury in several clinical situations, such as critical diseases, congestive heart failure, and chronic kidney disease. Ultrasonography and abnormal Doppler flow patterns diagnose clinically significant systemic venous congestion. Cardiologists and nephrologists might use this valuable, non-invasive, bedside diagnostic tool to establish fluid status and guide clinical choices.

Key Words: Cardio-renal syndrome; Fluid overload; Venous congestion; Acute kidney injury; Ultrasound; Doppler flow patterns

Core Tip: Fluid overload and venous congestion, including renal venous hypertension, play a major role in the pathogenesis of acute and chronic renal dysfunction occurring in heart disease. Physical assessment sensitivity alone to determine fluid status is scarce, limiting success in clinical decision-making. Ultrasonography and venous Doppler flow patterns evaluation is a valuable, non-invasive, bedside diagnostic tool for establishing fluid status, and guide its treatment.

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INTRODUCTION

The paper written by Kuwahara *et al*[1] analyzed the relationship between portal vein pulsatility ratio (PVPR) and acute heart failure. The authors calculated the PVPR ratio in the right portal branch of 56 patients hospitalized with acute heart failure and 17 controls and found that reducing PVPR due to improving venous congestion was associated with better outcomes. PVPR was suggested to be a novel prognostic marker for hospitalized patients with acute heart failure.

Interestingly, the mean estimated glomerular filtration rate of the subjects investigated was between 39 and 47 mL/min/1.73 m^2 in the three groups of patients with different PVPR values. The paper does not report whether the patients suffered only acute kidney injury or had an exacerbation of pre-existing chronic kidney disease. It is necessary to underline this problem because the vicious circle between heart and renal disease is a well-known clinical condition[2].

CARDIO-RENAL SYNDROME

The relationship between heart and renal disease is defined as cardio-renal syndrome (CRS), a term describing the complex interactions between heart and kidney dysfunction. CRS is a challenging and evolving field, and more research is needed to understand better the pathophysiology, diagnosis, prevention, and treatment of this complex condition. CRS is classified into five subtypes, depending on the primary organ involved and the acute or chronic nature of the condition [3].

The epidemiology of CRS is not well established, as few prospective studies have assessed the prevalence, incidence, risk factors, and outcomes of different CRS subtypes. However, some estimates suggest that CRS is a common and severe complication of cardiovascular and renal diseases affecting people worldwide[4].

Aging, hypertension, diabetes, obesity, inflammation, oxidative stress, neurohormonal activation, and medications could contribute to the development of CRS. However, the cardiorenal connection is more complex than the hemodynamic model alone; it should be considered the effects of a network including the renin-angiotensin system, the nitric oxide, the reactive oxygen species, the inflammation, the anemia, and the sympathetic nervous system[5,6].

It could be argued that patients enrolled in the Kuwahara *et al*[1] study could be classified as acute or type 1 cardio-renal syndrome. In this clinical condition, acute worsening of heart function causes reduced kidney function. Acute renal dysfunction is diagnosed in 27%-40% of patients hospitalized for acute heart failure[7,8]; this clinical entity leads to higher morbidity and mortality, increasing the duration of admission[9]. Also, in internal medicine units, CRS type 1 is common, especially in elderly patients with stage 3-4 chronic kidney disease[10].

VENOUS CONGESTION ASSESSMENT

Using Doppler modalities during ultrasound investigations, the clinician could assess venous flow patterns relating the signal to the cardiac cycle. In the presence of hemodynamic changes within the systemic venous circulation leading to high venous pressure, venous Doppler profile abnormalities at multiple sites are detected (Figure 1). Clinically significant systemic venous congestion is diagnosed by abnormal Doppler flow patterns. Venous excess ultrasound (VExUS) score was studied in patients assessed with right heart catheterization, and proper atrial pressure was significantly associated with VExUS grade[11]. Organ congestion from venous hypertension could be involved in the development of organ injury in several clinical situations, such as critical diseases, congestive heart failure, and chronic kidney disease[12].

VENOUS CONGESTION IN DIFFERENT CLINICAL CONDITIONS

Fluid overload and venous congestion, including renal venous hypertension, are major determinants of acute and chronic renal dysfunction arising in heart disease[2]. Due to the limitations of traditional methods in evaluating venous congestion, detecting venous Doppler profile abnormalities (at multiple sites) related to elevated venous pressure is becoming very important in clinical assessment, mainly because it can be performed at the bedside[12].

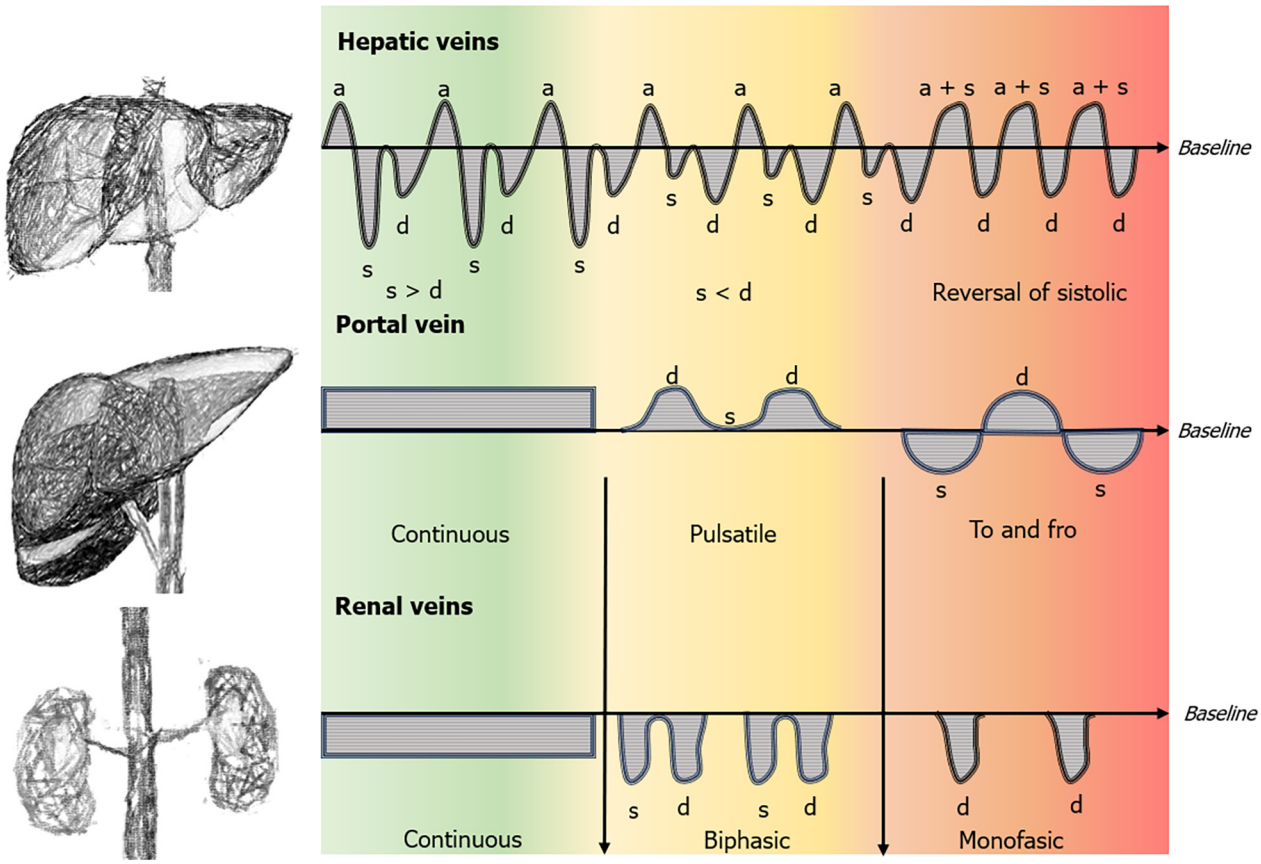

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Figure 1 Venous Doppler profiles detected at multiple sites in normal conditions and in the case of venous and severe venous congestion.

In 2019, Husain-Syed *et al*[13] evaluated 205 subjects with suspected or pre-diagnosed pulmonary hypertension who underwent right heart catheterization. They also evaluated intrarenal venous patterns and concluded that the renal venous stasis index could predict the development of right heart failure.

In 2020, Spiegel *et al*[14] compared the morphology of hepatic veins, portal veins, and intra-renal veins waveform abnormalities VExUS for predicting major kidney events at 30 d in 114 adult patients admitted to an intensive care unit. They found that significant kidney events at 30 d were associated with abnormalities in hepatic and portal venous Doppler.

Severe venous congestion shown by flow abnormalities in Doppler patterns was associated with acute kidney injury (AKI) in 145 patients who underwent cardiac surgery. VExUS grade outperformed central venous pressure measurements[15].

Inferior vena cava and hepatic vein waveform, and portal vein pulsatility were investigated aiming at determining VExUS, in thirty CRS patients aged 59 years in order to evaluate the association between fluid overload and AKI. Authors found that improved renal function was related to improvement in VExUS grade[16].

Argaiz *et al*[17] suggested that in patients with acute left heart failure, the normalization of the size of the inferior vena cava, the restoration of its collapsibility, and the improvement of portal vein flow were related to the decrease in serum creatinine levels.

Hermansen *et al*[18] conducted a prospective, observational study to assess the connection between Doppler signals of renal perfusion and the development of AKI. Abnormal renal venous flow pattern on the first postoperative day and portal vein pulsatility fraction were associated with severe AKI development.

During 2023, at least four papers investigated the relationship between AKI and venous congestion. After cardiac surgery, abnormalities in intra-renal venous flow, portal vein pulsatility fraction, hepatic vein flow patterns, and central venous pressure were associated with the development of AKI[19]. In a prospective study evaluating subjects suffering from acute coronary syndrome, the increasing degree of VExUS was associated with AKI[20].

Patients admitted to intensive care units with a VExUS score greater than one were treated with diuretics more frequently than those with a VExUS score equal to or lower than 1. Moreover, subjects showing decreasing VExUS scores had more renal replacement therapy-free days in 28 d[21].

On the other hand, Andrei *et al*[22] could not detect any association between VExUS score and AKI and 28-d mortality.

CONCLUSION

Chronic kidney disease increases the risk of death during hospitalization in several clinical conditions, such as myocardial infarction[23], chronic obstructive pulmonary disease[24], stroke[25], and CRS[26]. Some of the strategies that may be beneficial in order to improve outcomes include optimizing fluid balance, reducing congestion, improving hemodynamics, preserving renal perfusion, preventing or treating acute kidney injury, and using cardioprotective and renoprotective drugs. Managing kidney failure and different clinical conditions, particularly those involving the heart, requires a multidisciplinary approach that addresses the underlying causes and the specific features of each subtype. Cardiologists and nephrologists should correctly manage the complex fluid problem due to its centrality in everyday clinical practice. Physical assessment sensitivity alone to determine fluid status is scarce, limiting success in clinical decision-making. Ultrasonography and venous Doppler flow pattern evaluation are valuable, non-invasive, bedside diagnostic tools for establishing fluid status and guiding the treatment of venous congestion[27].

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MINIREVIEWS

Unveiling the silent link: Normal-tension glaucoma's enigmatic bond with cardiac blood flow

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Abstract

This comprehensive review embarks on a captivating journey into the complex relationship between cardiology and normal-tension glaucoma (NTG), a condition that continues to baffle clinicians and researchers alike. NTG, characterized by optic nerve damage and visual field loss despite normal intraocular pressure, has long puzzled clinicians. One emerging perspective suggests that alterations in ocular blood flow, particularly within the optic nerve head, may play a pivotal role in its pathogenesis. While NTG shares commonalities with its high-tension counterpart, its unique pathogenesis and potential ties to cardiovascular health make it a fascinating subject of exploration. It navigates through the complex web of vascular dysregulation, blood pressure and perfusion pressure, neurovascular coupling, and oxidative stress, seeking to uncover the hidden threads that tie the heart and eyes together in NTG. This review explores into the intricate mechanisms connecting cardiovascular factors to NTG, shedding light on how cardiac dynamics can influence ocular health, particularly in cases where intraocular pressure remains within the normal range. NTG's enigmatic nature, often characterized by seemingly contradictory risk factors and clinical profiles, underscores the need for a holistic approach to patient care. Drawing parallels to cardiac health, we examine into the shared vascular terrain connecting the heart and the

eyes. Cardiovascular factors, including systemic blood flow, endothelial dysfunction, and microcirculatory anomalies, may exert a profound influence on ocular perfusion, impacting the delicate balance within the optic nerve head. By elucidating the subtle clues and potential associations between cardiology and NTG, this review invites clinicians to consider a broader perspective in their evaluation and management of this elusive condition. As the understanding of these connections evolves, so too may the prospects for early diagnosis and tailored interventions, ultimately enhancing the quality of life for those living with NTG.

Key Words: Normal tension glaucoma; Vascular dysregulation; Ocular blood flow; Blood pressure; Perfusion pressure; Oxidative stress

Core Tip: Cardiovascular disease and glaucoma may appear unrelated at first glance, but recent research suggests a potential link between the two seemingly distinct health issues. This review delves into the complex interplay of vascular dysregulation, blood pressure, perfusion pressure, neurovascular coupling, and oxidative stress. Furthermore, certain medications frequently prescribed for managing cardiovascular disease and high blood pressure, such as beta-blockers, may influence blood flow to the eyes. This, in turn, could potentially increase the risk of glaucoma in some individuals. This research highlights how cardiac dynamics can impact ocular health, even when intraocular pressure remains within the normal range.

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INTRODUCTION

Cardiovascular disease and glaucoma may appear unrelated at first glance, but recent research suggests a potential link between the two seemingly distinct health issues. Glaucoma is a progressive optic neuropathy with an unknown origin. There's a hypothesis suggesting that vascular factors play a role in glaucoma's pathophysiology. This review delves into the complex interplay of vascular dysregulation, blood pressure, perfusion pressure, neurovascular coupling, and oxidative stress. These factors may have significant roles in connecting the cardiovascular system with the eyes, especially in normal-tension glaucoma (NTG). Furthermore, certain medications frequently prescribed for managing cardiovascular disease and high blood pressure, such as beta-blockers, may influence blood flow to the eyes. This, in turn, could potentially increase the risk of glaucoma in some individuals. This research highlights how cardiac dynamics can impact ocular health, even when intraocular pressure remains within the normal range.

THE VASCULAR WEB OF NTG

Exploring the intricacies of normal tension glaucoma, we delve into the 'Vascular Web' that underlies this condition, where ocular blood flow, perfusion pressure, and autonomic control come together. In the complex vascular system of NTG, a study revealed asymmetric visual field damage despite stable intraocular pressure. Using color Doppler imaging, the study confirmed that retrobulbar vascular dysregulation significantly contributes to glaucoma progression, particularly in normal tension glaucoma patients with progressive visual field damage. Vascular dysregulation, the inadequate regulation of blood flow for tissue needs, includes primary vascular dysregulation (PVD, formerly called vasospastic syndrome) and secondary vascular dysregulation. In subjects with PVD, retinal vessels are stiffer and more irregular, and both neurovascular coupling and autoregulation capacity are reduced while retinal venous pressure is often increased. Asymmetric glaucomatous damage was associated with lower retrobulbar hemodynamics in the eye with more advanced damage, highlighting the role of vascular factors in the progression of glaucoma[1,2]. In a four-year prospective study involving glaucoma patients, systemic vascular abnormalities significantly impacted glaucoma progression, even with well-controlled intraocular pressure. Patients with vascular comorbidities had a substantial likelihood of glaucoma deterioration, highlighting the importance of comprehensive patient management beyond intraocular pressure control[3]. In a study on vascular factors in NTG within a South Indian population, assessments included medical histories, blood pressure, lipid profiles, intraocular pressure (IOP), and central corneal thickness. Perimetry was conducted to assess visual field defects. The results highlighted a significant association between diastolic perfusion pressure and visual field defects, emphasizing the relevance of vascular factors in NTG progression. Hypertension emerged as a notable risk factor in NTG, reinforcing the pivotal role of vascular considerations in understanding this condition[4].

Various studies have demonstrated reduced blood flow in ocular and systemic vessels observed in glaucoma, leading to dysregulation. This can result in overperfusion or underperfusion, inducing oxidative stress through unstable perfusion cycles. PVD affects autoregulation, contributing to glaucomatous optic neuropathy (GON). Systemic vascular dysregulation leads to sustained reduction in ocular blood flow, affecting the choroid and optic nerve head. Overall, vascular dysregulation plays a significant role in the progression of GON[5]. In understanding the development and progression of NTG, it's crucial to acknowledge multi-level circulation-related pathologies. Early-stage NTG patients exhibit subclinical vascular abnormalities at both macro- and micro-vascular levels. This includes altered retinal vascular responses to flickering light, enhanced arterial constriction, reduced venous dilation, increased carotid intima-media thickness, and an elevated pulse wave analysis augmentation index. These findings emphasize the complex interplay of vascular factors in the early stages of NTG, providing insights for comprehensive diagnostic and therapeutic approaches [6].

THE BLOOD PRESSURE FACTOR

The Skrzypecki *et al*'s study explores in detail, the complex relationship between arterial blood pressure (ABP), IOP, and the risk of glaucoma[7]. It suggests that both low and high ABP levels may impact optic nerve health, but evidence-based guidelines for managing ABP in glaucoma patients are lacking. Notably, hypertension trials, such as the SPRINT study, have not included eye-related endpoints, missing an opportunity to investigate the effect of intensive ABP reduction on glaucoma progression and optimal antihypertensive medications. The concept of ocular perfusion pressure (OPP) is introduced to better understand the relationship between low ABP and glaucoma progression. OPP is defined as the difference between systolic blood pressure or diastolic blood pressure and IOP[7]. A number of studies have shown that a reduced OPP and increased fluctuation of OPP are risk factors for glaucoma progression. Retinal venous pressure (RVP), which refers to the blood pressure within the veins of the retina, has been commonly presumed to be equivalent to IOP in most of these studies. Meanwhile, it has been shown that in the majority of glaucoma patients, RVP is far above IOP therefore, the OPP in such cases is much lower than was previously assumed. High RVP reduces the OPP and therefore reduces circulation of both the retina and the optic nerve head (ONH). The reduction of ONH perfusion contributes to glaucomatous damage[8].

Blood pressure fluctuations play a significant role in normal-tension glaucomatous optic neuropathy. Two studies emphasize the importance of 24-h ambulatory blood pressure monitoring. The first study by Melgarejo found a strong association between blood pressure variability, particularly in mean arterial pressure readings, and the risk of GON, independent of blood pressure levels. The second study by Plange observed that patients with NTG had higher night-time diastolic and mean arterial blood pressure values and increased variability in night-time blood pressure. This increased blood pressure fluctuation may contribute to ocular perfusion pressure variations and potential ischemic episodes at the optic nerve head, linking blood pressure variability to NTG[9,10].

A recent prospective study investigated ambulatory fluctuations in IOP and blood pressure (BP) in patients with NTG. The study uncovered that many NTG patients displayed signs of vascular dysregulation, including systemic hypertension, reduced night time BP drop, and a morning BP surge. This highlights the importance of considering these vascular factors in NTG. These findings emphasize the importance of considering BP fluctuations in the context of NTG, shedding light on the broader vascular implications in glaucoma pathogenesis[11].

THE SIGNIFICANCE OF BLOOD FLOW IN NORMAL-TENSION GLAUCOMA

Two principal theories for the pathogenesis of GON have been described - a mechanical and a vascular theory. Both have been defended by various research groups over the past 150 years. The mechanical theory of glaucoma links optic nerve damage to increased IOP. However, the vascular theory suggests that GON arises from insufficient blood supply, either due to elevated IOP or other factors reducing ocular blood flow. While conditions like congenital or angle-closure glaucoma demonstrate IOP's role in GON, NTG challenges this pressure-centric view. Numerous studies in NTG patients highlight reduced ocular perfusion compared to normal subjects, implying factors beyond pressure may contribute significantly to NTG's development[12]. The exact mechanisms connecting cardiovascular disease, blood pressure, and glaucoma remain the subject of ongoing investigation. One prevailing theory is that these conditions share a common denominator: Blood vessels. Alterations in blood vessels are central to both cardiovascular disease and glaucoma. Studies indicate that glaucoma patients exhibit reduced ocular blood flow biomarkers, especially peak systolic velocity and mean flow velocity, linked to lamina cribrosa deformation. However, glaucoma suspects with similar lamina cribrosa shapes did not show this correlation, revealing a complex relationship between ocular blood flow and lamina cribrosa morphology. Vascular factors play a vital role in NTG and related conditions. Abnormal ocular blood flow detected through various imaging techniques is associated with glaucomatous optic neuropathy. Systemic disorders like migraine, systemic hypotension, Alzheimer's disease, primary vascular dysregulation, and Flammer syndrome contribute to NTG progression. Flammer syndrome, describes a phenotype characterized by primary vascular dysregulation, involves various symptoms triggered by stimuli like cold or stress. Nearly all organs, particularly the eye, can be involved. While it has protective aspects against conditions like atherosclerosis, it's also associated with diseases such as NTG[13]. Mechanisms of abnormal ocular blood flow include oxidative stress, vasospasm, and endothelial dysfunction, impacting mitochondrial function in the optic nerve head. Improving ocular blood flow may offer neuroprotective benefits in addition to lowering IOP in glaucoma treatment[14,15]. Optic nerve blood flow responses to perfusion pressure changes

were examined in individuals with NTG and controls. The study indicated no significant changes in the optic nerve blood flow in either group, but NTG patients showed a trend towards increased vascular resistance compared to controls, suggesting potential alterations in vessel tone regulation mechanisms, shedding light on the pathophysiology of NTG, which requires further investigation[16].

EXPLORING THE CONNECTION; GLAUCOMA AND SYSTEMIC FACTORS

In the realm of glaucoma, systemic factors significantly influence its development. Diabetes and elevated blood sugar levels could affect lipid metabolism, raising oxidative stress and cell apoptosis, resembling mechanisms in glaucoma-related retinal cell loss. Alterations in diabetes-related connective tissue might impact both the lamina cribrosa and potentially the trabecular meshwork, possibly influencing optic nerve biomechanics and fluid drainage, potentially raising the risk of glaucoma[17]. Diabetic retinopathy (DR) and hypertension are pivotal risk factors. Proliferative diabetic retinopathy can lead to neovascular glaucoma (NVG) with a sudden IOP surge. Hypertension raises glaucoma risk through central retinal vein occlusion, a precursor to NVG. Hypotension increases the risk to the optic nerve, causing ischemic injury and higher glaucoma risk. Carotid-cavernous fistulas disrupt IOP dynamics. The primary vascular dysregulation syndrome, often accompanied by systemic hypotension, disrupts the autoregulation of ocular blood flow. This vascular abnormality and associated autonomic dysfunction can lead to oxidative stress in glaucomatous neuropathy. Understanding these connections highlights the multifaceted nature of glaucoma and potential therapeutic interventions[18,19]. In the 2010-2012 KNHANES Survey, we used the Framingham risk score to assess the association between glaucoma and cardiovascular diseases. Regardless of the glaucoma subtype, individuals with glaucoma showed a significantly higher 10-year risk of general cardiovascular disease compared to the control group. This indicates an increased susceptibility to cardiovascular events in glaucoma patients, emphasizing the positive interplay with compromised autoregulatory capacity[20].

The examination of autonomic dysfunction, assessed through heart rate variability (HRV) as a possible factor contributing to the reduction of mean ocular perfusion pressure (MOPP), is a notable focus in two studies. These studies shed light on autonomic dysfunction and HRV in glaucoma, including NTG. Both high tension glaucoma and NTG patients exhibited reduced MOPP and lower diastolic blood pressure. HRV assessments indicated increased sympathetic innervation in glaucoma patients, particularly during a stress test, revealing autonomic disturbance in NTG patients. This disturbance is closely tied to ocular blood flow dynamics and structural damage[21,22]. Elevated sympathetic neural activity raises vascular resistance, particularly in cases of endothelial dysfunction, impacting glaucoma development. Blood supply to different organs or vascular beds is regulated by the vascular endothelium. Endothelial dysfunction can lead to inadequate organ perfusion due to vascular dysregulation, especially in individuals with a predisposition. This may result in characteristic vascular -mediated diseases such as normal-tension glaucoma[23].

MEDICATIONS AND EYE HEALTH

Certain medications have been postulated to increase the risk of development of glaucoma. Studies suggest that both high and low blood pressure can elevate the risk of developing glaucoma. While the precise mechanisms behind this connection remain unclear, it is believed to involve pathological changes in blood vessels, which are relevant in both cardiovascular disease and glaucoma. Two studies suggest a connection between cardiovascular medications and glaucoma. Commonly used medications for cardiovascular health and hypertension such as Beta-blockers, may influence blood flow to the eyes, potentially increasing the risk of glaucoma. All β-blockers lower IOP *via* inhibition of β2-adrenoceptors present on the ciliary epithelium, thus reducing aqueous humor flow. Beta-blockers can be classified into non-selective and selective types based on their affinity for β1 and β2 receptors. Non-selective β-blockers like propranolol block both β1 and β2 receptors, affecting not only the eye but also other organs like the heart and lungs. Selective β-blockers, such as betaxolol, predominantly target β1 receptors and have a lesser impact on β2 receptors in comparison to non-selective blockers (Table 1)[24].

Calcium channel blockers (CCBs) were also linked to higher glaucoma prevalence, but the causal relationship remains unclear. For glaucoma patients on systemic antihypertensive medications, these findings have important implications. A differentiation is necessary between normal doses for arterial hypertension and the significantly smaller doses used for treating vascular dysregulation. This distinction is vital considering that very low doses are employed, which minimally impact BP. CCB may have negligible BP-lowering effects in individuals with already low BP. Despite individuals with Flammer syndrome often having lower BP, some may develop high BP with age. In such instances, a cautious approach with a low-dose CCB in antihypertensive treatment is recommended[25,26].

CONCLUSION

Intriguing as this research may be, there is much yet to be uncovered regarding the relationship between cardiovascular disease, blood pressure, and the development and progression of glaucoma. NTG is not solely an IOP-dependent condition; vascular dysregulation, systemic comorbidities, and blood pressure variability contribute significantly, reduced blood flow to the optic nerve head potentially leading to ischemia and optic nerve damage, even in cases with

Table 1 Table showing the medication impact on glaucoma risk and mechanisms

Medication	Impact on glaucoma risk
Beta-blockers	Influence blood flow to the eyes, potentially increasing glaucoma risk
	Lower intraocular pressure *via* inhibition of β2-adrenoceptors on ciliary epithelium, reducing aqueous humor flow
	Non-selective β-blockers (*e.g.*, propranolol) affect β1 and β2 receptors, impacting multiple organs including the eye, heart, and lungs
	Selective β-blockers (*e.g.*, betaxolol) primarily target β1 receptors, with a lesser impact on β2 receptors
CCB	CCB may have negligible BP-lowering effects in individuals with already low BP
	In Flammer syndrome, some may transition from low to high blood pressure with age, prompting the use of low-dose CCBs for hypertension treatment

BP: Blood pressure; CCB: Calcium channel blocker.

apparently normal IOP. As further research unravels the intricate connections between these seemingly disparate health issues, individuals with a history of cardiovascular disease and varying blood pressure levels need to remain vigilant about their eye health. By elucidating subtle clues and potential associations between cardiology and NTG, we open the door to improved early diagnosis and tailored interventions, ultimately enhancing the quality of life for individuals living with NTG. Medications for cardiovascular health, including beta-blockers, may influence blood flow to the eyes and potentially increase the risk of glaucoma. Further research will provide invaluable insights into this complex relationship, potentially leading to enhanced prevention and treatment strategies.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Do changes in intracoronary pressure aid coronary spasm diagnosis using the spasm provocation test?

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Abstract

BACKGROUND

Although the spasm provocation test (SPT) can diagnose coronary spasms, it would be helpful if it could also predict their occurrence.

AIM

To investigate whether coronary spasms can be predicted using changes in intracoronary artery pressure measured using a pressure wire during the SPT.

METHODS

Seventy patients underwent SPTs with pressure-wire measurement of intracoronary artery pressure. During each SPT, the pressure wire was advanced into the distal portion of the right coronary artery (RCA) and left anterior descending coronary artery, and the ratio of intracoronary pressure to aortic pressure (Pd/Pa) was monitored. Coronary spasm was defined as an arterial narrowing of > 90% in response to the administration of acetylcholine (ACh), with chest symptoms and/or ischemic electrocardiographic changes. ACh was administered to the RCA at low, moderate, or high doses of 20, 50, or 80 μg, respectively, and to the left coronary artery (LCA) at low, moderate, or high doses of 50, 100, or 200 μg, respectively. Coronary arteries with coronary spasms at low doses of ACh were defined as group L, and those with coronary spasms at moderate or high doses were defined as group MH. Those who did not occur coronary spasms at any ACh dose were designated as group N.

RESULTS

Among the 132 coronary arteries assessed using a pressure wire, there were 49 in group N, 25 in group L, and 58 in group MH. Baseline Pd/Pa was the lowest in group L ($P = 0.001$). The decrease in the Pd/Pa between baseline to low doses of ACh was lower in group MH than in group N ($P < 0.001$). A receiver-operating characteristics analysis showed that the cutoff baseline Pd/Pa value for predicting group L was 0.95, with a sensitivity of 0.600 (15/25) and a specificity of 0.713

(76/107) and that the cutoff value of Pd/Pa from baseline to low doses of ACh for predicting group MH was −0.04, with a sensitivity of 0.741 (43/58) and a specificity of 0.694 (34/49).

CONCLUSION
These findings suggest that indices of intracoronary pressure during SPT may be useful means for predicting the occurrence of coronary spasms.

Key Words: Acetylcholine; Coronary spasm; Intracoronary pressure; Pressure wire; Spasm provocation test; Vasospastic angina

Core Tip: The spasm provocation test (SPT) is a well-established tool for diagnosing coronary spasms. However, it is associated with several complications that can make the test a stressful experience. We investigated whether coronary spasms detected in the SPT can be estimated using intracoronary artery pressure measured with a pressure wire. We found that coronary spasms induced by low acetylcholine doses were associated with decreased intracoronary pressure at baseline. Coronary spasms induced by moderate-to-high acetylcholine doses showed decreased intracoronary pressure from baseline to low acetylcholine doses. These indices of intracoronary pressure may be used to predict coronary spasms.

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INTRODUCTION

Vasospastic angina (VSA) is a condition in which transient vasoconstriction of the epicardial coronary arteries causes myocardial ischemia[1-4]. In recent years, VSA, angina with nonobstructive coronary artery disease (ANOCA)[5,6], and myocardial infarction with nonobstructive coronary artery (MINOCA)[7] have attracted increasing research attention. A diagnosis of VSA is made when transient electrocardiographic changes are observed in addition to typical anginal pain [8]. However, in actual clinical practice, electrocardiographic changes cannot always be detected[9,10] and the final diagnosis of VSA is made by performing a spasm provocation test (SPT).

In SPT, acetylcholine (ACh) or ergonovine maleate are used as provocative drugs. ACh is usually administered in small, gradual doses[6,11]. The physical response to this allows the diagnosis of VSA based on chest symptoms, electrocardiographic changes, and significant coronary vasoconstriction. However, VSA and/or SPT-related complications have also been reported to occur[12,13]. It is undeniable that SPT can be stressful, even for the person performing the test. Therefore, if the cardiologist performing the SPT can predict that coronary spasm will occur with the next provocation, they can respond quickly. The ability to predict coronary spasm during the test would be highly useful and allow both practical and mental preparation.

In some cases, coronary spasm tests are performed after evaluation of coronary microcirculatory dysfunction (CMD) [14,15]. In such cases, the SPT is often performed with a pressure wire in place. In our previous research, we demonstrated the utility of measuring changes in intracoronary pressure using a pressure wire during SPTs for the diagnosis of VSA or assessment of VSA status[16]. In the present study, we investigated whether spasm provocation could be predicted by changes in intracoronary pressure measured using a pressure wire.

MATERIALS AND METHODS

Study patients

This observational retrospective study included patients who underwent coronary angiography (CAG) and the SPT using a pressure wire at our institution between January 2012 and August 2015 (n = 79). The exclusion criteria were as follows: Significant coronary stenosis (% stenosis > 50%, n = 5) or a history of percutaneous coronary intervention (n = 4). Finally, 70 patients (mean age, 68 years; 36 men, 34 women) were enrolled (Figure 1). The study protocol was approved by the ethics committee of our institution, No. 2023-11. Written informed consent was obtained from all participants for SPT. The opt-out method (http://www.jrhh.sakura.ne.jp/annnai/torikumi.html) was used to confirm final agreement to participate.

CAG and SPT using a pressure wire

The SPT procedure has previously been described[16]. Coronary vasodilators were withdrawn at least 48 h before each SPT. Subsequently, the SPT was performed on the right coronary artery (RCA). After the initial CAG, a 5-Fr catheter was

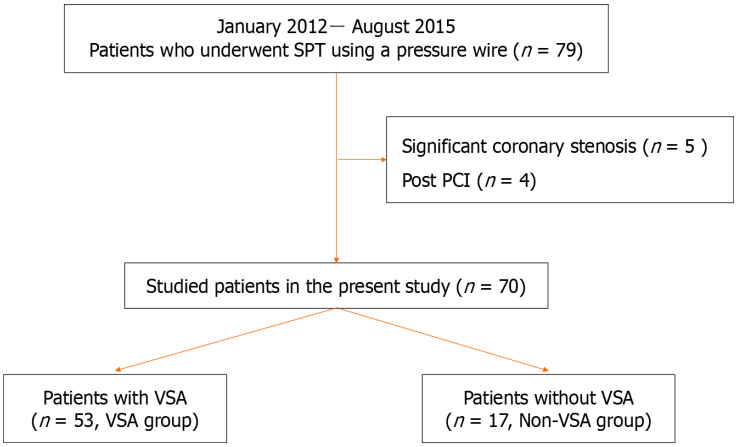

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Figure 1 Flowchart of the present study. PCI: Percutaneous coronary intervention; SPT: Spasm provocation test; VSA: Vasospastic angina.

used to insert a 0.014-inch pressure wire (PrimeWire Prestige Plus guidewire or Verrata Pressure guidewire; Phillips Volcano, Amsterdam, Holland) into the distal part of the RCA. The pressure between the catheter tips and pressure wire was previously calibrated at the ostium of the coronary arteries. The ratio of distal intracoronary pressure (Pd) detected by the pressure wire to the proximal intracoronary pressure (Pa) detected by the catheter tips was continuously monitored using the Pd/Pa indices. Then, an injection of 20 μg was made into the RCA, followed by another of 50 μg. If 50 μg ACh failed to induce coronary spasm, an 80 μg of ACh was injected. When the Pd/Pa index dropped during a coronary spasm, the lowest Pd/Pa value in response to each ACh dose was recorded, as were the Pd/Pa values immediately prior to the angiogram. CAG was performed after coronary spasm or maximum ACh infusion. When coronary spasms occurred but disappeared on their own without intracoronary 0.3 mg nitroglycerin (NTG) injection into the RCA, SPT of the left coronary artery (LCA) was performed. In such cases, NTG was injected into the RCA and, after completion of the LCA SPT, CAG was performed once more. If coronary spasms were prolonged or severe enough to result in hemodynamic instability, an intracoronary NTG injection was administered to treat them. SPT was subsequently performed on the LCA. A pressure wire was introduced into the distal segments of the left anterior descending coronary artery (LAD) during the LCA SPT, following the second pressure calibration at the LCA ostium. Similar to the RCA SPT, the LCA was infused with ACh doses. In the LCA test, the ACh doses were 50 and 100 μg, followed by 200 μg if the previous doses did not induce a coronary spasm. Following the commencement of a coronary spasm or the maximum ACh infusion, whichever came first, CAG was administered. A 0.3 mg NTG intracoronary injection and the last CAG for the LCA were then performed. According to this study, the appropriate low, moderate, and high ACh dosages for the RCA and LCA were 20, 50, and 80 μg and 50, 100, and 200 μg, respectively. Since the number of spasm-positive cases at high doses was not large, we divided the lesions into three groups: Group N consisted of lesions that did enter the coronary spasm, group L consisted of lesions in which coronary spasm was induced by the lowest dose of ACh, and group MH consisted of lesions in which coronary spasm was induced by the moderate or high-dose ACh.

When the Pd/Pa index decreased during a coronary spasm, the data immediately before the angiogram were used instead of the minimal Pd/Pa index in response to each ACh dose. The minimal Pd/Pa at low doses of ACh minus the Pd/Pa at baseline was used to define the difference in the Pd/Pa at low doses of ACh. When a PrimeWire Prestige Plus guidewire was available, the instantaneous free-wave ratio (iFR) was assessed immediately before ACh administration. The usual technique for the intravenous administration of adenosine triphosphate was used to test the fractional flow reserve (FFR) in patients with coronary atherosclerosis. We employed an autoinjector using a previously described method[16]. The diameter of the coronary artery was measured. Atherosclerotic lesions were defined as those with between a stenosis between 20% and 50%.

Definitions of VSA-related parameters

There are three categories of angina pectoris activity: Resting, exertion, and combined rest and exertion. When induced, VSA was defined as > 90% constriction of the coronary arteries as measured by angiogram, along with typical chest symptoms and/or an ST-segment deviation on electrocardiogram[6]. Those who had a coronary spasm in at least one major coronary artery were classified as the VSA group, and those who had no spasms in any coronary artery as the non-VSA group. Based on the classifications of the American Heart Association (AHA), focal spasms are defined as temporary arterial narrowing of more than 90% that remains within the boundaries of a single isolated coronary segment[17]. Diffuse vasoconstriction is defined by the AHA as > 90% arterial narrowing in two coronary artery segments[17]. The coronary spasm endotype observed in the RCA and LCA of each patient can differ. Coronary spasms that affect more than two major coronary arteries are referred to as multivessel spasms. We were unable to identify multivessel spasms in cases in which the unavoidable use of NTG was followed by a negative SPT. Each coronary artery at the site of the coronary spasm was separated into three sections (proximal, mid, and distal) for lesion studies, and the central area of the coronary spasm was labeled as diffuse.

Other clinical characteristics measured

Patient information was collected regarding current and former smoking habits and alcohol consumption, family history of coronary artery disease (CAD)[16], and comorbid hypertension, dyslipidemia, diabetes mellitus, or chronic kidney disease (CKD), all defined using the accepted criteria[16,18-20]. Using cardiac ultrasonography (UCG), the left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's method. Flow-mediated dilation (FMD), endothelium-dependent function, endothelium-independent function, and NTG-induced dilation (NID), were also measured and recorded in the majority of the patients (n = 62)[16,21].

Statistical analyses

For nonnormally distributed data and noncontinuous variables, data were presented as mean and SD or median and interquartile range. Student's unpaired t-tests, Wilcoxon signed-rank tests, or 2 analyses were used for between-group comparisons of variables at baseline. The causes of coronary spasms caused by low-dose or moderate-to-high doses of ACh were identified using logistic regression analyses. Optimal cutoff values were determined using receiver-operating characteristic (ROC) analyses. JMP version 17 was used to perform statistical analyses (SAS Institute Inc., United States). Statistical significance was set as P values < 0.05.

RESULTS

Characteristics of patients in the VSA and non-VSA groups

There were 53 patients (76%) in the VSA group and 17 patients (24%) in the non-VSA group. Patient characteristics are summarized in Table 1. There were no significant differences in age, body mass index, coronary risk factors, alcohol consumption, smoking, family history of CAD, or CKD between the two groups, but there were significantly more males in the VSA group than in the non-VSA group (P = 0.001). UCG showed no significant difference in LVEF. Brachial artery ultrasonography showed no difference in brachial artery diameter at baseline between the two groups; however, in the VSA group, FMD was significantly lower (P = 0.008) and NID tended to be lower (P = 0.061). Coronary vasodilator use, which was stopped at least 48 h before the SPT, was clearly lower in the VSA group (P = 0.018), but no differences were observed for other medications.

Changes in intracoronary pressure with coronary spasms and ACh

In most patients, a pressure wire was inserted into the RCA and LAD. However, eight coronary vessels were excluded. This was because the RCA was too small to perform the SPT (n = 2), the catheter could not engage into the RCA (n = 2), the pressure wire could not be inserted into the distal portion of RCA due to meandering (n = 3), or the pressure wire could not be inserted into the LAD (n = 1). Thus, a pressure wire was inserted into the remaining 132 coronary vessels, including 63 RCA and 69 LAD.

Coronary spasms were induced by low, moderate, and high doses of ACh in 25, 51, and 7 vessels, respectively. No coronary spasms occurred in the remaining 49 vessels (group N). In seven vessels, spasms were induced by the high dose but were insufficient to clarify the statistical results. Thus, as described in the Methods, vessels in which coronary spasms were induced by moderate and high doses of ACh were combined into group MH. There were 49 vessels in group N, 25 in group L, and 58 in group MH. The lesion characteristics are listed in Table 2. There were no differences between the RCA and LAD in coronary vessels, in the rate of atherosclerosis, or in the unavoidable need for NTG administration. There was no difference between group L and MH in whether induced coronary spasms were focal or diffuse (P = 0.456) and whether the coronary arteries were proximal, mid, or distal (P = 0.610). We found no significant differences in iFR (P = 0.104) or FFR (P = 0.093) among the three groups. The Pd/Pa values at baseline were the lowest in group L (P = 0.001) (Figure 2). The Pd/Pa value at low doses of ACh was lowest in group L and highest in group N (Figure 3A). The difference between baseline and low-dose ACh was lowest in group L and highest in group N (Figure 3B). Pd/Pa at moderate-to-high doses of ACh was significantly lower in group MH than in N (P < 0.001).

Predictions of coronary spasms at low and moderate-high doses of ACh were made based on Pd/Pa at baseline and changes in Pd/Pa.

In univariate analysis, the only significant indicator of coronary spasm induced by low doses of ACh was Pd/Pa at baseline (P = 0.002). Pd/Pa at baseline was negatively correlated with LAD (P < 0.001) and the presence of atherosclerosis (P = 0.030). Logistic regression analysis of positive SPT at the low dose of ACh, using Pd/Pa at baseline, the LAD, and the presence of atherosclerosis found Pd/Pa at baseline was the only significant predictor (P = 0.003). ROC analysis showed an area under the curve (AUC) of 0.688 and a cutoff Pd/Pa at baseline of 0.95 for predicting the induction of coronary spasm by low doses of ACh (group L), with sensitivity and specificity of 0.600 (15/25) and 0.713 (76/107), respectively (Figure 4A). In an analysis of the 107 Lesions in group N and MH, the factors that predicted the induction of coronary spasms by moderate or high doses of ACh were Pd/Pa at baseline (P = 0.019, AUC 0.626), Pd/Pa at low doses of ACh (P < 0.001, AUC 0.739), and the ΔPd/Pa from baseline to low ACh dose (P < 0.001, AUC 0.742). ΔPd/Pa, which had the highest AUC, did not correlate with the presence of atherosclerosis (P = 0.141) or with the LAD (P = 0.393). ROC analysis showed that the optimal ΔPd/Pa from baseline to the low dose of ACh was −0.04, with a sensitivity of 0.741 (43/58) and a specificity of 0.694 (34/49) (Figure 4B).

Table 1 Patients' characteristics

	Non-VSA	VSA	*P* value
n (%)	17 (24)	53 (18)	
Age (yr)	68 ± 10	68 ± 9	0.775
Male/Female	3/14	33/20	0.001
Body mass index	24.4 ± 4.1	24.5 ± 3.8	0.914
Coronary risk factors (%)			
Smoking (active/former/never)	2/2/13	11/16/26	0.134
Hypertension	14 (82)	39 (74)	0.463
Dyslipidemia	11 (65)	32 (60)	0.750
Diabetes mellitus	4 (24)	18 (34)	0.420
Alcohol consumer (%)	10 (13)	5 (29)	0.09
Family history of CAD (%)	4 (24)	14 (26)	0.813
CKD (%)	7 (41)	17 (32)	0.492
LVEF on UCG (%)	69 ± 7	66 ± 9	0.200
Brachial artery ultrasonography (*n*)	14	48	
Brachial artery diameter at baseline (mm)	3.8 ± 0.8	3.9 ± 0.7	0.711
FMD (%)	6.2 ± 4.8	3.0 ± 3.6	0.008
NID (%)	17.7 ± 7.7	13.6 ± 6.9	0.061
Medications			
Any kind of coronary vasodilator (%)	13 (76)	23 (43)	0.018
No. of coronary vasodilators	1 (0.5, 1)	0 (0, 1)	0.059
Beta-receptor blockers (%)	1 (6)	4 (8)	0.817
RAS inhibitors (%)	7 (41)	12 (23)	0.135
Lipid-lowering drugs (%)	4 (41)	17 (32)	0.492
Anti-platelet drugs (%)	4 (24)	18 (34)	0.420

CAD: Coronary artery disease; CKD: Chronic kidney disease; FMD: Flow-mediated dilation; LVEF: Left ventricular ejection fraction; NID: Nitroglycerin-induced dilation; RAS: Renin-angiotensin system; UCG: Cardiac ultrasonography; VSA: Vasospastic angina.

DISCUSSION

This study examined whether baseline Pd/Pa values and changes in this value, as measured by a pressure wire, could be used to predict the next coronary spasm when the SPT was performed using a pressure wire. We found that intracoronary pressure at baseline decreased in cases where coronary spasms were induced by a low dose of ACh, indicating that decreased intracoronary pressure at baseline may predict these coronary spasms. Furthermore, coronary spasms induced by moderate-to-high doses of ACh were not only correlated with lower intracoronary pressure at baseline, but also with lower intracoronary pressure from baseline to low-dose ACh administration, indicating that this intracoronary pressure trend is useful in the prediction of coronary spasms induced by moderate-to-high dose ACh provocation. When pressure wires are used in the SPT, these indices may be useful for predicting coronary spasms.

The SPT is a reliable and well-established test that is useful for the diagnosis of coronary spasms and the evaluation of their activity and prognosis[6,17,22-25]. However, a certain percentage of SPTs have known complications, some of which are the result of the induced spasms. In this sense, the test is by no means stress-free for either the patient or the cardiologist. The ability to predict the likelihood of coronary spasms at the next provocation in SPT has the potential to attenuate this stress to some degree. We attempted to determine whether the next coronary spasm during the SPT could be predicted based on the Pd/Pa value and its changes measured using a pressure wire.

To date, there have been no reports on the measurement of changes in intracoronary pressure during SPT. However, several studies have examined this pressure using quantitative CAG and coronary blood flow velocity using Doppler wires[26,27]. In our previous study[26], the baseline coronary artery diameter in patients with VSA (mean, 2.95 mm) was slightly lower than that of non-VSA patients (mean, 3.14 mm), although not significantly. We also showed that a 2 min infusion of ACh at a dose of 3 μg/min caused significant vasocontraction of the coronary artery but did not induce

Table 2 Characteristics of lesions based on the occurrence of coronary spasms during spasm provocation tests and the dose of acetylcholine

	Group N	Group L	Group MH	*P* value
n	49	25	58	
RCA/LAD	27/22	9/16	27/31	0.290
Atherosclerosis (%)	23 (47)	9 (36)	28 (48)	0.568
Unavoidable use of NTG	4 (8)	3 (12)	5 (9)	0.851
Coronary spasm				
Focal/diffuse		8/17	14/44	
Proximal/mid/distal		4/15/6	5/35/18	
iFR	0.98 ± 0.04	0.92 ± 0.09	0.98 ± 0.06	0.104
n	15	5	11	
Pd/Pa				
Baseline	0.98 ± 0.04	0.94 ± 0.05	0.96 ± 0.05	0.001
Low dose of ACh	0.96 ± 0.05	0.72 ± 0.14	0.90 ± 0.06	< 0.001
Pd/Pa (Low dose-baseline)	−0.03 ± 0.03	−0.22 ± 0.14	−0.06 ± 0.05	< 0.001
Moderate-high doses of ACh	0.93 ± 0.06		0.78 ± 0.13	< 0.001
FFR	1.01	0.81 ± 0.09	0.87 ± 0.09	0.093
n	1	6	13	

Coronary arteries with coronary spasms at low doses of Acetylcholine (Ach) were defined as group L, and those with coronary spasms at moderate or high doses were defined as group MH. Those who did not occur coronary spasms at any ACh dose were designated as group N. ACh: Acetylcholine; FFR: Fractional flow reserve; iFR: Instantaneous free-wave ratio; LAD: Left anterior descending coronary artery; NTG: Nitroglycerin; Pa: Aortic pressure; Pd: Distal pressure; RCA: Right coronary artery.

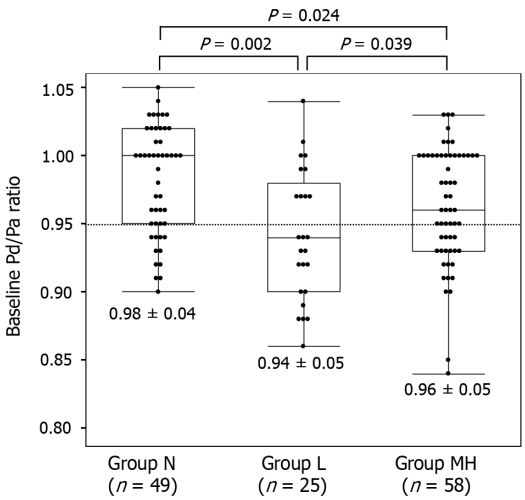

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Figure 2 The distal pressure/aortic pressure ratio at baseline in lesions with no coronary spasm in response to spasm provocation test (group N), lesions in which coronary spasm was induced by a low dose of acetylcholine (group L), and lesions in which coronary spasm was induced by a moderate or high-dose acetylcholine (group MH). This value was lower in group L than in groups MH and N. ACh: Acetylcholine; Pa: Aortic pressure; Pd: Distal pressure; SPT: Spasm provocation test.

coronary spasms[26]. Similarly, Feenstra *et al*[27] found that an 8.6 μg/min dose of ACh for 3 min causes a nonsignificant coronary artery contraction in patients with epicardial coronary spasm. Despite the differences due to the part of the measured coronary artery and the dose of ACh infusion, the baseline coronary artery diameter and changes in this diameter in response to small doses of ACh can cause a decrease in baseline intracoronary pressure, with greater decreases in patients with VSA.

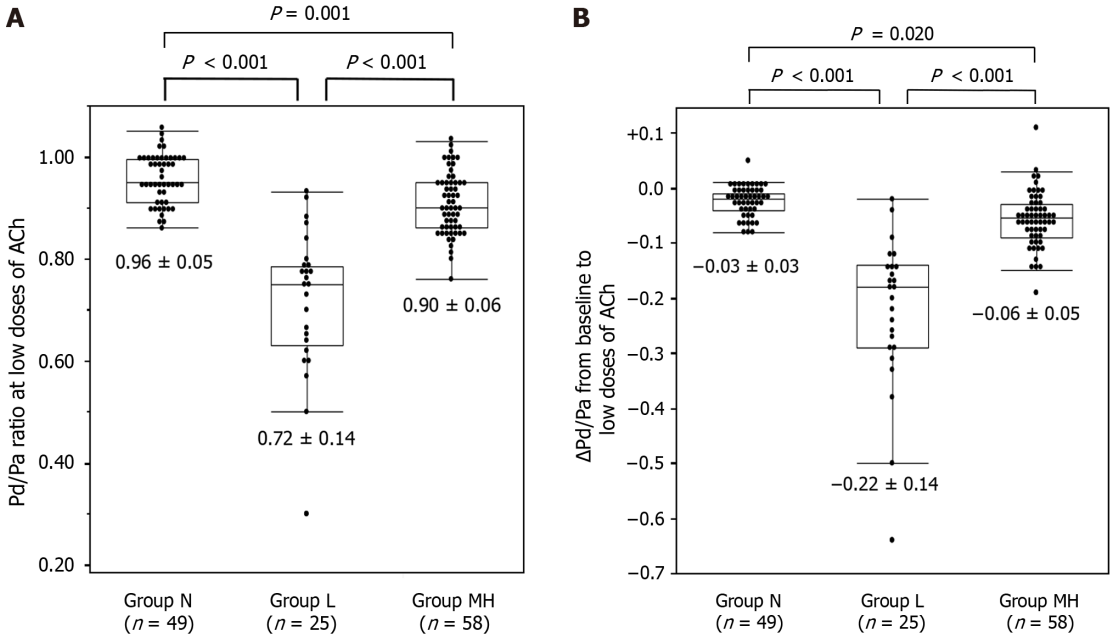

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Figure 3 The distal pressure/aortic pressure ratio at low doses of acetylcholine and Pd/Pa between baseline and low doses of acetylcholine in the three coronary spasm groups. A: Shows distal pressure/aortic pressure (Pd/Pa) at low doses of acetylcholine (ACh). The value was lowest in group L and highest in group N; B: Shows the Pd/Pa between baseline and low doses of ACh. This value was also lowest in group L and highest in group N. ACh: Acetylcholine; Pa: Aortic pressure; Pd: Distal pressure.

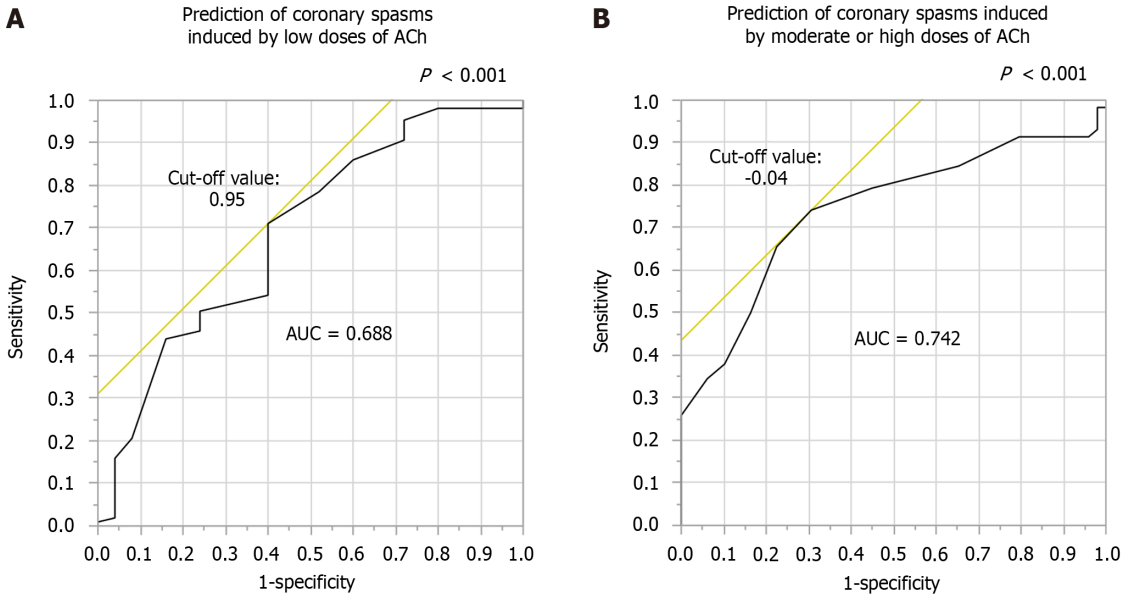

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Figure 4 The results of a receiver-operating characteristics analysis of the data from this study. A: Shows the cutoff value of the distal pressure/aortic pressure (Pd/Pa) ratio at baseline for the prediction of coronary spasms induced by low doses of acetylcholine (ACh); B: Shows the cutoff value of the Pd/Pa between baseline and low-doses ACh. ACh: Acetylcholine; Pa: Aortic pressure; Pd: Distal pressure; ROC: Receiver-operating characteristics; AUC: Area under the curve.

There are several reasons why performing the SPT with a pressure wire can be useful: (1) A decrease in intracoronary pressure when a coronary spasm occurs, indicating that a spasm has occurred before CAG; (2) Improvements in intracoronary pressure following NTG administration shows whether a coronary spasm is immediately relieved, reducing the need for additional NTG and/or contrast medium; and (3) The insertion of a pressure wire stabilizes the catheter's engagement, especially in the RCA. The present study showed the feasibility of predicting coronary spasm provocation using intracoronary pressure at baseline and its changes during low-dose ACh infusion. However, we do not recommend routine use of a pressure wire with SPT. Insertion of a pressure wire prolongs fluoroscopy time and increases

medical costs. In addition, there is a risk of coronary artery trauma due to pressure-wire insertion, which cannot always be inserted all the way to the distal end of the coronary artery. The insertion of the wire can potentially obscure the findings of the SPT or cause the accordion phenomenon. Hence, there are many possible disadvantages of pressure-wire insertion. In recent years, there has been increased research attention on the SPT and the functional testing of CMD, as many patients with ANOCA or MINOCA conditions do not have significant stenosis of the coronary arteries[5,6] and clarification of causes can improve prognosis[28]. A pressure wire is sometimes used to evaluate CMD before the SPT[14, 15]. The number of cases in which a pressure wire is used to induce coronary spasm is likely to increase in the future. In such cases, the results of the present study can be used as a reference for predicting coronary spasms. We hope that the validity of the results of this study will be strengthened in future research.

This study had several limitations. First, because this was a single-center study with a small sample size, our results may not be generalizable to all patients with coronary spasms. Second, although coronary artery diameters should be measured during drug provocation from quantitative CAG, in asymptomatic cases, no electrocardiographic changes, or no changes in intracoronary pressure, CAG was omitted or only a test shot was taken, and changes in coronary artery diameters were not evaluated. This was a significant impediment to our findings. Third, some negative coronary spasm cases may have completed provocation following a moderate dose of ACh. Recently, the usefulness of high-dose ACh provocation[29,30] and sequential provocation proposed by Sueda *et al*[31] was reported, and it is possible that such provocation would have changed the results to positive. The rates of coronary vasodilators in the VSA and non-VSA groups differed, which may have had some effect on the SPT results, although their use was stopped for at least 48 h before the SPT. Fourth, the present study included patients with chest symptoms but no significant stenosis in the coronary arteries. Some patients had positive Holter ECG or exercise stress ECG results, but not all patients had confirmed ischemic findings. From this point of view, the patients included in the study were ANOCA patients. Finally, the use of pressure wires during the SPT may have been higher in our sample because the SPT was performed after CMD assessment, in which case, ACh provocation would occur after NTG administration. Because of the small number of patients in this study who required NTG, the changes in intracoronary pressure during ACh provocation recorded after NTG administration may not have been consistent with our main results.

CONCLUSION

We performed SPT using a pressure wire to investigate whether coronary spasm could be predicted from changes in the intracoronary artery pressure during the test. Decreased intracoronary pressure at baseline may be a useful means of inferring coronary spasms induced by a low-dose ACh provocation. A decrease in intracoronary pressure from baseline following low-dose ACh provocation may be useful for predicting subsequent moderate-to-high dose ACh-induced coronary spasms. Although pressure wires are not recommended for routine use in the SPT, when they are used, the intracoronary pressure findings appear to be useful in the prediction of coronary spasms. We hope that the validity of our results will be evaluated in future studies.

ARTICLE HIGHLIGHTS

Research background

Although the spasm provocation test (SPT) can diagnose coronary spasms, there are some complications related to SPT.

Research motivation

To reduce complications related to SPT, it would be helpful if it could also predict the occurrence of coronary spasm during the SPT.

Research objectives

We investigated whether coronary spasms can be predicted using changes in intracoronary artery pressure measured using a pressure wire during the SPT.

Research methods

Seventy patients underwent SPTs with pressure-wire measurement of intracoronary artery pressure. During each SPT, the pressure wire was advanced into the distal portion of the right coronary artery (RCA) and left anterior descending coronary artery, and the ratio of intracoronary pressure to aortic pressure (Pd/Pa) was monitored. Coronary spasm was defined as an arterial narrowing of > 90% in response to the administration of acetylcholine (ACh), with chest symptoms and/or ischemic electrocardiographic changes. ACh was administered to the RCA at low, moderate, or high doses of 20, 50, or 80 μg, respectively, and to the left coronary artery (LCA) at low, moderate, or high doses of 50, 100, or 200 μg, respectively. Coronary arteries with coronary spasms at low doses of ACh were defined as group L, and those with coronary spasms at moderate or high doses were defined as group MH. Those who did not occur coronary spasms at any ACh dose were designated as group N.

Research results

Among the 132 coronary arteries assessed using a pressure wire, there were 49 in group N, 25 in group L, and 58 in group MH. Baseline Pd/Pa was the lowest in group L (P = 0.001). The decrease in the Pd/Pa between baseline to low doses of ACh was lower in group MH than in group N (P < 0.001). A receiver-operating characteristics analysis showed that the cutoff baseline Pd/Pa value for predicting group L was 0.95, with a sensitivity of 0.600 (15/25) and a specificity of 0.713 (76/107) and that the cutoff value of Pd/Pa from baseline to low doses of ACh for predicting group MH was −0.04, with a sensitivity of 0.741 (43/58) and a specificity of 0.694 (34/49).

Research conclusions

These findings suggest that indices of intracoronary pressure during SPT may be useful for predicting coronary spasms induced by both low doses and moderate-high doses of ACh.

Research perspectives

We do not recommend that all patients undergo SPT testing with a pressure wire in all cases. However, if SPT is performed after evaluation of coronary microvascular function using a pressure wire, it may be possible to leave the pressure wire in place, which may help predict coronary spasm. It is necessary to confirm the results of this study by accumulating more data in the future.

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FOOTNOTES

Author contributions: Oshita C and Uchimura Y contributed to the acquisition of data and Teragawa H contributed to the writing and revision of the manuscript; All the authors approved the final version of the manuscript.

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SYSTEMATIC REVIEWS

Safety and effectiveness of neuromuscular electrical stimulation in cardiac surgery: A systematic review

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Abstract

BACKGROUND

Lack of mobilization and prolonged stay in the intensive care unit (ICU) are major factors resulting in the development of ICU-acquired muscle weakness (ICUAW). ICUAW is a type of skeletal muscle dysfunction and a common complication of patients after cardiac surgery, and may be a risk factor for prolonged duration of mechanical ventilation, associated with a higher risk of readmission and higher mortality. Early mobilization in the ICU after cardiac surgery has been found to be low with a significant trend to increase over ICU stay and is also associated with a reduced duration of mechanical ventilation and ICU length of stay. Neuromuscular electrical stimulation (NMES) is an alternative modality of exercise in patients with muscle weakness. A major advantage of NMES is that it can be applied even in sedated patients in the ICU, a fact that might enhance early mobilization in these patients.

AIM

To evaluate safety, feasibility and effectiveness of NMES on functional capacity and muscle strength in patients before and after cardiac surgery.

METHODS

We performed a search on Pubmed, Physiotherapy Evidence Database (PEDro), Embase and CINAHL databases, selecting papers published between December 2012 and April 2023 and identified published randomized controlled trials (RCTs)

that included implementation of NMES in patients before after cardiac surgery. RCTs were assessed for methodological rigor and risk of bias *via* the PEDro. The primary outcomes were safety and functional capacity and the secondary outcomes were muscle strength and function.

RESULTS

Ten studies were included in our systematic review, resulting in 703 participants. Almost half of them performed NMES and the other half were included in the control group, treated with usual care. Nine studies investigated patients after cardiac surgery and 1 study before cardiac surgery. Functional capacity was assessed in 8 studies *via* 6MWT or other indices, and improved only in 1 study before and in 1 after cardiac surgery. Nine studies explored the effects of NMES on muscle strength and function and, most of them, found increase of muscle strength and improvement in muscle function after NMES. NMES was safe in all studies without any significant complication.

CONCLUSION

NMES is safe, feasible and has beneficial effects on muscle strength and function in patients after cardiac surgery, but has no significant effect on functional capacity.

Key Words: Neuromuscular electrical stimulation; Cardiac surgery; coronary artery bypass grafting; Heart valve replacement; Peak VO_2; Safety

Core Tip: Data regarding the effects of neuromuscular electrical stimulation (NMES) in cardiac surgery patients still remains limited. We investigated the safety and the effectiveness of NMES on functional capacity and muscle strength and function in patients before and after cardiac surgery. We observed that NMES has beneficial effects on muscle strength and function, but its effect on functional capacity is not clear. Moreover, NMES is safe and feasible for cardiac surgery patients without any major adverse events.

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INTRODUCTION

Polyneuromyopathy, defined as a disorder of both the muscle and the peripheral nerve or lower motor neuron, is a common complication in the majority of patients during their stay in the intensive care unit (ICU) before and after cardiac surgery[1,2]. It is characterized by muscle weakness, increased loss of muscle mass, as well as degeneration of the deep ligaments and tendons[3,4]. During the last decade, the term that was proposed and used to characterize this neuromuscular weakness was intensive care unit acquired weakness (ICUAW)[5]. Lack of mobilization and prolonged stay in the ICU are major factors resulting in the development of muscle weakness[6]. Weaning from mechanical ventilation is quite difficult and muscle strength is limited for several months in patients with ICUAW, with tremendous effects on their quality of life and their mortality rates[7]. Muscle mass is associated with increased muscle strength and therefore, it is a prognostic marker for the clinical outcomes in patients with polyneuromyopathy[3].

Most therapeutical strategies of polyneuromyopathy are focused on prevention of muscle atrophy and degeneration of muscle proteins. Early mobilization has been associated with increased muscle strength and functional capacity[8,9]. Active exercise is not feasible for most patients due to difficulty in producing sufficient muscle contractions and hemodynamic instability[10]. Recent research has shown that neuromuscular electrical stimulation (NMES) is an alternative modality of exercise in patients with muscle weakness due to chronic obstructive pulmonary disease and chronic heart failure[11,12]. NMES causes muscle contraction without patient's effort, so it can be implemented even in intubated patients under mechanical ventilation. It has beneficial effects as its daily application prevents the progression of neuromyopathy and results in shorter length of stay in the ICU[13]. It also increases muscle strength, exercise endurance and maximum oxygen uptake (peak VO_2), reduces protein catabolism and sympathetic nervous system activity in patients with chronic heart failure[11,12,14] and has positive influence on the peripheral microcirculation of skeletal muscles[11,15], which is directly related to the endothelial function[16,17]. All these effects on clinical outcomes may lead to improvement of patients' quality of life.

NMES could be an alternative method of activating skeletal muscles and improving muscle function in patients who cannot exercise after cardiac surgery and present high risk of ICUAW. It may also prevent the progression of ICU-related muscular dystrophy and post-intensive care syndrome. We hypothesized that NMES is safe and feasible in patients before and after cardiac surgery, leading in improvement in functional capacity and prevention or reduction of neuromyopathy. The aim of this systematic review was to evaluate safety and effectiveness of NMES on functional capacity and

mobility in patients before or after undergoing cardiac surgery.

MATERIALS AND METHODS

Search strategy

Authors searched literature for suitable articles that included in-hospital implementation of NMES in patients before and after cardiac surgery. The search was conducted between April of 2023 and May of 2023 in 4 science databases; Pubmed, Physiotherapy Evidence Database (PEDro), Embase and CINAHL. Terms which were used included ("cardiac surgery" OR "left ventricular assist device" OR "LVAD" OR "ECMO" OR "extracorporeal membrane oxygenation" OR "coronary artery bypass grafting" OR "CABG" OR "heart valve replacement") AND ("electrotherapy" OR "electrical stimulation" OR "electrical muscle stimulation" OR "electromyostimulation" OR "electrostimulation" OR "neuromuscular stimulation" OR "Functional Electrical Stimulation" OR "FES" OR "Neuromuscular Electrical Stimulation" OR "NMES"). Studies were selected according to the PRISMA and the PRISMA checklist. Duplicates were removed from the initial number of studies and the rest were initially screened using only the title and the abstract and then, the full text of the articles. Two independent reviewers reviewed all these articles for eligibility. The final evaluation of the process was performed by a third independent reviewer.

Study selection criteria

Inclusion criteria were: (1) Studies available as full texts in English; (2) published randomized controlled trials (RCTs) in peer-reviewed journals; (3) study groups including patients before and after cardiac surgery such as CABG, valve replacement, LVAD, cardiac transplantation, *etc.*; (4) patients aged ≥ 18 years, (5) NMES protocols of at least 1 session compared to usual care or sham NMES of the control group, and (6) outcome measures focused on safety, functional capacity assessed by 6MWT or other indices and muscle strength (ambulation ability, MRC values, *etc.*).

Exclusion criteria were: (1) Non RCTs, reviews, guidelines, commentaries, case reports, editorials or conference abstracts; (2) additional interventions in study groups except for NMES; (3) studies including patients with hemodynamic instability of high risk; (4) studies including patients with other types of surgeries, (5) studies including patients aged < 18 years; and (6) studies including NMES and other exercise modalities that were unable to be quantified.

Quality assessment

Two independent reviewers used PEDro in order to assess all the included RCTs for methodological rigor and risk of bias, using similar methods with a recently published study[18]. PEDro is an 11-point scale for assessing RCTs for internal validity and control of bias. Maximum score is 10 as the first question does not contribute to total score. A study with a score of 6-10 is considered of excellent quality, a study with 4-5 of fair quality, and a score of 3 or less gives a poor-quality study. If the 2 reviewers did not agree for their quality score, then an independent third reviewer made the final decision.

Outcome measures

The primary outcome measures were functional capacity, assessed by 6MWT or other indices, and safety of NMES. The secondary outcome measure was muscle strength and mass assessed by several indices such as the 1 repetition maximum test (1RM test), the sit-and-stand test (SST), perimeter of the thighs, grip strength, knee extensors strength, cross-sectional area of the quadriceps femoris, *etc.* All outcomes were evaluated at baseline and after NMES intervention.

RESULTS

Screening of the articles

From the initial 7870 studies derived from Pubmed, Embase, Physiotherapy Evidence Database (PEDro) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) database, 877 duplicates were removed and 6993 studies remained for title and abstract screening. Among these, 187 studies were eligible for full text review. After the full text review of these 187 studies, 152 were excluded because they did not include NMES, 12 presented different endpoints, 3 included other surgeries, 2 articles were RCT protocols without results, while 8 studies were clinical trials without randomization. As a result, we finally found 10 RCTs eligible for our systematic review[19-28] (Figure 1).

Quality assessment

Scores from the PEDro scale, which was used as a quality assessment tool, ranged from 3 to 9 for these studies (Table 1). A single study scored 3 points, being assessed as poor-quality study. Seven studies out of 10 scored 6-8 points being assessed as good-quality studies, while 2 out of 10 studies scored 9 points and were of excellent quality. Blindness of therapists and participants, concealed allocation and adequate follow-up had the lowest scores.

Characteristics of participants

The 10 RCTs resulted in 703 patients before and after cardiac surgery separated almost equally between the interventional and the control group. The majority of them were males (475 *vs* 228 females). Patients were from 42 to 74 years with a

Table 1 Quality assessment of the included studies using the physiotherapy evidence database

	Fischer *et al*[19]	Schardong *et al*[20]	Kitamura *et al*[21]	Fontes Cerqueira *et al*[22]	Fontes Cerqueira *et al*[23]	Sumin *et al*[24]	Rengo *et al*[25]	Cerqueira *et al*[26]	Takino *et al*[27]	Sumin *et al*[28]
Eligibility criteria[1]	√	√	√	√	√	√	√	√	√	√
Random allocation	√	√	√	√	√	√	√	√	√	√
Concealed allocation	√	√			√			√	√	
Baseline comparability	√	√	√	√	√	√		√	√	√
Blinded subjects	√	√			√				√	
Blinded therapists										
Blinded assessors		√	√	√		√		√	√	
Adequate follow-up	√	√	√						√	√
Intention-to-treat analysis	√	√	√	√	√	√		√	√	√
Between-group comparisons	√	√	√	√	√	√	√	√	√	√
Point estimates and variability	√	√	√	√	√	√	√	√	√	√
Total score	8/10	9/10	7/10	6/10	7/10	6/10	3/10	7/10	9/10	6/10

[1]Eligibility criteria item does not contribute to total score.

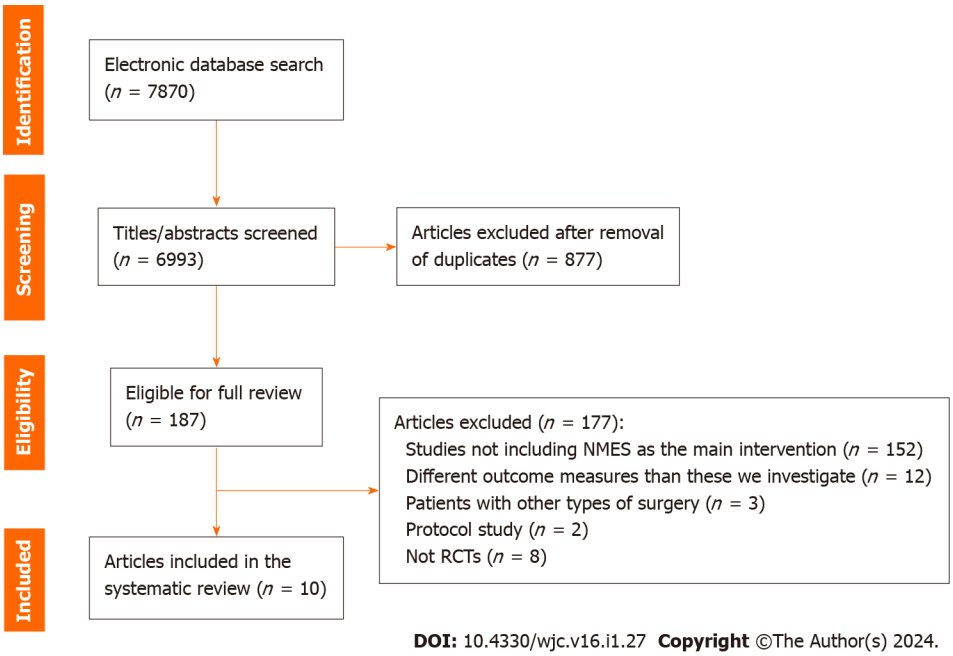

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Figure 1 PRISMA flowchart regarding the screening results of the systematic review. RCT: Randomized controlled trial; NMES: Neuromuscular electrical stimulation.

mean BMI ranging from 19.3 to 29.1 kg/m^2. Cardiac surgeries included a variety of cases such as aortic valve replacement, CABG, heart transplantation, mitral/aortic/tricuspid valve replacement or reconstruction and Bentall surgery. Studies were conducted in 5 countries; Brazil[20,22,23,26], Japan[21,27], the United States[25], Austria[19] and Russia[24,28]. Table 2 demonstrates baseline characteristics of patients.

NMES protocols

Table 3 demonstrates details regarding NMES protocols, as well as populations, intervention, comparison, outcomes and study designs (PICOS). NMES was performed in the intervention group in all studies with differences however, in intensity and sessions duration among studies. In 3 studies, stimulator electrodes were applied to the control group but no electricity was delivered[19,20,23] while in the rest 7 studies the control group received only usual care after the surgery[21,22,24-28]. Most studies included at least 5 sessions of NMES except for one that included a single session of NMES[23]. Sessions were performed from 2 to 5 times weekly with a duration from 30 min to 90 min.

Effectiveness of NMES on functional capacity

Effects of NMES on functional capacity were assessed by several indices in 9 studies out of 10. Only a single study did not investigate functional capacity[23]. Functional capacity seemed to improve only in 2 recent studies out of 9 examined; in the first case in patients before cardiac surgery who received NMES as prehabilitation[28] and in the second case in older individuals with diabetes mellitus with postsurgical muscle weakness[27].

Specifically, Fischer *et al*[19] did not found significant differences in the average mobility level, functional independence measure (FIM) score, the Timed Up and Go Test as well as the mental component score (MCS-12) and physical component score (PCS-12) of the SF-12 between the intervention and the control group from preoperative day to ICU or hospital discharge. Similarly, Schardong *et al*[20] assessed 6MWT and, although they found an increase in the distance to 6MWT by 11.0% (49.6 m, 95%CI: 15.9-83.3) in the FES group and by 10.4% (41.5 m, 95%CI: 7.8-75.2) in the control group, no significant difference between groups was observed. Kitamura *et al*[21] also assessed functional capacity *via* walking speed and found no significant difference between groups after the surgery (NMES: 1.04 ± 0.24 m/s *vs* Control group: 0.99 ± 0.23 m/s, $P = 0.294$).

Fontes Cerqueira *et al*[22] found no influence of NMES on functional capacity as there was no statistically significant difference in distance walked (0.10 m, 95%CI: -64.87 to 65.97) and walking speed (0.01m/s, 95%CI: -0.55 to 0.57) between intervention and control group in cardiac valve surgery patients in the immediate postoperative period. Four years later, Fontes Cerqueira *et al*[23] examined the effect of NMES on functional capacity of patients in the immediate postoperative period of cardiac surgery again and found similar conclusions; no significant difference in the distance walked ($P = 0.650$) between NMES group (239.06 ± 88.55) and control group (254.43 ± 116.67) as well as gait speed ($P = 0.363$) and FIM score ($P = 0.059$).

In another study of Rengo *et al*[25], physical function measures improved from discharge to 4 wk post-surgery ($P < 0.001$) in the total sample and, NMES group showed greater improvements in 6MWT distance and power output compared with controls ($P < 0.01$). However, no differences between NMES and control groups were found in total Short Physical Performance Battery score or 6MWT measured pre-surgery (range of P values: 0.19-0.61), or at post-surgery discharge (range of P values: 0.21-0.56).

Sumin *et al*[24] did not find any significant difference in the 6MWT at discharge between NMES and control group ($P = 0.166$) in early rehabilitation of patients with postoperative complications after cardiovascular surgery. In the contrary, some years later, the same investigators found a statistically significant increase in the 6MWT within NMES group [from 300.0 m (261.0-371.0) to 331.0 m (280.0-375.0); $P < 0.01$] compared to the control group [from 304.5 m (253.0-380.0) to 285.5 m (246.0-342.0); $P < 0.01$], as well as between groups ($P < 0.001$) in patients before cardiac surgery as a kind of prehabilitation[28].

Finally, Takino *et al*[27] managed to show a statistically significant improvement in the percent change in maximum walking speed from preoperative to postoperative day 7 [treatment effect: 6.2 (0.3 to 12.1); $P = 0.04$], but the percent change in usual walking speed from preoperative to postoperative day 7 remained unchanged [treatment effect: 3.6 (-0.7 to 7.9); $P = 0.10$] between groups.

Safety of NMES

Regarding safety, there was no study that demonstrated severe complications during NMES sessions. Adverse events included only minor events and concerned only a very small number of patients. Specifically, 5 patients in the NMES group mentioned a feeling of discomfort in the study of Fischer *et al*[19], 1 patient mentioned muscle soreness in the study of Kitamura *et al*[21], and 2 patients reported hypotension and 1 patient complained of pain in the study of Fontes Cerqueira *et al*[22]. In the rest of the studies, no complications were mentioned.

Effectiveness of NMES on muscle function, strength and endurance

All of the above studies investigated the effectiveness of NMES on muscle mass and/or strength except for 2 studies[23,25].

Fischer A *et al*[19] assessed muscle layer thickness of the quadriceps muscle of both thighs using two-dimensional B-mode ultrasound and muscle strength *via* the Medical Research Council (MRC) scale and found that at hospital discharge, NMES patients regained preoperative levels of muscle strength [NMES compared to controls: 0.09 points (0.03 to 0.14); $P = 0.002$], but not of MLT [NMES compared to controls: 0.02 cm (−0.01 to 0.06); $P = 0.21$]. As a result, NMES had no significant effect on MLT although patients in the NMES group regained muscle strength 4.5 times faster than patients in the control group. Moreover, there was no difference in grip strength between groups [NMES compared to controls: 0.89

Table 2 The main baseline characteristics among patients after cardiac surgery in each study included in the systematic review

Ref.	Groups	Males/ Females (*N*)	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m^2)	Type of surgery
Fischer *et al* [19]	NMES (*n* = 27); CG (*n* = 27)	18/9; 20/7	63.3 ± 15.5; 69.7 ± 13.1	NA	NA	27.6 ± 3.7; 27.7 ± 4.6	Aortic valve replacement; CABG; Heart transplantation; Other cardiothoracic surgery; Mitral valve replacement; Mitral valve reconstruction; Tricuspid valve reconstruction; Bentall surgery
Schardong *et al*[20]	FES (*n* = 10); CG (*n* = 10)	7/3; 7/3	60 ± 7.3; 63.5 ± 5	NA	NA	27.3 ± 3.1; 29.1 ± 6.2	CABG; Heart valve surgery
Kitamura *et al*[21]	NMES (*n* = 60); CG (*n* = 59)	39/21; 37/22	67 (55-74); 70 (61-77)	NA	NA	25.5 (20.4-24.8); 22.3 (20.4-24.9)	CABG; Valvular surgery; Thoracic Aorta
Fontes Cerqueira *et al* [22]	NMES (*n* = 26); CG (*n* = 33)	18/8; 23/10	41.8 ± 13.17; 42.21 ± 14.36	66.12 ± 13.29; 61.85 ± 12.69	160 ± 6; 165 ± 8	25. ± 4.72; 21.96 ± 4.2	Mitral valve replacement; Aortic valve replacement; Mitral valve reconstruction; Aortic valve reconstruction; Mitral valve replacement + Aortic valve reconstruction
Fontes Cerqueira *et al* [23]	NMES (*n* = 15); CG (*n* = 15)	9/6; 5/10	49.87 ± 14.37; 50.93 ± 14.56	NA	NA	NA	CABG; Valve replacement; CABG + Valve replacement
Sumin *et al* [24]	NMES (*n* = 18); CG (*n* = 19)	12/6; 13/6	61.5 [52-70]; 64 [60-68]	NA	NA	28.4 [25.2-30.9]; 28.4 [25.8-32.5]	CABG; Aortic valve replacement; Mitral valve replacement; CABG + valve replacement; Multivalve operations; Bentall surgery; Aortic dissection; Heart transplantation
Rengo *et al* [25]	NMES (*n* = 18); CG (*n* = 19)	16/2; 17/2	66.5 ± 1.6; 66.2 ± 1.4	89.4 ± 2.7; 90.9 ± 3.8	173 ± 1; 176 ± 3	29.7 ± 0.8; 29.0 ± 0.8	CABG; CABG + Valve replacement
Cerqueira *et al* [26]	NMES (*n* = 23); CG (*n* = 22)	12/11; 15/7	47.8 ± 13.9; 46.4 ± 13.5	72.3 ± 14.8; 68.5 ± 13.6	163.1 ± 10.4; 165.2 ± 7.2	27.2 ± 4.9; 25.1 ± 4.5	CABG; Aortic valve replacement; Mitral valve replacement; Mitral valve replacement; + Aortic valve reconstruction
Takino *et al* [27]	NMES (*n* = 90); CG (*n* = 90)	61/29; 63/27	74 ± 5; 74 ± 5	NA	NA	19.8 (18.0-21.8); 19.3 (18.2-20.8)	CABG; Valvular surgery; Thoracic aorta; Other surgery; Combined surgery
Sumin *et al* [28]	NMES *n* = 62); CG (*n* = 60)	44/18; 39/21	62.0 [57.5-66.6]; 63.5 [59.0-69.0]	NA	NA	27.4 [25.4-31.5]; 28.7 [25.9-33.3]	Prehabilitation (before cardiac surgery)

Values are presented as a mean ± SD or median (interquartile range). CABG: Coronary artery bypass grafting; CG: Control group; FES: Functional electrical stimulation; NMES: Neuromuscular electrical stimulation group; NA: Not available.

kgf (−5.16 to 6.94); P = 0.77]. In the study of Schardong *et al*[20], there were significant between-group differences for quadriceps muscle strength (7.2 kg, 95%CI: 0.2-14.2) assessed by the 1RM test and muscle endurance (2.2 repetitions, 95%CI: 1.0-3.4) assessed by the SST test, in favor of the NMES group. Muscle mass above the patella did not differ between the 2 groups (P > 0.05).

Sumin *et al*[24] examined muscle strength in 37 patients with postoperative complications after cardiovascular surgery. They showed that knee extensors strength at discharge was significantly higher in the NMES group [28.1 kg (23.8; 36.2) on the right and 27.45 kg (22.3; 33.1) on the left] than in the control group [22.3 kg (20.1; 27.1) and 22.5 kg (20.1; 25.9), respectively; P < 0.001) while there was no difference in the handgrip strength, knee flexor strength and quadriceps cross-sectional area between groups (P > 0.05). In the other modality of exercise, prehabilitation, Sumin *et al*[28] demonstrated statistically significant increase in right and left knee extensors and knee flexors strength in the NMES group compared to the controls (P < 0.001), but handgrip strength was similar between the 2 groups (P = 0.054 on the right hand and P = 0.062 on the left hand).

Finally, Takino *et al*[27] showed that isometric knee extension strength from preoperative to postoperative day 7 was significantly lower in the NMES than the SHAM group [NMES: mean -2%, 95%CI: -6 to 1 *vs* sham: Mean -13%, 95%CI: -17 to -9; P < 0.001], indicating the benefits of NMES in postsurgical muscle weakness and functional decline in older persons with diabetes mellitus after cardiac surgery. However, the percent change in grip strength from preoperative to postoperative day 7 did not differ statistically significant between the 2 groups.

There were studies that did not show statistically significant differences on muscle strength and muscle function after NMES. Specifically, Kitamura *et al*[21] assessed muscle function *via* knee extensor isometric strength (KEIS) and the mean concentration of 3-methylhistidine concentration corrected for urinary creatinine (Cre) content (3-MH/Cre), which is an objective measure of muscle proteolysis[29]. Authors concluded that there was no significant difference in the mean 3-MH/Cre from post-operative day 1 to post-operative day 6 [225.3 μmol/g (204.0-248.3) *vs* 227.3 μmol/g (206.3-259.9); P =

Table 3 Population, intervention, comparison, outcomes, and study design of each study included in the systematic review

Ref.	Interventions by group	Frequency	Session duration	Intervention Duration	Outcomes	Main results	Adverse events
Fischer *et al*[19]	**NMES**: biphasic rectangular pulses at 66 Hz, pulse duration 0.4 ms, duty cycle 3.5 s on and 4.5 s off to quadriceps muscle bilaterally. **CG:** stimulator electrodes were applied but no electricity was delivered	2 times/d for 7 d/wk	30 min	From POD 1 until ICU exit or POD 14	Muscle layer thickness, Muscle strength; Functional capacity	No significant effect on MLT. ↑ 4.5 times in recovering muscle strength to NMES group during ICU stay. Positive correlation between change in MLT and cumulative fluid balance (r = 0.43, P = 0.01) the first 3 PODs. No significant effect on functional ability	5 patients in the NMES group mentioned a feeling of discomfort
Schardong *et al*[20]	[1]**FES:** symmetric biphasic rectangular pulses at 15 Hz, pulse duration 0.5 ms, duty cycle 5 s on and 10 s off to vastus medialis and lateralis muscle bilaterally. **CG:** Stimulator electrodes were applied but no electricity was delivered	2 times/wk	40 min	8 wk	Functional capacity; Muscle strength; Muscle endurance; Muscle mass	↑ Distance to 6MWT in the FES group by 11.0% (49.6 m, 95%CI: 15.9-83.3) and in the CG by 10.4% (41.5 m, 95%CI: 7.8-75.2) with no significant between-groups. ↑ muscle strength (7.2 kg, 95%CI: 0.2-14.2). ↑ Muscle endurance (2.2 repetitions, 95%CI: 1.0-3.4)	No complications
Kitamura *et al*[21]	**NMES:** Symmetric biphasic square pulses, duty cycle 0.4 s on and 0.6 s off, 10 pulse trains (10 s) with 30 s intervals to quadriceps femoris and triceps surae muscle bilaterally. Usual postoperative rehabilitation program. **CG:** Usual postoperative rehabilitation program	1 time/d	30 min	3 d before surgery and from POD 1 to POD 5 (8 sessions)	The mean concentration of 3-MH/Cre; Physical function; Walking speed; Grip strength	No significant difference in the mean 3-MH/Cre from POD 1 to POD 6 between groups (225.3 [204.0-248.3] μmol/g *vs* 227.3 [206.3-259.9] μmol/g, P = 0.531). No significant difference in the KEIS on POD 7 between groups (0.44 ± 0.13 kgf/kg *vs* 0.41 ± 0.12 kgf/kg, P = 0.149. No significant difference in walking speed between groups (1.04 ± 0.24 m/s *vs* 0.99 ± 0.23 m/s, P = 0.294). No significant difference in grip strength between groups (29.1 ± 10.5 kg *vs* 26.9 ± 8.7 kg, P = 0.213)	1 patient mentioned muscle soreness
Cerqueira *et al*[22]	**NMES:** Stimulation at 50 Hz, duration 400 ms duty cycle 3 s on and 9 s off, to quadriceps and gastrocnemius muscle bilaterally. Regular physiotherapy care. **CG:** Usual physiotherapy care twice a day	2 times/d	60 min	from POD 1 to POD 5	Ambulation ability; Muscle strength; Functional independence; Quality of life	No significant difference in distance walked (95%CI: -64.87 to 65.97) and walking speed (95%CI: -0.55 to 0.57) between groups. No significant difference in muscle strength in the upper- limb, lower limb, and total MRC values, functional independence, and quality of life between groups	2 patients reported hypotension, and 1 patient complained of pain
Cerqueira *et al*[23]	**NMES:** Stimulation at 50 Hz, duration 200 ms duty cycle 3 s on and 9 s off, to quadriceps and gastrocnemius muscle bilaterally. Regular physiotherapy care. **CG:** stimulator electrodes were applied but no electricity was delivered	Once during the first 48 h of ICU stay	60 min	60 min	Hemodynamic responses; Respiratory responses	No difference in heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure respiratory rate, and oxygen saturation between groups	No complications
Sumin *et al*[24]	**NMES**: biphasic rectangular pulses at 45 Hz, duty cycle 12 s on and 5 s off to quadriceps muscle bilaterally. **CG:** Usual postoperative rehabilitation program	1 time/d	90 min	from POD 3 to exit the hospital (12 sessions or more)	Knee extensors strength; Handgrip strength; Knee flexor strength CSA of quadriceps femoris	↑ Knee extensors strength in the NMES group [28.1 (23.8; 36.2) kg on the right and 27.45 (22.3; 33.1) kg on the left] *vs* CG [22.3 (20.1; 27.1) and 22.5 (20.1; 25.9) kg, respectively; P < 0.001]. No difference in handgrip strength, knee flexor strength,	Non mentioned

						quadriceps CSA, and 6MWT at discharge between groups	
Rengo *et al*[25]	[2]**NMES**: biphasic rectangular pulses at 25 Hz, pulse duration 400 ms, duty cycle 10 s on and 30 s off to quadriceps muscle bilaterally. **CG:** no intervention	1 times/d for 5 d/wk	45 min	4 wk	Physical function Mental and physical health	From discharge to 4-wk post-discharge: No significant interaction effect for total SPPB score (P = 0.11; ηp^2 = 0.073; CG: 2.89 ± 0.50 *vs* NMES: 4.11 ± 0.54 units). Time effects for 6MWT distance (P < 0.01; ηp^2 = 0.207; CG: 194 ± 18 *vs* NMES: 267 ± 16 m) and 6MWT power output (P = 0.01; ηp^2 = 0.168; CG: 0.4 ± 0.1 *vs* NMES: 0.6 ± 0.1 W; P = 0.01)	No complications
Cerqueira *et al*[26]	**NMES:** Stimulation at 50 Hz, duration 400 ms duty cycle 3 s on and 9 s off, to rectus femoris and gastrocnemius muscle bilaterally. Regular physiotherapy care twice a day. **CG:** Usual physiotherapy care twice a day	2 times/d	60 min	From POD 1 to POD 5	Distance walked; Gait speed; Lactate levels Muscle strength Electromyographic activity of the rectus femoris; Functional Independence Measure	No significant difference in the distance walked (P = 0.650) between NMES group (239.06 ± 88.55) and CG (254.43 ± 116.67) as well as gait speed (P = 0.363), lactate levels (P = 0.302), knee extensor strength (P = 0.117), handgrip strength (P = 0.882), global muscle strength (P = 0.104), electromyographic activity (P = 0.179) and Functional Independence Measure (P = 0.059)	No complications
Takino *et al*[27]	**NMES**: Biphasic symmetric square pulses at 20 and 200 Hz, duty cycle 0.4 s on and 0.6 s off to vastus lateralis, vastus medialis and triceps surae muscle bilaterally. Standard post- surgical rehabilitation. **CG:** Standard post- surgical rehabilitation.	1 time/d	60 min	from POD 1 to POD 7	% change in isometric knee strength; % change in usual and maximum walking speed; % change in grip strength	↓ %ΔIKES in the NMES than CG [NMES: Mean -2%, 95% confidence interval (CI) -6 to 1; CG: -13%, 95% CI -17 to -9, P < 0.001]. ↓ %ΔMWS (P = 0.04). ↓ %ΔUWS and %ΔGS in the NMES compare to CG but not statistically significant	Non mentioned
Sumin *et al*[28]	**NMES**: rectangular pulses at 45 Hz, duty cycle 12 s on and 5 s off to quadriceps muscle bilaterally. Standard preoperative rehabilitation program; **CG:** Standard preoperative rehabilitation program	1 time/d	90 min	from the 2nd day of hospital stay until the day before surgery (7–10 sessions)	Exercise capacity; Muscle strength	↑ in KES, KFS, and 6MWT distance (all P < 0.001) in the NMES group compared to the CG. Slight ↑ in HS to the NMES group and slight ↓ to the CG but not statistically significant (P = 0.054 on the right hand and P = 0.062 on the left)	No complications

[1]Patients were discharged from hospital and submitted to phase I of cardiac rehabilitation.

[2]Home-based intervention after hospital discharge.

CG: Control group; CSA: Cross-sectional area; FES: Functional electrical stimulation; ICU: Intensive care unit; KEIS: Knee extensor isometric strength; MLT: Muscle layer thickness; NMES: Neuromuscular electrical stimulation POD: Post operative day; SPPB: Short physical performance battery; 3-MH/Cre: 3-methylhistidine concentration corrected for urinary creatinine content; 6MWT: Six minutes walking test; KFS: Knee flexor strength; KES: Knee extensor strength; NA: Not available.

0.531), in the KEIS on post-operative day 7 (0.44 ± 0.13 kgf/kg *vs* 0.41 ± 0.12 kgf/kg; P = 0.149) and in grip strength (29.1 ± 10.5 kg *vs* 26.9 ± 8.7 kg; P = 0.213) between groups. Fontes Cerqueira *et al*[22] came in agreement with the findings of Kitamura *et al*[21] in their study, as no significant difference in muscle strength in the upper- limb (P = 0.54), lower limb(P = 0.67), and total MRC values (P = 0.57) were observed between NMES and control group in post-cardiac surgery patients. Muscle strength was assessed by measuring the peak strength and representative maximum voluntary contraction through manual testing, ranging from 0 (no muscular contraction) to 5 (active movement against complete resistance) for 6 lower and upper limbs movements. In the other RCT they performed some years later[26], the same investigators confirmed their previous results as they also did not find differences in knee extensor strength (P = 0.117), handgrip strength (P = 0.882), global muscle strength (P = 0.104) and electromyographic activity (P = 0.179) between NMES and controls.

DISCUSSION

Safety, feasibility and effectiveness of NMES on functional capacity and muscle strength in patients before undergoing or immediately after cardiac surgery, and comparison between NMES and SHAM or usual care, were assessed in this article. Through our systematic review, we demonstrated that NMES is safe and feasible for patients before and after cardiac surgery and seems to be beneficial in muscle strength in order to prevent ICUAW. However, it did not seem to be beneficial on functional capacity after cardiac surgery, but, mainly before cardiac surgery as a type of prehabilitation.

ICUAW is a type of skeletal muscle dysfunction and a common complication of patients after cardiac surgery, and has been associated with a poor 2-year survival of critically ill patients[30]. It may be a risk factor for prolonged duration of mechanical ventilation[31], associated with a higher risk of readmission[32] and higher mortality[33]. The incidence of ICUAW ranges from 25% to 31% worldwide[34,35]. Patients with ICUAW may have critical illness polyneuropathy and critical illness myopathy, followed by muscle atrophy[36]. A previous study from our Institution showed that skeletal quadriceps muscle mass tends to decrease in ICU patients after cardiac surgery and seems to be associated with prolonged duration of mechanical ventilation and ICU length of stay[37]. Muscle atrophy may occur due to reduced synthesis and increased degradation of muscle proteins. Muscle mass and volume decrease, shrinkage of the muscle fiber cross-section area, and transformation of the type of muscle fibers from I to II are some of the pathophysiological mechanisms of muscle atrophy, also correlated with age[38]. Moreover, muscle atrophy and dysfunction is a result of increased reactive oxygen species due to long-term muscle inactivity[39]. The ubiquitin–proteasome system, calpain, caspase 3, and the autophagy–lysosome system are the major proteolytic systems causing massive loss of myosin and myoglobin-related proteins and leading to muscle atrophy[36,40]. Structural remodeling of the neuromuscular junction is also an important cause of aging-related muscle atrophy[41].

Early mobilization in the ICU after cardiac surgery has been found to be low with a significant trend to increase over ICU stay and is also associated with a reduced duration of mechanical ventilation and ICU length of stay[9,42-44]. In Greek ICUs, only 19% of ICU physiotherapists practice early mobilization in critical ill patients[45]. Similarly, low mobilization rates are also referred in ICUs in Australia, New Zealand and Scotland[46,47]. NMES is safe and feasible as an alternative form of exercise with beneficial effects on preserving muscle mass and strength[9,12], local and systemic microcirculation[15,16] in critically ill patients and may also reduce the duration of mechanical ventilation and ICU stay [11,14]. A major advantage of NMES is that it can be applied even in sedated patients in the ICU, a fact that might enhance early mobilization in these patients. Most RCTs included in our systematic review showed that early implementation of NMES increases muscle strength and endurance of the upper and lower limbs, and improves muscle function in patients after cardiac surgery[19,20,24,27]. However, none of these studies demonstrated significant increase of the muscle mass and handgrip strength remained also unchanged. A possible explanation of these findings may be the small number of sessions performed by patients due to their short length of stay in the ICU. Moreover, functional capacity did not improve after NMES in most studies except for one[28]. This may happen due to the fact that NMES is applied locally in the upper or lower extremities for a short time and thus, its effect is not satisfying on functional capacity. Our findings come in agreement with the findings of a recent meta-analysis by Zhang *et al*[48] who found no effects of NMES on 6MWT (MD = 44.08; $P = 0.22$) and walking speed (MD = 0.05; $P = 0.24$) in 400 cardiac surgery patients.

There are many factors influencing length of stay in ICU after adult cardiac surgery including age, gender, increased BMI, smoking and other cardiovascular and non-cardiovascular risk factors[49]. Preoperative functional capacity and exercise tolerance are among them[49]. NMES, as a form of prehabilitation, could be a crucial approach in order to prevent muscle atrophy and polyneuromyopathy. A recently published RCT showed that 62 patients who underwent 7–10 sessions of NMES prior to cardiac surgery, significantly increased knee extensor strength, knee flexor strength, and 6MWT distance compared to 60 controls who carried out only breathing exercises and an educational program ($P < 0.001$), indicating improvement on functional capacity and muscle strength[28]. These findings could be quite promising and guide clinicians to target prehabilitation as a significant part of the therapeutic strategy of ICUAW. Unfortunately, data regarding the use of NMES as a form of prehabilitation is still limited.

Potential pathophysiological mechanisms regarding the effects of NMES on functional capacity and muscle function have been proposed over the years. NMES activates muscle fibers by bypassing motor neurons. A positive correlation between the intensity, the electrical filed and the number of recruited type I and II muscle fibers has been found[50]. Moreover, it seems that higher benefits are derived by higher current intensity[51]. NMES should be applied specifically to the muscles of the lower limbs of frail patients with the maximal tolerable intensities, high frequencies (> 30 Hz and rather 50–80 Hz), optimal width pulses, short contractions interspersed with long recovery times[51]. NMES both stimulates anabolic pathways and negatively modulates muscle catabolism, which increases protein synthesis and reduces protein degradation and activates satellite cells in aged individuals[52-54]. As a result, NMES induces an increase in the size of type II muscle fibers[53]. Finally, there is a hypothesis that peripheral application of NMES can evoke a wide range of activities in the central nervous system, which can lead to a series of neural adjustments and adaptations[55].

Clinical perspectives

Patients after cardiac surgery may present impaired functional capacity and muscle function, reduced muscle strength, exercise intolerance and poor prognosis due to complications including ICUAW and polyneuromyopathy. The present systematic review evaluated the beneficial effects of NMES on functional capacity, muscle strength and muscle function. The most significant fact is that NMES is safe and feasible for these patients, without severe complications or major adverse effects even in high-risk patients. Moreover, it was proven to efficient, too. NMES should be initiated in patients as a form of prehabilitation before a major cardiac surgery and be continued immediately after the surgery until hospital discharge. A multidisciplinary team approach is necessary for its implementation. Preventing ICUAW and polyneuromyopathy *via* NMES could result in better prognosis, reduced length of stay in the ICU, less complications and improved

exercise tolerance and mobility of cardiac surgery patients. Other additional benefits of NMES could be better quality of life and improved hemodynamic and respiratory responses.

Limitations

More RCTs regarding the effects of NMES after cardiac surgery are required. Especially as a form of prehabilitation before cardiac surgery, NMES has been investigated only in one single study[28]. Another significant limitation is that the different samples from the included RCTs may present heterogeneity due to different mean age, type of surgery and functional capacity at baseline. Moreover, the number of NMES sessions was low in most studies and, as a result, the effectiveness of NMES on functional capacity may not have been shown in these studies. Finally, the lack of adjustment for multiple comparisons and possible confounders in the analysis makes it difficult for researchers to conclude whether these results are generalizable for the whole population of these patients. However, all these limitations are related mostly with each RCT separately, and not directly with our systematic review. The reason we preferred a systematic review over a meta-analysis was due to the fact that access to data of all the included RCTs was not feasible.

CONCLUSION

NMES is safe and feasible for patients before and after cardiac surgery and seems to be beneficial in muscle strength in order to prevent ICUAW in these patients. NMES did not present beneficial effects on functional capacity and muscle mass after cardiac surgery, possibly due to the low number of sessions that patients performed. However, NMES before cardiac surgery, as a form of prehabilitation, showed promising results on functional capacity and muscle strength and function. This form of rehabilitation could be a valuable strategy of preventing ICUAW after cardiac surgery. In order to discover all beneficial effects of NMES, fully understand its pathophysiological mechanisms in muscle function and functional capacity, and define the appropriate dose including duration, frequency and intensity, bigger number of multicenter RCTs with higher number of patients are required.

ARTICLE HIGHLIGHTS

Research background

Lack of mobilization and prolonged stay in the intensive care unit (ICU) are major factors resulting in the development of ICU-acquired muscle weakness (ICUAW). Early mobilization in the ICU after cardiac surgery is associated with a reduced duration of mechanical ventilation and ICU length of stay.

Research motivation

Neuromuscular electrical stimulation (NMES) is an alternative modality of exercise in patients with muscle weakness. A major advantage of NMES is that it can be applied even in sedated patients in the ICU, a fact that might enhance early mobilization in these patients.

Research objectives

To evaluate safety, feasibility and effectiveness of NMES on functional capacity and muscle strength in patients before and after cardiac surgery.

Research methods

We performed a search on Pubmed, PEDro, Embase and CINAHL databases, selecting papers published between December 2012 and April 2023 and identified published randomized controlled trials (RCTs) that included implementation of NMES in patients before after cardiac surgery. RCTs were assessed for methodological rigor and risk of bias *via* the Physiotherapy Evidence Database. The primary outcomes were safety and functional capacity and the secondary outcomes were muscle strength and function.

Research results

Ten studies were included in our systematic review, resulting in 703 participants. Almost half of them performed NMES and the other half were included in the control group, treated with usual care. Nine studies investigated patients after cardiac surgery and 1 study before cardiac surgery. Functional capacity was assessed in 8 studies *via* 6MWT or other indices, and improved only in 1 study before and in 1 after cardiac surgery. Nine studies explored the effects of NMES on muscle strength and function and, most of them, found increase of muscle strength and improvement in muscle function after NMES. NMES was safe in all studies without any significant complication.

Research conclusions

NMES is safe, feasible and has beneficial effects on muscle strength and function in patients after cardiac surgery, but has no significant effect on functional capacity.

Research perspectives

The present systematic review evaluated the beneficial effects of NMES on functional capacity, muscle strength and muscle function. NMES should be initiated in patients as a form of prehabilitation before a major cardiac surgery and be continued immediately after the surgery until hospital discharge. A multidisciplinary team approach is necessary for its implementation. Preventing ICUAW and polyneuromyopathy *via* NMES could result in better prognosis, reduced length of stay in the ICU, less complications and improved exercise tolerance and mobility of cardiac surgery patients.

FOOTNOTES

Co-first authors: Christos Kourek and Marios Kanellopoulos.

Author contributions: Kourek C, Kanellopoulos M and Dimopoulos S conceptualized and designed the research; Kourek C, Kanellopoulos M and Raidou V performed the research; Kourek C, Kanellopoulos M, Raidou V and Dimopoulos S analyzed the data; Kourek C and Kanellopoulos M wrote the paper. All the authors have read and approved the final manuscript. Kourek C and Kanellopoulos M proposed and designed the research, performed data analysis and prepared the first draft of the manuscript. Both authors have made crucial and indispensable contributions towards the completion of the project and thus qualified as the co-first authors of the paper.

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META-ANALYSIS

Left bundle branch pacing *vs* biventricular pacing in heart failure patients with left bundle branch block: A systematic review and meta-analysis

Farah Yasmin, Abdul Moeed, Rohan Kumar Ochani, Hamna Raheel, Malik Ali Ehtsham Awan, Ayesha Liaquat, Arisha Saleem, Muhammad Aamir, Nael Hawwa, Salim Surani

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Abstract

BACKGROUND

Left bundle branch pacing (LBBP) is a novel pacing modality of cardiac resynchronization therapy (CRT) that achieves more physiologic native ventricular activation than biventricular pacing (BiVP).

AIM

To explore the validity of electromechanical resynchronization, clinical and echocardiographic response of LBBP-CRT.

METHODS

Systematic review and Meta-analysis were conducted in accordance with the standard guidelines as mentioned in detail in the methodology section.

RESULTS

In our analysis, the success rate of LBBP-CRT was determined to be 91.1%. LBBP-

CRT significantly shortened QRS duration, with significant improvement in echocardiographic parameters, including left ventricular ejection fraction, left ventricular end-diastolic diameter and left ventricular end-systolic diameter in comparison with BiVP-CRT.

CONCLUSION

A significant reduction in New York Heart Association class and B-type natriuretic peptide levels was also observed in the LBBP-CRT group *vs* BiVP-CRT group. Lastly, the LBBP-CRT cohort had a reduced pacing threshold at follow-up as compared to BiVP-CRT.

Key Words: Left bundle branch pacing; Biventricular pacing; QRS duration; Left ventricular ejection fraction; Heart failure

Core Tip: Left bundle branch pacing (LBBP) is a unique pacing modality in cardio resynchronization therapy. LBBP-cardiac resynchronization therapy (CRT) improves the left ventricular ejection fraction, echocardiographic parameters, and clinical outcomes when compared to biventricular pacing (BiVP). It causes significant reduction in New York Heart Association class, pacing threshold and B-type natriuretic peptide. This systematic review and meta-analysis reviews and analyze the data comparing LBBP *vs* BiVP-CRT.

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INTRODUCTION

Left bundle branch block (LBBB) is of paramount importance given the evidence of worse prognosis in severe, symptomatic heart failure (HF) patients[1,2]. Cardiac resynchronization therapy (CRT) carries a strong recommendation for symptomatic patients with sinus rhythm, QRS duration (QRSd) ≥ 150 ms with LBBB morphology, and left ventricular ejection fraction (LVEF) ≤ 35% despite optimal medical therapy, with the goal of relieving symptoms and minimizing morbidity and mortality[3]. Biventricular pacing (BiVP) is the conventional CRT for LBBB, with HF showing significantly improved patient mortality[4]. However, not all patients respond to it, with an alarming non-response rate of approximately one-third[5]. Left bundle branch pacing (LBBP), a sub-type of conduction system pacing (CSP), has increasingly gained traction lately as an emerging, effective mode of CRT since it first showed a complete reversal of LBBB in HF patients[6]. Both procedures are subjected to non-responses due to variable patterns of mechanical desynchrony in HF patients, left ventricular pacing site, and cause of HF[5]. LBBP is deemed to be a less complex procedure and can target distal and deeper to the bundle of His such that it now serves as a potential alternative to His bundle pacing (HBP), *i.e.*, the more traditionally used type of CSP for LBBB[6]. Very recently, Wang *et al*[7] conducted the first randomized control trial (RCT) evaluating the efficacy of LBBP-CRT in improving echocardiographic parameters among patients with HF and reduced LVEF and demonstrated a greater degree of LVEF improvement with LBBP-CRT in comparison to BiVP-CRT. Another recent analysis by Chen *et al*[8] showed LBBP-CRT to have better electromechanical resynchronization, higher clinical and echocardiographic response, and especially higher rate of super-response than BiVP-CRT in patients with LVEF ≤ 35%, and LBBB with HF. A previous meta-analysis conducted by Cheng *et al*[9] excluded these studies, thus resulting in lower statistical power and inconsistent results. Hence, we performed an updated analysis pooling the first ever RCT published in the literature to provide a comprehensive clinical evaluation of the efficacy of LBBP-CRT and confirm the validity of the improved electromechanical resynchronization and clinical outcomes in comparison to BiVP-CRT.

MATERIALS AND METHODS

This systematic review and meta-analysis were conducted in accordance with the established methods recommended by the PRISMA, Cochrane, and AMSTAR-2 guidelines[10-12].

Data source and search strategy

An extensive literature search was conducted using MEDLINE (PubMed), Cochrane Library, and Scopus from inception through October 2022 to identify relevant studies evaluating the clinical and echocardiographic metrics between LBBP-CRT *vs* BiVP-CRT among HF patients with LBBB. We applied Boolean Operators 'OR' and 'AND' among synonymous

and different Medical subject headings terms and keywords, including 'left bundle branch pacing' OR 'left bundle branch area pacing' AND 'left bundle branch block' AND 'heart failure'. We placed no restrictions based on time, language, year, or geographical location/country of publication. We further manually searched reference lists of retrieved original publications, review articles, editorials, and online databases comprising Clinicaltrials.gov and preprints *via* MedRix.org to identify any grey literature.

Study selection and eligibility criteria

All the articles that were retrieved after the systematic search were exported to Endnote Reference Manager (Version X4; Clarivate Analytics, Philadelphia, PA, United States), where duplicates were identified and removed. Two independent reviewers (Moeed A and Raheel H) carefully examined the articles initially by title and abstract and then by full text to ensure relevance, and any disagreement was resolved through mutual consensus with the involvement of the senior investigator (Yasmin F). Articles with the following inclusion criteria were added to the review: (1) HF patients with LBBB; (2) comparative studies between LBBP and BVP; (3) studies reporting at least one of the outcomes of interest; and (4) retrospective or prospective cohort and RCT's.

Data extraction and study quality assessment

Two investigators (Moeed A and Raheel H) independently extracted data from shortlisted studies using pre-specified collection forms. All data related to the population and study characteristics were collected in addition to the outcomes of interest. The primary outcome of interest was QRSd. Secondary outcomes included pacing threshold, New York Heart Association (NYHA) classification, B-type natriuretic peptide (BNP) level, and echocardiographic parameters, including LVEF, left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD). The quality assessment of the observational studies was performed using the Newcastle-Ottawa scale[13], based on the pre-specified criterion of comparability, selection, and outcome or exposure of included studies, while Cochrane Collaboration's risk of bias tool for randomized controlled trials[14] was used to assess the quality of the RCT.

Statistical analysis

Review Manager (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was utilized for all statistical analyses. A random-effects model was employed, and the effect size was pooled as mean differences (MD) with corresponding 95% confidence intervals (95%CIs). Heterogeneity across studies was evaluated using Higgins I^2 statistics (I^2 = 25%-50% was considered mild, 50%-75% moderate, and > 75% severe heterogeneity)[15]. Sensitivity analysis was performed in which outlier studies having disproportionate effects on the overall effect size were excluded to address critical heterogeneity. A publication bias assessment could not be conducted as there were less than ten studies included in the meta-analysis as per the Cochrane guidelines[12]. A $P < 0.05$ was considered statistically significant in all cases.

RESULTS

Study characteristics

A preliminary search of the electronic databases yielded a total of 790 results. Applying the aforementioned eligibility criteria, 6 studies were included in the review[8,7,16-19]. A detailed description of the complete search strategy applied for each database is given in Supplementary Table 1, and the PRISMA flow chart summarizing the search and study selection process is given in Figure 1. A total of 6 studies (1 RCT and 5 comparative observational studies) with 389 participants (159 in LBBP-CRT *vs* 230 in BiVP-CRT) across 12 centers were included with a median follow-up of 9 mo (IQR 6-12.6)[8,7,16-19]. The LBBP-CRT success rate was 91.1%. Overall, 50.3% of the population constituted of males, and the mean age was 64 ± 4 years. Detailed study and patient characteristics are given in Table 1.

Primary outcome

All articles reported QRSd as an outcome. QRSd was significantly decreased with LBBP-CRT *vs* BiVP-CRT (LBBP-CRT mean 115.4 *vs* BiVP-CRT mean 138.0; MD = -22.65, 95%CI: -30.87 to -14.44, $P < 0.00001$, I^2 = 88%) (Figure 2).

Secondary outcomes and sensitivity analysis

Pacing threshold was also significantly lower in LBBP-CRT group compared to BiVP-CRT (LBBP-CRT mean 0.69 *vs* BiVP-CRT mean 1.24; MD = -0.56, 95%CI: -0.69 to 0.43, $P < 0.00001$, I^2 = 59%) (Figure 3). LBBP-CRT resulted in significantly increased LVEF (LBBP-CRT mean 43.8 *vs* BiVP-CRT mean 37.6; MD = 6.73, 95%CI: 4.48 to 8.97, $P < 0.00001$, I^2 = 0%), significantly decreased LVEDD (LBBP-CRT mean 55.9 *vs* BiVP-CRT mean 60.6; MD = -5.12, 95%CI: -7.21 to -3.03, $P < 0.00001$, I^2 = 5%), and reduced LVESD (LBBP-CRT mean 42.0 *vs* BiVP-CRT mean 47.3; MD = -5.57, 95%CI: -8.80 to -2.35, $P < 0.00007$, I^2 = 0%) compared to BiVP-CRT (Figures 4-6). The pooled analysis showed a significant decrease in NYHA class in LBBP-CRT *vs* BiVP-CRT patients (LBBP-CRT mean 1.3 *vs* BiVP-CRT mean 1.8; MD = -0.47, 95%CI: -0.73 to -0.21, $P < 0.00003$, I^2 = 65%) (Figure 7). LBBP-CRT showed a statistically significant decrease in BNP concentration on follow-up compared to BiVP-CRT (LBBP-CRT mean 311.3 *vs* BiVP-CRT mean 1145.3; SMD = -0.66, 95%CI: -0.96 to -0.35, $P < 0.00001$, I^2 = 0%) (Figure 8).

We additionally performed a series of sensitivity analysis to determine if any outlier study had disproportionate effects on the pooled estimates for the outcomes of QRSd, pacing threshold, and NYHA class. We found no change in the

Table 1 General characteristics of the included studies

Ref.	Area	Centre	Study design	Number of participants in LBBP	Number of participants in BiVP	Patients	Male sex in LBBP (%)	Age (yr) in LBBP	Success rate in LBBP (%)	Follow up (mo)	ICM (%) in LBBP
Wang *et al*[16], 2020	China	1	Matched case-control	10	30	HF, LBBB	90.0	64.8 ± 7.1	100.0	6.0	10
Guo *et al*[17], 2020	China	1	Prospective observational	21	21	HF, LBBB	42.9	66.1 ± 9.7	87.5	14.3	9.5
Wu *et al* [18], 2021	China	1	Prospective non-randomized	32	54	HF, LBBB	43.8	67.2 ± 13	100.0	12.0	3.1
Li *et al* [19], 2020	China	3	Prospective observational	27	54	HF, LBBB	58.1	56.8 ± 10.1	81.1	6.0	18.9
Chen *et al*[8], 2022	China	4	Prospective observational	49	51	HF, LBBB	50.0	67.1 ± 8.9	91.1	12.0	0
Wang *et al*[7], 2022	China	2	Randomized controlled trial	20	20	HF, LBBB	35.0	62.3 ± 11.2	90.0	6.0	0

LBBP: Left bundle branch pacing; BiVP: Biventricular pacing; ICM: Implantable Cardiac Monitor; HF: Heart failure; LBBB: Left bundle branch block.

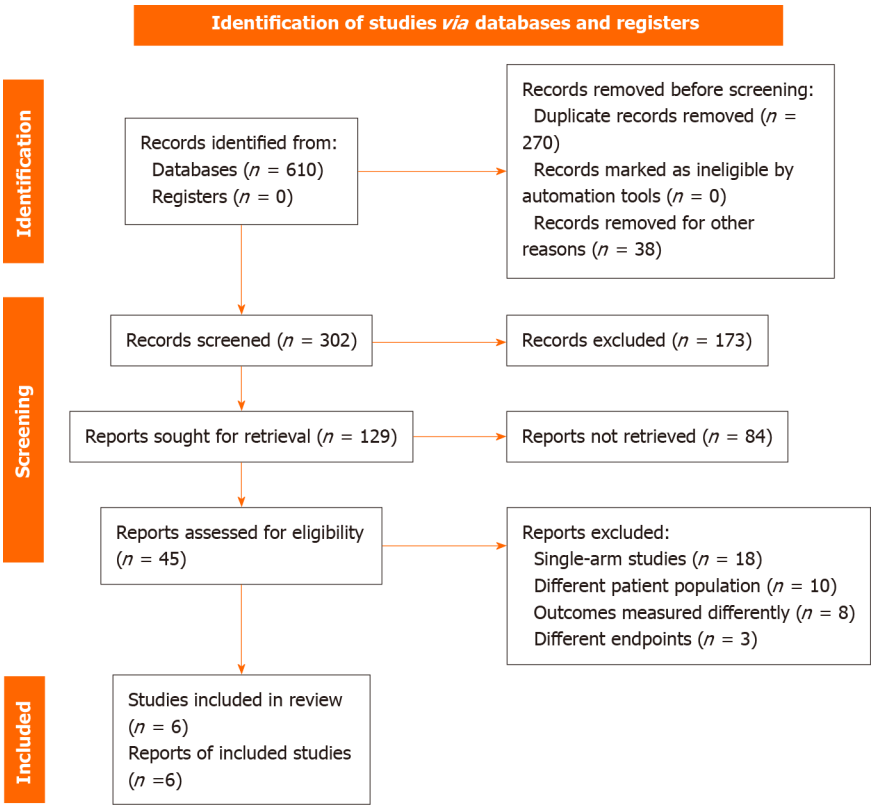

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Figure 1 PRISMA flowchart.

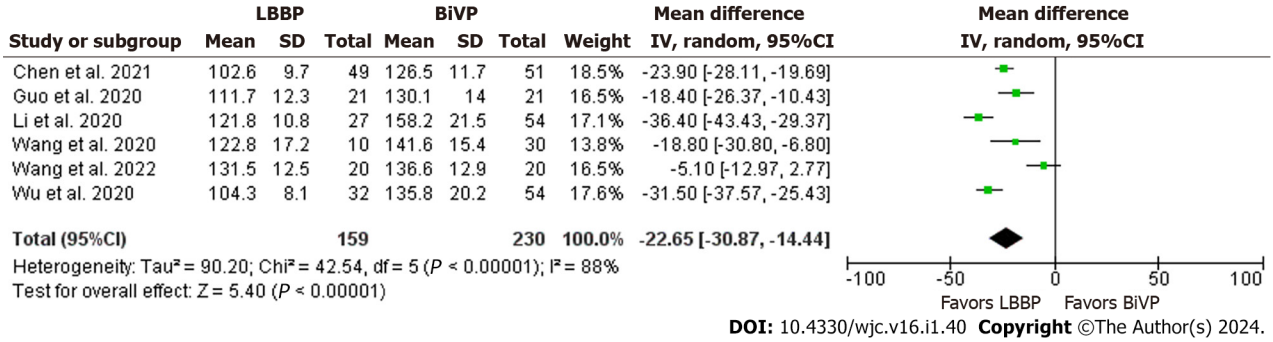

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Figure 2 Forest plot comparing paced QRS duration between left bundle branch pacing and biventricular pacing groups. 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.

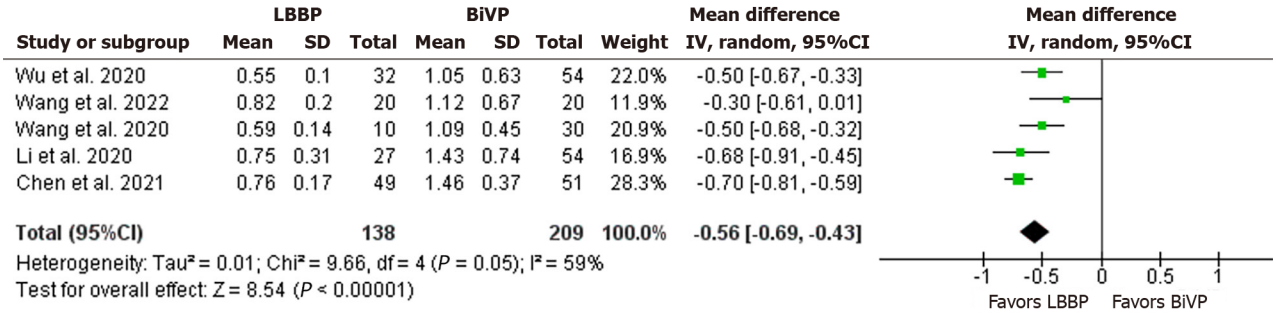

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Figure 3 Forest plot comparing pacing threshold at follow-up between left bundle branch pacing and biventricular pacing groups. 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.

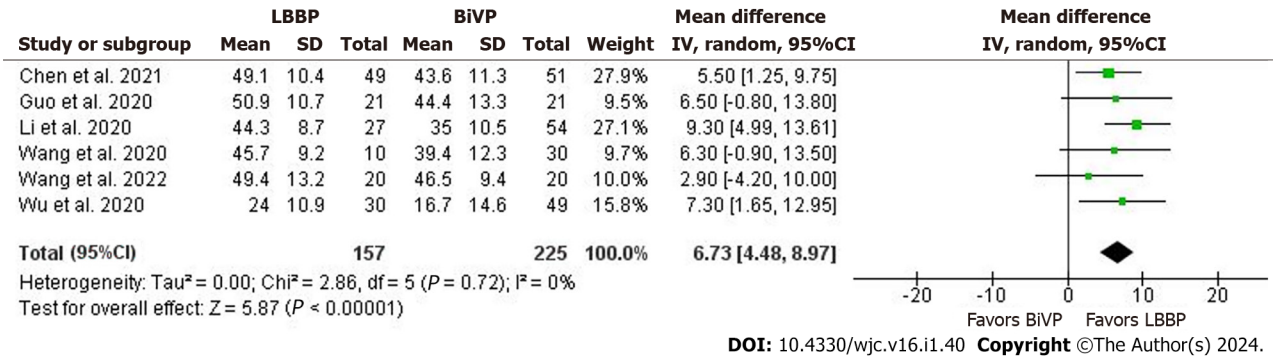

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Figure 4 Forest plot comparing paced left ventricular ejection fraction between left bundle branch pacing and biventricular pacing groups. 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.

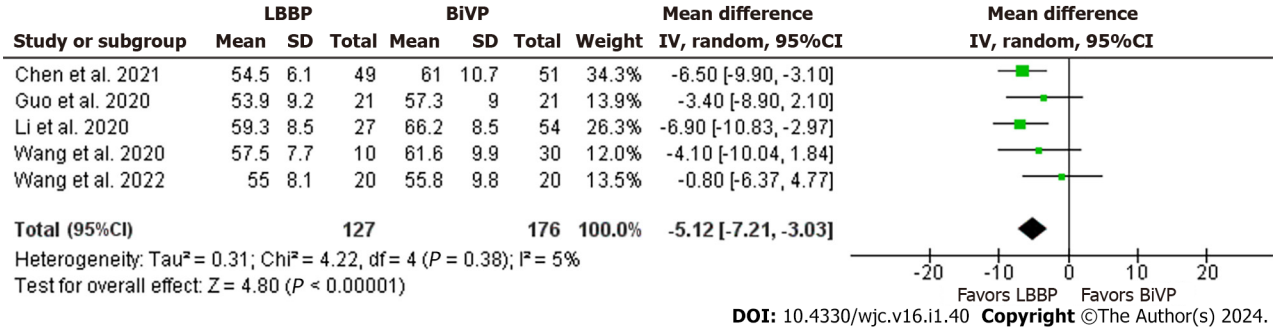
significance of the pooled results (Supplementary Figures 1-3).

Quality assessment

Owing to the robust methodology, most cohort studies were categorized as moderate to high quality on the NOS assessment tool. Wang *et al*[7] 2022 study was the only clinical trial included in the review, which was assessed through Cochrane risk of bias. All domains had a low risk of bias except the deviation from the intended interventions domain. The results of the quality assessment are mentioned in Supplementary Tables 2 and 3. The PRISMA and AMSTAR checklists have been included in Supplementary Tables 4 and 5.

DISCUSSION

In comparison to BiVP-CRT, LBBP-CRT was demonstrated to be safe and effective in enhancing LVEF with a low and consistent threshold. A smaller QRSd has been linked to improved mechanical synchronization of the ventricle[20]. Thus,



DOI: 10.4330/wjc.v16.i1.40

Figure 5 Forest plot comparing paced left ventricular end-diastolic diameter between left bundle branch pacing and biventricular pacing groups. 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.

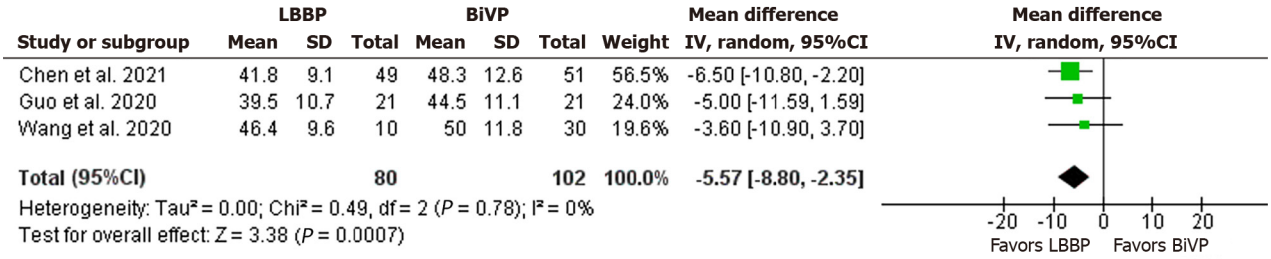


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Figure 6 Forest plot comparing paced left ventricular end-systolic diameter between left bundle branch pacing and biventricular pacing groups. 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.

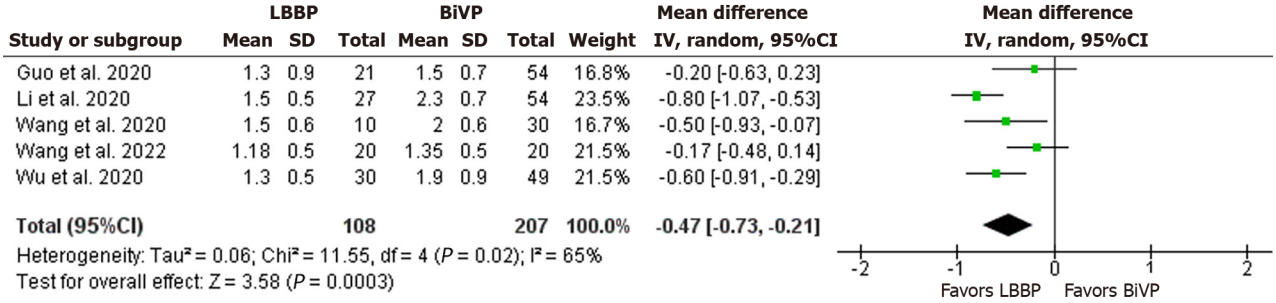

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Figure 7 Forest plot comparing New York Heart Association classification between left bundle branch pacing and biventricular pacing groups. 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.

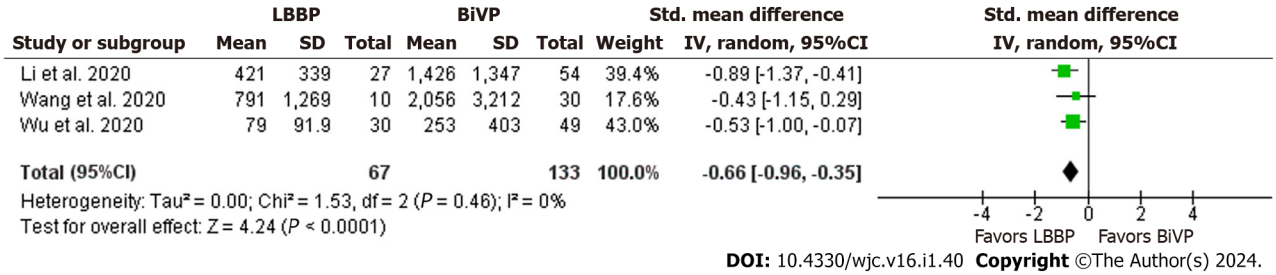

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Figure 8 Forest plot comparing B-type natriuretic peptide levels between left bundle branch pacing and biventricular pacing groups. 95%CI: 95% confidence interval; LBBP: Left bundle branch pacing; BiVP: Biventricular pacing.

our meta-analysis revealed that CRT provided more effective electrical and mechanical resynchronization *via* LBBP. Our study analyzed the pacing threshold at the time of implant and the pacing threshold at the time of follow-up. Five studies included in our analysis reported that the pacing threshold in LBBP-CRT was much lower than in BiVP-CRT. This is consistent with previous studies in which the pacing threshold at implant was lower in LBBP-CRT *vs* BiVP-CRT, and remained considerably lower in LBBP-CRT at 6-months and 1-year follow-up[8]. All six of our studies reported LVEF data. When compared to BiVP-CRT, LBBP-CRT dramatically raised LVEF. This is consistent with earlier studies in which patients in the LBBP-CRT group had significantly greater LVEF at 6-month follow-up than patients in the BiVP-CRT group[8], and a recent study by Vijayaraman *et al*[21] found a greater increase in LVEF with LBBP. In our analysis, five studies reported a substantial reduction in LVEDD with LBBP-CRT compared to BiVP-CRT. This is consistent with prior research, including a report by Huang *et al*[6], who first described LBBB and dilated cardiomyopathy in a 72-year-old lady with HF treated with LBBP.

They employed a low-pacing output to rectify the LBBB on the electrocardiogram, which RBBB accompanied. At one year, they discovered that LVEDD decreased to 42 mm from a baseline 76 mm[6].

Three studies reported on follow-up LVESD, which was much lower in LBBP-CRT patients compared to BiVP-CRT, which is consistent with earlier research in which LVESD was also significantly lower[22,23]. Furthermore, three studies reported increased BNP levels to have a strong clinical and hemodynamic correlation with the degree of left ventricular dysfunction. Our study demonstrated that LBBP-CRT patients had a statistically significant lower BNP concentration on follow-up than BiVP-CRT patients. Similar prior studies, such as Huang *et al*[6], reported a decrease in the BNP concentration from baseline. Moreover, NYHA classification was assessed when patients were followed up, and five studies revealed a substantial drop-in NYHA class in LBBP-CRT patients compared to BiVP-CRT patients. This is consistent with previous studies, which have shown that in comparison to BiVP-CRT, LBBP-CRT may reduce NYHA class[9].

Limitations

This meta-analysis has some limitations. All of the studies included in the quantitative synthesis were conducted in China. Thus, the results may not be applicable to a more diverse population. The median follow-up time of the included studies was 9 mo, serving as a limitation in judging the long-term efficacy of either of the two pacing methods. Although we included the first and only RCT published in the literature in our analysis, the majority of our pooled comparative studies were observational with small to moderate sample sizes. This could have introduced significant heterogeneity, however, to mitigate this compromise, we chose a random-effects methodology for our analysis. Thus, to ascertain the benefit of LBBP or BiVP in LBBB patients, it is imperative to conduct large-scale RCTs to solidify which pacing method is more appropriate in HF patients.

CONCLUSION

To conclude, our meta-analysis provided further clarity regarding the benefits of the novel LBBP-CRT in improving LVEF, cardiac echocardiographic parameters, and clinical outcomes when compared to BiVP-CRT.

ARTICLE HIGHLIGHTS

Research background

Biventricular pacing (BiVP) is the conventional mode of cardiac resynchronization therapy (CRT) for left bundle branch block (LBBB) with heart failure (HF), and shows significantly improved patient mortality. However, approximately one-third of the patients fail to response to it. Left bundle branch pacing (LBBP) has gained increasing attention recently as an effective mode of CRT showing complete reversal of LBBB among HF patients.

Research motivation

Several clinical studies evaluating the efficacy of LBBP-CRT in improving electromechanical resynchronization, clinical, and echocardiographic response in comparison to BiVP-CRT among patients with reduced left ventricular ejection fraction (LVEF), LBBP, and HF have been published but the results remain inconclusive. Hence, we performed an updated analysis pooling the recent clinical data to provide a comprehensive clinical evaluation of the efficacy of LBBP-CRT and confirm the validity of the improved electromechanical resynchronization and clinical outcomes in comparison to BiVP-CRT.

Research objectives

The primary outcome of interest was QRS duration. Secondary outcomes included pacing threshold, New York Heart Association (NYHA) classification, B-type natriuretic peptide (BNP) level, and echocardiographic parameters, including LVEF, l left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD).

Research methods

An extensive literature search was conducted using MEDLINE (PubMed), Cochrane Library, and Scopus from inception through October 2022 to identify relevant studies evaluating the clinical and echocardiographic metrics between LBBP-

CRT *vs* BiVP-CRT among HF patients with LBBB. A random-effects model was employed, and the effect size was pooled as mean differences with corresponding 95% confidence intervals. A $P < 0.05$ was considered statistically significant in all cases.

Research results

The success rate of LBBP-CRT was observed to be 91.1% in our analysis. LBBP-CRT resulted in increased LVEF, reduction in LVEDD, and LVESD compared to BiVP-CRT. Significantly reduced BNP levels, and NYHA class was also noted in the LBBP-CRT group *vs* BiVP-CRT group. Lastly, the LBBP-CRT cohort had a reduced pacing threshold at follow-up as compared to BiVP-CRT.

Research conclusions

Our analysis compared success rate, echocardiographic parameters and clinical response between LBBP-CRT *vs* BiVP-CRT and demonstrated LBBP-CRT to result in significantly improved cardiac echocardiographic parameters, and clinical outcomes when compared to BiVP-CRT.

Research perspectives

LBBP-CRT resulting in significant improvement in the echocardiographic parameters and clinical outcomes can help shape the clinical practice. Further larger randomized control trials are needed.

FOOTNOTES

Author contributions: Yasmin F, Moeed A, Ochani RK participated in the conceptualization, data curation, investigation, methodology, project administration, resources, supervision, validation, visualization, and writing of the original draft; Raheel H, Awan MAE, Liaquat A, Saleem A were involved in project administration, and writing of the original draft; Yasmin F, Moeed A, Aamir M, Hawwa N, and Surani S were involved in the formal analysis, project administration, supervision, validation, visualization, and writing - review & editing.

Conflict-of-interest statement: None of the authors have any conflict of interest to disclose.

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