ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2021 October 26; 13(10): 526-598

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 13 Number 10 October 26, 2021

MINIREVIEWS

ORIGINAL ARTICLE

Observational Study

Prospective Study

META-ANALYSIS

CASE REPORT

World Journal of Cardiology

Monthly Volume 13 Number 10 October 26, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Cardiology*, Massimo Iacoviello, MD, PhD, Associate Professor, Doctor, Department of Medical and Surgical Sciences, University of Foggia, Foggia 71122, Italy. massimo.iacoviello@unifg.it

AIMS AND SCOPE

The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJC mainly publishes articles reporting research results and findings obtained in the field of cardiology and covering a wide range of topics including acute coronary syndromes, aneurysm, angina, arrhythmias, atherosclerosis, atrial fibrillation, cardiomyopathy, congenital heart disease, coronary artery disease, heart failure, hypertension, imaging, infection, myocardial infarction, pathology, peripheral vessels, public health, Raynaud's syndrome, stroke, thrombosis, and valvular disease.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for *WJC* as 0.36. The *WJC*'s CiteScore for 2020 is 0.3, and Scopus CiteScore rank 2020: Cardiology and Cardiovascular Medicine is 289/317.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

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

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

PUBLICATION DATE
October 26, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Cardiology

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

World J Cardiol 2021 October 26; 13(10): 526-532

DOI: 10.4330/wjc.v13.i10.526

ISSN 1949-8462 (online)

MINIREVIEWS

Lipid lowering in patients 75 years and older

Umidakhon Makhmudova, P Christian Schulze, Harry R Davis, Oliver Weingärtner

ORCID number: Umidakhon Makhmudova 0000-0001-8746-5465; P Christian Schulze 0000-0001-9442-7141; Harry R Davis 0000-0003-2204-7232; Oliver Weingärtner 0000-0002-0236-206X.

Author contributions: Makhmudova U, Schulze PC, Davis HR and Weingärtner O wrote the manuscript and designed figures; All authors have read and approved the final manuscript.

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

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Umidakhon Makhmudova, P Christian Schulze, Oliver Weingärtner, Klinik für Innere Medizin I, Universitätsklinikum Jena, Jena 07747, Germany

Harry R Davis, Synergy Partners RD Solutions, Synergy Partners RD Solutions, Gaithersburg, MD 20850, United States

Corresponding author: Oliver Weingärtner, MD, PhD, Adjunct Professor, Klinik für Innere Medizin I, Universitätsklinikum Jena, Jena 07747, Germany. oliver.weingaertner@med.uni-jena.de

Abstract

More than twenty years ago, knowledge about the importance of cholesterol absorption and the potential therapeutic effect of its inhibition led to the discovery and clinical application of the first and only cholesterol absorption inhibitor to date – ezetimibe. Since then, ezetimibe has become a well-recognized player in lipid-lowering therapy. Recent findings of IMPROVE-IT and EWTOPIA 75 imply that elderly patients over the age of 75 years in particular benefit from ezetimibe. This review summarizes the evidence, discusses the possible underlying pathophysiological mechanisms and calls for a change in future dyslipidemia guidelines.

Key Words: Cholesterol; Cholesterol absorption; Cholesterol synthesis; Ezetimibe; Elderly

Core Tip: The review summarizes the evidence of lipid-lowering therapies in patients 75 years and older, and discusses the possible underlying pathophysiological mechanisms and calls for a change in future dyslipidemia guidelines.

Citation: Makhmudova U, Schulze PC, Davis HR, Weingärtner O. Lipid lowering in patients 75 years and older. *World J Cardiol* 2021; 13(10): 526-532

URL: https://www.wjgnet.com/1949-8462/full/v13/i10/526.htm

DOI: https://dx.doi.org/10.4330/wjc.v13.i10.526

Country/Territory of origin: Germany

Peer-review report's scientific quality classification

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

Received: April 1, 2021
Peer-review started: April 1, 2021
First decision: July 6, 2021
Revised: July 12, 2021
Accepted: September 8, 2021
Article in press: September 8, 2021
Published online: October 26, 2021

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

INTRODUCTION

Aging is a risk factor for cardiovascular morbidity, as the prevalence of atherosclerosis, myocardial infarction, and stroke increases with age[1]. Among all the physiological alterations that occur during the lifespan of a human being, changes in cholesterol metabolism are among the most important. Total cholesterol levels increase beginning from age 18-19 in men and age 20-21 in women and reach their climax at 50-51 and 56-57 years of age, respectively[2]. Although the concentration of endogenously synthesized cholesterol exceeds the amount of exogenous dietary cholesterol in the bloodstream, the inhibition of cholesterol absorption by ezetimibe reduces both low density lipoprotein (LDL)-c levels and the occurrence of cardiovascular events[3-5]. The particular benefit of ezetimibe treatment in regard to hard cardiovascular outcomes in patient populations over 75 years of age was only recently demonstrated in large cardiovascular outcome trials, such as IMPROVE-IT[6] (secondary prevention) and EWTOPIA 75[7] (primary prevention).

CHOLESTEROL METABOLISM

Cholesterol is one of the key components of the cell membrane and a precursor of steroid hormones, bile acids and vitamin D. Plasma cholesterol levels are regulated by three factors: Dietary absorption, endogenous biosynthesis in the liver and bile acids that are reabsorbed in the small intestine. Endogenous cholesterol synthesis begins with the 18-step formation of mevalonate through its conversion by HMG (3-hydroxy-3-methyl-glutaryl-) CoA reductase, which is a target of statin therapy, and ends with the 19-step synthesis of cholesterol from lanosterol. This cascade of reactions occurs in all nucleated cells and is catalyzed by a diversity of enzymes. Late precursors of cholesterol, such as squalene, cholestanol, desmosterol and lathosterol, are traditionally used as cholesterol synthesis markers. Due to its structure, cholesterol cannot be easily transported to tissues. Therefore, it is transported by lipoproteins, which contain triglycerides and cholesterol in their cores and apolipoproteins on their surface. Very low-density lipoprotein is synthesized in the liver and hydrolyzed to LDL in two steps. LDL is the major transporter of cholesterol in the plasma.

In addition to be endogenously synthesized, cholesterol is absorbed from the diet. In the small intestine, esterified cholesterol is converted to free cholesterol, which is absorbed *via* transport and endocytosis by NPC1L1 (Niemann-Pick C1-Like 1). In enterocytes, chylomicrons are formed from cholesterol, phospholipids, and triacylglycerol by apoprotein B48. Chylomicrons are transported *via* the lymphatic system to the bloodstream, where they deliver fatty acids to peripheral tissues and are eventually degraded by the liver. Moreover, nonesterified plant sterols and "excess cholesterol" are excreted back into the small intestine *via* the ATP-binding cassette transporter (ABCG5/G8) heterodimer. This results in large differences between cholesterol and plant sterol concentrations in the bloodstream, with plasma cholesterol levels being approximately 1000-fold higher than plant sterol levels.

PATHOPHYSIOLOGIC ASPECTS OF CHOLESTEROL METABOLISM IN AGING

The increase in LDL-c levels with age can be explained by several factors: A decrease in LDL receptor levels, an increase in the levels of apoB-100 in the liver and serum[8], an increase in cholesterol absorption, and a decrease in bile acid synthesis[9].

Animal studies have demonstrated that the cholesterol absorption rate increases with age[10,11]. According to Duan *et al*[11], cholesterol absorption in older mice (measured by the plasma dual isotope ratio method) is higher than that in younger mice, which is mechanistically explained by an increase in NPC1L1 mRNA expression with aging. Interestingly, the expression of ABCG5/G8, a transporter that pumps plant sterols back into the intestinal lumen and thus decreases plant sterol concentrations in the plasma, is negatively correlated with aging[11].

Another important age-related alteration is a reduction in CYP7A1 expression, an enzyme involved in bile acid synthesis. This leads to a decrease in bile acid synthesis, which in turn results in a lower cholesterol utilization rate[9].

Unfortunately, the number of human studies in this context is very limited. One study reported a positive correlation between cholesterol synthesis marker levels and

aging in a Northern Italian population. In that study, cholesterol absorption marker levels were also elevated in elderly individuals but not in patients with gallstones[12] (Figure 1).

METHODS OF CHOLESTEROL ABSORPTION MEASUREMENT

Methods to quantify cholesterol absorption were established as early as 1960[13,14]. Almost all of the early methods were based on isotope labeling of plasma and fecal probes: Cholesterol balance, single-dose isotopic feeding, dual isotope plasma ratio, continuous isotope feeding, and intestinal perfusion[13]. Another validated method that does not require isotope feeding is the measurement of the ratio of plant sterol levels (campesterol and sitosterol) and cholestanol levels (metabolite of cholesterol), which is performed mainly *via* high-performance liquid chromatography. Plant sterol concentrations have been shown in several studies to be markers of cholesterol absorption[15].

INHIBITION OF CHOLESTEROL ABSORPTION IN ELDERLY INDIVIDUALS

Early studies

A landmark study addressing the importance of cholesterol metabolism in elderly patients was the DEBATE-Study[16]. Strandberg and colleagues conducted a prospective cohort study of home-dwelling elderly individuals to assess the prognostic value of markers of cholesterol metabolism (absorption *vs* synthesis). They found that low cholesterol absorption in individuals older than 75 years of age was associated with fewer cardiovascular events and better survival. In that study, the levels of markers of cholesterol synthesis were negatively associated with cardiovascular outcomes[16]. Strandberg and colleagues speculated that lower cholesterol absorption was associated with better prognosis since these individuals had a lower cholesterol burden during their lifespan. On the other hand, the worse prognosis may have also been due to increased plant sterol absorption. Similar results were reported by our group in elderly patients with aortic stenosis and patients with diabetes mellitus[17,18].

Statins

Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase in the liver, thus preventing the formation of mevalonate, which determines the rate of endogenous cholesterol synthesis[19]. Statins reduce LDL-c levels by up to 60% depending on the specific drug and dose (rosuvastatin is the most potent statin, as 40 mg of rosuvastatin reduces LDL-c levels by 55%)[20]. Although statins are the cornerstone of lipid-lowering therapy, target goal attainment with statin monotherapy is often unsatisfactory. In JUPITER (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin), approximately 10% of the patients showed no change in LDL-c levels, and over 40% had a LDL-c level reduction below 50%[21]. Several loci were identified by genome-wide association studies to be responsible for "nonresponsiveness" to statin therapy[21,22]. On the other hand, ezetimibe treatment is particularly effective in these patients since low endogenous synthesis is associated with high cholesterol absorption[23,24].

The secondary analysis of ALLHAT-LTT demonstrated that statins (pravastatin) conveyed no benefit in a primary prevention setting. Moreover, there was a nonsignificant trend toward increased all-cause mortality in the pravastatin group vs. the placebo group. PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) evaluated hard cardiovascular outcomes in pravastatin- *vs* placebo-treated patients. Pravastatin reduced primary endpoints (a composite of coronary death, nonfatal myocardial infarction, and nonfatal stroke occurrence) after 3 years of follow-up. The subgroup analysis in the study revealed that this effect was stronger among those with established cardiovascular disease than among those without cardiovascular diseases, implying that statins are less effective in a primary prevention setting. However, no significant difference was observed in the interaction test between groups. Moreover, in pravastatin-treated patients, the incidence of newly diagnosed cancer was 25% higher than in the placebo group, although a meta-analysis did not show any significant association with cancer[25].

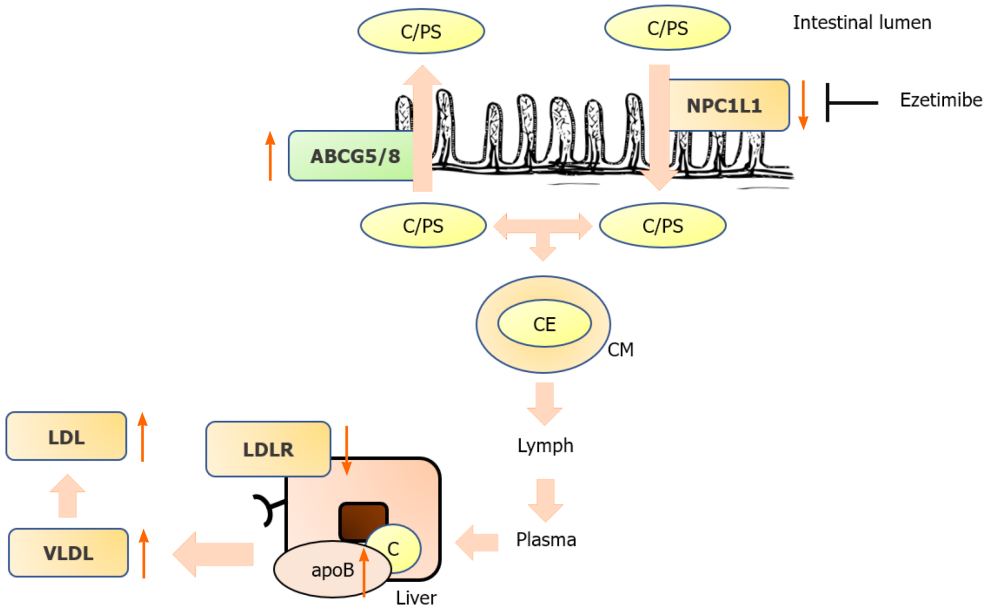


Figure 1 Alteration of cholesterol metabolism during lifetime. Dietary cholesterol is absorbed in the intestinal lumen *via* transport and endocytosis, which is regulated by NPC1L1. NPC1L1 mRNA expression decreases with increasing age. On the other hand, about 50% of dietary cholesterol and about 95% of plant sterols are pumped back into the intestinal lumen by ABCG5/8, which is upregulated in elderly individuals. Cholesterol is packed into the chylomicrons and transported to the liver. Chylomicron remnants are taken up by the low density lipoprotein (LDL)-receptor in the liver. Moreover, endogenous cholesterol is synthesized in the liver. Endogenously synthesized cholesterol is transported to peripheral tissues *via* LDL. The red arrow shows age-related up- or downregulation of different genes/proteins in cholesterol metabolism. C: Cholesterol; PS: Plant sterols, CM: Chylomicrone; LDL: Low density lipoprotein; VLDL: Very low-density lipoprotein; NPC1L1: Niemann-Pick C1-like 1; ABCG5/8-ATP: Binding cassette transporter G5/G8.

Ezetimibe

Ezetimibe targets NPC1L1 in the small intestine, resulting in the inhibition of cholesterol and plant sterol absorption. In humans, ezetimibe also inhibits hepatic NPC1L1 to prevent reabsorption of cholesterol and plant sterols from the bile and increases their excretion. Ezetimibe is metabolized to ezetimibe-glucuronide, which is also a potent inhibitor of NPC1L1. The maximal concentration is reached 1–2 h after oral administration, and it has a terminal half-life of 22 h[3]. Ezetimibe lowers LDL-c levels by approximately 20%[3,4]. PRECISE-IVUS demonstrated that ezetimibe in combination with atorvastatin resulted in greater coronary plaque regression than atorvastatin monotherapy in patients with coronary artery disease[26]. The SHARP trial demonstrated that the combination of statins and ezetimibe reduced LDL-c levels and cardiovascular outcomes in patients with chronic kidney disease[27]. According to the current ESC/EAS guidelines, ezetimibe is recommended as an adjuvant to statin therapy when LDL-c goals cannot be achieved by statin monotherapy[28].

A post hoc analysis of the Scandinavian Simvastatin Survival Study (4S) suggested that patients with high cholesterol absorption and low cholesterol synthesis did not benefit from statins in terms of cardiovascular event reduction[29]. HIJ-Proper, on the other hand, demonstrated that patients with high cholesterol absorption benefited from the addition of ezetimibe in terms of cardiovascular event reduction, whereas patients with low cholesterol absorption did not[30].

IMPROVE-IT secondary analysis – addition of ezetimibe to a statin in elderly patients after acute coronary syndrome

IMPROVE-IT demonstrated for the first time that ezetimibe, a nonstatin drug, reduces LDL-c levels and hard cardiovascular outcomes[5]. In a recent secondary analysis, the outcomes of IMPROVE-IT were analyzed according to age. Interestingly, in patients older than 75 years of age, ezetimibe treatment was much more effective in reducing cardiovascular events. In patients over 75 years of age, the number "needed to treat" was 11, whereas it was 125 in patients younger than 75 years of age[6]. These findings illustrate the preventive capacity of adding a cholesterol absorption inhibitor in elderly individuals over 75 years of age[31].

EWTOPIA 75 – ezetimibe in the primary prevention of cardiovascular disease in elderly individuals

The EWTOPIA 75 study is a prospective, double-blind, placebo-controlled randomized trial that was conducted in Japan and demonstrated the benefit of ezetimibe in elderly patients without a history of coronary artery disease[7]. In this primary prevention trial, ezetimibe reduced both LDL-C levels and hard cardiovascular outcomes. This further adds to the notion that individuals over 75 years of age with elevated cholesterol levels benefit in particular from ezetimibe treatment[32]. This is of particular interest since all statin trials of primary prevention in patients over 75 years of age failed to reduce cardiovascular events[25,33].

Possible role of plant sterols

In a recently published large-scale genetic analysis of over 1 million individuals with and without cardiovascular diseases, Helgadottir and colleagues reported genetic variants of ABCG5/G8 and NPC1L1 that increase plasma plant sterol levels, and plasma cholesterol levels have a greater impact on cardiovascular risk than the levels of other lipid genes that increase only serum cholesterol levels (LDL-c receptor, HMG-CoA-reductase, apoB, *etc*.). Genes that increased non-HDL cholesterol levels by 1 mmol/L and also increased serum plant sterol levels increased cardiovascular risk 2.0-fold. However, genes that increased serum non-HDL cholesterol levels by 1 mmol/L but had no impact on serum plant sterol levels increased cardiovascular risk only 1.5-fold[34]. These findings are important since they demonstrate that plant sterols "per se" are atherogenic. On the basis of these findings, determination of the levels of markers of cholesterol metabolism, such as campesterol, sitosterol and lathosterol, should play a more important role in future cardiovascular risk stratification and a more personalized and individualized treatment approach for hyperlipidemia[24,35]. As early as 2016, we suggested evaluating the ratio of cholesterol synthesis and absorption in IMPROVE-IT[36]. This analysis is under way, as assured by the TIMI Study group, and will provide important mechanistic insights[37].

CONCLUSION

Evidence from animal studies and human trials indicates that cholesterol and plant sterol absorption increase with age. Findings from large-scale prospective, randomized trials on primary and secondary prevention demonstrate that patients over 75 years of age benefit in particular from the addition of a cholesterol absorption inhibitor, such as ezetimibe. Therefore, ezetimibe should be the lipid-lowering drug of choice in patients 75 years and older.

REFERENCES

1 **Rodgers JL**, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, Karia K, Panguluri SK. Cardiovascular Risks Associated with Gender and Aging. *J Cardiovasc Dev Dis* 2019; **6** [PMID: 31035613 DOI: 10.3390/jcdd6020019]

2 **Yi SW**, Yi JJ, Ohrr H. Total cholesterol and all-cause mortality by sex and age: a prospective cohort study among 12.8 million adults. *Sci Rep* 2019; **9**: 1596 [PMID: 30733566 DOI: 10.1038/s41598-018-38461-y]

3 **Kosoglou T**, Statkevich P, Johnson-Levonas AO, Paolini JF, Bergman AJ, Alton KB. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2005; **44**: 467-494 [PMID: 15871634 DOI: 10.2165/00003088-200544050-00002]

4 **Morrone D**, Weintraub WS, Toth PP, Hanson ME, Lowe RS, Lin J, Shah AK, Tershakovec AM. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. *Atherosclerosis* 2012; **223**: 251-261 [PMID: 22410123 DOI: 10.1016/j.atherosclerosis.2012.02.016]

5 **Cannon CP**, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015; **372**: 2387-2397 [PMID: 26039521 DOI: 10.1056/NEJMoa1410489]

6 **Bach RG**, Cannon CP, Giugliano RP, White JA, Lokhnygina Y, Bohula EA, Califf RM, Braunwald E, Blazing MA. Effect of Simvastatin-Ezetimibe Compared With Simvastatin Monotherapy After Acute Coronary Syndrome Among Patients 75 Years or Older: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol* 2019; **4**: 846-854 [PMID: 31314050 DOI:

10.1001/jamacardio.2019.2306]
7 **Ouchi Y**, Sasaki J, Arai H, Yokote K, Harada K, Katayama Y, Urabe T, Uchida Y, Hayashi M, Yokota N, Nishida H, Otonari T, Arai T, Sakuma I, Sakabe K, Yamamoto M, Kobayashi T, Oikawa S, Yamashita S, Rakugi H, Imai T, Tanaka S, Ohashi Y, Kuwabara M, Ito H. Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized, Controlled Trial. *Circulation* 2019; **140**: 992-1003 [PMID: 31434507 DOI: 10.1161/CIRCULATIONAHA.118.039415]
8 **Higuchi K**, Kitagawa K, Kogishi K, Takeda T. Developmental and age-related changes in apolipoprotein B mRNA editing in mice. *J Lipid Res* 1992; **33**: 1753-1764 [PMID: 1479285 DOI: 10.1016/S0022-2275(20)41333-1]
9 **Morgan AE**, Mooney KM, Wilkinson SJ, Pickles NA, Mc Auley MT. Cholesterol metabolism: A review of how ageing disrupts the biological mechanisms responsible for its regulation. *Ageing Res Rev* 2016; **27**: 108-124 [PMID: 27045039 DOI: 10.1016/j.arr.2016.03.008]
10 **Hollander D**, Morgan D. Increase in cholesterol intestinal absorption with aging in the rat. *Exp Gerontol* 1979; **14**: 201-204 [PMID: 477764 DOI: 10.1016/0531-5565(79)90020-2]
11 **Duan LP**, Wang HH, Ohashi A, Wang DQ. Role of intestinal sterol transporters Abcg5, Abcg8, and Npc1 L1 in cholesterol absorption in mice: gender and age effects. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G269-G276 [PMID: 16179600 DOI: 10.1152/ajpgi.00172.2005]
12 **Bertolotti M**, Mussi C, Pellegrini E, Magni A, Del Puppo M, Ognibene S, Carulli L, Anzivino C, Baldelli E, Loria P, Carulli N. Age-associated alterations in cholesterol homeostasis: evidence from a cross-sectional study in a Northern Italy population. *Clin Interv Aging* 2014; **9**: 425-432 [PMID: 24669190 DOI: 10.2147/CIA.S57714]
13 **Matthan NR**, Lichtenstein AH. Approaches to measuring cholesterol absorption in humans. *Atherosclerosis* 2004; **174**: 197-205 [PMID: 15136049 DOI: 10.1016/S0021-9150(03)00248-X]
14 **Wang DQ**, Carey MC. Measurement of intestinal cholesterol absorption by plasma and fecal dual-isotope ratio, mass balance, and lymph fistula methods in the mouse: an analysis of direct *vs* indirect methodologies. *J Lipid Res* 2003; **44**: 1042-1059 [PMID: 12588946 DOI: 10.1194/jlr.D200041-JLR200]
15 **Tilvis RS**, Miettinen TA. Serum plant sterols and their relation to cholesterol absorption. *Am J Clin Nutr* 1986; **43**: 92-97 [PMID: 3942097 DOI: 10.1093/ajcn/43.1.92]
16 **Strandberg TE**, Tilvis RS, Pitkala KH, Miettinen TA. Cholesterol and glucose metabolism and recurrent cardiovascular events among the elderly: a prospective study. *J Am Coll Cardiol* 2006; **48**: 708-714 [PMID: 16904538 DOI: 10.1016/j.jacc.2006.04.081]
17 **Weingärtner O**, Weingärtner N, Scheller B, Lütjohann D, Gräber S, Schäfers HJ, Böhm M, Laufs U. Alterations in cholesterol homeostasis are associated with coronary heart disease in patients with aortic stenosis. *Coron Artery Dis* 2009; **20**: 376-382 [PMID: 19620855 DOI: 10.1097/MCA.0b013e32832fa947]
18 **Weingärtner O**, Lütjohann D, Vanmierlo T, Müller S, Günther L, Herrmann W, Böhm M, Laufs U, Herrmann M. Markers of enhanced cholesterol absorption are a strong predictor for cardiovascular diseases in patients without diabetes mellitus. *Chem Phys Lipids* 2011; **164**: 451-456 [PMID: 21501602 DOI: 10.1016/j.chemphyslip.2011.03.008]
19 **Endo A**. The discovery and development of HMG-CoA reductase inhibitors. *J Lipid Res* 1992; **33**: 1569-1582 [PMID: 1464741 DOI: 10.1016/S0022-2275(20)41379-3]
20 **Hou R**, Goldberg AC. Lowering low-density lipoprotein cholesterol: statins, ezetimibe, bile acid sequestrants, and combinations: comparative efficacy and safety. *Endocrinol Metab Clin North Am* 2009; **38**: 79-97 [PMID: 19217513 DOI: 10.1016/j.ecl.2008.11.007]
21 **Ridker PM**, Mora S, Rose L; JUPITER Trial Study Group. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. *Eur Heart J* 2016; **37**: 1373-1379 [PMID: 26916794 DOI: 10.1093/eurheartj/ehw046]
22 **Postmus I**, Trompet S, Deshmukh HA, Barnes MR, Li X, Warren HR, Chasman DI, Zhou K, Arsenault BJ, Donnelly LA, Wiggins KL, Avery CL, Griffin P, Feng Q, Taylor KD, Li G, Evans DS, Smith AV, de Keyser CE, Johnson AD, de Craen AJ, Stott DJ, Buckley BM, Ford I, Westendorp RG, Slagboom PE, Sattar N, Munroe PB, Sever P, Poulter N, Stanton A, Shields DC, O'Brien E, Shaw-Hawkins S, Chen YD, Nickerson DA, Smith JD, Dubé MP, Boekholdt SM, Hovingh GK, Kastelein JJ, McKeigue PM, Betteridge J, Neil A, Durrington PN, Doney A, Carr F, Morris A, McCarthy MI, Groop L, Ahlqvist E; Welcome Trust Case Control Consortium, Bis JC, Rice K, Smith NL, Lumley T, Whitsel EA, Stürmer T, Boerwinkle E, Ngwa JS, O'Donnell CJ, Vasan RS, Wei WQ, Wilke RA, Liu CT, Sun F, Guo X, Heckbert SR, Post W, Sotoodehnia N, Arnold AM, Stafford JM, Ding J, Herrington DM, Kritchevsky SB, Eiriksdottir G, Launer LJ, Harris TB, Chu AY, Giulianini F, MacFadyen JG, Barratt BJ, Nyberg F, Stricker BH, Uitterlinden AG, Hofman A, Rivadeneira F, Emilsson V, Franco OH, Ridker PM, Gudnason V, Liu Y, Denny JC, Ballantyne CM, Rotter JI, Adrienne Cupples L, Psaty BM, Palmer CN, Tardif JC, Colhoun HM, Hitman G, Krauss RM, Wouter Jukema J, Caulfield MJ. Pharmacogenetic meta-analysis of genome-wide association studies of LDL cholesterol response to statins. *Nat Commun* 2014; **5**: 5068 [PMID: 25350695 DOI: 10.1038/ncomms6068]
23 **Weingärtner O**, Lütjohann D, Böhm M, Laufs U. Relationship between cholesterol synthesis and intestinal absorption is associated with cardiovascular risk. *Atherosclerosis* 2010; **210**: 362-365 [PMID: 20116793 DOI: 10.1016/j.atherosclerosis.2010.01.003]

24 **Lütjohann D**, Stellaard F, Mulder MT, Sijbrands EJG, Weingärtner O. The emerging concept of "individualized cholesterol-lowering therapy": A change in paradigm. *Pharmacol Ther* 2019; **199**: 111-116 [PMID: 30877023 DOI: 10.1016/j.pharmthera.2019.03.004]

25 **Shepherd J**, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG; PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; **360**: 1623-1630 [PMID: 12457784 DOI: 10.1016/s0140-6736(02)11600-x]

26 **Tsujita K**, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, Komura N, Sakamoto K, Ono T, Oka H, Nakao K, Nakamura S, Ishihara M, Matsui K, Sakaino N, Nakamura N, Yamamoto N, Koide S, Matsumura T, Fujimoto K, Tsunoda R, Morikami Y, Matsuyama K, Oshima S, Kaikita K, Hokimoto S, Ogawa H; PRECISE-IVUS study investigators. Plaque REgression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by IntraVascular UltraSound (PRECISE-IVUS Trial): Study protocol for a randomized controlled trial. *J Cardiol* 2015; **66**: 353-358 [PMID: 25577723 DOI: 10.1016/j.jjcc.2014.12.011]

27 **Baigent C**, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011; **377**: 2181-2192 [PMID: 21663949 DOI: 10.1016/S0140-6736(11)60739-3]

28 **Mach F**, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; **41**: 111-188 [PMID: 31504418 DOI: 10.1093/eurheartj/ehz455]

29 **Miettinen TA**, Gylling H, Strandberg T, Sarna S. Baseline serum cholestanol as predictor of recurrent coronary events in subgroup of Scandinavian simvastatin survival study. Finnish 4S Investigators. *BMJ* 1998; **316**: 1127-1130 [PMID: 9552949 DOI: 10.1136/bmj.316.7138.1127]

30 **Hagiwara N**, Kawada-Watanabe E, Koyanagi R, Arashi H, Yamaguchi J, Nakao K, Tobaru T, Tanaka H, Oka T, Endoh Y, Saito K, Uchida T, Matsui K, Ogawa H. Low-density lipoprotein cholesterol targeting with pitavastatin + ezetimibe for patients with acute coronary syndrome and dyslipidaemia: the HIJ-PROPER study, a prospective, open-label, randomized trial. *Eur Heart J* 2017; **38**: 2264-2276 [PMID: 28430910 DOI: 10.1093/eurheartj/ehx162]

31 **Weingärtner O**, Sijbrands EJG, Lütjohann D. Interpreting the Benefit of Simvastatin-Ezetimibe in Patients 75 Years or Older. *JAMA Cardiol* 2020; **5**: 234 [PMID: 31895451 DOI: 10.1001/jamacardio.2019.5197]

32 **Weingärtner O**, Sijbrands E, Lütjohann D. Letter by Weingärtner *et al* Regarding Article, "Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized, Controlled Trial". *Circulation* 2020; **141**: e65-e66 [PMID: 32078427 DOI: 10.1161/CIRCULATIONAHA.119.043726]

33 **Han BH**, Sutin D, Williamson JD, Davis BR, Piller LB, Pervin H, Pressel SL, Blaum CS; ALLHAT Collaborative Research Group. Effect of Statin Treatment *vs* Usual Care on Primary Cardiovascular Prevention Among Older Adults: The ALLHAT-LLT Randomized Clinical Trial. *JAMA Intern Med* 2017; **177**: 955-965 [PMID: 28531241 DOI: 10.1001/jamainternmed.2017.1442]

34 **Helgadottir A**, Thorleifsson G, Alexandersson KF, Tragante V, Thorsteinsdottir M, Eiriksson FF, Gretarsdottir S, Björnsson E, Magnusson O, Sveinbjornsson G, Jonsdottir I, Steinthorsdottir V, Ferkingstad E, Jensson BÖ, Stefansson H, Olafsson I, Christensen AH, Torp-Pedersen C, Køber L, Pedersen OB, Erikstrup C, Sørensen E, Brunak S, Banasik K, Hansen TF, Nyegaard M, Eyjolfssson GI, Sigurdardottir O, Thorarinsson BL, Matthiasson SE, Steingrimsdottir T, Bjornsson ES, Danielsen R, Asselbergs FW, Arnar DO, Ullum H, Bundgaard H, Sulem P, Thorsteinsdottir U, Thorgeirsson G, Holm H, Gudbjartsson DF, Stefansson K. Genetic variability in the absorption of dietary sterols affects the risk of coronary artery disease. *Eur Heart J* 2020; **41**: 2618-2628 [PMID: 32702746 DOI: 10.1093/eurheartj/ehaa531]

35 **Weingärtner O**, Patel SB, Lütjohann D. It's time to personalize and optimize lipid-lowering therapy. *Eur Heart J* 2020; **41**: 2629-2631 [PMID: 32702747 DOI: 10.1093/eurheartj/ehaa445]

36 **Weingärtner O**, Lütjohann D, Elsässer A. Personalize and Optimize Lipid-Lowering Therapies. *J Am Coll Cardiol* 2016; **68**: 325-326 [PMID: 27417013 DOI: 10.1016/j.jacc.2016.02.086]

37 **Murphy SA**, Cannon CP, Blazing MA, Giugliano RP, Tershakovec AM, Braunwald E. Reply: Personalize and Optimize Lipid-Lowering Therapies. *J Am Coll Cardiol* 2016; **68**: 326 [PMID: 27417014 DOI: 10.1016/j.jacc.2016.04.043]

World Journal of Cardiology

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

World J Cardiol 2021 October 26; 13(10): 533-545

DOI: 10.4330/wjc.v13.i10.533

ISSN 1949-8462 (online)

MINIREVIEWS

Electrocardiographic changes in Emphysema

Puneet Gupta, Hitangee Jain, Misbah Gill, Gurpreet Bharaj, Nauman Khalid, Waseem Chaudhry, Lovely Chhabra

ORCID number: Puneet Gupta 0000-0001-9298-3443; Hitangee Jain 0000-0001-6975-6146; Misbah Gill 0000-0001-5373-3601; Gurpreet Bharaj 0000-0002-8205-6547; Nauman Khalid 0000-0003-4159-555X; Waseem Chaudhry 0000-0003-0430-6886; Lovely Chhabra 0000-0002-9193-5981.

Author contributions: Gupta P performed the research and a major contribution to the manuscript draft; Jain H contributed to the manuscript draft, schematic illustrations copyright approvals and minor revisions; Gill M and Bharaj G contributed to draft revisions; Khalid N and Waseem C contributed to the analysis and revisions; Chhabra L conceptualized the project, supervised the research, contributed substantially to the manuscript draft, and performed major revisions.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Puneet Gupta, Department of Interventional Cardiology, Northeast Ohio Medical University, Canton, OH 44272, United States

Hitangee Jain, BA-MD, Brooklyn College, Brooklyn, NY 11210, United States

Misbah Gill, Department of Family Medicine, Memorial Hospital of Carbondale, Carbondale, IL 62901, United States

Gurpreet Bharaj, Psychiatry, Loretto Hospital, Chicago, IL 60644, United States

Nauman Khalid, Department of Interventional Cardiology, St. Francis Medical Center, Monroe, LA 71201, United States

Waseem Chaudhry, Lovely Chhabra, Department of Cardiology, Westchester Medical Center Network Advanced Physician Services, Poughkeepsie, NY 12601, United States

Corresponding author: Lovely Chhabra, FACC, MD, Doctor, Department of Cardiology, Westchester Medical Center Network Advanced Physician Services, 241 North Road, Poughkeepsie, NY 12601, United States. lovids@hotmail.com

Abstract

Chronic obstructive lung disease (COPD), predominantly emphysema, causes several thoracic anatomical and hemodynamic changes which may cause changes in various electrocardiographic parameters. A 12-lead electrocardiogram (ECG), which is often a part of routine evaluation in most clinical settings, may serve as a useful screening modality for diagnosis of COPD or emphysema. Our current article aims to provide a comprehensive review of the electrocardiographic changes encountered in COPD/emphysema utilizing published PubMed and Medline literature database. Several important ECG changes are present in COPD/emphysema and may serve as a good diagnostic tool. Verticalization of P-vector, changes in QRS duration, pattern recognition of precordial R-wave progression and axial shifts can be considered some of the most valuable markers among other changes. In conclusion, 12-lead surface electrocardiogram can serve as a valuable tool for the diagnosis of COPD and/or emphysema. An appropriate knowledge of these ECG changes can not only help in the diagnosis but can also immensely help in an appropriate clinical management of these patients.

Key Words: Emphysema; Chronic obstructive pulmonary disease; Electrocardiogram; P-wave axis; Sensitivity; Specificity

Manuscript source: Unsolicited manuscript

Specialty type: Cardiac and Cardiovascular Systems

Country/Territory of origin: United States

Peer-review report's scientific quality classification

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

Received: May 1, 2021
Peer-review started: May 1, 2021
First decision: June 7, 2021
Revised: June 25, 2021
Accepted: September 26, 2021
Article in press: September 26, 2021
Published online: October 26, 2021

P-Reviewer: Yamamoto H
S-Editor: Chang KL
L-Editor: A
P-Editor: Wang LYT

Core Tip: Chronic obstructive pulmonary disease (COPD) remains a major cause of morbidity and mortality in the United States. With COPD, a timely diagnosis and treatment are crucial to prevent increasing severity. COPD can cause electrocardiographic changes due to factors including lung hyperinflation. These changes can be present on the electrocardiograms of patients without COPD; however, specific parameters not seen in those with COPD will be indicative of other diseases such as congenital heart disease. The present review focuses on the use of 12-lead electrocardiogram with an emphasis on vertical frontal plane P-wave axis, combined with other minor abnormalities, which can aid in the diagnosis of COPD.

Citation: Gupta P, Jain H, Gill M, Bharaj G, Khalid N, Chaudhry W, Chhabra L. Electrocardiographic changes in Emphysema. *World J Cardiol* 2021; 13(10): 533-545
URL: https://www.wjgnet.com/1949-8462/full/v13/i10/533.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i10.533

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common respiratory condition and is ranked among the top five causes of death in the United States[1]. It causes significant obstructive airflow limitation and is associated with chronic oxygen dependence, functional limitation, recurrent hospitalizations as well as increased morbidity. Prompt diagnosis and treatment can prevent worsening of the disease and offer morbidity and mortality benefit. As such, it is important for clinicians to promptly recognize this condition even if the patient is getting evaluated for other reasons.

COPD causes several thoracic anatomical and hemodynamic changes which may produce changes in the different electrocardiographic parameters. Increased airway obstruction, right ventricular afterload, diaphragmatic displacement due to hyperinflation, clockwise rotation of the right heart, and body mass index changes correlated with clockwise rotation of the frontal QRS-vector are some of the underlying factors which play a major role in the electrocardiographic changes observed in patients with COPD[2]. A 12-lead electrocardiogram (ECG), which is often a part of routine evaluation in many clinical settings, can yield useful diagnostic clues and may serve as an initial screening modality as well as aid in further evaluation and management of COPD or emphysema. However, some of the ECG changes observed in patients with known COPD/emphysema may carry an independent prognostic value.

This comprehensive review aims at discussing characteristic electrocardiographic findings in COPD, some of which may offer a high sensitivity and specificity as standalone criteria in the diagnosis of COPD.

LITERATURE RESEARCH/MATERIALS AND METHODS

We searched PubMed and Medline for published articles focusing on COPD, emphysema, and electrocardiography. The search terms used in different combinations, were "chronic obstructive lung disease and ECG changes", "emphysema and ECG changes", "COPD and ECG changes", "COPD and ECG", "COPD and electrocardiogram", "emphysema and electrocardiogram", "emphysema and ECG", "COPD and electrocardiographic changes", and " emphysema and electrocardiographic changes", yielding us 177, 70, 175, 1154, 1098, 535, 549, 50 and 31 articles respectively indexed in PubMed and Medline at the time of writing this publication. These articles were further screened for subject relevancy and used if they were English-language full-text papers. Both review articles and original papers were included. Finally, the data from these articles used for writing of this review paper were those that were most relevant and pertinent to our current subject of discussion.

IMPORTANT ECG PARAMETERS

Emphysema produces a variety of electrocardiographic changes which are discussed in details below. A summary of these changes is enclosed at the end of the manuscript in a tabular format (Table 1).

Frontal plane P-wave axis

The changes in the frontal plane P wave axis are among one of the most important changes produced in the standard 12-lead ECG by emphysema. In most normal adults, the frontal P axis is considered to be within a very narrow range, +45° to +65°[2,3]. Studies from the 1940s and 1950s suggested that in patients with chronic lung disease, the mean frontal P vector was shifted rightward or vertically[2,4]. A study of 50 cases of chronic cor pulmonale found that all but 8 cases had a mean manifest frontal P axis of 60° or more[4]. Spodick and colleagues[2] analyzed ECGs of 79 consecutive hospital admissions for diffuse lung disease (predominantly emphysema) and found that the mean manifest P axis was to the right of +70° in 83% of these cases. A vertical P wave axis (> 60°) in the frontal plane especially in individuals over age 45 years has been considered highly suggestive of emphysema by many studies since then[5-12].

As depicted in Figure 1 and Figure 2, a vertical P vector can be primarily determined by two methods on a standard 12-lead electrocardiogram—P wave amplitude in lead III greater than in lead I (bipolar lead set) and/or a predominantly negative P wave in lead aVL (unipolar lead set)[2,13,14]. Out of these two criteria, the bipolar lead set appears to be more sensitive. A recent study from our group reviewed 100 consecutive ECGs of patients with a known diagnosis of emphysema found the bipolar lead set to be a more sensitive marker of vertical P-wave axis in emphysema than the unipolar lead set (sensitivity 88% *vs* 66% respectively)[13]. This study excluded patients younger than 45 years because a vertical P vector may be a normal finding in these patients[13].

Several studies have investigated the sensitivity and specificity of P vector verticalization as a criterion in screening for emphysema. A large study evaluated ECGs of 600 patients with vertical P avector and compared with age and sex matched control cohort with P-vector of < 60° which demonstrated that the sensitivity and specificity of vertical P-vector in diagnosing emphysema to be 94% and 87% respectively[5]. Other studies have shown comparable results[12,14]. Another study showed that frontal P axis > 80° was the single best criterion (among many other P and QRS criteria) for the separation of patients with and without COPD[15]. When the vertical P axis (> 60°) was combined with a QRS duration of < 75 ms, the specificity increased to 100% at the cost of significant decrease in sensitivity[7]. Similar findings of increased specificity and decreased sensitivity have been noted when vertical P axis was used in conjunction with one of the QRS criteria such as vertical QRS axis, low voltage in Leads V6 and/or Vs, as well as R/S ratio in Leads V5 and/or V6 < 1[15].

In addition to carrying a high sensitivity for screening of emphysema, the degree of P axis verticalization has also been found to strongly correlate with the severity of emphysema[5,8,10]. In a study of 154 patients with chronic bronchitis, and with or without emphysema, P axes > +75° correlated negatively with severity of lung disease measured by forced expiratory volume/vital capacity (FEV1/VC%, r = -0.724, P < 0.05)[8]. Calatayud *et al*[10] showed that the frontal P axis negatively correlated (r = -0.35, P < 0.01) with maximum voluntary ventilation (MVV) in a group of 173 patients with COPD referred for pulmonary function testing. In some recent studies, a significant positive correlation has been observed between the radiographic quantification of severity of emphysema and electrocardiographic P-vector verticalization in patients with established clinical diagnosis of emphysema[5]. In a small retrospective study of 26 patients with emphysema who underwent high resolution computed tomography (CT) scans, the computed tomographic visual score of emphysema and orientation of the P vector had a significant overall positive correlation (r = +0.68, P = 0.0001)[5]. This was particularly strong in patients with predominantly lower lobe emphysema (r = +0.88, P = 0.000, FEV1, and orientation of P vector had almost linear negative correlation in this subgroup (r = -0.92, P < 0.0001). Another study showed significant positive correlations with radiographic percent emphysematous area estimated by high-resolution CT and degree of P vector (r = +0.77, P < 0.0001), a stronger correlation was again found in patients with predominantly lower lobe emphysema.

The mechanisms responsible for verticalization of P vector in emphysema have long been debated. P axis in restrictive lung disease tends to be more horizontal than in obstructive lung disease[6,9]. A series of consecutive patients with pure restrictive and pure obstructive lung disease demonstrated that diaphragmatic levels were

Table 1 Common electrocardiographic changes commonly related to chronic obstructive pulmonary disease/emphysema

Vertical P-wave	P-wave axis > 60°
P-pulmonale	P-amplitude in II, III or aVF ≥ 2.5 mm
	P-amplitude in V1 ≥ 1.5 mm
Right ventricular hypertrophy	R in V1 ≥ 7 mm
	R/S in V1 > 1
	VAT in V1 > 35 ms
Sokolow-Lyon: Right ventricular hypertrophy	R in V1 + S in V5 or V6 > 10.5 mm
Clockwise rotation	R/S ratio in V5 ≤ 1
Low voltage limb leads	QRS (R+S) < 5 mm in I, II, aVF, III (all)
Low voltage precordial leads	QRS < 10 mV in V1–V6 (all)
S1S2S3 pattern	Dominant S in I, II, III (all)1
QS complex	Lead III
Rightward QRS-axis deviation:	> 90°
Short QRS duration	< 75 ms
Elevated resting heart rate (especially during exacerbation)	HR > 80 beats/min

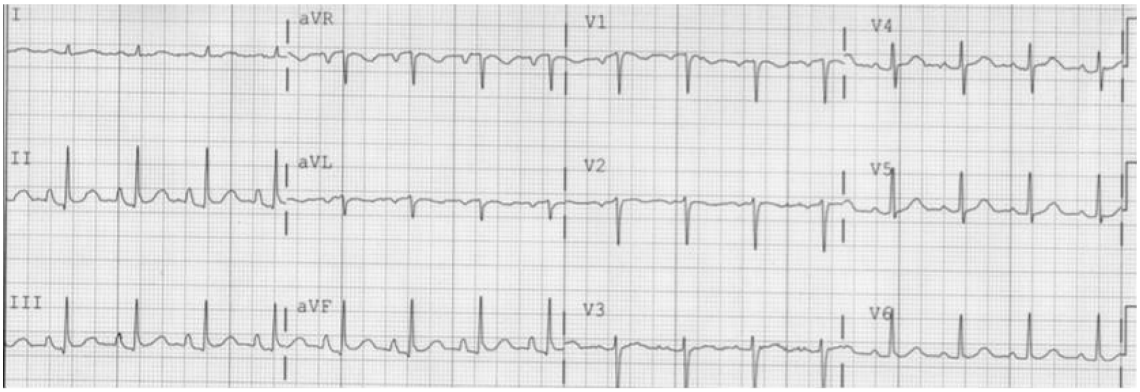


Figure 1 Electrocardiogram showing vertical P wave axis suggested by P wave amplitude in lead III greater than P wave in lead I and a negative P wave in lead aVL. Adapted from Bajaj *et al*[13].

significantly higher in patients with restrictive disease compared with obstructive disease (in the same series, P axes in obstructive disease were predominantly vertical and those in restrictive disease were predominantly horizontal or intermediate)[16]. It was hypothesized that opposite effects on diaphragm level by obstructive disease (low diaphragm) and by restrictive disease (high diaphragm) could explain the axis differences, because the right atrium is attached *via* the inferior vena cava and adjacent pericardium to the right leaf of the diaphragm. Other hypotheses attribute P vector verticalization to the presence of right atrial and right ventricular hypertrophy (RVH) from cor pulmonale.

Hypertension and left ventricular hypertrophy (LVH) represent some clinical scenarios in which a vertical P vector may be observed without the presence of emphysema[2,12]. Conversely, some patients with hypertension and LVH may have leftward P axes in the setting of emphysema[2,12]. Although it could be inferred that LVH may reduce the sensitivity of vertical P axis when used for detection of emphysema, this was refuted in a recent retrospective study[17]. It did not find any statistically significant difference in the mean P vector between emphysema patients with and without echocardiographic evidence of LVH, and concluded that the presence of LVH may not significantly alter the sensitivity of P wave verticalization when used as a sole criterion for the diagnosis of emphysema.

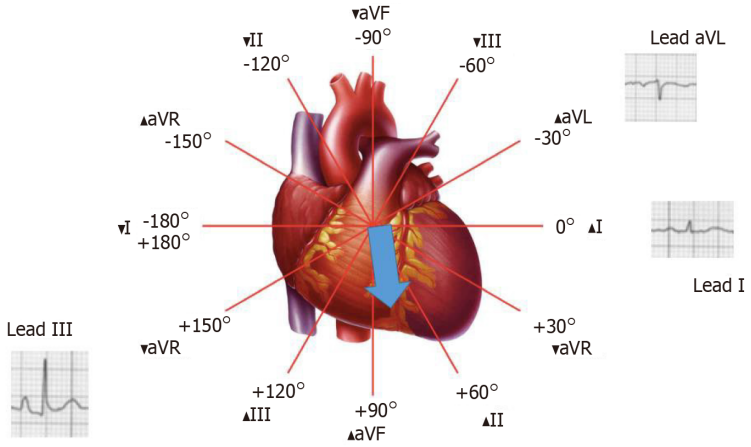


Figure 2 Depiction of vertical P axis in Hexaxial reference system.

It has been noted that many patients with congenital heart disease (CHD) that causes right atrial enlargement, right ventricular enlargement, and right bundle branch block, a vertical P axis may be commonly noted in the absence of emphysema [11]. While most patients with emphysema tend to have posteriorly and superiorly displaced QRS vectors, those with CHD and RVH have anteriorly, rightward, and slightly inferiorly displaced late QRS vectors[11]. The presence of low voltage of QRS (< 0.7 mV in limb leads and V6) and posterior and superior displacement of the mean QRS axis can help differentiate cases of emphysema and CHD with vertical P axis.

Frontal plane P wave amplitude

In addition to changes in the P wave axis, a more vertical position of the heart from diaphragmatic depression in obstructive lung disease can be associated with increased amplitude of P waves in inferior leads (II, III, aVF)[9]. This mechanism has been substantiated by scientific data. "P-pulmonale" is much more common in obstructive lung disease and in fact, it has not been noted at all in cases of restrictive lung disease in some studies[17]. A study of patients with chronic lung disease[18] and P-pulmonale on ECGs who underwent right heart catheterization showed no significant increase in right atrial or pulmonary artery pressures among these patients. In contrast, none of the patients with atrial septal defect or pulmonary hypertension had P-pulmonale on ECG. Given that all the patients with P-pulmonale had low cardio-thoracic ratio on chest radiograph and a considerably depressed diaphragm, the authors concluded that a more vertical position of the heart (particularly right atrium) was the major factor responsible for generation of P-pulmonale in patients with chronic lung disease[18]. Although P-pulmonale is an important finding in the chronic lung disease, it should be noted that there are some important differential diagnoses which should be entertained in cases of P-pulmonale. P-pulmonale may be observed in congenital heart disorders such as tricuspid atresia, rarely some electrolyte derangements and even in left sided cardiac dysfunction probably due to concomitant right atrial strain produced by underlying type-2 or mixed form of pulmonary hypertension[19,20]. It is also plausible that many of these patients in prior studies who had reported P-pulmonale in left heart failure may have previously undocumented co-existing chronic lung disease. It is also to be remembered that P-pulmonale is not necessarily a sign of right atrial enlargement in emphysema, but may be even likely the result of underlying pulmonary hyperinflation, right atrial hypoxia, and transient atrial strain or mechanical load directly resulting from the bronchospasm.

Spodick in his pioneer series of 79 consecutive hospital admissions for diffuse lung disease (almost all had emphysema) noted that classical P-pulmonale and "Gothic" P wave occurred only in cases with frontal P axis of +70° or greater[2]. A classic P-pulmonale refers to P wave amplitude > 2.5 mm in the inferior leads (II, III, aVF), while a "Gothic" P wave[2,4] refers to definite single peaking of P wave of normal amplitude in leads II, III and aVF. A schematic illustration is demonstrated in Figure 3. Although the presence of P-pulmonale and "Gothic" P waves is characteristic of obstructive disease, this finding is much less sensitive as compared to vertical P axis and is found in a little over half of the cases[2,10].

In some studies[9,10], increasing P amplitudes in inferior leads have been associated with decreasing FEV1%[9] and with MVV[11]. Thus, higher P amplitudes in inferior

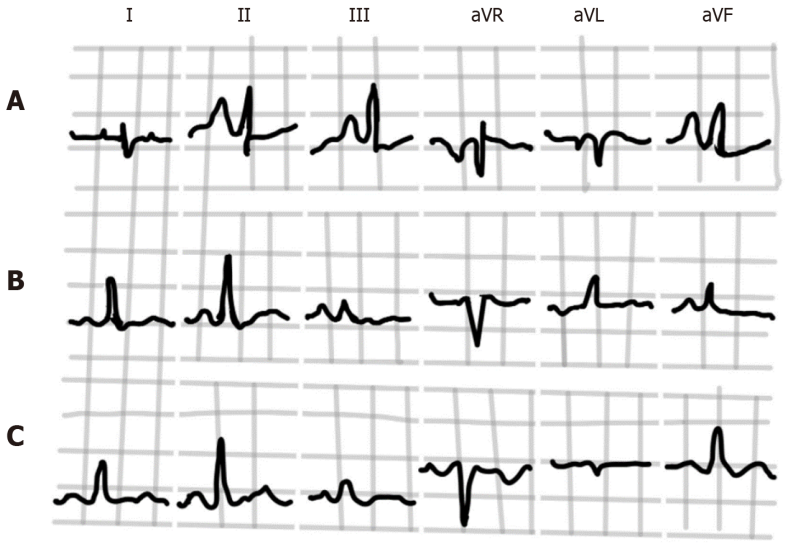


Figure 3 A schematic illustration of "P-pulmonale" (A), "Gothic" P waves (B) and normal "Cupola" P wave (rounded in contour).

leads may be a marker of decreasing lung function in emphysema, although these inverse correlations were weaker than those with increasing P wave axes.

P wave changes in precordial leads

Initial increased P-wave amplitude in lead V1 may be a sign of right atrial abnormality associated with emphysema. An increased P-terminal force in V1 (V1PTF) is usually a sign of left atrial enlargement[21-23], however an increased V1PTF was also frequently found in patients with cor pulmonale (Figure 4)[24]. Thus, increased V1PTF should be interpreted with caution in patients with known emphysema. A former retrospective study showed that V1PTF correlated with vertical P vectors in patients with emphysema and may be a function of downward right atrial displacement in this population rather than left atrial enlargement[25].

Spodick *et al*[2] noted that 51% cases of diffuse lung disease had biphasic (+/-) P waves in at least V1 and V2 and in some cases as far as V4, 78% of these were associated with vertical P axis of +70° or more. In another series of patients with fibrosing lung disease and COPD, P wave changes in lead V1 were not significantly different between the two groups[9].

Although P-wave indices constitute an important diagnostic criterion in patients with emphysema, the application of such criteria is limited in those patients with emphysema who have atrial arrhythmias including atrial fibrillation. In those patients, other criteria such as QRS voltage, QRS axis and QRS duration changes may be used to supplement the diagnosis of chronic lung disease.

Abnormalities of the PR segment

When compared to normal individuals, increased PR depression in leads II and III has been noted in patients with cor pulmonale in some older studies[4]. It was attributed to abnormal atrial repolarization because these tracings were similar to experimental tracings when atrial muscle was injured. Most such cases also exhibited P waves of high voltage, presumably due to atrial hypertrophy. One study reported strong negative correlation of PR depression of 0.5 mm or more (referred to as Ta waves) with FEV1/VC% in a series comprising of 154 patients with chronic bronchitis[8]. PR interval has been reported to be normal in patients with COPD[4,10].

However, in severe cases where COPD is coupled with pulmonary hypertension, the PR interval may be prolonged. A study examined ECG differences of 142 patients with COPD with or without pulmonary hypertension[26]. Of these, 63% of the patients that had pulmonary hypertension exhibited a longer PR interval than those without pulmonary hypertension. The prolonged PR interval in those patients was also linked to patients having an abnormal mean Papanicolaou (PAP) ≥ 40 mmHg. The combination of a mean PAP ≥ 40 mmHg and a lengthened PR interval has been shown to be a predictor of adverse outcomes for COPD patients with pulmonary hypertension[27].

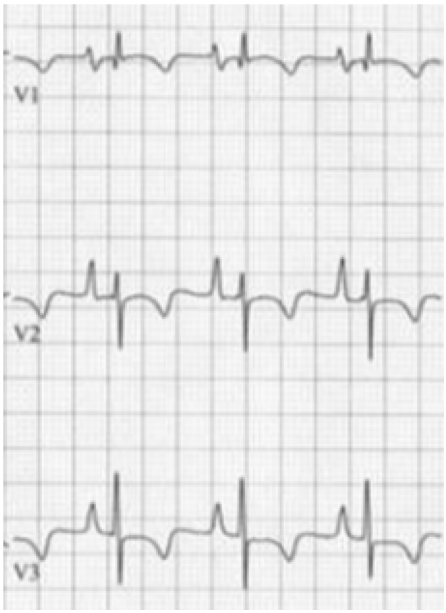


Figure 4 Note the presence of right ventricular hypertrophy, significant P-terminal force and negative T waves in right precordial leads in this patient with pulmonary hypertension. Adapted from Yanowitz[39].

QRS duration

The ECGs of patients with COPD tend to demonstrate shorter duration of QRS complexes[7,28]. One study in 1970s showed the QRS duration to be shorter in all 12 standard leads in COPD patients when compared to controls (mean 0.061 ± 0.005 s *vs* 0.074 ± 0.003 s, $P < 0.001$)[28]. In another recent study, QRS duration with emphysema was found to be shorter than controls (78 ± 8 *vs* 89 ± 6 ms, $P < 0.01$)[7]. The combination of QRS duration < 75 ms in conjunction with a P axis of > 60° achieved a specificity of 100% for the diagnosis of emphysema, although the sensitivity decreased to 33%[7].

The exact mechanism by which QRS duration becomes shorter in emphysema patients remains elusive, but several hypotheses have been advocated by various authors. Low voltage QRS in emphysema may result in partial loss of the initial and terminal QRS forces which become indistinguishable from baseline, resulting in shorter QRS duration[7,28]. Postmortem investigations in emphysematous patients have suggested diminished left ventricular coronal area and left ventricular cavity, consistent with "left ventricular disuse atrophy"[29]. Some authors have hypothesized that in the absence of significant RVH, a tendency might exist for rapid completion of depolarization in these patients because of "less" left ventricular mass and size[7,25].

QRS axis in horizontal and frontal planes

In emphysema, various changes occur in the anatomic position of the heart. It descends downward due to depression of the diaphragm from hyperinflation of the lungs, assumes a vertical position, rotates clockwise along its longitudinal axis and its apex gets displaced posteriorly[4]. These anatomic changes produce significant changes in the QRS axis in the frontal and horizontal planes. In general, the frontal plane QRS axis tends to be more rightward and the horizontal plane QRS axis tends to be directed more posteriorly (Figure 5 and 6).

Spodick *et al*[2] in his series of 79 consecutive patients with diffuse lung disease noticed that the mean frontal QRS axis was to the right of +70° or indeterminate in almost 50% of the cases, which was quite uncommon for their age group. Among those with relatively leftward QRS axis, many patients had evidence of concomitant left heart disease or congenital chest deformity. In the same study, posterior orientation of the QRS axis in the horizontal plane was evidenced by an S wave of ≥ 2 mm in leads V5 or V6 in 65% of the patients. Moreover, high correlation between posteriorly oriented QRS axis and vertical frontal plane QRS axis as well as vertical frontal plane P axis (> 70°) was noted, indicating that these changes were likely related to emphysema and related anatomic changes in heart position.

Another series of patients with cor pulmonale made several observations regarding QRS changes in such patients[4]. When compared to the normal population, the

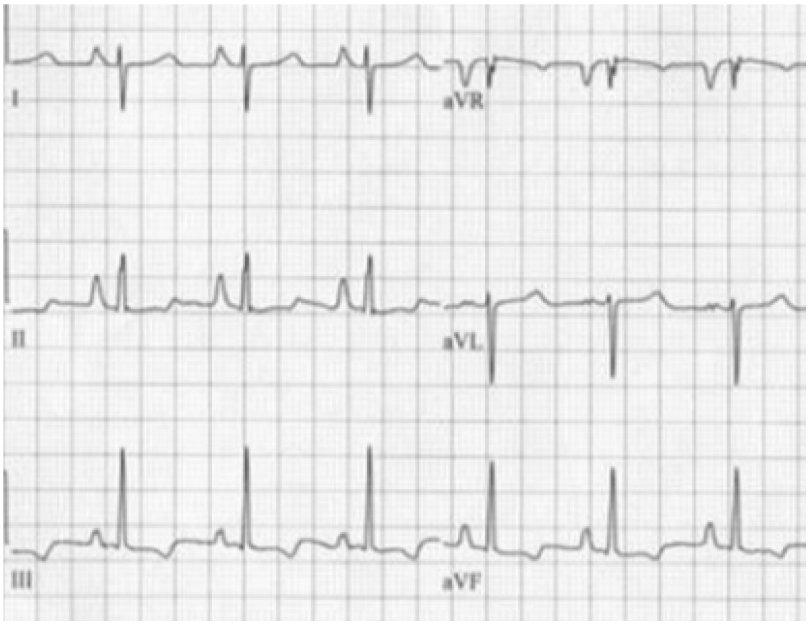


Figure 5 Right axis deviation of frontal plane QRS is noted along with P-pulmonale in a patient with pulmonary hypertension. Adapted from Yanowitz[39].

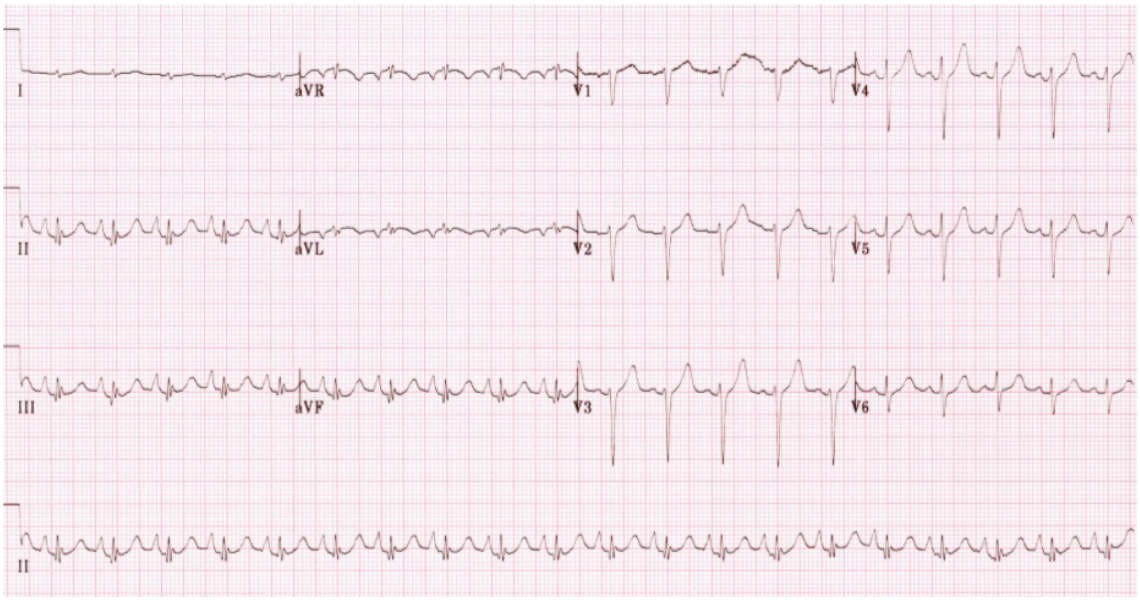


Figure 6 ECG of a patient with chronic lung disease showing precordial QRS changes suggestive of emphysema—poor R wave progression, R < 0.5 mv in lead V6, R/S < 1 in lead V6 and S wave > 5 mm in leads V5-6. Also note—P-pulmonale, lead I sign and negative P in aVL. Adapted from Burns[40].

average voltage of R wave in leads V2-V6 was lower while the average voltage of S wave was higher in leads V3-V6. These changes were attributed to the clockwise rotation of the heart (found to be much more common than in normal hearts in this study and because of frequent finding of left shifting of transitional complexes to leads V5-6). A study from Japan investigated the relationship between shift of transitional zone on precordial leads of electrocardiogram with anatomic rotation of the heart along its long axis by cardiac CT[30]. They measured the left sided angle between interventricular septum and the horizontal axis of the body based on CT and found that the mechanism of clockwise and counterclockwise rotation of the transitional zone could be attributed to the septal angle in about two-thirds of the cases. Relatively higher position of the precordial electrocardiography leads due to vertical heart position was thought to be responsible for clockwise rotation (which typically happens in emphysema) in the remaining cases. This supports the notion that these findings in

precordial leads are related to anatomic changes in heart position.

Poor R wave progression in precordial leads can be found in a variety of clinical conditions other than emphysema. One important differential is an old antero-septal myocardial infarction. One interesting study calculated R/S ratio in all precordial leads in a series of patients with emphysema and previous anteroseptal MI[31]. While the R/S ratio was significantly higher in emphysema from leads V1-V4, the pattern was reversed in leads V5-V6 where it was significantly higher in patients with MI. An R/S ratio > 3.5 in lead V5 was found to be most sensitive (87%), specific (83%) and accurate (85%) in differentiating poor R wave progression because of old anteroseptal myocardial infarction from that due to emphysema. A similar ECG pattern may sometimes be observed in patients with large right sided or tension pneumothorax which should be considered in differential diagnosis as clinically considered relevant [32].

Some other precordial QRS criteria have been studied in relation to emphysema (Figure 6). One study of COPD patients with electrocardiograms and lung function tests determined which QRS complex criteria were most useful in diagnosing COPD [33]. The best QRS criteria were R V6 amplitude of ≤ 0.5 mV and R/S ratio in V6 ≤ 1, which were present five times more in patients in quartile IV (most impaired with COPD) than quartile I. QRS axis greater than 75° or greater than 90° was present twice as often in quartile IV. Although R V6 amplitude of ≤ 0.5 mv and R/S ratio in V6 ≤ 1 were found to have a better discriminatory ratio between quartile IV and I than P axis ≥ 75°, these criteria were not applicable to almost half of the cases due to absence of S wave in V6. Another study found significant negative correlations between S wave ≥ 5 mm in V5-V6 and QRS axis over +75° with FEV1/VC%[8].

QRS amplitude

Some authors have also tried to establish QRS amplitude criteria for diagnosis of emphysema[15]. They studied the reliability of QRS amplitude ≤ 5 mm in limb leads, QRS amplitude ≤ 5 mm in leads V5 and/or V6 and R wave ≤ 7 mm in V5 and ≤ 5 mm in V6. Approximately one-half of the patients were categorized as false positive by these criteria, mostly due to atherosclerotic cardiovascular disease. Other studies did not find QRS amplitude criteria in limb leads to be useful in discriminating between different quartiles of lung function[33]. The average voltage of R+S in precordial leads was normal in cor pulmonale patients in one study[4].

The S1S2S3 syndrome

Older studies found that the average amplitude of R waves was lower while the amplitude of S waves was higher in leads I, II and III among patients with cor pulmonale when compared with normal population[4]. This is in keeping with the higher frequency of right axis deviation of QRS in the frontal plane in patients with emphysema. Some patients may demonstrate the S1-S2-S3 pattern (Figure 7) in leads I, II and III, where the S is of near to or greater magnitude than the R in each of these leads. This is often a normal finding in young individuals and frequently seen in patients with RVH due to other congenital and acquired lesions[34], although appears to have a relatively lower incidence in patients with emphysema (9-22%)[4,15,34,35]. When present, it is usually indicative of severe lung disease[15].

Pseudo left axis deviation / axis illusion phenomenon

Although the majority of patients with chronic lung disease have rightward deviation of frontal QRS axis, some patients may exhibit significant left axis deviation (-80° to -90°) or "indeterminate" axis in the absence of significant left ventricular disease or old myocardial infarction[2,34]. When viewed in the horizontal plane, it becomes apparent that this is due to the posteriorly directed ventricular activation and these axes are in fact not very different from an axis of +80° or +90°, as illustrated in the Figure 8[2]. This has been referred to as "pseudo left axis deviation" because left anterior fascicular block and coronary disease are usually not present[35,36].

"Lead I sign"

The presence of an isoelectric P wave, QRS amplitude < 1.5 mm, and T wave amplitude < 0.5 mm in lead I is usually referred to as "nearly isoelectric lead I" sign, which when present is highly indicative of underlying COPD[15,35,36]. A schematic illustration is provided in Figure 9.

T-wave changes

T wave changes in emphysema have not been extensively studied. One study

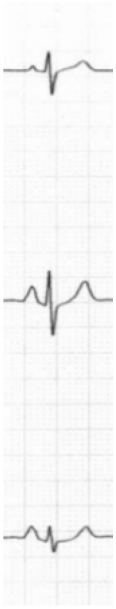


Figure 7 S1S2S3 pattern.

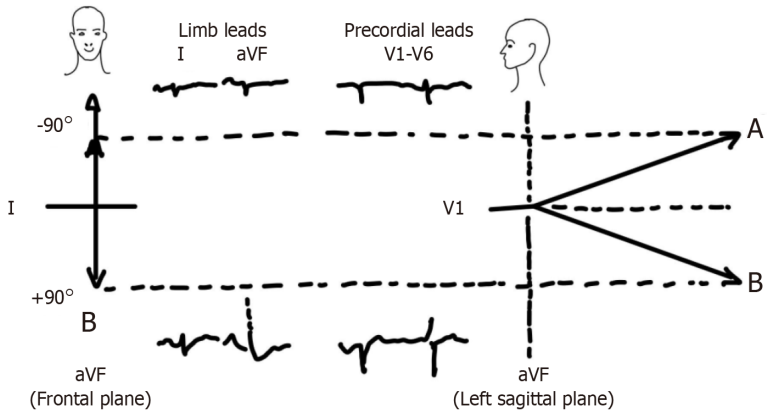


Figure 8 This is a schematic illustration of the axis-illusion phenomenon. A and B are frontal mean QRS axes of -90° and +90° respectively, suggesting a 180° divergence. Their sagittal projections reveal that this is illusory since they are actually much closer in space. Concept adapted from David Spodick's work.

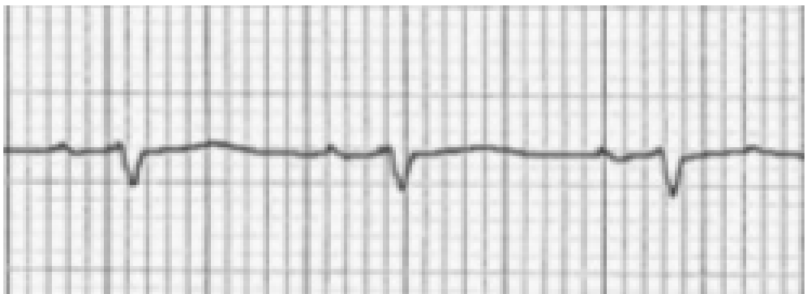


Figure 9 Schematic illustration of Lead I sign in emphysema.

conducted in the 1940s pointed out some T wave changes in a series of patients with cor pulmonale[4]. A negative T wave was found in 59% of cases in lead V1 and in 46% in leads V1 and V2, while it was usually positive in leads V3-V6. These negative T waves (Figure 4) were thought to be related to the position of the heart and not entirely to RVH because of the low incidence of delayed intrinsic deflection

accompanying such negative T waves[4]. In the inferior limb leads, the RS-T segment frequently (66.6%) showed a negative displacement and was rarely positive. In leads III and aVF, diphasic T wave was more often seen (48%) than negative T waves (which can also be seen in normal hearts, 16%), the significance of which was not clear, but could have been related to heart position as well.

RVH

In advanced COPD, the presence of tall right precordial R waves on the ECG are indicators of progression of RVH and pulmonary hypertension[34]. This is especially true if they are accompanied by T wave inversions in the same leads (Figure 4). Also, progression of RVH is typically associated with accentuation of right deviation of frontal plane P and QRS axes, an increased voltage of P wave in the inferior leads (P-pulmonale), small R waves and increased depth of S waves in leads V5 and V6 as well as negativity of T waves in leads V1 and V2[4].

Cardiac arrhythmias in COPD

A recent study showed that heart rate was significantly higher in patients with COPD compared with the healthy age-matched controls[35]. The frequency of arrhythmias in stable patients with COPD has been studied in some patients enrolled in nocturnal oxygen therapy trial group using 24-h ambulatory ECG monitoring[37]. The results suggested that both ventricular and supraventricular premature beats (including bigeminy, multiform premature ventricular contractions, runs of ventricular tachycardia) were frequent in patients with COPD. In addition, sinus tachycardia and supraventricular tachycardia including multifocal atrial tachycardia were noted in 38% and 69% of patients respectively[38]. Interestingly, history of coronary artery disease, increased sinus heart rate and decreased maximum workload were found to be predictors of death, rather than the presence of arrhythmias[38-40]. Multifocal atrial tachycardia may be noted in cases with significant underlying lung disease, particularly during COPD exacerbation[34].

CONCLUSION

The 12-lead ECG can be extremely valuable to the clinician in pointing towards undiagnosed COPD. A vertical frontal plane P wave axis is an extremely helpful electrocardiographic finding of COPD and appears to be highly sensitive and specific when used as a lone criterion for diagnosis. It has also been shown to correlate strongly with the severity of COPD as measured by spirometric and the CT criteria. Other noted abnormalities include increased P wave amplitude in inferior leads (P-pulmonale and Gothic P waves), increased P terminal force in V1, depression of PR segment, short QRS duration, rightward and posterior QRS axis, S1S2S3 sign, lead I sign and signs of RVH. These findings are less sensitive and specific but substantiate the diagnosis when present in conjunction with vertical P wave axis in frontal plane. All these changes appear to result from more vertical orientation of the heart due to depression of the diaphragm as well as clockwise and posterior rotation along its horizontal axis.

REFERENCES

1 **Miniño AM**, Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2008. *Natl Vital Stat Rep* 2011; **59**: 1-126 [PMID: 22808755]

2 **SPODICK DH**. Electrocardiographic studies in pulmonary disease. I. Electrocardiographic abnormalities in diffuse lung disease. *Circulation* 1959; **20**: 1067-1072 [PMID: 13833426 DOI: 10.1161/01.cir.20.6.1067]

3 **Sodi-Pallares D**. New Bases of Electrocardiography. Philadelphia: CV Mosby, 1956

4 **Zuckermann R**, Cabrera CE. Electrocardiogram in chronic cor pulmonale. *Am Heart J* 1948; **35**: 421-437 [PMID: 18903667 DOI: 10.1016/0002-8703(48)90118-5]

5 **Chhabra L**, Sareen P, Gandagule A, Spodick DH. Visual computed tomographic scoring of emphysema and its correlation with its diagnostic electrocardiographic sign: the frontal P vector. *J Electrocardiol* 2012; **45**: 136-140 [PMID: 22244933 DOI: 10.1016/j.jelectrocard.2011.12.005]

6 **Shah NS**, Velury S, Mascarenhas D, Spodick DH. Electrocardiographic features of restrictive pulmonary disease, and comparison with those of obstructive pulmonary disease. *Am J Cardiol* 1992; **70**: 394-395 [PMID: 1632412 DOI: 10.1016/0002-9149(92)90628-c]

7 **Thomas AJ**, Apiyasawat S, Spodick DH. Electrocardiographic detection of emphysema. *Am J*

Cardiol 2011; **107**: 1090-1092 [PMID: 21306694 DOI: 10.1016/j.amjcard.2010.11.039]
8 **Tandon MK**. Correlations of electrocardiographic features with airway obstruction in chronic bronchitis. *Chest* 1973; **63**: 146-148 [PMID: 4688056 DOI: 10.1378/chest.63.2.146]
9 **Ikeda K**, Kubota I, Takahashi K, Yasui S. P-wave changes in obstructive and restrictive lung diseases. *J Electrocardiol* 1985; **18**: 233-238 [PMID: 4031726 DOI: 10.1016/s0022-0736(85)80047-9]
10 **Calatayud JB**, Abad JM, Khoi NB, Stanbro WW, Silver HM. P-wave changes in chronic obstructive pulmonary disease. *Am Heart J* 1970; **79**: 444-453 [PMID: 4244706 DOI: 10.1016/0002-8703(70)90248-6]
11 **Selvester RH**, Rubin HB. New criteria for the electrocardiographic diagnosis of emphysema and cor pulmonale. *Am Heart J* 1965; **69**: 437-447 [PMID: 14270092 DOI: 10.1016/0002-8703(65)90413-8]
12 **SPODICK DH**. Electrocardiographic studies in pulmonary disease. II. Establishment of criteria for the electrocardiographic inference of diffuse lung diseases. *Circulation* 1959; **20**: 1073-1074 [PMID: 13833427 DOI: 10.1161/01.cir.20.6.1073]
13 **Bajaj R**, Chhabra L, Basheer Z, Spodick DH. Optimal electrocardiographic limb lead set for rapid emphysema screening. *Int J Chron Obstruct Pulmon Dis* 2013; **8**: 41-44 [PMID: 23378754 DOI: 10.2147/COPD.S37776]
14 **Baljepally R**, Spodick DH. Electrocardiographic screening for emphysema: the frontal plane P axis. *Clin Cardiol* 1999; **22**: 226-228 [PMID: 10084066 DOI: 10.1002/clc.4960220313]
15 **Kamper D**, Chou TC, Fowler NO, Witt RL, Bloomfield S. The reliability of electrocardiographic criteria of chronic obstructive lung disease. *Am Heart J* 1970; **80**: 445-452 [PMID: 5471205 DOI: 10.1016/0002-8703(70)90190-0]
16 **Shah NS**, Koller SM, Janower ML, Spodick DH. Diaphragm levels as determinants of P axis in restrictive vs obstructive pulmonary disease. *Chest* 1995; **107**: 697-700 [PMID: 7874939 DOI: 10.1378/chest.107.3.697]
17 **Lanjewar SS**, Chhabra L, Chaubey VK, Joshi S, Kulkarni G, Kothagundla C, Kaul S, Spodick DH. Diagnostic electrocardiographic dyad criteria of emphysema in left ventricular hypertrophy. *Int J Chron Obstruct Pulmon Dis* 2013; **8**: 591-594 [PMID: 24293995 DOI: 10.2147/COPD.S50680]
18 **Maeda S**, Katsura H, Chida K, Imai T, Kuboki K, Watanabe C, Kida K, Ohkawa S, Matsushita S, Ueda K. Lack of correlation between P pulmonale and right atrial overload in chronic obstructive airways disease. *Br Heart J* 1991; **65**: 132-136 [PMID: 2015120 DOI: 10.1136/hrt.65.3.132]
19 **Chhabra L**, Spodick DH. Transient Super-Himalayan P-waves in severe pulmonary emphysema. *J Electrocardiol* 2012; **45**: 26-27 [PMID: 21907999 DOI: 10.1016/j.jelectrocard.2011.07.016]
20 **Hayashi H**, Miyamoto A, Kawaguchi T, Naiki N, Xue JQ, Matsumoto T, Murakami Y, Horie M. P-pulmonale and the development of atrial fibrillation. *Circ J* 2014; **78**: 329-337 [PMID: 24284921 DOI: 10.1253/circj.cj-13-0654]
21 **Kishimoto C**, Tamaru K, Kuwahara H. Tall P waves associated with severe hypokalemia and combined electrolyte depletion. *J Electrocardiol* 2014; **47**: 93-94 [PMID: 24099885 DOI: 10.1016/j.jelectrocard.2013.09.002]
22 **Conde D**, Seoane L, Gysel M, Mitrione S, Bayés de Luna A, Baranchuk A. Bayés' syndrome: the association between interatrial block and supraventricular arrhythmias. *Expert Rev Cardiovasc Ther* 2015; **13**: 541-550 [PMID: 25907617 DOI: 10.1586/14779072.2015.1037283]
23 **Surawicz B**, Knilans T. Atrial abnormalities. In: Chou's Electrocardiography in Clinical Practice: Adult and Pediatric. 6th ed. Philadelphia: Saunders Elsevier, 2008: 33-36
24 **Bayés de Luna A**, Platonov P, Cosio FG, Cygankiewicz I, Pastore C, Baranowski R, Bayés-Genis A, Guindo J, Viñolas X, Garcia-Niebla J, Barbosa R, Stern S, Spodick D. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. *J Electrocardiol* 2012; **45**: 445-451 [PMID: 22920783 DOI: 10.1016/j.jelectrocard.2012.06.029]
25 **Lynch P**, Webb-Peploe MM. The P terminal vector in lead V1 of the electrocardiogram in cor pulmonale. *J Electrocardiol* 1982; **15**: 205-208 [PMID: 6214600 DOI: 10.1016/s0022-0736(82)80020-4]
26 **Chhabra L**, Chaubey VK, Kothagundla C, Bajaj R, Kaul S, Spodick DH. P-wave indices in patients with pulmonary emphysema: do P-terminal force and interatrial block have confounding effects? *Int J Chron Obstruct Pulmon Dis* 2013; **8**: 245-250 [PMID: 23690680 DOI: 10.2147/COPD.S45127]
27 **Alkukhun L**, Baumgartner M, Budev M, Dweik RA, Tonelli AR. Electrocardiographic differences between COPD patients evaluated for lung transplantation with and without pulmonary hypertension. *COPD* 2014; **11**: 670-680 [PMID: 24983839 DOI: 10.3109/15412555.2014.898047]
28 **Tonelli AR**, Baumgartner M, Alkukhun L, Minai OA, Dweik RA. Electrocardiography at diagnosis and close to the time of death in pulmonary arterial hypertension. *Ann Noninvasive Electrocardiol* 2014; **19**: 258-265 [PMID: 24372670 DOI: 10.1111/anec.12125]
29 **Zambrano SS**, Moussavi MS, Spodick DH. QRS duration in chronic obstructive lung disease. *J Electrocardiol* 1974; **7**: 35-36 [PMID: 4811647 DOI: 10.1016/s0022-0736(74)80006-3]
30 **Foraker AG**, Bedrossian CW, Anderson AE Jr. Myocardial dimensions and proportions in pulmonary emphysema. *Arch Pathol* 1970; **90**: 344-347 [PMID: 4248257]
31 **Tahara Y**, Mizuno H, Ono A, Ishikawa K. Evaluation of the electrocardiographic transitional zone by cardiac computed tomography. *J Electrocardiol* 1991; **24**: 239-245 [PMID: 1919383 DOI: 10.1016/0022-0736(91)90029-l]
32 **Mittal SR**, Srivastava P. Differentiation of poor R wave progression of old anteroseptal myocardial infarction from that due to emphysema. *Int J Cardiol* 1986; **13**: 92-94 [PMID: 3771008 DOI:

10.1016/0167-5273(86)90085-9]
33 **Yamamoto H**, Satomi K, Aizawa Y. Electrocardiographic manifestations in a large right-sided pneumothorax. *BMC Pulm Med* 2021; **21**: 101 [PMID: 33757495 DOI: 10.1186/s12890-021-01470-1]
34 **Silver HM**, Calatayud JB. Evaluation of QRS criteria in patients with chronic obstructive pulmonary disease. *Chest* 1971; **59**: 153-159 [PMID: 5542926 DOI: 10.1378/chest.59.2.153]
35 **Rodman DM**, Lowenstein SR, Rodman T. The electrocardiogram in chronic obstructive pulmonary disease. *J Emerg Med* 1990; **8**: 607-615 [PMID: 2254610 DOI: 10.1016/0736-4679(90)90458-8]
36 **Larssen MS**, Steine K, Hilde JM, Skjørten I, Hodnesdal C, Liestøl K, Gjesdal K. Mechanisms of ECG signs in chronic obstructive pulmonary disease. *Open Heart* 2017; **4**: e000552 [PMID: 28533915 DOI: 10.1136/openhrt-2016-000552]
37 **Schaeffer JW**, Pryor R. Pseudo left axis deviation and the S1S2S3 syndrome in chronic airway obstruction. *Chest* 1977; **71**: 453-455 [PMID: 852319 DOI: 10.1378/chest.71.4.453]
38 **Shih HT**, Webb CR, Conway WA, Peterson E, Tilley B, Goldstein S. Frequency and significance of cardiac arrhythmias in chronic obstructive lung disease. *Chest* 1988; **94**: 44-48 [PMID: 2454781 DOI: 10.1378/chest.94.1.44]
39 **Yanowitz FG**. Introduction to ECG interpretation. 10th ed. Salt Lake City: Spenser S. Eccles Health Sciences Library, 2017
40 **Burns E**. ECG in Chronic Obstructive Pulmonary Disease [cited Sep 6, 2020]. Available from: https://litfl.com/ecg-in-chronic-obstructive-pulmonary-disease/

World Journal of Cardiology

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

World J Cardiol 2021 October 26; 13(10): 546-555

DOI: 10.4330/wjc.v13.i10.546

ISSN 1949-8462 (online)

MINIREVIEWS

Artificial intelligence and machine learning in cardiovascular computed tomography

Karthik Seetharam, Premila Bhat, Maxine Orris, Hejmadi Prabhu, Jilan Shah, Deepak Asti, Preety Chawla, Tanveer Mir

ORCID number: Karthik Seetharam 0000-0001-8006-6445; Premila Bhat 0000-0002-7384-2300; Maxine Orris 0000-0002-0898-3991; Hejmadi Prabhu 0000-0001-9374-7952; Jilan Shah 0000-0002-0863-8979; Deepak Asti 0000-0003-2205-7529; Preety Chawla 0000-0002-1578-6697; Tanveer Mir 0000-0002-8550-5555.

Author contributions: Seetharam K and Bhat P contributed equally to this work; Seetharam K, Bhat P, Orris M, Prabhu H, Shah J, Asti D, Chawla P, and Mir T designed the research study; Seetharam K, Bhat P, Asti D, and Mir T performed the research; Seetharam K and Bhat P wrote the manuscript; all authors have read and approve the final manuscript.

Conflict-of-interest statement: The authors declare that there is no any conflicts of interest.

Karthik Seetharam, Department of Cardiology, West Virgina University, Morgan Town, NY 26501, United States

Premila Bhat, Maxine Orris, Jilan Shah, Department of Medicine, Wyckoff Heights Medical Center, Brooklyn, NY 11237, United States

Hejmadi Prabhu, Deepak Asti, Preety Chawla, Department of Cardiology, Wyckoff Heights Medical Center, Brooklyn, NY 11237, United States

Tanveer Mir, Department of Internal Medicine, Wyckoff Heights Medical Center, Brooklyn, NY 11237, United States

Corresponding author: Karthik Seetharam, MD, Academic Research, Department of Cardiology, West Virgina University, Heart and Vascular Institute West Virginia University 1 Medical Center Drive, Morgan Town, NY 26501, United States. skarthik87@yahoo.com

Abstract

Computed tomography (CT) is emerging as a prominent diagnostic modality in the field of cardiovascular imaging. Artificial intelligence (AI) is making significant strides in the field of information technology, the commercial industry, and health care. Machine learning (ML), a branch of AI, can optimize the performance of CT and augment the assessment of coronary artery disease. These ML platforms can automate multiple tasks, perform calculations, and integrate information from a variety of data sources. In this review article, we explore the ML in CT imaging.

Key Words: Computed tomography; Machine learning; Artificial intelligence; Cardiovascular imaging

Core Tip: Machine learning (ML), a subset of artificial intelligence, contains multiple algorithms which include supervised, unsupervised, reinforcement and deep learning. These algorithms can greatly augment multiple aspects in computed tomography which

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: United States

Peer-review report's scientific quality classification

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

Received: May 8, 2021
Peer-review started: May 8, 2021
First decision: June 29, 2021
Revised: July 10, 2021
Accepted: August 13, 2021
Article in press: August 13, 2021
Published online: October 26, 2021

P-Reviewer: Ankrah AO
S-Editor: Ma YJ
L-Editor: A
P-Editor: Wang LYT

include automated segmentation, diagnosis, and stratification based on risk. Outputs need to be carefully assessed by the medical team for any potential biases. For the future of computed tomography and cardiovascular imaging, ML algorithms need to be integrated in clinical care.

Citation: Seetharam K, Bhat P, Orris M, Prabhu H, Shah J, Asti D, Chawla P, Mir T. Artificial intelligence and machine learning in cardiovascular computed tomography. *World J Cardiol* 2021; 13(10): 546-555
URL: https://www.wjgnet.com/1949-8462/full/v13/i10/546.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i10.546

INTRODUCTION

In this digital era, distance is no longer a limiting factor and information is emanating from a variety of devices and sources[1]. These technological innovations have considerably transformed our perception, culture, and our daily lifestyles[2]. Similarly, many of these changes have trickled downwards in healthcare and are especially apparent in the field of cardiovascular imaging. Over the last 10 years, the field of computed tomography (CT) has expanded tremendously with significant changes in diagnostic performance and prognostic implications in coronary artery disease[3,4]. Coronary CT angiography (CTA) is now heralded as an established diagnostic modality in the evaluation of coronary artery disease (CAD)[4,5]. With each year, data arising from each imaging scan is increasing exponentially in intricacy and size[6]. As we approach this technological ceiling, the sheer complexity of this information will supersede the analytic capabilities of conventional statistical software[7].

Artificial Intelligence (AI) refers to a set of actions that can mimic human cognitive thinking and decision making[8]. Machine learning (ML), a branch of AI, can extrapolate hidden characteristics or relationships present in vast expanses of data[2]. It can analyze data from a multitude of sources and link the information in user-friendly approaches[9]. In addition, it can automate several processes and perform many calculations[10]. With the application of ML algorithms in CT for cardiology, it can elevate the modality to unprecedented new heights which can improve the quality of patient care. In our review, we evaluate recent advances and progression of ML in cardiac CT over recent years.

BROAD CLASSIFICATION OF ML

ML is an aggregate term which collectively encompasses a wide variety of analytical algorithms[11]. They can be simply divided into supervised learning, unsupervised learning, semi-supervised learning, deep learning and reinforcement learning[12,13] (Figure 1 and Table 1). Supervised learning requires labeled datasets or domains within the dataset to perform analytical actions[14]. Unsupervised learning does not require labels within a dataset and can analyze information in a very independent manner. For discussion purposes, it can be referred to as agnostic[2,15]. Hierarchical clustering, a type of unsupervised learning, can identify and distinguish new phenotypes within various cardiac diseases[2]. It has gained significant traction recently. Semi-supervised learning is a hybrid approach that utilizes properties present within supervised and unsupervised learning[16]. Reinforcement learning uses definitive reward conditions for the ML architecture to perform certain functions. Nevertheless, frequently not used in the field of cardiology[7]. Multiple studies have been documented to show the potential of ML in CT and CTA (Table 2).

Among all the available ML algorithms, deep learning is considered to have the most revolutionary potential[17]. In various sectors of commerce and industry, deep learning is being heavily utilized to unravel information within large troves of data [18]. From voice recognition software in Siri or Alexa to self-driving cars in google, deep learning is garnering significant interest[12]. The architecture of deep learning algorithms is similar to the arrangement of a human neuron[19,20]. It is structured in a series of layers, there is significant communication between the preceding and subsequent layers. It processes information in multiple layers and is more independent

Table 1 Type of machine learning

Types of machine learning	Function	Examples
Supervised learning (55)	Contains labels and outcomes, deduces inferences for prediction purpose	Includes logistic regression, ridge regression, elastic net regression, Bayesian and artificial neural networks
Unsupervised learning (55)	No labels, independently detects significant relationships.	Includes hierarchical clustering, k- means clustering, principal component analysis
Semi-supervised learning (55)	Properties of both supervised and unsupervised learning	Utilized in image and speech recognition
Re-enforcement learning (55)	Utilizes reward function to execute tasks	Utilized in medical imaging, analytics, and prescription selection

Table 2 Machine learning studies in computed tomography

Ref.	ML approach	Brief study description
ML derived CAC assessment		
Al'Aref *et al*[24]	Multiple ML algorithm	To use CAC and clinical factors for CAD prediction
Tesche *et al*[26]	ML algorithm	To compare ML derived CT FFR and CAC in CT
Kay *et al*[27]	ML algorithm	To identify phenotypes of left ventricular hypertrophy in combination with CAC
ML derived CT FFR assessment		
Zhou *et al*[31]	Multiple ML algorithms	To employ CT FFR for myocardial bridge formation prediction
Tang *et al*[32]	ML algorithm	To compare ML CT FFR, CTA and invasive angiography
Coenen *et al*[33]	Supervised learning	To identify CAD
ML derived evaluation of plaque characteristics		
Dey *et al*[34]	ML algorithm	To generate ML derived scores from plaque characteristics
Hell *et al*[35]	ML algorithm	To predict cardiac death from plaque characteristics from CTA
ML derived evaluation of epicardial adipose tissue		
Rodrigues *et al*[38]	ML algorithm	To segment and distinguish between different varieties of EAT
Commandeur *et al*[39]	Deep learning	To quantify EAT in CT
Otaki *et al*[40]	Supervised learning	To assess the relationship between EAT in CT and MFR in PET
Miscellaneous applications of ML in CT		
Baskaran *et al*[41]	Deep learning	To assess automatic and manual assessment of left and right cardiac structure and function
Al'Aref *et al*[42]	Supervised learning	To identify culprit coronary lesions in CT
Beecy *et al*[43]	Deep learning	To detect acute ischemic stroke in CT
Oikonomou *et al*[44]	Supervised learning	To utilize perivascular fat for cardiac risk prediction
Eisenberg *et al*[45]	Deep learning	To evaluate epicardial tissue for MACE events

CT: Computed tomography; CTA: Computed tomography angiography; CAC: Coronary artery calcium; ML: Machine learning; CAD: Coronary artery disease; FFR: Fractional flow reserve; EAT: Epicardial adipose tissue.

compared to other ML algorithms. As the complexity and size of the dataset increase, the performance of the algorithm improves significantly[21,22].

AUGMENTED CORONARY CALCIUM ASSESSMENT

Coronary artery calcium (CAC) measurement is heralded as a fundamental metric in coronary CT because it serves as a pivotal predictor of mortality and cardiac complic-

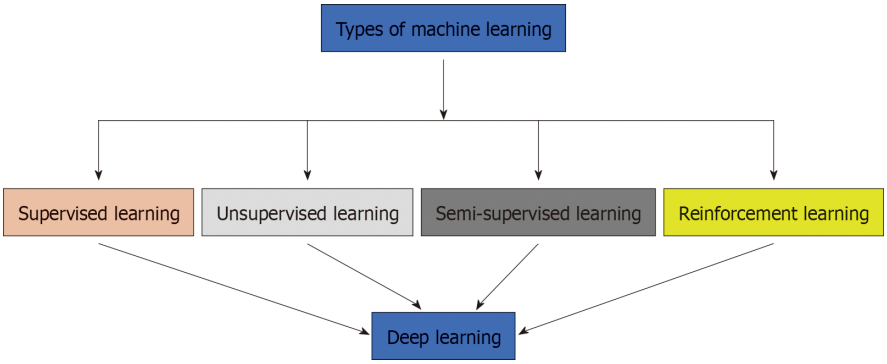


Figure 1 Brief overview of the progression of machine learning.

ations[23]. The Agatston scoring method is the conventional approach utilized to quantify CAC in coronary CT[19]. Furthermore, the CAC plays a diagnostic role in medical management, the CAC scores can be used to stratify patients and monitor medical therapy. However, CAC measurement can be quite tedious due to underlying artifacts, image noise, an abundance of calcifications, interobserver variability, and other factors[24]. The application of ML can significantly elevate the potential of CAC in CT.

Al'Aref *et al*[24] applied an ML architecture incorporating clinical factors in the CONFIRM registry with CAC for calculating the probability of CAD with CTA in a total of 35821 patients. It clearly showcased excellent AUC for ML and (CAC) (0.881) to other conventional approaches in their study [ML independently (0.773), updated Diamond- Forrester Score (0.682) coronary calcium (0.886)]. Hou *et al*[25] assessed the role of supervised ML to evaluate pretest likelihood of CAD in CTA with 6274 individuals. Their ML algorithm demonstrated superior discriminative capacity for CAD occlusion in comparison to traditional scoring metrics such as Modified Diamond Forester scores and CAD consortium score ($P < 0.001$). Tesche *et al*[26] exhibited superior performance of ML derived CT fractional flow reserve (FFR) in comparison to CTA with CAC, substantial distinctions in capability were noted and with propionate increases in Agatston scores ($P < 0.001$). Kay *et al*[27] integrated various algorithmic frameworks with radiomics for identifying new phenotypic characteristics regarding left ventricular hypertrophy (LVH) severity in CT with (CAC) assessment. As a result, ML frameworks are found to be efficacious in identification of LVH.

APPLICATION OF MACHINE LEARNING FOR CT FRACTIONAL FLOW RESERVE

Although CTA enables visual evaluation of a stenotic lesion, it lags behind invasive FFR for assessing the hemodynamic significance of coronary stenosis[28]. Coronary fractional flow reserve (CT-FFR) has become a suitable non-invasive modality for evaluating ischemic heart disease and chest pain[29]. Furthermore, it can perform this task without the requirement of additional medications or imaging. It provides functional and anatomic evaluation, this approach is steadily gaining momentum in CT imaging[30]. ML algorithms can calculate FFR in the absence of computational fluid dynamics and yield additional prognostic information[3]. It can substantially expand the arena of CT-FFR in CT imaging.

Zhou *et al*[31] evaluated CT fractional flow reserve (CT FFR) for estimating myocardial bridge formation by integrating several algorithms. Interestingly, the framework chose properties which contained superior AUC (0.75 ± 0.04) in comparison to clinical attributes (0.53 ± 0.09, $P < 0.0001$), or CT- FFR prosperities (0.62 ± 0.06, $P = 0.0127$). Tang *et al*[32] demonstrated that CT FFR with computational fluid dynamics was superior CTA and invasive angiography for detecting vessel-specific ischemia. This was particularly seen in intermediate lesions ($P < 0.001$ for all). Coenen *et al*[33] demonstrated excellent correlation between ML based CT FFR and deep learning in CAD ($r = 0.997$).

PLAQUE CHARACTERIZATION AND SEGMENTATION IN CAD

ML algorithms can provide additional insight regarding plaque characteristics in CAD and augment our understanding[2]. Dey *et al*[34] utilized a logitboost algorithm to produce an ML-derived risk score from plaque characteristics in CTA for 254 patients. The ML algorithm displayed a higher AUC (0.84) than individual CTA parameters including stenosis (0.76), total plaque volume (0.74), and low likelihood of CAD (P < 0.0006) (0.63). Hell *et al*[35] investigated the role of ML algorithms to predict cardiac death from coronary CTA through the utilization of plaque features in 2748 patients. The non-calcified plaque > 146 mm^3 (P = 0.027), low density non-calcified plaque (P = 0.025), total plaque volume > 179 mm^3, and CDD > 35% in any vessel were significantly associated with elevated risk of future cardiac death.

ML AUGMENTED EVALUATION OF EPICARDIAL AND THORACIC ADIPOSE TISSUE

Cardiac CT is deemed as the gold standard for evaluation of epicardial adipose tissue (EAT) quantification and assessment. EAT is a layer of adipose surrounding the heart and the accompanying coronary arteries. In addition, EAT is significantly linked with various cardiovascular risk factors, atherosclerosis of the coronary arteries, and CAD [36,37]. The application of ML algorithms can automate the quantification of EAT and greatly reduce the time of manual measurements. This can translate into greater clinical implementation in coronary CT.

Rodrigues *et al*[38] applied ML algorithms for segmenting and differentiating types of fat in CT. The ML platform was able to achieve 98.4% mean accuracy and a DICE similarity index of 96.8%. Commandeur *et al*[39] utilized a deep learning algorithm for quantifying EAT in coronary CT. Strong agreement was observed between automatic and expert manual quantification with a mean DICE score coefficient of 0.823 and an excellent correlation of 0.923 with EAT volume. Otaki *et al*[40] utilized a boost ensemble machine learning algorithm for assessing the association of epicardial fat volume from myocardial flow reserve (MFR) in non- contrast CT in positive emission tomography (PET). The ML composite risk score substantially increased risk reclassification of impaired MFR to EAT volume or coronary calcium score (IDI = 0.19 and P = 0.007, IDI = 0.22 and P = 0.002).

MISCELLANEOUS APPLICATIONS OF ML

In CT, ML has been applied in a variety of different situations with overwhelmingly positive results. Baskaran *et al*[41] assessed deep learning for assessing cardiovascular structures for CTA in 166 patients. The ML architecture corroborated in parallel to manual annotation in CTA for left ventricular volume (r = 0.98), right ventricular volume (r = 0.97) (P < 0.05). Al'Aref *et al*[42] utilized ML in CTA to detect precursor culprit lesion from patients with CAD. It exhibited a superior AUC for discriminating lesions in comparison to other ML derived frameworks (P < 0.01). Beecy *et al*[43] on CT for detecting acute ischemic stroke events. Interestingly, their AUC was 0.91 for automatic detection of infarction and had a 93% accuracy with interpretation of experienced physicians. Oikonomou *et al*[44] examined the capability of the random forest ML architecture from the radiomic profile of CTA derived coronary perivascular adipose tissue (PVAT) for identifying cardiac risk. It exceeded traditional risk stratification metrics for MACE prediction (P < 0.001). Eisenberg used deep learning for MACE prediction with EAT and other characteristics. The EAT in CT predicted MACE effectively (HR, 1.35, P < 0.01), inversely with attenuation (0.83, P = 0.01)[45].

BIG DATA UTILIZATION FOR PREDICTION OF OUTCOMES IN CT

Big data has emerged as a valuable resource that provides significant depth and understanding and is instrumental to the growth of ML in clinical medicine (Table 3) [5]. Due to size and magnitude, many important characteristics are often unnoticed by conventional approaches[6,46]. The implementation of AI with these immense expanses of data can yield additional information which can aid in medical management and clinical care.

Table 3 Big data utilization by machine learning in computed tomography

Ref.	ML approach	Number	Brief study description
Motwani *et al*[47]	Supervised Learning	10030	To predict 5-yr mortality from CT
Rosandael *et al*[48]	Supervised Learning	8844	To predict major cardiac events from CT
Han *et al*[49]	ML algorithm	86155	To predict all-cause mortality from CT

CT: Computed tomography; ML: Machine learning.

Motwani *et al*[47] evaluated an ML framework to predict CAD in 10,030 patients for five-year mortality in comparison to traditional cardiac metrics in CT. Interestingly, the ML architecture exhibited a superior AUC (0.79) than CT severity scores (SSS = 0.64, SIS = 0.64, DI = 0.62) for five-year all-cause mortality prediction ($P < 0.0001$). Similarly, van Rosendael *et al*[48] utilized an ML framework in CT with 8844 patients for detecting major cardiovascular events encompassing various attributes in relation to severity scores for CAD prediction. The ML derived AUC (0.771) was significantly higher in CT than conventional scoring parametric systems (0.685-0.701) for anticipating major cardiovascular events, with a notable difference ($P < 0.001$). Han *et al*[49] assessed an ML-derived predictive capacity for all-cause mortality in 86155 patients. Notably, the AUC (0.82) noted to be higher than Framingham risk score and other traditional metrics ($P < 0.05$).

EVOLVING BELIEFS AND FUTURE DIRECTIONS OF ML

It must be emphasized with great importance that cardiovascular disease is heterogeneous in nature[50]. It cannot be perceived as straightforward because disease mechanisms have intricate interactions among molecular, genetic, and environmental factors[22]. The process is very dynamic, it truly reflects the essence of ML algorithms. ML can integrate this information from multiple sources and analyze it in a variety of approaches. This can lead to the development of various genetic markers which can help guide medical management and monitor responses after therapy[6,51]. Furthermore, we can tailor treatment regimens appropriate to the genetic constitutional makeup of an individual, ML algorithms will facilitate the growth of precision medicine[12].

In current times, mobile devices, smartphone apps, and wearable devices are part and parcel of our daily lifestyles[52]. Telemedicine and ML algorithms are clearly intertwined in cardiovascular imaging and CT[1]. The information from these devices can be integrated with various parameters in cardiovascular imaging to yield additional insight regarding various cardiovascular diseases. In many underserved regions of the world, these devices can provide medical care and help direct patients towards appropriate intervention[1,53]. ML algorithms can analyze this information in real-time and help expedite this process[1]. These algorithms can serve as a bridge between different types of technology and cardiovascular imaging.

Although several algorithms have significant potential in computed tomography, deep learning has the most overwhelming potential[54]. It captures information through hierarchical levels of abstraction. As the computational prowess of graphical processing units (GPUs) continue to progressively evolve in conjunction with big data, the relevance of deep learning in computed tomography is becoming imminent. It is very effective in robust tasks such as image classification, image segmentation, and identification of various cardiovascular structures in CT, CTA, and cardiovascular imaging[20]. Furthermore, it does not require extensive training. The accuracy can be achieved by elevating the capability of the network or increasing the training set. This is a stark distinction in comparison to other ML algorithms[55]. Other algorithms entail a significant number of observations, computations, manual labor, and training to achieve optimal efficiency.

Randomized clinical trials (RCTs) are the gold standard in clinical research. The integration of ML algorithms could prove to be exceeding useful if implemented appropriately. Numerous RCTs fail to reach completion due to several factors which could include improper study design, inadequate number of participants, or lack of funding[56]. The integration of ML algorithms during the early or intermediate stage of an RCT could provide an outlook of different outcomes[5]. This information could

be used to restructure the RCT to obtain more successful outcomes. In addition, ML algorithms can enhance the randomization process in RCT[56].

LIMITATIONS OF ML

Though ML algorithms offer a significant promise for the future, it is far from straightforward. Several issues need to be resolved for successful implementation in clinical medicine. The potential of false discovery can occur with small databases, there is not enough information to properly train the algorithm[55]. Unfortunately, AI lacks a moral compass[57]. In addition, several unintentional biases can emerge during the process and could alter interpretation. The "black box" nature has always been an enigmatic property of ML algorithms, this has impeded its adoption in the medical field[2]. Investigators must have a proper research concept and plan before embarking on any ML-related task. As a result, engineers, physicians, and other members of a research team must play an active role in every stage of the ML algorithm[15,58]. Adjustments can be made to the algorithm to deliver clinically relevant information.

For any ML algorithm to thrive and grow, large information or databases is mandatory[15]. Obtaining this information can be complex and tedious. Data needs to be shared among institutions to allow training of the ML model[15]. This might require multiple IRB approvals. Information also needs to be de-identified before it can be shared. Many of these tasks can be time-consuming. Many types of imaging systems are frequently used for storing cardiovascular images. Nevertheless, each institution has their own unique protocols and there are differences in the acquisition process as well[2]. Some form of data standardization is required to facilitate data sharing and ML algorithm growth. If more information can be publicly available, it would be beneficial.

CONCLUSION

ML algorithms will have limitless potential in cardiovascular imaging, this has been evidenced in the field of CT. It will cause multiple paradigm shifts which will have a revolutionary impact in the field of medicine. These frameworks will automate several tasks, perform calculations, and aid as a supplementary tool for medical diagnosis and prognostication. By performing multiple tasks, physicians will have more time to spend with patients and be more focused on proper medical management. ML will serve as a long-lasting bridge between physicians and technology in clinical medicine.

REFERENCES

1 **Seetharam K**, Kagiyama N, Sengupta PP. Application of mobile health, telemedicine and artificial intelligence to echocardiography. *Echo Res Pract* 2019; **6**: R41-R52 [PMID: 30844756 DOI: 10.1530/ERP-18-0081]

2 **Seetharam K**, Brito D, Farjo PD, Sengupta PP. The Role of Artificial Intelligence in Cardiovascular Imaging: State of the Art Review. *Front Cardiovasc Med* 2020; **7**: 618849 [PMID: 33426010 DOI: 10.3389/fcvm.2020.618849]

3 **Al'Aref SJ**, Anchouche K, Singh G, Slomka PJ, Kolli KK, Kumar A, Pandey M, Maliakal G, van Rosendael AR, Beecy AN, Berman DS, Leipsic J, Nieman K, Andreini D, Pontone G, Schoepf UJ, Shaw LJ, Chang HJ, Narula J, Bax JJ, Guan Y, Min JK. Clinical applications of machine learning in cardiovascular disease and its relevance to cardiac imaging. *Eur Heart J* 2019; **40**: 1975-1986 [PMID: 30060039 DOI: 10.1093/eurheartj/ehy404]

4 **Abdelrahman KM**, Chen MY, Dey AK, Virmani R, Finn AV, Khamis RY, Choi AD, Min JK, Williams MC, Buckler AJ, Taylor CA, Rogers C, Samady H, Antoniades C, Shaw LJ, Budoff MJ, Hoffmann U, Blankstein R, Narula J, Mehta NN. Coronary Computed Tomography Angiography From Clinical Uses to Emerging Technologies: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2020; **76**: 1226-1243 [PMID: 32883417 DOI: 10.1016/j.jacc.2020.06.076]

5 **Seetharam K**, Min JK. Artificial Intelligence and Machine Learning in Cardiovascular Imaging. *Methodist Debakey Cardiovasc J* 2020; **16**: 263-271 [PMID: 33500754 DOI: 10.14797/mdcj-16-4-263]

6 **Shameer K**, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. Machine learning in cardiovascular medicine: are we there yet? *Heart* 2018; **104**: 1156-1164 [PMID: 29352006 DOI: 10.1136/heartjnl-2017-311198]

7 **Seetharam K**, Raina S, Sengupta PP. The Role of Artificial Intelligence in Echocardiography. *Curr*

Cardiol Rep 2020; **22**: 99 [PMID: 32728829 DOI: 10.1007/s11886-020-01329-7]
8 **Hamet P**, Tremblay J. Artificial intelligence in medicine. *Metabolism* 2017; **69S**: S36-S40 [PMID: 28126242 DOI: 10.1016/j.metabol.2017.01.011]
9 **Seetharam K**, Sengupta PP, Bianco CM. Cardiac mechanics in heart failure with preserved ejection fraction. *Echocardiography* 2020; **37**: 1936-1943 [PMID: 32594605 DOI: 10.1111/echo.14764]
10 **Kagiyama N**, Shrestha S, Farjo PD, Sengupta PP. Artificial Intelligence: Practical Primer for Clinical Research in Cardiovascular Disease. *J Am Heart Assoc* 2019; **8**: e012788 [PMID: 31450991 DOI: 10.1161/JAHA.119.012788]
11 **Seetharam K**, Shrestha S, Sengupta P. Artificial Intelligence in Cardiac Imaging. *US Cardiol Rev* 2020; **13**: 110-116 [DOI: 10.15420/usc.2019.19.2]
12 **Johnson KW**, Torres Soto J, Glicksberg BS, Shameer K, Miotto R, Ali M, Ashley E, Dudley JT. Artificial Intelligence in Cardiology. *J Am Coll Cardiol* 2018; **71**: 2668-2679 [PMID: 29880128 DOI: 10.1016/j.jacc.2018.03.521]
13 **Krittanawong C**, Zhang H, Wang Z, Aydar M, Kitai T. Artificial Intelligence in Precision Cardiovascular Medicine. *J Am Coll Cardiol* 2017; **69**: 2657-2664 [PMID: 28545640 DOI: 10.1016/j.jacc.2017.03.571]
14 **Seetharam K**, Kagiyama N, Shrestha S, Sengupta PP. Clinical Inference From Cardiovascular Imaging: Paradigm Shift Towards Machine-Based Intelligent Platform. *Curr Treat Options Cardiovasc Med* 2020; **22**: 8 [DOI: 10.1007/s11936-020-0805-5]
15 **Seetharam K**, Shresthra S, Mills JD, Sengupta PP. Artificial Intelligence in Nuclear Cardiology: Adding Value to Prognostication. *Curr Cardiovasc Imag Rep* 2019; 12 [DOI: 10.1007/s12410-019-9490-8]
16 **Sengupta PP**, Shrestha S. Machine Learning for Data-Driven Discovery: The Rise and Relevance. *JACC Cardiovasc Imaging* 2019; **12**: 690-692 [PMID: 30553684 DOI: 10.1016/j.jcmg.2018.06.030]
17 **Bizopoulos P**, Koutsouris D. Deep Learning in Cardiology. *IEEE Rev Biomed Eng* 2019; **12**: 168-193 [PMID: 30530339 DOI: 10.1109/RBME.2018.2885714]
18 **Krittanawong C**, Johnson KW, Rosenson RS, Wang Z, Aydar M, Baber U, Min JK, Tang WHW, Halperin JL, Narayan SM. Deep learning for cardiovascular medicine: a practical primer. *Eur Heart J* 2019; **40**: 2058-2073 [PMID: 30815669 DOI: 10.1093/eurheartj/ehz056]
19 **Sengupta PP**, Shrestha S, Zeb I. Solving coronary risk: time to feed machines some calcium (score) supplements. *Eur Heart J* 2020; **41**: 368-370 [PMID: 31603192 DOI: 10.1093/eurheartj/ehz708]
20 **Litjens G**, Ciompi F, Wolterink JM, de Vos BD, Leiner T, Teuwen J, Išgum I. State-of-the-Art Deep Learning in Cardiovascular Image Analysis. *JACC Cardiovasc Imaging* 2019; **12**: 1549-1565 [PMID: 31395244 DOI: 10.1016/j.jcmg.2019.06.009]
21 **Shrestha S**, Sengupta PP. Machine learning for nuclear cardiology: The way forward. *J Nucl Cardiol* 2019; **26**: 1755-1758 [PMID: 29679221 DOI: 10.1007/s12350-018-1284-x]
22 **Shrestha S**, Sengupta PP. The Mechanics of Machine Learning: From a Concept to Value. *J Am Soc Echocardiogr* 2018; **31**: 1285-1287 [PMID: 30522604 DOI: 10.1016/j.echo.2018.10.003]
23 **Al'Aref SJ**, Min JK. Cardiac CT: current practice and emerging applications. *Heart* 2019; **105**: 1597-1605 [PMID: 31142595 DOI: 10.1136/heartjnl-2018-314229]
24 **Al'Aref SJ**, Maliakal G, Singh G, van Rosendael AR, Ma X, Xu Z, Alawamlh OAH, Lee B, Pandey M, Achenbach S, Al-Mallah MH, Andreini D, Bax JJ, Berman DS, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Chinnaiyan K, Chow BJW, Cury RC, DeLago A, Feuchtner G, Hadamitzky M, Hausleiter J, Kaufmann PA, Kim YJ, Leipsic JA, Maffei E, Marques H, Gonçalves PA, Pontone G, Raff GL, Rubinshtein R, Villines TC, Gransar H, Lu Y, Jones EC, Peña JM, Lin FY, Min JK, Shaw LJ. Machine learning of clinical variables and coronary artery calcium scoring for the prediction of obstructive coronary artery disease on coronary computed tomography angiography: analysis from the CONFIRM registry. *Eur Heart J* 2020; **41**: 359-367 [PMID: 31513271 DOI: 10.1093/eurheartj/ehz565]
25 **Hou ZH**, Lu B, Li ZN, An YQ, Gao Y, Yin WH, Liang S, Zhang RG. Machine Learning for Pretest Probability of Obstructive Coronary Stenosis in Symptomatic Patients. *JACC Cardiovasc Imaging* 2019; **12**: 2584-2586 [PMID: 31734209 DOI: 10.1016/j.jcmg.2019.07.030]
26 **Tesche C**, Otani K, De Cecco CN, Coenen A, De Geer J, Kruk M, Kim YH, Albrecht MH, Baumann S, Renker M, Bayer RR, Duguay TM, Litwin SE, Varga-Szemes A, Steinberg DH, Yang DH, Kepka C, Persson A, Nieman K, Schoepf UJ. Influence of Coronary Calcium on Diagnostic Performance of Machine Learning CT-FFR: Results From MACHINE Registry. *JACC Cardiovasc Imaging* 2020; **13**: 760-770 [PMID: 31422141 DOI: 10.1016/j.jcmg.2019.06.027]
27 **Kay FU**, Abbara S, Joshi PH, Garg S, Khera A, Peshock RM. Identification of High-Risk Left Ventricular Hypertrophy on Calcium Scoring Cardiac Computed Tomography Scans: Validation in the DHS. *Circ Cardiovasc Imaging* 2020; **13**: e009678 [PMID: 32066275 DOI: 10.1161/CIRCIMAGING.119.009678]
28 **Pijls NH**, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, el Gamal MI. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation* 1995; **92**: 3183-3193 [PMID: 7586302 DOI: 10.1161/01.cir.92.11.3183]
29 **Leipsic J**, Weir-McCall J, Blanke P. FFR_{CT} for Complex Coronary Artery Disease Treatment Planning: New Opportunities. *Interv Cardiol* 2018; **13**: 126-128 [PMID: 30443268 DOI: 10.15420/icr.2018.14.3]
30 **Hirshfeld JW Jr**, Nathan AS. QFR and FFR_{CT}: Accurate Enough? *JACC Cardiovasc Interv* 2019; **12**:

2060-2063 [PMID: 31648767 DOI: 10.1016/j.jcin.2019.07.029]
31 **Zhou F**, Tang CX, Schoepf UJ, Tesche C, Rollins JD, Liu H, Zhou CS, Yan J, Lu MJ, Lu GM, Ni QQ, Zhang LJ. Machine Learning Using CT-FFR Predicts Proximal Atherosclerotic Plaque Formation Associated With LAD Myocardial Bridging. *JACC Cardiovasc Imaging* 2019; **12**: 1591-1593 [PMID: 30878419 DOI: 10.1016/j.jcmg.2019.01.018]
32 **Tang CX**, Liu CY, Lu MJ, Schoepf UJ, Tesche C, Bayer RR 2nd, Hudson HT Jr, Zhang XL, Li JH, Wang YN, Zhou CS, Zhang JY, Yu MM, Hou Y, Zheng MW, Zhang B, Zhang DM, Yi Y, Ren Y, Li CW, Zhao X, Lu GM, Hu XH, Xu L, Zhang LJ. CT FFR for Ischemia-Specific CAD With a New Computational Fluid Dynamics Algorithm: A Chinese Multicenter Study. *JACC Cardiovasc Imaging* 2020; **13**: 980-990 [PMID: 31422138 DOI: 10.1016/j.jcmg.2019.06.018]
33 **Coenen A**, Kim YH, Kruk M, Tesche C, De Geer J, Kurata A, Lubbers ML, Daemen J, Itu L, Rapaka S, Sharma P, Schwemmer C, Persson A, Schoepf UJ, Kepka C, Hyun Yang D, Nieman K. Diagnostic Accuracy of a Machine-Learning Approach to Coronary Computed Tomographic Angiography–Based Fractional Flow Reserve. *Circ Cardiovasc Imag* 2018; **11**: e007217 [DOI: 10.1161/CIRCIMAGING.117.007217]
34 **Dey D**, Gaur S, Ovrehus KA, Slomka PJ, Betancur J, Goeller M, Hell MM, Gransar H, Berman DS, Achenbach S, Botker HE, Jensen JM, Lassen JF, Norgaard BL. Integrated prediction of lesion-specific ischaemia from quantitative coronary CT angiography using machine learning: a multicentre study. *Eur Radiol* 2018; **28**: 2655-2664 [PMID: 29352380 DOI: 10.1007/s00330-017-5223-z]
35 **Hell MM**, Dey D, Marwan M, Achenbach S, Schmid J, Schuhbaeck A. Non-invasive prediction of hemodynamically significant coronary artery stenoses by contrast density difference in coronary CT angiography. *Eur J Radiol* 2015; **84**: 1502-1508 [PMID: 26001435 DOI: 10.1016/j.ejrad.2015.04.024]
36 **Rosito GA**, Massaro JM, Hoffmann U, Ruberg FL, Mahabadi AA, Vasan RS, O'Donnell CJ, Fox CS. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. *Circulation* 2008; **117**: 605-613 [PMID: 18212276 DOI: 10.1161/CIRCULATIONAHA.107.743062]
37 **de Vos AM**, Prokop M, Roos CJ, Meijs MF, van der Schouw YT, Rutten A, Gorter PM, Cramer MJ, Doevendans PA, Rensing BJ, Bartelink ML, Velthuis BK, Mosterd A, Bots ML. Peri-coronary epicardial adipose tissue is related to cardiovascular risk factors and coronary artery calcification in post-menopausal women. *Eur Heart J* 2008; **29**: 777-783 [PMID: 18156138 DOI: 10.1093/eurheartj/ehm564]
38 **Rodrigues ÉO**, Morais FF, Morais NA, Conci LS, Neto LV, Conci A. A novel approach for the automated segmentation and volume quantification of cardiac fats on computed tomography. *Comput Methods Programs Biomed* 2016; **123**: 109-128 [PMID: 26474835 DOI: 10.1016/j.cmpb.2015.09.017]
39 **Commandeur F**, Goeller M, Betancur J, Cadet S, Doris M, Chen X, Berman DS, Slomka PJ, Tamarappoo BK, Dey D. Deep Learning for Quantification of Epicardial and Thoracic Adipose Tissue From Non-Contrast CT. *IEEE Trans Med Imaging* 2018; **37**: 1835-1846 [PMID: 29994362 DOI: 10.1109/TMI.2018.2804799]
40 **Otaki Y**, Hell M, Slomka PJ, Schuhbaeck A, Gransar H, Huber B, Nakazato R, Germano G, Hayes SW, Thomson LE, Friedman JD, Achenbach S, Berman DS, Dey D. Relationship of epicardial fat volume from noncontrast CT with impaired myocardial flow reserve by positron emission tomography. *J Cardiovasc Comput Tomogr* 2015; **9**: 303-309 [PMID: 25977114 DOI: 10.1016/j.jcct.2015.03.005]
41 **Baskaran L**, Maliakal G, Al'Aref SJ, Singh G, Xu Z, Michalak K, Dolan K, Gianni U, van Rosendael A, van den Hoogen I, Han D, Stuijfzand W, Pandey M, Lee BC, Lin F, Pontone G, Knaapen P, Marques H, Bax J, Berman D, Chang HJ, Shaw LJ, Min JK. Identification and Quantification of Cardiovascular Structures From CCTA: An End-to-End, Rapid, Pixel-Wise, Deep-Learning Method. *JACC Cardiovasc Imaging* 2020; **13**: 1163-1171 [PMID: 31607673 DOI: 10.1016/j.jcmg.2019.08.025]
42 **Al'Aref SJ**, Singh G, Choi JW, Xu Z, Maliakal G, van Rosendael AR, Lee BC, Fatima Z, Andreini D, Bax JJ, Cademartiri F, Chinnaiyan K, Chow BJW, Conte E, Cury RC, Feuchtner G, Hadamitzky M, Kim YJ, Lee SE, Leipsic JA, Maffei E, Marques H, Plank F, Pontone G, Raff GL, Villines TC, Weirich HG, Cho I, Danad I, Han D, Heo R, Lee JH, Rizvi A, Stuijfzand WJ, Gransar H, Lu Y, Sung JM, Park HB, Berman DS, Budoff MJ, Samady H, Stone PH, Virmani R, Narula J, Chang HJ, Lin FY, Baskaran L, Shaw LJ, Min JK. A Boosted Ensemble Algorithm for Determination of Plaque Stability in High-Risk Patients on Coronary CTA. *JACC Cardiovasc Imaging* 2020; **13**: 2162-2173 [PMID: 32682719 DOI: 10.1016/j.jcmg.2020.03.025]
43 **Beecy AN**, Chang Q, Anchouche K, Baskaran L, Elmore K, Kolli K, Wang H, Al'Aref S, Peña JM, Knight-Greenfield A, Patel P, Sun P, Zhang T, Kamel H, Gupta A, Min JK. A Novel Deep Learning Approach for Automated Diagnosis of Acute Ischemic Infarction on Computed Tomography. *JACC Cardiovasc Imaging* 2018; **11**: 1723-1725 [PMID: 29778866 DOI: 10.1016/j.jcmg.2018.03.012]
44 **Oikonomou EK**, Williams MC, Kotanidis CP, Desai MY, Marwan M, Antonopoulos AS, Thomas KE, Thomas S, Akoumianakis I, Fan LM, Kesavan S, Herdman L, Alashi A, Centeno EH, Lyasheva M, Griffin BP, Flamm SD, Shirodaria C, Sabharwal N, Kelion A, Dweck MR, Van Beek EJR, Deanfield J, Hopewell JC, Neubauer S, Channon KM, Achenbach S, Newby DE, Antoniades C. A novel machine learning-derived radiotranscriptomic signature of perivascular fat improves cardiac risk prediction using coronary CT angiography. *Eur Heart J* 2019; **40**: 3529-3543 [PMID: 31504423

DOI: 10.1093/eurheartj/ehz592]

45 **Eisenberg E**, McElhinney PA, Commandeur F, Chen X, Cadet S, Goeller M, Razipour A, Gransar H, Cantu S, Miller RJH, Slomka PJ, Wong ND, Rozanski A, Achenbach S, Tamarappoo BK, Berman DS, Dey D. Deep Learning-Based Quantification of Epicardial Adipose Tissue Volume and Attenuation Predicts Major Adverse Cardiovascular Events in Asymptomatic Subjects. *Circ Cardiovasc Imaging* 2020; **13**: e009829 [PMID: 32063057 DOI: 10.1161/CIRCIMAGING.119.009829]

46 **Shameer K**, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. The whole is greater than the sum of its parts: combining classical statistical and machine intelligence methods in medicine. *Heart* 2018; **104**: 1228 [PMID: 29945951 DOI: 10.1136/heartjnl-2018-313377]

47 **Motwani M**, Dey D, Berman DS, Germano G, Achenbach S, Al-Mallah MH, Andreini D, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Chinnaiyan K, Chow BJ, Cury RC, Delago A, Gomez M, Gransar H, Hadamitzky M, Hausleiter J, Hindoyan N, Feuchtner G, Kaufmann PA, Kim YJ, Leipsic J, Lin FY, Maffei E, Marques H, Pontone G, Raff G, Rubinshtein R, Shaw LJ, Stehli J, Villines TC, Dunning A, Min JK, Slomka PJ. Machine learning for prediction of all-cause mortality in patients with suspected coronary artery disease: a 5-year multicentre prospective registry analysis. *Eur Heart J* 2017; **38**: 500-507 [PMID: 27252451 DOI: 10.1093/eurheartj/ehw188]

48 **van Rosendael AR**, Maliakal G, Kolli KK, Beecy A, Al'Aref SJ, Dwivedi A, Singh G, Panday M, Kumar A, Ma X, Achenbach S, Al-Mallah MH, Andreini D, Bax JJ, Berman DS, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Chinnaiyan K, Chow BJW, Cury RC, DeLago A, Feuchtner G, Hadamitzky M, Hausleiter J, Kaufmann PA, Kim YJ, Leipsic JA, Maffei E, Marques H, Pontone G, Raff GL, Rubinshtein R, Shaw LJ, Villines TC, Gransar H, Lu Y, Jones EC, Peña JM, Lin FY, Min JK. Maximization of the usage of coronary CTA derived plaque information using a machine learning based algorithm to improve risk stratification; insights from the CONFIRM registry. *J Cardiovasc Comput Tomogr* 2018; **12**: 204-209 [PMID: 29753765 DOI: 10.1016/j.jcct.2018.04.011]

49 **Han D**, Beecy A, Anchouche K, Gransar H, Dunham PC, Lee JH, Achenbach S, Al-Mallah MH, Andreini D, Berman DS, Bax JJ, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Chinnaiyan K, Chow BJW, Cury RC, DeLago A, Feuchtner G, Hadamitzky M, Hausleiter J, Kaufmann PA, Kim YJ, Leipsic JA, Maffei E, Marques H, de Araújo Gonçalves P, Pontone G, Raff GL, Rubinshtein R, Villines TC, Lu Y, Peña JM, Shaw LJ, Min JK, Lin FY. Risk Reclassification With Coronary Computed Tomography Angiography-Visualized Nonobstructive Coronary Artery Disease According to 2018 American College of Cardiology/American Heart Association Cholesterol Guidelines (from the Coronary Computed Tomography Angiography Evaluation for Clinical Outcomes : An International Multicenter Registry [CONFIRM]). *Am J Cardiol* 2019; **124**: 1397-1405 [PMID: 31547994 DOI: 10.1016/j.amjcard.2019.07.045]

50 **Shrestha S**, Sengupta PP. Imaging Heart Failure With Artificial Intelligence: Improving the Realism of Synthetic Wisdom. *Circ Cardiovasc Imaging* 2018; **11**: e007723 [PMID: 29661796 DOI: 10.1161/CIRCIMAGING.118.007723]

51 **Dey D**, Slomka PJ, Leeson P, Comaniciu D, Shrestha S, Sengupta PP, Marwick TH. Artificial Intelligence in Cardiovascular Imaging: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019; **73**: 1317-1335 [PMID: 30898208 DOI: 10.1016/j.jacc.2018.12.054]

52 **Bhavnani SP**, Narula J, Sengupta PP. Mobile technology and the digitization of healthcare. *Eur Heart J* 2016; **37**: 1428-1438 [PMID: 26873093 DOI: 10.1093/eurheartj/ehv770]

53 **Bhavnani SP**, Sola S, Adams D, Venkateshvaran A, Dash PK, Sengupta PP; ASEF-VALUES Investigators. A Randomized Trial of Pocket-Echocardiography Integrated Mobile Health Device Assessments in Modern Structural Heart Disease Clinics. *JACC Cardiovasc Imaging* 2018; **11**: 546-557 [PMID: 28917688 DOI: 10.1016/j.jcmg.2017.06.019]

54 **Sabharwal NK**. Could Deep Learning Change Our Working Lives? *JACC Cardiovasc Imaging* 2018; **11**: 1664-1665 [PMID: 29550322 DOI: 10.1016/j.jcmg.2018.02.010]

55 **Seetharam K**, Shrestha S, Sengupta PP. Artificial Intelligence in Cardiovascular Medicine. *Curr Treat Options Cardiovasc Med* 2019; **21**: 25 [PMID: 31089906 DOI: 10.1007/s11936-019-0728-1]

56 **Krittanawong C**, Johnson KW, Tang WW. How artificial intelligence could redefine clinical trials in cardiovascular medicine: lessons learned from oncology. *Per Med* 2019; **16**: 83-88 [PMID: 30838909 DOI: 10.2217/pme-2018-0130]

57 **Bostrom N**, Yudkowsky E. The ethics of artificial intelligence. The Cambridge Handbook of Artificial Intelligence. Cambridge University Press, 2014 [DOI: 10.1017/CBO9781139046855]

58 **Sengupta PP**, Shrestha S, Berthon B, Messas E, Donal E, Tison GH, Min JK, D'hooge J, Voigt JU, Dudley J, Verjans JW, Shameer K, Johnson K, Lovstakken L, Tabassian M, Piccirilli M, Pernot M, Yanamala N, Duchateau N, Kagiyama N, Bernard O, Slomka P, Deo R, Arnaout R. Proposed Requirements for Cardiovascular Imaging-Related Machine Learning Evaluation (PRIME): A Checklist: Reviewed by the American College of Cardiology Healthcare Innovation Council. *JACC Cardiovasc Imaging* 2020; **13**: 2017-2035 [PMID: 32912474 DOI: 10.1016/j.jcmg.2020.07.015]

World Journal of Cardiology

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

World J Cardiol 2021 October 26; 13(10): 556-565

DOI: 10.4330/wjc.v13.i10.556

ISSN 1949-8462 (online)

MINIREVIEWS

Coronavirus and cardiovascular manifestations- getting to the heart of the matter

Monika Bhandari, Akshyaya Pradhan, Pravesh Vishwakarma, Rishi Sethi

ORCID number: Monika Bhandari 0000-0002-4699-8633; Akshyaya Pradhan 0000-0002-2360-7580; Pravesh Vishwakarma 0000-0003-4454-2189; Rishi Sethi 0000-0002-6745-6235.

Author contributions: Pradhan A and Bhandari M conceived the project; Pradhan A and Vishwakarma P did the literature review; Bhandari M prepared the first draft; Sethi R critically reviewed it; Bhandari M and Vishwakarma P prepared the revised manuscript; Pradhan A submitted the original manuscript and collaborated with Bhandari M for revising the manuscript and submitted it.

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

Monika Bhandari, Akshyaya Pradhan, Pravesh Vishwakarma, Rishi Sethi, Department of Cardiology, King George's Medical University, Lucknow 226003, Uttar Pradesh, India

Corresponding author: Akshyaya Pradhan, MBBS, MD, DM, FACC, FSCAI Additional Professor, Department of Cardiology, King George's Medical University, Shahmina Road, Chowk, Lucknow 226003, Uttar Pradesh, India. akshyaya33@gmail.com

Abstract

Coronavirus disease has unarguably been the largest pandemic of recent times. Over 150 million cases have occurred worldwide, and more than 3 million have succumbed to the disease. Cardiac manifestations can have varied presentations from an asymptomatic troponin rise to fulminant myocarditis. The pathogenesis of myocardial damage could be direct or indirect, including inflammation, coronary spasm, plaque rupture, and cytokine storm. Thromboembolism is also an important feature of cardiovascular affliction with both arterial and venous systems being affected. Hence, anticoagulation has also been a matter of debate. Fulminant myocarditis is the most severe form and can lead to circulatory shock with a high mortality. Management of cardiac patients with coronavirus disease 2019 (COVID-19) infection is not considerably different from non-COVID-19 cardiovascular disease, but interaction between cardiovascular drugs and anti-COVID-19 therapy requires careful attention. More recently, vaccines have emerged as a ray of hope for the disease. But simultaneously, there have been reports of thromboembolism following vaccination. In this review, we discuss the various aspects of coronavirus disease affecting of heart and its management.

Key Words: Myocarditis; Cytokine storm; Angiotensin-converting enzymes-2; Acute coronary syndrome; Hypercoagulable state; Vaccine

Core Tip: Coronavirus affects various parts of cardiovascular (CV) system. Acute coronary syndromes, myocarditis, tachyarrhythmia, heart failure and shock can be the various manifestations. The mechanism of cardiac involvement can be direct or indirect *via* cytokine storm ,inflammation and thromboembolism. Thromboembolism is particularly more common in coronavirus disease (COVID) infection and so is

Manuscript source: Unsolicited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: India

Peer-review report's scientific quality classification

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

Received: June 21, 2021
Peer-review started: June 21, 2021
First decision: July 30, 2021
Revised: August 7, 2021
Accepted: September 16, 2021
Article in press: September 16, 2021
Published online: October 26, 2021

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

bleeding making anticoagulation a daunting task. Management of cardiac manifestations is not very different from a non COVID patient and needs diligent effort due to the need for preventing transmission to health care workers. Undoubtedly, cardiac involvement portends poor prognosis and antecedent cardiovascular disease is abundant among non-survivors. Adequate control of CV risk factors, prompt recognition of symptoms, timely management and early vaccination hold the key to victory against the coronavirus onslaught on the heart. Reports of thromboembolism have also emerged after COVID-19 vaccination but the incidence is rare.

Citation: Bhandari M, Pradhan A, Vishwakarma P, Sethi R. Coronavirus and cardiovascular manifestations- getting to the heart of the matter. *World J Cardiol* 2021; 13(10): 556-565
URL: https://www.wjgnet.com/1949-8462/full/v13/i10/556.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i10.556

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The disease has evolved into a global pandemic and has affected more than 150 million people worldwide. Unfortunately, more than 3.5 million people have succumbed to the disease till now[1].

Infection with the SARS-CoV-2 virus mainly causes fever (77%–98% of cases), fatigue (52%–75%), and cough (62%–81%). It primarily affects the respiratory system, but its effects on the cardiovascular (CV) system have also been noted. While those with pre-existing CV disease are at an increased risk of mortality, the disease also contributes to CV complications. These may be acute coronary syndrome (ACS), including myocardial infarction (MI), arrhythmias, myocarditis, acute heart failure (HF), cardiogenic shock, and even death[2-4].

CARDIAC INVOLVEMENT IN COVID-19

Cardiac injury is described by the presence of raised cardiac troponins (cTn) in COVID-19. Cardiac biomarkers are elevated in 7%–28% of COVID-19 patients. It can be either due to MI or due to myocardial injury from myocarditis and hemodynamic shock[5-8].

According to the American College of Cardiology (ACC), patients with cTn elevation (myocardial injury) can be classified as (1) Chronic myocardial injury; (2) Acute nonischemic myocardial injury; or (3) Acute myocardial infarction (MI)[9].

An association between ACS is already described for influenza virus and other respiratory viruses. Thus, it is of extreme importance to understand the pathophysiological mechanism of ACS in COVID-19[10,11].

Many patients with COVID-19 present with symptoms mimicking ACS. According to the study of Huang *et al*[4], prevalence of myocardial injury in SARS-CoV-2 is 12%. In another study, cardiac injury is observed in 7.2% overall and 22.2% of intensive care unit (ICU) patients infected with the SARS-COV-2 virus[2].

From a retrospective analysis of 191 COVID-19 pneumonia patients by Zhou *et al* [12], it can inferred that those who develop acute myocardial injury are more likely to die (odd ratio of 21.4, $P < 0.0001$). Thus, myocardial injury is an independent predictor of mortality.

MECHANISM OF CARDIOVASCULAR INVOLVEMENT IN COVID-19

Several mechanisms are postulated to cause CV events in SARS-COV-2 infection (Figure 1). These include a pro-inflammatory state and cytokine storm, which leads to plaque instability in patients with pre-existing CAD. In addition to this, COVID-19 infection induces a prothrombotic state as evidenced by raised D-dimer levels and hypoxemia-related myocardial ischemia due to respiratory failure. All these mechanisms cause myocardial ischemia even in patients without pre-existing CV

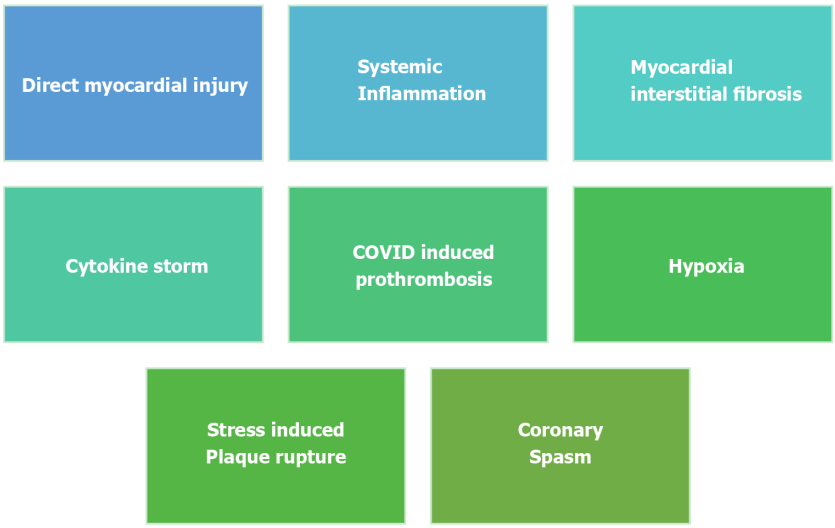


Figure 1 Various mechanisms of myocardial injury associated with coronavirus disease 2019 disease. COVID: Coronavirus disease.

disease[13].

Pro-inflammatory state

In a recently published case of series of COVID-19 patients, Varga *et al*[14] demonstrated evidence of direct viral infection of the endothelial cells. This leads to endothelitis along with micro- and macro-thrombosis in both the arterial and venous circulation. This in addition to the hypercoagulability predisposes to ACS[15].

Cytokine storm

An excessive immune response to SARS-COV 2 virus has been demonstrated in certain patients, which leads to a cytokine storm[4]. In a study of 53 patients with clinically moderate to severe COVID-19 disease, 14 types of cytokines were elevated. Of them, interferon gamma-induced protein 10 (IP-10), monocyte chemotactic protein 3 (MCP-3), and interleukin-1 receptor antagonist (IL-1ra), are independently associated with hypoxaemia, disease progression, and death[16]. Cytokine production damages the healthy cells initially in the lungs. Subsequently, it involves other organs, such as the kidney, heart blood vessels, and brain. Due to this hypercytokinemia, there is an increase in hypercoagulability contributing to a 31% increase in incidence of thrombosis. This eventually manifests as ischemic stroke, deep vein thrombosis, acute pulmonary embolism, MI, and systemic arterial embolism[14].

Angiotensin-converting enzymes

The pathophysiology of COVID-19 infection involves binding of the SARS-COV2 virus to the host ACE-2 receptor, which mediates virus entry into the cell. Angiotensin-converting enzymes (ACE)-2 receptors are present in the epithelial cells of the lungs, kidneys, heart, intestines, and blood vessels. ACE is also an important component in the pathophysiology of CAD[17,18].

In COVID-19 infection, there is dysregulation of the rennin-angiotensin-aldosterone system (RAAS)/ ACE-2 *via* the SARS-COV-2 virus, leading to CV involvement[19]. This may be a primary manifestation of COVID-19 or may be secondary to lung involvement, leading to hypoxemia-induced myocardial damage. Patients with pre-existing cardiac disease are especially prone for this. Additionally, the downregulation of ACE-2 with concomitant upregulation of angiotensin II results in RAS overactivation. The ultimate result is loss of the beneficial effects of angiotensin (1-7), aggravating and perpetuating cardiac injury.

Relationship between COVID-19, ACE-2, and hypertension

ACE inhibitors (ACE-I) lead to upregulation of ACE-2 receptors; thus causative role in severe COVID-19 disease is postulated. However, in the study of Guo *et al*[8] in patients with COVID-19, mortality is not impacted by use of ACE-I. In contrast, a retrospective analysis of 1128 hypertensive patients with COVID-19 the inpatient use of ACE-I reduced the all-cause mortality[20]. Thus, patients with pre-existing hypertension who are on ACE-I should continue to take it.

ACS

Decrease in ACS cases

Although COVID-19 has led to an increase in hospitalizations, the amount of ACS admissions has substantially decreased. This decline is more for ST elevation myocardial infarction (STEMI) than for non-ST elevation myocardial infarction (NSTEMI). This finding is observed in multiple countries and is believed to be due to multiple factors. These include hesitance of patients to visit hospitals despite initial symptoms for fear of contracting the COVID-19 infection and confusion regarding symptoms. Other factors include better medication adherence, lower pollution levels, less smoking, and less physical strain[21,22].

In one study, 40% decline in hospital admission for ACS is reported. Another finding of interest is the late presentation for STEMI compared to the pre-COVID-19 era. Fortunately enough, there is no difference in door to balloon time. Mortality rates are also high for STEMI during the COVID-19 pandemic ($P < 0.05$)[23].

Presentation of ACS during COVID-19

In one case series, of 18 patients of ACS with COVID-19, 56% of the patients presented with STEMI and the remaining developed it during the course of illness. ST elevations could be diffuse or focal and there was high prevalence of LV dysfunction in latter. However, obstructive CAD is seen only in a minority of patients, as seen in 6 (33%) out of 9 patients in the study. Of note, all 18 patients had elevated D-dimer levels[24]. In a retrospective single center study by Shi *et al*[25], of 416 patients with COVID-19, prevalence of ACS was 3.6%, and all were NSTEMI.

Management of ACS in COVID-19

According to the latest European Society of Cardiology (ESC) guidelines for management of CAD during the COVID-19 pandemic, primary PCI is the norm if they are in the window period (< 12 h from symptom onset). The primary PCI should be performed with a door to balloon time of 120 min. However, owing to the delay in transfer to a catheterization lab-facilitated hospital during the COVID-19 pandemic, a delay of up to 60 min can be accepted due in many instances. If the delay is more than this and there is no contraindication for thrombolysis, then patient can be thrombolyzed. In any circumstance, treatment should not be delayed ensuring necessary COVID-19 safety precautions[26].

Patients presenting with NSTEMI, should be risk stratified initially depending on the presence of recurrent chest pain, elevation of biomarkers, recurrent ST-T changes, heart failure, and LV dysfunction. COVID-19 testing should be performed as soon as possible regardless of treatment strategy. Patients having very high risk features should undergo immediate invasive management as for STEMI with COVID safety norms. Patients at high risk should be managed in a separate ICU while waiting for the COVID-19 results, and invasive management should be done within 24 h. Patients with intermediate and low risk can undergo non-invasive testing, such as CT coronary angiography, to rule out obstructive CAD. If patients with high risk and intermediate risk NSTEMI are COVID-19 positive, they should be transferred to equipped COVID-19 hospitals for cardiac intervention so that that along with cardiac illness they can also be treated for COVID[26].

MYOCARDITIS

The exact mechanism of myocarditis in COVID-19 is not clear. Some studies suggest high viral load as the possible mechanism. The cytokine storm and inflammatory state in COVID-19 may lead to myocarditis. It is suspected if a COVID-19 patient without pre-existing cardiac disease develops fulminant HF. Echocardiography shows marked depression in LVEF with global hypokinesia, LV dilatation, and pericardial effusion. Patients respond to anti-inflammatory therapy including parenteral glucocorticoids and immunoglobins[26,27].

STRESS-INDUCED CARDIOMYOPATHY

There is a strong relationship between psychosocial stress and cardiomyopathy. In a study published in JAMA, a significant rise in the incidence of stress cardiomyopathy

is observed during the COVID-19 pandemic (incidence proportion: 7.8% of total ACS patients). However, in comparison to the pre-pandemic time, the incidence proportion range is only 1.5%–1.8%. Nevertheless, there is no difference in mortality as compared to that of the pre-pandemic era[28].

CARDIOGENIC SHOCK

All patients presenting with cardiogenic shock or out of hospital arrest, must be considered COVID-19 positive until results are available. Those who are COVID-19 negative should be managed according to the latest guidelines. Patients should be admitted to the ICU, and mechanical circulatory support (MCS) should be provided. For COVID-19-positive patients, ICU admission should be given to those who require ventilatory support, use of MCS should be more restrictive, and health care personnel protection should be the priority[26,29].

HEART FAILURE

Patients with pre-existing cardiovascular disease (CVD) are at increased risk of severe COVID-19 infection. Hypertension and CVD is seen in approximately 17.1% and 16.4% of hospitalized COVID-19 patients as suggested in a meta-analysis of 6 studies and contributes to a 2–3 fold increased risk of mortality[30] (Table 1).

Acute heart failure (HF) can complicate COVID-19 cases. It is diagnosed by the classical signs and symptoms like chest rales, increased jugular venous pressure cardiomegaly, and bilateral pleural effusion. Significant elevation of brain natriuretic peptide (BNP) and NT-pro BNP also suggest HF.

There are various mechanisms responsible for HF in COVID-19, including myocardial ischemia, myocarditis, acute respiratory distress syndrome, acute kidney injury, stress induced cardiomyopathy and arrhythmias. Treatment should be administered according to the standard HF treatment guidelines.

ARRHYTHMIAS

The incidence of cardiac arrhythmias in COVID-19 patients was found to be approximately 16.7% in a single center study of 138 patients. The incidence is higher in seriously ill patients admitted to the ICU[2]. The management of arrhythmias in COVID-19 patients is essentially similar to as in COVID-19-negative patients.

Follow-up and monitoring of patients with implantable intracardiac devices should be done remotely. In COVID patients presenting with atrial arrhythmias, rate-controlling agents should be used in place of anti-arrhythmic therapy. This is because there may be need for the concomitant use of hydroxychloroquine/azithromycin which can lead to QT-c prolongation and torsades de pointes.

In patients presenting with VT/VF, amiodarone is the drug of choice. The implantation of an intracardiac device should be postponed for as long as possible.

For patients with bradyarrhythmias, if pacemaker implantation is required, all the necessary precautions should be taken for protection of health care personnel and to prevent nosocomial infections[26].

PULMONARY EMBOLISM

Strong evidence suggesting the increased risk of pulmonary embolism (PE) in COVID-19 is lacking. Some case reports have suggested that the incidence of pulmonary embolism may be high in hospitalized patients with COVID-19[31,32]. Owing to the high inflammatory state, enhanced hypercoagulability and immobilization, prophylactic anticoagulation should be given to hospitalized patients.

Because patients with COVID-19 pneumonia also have respiratory distress and chest pain, it is possible to miss PE. However, in the case of any unexpected tachycardia, deterioration of respiratory symptoms, and a decrease in blood pressure, PE should be suspected. This is specially important if there are new ECG changes suggestive of PE or there is deep vein thrombosis. Although the D-dimer is not reliable

Table 1 Cardiac involvement in coronavirus disease 2019 patients among various studies

Ref.	Study type	Number of patients	Cardiac involvement	Cardiovascular comorbidities
Wang *et al* [2]	Case series	138	7.2%	Diabetes (10.1%); Hypertension (31.2%); CVD (14.5%); CVA
Huang *et al* [4]	Prospective	41	12%	Hypertension
Guo *et al*[8]	Retrospective	187	27.8%	Hypertension (32.6%); Diabetes (15%); CVD (11.2%); Cardiomyopathy (4.3%)
Zhou *et al* [12]	Retrospective	191	17%	Hypertension (30%); Diabetes (19%); CAD (8%)
Shi *et al*[25]	Descriptive	416	19.7%	Hypertension (30.5%); Diabetes (14.4%); CVA (5.3%); CAD (10.6%)
Yang *et al* [33]	Retrospective, observational study	52	23%	Diabetes (17%); CVD (10%); CVA (13.5%)

CVD: Cardiovascular disease; CVA: Cardiovascular accident.

in COVID-19, it can still be used to rule out PE. In case of high suspicion and normal CT chest despite respiratory worsening, CT pulmonary angiography should be performed. The treatment protocol is similar to as in COVID-19-negative patients[32, 33].

INDICATIONS OF ANTICOAGULATION WITH COVID-19 INFECTION

Parenteral anticoagulants are indicated in all acutely ill hospitalized patients[34].

Dosing of anticoagulation: (1) Moderate disease (standard risk patients): standard weight-adjusted prophylactic dose (*e.g.*, enoxaparin at 40 mg once daily for a 70-kg adult with CrCl > 30 mL/min); (2) Severe and critical disease (high-risk patients requiring invasive ventilation/continuous positive airway pressure (CPAP)/non-invasive ventilation (NIV)/high-flow nasal oxygen): intermediate dose Low Molecular Weight Heparin (enoxaparin at 40 mg two times per day for a 70-kg adult with CrCl > 30 mL/min); (3) Diagnosed/highly suspected macro-thrombosis (PE/DVT): therapeutic dose (enoxaparin at 1 mg/kg with 12 h subcutaneous or 1.5 mg/kg subcutaneously once daily); and (4) Renal insufficiency: Enoxaparin with dose reduction is the preference over other LMWH drugs/fondaparinux. UFH with aPTT monitoring indicated at eGFR < 15 mL/min.

Decisions regarding post discharge prophylactic anticoagulation should be individualized. Based on past and ongoing trials regarding usage of anticoagulants, it can be concluded that patients with moderate to severe disease and fulfilling any one of the below criteria should receive post discharge thromboprophylaxis (Table 2)[34]: (1) Modified IMPROVE venous thromboembolism (VTE) (MIV) score ≥ 4; (2) MIV ≥ 2 with a D-dimer value > 2 times the upper limit of the normal range; (3) Age ≥ 75 years; (4) Age > 60 years with a D-dimer value > 2 times the upper limit of the normal range (ULN); and (5) Age 40–60 years with a D-dimer value > 2 times (ULN) and a history of VTE or with diagnosed malignancy.

PROGNOSTIC IMPLICATION

Many serum biomarkers can be utilized for both diagnosis and prognosis in COVID-19 with cardiovascular affliction (Figure 2). In a study by Liu *et al*[35], C-reactive protein (CRP), lactate dehydrogenase, and D-dimer were elevated in 85.5%, 65.2%, and 65.2% of patients, respectively, in the severe category. In another study, the proportions of patients with increased IL-6, CRP, and procalcitonin levels were significantly higher in the severe COVID-19 group than in mild COVID-19 patients. The Cox proportional hazard model showed that IL-6 and CRP are independent factors in predicting the severity of COVID-19. Based on their analysis, patients with IL-6 > 32.1 pg/mL or CRP > 41.8 mg/L are more likely to have severe complications[36].

Table 2 Modified venous thrombo-embolism score for risk stratification in pulmonary embolism/deep vein thrombosis

VTE risk factor	VTE risk score
Previous VTE	3
Known thrombophilia[1]	2
Current lower limb paralysis or paresis	2
History of cancer	2
ICU/CCU stay	1
Complete immobilization > 24 h	1
Age > 60 yr	1

[1]Congenital or acquired.
VTE: Venous thromboembolism; ICU: Intensive care unit; CCU: Coronary care unit.

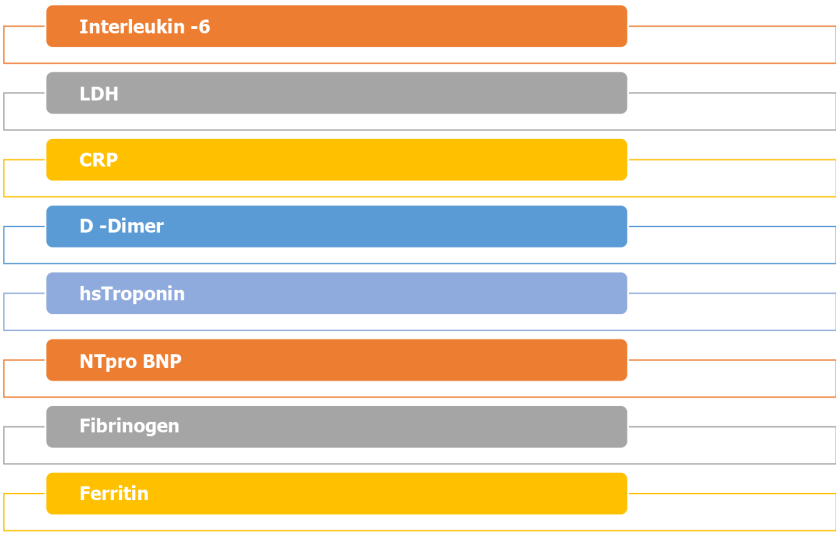


Figure 2 Biomarkers of inflammation/injury commonly utilized for prognostic implications in coronavirus disease 2019 infection. LDH: Lactate dehydrogenase; CRP: C-reactive protein; BNP: Brain natriuretic peptide.

Troponin elevation during a hospital stay enhances the risk of arrhythmias, mechanical ventilation, and indicated a subgroup poised for high mortality[36].

Deranged coagulation parameters (D-dimer, fibrinogen, activated partial thromboplastin time, and prothrombin time) are also predictors of poor prognosis as evidenced in a study from Wuhan[37]. Critically ill patients and deceased patients demonstrate more frequently elevated levels of D-dimer, PT/INR, and lower fibrinogen levels. Interestingly, D-dimer levels also correlated with the CT findings.

COVID-19 VACCINE AND THROMBOEMBOLISM

Vaccination is thought to be the most promising approach for containing or ending the COVID-19 pandemic. The efficacy of the COVID-19 vaccine in preventing COVID-19 infection varies from 50% to 70%, while the efficacy in preventing serious disease is 70–90%. No major safety warnings, other than rare cases of anaphylaxis, are reported in large trials. In February 2021, the first case of prothrombotic syndrome appeared with the AstraZeneca vaccine (COVISHIELD), which is an adenoviral vector-based vaccine. Subsequently, Ad26.COV2.S vaccine (Janssen; Johnson and Johnson) also reported similar issues[38]. Both arterial and VTE are noted with COVID-19 vaccines. However, the distribution is symmetrical for COVISHIELD, while it is skewed in favor of arterial thromboembolism with mRNA vaccines (Pfizer-BioNTech and Moderna) [39]. The underlying mechanism discovered is an immune-mediated thrombotic thrombocytopenia and is similar to that observed with heparin-induced thrombocyt-

openia. The condition starts usually within 1–2 wk after vaccination and is common in young females[40].

The incidence of VTE is 1 case per 100000 exposure. The frequency of COVID-19-related VTE is 14.7% to 17.6%, and the frequency rates of overall arterial thromboembolism is approximately 3.9%[41].Thus, the chances of thromboembolic episodes are far lower as compared to COVID-19 infection itself[]. Thus, the vaccines available are safe and effective.

COVID-19 VACCINE AND ACCELERATED HYPERTENSION

Meylan *et al*[42] reported a case series of 9 patients who developed accelerated hypertension (Stage III) shortly after their vaccinations. However, the majority were being treated for hypertension with drugs beforehand. Anxiety and allergic reactions to vaccine components have been proposed, but in the absence of tachycardia, the former is less likely.

CONCLUSION

The COVID-19 pandemic is producing an adverse impact on health care systems. Studies have demonstrated that this disease not only involves the respiratory system but also multiple organs, including the heart, brain, and kidneys. Cardiovascular involvement is quite common and can be a source of mortality. Thus, there should be a high index of suspicion for cardiac involvement in severe COVID-19 cases, and appropriate measures should be taken. Because the acuteness of pandemic, there is dearth of randomized studies. For patients with primary cardiac presentation, such as ACS, first preference should be given for cardiac management pending a COVID testing. STEMI patients should undergo revascularization either by primary PCI or by thrombolysis according to the window periods and time delays. For NSTEMI patients, treatment should be according to the risk category. For heart failure, arrhythmias, and myocarditis, the standard treatment protocol should be followed.

REFERENCES

1 **World health organization**. Weekly operational update on COVID-19. [cited 7 September, 2021] https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---6-september-2021

2 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

3 **Livingston E**, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. *JAMA* 2020; **323**: 1335 [PMID: 32181795 DOI: 10.1001/jama.2020.4344]

4 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

5 **Lippi G**, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. *Prog Cardiovasc Dis* 2020; **63**: 390-391 [PMID: 32169400 DOI: 10.1016/j.pcad.2020.03.001]

6 **Bhatraju PK**, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Wurfel MM, Evans L, Kritek PA, West TE, Luks A, Gerbino A, Dale CR, Goldman JD, O'Mahony S, Mikacenic C. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. *N Engl J Med* 2020; **382**: 2012-2022 [PMID: 32227758 DOI: 10.1056/NEJMoa2004500]

7 **Phua J**, Weng L, Ling L, Egi M, Lim CM, Divatia JV, Shrestha BR, Arabi YM, Ng J, Gomersall CD, Nishimura M, Koh Y, Du B; Asian Critical Care Clinical Trials Group. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. *Lancet Respir Med* 2020; **8**: 506-517 [PMID: 32272080 DOI: 10.1016/S2213-2600(20)30161-2]

8 **Guo T**, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 811-818 [PMID: 32219356 DOI: 10.1001/jamacardio.2020.1017]

9 **Yader Sandoval**. Key Points About Myocardial Injury and Cardiac Troponin in COVID-19. [cited 3 February 2021] Available from: https://www.acc.org/Latest-in-cardiology/articles/2020/07/17/08/00/key-points-about-myocardial-injury-and-cardiac-troponin-in-

covid-19

10 **Kwong JC**, Schwartz KL, Campitelli MA. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. *N Engl J Med* 2018; **378**: 2540-2541 [PMID: 29949484 DOI: 10.1056/NEJMc1805679]

11 **Violi F**, Cangemi R, Falcone M, Taliani G, Pieralli F, Vannucchi V, Nozzoli C, Venditti M, Chirinos JA, Corrales-Medina VF; SIXTUS (Thrombosis-Related Extrapulmonary Outcomes in Pneumonia) Study Group. Cardiovascular Complications and Short-term Mortality Risk in Community-Acquired Pneumonia. *Clin Infect Dis* 2017; **64**: 1486-1493 [PMID: 28205683 DOI: 10.1093/cid/cix164]

12 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]

13 **Clerkin KJ**, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, Jain SS, Burkhoff D, Kumaraiah D, Rabbani L, Schwartz A, Uriel N. COVID-19 and Cardiovascular Disease. *Circulation* 2020; **141**: 1648-1655 [PMID: 32200663 DOI: 10.1161/CIRCULATIONAHA.120.046941]

14 **Varga Z**, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417-1418 [PMID: 32325026 DOI: 10.1016/S0140-6736(20)30937-5]

15 **Violi F**, Pastori D, Cangemi R, Pignatelli P, Loffredo L. Hypercoagulation and Antithrombotic Treatment in Coronavirus 2019: A New Challenge. *Thromb Haemost* 2020; **120**: 949-956 [PMID: 32349133 DOI: 10.1055/s-0040-1710317]

16 **Vaninov N**. In the eye of the COVID-19 cytokine storm. *Nat Rev Immunol* 2020; **20**: 277 [PMID: 32249847 DOI: 10.1038/s41577-020-0305-6]

17 **Walls AC**, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* 2020; **181**: 281-292.e6 [PMID: 32155444 DOI: 10.1016/j.cell.2020.02.058]

18 **Li W**, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003; **426**: 450-454 [PMID: 14647384 DOI: 10.1038/nature02145]

19 **Wu Y**. Compensation of ACE2 Function for Possible Clinical Management of 2019-nCoV-Induced Acute Lung Injury. *Virol Sin* 2020; **35**: 256-258 [PMID: 32034638 DOI: 10.1007/s12250-020-00205-6]

20 **Zhang P**, Zhu L, Cai J, Lei F, Qin JJ, Xie J, Liu YM, Zhao YC, Huang X, Lin L, Xia M, Chen MM, Cheng X, Zhang X, Guo D, Peng Y, Ji YX, Chen J, She ZG, Wang Y, Xu Q, Tan R, Wang H, Lin J, Luo P, Fu S, Cai H, Ye P, Xiao B, Mao W, Liu L, Yan Y, Liu M, Chen M, Zhang XJ, Wang X, Touyz RM, Xia J, Zhang BH, Yuan Y, Loomba R, Liu PP, Li H. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19. *Circ Res* 2020; **126**: 1671-1681 [PMID: 32302265 DOI: 10.1161/CIRCRESAHA.120.317134]

21 **Garcia S**, Albaghdadi MS, Meraj PM, Schmidt C, Garberich R, Jaffer FA, Dixon S, Rade JJ, Tannenbaum M, Chambers J, Huang PP, Henry TD. Reduction in ST-Segment Elevation Cardiac Catheterization Laboratory Activations in the United States During COVID-19 Pandemic. *J Am Coll Cardiol* 2020; **75**: 2871-2872 [PMID: 32283124 DOI: 10.1016/j.jacc.2020.04.011]

22 **De Filippo O**, D'Ascenzo F, Angelini F, Bocchino PP, Conrotto F, Saglietto A, Secco GG, Campo G, Gallone G, Verardi R, Gaido L, Iannaccone M, Galvani M, Ugo F, Barbero U, Infantino V, Olivotti L, Mennuni M, Gili S, Infusino F, Vercellino M, Zucchetti O, Casella G, Giammaria M, Boccuzzi G, Tolomeo P, Doronzo B, Senatore G, Grosso Marra W, Rognoni A, Trabattoni D, Franchin L, Borin A, Bruno F, Galluzzo A, Gambino A, Nicolino A, Truffa Giachet A, Sardella G, Fedele F, Monticone S, Montefusco A, Omedè P, Pennone M, Patti G, Mancone M, De Ferrari GM. Reduced Rate of Hospital Admissions for ACS during Covid-19 Outbreak in Northern Italy. *N Engl J Med* 2020; **383**: 88-89 [PMID: 32343497 DOI: 10.1056/NEJMc2009166]

23 **Braiteh N**, Rehman WU, Alom M, Skovira V, Breiteh N, Rehman I, Yarkoni A, Kahsou H, Rehman A. Decrease in acute coronary syndrome presentations during the COVID-19 pandemic in upstate New York. *Am Heart J* 2020; **226**: 147-151 [PMID: 32569892 DOI: 10.1016/j.ahj.2020.05.009]

24 **Bangalore S**, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, Ibrahim H, Friedman GH, Thompson C, Alviar CL, Chadow HL, Fishman GI, Reynolds HR, Keller N, Hochman JS. ST-Segment Elevation in Patients with Covid-19 - A Case Series. *N Engl J Med* 2020; **382**: 2478-2480 [PMID: 32302081 DOI: 10.1056/NEJMc2009020]

25 **Shi S**, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; **5**: 802-810 [PMID: 32211816 DOI: 10.1001/jamacardio.2020.0950]

26 ESC guidance for diagnosis and management of CV disease during COVID-19 pandemic. [cited 5 February, 2021] Available form: https://www.escardio.org/Education/COVID-19 and Cardiology/ESC-COVID-19-Guidance

27 **Liu Y**, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Feng C, Zhang Z, Wang L, Peng L, Chen L, Qin Y, Zhao D, Tan S, Yin L, Xu J, Zhou C, Jiang C, Liu L. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* 2020; **63**: 364-374 [PMID: 32048163 DOI: 10.1007/s11427-020-1643-8]

28 **Jabri A**, Kalra A, Kumar A, Alameh A, Adroja S, Bashir H, Nowacki AS, Shah R, Khubber S, Kanaa'N A, Hedrick DP, Sleik KM, Mehta N, Chung MK, Khot UN, Kapadia SR, Puri R, Reed GW. Incidence of Stress Cardiomyopathy During the Coronavirus Disease 2019 Pandemic. *JAMA Netw Open* 2020; **3**: e2014780 [PMID: 32644140 DOI: 10.1001/jamanetworkopen.2020.14780]

29 **Christian MD**, Hawryluck L, Wax RS, Cook T, Lazar NM, Herridge MS, Muller MP, Gowans DR, Fortier W, Burkle FM. Development of a triage protocol for critical care during an influenza pandemic. *CMAJ* 2006; **175**: 1377-1381 [PMID: 17116904 DOI: 10.1503/cmaj.060911]

30 **Li B**, Yang J, Zhao F, Zhi L, Wang X, Liu L, Bi Z, Zhao Y. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020; **109**: 531-538 [PMID: 32161990 DOI: 10.1007/s00392-020-01626-9]

31 **Danzi GB**, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J* 2020; **41**: 1858 [PMID: 32227120 DOI: 10.1093/eurheartj/ehaa254]

32 **Xie Y**, Wang X, Yang P, Zhang S. COVID-19 Complicated by Acute Pulmonary Embolism. *Radiol Cardiothorac Imaging* 2020; **2**: e200067 [PMID: 33778561 DOI: 10.1148/ryct.2020200067]

33 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/S2213-2600(20)30079-5]

34 **Chandra A**, Chakraborty U, Ghosh S, Dasgupta S. Anticoagulation in COVID-19: current concepts and controversies. *Postgrad Med J* 2021 [PMID: 33850011 DOI: 10.1136/postgradmedj-2021-139923]

35 **Liu T**, Zhang J, Yang Y, Ma H, Li Z, Cheng J, Zhang X, Zhao Y, Xia Z, Zhang L, Wu G, Yi J. The role of interleukin-6 in monitoring severe case of coronavirus disease 2019. *EMBO Mol Med* 2020; **12**: e12421 [PMID: 32428990 DOI: 10.15252/emmm.202012421]

36 **Liu F**, Li L, Xu M, Wu J, Luo D, Zhu Y, Li B, Song X, Zhou X. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J Clin Virol* 2020; **127**: 104370 [PMID: 32344321 DOI: 10.1016/j.jcv.2020.104370]

37 **Long H**, Nie L, Xiang X, Li H, Zhang X, Fu X, Ren H, Liu W, Wang Q, Wu Q. D-Dimer and Prothrombin Time Are the Significant Indicators of Severe COVID-19 and Poor Prognosis. *Biomed Res Int* 2020; **2020**: 6159720 [PMID: 32596339 DOI: 10.1155/2020/6159720]

38 **Greinacher A**, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *N Engl J Med* 2021; **384**: 2092-2101 [PMID: 33835769 DOI: 10.1056/NEJMoa2104840]

39 **Smadja DM**, Yue QY, Chocron R, Sanchez O, Lillo-Le Louet A. Vaccination against COVID-19: insight from arterial and venous thrombosis occurrence using data from VigiBase. *Eur Respir J* 2021; **58** [PMID: 33863748 DOI: 10.1183/13993003.00956-2021]

40 **Cines DB**, Bussel JB. SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia. *N Engl J Med* 2021; **384**: 2254-2256 [PMID: 33861524 DOI: 10.1056/NEJMe2106315]

41 **Tan BK**, Mainbourg S, Friggeri A, Bertoletti L, Douplat M, Dargaud Y, Grange C, Lobbes H, Provencher S, Lega JC. Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis. *Thorax* 2021; **76**: 970-979 [PMID: 33622981 DOI: 10.1136/thoraxjnl-2020-215383]

42 **Meylan S**, Livio F, Foerster M, Genoud PJ, Marguet F, Wuerzner G; CHUV COVID Vaccination Center. Stage III Hypertension in Patients After mRNA-Based SARS-CoV-2 Vaccination. *Hypertension* 2021; **77**: e56-e57 [PMID: 33764160 DOI: 10.1161/HYPERTENSIONAHA.121.17316]

World Journal of Cardiology

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

World J Cardiol 2021 October 26; 13(10): 566-573

DOI: 10.4330/wjc.v13.i10.566

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Observational Study

Elderly patients with non-cardiac admissions and elevated high-sensitivity troponin: the prognostic value of renal function

Ioanna Samara, Stavroula Tsiara, Michail I Papafaklis, Konstantinos Pappas, Georgios Kolios, Nikolaos Vryzas, Lampros K Michalis, Eleni T Bairaktari, Christos S Katsouras

ORCID number: Ioanna Samara 0000-0001-8840-4349; Stavroula Tsiara 0000-0002-1461-9272; Michail I Papafaklis 0000-0002-5646-0378; Konstantinos Pappas 0000-0003-4272-5256; Georgios Kolios 0000-0001-5885-658X; Nikolaos Vryzas 0000-0002-6057-743X; Lampros K Michalis 0000-0001-8834-4462; Eleni T Bairaktari 0000-0003-3231-8649; Christos S Katsouras 0000-0001-7638-9217.

Author contributions: Samara I, Katsouras CS, Tsiara S, and Papafaklis MI wrote the first draft; all authors were involved in data collection, analysis, interpretation, final drafting of this manuscript and contributed to the submission.

Institutional review board statement: The study was reviewed and approved by the University Hospital of Ioannina Institutional Review Board, No. 123, 25-02-2019 / 6303.

Informed consent statement: Signed informed consent form was not needed for this study, University Hospital of Ioannina has given permission to conduct this study.

Conflict-of-interest statement: None of the authors has any conflicts of interest.

Ioanna Samara, Michail I Papafaklis, Konstantinos Pappas, Nikolaos Vryzas, Lampros K Michalis, Christos S Katsouras, Second Department of Cardiology, University Hospital of Ioannina, Ioannina 45110, Greece

Stavroula Tsiara, Second Department of Internal Medicine, University Hospital of Ioannina, Ioannina 45110, Greece

Georgios Kolios, Laboratory of Biochemistry, University Hospital of Ioannina, Ioannina 45110, Greece

Eleni T Bairaktari, Laboratory of Clinical Chemistry, School of Health Sciences, Faculty of Medicine, University of Ioannina, Ioannina 45110, Greece

Corresponding author: Christos S Katsouras, MD, PhD, Associate Professor, Second Department of Cardiology, University Hospital of Ioannina, Stavros Niarchos avenue, Ioannina 45110, Greece. cskats@yahoo.com

Abstract

BACKGROUND

High-sensitivity cardiac troponin (hs-cTn) levels are frequently elevated in elderly patients presenting to the emergency department for non-cardiac events. However, most studies on the role of elevated hs-cTn in elderly populations have investigated the prognostic value of hs-cTn in patients with a specific diagnosis or have assessed the relationship between hs-cTn and comorbidities.

AIM

To investigate the in-hospital prognosis of consecutive elderly patients admitted to the Internal Medicine Department with acute non-cardiac events and increased hs-cTnI levels.

METHODS

In this retrospective study, we selected patients who were aged ≥ 65 years and admitted to the Internal Medicine Department of our hospital between January 2019 and December 2019 for non-cardiac reasons. Eligible patients were those who had hs-cTnI concentrations ≥ 100 ng/L. We investigated the independent predictors of in-hospital mortality by multivariable logistic regression analysis.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Manuscript source: Invited manuscript

Specialty type: Geriatrics and Gerontology

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

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

Received: April 25, 2021
Peer-review started: April 25, 2021
First decision: June 17, 2021
Revised: June 27, 2021
Accepted: September 8, 2021
Article in press: September 8, 2021
Published online: October 26, 2021

P-Reviewer: Xi K
S-Editor: Wu YXJ
L-Editor: A
P-Editor: Wang LYT

RESULTS

One hundred and forty-six patients (59% female) were selected with an age range from 65 to 100 (mean ± SD: 85.4 ± 7.61) years. The median hs-cTnI value was 284.2 ng/L. For 72 (49%) patients the diagnosis of hospitalization was an infectious disease. The overall in-hospital mortality was 32% (47 patients). Individuals who died did not have higher hs-cTnI levels compared with those who were discharged alive (median: 314.8 *vs* 282.5 ng/L; $P = 0.565$). There was no difference in mortality in patients with infectious *vs* non-infectious disease (29% *vs* 35%). Multivariable analysis showed that age (OR 1.062 per 1 year increase, 95%CI: 1.000-1.127; $P = 0.048$) and creatinine levels (OR 2.065 per 1 mg/dL increase, 95%CI: 1.383-3.085; $P < 0.001$) were the only independent predictors of death. Mortality was 49% in patients with eGFR < 30 mL/min/1.73 m^2.

CONCLUSION

Myocardial injury is a malignant condition in elderly patients admitted to the hospital for non-cardiac reasons. The presence of severe renal impairment is a marker of extremely high in-hospital mortality.

Key Words: Internal medicine; High sensitivity troponin; Elderly; Non-cardiac admissions; Renal function; Prognosis

Core Tip: Many reports have shown that there is an association between acute myocardial injury and adverse outcomes in almost every clinical setting. However, data from consecutive elderly patients admitted to Internal Medicine Departments with acute non-cardiac events are limited. We found that these patients are at high risk of in-hospital death and that age and renal dysfunction were the only independent predictors of death. Elderly patients with acute myocardial injury from non-cardiac cause and chronic kidney disease stages IV or V had an extremely high risk (approximate 50%) of in-hospital death.

Citation: Samara I, Tsiara S, Papafaklis MI, Pappas K, Kolios G, Vryzas N, Michalis LK, Bairaktari ET, Katsouras CS. Elderly patients with non-cardiac admissions and elevated high-sensitivity troponin: the prognostic value of renal function. *World J Cardiol* 2021; 13(10): 566-573
URL: https://www.wjgnet.com/1949-8462/full/v13/i10/566.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i10.566

INTRODUCTION

Since the introduction of high-sensitive cardiac troponin (hs-cTn) assays, troponin testing has been used in a broad spectrum of patients to detect minor myocardial injury[1,2]. A variety of non-cardiac clinical conditions is accompanied by "troponinemia"[2,3] and many reports have investigated the association between serum hs-cTn concentrations and adverse outcomes in almost every clinical setting[4-6].

Hs-cTn levels increase over time in asymptomatic elderly individuals[7,8]. Moreover, they are frequently elevated in elderly patients presenting to the emergency department for non-cardiac events[9]. However, the 99th centile for the hospital population is not well defined and varies depending on the clinical setting, age and location when the test is requested[9-13]. Most studies on the role of elevated hs-cTn in elderly populations have investigated the prognostic value of hs-cTn in patients with a specific diagnosis or have assessed the relationship between hs-cTn and comorbidities [14-16].

The objective of this study was to investigate: (1) The in-hospital survival of consecutive elderly patients presenting to the emergency department with acute non-cardiac events, elevated hs-cTnI levels and admitted to the Internal Medicine Department; and (2) The independent predictors (*i.e.*, comorbidities) of in-hospital mortality.

MATERIALS AND METHODS

Study design and population

We conducted a retrospective observational study at the University Hospital of Ioannina in Greece. The study protocol conformed to the Declaration of Helsinki and was approved by the institutional ethics committee.

First, we searched the electronic medical records and we selected patients who were aged ≥ 65 years, admitted to the Internal Medicine Department between January 2019 and December 2019, and had hs-TnI levels ≥ 100 ng/L. Then, the paper medical records of the included patients were also reviewed. In our tertiary hospital elderly patients presenting with acute coronary syndromes or other acute cardiac events are admitted exclusively in the Cardiology Department. Additionally, all patients with a final diagnosis of acute myocardial infarction (based on serial troponin measurements, symptoms, and electrocardiogram) after admission were excluded from the study. Patients on hemodialysis or peritoneal dialysis were also excluded.

Demographic, clinical and biochemical data were extracted from patient records. Serum creatinine at presentation was used to calculate the estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease study equation [17]. High-sensitivity-cTnI was measured using two-site immunoenzymatic ("sandwich") assay (Beckman Coulter, Inc. Brea, CA, United States). The assay's 99th centile is 19.8 ng/L for men and 11.6 ng/L for women according to the manufacturer. However, troponin concentrations and the 99th percentile upper reference limits (URL) depend on several other factors including age and ethnicity/race[18].

Statistical analysis

Continuous variables were expressed as means ± SD or median (interquartile range) as appropriate. Deviation of continuous variables from the normal distribution was tested using the Shapiro-Wilk test (for a chosen alpha level of 0.05). The student's *t*-test and the Mann-Whitney test were used to compare normally and not normally distributed data, respectively. Only the first hs-cTnI measurement ≥ 100 ng/L of the included patients was considered for the analysis, and log transformation was also used for troponin values (because of non-normal distribution with positive skew). Categorical data were presented as counts and percentages and were compared using the χ^2 or the Fischer's exact test as appropriate. Correlation between continuous variables was determined with the Pearson's correlation coefficient. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of parameters for predicting in-hospital death. We performed binary logistic regression analysis to identify independent predictors of in-hospital death. A P value < 0.05 was considered statistically significant and all tests were two-sided. Statistical analysis was performed with the SPSS/PC (version 22.0, IBM Corp, Armonk, NY, United States) software package.

RESULTS

During the study period (January 2019 to December 2019), 146 patients (59% female) fulfilled our inclusion criteria. Patient age ranged from 65 years to 100 years (median: 87, mean ± SD: 85.4 ± 7.61). There was a substantial burden of comorbidities: 53 (36%) patients had diabetes mellitus, 38 (26%) coronary artery disease, 64 (44%) atrial fibrillation, and 46 (32%) chronic kidney disease (CKD). For 72 (49%) patients the diagnosis of hospitalization was an infectious disease. The second most commonly diagnosis was stroke (15 patients, 10%). Eleven patients (8%) were admitted due to gastrointestinal causes, 8 (5%) due to explained or unexplained falls, 7 (5%) due to pulmonary embolism, 6 (4%) due to severe anemia or pancytopenia, 5 (3%) due to "senility", 4 (3%) due to hypoglycemia or hyperglycemia, 4 (3%) due to cancer, and 14 (10%) due to other causes.

The median hs-cTnI value was 284.25 ng/L (interquartile range 553.4), while the mean was 946.4 (± 2336.07) ng/L. High-sensitivity-cTnI was correlated with creatinine levels (r = 0.169, P = 0.042) and eGFR (r = -0.240, P = 0.004).

The overall in-hospital mortality was 32% (47 patients). Differences between patients who died in-hospital and those who were discharged alive are shown in Table 1. Individuals who died did not have significantly higher hs-cTnI levels (median: 314.8 *vs* 282.5 ng/L; Mann-Whitney U test, P = 0.565). There were no significant differences in mortality according to diagnosis (infectious *vs* non-infectious disease: 29% *vs* 35%), gender (males *vs* females: 35% *vs* 30%), diabetes (30% *vs* 33%), history of

Table 1 Differences between patients who died in-hospital and those who were discharged alive

	Patients who died (*n* = 47)	Discharged alive (*n* = 99)	*P* value
Age (yr), mean ± SD	87.5 ± 5.3	83.4 ± 8.3	0.001
Gender, *n* (%)			0.59
Female	26 (30)	60 (70)	
Male	21 (35)	39 (65)	
History of CAD, *n*	12	26	1
Atrial fibrillation/flutter, *n*	18	46	0.38
Renal function, *n* (%)			
Known history of CKD	24 (52)	22 (48)	0.001
No history of CKD	23 (23)	77 (77)	
Creatinine levels, mg/dL	2.10 (1.03)	1.66 (0.95)	0.008
eGFR (mL/min/1.73 m^2), mean ± SD	35.32 ± 19.85	47.17 ± 24.22	0.002
On antihypertensive therapy, *n*	28	74	0.082
Diabetes Mellitus, *n*	16	37	0.69
On statin therapy, *n*	19	45	0.6
Diagnosis on admission, *n* (%)			0.86
Infectious diseases	21 (31)	46 (69)	
Non-infectious diseases	26 (33)	53 (67)	
CRP (mg/L), mean ± SD	178.16 ± 130.81	154.27 ± 125.30	0.26
hs-TnI (ng/L)			
Median	314.8	282.5	0.57
Log-hsTnI, mean ± SD	2.57 ± 0.57	2.59 ± 0.42	0.89

CAD: Coronary artery disease; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtrated rate; SD: Standard deviation; CRP: C-reactive protein; hs-cTnI: High sensitive cardiac troponin I; Log: Logarithm 10.

coronary artery disease (32% *vs* 32%), and atrial fibrillation (28% *vs* 35%). Mortality was higher among patients with known CKD (52% *vs* 23%, P = 0.001). Moreover, individuals who died had higher creatinine levels (2.10 ± 1.03 *vs* 1.66 ± 0.95 mg/dL, P = 0.008) and lower eGFR (35.32 ± 19.85 *vs* 47.17 ± 24.22 mL/min/1.73 m^2, P = 0.002). In ROC analysis, the area under the curves was 0.527 for hs-cTnI, and 0.711 for creatinine (Figure 1).

Multivariable analysis showed that age (OR 1.062 per 1 year increase, 95%CI: 1.00-1.13; P = 0.048) and creatinine levels (OR 2.07 per 1 mg/dL increase, 95%CI: 1.38-3.09; P < 0.001) were the only independent predictors of death. When renal function was estimated as eGFR, it was also a significant independent predictor of mortality (OR 1.04 per 1 mL/min/1.73 m^2 decrease, 95%CI: 1.01-1.06; P = 0.001). Figure 2 shows the percentages of patients who died in-hospital according to the CKD stages. Mortality was 49% in patients with severe CKD (eGFR < 30 mL/min/1.73 m^2).

DISCUSSION

We performed a retrospective investigation of in-hospital mortality in elderly patients admitted to the Internal Medicine Department with non-acute cardiac events and elevated hs-cTnI levels. Our major findings are that (1) these patients were at high risk of in-hospital death; (2) age and renal dysfunction were the only independent predictors of death among the parameters assessed; and (3) patients who died did not have higher hs-cTnI levels compared with those who were discharged alive.

Previous studies have reported that hs-cTnI concentrations and their 99th percentile strongly depend on the characteristics of the population being assessed[7] and that

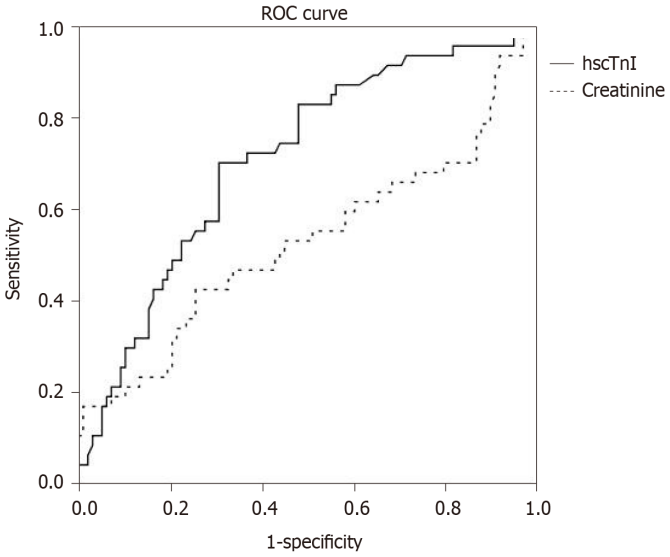


Figure 1 The area under the curves in receiver operating characteristic analysis. ROC: Receiver operating characteristic; hs-cTnI: High-sensitivity cardiac troponin I.

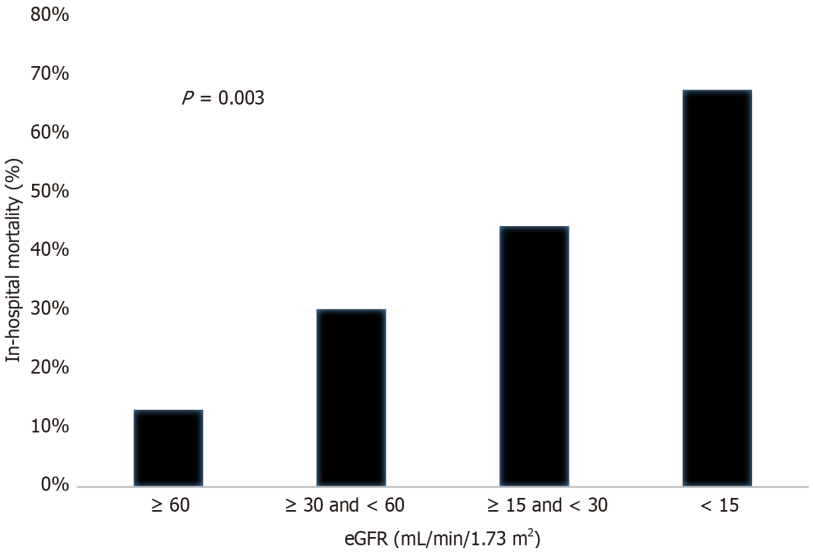


Figure 2 The percentages of patients who died in-hospital according to the chronic kidney disease stages.

more than 20% of elderly inpatients may have hs-TnI levels above URL[11]. Advancing age and decreasing eGFR were shown to be independent predictors of hs-TnI concentration greater than the recommended URL[11]. Moreover, the 99th percentile of elderly inpatients (after excluding participants diagnosed as having acute myocardial infarction) may be 10 times higher than the recommended URL[11]. Eggers *et al*[7] reported the 99th percentile for hs-cTnI near our cut-off value (*i.e.*, 100 ng/L) regarding individuals with age distribution and cardiac history similar to our study group.

The high in-hospital mortality in patients with high troponin levels admitted for non-cardiac causes is in line with previously published studies[5,6,12,19]. The relatively higher mortality in our study could be mainly explained by differences in baseline characteristics of the included patients, since our study population was older, had more frequently a history of CKD and higher creatinine levels (and thus, lower eGFR)[5,6,12,19]. We showed that age and renal function were the only independent predictors of in-hospital mortality in elderly patients admitted with high hs-cTnI levels and non-cardiac causes in the Internal Medicine Department. It is worth noting that the majority of prior research has been conducted in patients with infectious diseases, while in our unselected elderly study group, 50% of the elderly inpatients suffered from other diseases. However, there were no significant differences regarding

mortality according to the cause of admission (infectious *vs* non-infectious disease) and no differences regarding the CRP concentrations between patients who died and patients who were discharged alive.

Our study showed that although elderly patients with non-cardiac events and hs-cTnI ≥ 100 ng/L have a high risk of in-hospital death, individuals who died did not have higher hs-cTnI levels compared with those who were discharged alive. Similarly, Frencken *et al*[5] also showed that troponin release beyond hs-cTnI plasma concentrations of approximate 100 ng/L does not carry an additional mortality risk in patients with sepsis. This non-linear relationship between troponin levels and mortality may be present even in patients with revascularized acute coronary syndromes[12]. The nonlinear relationship with mortality is difficult to explain. It is possible that in patients with non-cardiac acute events, the presence of myocardial injury (and not the extent of injury) maybe a marker of increased mortality. This hypothesis is supported from our ROC analysis, since the area under the curve for hs-cTnI was approximately 0.5, thereby indicating that the level of the troponin (the level of myocardial injury) has no discrimination capacity for further distinguish the risk of in-hospital death.

Cardiac troponin concentrations are often increased in CKD patients[20]. Although the reasons are not clear, higher troponin values in CKD patients are considered to be primarily caused by chronic myocardial injury, and thus troponin release to the circulation, and secondarily by decreased clearance. Miller-Hodges *et al*[21] evaluated hs-TnI testing in patients with suspected acute coronary syndrome with and without renal impairment. They reported that patients with elevated troponin and renal impairment had a greater risk for cardiac events at 1 year. Although previous studies have investigated the prognostic role of troponins in elderly patients[7,8,12], data regarding the evaluation of CKD in elderly patients with non-cardiac admissions and elevated hs-Tn measurements are sparse. We report an extremely high risk of in-hospital death among elderly patients with renal impairment admitted to the hospital for non-cardiac causes with elevated hs-cTnI levels. Elderly inpatients with CKD stages IV or V had a risk of approximate 50% for in-hospital death. This may emphasize the need for more aggressive monitoring and treatment in this group in order to avoid complications and death.

Our study had several limitations. First, all retrospective studies using electronic/paper medical records have inherent methodological problems[22]. Second, we did not use a control group (*e.g.*, patients with "normal" hs-cTnI levels) for comparison purposes. Third, other potential prognostic indices (*e.g.*, brain natriuretic peptides) were available only in a very small number of patients, hence we did not include them in the analysis. Finally, although in almost all the cases cardiology examination was performed, in clinical practice it is often difficult to exclude from the diagnosis an acute coronary syndrome, especially in elderly patients with non-specific symptoms.

CONCLUSION

Myocardial injury is a malignant condition in elderly patients admitted to the hospital for non-cardiac reasons and indicates poor overall prognosis. The presence of severe renal impairment remains as an independent marker of extremely high in-hospital mortality in this selected patient group.

ARTICLE HIGHLIGHTS

Research background

Many reports have shown that there is an association between acute myocardial injury and adverse outcomes in almost every clinical setting.

Research motivation

Data from consecutive elderly patients admitted to the Internal Medicine Department with acute non-cardiac events and acute myocardial injury are limited.

Research objectives

To investigate: (1) The in-hospital survival of consecutive elderly patients presenting to the emergency department with acute non-cardiac events, elevated high-sensitivity

cardiac troponin I (hs-cTnI) levels and admitted to the Internal Medicine Department; and (2) The independent predictors (*i.e.*, comorbidities) of in-hospital mortality.

Research methods

This was a single centre, retrospective, observational study, involving 146 elderly (≥ 65 years) patients (59% female) admitted to the Internal Medicine Department with acute non-cardiac events and elevated hs-cTnI (≥ 100 ng/L).

Research results

Patient age ranged from 65 to 100 (mean ± SD: 85.4 ± 7.61) years. The median hs-cTnI value was 284.2 ng/L. The overall in-hospital mortality was 32% (47 patients). Multivariate analysis showed that age (OR 1.062 per 1 year increase, 95%CI: 1.000-1.127; $P = 0.048$) and creatinine levels (OR 2.065 per 1 mg/dL increase, 95%CI: 1.383-3.085; $P < 0.001$) were the only independent predictors of death. Mortality was 49% in patients with eGFR < 30 mL/min/1.73 m^2.

Research conclusions

Myocardial injury is a malignant condition in elderly patients admitted to the hospital for non-cardiac reasons and indicates poor overall prognosis. The presence of severe renal impairment remains as an independent marker of extremely high in-hospital mortality in this selected patient group.

Research perspectives

Our results emphasize the need for more aggressive monitoring and treatment in elderly patients with severe renal impairment admitted to the hospital for non-cardiac reasons in order to avoid complications and death.

REFERENCES

1 **Thygesen K**, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, Huber K, Plebani M, Biasucci LM, Tubaro M, Collinson P, Venge P, Hasin Y, Galvani M, Koenig W, Hamm C, Alpert JS, Katus H, Jaffe AS; Study Group on Biomarkers in Cardiology of ESC Working Group on Acute Cardiac Care. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J* 2012; **33**: 2252-2257 [PMID: 22723599 DOI: 10.1093/eurheartj/ehs154]

2 **Collinson PO**, Apple F, Jaffe AS. Use of troponins in clinical practice: Evidence in favour of use of troponins in clinical practice: Evidence in favour of use of troponins in clinical practice. *Heart* 2020; **106**: 253-255 [PMID: 31672780 DOI: 10.1136/heartjnl-2019-315622]

3 **Mariathas M**, Curzen N. Use of troponins in clinical practice: Evidence against the use of troponins in clinical practice. *Heart* 2020; **106**: 251-252 [PMID: 31672777 DOI: 10.1136/heartjnl-2019-315765]

4 **Blankenberg S**, Salomaa V, Makarova N, Ojeda F, Wild P, Lackner KJ, Jørgensen T, Thorand B, Peters A, Nauck M, Petersmann A, Vartiainen E, Veronesi G, Brambilla P, Costanzo S, Iacoviello L, Linden G, Yarnell J, Patterson CC, Everett BM, Ridker PM, Kontto J, Schnabel RB, Koenig W, Kee F, Zeller T, Kuulasmaa K; BiomarCaRE Investigators. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium. *Eur Heart J* 2016; **37**: 2428-2437 [PMID: 27174290 DOI: 10.1093/eurheartj/ehw172]

5 **Frencken JF**, Donker DW, Spitoni C, Koster-Brouwer ME, Soliman IW, Ong DSY, Horn J, van der Poll T, van Klei WA, Bonten MJM, Cremer OL. Myocardial Injury in Patients With Sepsis and Its Association With Long-Term Outcome. *Circ Cardiovasc Qual Outcomes* 2018; **11**: e004040 [PMID: 29378734 DOI: 10.1161/CIRCOUTCOMES.117.004040]

6 **Vestjens SMT**, Spoorenberg SMC, Rijkers GT, Grutters JC, Ten Berg JM, Noordzij PG, Van de Garde EMW, Bos WJW; Ovidius Study Group. High-sensitivity cardiac troponin T predicts mortality after hospitalization for community-acquired pneumonia. *Respirology* 2017; **22**: 1000-1006 [PMID: 28221010 DOI: 10.1111/resp.12996]

7 **Eggers KM**, Lind L, Venge P, Lindahl B. Factors influencing the 99th percentile of cardiac troponin I evaluated in community-dwelling individuals at 70 and 75 years of age. *Clin Chem* 2013; **59**: 1068-1073 [PMID: 23462029 DOI: 10.1373/clinchem.2012.196634]

8 **Eggers KM**, Venge P, Lindahl B, Lind L. Cardiac troponin I levels measured with a high-sensitive assay increase over time and are strong predictors of mortality in an elderly population. *J Am Coll Cardiol* 2013; **61**: 1906-1913 [PMID: 23500239 DOI: 10.1016/j.jacc.2012.12.048]

9 **Wang AZ**, Schaffer JT, Holt DB, Morgan KL, Hunter BR. Troponin Testing and Coronary Syndrome in Geriatric Patients With Nonspecific Complaints: Are We Overtesting? *Acad Emerg Med* 2020; **27**: 6-14 [PMID: 31854117 DOI: 10.1111/acem.13766]

10 **Zhang SJ**, Wang Q, Cui YJ, Wu W, Zhao QH, Xu Y, Wang JP. High-sensitivity cardiac troponin T in geriatric inpatients. *Arch Gerontol Geriatr* 2016; **65**: 111-115 [PMID: 27017416 DOI:

10.1016/j.archger.2016.03.010]

11 **Mariathas M**, Allan R, Ramamoorthy S, Olechowski B, Hinton J, Azor M, Nicholas Z, Calver A, Corbett S, Mahmoudi M, Rawlins J, Simpson I, Wilkinson J, Kwok CS, Cook P, Mamas MA, Curzen N. True 99th centile of high sensitivity cardiac troponin for hospital patients: prospective, observational cohort study. *BMJ* 2019; **364**: l729 [PMID: 30867154 DOI: 10.1136/bmj.l729]

12 **Kaura A**, Panoulas V, Glampson B, Davies J, Mulla A, Woods K, Omigie J, Shah AD, Channon KM, Weber JN, Thursz MR, Elliott P, Hemingway H, Williams B, Asselbergs FW, O'Sullivan M, Kharbanda R, Lord GM, Melikian N, Patel RS, Perera D, Shah AM, Francis DP, Mayet J. Association of troponin level and age with mortality in 250 000 patients: cohort study across five UK acute care centres. *BMJ* 2019; **367**: l6055 [PMID: 31748235 DOI: 10.1136/bmj.l6055]

13 **Wu W**, Li DX, Wang Q, Xu Y, Cui YJ. Relationship between high-sensitivity cardiac troponin T and the prognosis of elderly inpatients with non-acute coronary syndromes. *Clin Interv Aging* 2018; **13**: 1091-1098 [PMID: 29922047 DOI: 10.2147/CIA.S157048]

14 **Tang O**, Daya N, Matsushita K, Coresh J, Sharrett AR, Hoogeveen R, Jia X, Windham BG, Ballantyne C, Selvin E. Performance of High-Sensitivity Cardiac Troponin Assays to Reflect Comorbidity Burden and Improve Mortality Risk Stratification in Older Adults With Diabetes. *Diabetes Care* 2020; **43**: 1200-1208 [PMID: 32161049 DOI: 10.2337/dc19-2043]

15 **Di Micoli A**, Scarciello C, De Notariis S, Cavazza M, Muscari A. Determinants of troponin T and I elevation in old patients without acute coronary syndrome. *Emergency Care J* 2019; **15**: 1 [DOI: 10.4081/ecj.2019.7798]

16 **Sedighi SM**, Nguyen M, Khalil A, Fülöp T. The impact of cardiac troponin in elderly patients in the absence of acute coronary syndrome: A systematic review. *Int J Cardiol Heart Vasc* 2020; **31**: 100629 [PMID: 32964099 DOI: 10.1016/j.ijcha.2020.100629]

17 **Froissart M**, Rossert J, Jacquot C, Paillard M, Houillier P. Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. *J Am Soc Nephrol* 2005; **16**: 763-773 [PMID: 15659562 DOI: 10.1681/ASN.2004070549]

18 **Clerico A**, Ripoli A, Masotti S, Musetti V, Aloe R, Dipalo M, Rizzardi S, Dittadi R, Carrozza C, Storti S, Belloni L, Perrone M, Fasano T, Canovi S, Correale M, Prontera C, Guiotto C, Cosseddu D, Migliardi M, Bernardini S. Evaluation of 99th percentile and reference change values of a high-sensitivity cTnI method: A multicenter study. *Clin Chim Acta* 2019; **493**: 156-161 [PMID: 30826369 DOI: 10.1016/j.cca.2019.02.029]

19 **Lala A**, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, Zhao S, Somani S, Van Vleck T, Vaid A, Chaudhry F, De Freitas JK, Fayad ZA, Pinney SP, Levin M, Charney A, Bagiella E, Narula J, Glicksberg BS, Nadkarni G, Mancini DM, Fuster V; Mount Sinai COVID Informatics Center. Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. *J Am Coll Cardiol* 2020; **76**: 533-546 [PMID: 32517963 DOI: 10.1016/j.jacc.2020.06.007]

20 **deFilippi CR**, Herzog CA. Interpreting Cardiac Biomarkers in the Setting of Chronic Kidney Disease. *Clin Chem* 2017; **63**: 59-65 [PMID: 27811207 DOI: 10.1373/clinchem.2016.254748]

21 **Miller-Hodges E**, Anand A, Shah ASV, Chapman AR, Gallacher P, Lee KK, Farrah T, Halbesma N, Blackmur JP, Newby DE, Mills NL, Dhaun N. High-Sensitivity Cardiac Troponin and the Risk Stratification of Patients With Renal Impairment Presenting With Suspected Acute Coronary Syndrome. *Circulation* 2018; **137**: 425-435 [PMID: 28978551 DOI: 10.1161/CIRCULATIONAHA.117.030320]

22 **Vassar M**, Holzmann M. The retrospective chart review: important methodological considerations. *J Educ Eval Health Prof* 2013; **10**: 12 [PMID: 24324853 DOI: 10.3352/jeehp.2013.10.12]

World Journal of Cardiology

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

World J Cardiol 2021 October 26; 13(10): 574-584

DOI: 10.4330/wjc.v13.i10.574

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Prospective Study

Patent hemostasis of radial artery: Comparison of two methods

Vassileios Kyriakopoulos, Andrew Xanthopoulos, Michail Papamichalis, Spyridon Skoularigkis, Chara Tzavara, Emmanouil Papadakis, Sotirios Patsilinakos, Filippos Triposkiadis, John Skoularigis

ORCID number: Vassileios Kyriakopoulos 0000-0001-8010-8174; Andrew Xanthopoulos 0000-0002-9439-3946; Michail Papamichalis 0000-0002-4994-7743; Spyridon Skoularigkis 0000-0003-4160-0064; Chara Tzavara 0000-0003-3242-9066; Emmanouil Papadakis 0000-0002-6038-1533; Sotirios Patsilinakos 0000-0002-9933-2675; Filippos Triposkiadis 0000-0001-6433-4016; John Skoularigis 0000-0001-7159-2478.

Author contributions: Kyriakopoulos V participated in design of the study, drafted the manuscript and was involved with data collection; Xanthopoulos A participated in design of the study, drafted the manuscript, and participated in oversight of the study; Papamichalis M drafted the manuscript and was involved with data collection; Skoularigkis S participated in design of the study, and was involved with data collection; Tzavara C participated in design of the study and performed statistical analysis; Papadakis E was involved with data collection and drafted the manuscript; Patsilinakos S participated in design and oversight of the study; Triposkiadis F participated in design of the study and drafted the manuscript; Skoularigis J participated in design and oversight of the study and drafted the manuscript; all authors read

Vassileios Kyriakopoulos, Emmanouil Papadakis, Sotirios Patsilinakos, Department of Cardiology, Konstantopoulio General Hospital, Athens 14233, Greece

Andrew Xanthopoulos, Michail Papamichalis, Spyridon Skoularigkis, Filippos Triposkiadis, John Skoularigis, Department of Cardiology, University Hospital of Larissa, Larissa 41110, Greece

Chara Tzavara, Department of Health, Medical School, University of Athens, Athens 11527, Greece

Corresponding author: Andrew Xanthopoulos, FACC, MD, PhD, Consultant Physician-Scientist, Department of Cardiology, University Hospital of Larissa, Mezourlo, PO Box 1425, Larissa 41110, Greece. andrewvxanth@gmail.com

Abstract

BACKGROUND

Radial artery obstruction is the most common complication of coronary angiography performed *via* transradial access. Patent hemostasis can significantly reduce the risk of radial artery occlusion. Previous studies utilized sophisticated methods to evaluate radial artery patency. Simplified and easily applicable methods for successful patent hemostasis are currently lacking.

AIM

To determine which method (pulse oximeter *vs* the traditional radial artery palpation) is better to achieve patent hemostasis.

METHODS

This prospective, single center study included 299 consecutive patients who underwent coronary angiography or percutaneous coronary intervention between November 2017 and July 2019. Patients less than 18 years old, with a history of radial artery disease, or no palpable artery pulse were excluded from the study. Patients were randomly assigned to two groups. In the first group, radial artery flow was assessed by palpation of the artery during hemostasis (traditional method). In the second group, radial artery patency was estimated with the use of a pulse oximeter. Two different compression devices were used for hemostasis (air chamber and pressure valve). The primary study endpoint was the achievement of successful patent hemostasis.

RESULTS

The two groups (pulse oximeter *vs* artery palpation) had no significant differences

and approved the final manuscript.

Institutional review board statement: The study protocol was approved by the hospital's ethics review board.

Informed consent statement: Patients participating in the study provided written informed consent.

Conflict-of-interest statement: The authors declare that they have no conflicting interests.

Data sharing statement: No additional data are available

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

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

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

Received: April 21, 2021
Peer-review started: April 21, 2021
First decision: May 13, 2021

in age, sex, body mass index, risk factors, or comorbidities except for supraventricular arrhythmias. The percentage of patients with successful patent hemostasis was significantly higher in the pulse oximeter group (82.2% *vs* 68.1%, $P = 0.005$). A lower percentage of patients with spasm was recorded in the pulse oximeter group (9.9% *vs* 19.0%, $P = 0.024$). The incidence of local complications, edema, bleeding, hematoma, vagotonia, or pain did not differ between the two groups. In the multivariate analysis, the use of a pulse oximeter (OR: 2.35, 95%CI: 1.34-4.13, $P = 0.003$) and advanced age (OR: 1.04, 95%CI: 1.01-1.07, $P = 0.006$), were independently associated with an increased probability of successful patent hemostasis. The type of hemostatic device did not affect patent hemostasis ($P = 0.450$).

CONCLUSION

Patent hemostasis with the use of pulse oximeter is a simple, efficient, and safe method that is worthy of further investigation. Larger randomized studies are required to consider its clinical implications.

Key Words: Radial access; Patent hemostasis; Palpation; Oximeter; Coronary angiography; Radial artery occlusion

Core Tip: This was a prospective, single center study with 299 consecutive patients who underwent coronary angiography or percutaneous coronary intervention. It aimed to evaluate the best method (pulse oximeter *vs* the traditional radial artery palpation) for successful patent hemostasis. The use of a pulse oximeter increased the probability of achieving patent hemostasis compared with artery palpation, and was associated with lower rates of artery spasm. In the multivariate analysis, the use of pulse oximeter and advanced age were independently associated with an increased probability of successful patent hemostasis.

Citation: Kyriakopoulos V, Xanthopoulos A, Papamichalis M, Skoularigkis S, Tzavara C, Papadakis E, Patsilinakos S, Triposkiadis F, Skoularigis J. Patent hemostasis of radial artery: Comparison of two methods. *World J Cardiol* 2021; 13(10): 574-584
URL: https://www.wjgnet.com/1949-8462/full/v13/i10/574.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i10.574

INTRODUCTION

Transradial access is increasingly used in coronary angiography *vs* transfemoral access as it has several advantages. Transradial access is associated with fewer vascular complications, lower bleeding complications, and reduced mortality in specific high-risk populations[1]. Furthermore, the technique offers earlier mobilization after the procedure, and the patient usually has a shorter hospital stay. The European guidelines for coronary angiography in patients with acute coronary syndrome favor transradial over transfemoral access with a Class IA indication[2,3].

Radial artery obstruction (RAO) is a frequent complication of coronary angiography performed *via* transradial access[4]. RAO may prevent radial artery access for future coronary angiography or as a conduit for coronary artery bypass grafting. At the same time, patients requiring hemodialysis lose an artery that can be used to create an arteriovenous fistula. Therefore, prevention of RAO is of particular clinical importance in patients undergoing coronary angiography *via* transradial access. Experts emphasize the need for the adoption of novel techniques that may reduce the incidence of RAO to less than 5%[5].

Complete obstruction of blood flow in the radial artery during hemostasis is a strong predictor of RAO occurrence[6]. On the contrary, maintaining circulatory anterograde flow in the radial artery during hemostasis, known as patent or nonobstructive hemostasis, reduces the risk of RAO[7,8]. Various methods of patent hemostasis have been described, but there is no current consensus on the optimal

Revised: May 24, 2021
Accepted: July 15, 2021
Article in press: July 15, 2021
Published online: October 26, 2021

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

method. Of note, the application of nonobstructive hemostasis is technically difficult as it requires intense staff mobilization, multiple evaluations of radial artery blood flow, and adjustment of hemostatic pressure in order to maintain patency. That is why patent hemostasis is not fully adopted in most laboratories[9]. The goal of this study was to evaluate a simplified and easily applicable method to achieve patent hemostasis in patients undergoing diagnostic coronary angiography or percutaneous coronary intervention (PCI).

MATERIALS AND METHODS

Patient population

A total of 299 consecutive patients undergoing cardiac catheterization between November 2017 and July 2019 and considered eligible for radial access were included in the study. Patients underwent a Barbeau test precatheterization, to assess collateral palmar arch sufficiency. Patients were randomly assigned to two groups. In the first group, radial artery flow was assessed by artery pulse palpation during hemostasis (traditional method). In the second group, radial artery patency was estimated with the use of a pulse oximeter. Two different compression devices were used for hemostasis, one with an air chamber and another with a pressure valve. The primary study endpoint was the achievement of successful patent hemostasis.

Randomization did not affect coronary angiography, either diagnostic or invasive, and operators were unaware of the patient allocation. RAO was assessed at 24 h and 30 d after the procedure. Patients younger than 18 years of age with a history of radial artery disease or absence of radial artery pulse were excluded from the study. Patients participating in the study provided written informed consent, and the study protocol was approved by the hospital's ethics review board.

Transradial catheterization procedure

Radial artery catheterization was performed using the Seldinger technique. The catheter diameter was 5/6-French.

Conventional hemostasis with radial artery pulse palpation

The introducer sheath was removed immediately after the procedure. The sheath was pulled out by 4 to 5 cm and a hemostatic bandage was applied around the wrist. The bandage was then tightened and the catheter was removed. In group 1, radial artery patency was assessed by radial artery pulse palpation. The bandage remained in place for 4 h and then was slowly removed. A light dressing was applied at the entry site after the procedure.

Patent hemostasis procedure with the aid of pulse oximeter

The sheath was pulled out by 4 to 5 cm and a hemostatic bandage was applied over the entry site. In group 2 a pulse oximeter sensor was placed on the index finger, the bandage was tightened, and the sheath was removed. The ulnar artery was compressed and the hemostatic bandage gradually began to relax. Radial artery patency was confirmed by plethysmographic signal reoccurrence. In case of bleeding before plethysmographic signal appearance, the hemostatic bandage compression was increased. If radial artery flow was confirmed by the oximeter and no bleeding complications occurred, then a bandage remained in place for 4 h. Radial artery patency was assessed on an hourly basis.

Assessment of radial artery patency

Radial artery flow was evaluated with a Barbeau test. The pulse oximeter sensor was placed on the index finger and the plethysmographic signal was observed. Ulnar and radial artery compression led to signal loss. Radial artery pressure was then removed while maintaining ulnar artery compression. Appearance of the plethysmographic signal was proof of radial artery patency, while absence of a signal indicated RAO. The test was performed precatheterization, at 24 h and at 30 d after coronary angiography. Radial artery patency was also assessed at 30 d by vascular ultrasonography with Doppler assessment.

Hemostatic efficacy

Hemorrhagic complications that resulted in blood loss from the puncture site and judged capable of causing hemodynamic instability, blood transfusion, or death were

regarded as significant. Hematomas at the puncture site were considered clinically significant when their diameter exceeded 3 cm.

Statistical analysis

Quantitative variables were expressed as means ± SD or as medians and interquartile range (IQR). Qualitative variables were reported with absolute and relative frequencies. Chi-square and Fisher's exact tests were used to compare proportions. Student's *t*-tests were used to compare mean values that were normally distributed. Mann-Whitney tests were used to compare median values when the distribution was not normal. Logistic regression analyses in a stepwise method (P for entry 0.05, P for removal 0.10) were performed in order to identify factors associated with the presence of specific outcomes. Unadjusted and adjusted odds ratios with 95%CI were computed from the results of the logistic regression analyses. Statistical significance was set at 0.05. The analyses were conducted using SPSS statistical software (version 22.0).

RESULTS

Demographic characteristics and risk factors/comorbidities

Radial artery patency during hemostasis was assessed by artery palpation (control group) in 147 patients (49.2%) and by pulse oximeter sensor in 152 patients (50.8%). The demographic characteristics of the study population are shown in Table 1. The study population consisted mainly of men (75%) with a mean age of 60.8 years. Dyslipidemia was the most common comorbidity followed by hypertension, coronary artery disease, and diabetes mellitus. One out of three patients (35%) had previously undergone PCIs and 6% had previously undergone coronary bypass surgery. The two groups of patients did not have significant differences in their baseline clinical characteristics (Table 1). Patients in the control group had a higher rate of supraventricular arrhythmia, mainly atrial fibrillation (26.5% *vs* 13.2%, $P = 0.004$).

Procedural characteristics

Table 2 shows the procedural characteristics of the two study groups. PCI was performed in 30% of the patients. There were no differences in the number of coronary vessels that received intervention. Half the patients underwent coronary angiography using a 5-french introducer sheath and the other half using a 6-french sheath. The two groups of patients did not differ in several other procedural characteristics (*e.g.*, right or left hand, duration of procedure, radiation time). Patients received similar doses of anticoagulants (heparin) and did not differ in the type of device used for hemostasis (Table 2).

Complications

Table 3 shows the coronary angiography complications. The group of patients in whom the radial artery patency was assessed with the traditional method (artery palpation) had a higher rate of radial artery spasm ($P = 0.024$). The two groups had similar rates of vagotonia, hematoma, bleeding, edema, local complications, and pain.

Patent hemostasis in the study groups

The group of patients whose radial artery patency was assessed using the pulse oximeter achieved significantly higher rates of patent hemostasis than those in the control group, using radial artery palpation (82.2% *vs* 68.1%, $P = 0.005$; Figure 1). The type of hemostatic device (air chamber or pressure valve device) did not affect patent hemostasis ($P = 0.450$). Radial artery flow was restored in a significant percentage of patients at 24 h and at 30 d after coronary angiography (Table 4).

Predictors of patent hemostasis

Multivariate logistic regression analysis revealed that pulse oximeter use (OR: 2.35, 95%CI: 1.34-4.13, $P = 0.003$) and patient age (per 1 year increase; OR: 1.04, 95%CI: 1.01-1.07, $P = 0.006$) as independent predictors of patent hemostasis (Table 5).

DISCUSSION

The main study findings were: (1) Successful patent hemostasis was significantly more frequent in the pulse oximeter group *vs* the radial artery palpation group; (2) A lower

Table 1 Baseline characteristics of the study population

Baseline characteristics	Control group (conventional hemostasis), *n* = 147	Oximetry – plethysmography group, *n* = 152	*P* value
Age (mean ± SD, yr)	61.5 ± 9.8	60.1 ± 11.6	0.273[1]
Male sex	109 (74.1)	115 (75.7)	0.764[2]
Body mass index (mean ± SD, kg/m^2)			0.343[2]
Normal (18.5-24.9)	31 ± 21.1	35 ± 23	
Overweight (25-29.9)	73 ± 49.7	63 ± 41.4	
Obese (> 30)	43 ± 29.3	54 ± 35.5	
Risk factors/Comorbidities, *n* (%)			
Hypertension	89 (60.5)	92 (60.5)	0.997[2]
Diabetes mellitus	29 (19.7)	40 (26.3)	0.176[2]
Insulin	6 (20.7)	14 (35.0)	0.196[3]
Dyslipidemia	112 (76.2)	114 (75.0)	0.811[2]
Smoking	69 (46.9)	74 (48.7)	0.850[2]
History of coronary artery disease	46 (31.3)	52 (34.2)	0.591[2]
Supraventricular arrhythmia	39 (26.5)	20 (13.2)	0.004[2]
History of interventions, *n* (%)			
Percutaneous coronary intervention	49 (33.3)	56 (36.8)	0.5252
Coronary artery bypass grafting	11 (7.5)	7 (4.6)	0.2963

[1]Student's *t*-test.
[2]Pearson's χ^2.
[3]Fisher's exact test.

percentage of complications (*i.e.* spasm) was recorded in the pulse oximeter group; and (3) Advanced age and the use of a pulse oximeter were independent predictors of successful patent hemostasis.

Many studies have reported the safety and efficacy of performing coronary angiography *via* the transradial access. Transradial access is preferred over transfemoral artery access for percutaneous diagnostic and interventional procedures because it is associated with lower rates of vascular and hemorrhagic complications that lead to transfusions[5,10-12]. A systematic review and meta-analysis including 11707 patients who presented with ST-segment elevation myocardial infarction, reported an association between transradial access and reduction in 30-d mortality (relative risk, 0.72), major bleeding (relative risk, 0.60), and access-site complications (relative risk, 0.40) compared with transfemoral access[11]. Interestingly, the transradial approach has the advantage of a rapid interval to patient mobilization[13].

RAO is a potential complication of coronary angiography using the transradial approach[5,10]. In randomized trials, RAO incidence ranged up to 10%[5]. However, in daily clinical practice RAO frequency is much higher[4,14-16]. Radial artery patency should be routinely checked before discharge of any patient who has undergone coronary angiography *via* transradial access[5]. Radial artery palpation is the most common technique used[17]. However, artery palpation may be misleading as the presence of collateral circulation from palmar arches in the upper extremity is likely to lead to a palpable pulse from the distal stump even in the presence of RAO[5]. RAO is more common at the end of hemostasis and thereafter gradually decreases in the first 24 h and even further in the 30 d after the procedure. In a meta-analysis of 112 studies including 46.631 patients, late revascularization occurred in a significant proportion of patients with RAO[18]. In this study, radial artery flow was restored in a significant percentage of patients at 24 h and at 30 d after coronary angiography.

Measures to reduce RAO incidence include smaller catheters, adequate anticoagulation, the adoption of patent hemostasis strategies with or without ulnar artery compression, and the reduction of hemostasis time to ≤ 120 min[5,16,18-24]. Patent

Table 2 Procedural data of the study population

Procedural data	Control group (conventional hemostasis) (*n* = 147)	Oximetry – plethysmography group (*n* = 152)	*P* value
PCI, *n* (%)	44 (29.9)	58 (38.2)	0.134[1]
Primary PCI, *n* (%)	12 (8.2)	15 (9.9)	0.607[1]
Heparin dose, median (IQR)	5000 (5000-7000)	5000 (5000-7000)	0.113[2]
INR, mean ± SD	1.1 ± 0.3)	1.1 ± 0.3)	0.958[3]
Significant coronary artery lesions, *n* (%)			
Left anterior descending artery	32 (21.8)	36 (23.7)	0.693[1]
Circumflex	10 (6.8)	12 (7.9)	0.718[1]
Right coronary artery	17 (11.6)	20 (13.2)	0.676[1]
Number of vessels[4], *n* (%)			0.707[3]
PCI in 1 vessel (%)	35 (81.4)	50 (87.7)	
PCI >1 vessels (%)	8 (18.6)	7 (12.3)	
Hemostatic device			0.223[1]
Air chamber, *n* (%)	80 (54.4)	72 (47.4)	
Valve with pressure plate, *n* (%)	67 (45.6)	80 (52.6)	
Right hand, *n* (%)	104 (70.7)	115 (75.7)	0.362[1]
Left hand, *n* (%)	43 (29.3)	37 (24.3)	
Puncture attempts, median (IQR)	1 (1-1)	1 (1-1)	0.354[2]
Puncture duration (min), median (IQR)	2.25 (1.42-3.3)	2.22 (1.44-3.37)	0.660[2]
Procedure time (min), median (IQR)	13 (8.4-27.3)	13.8 (9.2-26.9)	0.448[2]
Fluoro time (min), median (IQR)	3.1 (1.3-9.1)	3.4 (1.4-7.7)	0.663[2]
Sheath, *n* (%)			0.257[3]
5F	74 (50.3)	70 (46.1)	
6F	73 (49.7)	79 (52.0)	
7F	0 (0.0)	3 (2.0)	
Patent hemostasis, *n* (%)	94 (68.1)	125 (82.2)	0.005[1]

[1]Pearson's χ^2.
[2]Mann-Whitney test.
[3]Fisher's exact test.
[4]For those who underwent percutaneous coronary intervention.
INR: International normalized ratio; IQR: Interquartile range; PCI: Percutaneous coronary intervention.

hemostasis is the technique of maintaining radial artery forward flow through guided artery compression during hemostasis after coronary angiography[7]. In patients undergoing coronary angiography, complete absence of radial artery flow during hemostatic compression is a strong predictor of RAO[6,24]. On the contrary, maintaining radial artery antegrade flow during hemostasis, known as patent or nonocclusive hemostasis, is an important factor in preventing RAO, but its complexity has limited adoption[5,7,25]. Maintaining radial artery antegrade flow during hemostatic compression constitutes part of the recommended best practice after transradial access for coronary angiography[25].

The best technique to achieve patent hemostasis is a subject of ongoing research. Previous studies utilized relatively sophisticated methods to evaluate radial artery patency. In the landmark prevention of radial artery occlusion-patent hemostasis evaluation trial (the PROPHET study), 436 patients were randomized to undergo either conventional hemostasis or patent hemostasis after diagnostic coronary angiography *via* the transradial approach. Twelve percent of patients who underwent

Table 3 Coronary angiography complications between two hemostatic methods

Coronary angiography complications	Control group (Conventional Hemostasis)	Oximetry – plethysmography group	*P* value
Spasm	28 (19.0)	15 (9.9)	0.024[1]
Vagotonia	24 (16.3)	23 (15.1)	0.777[1]
Hematoma	25 (17.0)	15 (9.9)	0.070[1]
Hematoma diameter, median value (IQR)	0 (0 - 3)	0 (0 - 3)	0.462[2]
Bleeding	7 (4.8)	5 (3.3)	0.517[1]
Edema	26 (17.7)	29 (19.1)	0.756[1]
Local complication	18 (12.2)	24 (15.8)	0.378[1]
Pain	28 (19.0)	22 (14.4)	0.289[1]

[1]Pearson's χ^2.
[2]Mann-Whitney test.
Data are *n* (%)

Table 4 Patent radial artery by patient group

	Control group(conventional hemostasis)	Oximetry-plethysmography group	*P* value[3]
Patent radial artery			
Day 1[1] (*n* = 299)	126 (85.7)	137 (90.1)	0.241
Day 30[1] (*n* = 206)	100 (94.3)	89 (89.0)	0.164
Day 30[2] (*n* = 204)	100 (92.6)	87 (90.6)	0.612

[1]Evaluation with a Barbeau test.
[2]Evaluation with duplex ultrasonography.
[3]Pearson's χ^2.
Data are *n* (%)

Table 5 Predictors of patent hemostasis

	OR (95%CI)	*P* value
Patent hemostasis		
Age (per 1 yr increase)	1.04 (1.01-1.07)	0.006
Control group (reference)		
Oximetry-plethysmography group	2.35 (1.34-4.13)	0.003

conventional hemostasis experienced RAO at 24 h. The corresponding rate for patients in the patent hemostasis group was 5%[7]. The use of an oximetry-plethysmography test was the strongest predictor of achieving patent hemostasis. In the prophylactic hyperperfusion evaluation trial (PROPHET-II), ipsilateral ulnar artery compression during radial artery hemostatic compression increased the rate of patent hemostasis and reduced the incidence of RAO from 3.0% to 0.9%[25]. In the randomized radial compression guided by mean artery pressure *vs* standard compression with a pneumatic device (RACOMAP) trial, a significant reduction in RAO rates from 12.0% to 1.1% was observed in patients following the patent hemostasis protocol compared with traditional arterial obstructive compression[8]. In the RACOMAP trial, nonobstructive hemostasis was performed by compressing the radial artery during hemostasis, guided by the mean blood pressure[8].

In a study by Edris *et al*[26], patent hemostasis was achieved with rapid deflation of the compression band. The technique increased patent hemostasis rates from 40% to 95% and reduced RAO rates from 14.9% to 2.0% without bleeding complications. A study comparing nonobstructive hemostasis to conventional hemostasis reported

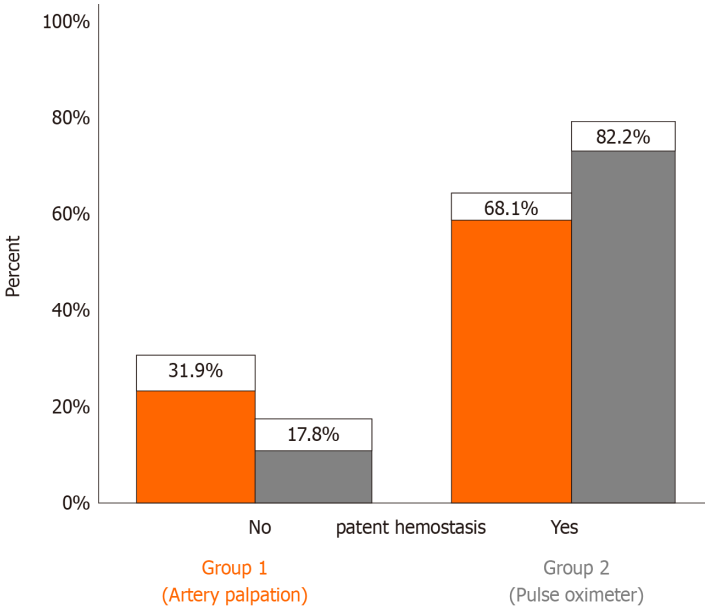


Figure 1 Percentage of patent hemostasis in each study group.

reduced RAO at 24 h in the patent hemostasis group, whereas the difference at 7 d between the two groups was not statistically significant[27]. The result is similar to that observed in this study in which RAO rates at 30 d did not differ between the two groups. The rates of patent hemostasis in this study are similar to those in previous studies (68.1% to 82.2%)[7,24]. Furthermore, in previous studies, nonocclusive hemostasis did not increase bleeding complications compared with conventional hemostasis[7,8]. Plethysmographic evaluation of radial artery flow allows easier achievement of patent hemostasis without adversely affecting the method safety. Similarly, in the present study, no difference was observed in the hemorrhagic events that occurred in the two treatment groups. Interestingly, in the current study, manual compression was not required to achieve hemostasis in the pulse oximeter group. In the PROPHET study manual compression was required in a small percentage of patients (3.6%) to achieve hemostasis[7]. Lastly, the rates of spasm in our study, which were lower in the oximeter *vs* the artery palpation group, were in accord with those reported in the literature[4].

In this study, we observed an association between increased age and successful patent hemostasis. Several speculations can be made regarding that finding. Firstly, radial artery spasm is more frequent in younger than in older patients undergoing PCI *via* radial access and therefore older adults are more likely to have a successful patent hemostasis[28-31]. Secondly, increased arterial stiffness in elderly patients produces a steeper increase in radial artery flow, resulting in reopening of the occlusion in the early period and maintaining vessel patency in the long-term[32]. Lastly, increased arterial stiffness in older patients may preclude the total interruption of flow during manual compression and therefore facilitate patent hemostasis[32].

The current study has several limitations that need to be addressed. Firstly, the study population was not large, but it was comparable to previous studies in the field. Secondly, at 30 d, radial artery patency was assessed with duplex ultrasonography in 204 out of 299 patients. We performed a telephone follow-up of the patients who did not return at 30 d. The three main reasons cited for follow-up interruptions were lack of understanding regarding the necessity of follow-up, social reasons (*e.g.*, distant hometown, financial barriers, relocation) and unawareness of the appointment schedule. Nevertheless, radial artery flow was restored in a significant percentage of patients who presented at follow-up, which is in accord with the current literature. Thirdly, patent hemostasis achieved in the current study by the use of pulse oximetry is relatively more simple than the techniques described in previous studies, and can be more widely implemented in everyday clinical practice.

CONCLUSION

Oximetry-plethysmography is an efficient and safe method to achieve patent hemostasis after coronary angiography *via* transradial access. Larger randomized control trials are urgently needed.

ARTICLE HIGHLIGHTS

Research background

Radial artery obstruction is a frequent complication of coronary angiography performed *via* transradial access. Maintaining circulatory anterograde flow in the radial artery during hemostasis (patent or nonobstructive hemostasis) reduces the risk of radial artery obstruction.

Research motivation

Simplified and easily applicable methods for successful patent hemostasis are currently lacking.

Research objectives

To determine which method, pulse oximeter *vs* the traditional radial artery palpation, is better to achieve patent hemostasis.

Research methods

This a prospective, single center study included 299 consecutive patients who underwent coronary angiography or percutaneous coronary intervention between November 2017 and July 2019. The exclusion criteria were: (1) Age of < 18 years; (2) History of radial artery disease; and (3) No palpable arterial pulse. Patients were randomly assigned to two groups. In the first group, radial artery flow was assessed by palpation of the artery during hemostasis (traditional method). In the second group, radial artery patency was estimated with a pulse oximeter. Two different compression devices were used for hemostasis (air chamber and pressure valve). The primary study endpoint was the successful achievement of patent hemostasis.

Research results

The two groups (pulse oximeter *vs* artery palpation) had no significant differences in age, sex, body mass index, risk factors, or comorbidities except for supraventricular arrhythmias. The percentage of patients with successful patent hemostasis was significantly higher in the pulse oximeter group (82.2% *vs* 68.1%, $P = 0.005$). A lower percentage of patients with spasm was recorded in the pulse oximeter group (9.9% *vs* 19.0%, $P = 0.024$). Multivariate analysis found that the use of pulse oximeter (OR: 2.35, 95%CI: 1.34-4.13, $P = 0.003$) and advanced age (OR: 1.04, 95%CI: 1.01-1.07, $P = 0.006$), were independently associated with an increased probability of successful patent hemostasis. The type of hemostatic device did not affect patent hemostasis ($P = 0.450$).

Research conclusions

Patent hemostasis with the use of pulse oximeter is a simple, efficient, and safe method, and is worthy of further investigation.

Research perspectives

Larger randomized studies are required to consider its clinical implications.

REFERENCES

1 **Ferrante G**, Rao SV, Jüni P, Da Costa BR, Reimers B, Condorelli G, Anzuini A, Jolly SS, Bertrand OF, Krucoff MW, Windecker S, Valgimigli M. Radial Versus Femoral Access for Coronary Interventions Across the Entire Spectrum of Patients With Coronary Artery Disease: A Meta-Analysis of Randomized Trials. *JACC Cardiovasc Interv* 2016; **9**: 1419-1434 [PMID: 27372195 DOI: 10.1016/j.jcin.2016.04.014]

2 **Collet JP**, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific

Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021; **42**: 1289-1367 [PMID: 32860058 DOI: 10.1093/eurheartj/ehaa575]

3 **Ibanez B**, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; **39**: 119-177 [PMID: 28886621 DOI: 10.1093/eurheartj/ehx393]

4 **Coghill EM**, Johnson T, Morris RE, Megson IL, Leslie SJ. Radial artery access site complications during cardiac procedures, clinical implications and potential solutions: The role of nitric oxide. *World J Cardiol* 2020; **12**: 26-34 [PMID: 31984125 DOI: 10.4330/wjc.v12.i1.26]

5 **Bernat I**, Aminian A, Pancholy S, Mamas M, Gaudino M, Nolan J, Gilchrist IC, Saito S, Hahalis GN, Ziakas A, Louvard Y, Montalescot G, Sgueglia GA, van Leeuwen MAH, Babunashvili AM, Valgimigli M, Rao SV, Bertrand OF; RAO International Group. Best Practices for the Prevention of Radial Artery Occlusion After Transradial Diagnostic Angiography and Intervention: An International Consensus Paper. *JACC Cardiovasc Interv* 2019; **12**: 2235-2246 [PMID: 31753298 DOI: 10.1016/j.jcin.2019.07.043]

6 **Sanmartin M**, Gomez M, Rumoroso JR, Sadaba M, Martinez M, Baz JA, Iniguez A. Interruption of blood flow during compression and radial artery occlusion after transradial catheterization. *Catheter Cardiovasc Interv* 2007; **70**: 185-189 [PMID: 17203470 DOI: 10.1002/ccd.21058]

7 **Pancholy S**, Coppola J, Patel T, Roke-Thomas M. Prevention of radial artery occlusion-patent hemostasis evaluation trial (PROPHET study): a randomized comparison of traditional *vs* patency documented hemostasis after transradial catheterization. *Catheter Cardiovasc Interv* 2008; **72**: 335-340 [PMID: 18726956 DOI: 10.1002/ccd.21639]

8 **Cubero JM**, Lombardo J, Pedrosa C, Diaz-Bejarano D, Sanchez B, Fernandez V, Gomez C, Vazquez R, Molano FJ, Pastor LF. Radial compression guided by mean artery pressure *vs* standard compression with a pneumatic device (RACOMAP). *Catheter Cardiovasc Interv* 2009; **73**: 467-472 [PMID: 19229978 DOI: 10.1002/ccd.21900]

9 **Shroff AR**, Fernandez C, Vidovich MI, Rao SV, Cowley M, Bertrand OF, Patel TM, Pancholy SB. Contemporary transradial access practices: Results of the second international survey. *Catheter Cardiovasc Interv* 2019; **93**: 1276-1287 [PMID: 30456913 DOI: 10.1002/ccd.27989]

10 **Aldoori JS**, Mohammed AI. Transradial approach for coronary angiography and percutaneos coronary intervention: personal experience. *Egypt Heart J* 2019; **71**: 10 [PMID: 31659542 DOI: 10.1186/s43044-019-0006-2]

11 **Di Santo P**, Simard T, Wells GA, Jung RG, Ramirez FD, Boland P, Marbach JA, Parlow S, Kyeremanteng K, Coyle D, Fergusson D, Russo JJ, Chong AY, Froeschl M, So DY, Dick A, Glover C, Labinaz M, Hibbert B, Le May M. Transradial Versus Transfemoral Access for Percutaneous Coronary Intervention in ST-Segment-Elevation Myocardial Infarction: A Systematic Review and Meta-Analysis. *Circ Cardiovasc Interv* 2021; **14**: e009994 [PMID: 33685220 DOI: 10.1161/CIRCINTERVENTIONS.120.009994]

12 **Agostoni P**, Biondi-Zoccai GG, de Benedictis ML, Rigattieri S, Turri M, Anselmi M, Vassanelli C, Zardini P, Louvard Y, Hamon M. Radial *vs* femoral approach for percutaneous coronary diagnostic and interventional procedures; Systematic overview and meta-analysis of randomized trials. *J Am Coll Cardiol* 2004; **44**: 349-356 [PMID: 15261930 DOI: 10.1016/j.jacc.2004.04.034]

13 **Spaulding C**, Lefèvre T, Funck F, Thébault B, Chauveau M, Ben Hamda K, Chalet Y, Monségu H, Tsocanakis O, Py A, Guillard N, Weber S. Left radial approach for coronary angiography: results of a prospective study. *Cathet Cardiovasc Diagn* 1996; **39**: 365-370 [PMID: 8958424 DOI: 10.1002/(SICI)1097-0304(199612)39:4<365::AID-CCD8>3.0.CO;2-B]

14 **Uhlemann M**, Möbius-Winkler S, Mende M, Eitel I, Fuernau G, Sandri M, Adams V, Thiele H, Linke A, Schuler G, Gielen S. The Leipzig prospective vascular ultrasound registry in radial artery catheterization: impact of sheath size on vascular complications. *JACC Cardiovasc Interv* 2012; **5**: 36-43 [PMID: 22230148 DOI: 10.1016/j.jcin.2011.08.011]

15 **Rao SV**. Observations from a transradial registry: our remedies oft in ourselves do lie. *JACC Cardiovasc Interv* 2012; **5**: 44-46 [PMID: 22230149 DOI: 10.1016/j.jcin.2011.10.005]

16 **Rashid M**, Kwok CS, Pancholy S, Chugh S, Kedev SA, Bernat I, Ratib K, Large A, Fraser D, Nolan J, Mamas MA. Radial Artery Occlusion After Transradial Interventions: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2016; **5** [PMID: 26811162 DOI: 10.1161/JAHA.115.002686]

17 **Bertrand OF**, Rao SV, Pancholy S, Jolly SS, Rodés-Cabau J, Larose E, Costerousse O, Hamon M, Mann T. Transradial approach for coronary angiography and interventions: results of the first international transradial practice survey. *JACC Cardiovasc Interv* 2010; **3**: 1022-1031 [PMID: 20965460 DOI: 10.1016/j.jcin.2010.07.013]

18 **Hahalis G**, Aznaouridis K, Tsigkas G, Davlouros P, Xanthopoulou I, Koutsogiannis N, Koniari I, Leopoulou M, Costerousse O, Tousoulis D, Bertrand OF. Radial Artery and Ulnar Artery Occlusions Following Coronary Procedures and the Impact of Anticoagulation: *ARTEMIS* (Radial and Ulnar *ARTE*ry Occlusion *M*eta-Analys*IS*) Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2017; **6** [PMID: 28838915 DOI: 10.1161/JAHA.116.005430]

19 **Pacchioni A**, Bellamoli M, Mugnolo A, Ferro J, Pesarini G, Turri R, Ribichini F, Saccà S, Versaci F,

Reimers B. Predictors of patent and occlusive hemostasis after transradial coronary procedures. *Catheter Cardiovasc Interv* 2021; **97**: 1369-1376 [PMID: 32761864 DOI: 10.1002/ccd.29066]

20 **Hahalis GN**, Leopoulou M, Tsigkas G, Xanthopoulou I, Patsilinakos S, Patsourakos NG, Ziakas A, Kafkas N, Koutouzis M, Tsiafoutis I, Athanasiadis I, Koniari I, Almpanis G, Anastasopoulou M, Despotopoulos S, Kounis N, Dapergola A, Aznaouridis K, Davlouros P. Multicenter Randomized Evaluation of High Versus Standard Heparin Dose on Incident Radial Arterial Occlusion After Transradial Coronary Angiography: The SPIRIT OF ARTEMIS Study. *JACC Cardiovasc Interv* 2018; **11**: 2241-2250 [PMID: 30391389 DOI: 10.1016/j.jcin.2018.08.009]

21 **Pancholy SB**. Comparison of the effect of intra-arterial *vs* intravenous heparin on radial artery occlusion after transradial catheterization. *Am J Cardiol* 2009; **104**: 1083-1085 [PMID: 19801029 DOI: 10.1016/j.amjcard.2009.05.057]

22 **Pancholy SB**, Ahmed I, Bertrand OF, Patel T. Frequency of radial artery occlusion after transradial access in patients receiving warfarin therapy and undergoing coronary angiography. *Am J Cardiol* 2014; **113**: 211-214 [PMID: 24210677 DOI: 10.1016/j.amjcard.2013.09.043]

23 **Plante S**, Cantor WJ, Goldman L, Miner S, Quesnelle A, Ganapathy A, Popel A, Bertrand OF. Comparison of bivalirudin *vs* heparin on radial artery occlusion after transradial catheterization. *Catheter Cardiovasc Interv* 2010; **76**: 654-658 [PMID: 20506483 DOI: 10.1002/ccd.22610]

24 **Pancholy SB**, Bertrand OF, Patel T. Comparison of a priori *vs* provisional heparin therapy on radial artery occlusion after transradial coronary angiography and patent hemostasis (from the PHARAOH Study). *Am J Cardiol* 2012; **110**: 173-176 [PMID: 22497680 DOI: 10.1016/j.amjcard.2012.03.007]

25 **Pancholy SB**, Bernat I, Bertrand OF, Patel TM. Prevention of Radial Artery Occlusion After Transradial Catheterization: The PROPHET-II Randomized Trial. *JACC Cardiovasc Interv* 2016; **9**: 1992-1999 [PMID: 27712733 DOI: 10.1016/j.jcin.2016.07.020]

26 **Edris A**, Gordin J, Sallam T, Wachsner R, Meymandi S, Traina M. Facilitated patent haemostasis after transradial catheterisation to reduce radial artery occlusion. *EuroIntervention* 2015; **11**: 765-771 [PMID: 26603985 DOI: 10.4244/EIJV11I7A153]

27 **Roghani F**, Tajik MN, Khosravi A. Compare Complication of Classic *vs* Patent Hemostasis in Transradial Coronary Angiography. *Adv Biomed Res* 2017; **6**: 159 [PMID: 29387670 DOI: 10.4103/abr.abr_164_16]

28 **Varenne O**, Jégou A, Cohen R, Empana JP, Salengro E, Ohanessian A, Gaultier C, Allouch P, Walspurger S, Margot O, El Hallack A, Jouven X, Weber S, Spaulding C. Prevention of arterial spasm during percutaneous coronary interventions through radial artery: the SPASM study. *Catheter Cardiovasc Interv* 2006; **68**: 231-235 [PMID: 16819768 DOI: 10.1002/ccd.20812]

29 **Jia DA**, Zhou YJ, Shi DM, Liu YY, Wang JL, Liu XL, Wang ZJ, Yang SW, Ge HL, Hu B, Yan ZX, Chen Y, Gao F. Incidence and predictors of radial artery spasm during transradial coronary angiography and intervention. *Chin Med J (Engl)* 2010; **123**: 843-847 [PMID: 20497675]

30 **Rathore S**, Stables RH, Pauriah M, Hakeem A, Mills JD, Palmer ND, Perry RA, Morris JL. Impact of length and hydrophilic coating of the introducer sheath on radial artery spasm during transradial coronary intervention: a randomized study. *JACC Cardiovasc Interv* 2010; **3**: 475-483 [PMID: 20488402 DOI: 10.1016/j.jcin.2010.03.009]

31 **Ho HH**, Jafary FH, Ong PJ. Radial artery spasm during transradial cardiac catheterization and percutaneous coronary intervention: incidence, predisposing factors, prevention, and management. *Cardiovasc Revasc Med* 2012; **13**: 193-195 [PMID: 22226169 DOI: 10.1016/j.carrev.2011.11.003]

32 **Buturak A**, Gorgulu S, Norgaz T, Voyvoda N, Sahingoz Y, Degirmencioglu A, Dagdelen S. The long-term incidence and predictors of radial artery occlusion following a transradial coronary procedure. *Cardiol J* 2014; **21**: 350-356 [PMID: 24142678 DOI: 10.5603/CJ.a2013.0128]

World Journal of Cardiology

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

World J Cardiol 2021 October 26; 13(10): 585-592

DOI: 10.4330/wjc.v13.i10.585

ISSN 1949-8462 (online)

META-ANALYSIS

Cardiovascular efficacy and safety of dipeptidyl peptidase-4 inhibitors: A meta-analysis of cardiovascular outcome trials

Dimitrios Ioannis Patoulias, Aristi Boulmpou, Eleftherios Teperikidis, Alexandra Katsimardou, Fotios Siskos, Michael Doumas, Christodoulos E Papadopoulos, Vassilios Vassilikos

ORCID number: Dimitrios Ioannis Patoulias 0000-0002-6899-684X; Aristi Boulmpou 0000-0002-5008-114X; Eleftherios Teperikidis 0000-0002-2146-1194; Alexandra Katsimardou 0000-0002-9180-6071; Fotios Siskos 0000-0002-4362-2219; Michael Doumas 0000-0002-7269-8044; Christodoulos E Papadopoulos 0000-0001-9643-9066; Vassilios Vassilikos 0000-0002-6982-4425.

Author contributions: Patoulias DI and Doumas M conceived and designed the study; Patoulias DI, Boulmpou A and Teperikidis E collected and analyzed data; Patoulias DI, Boulmpou A and Siskos F performed study quality and risk of bias assessment; Patoulias DI, Boulnpou A, Katsimardou A and Papadopoulos CE wrote the first draft of the study; Doumas M and Vassilikos V critically revised the final draft.

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

PRISMA 2009 Checklist statement: The present meta-analysis was conducted according to 2009 PRISMA Guidelines.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external

Dimitrios Ioannis Patoulias, Alexandra Katsimardou, Fotios Siskos, Michael Doumas, Second Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, Hippokration General Hospital, Thessaloniki 54642, Greece

Aristi Boulmpou, Eleftherios Teperikidis, Christodoulos E Papadopoulos, Vassilios Vassilikos, Third Department of Cardiology, Aristotle University of Thessaloniki, Hippokration General Hospital, Thessaloniki 54642, Greece

Corresponding author: Dimitrios Ioannis Patoulias, MD, MSc, Doctor, Research Fellow, Research Scientist, Second Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, Hippokration General Hospital, Konstantinoupoleos 49 Str., Thessaloniki 54642, Greece. dipatoulias@gmail.com

Abstract

BACKGROUND

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a generally safe and well tolerated antidiabetic drug class with proven efficacy in type 2 diabetes mellitus (T2DM). Recently, a series of large, randomized controlled trials (RCTs) addressing cardiovascular outcomes with DPP-4 inhibitors have been published.

AIM

To pool data from the aforementioned trials concerning the impact of DPP-4 inhibitors on surrogate cardiovascular efficacy outcomes and on major cardiac arrhythmias.

METHODS

We searched PubMed and grey literature sources for all published RCTs assessing cardiovascular outcomes with DPP-4 inhibitors compared to placebo until October 2020. We extracted data concerning the following "hard" efficacy outcomes: fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for heart failure, hospitalization for unstable angina, hospitalization for coronary revascularization and cardiovascular death. We also extracted data regarding the risk for major cardiac arrhythmias, such as atrial fibrillation, atrial flutter, ventricular fibrillation and ventricular tachycardia.

RESULTS

We pooled data from 6 trials in a total of 52520 patients with T2DM assigned either to DPP-4 inhibitor or placebo. DPP-4 inhibitors compared to placebo led to

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

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

Received: March 29, 2021
Peer-review started: March 29, 2021
First decision: June 25, 2021
Revised: July 8, 2021
Accepted: September 10, 2021
Article in press: September 10, 2021
Published online: October 26, 2021

P-Reviewer: Kawanami D, Wierzbicka A
S-Editor: Ma YJ
L-Editor: A
P-Editor: Li JH

a non-significant increase in the risk for fatal and non-fatal myocardial infarction [risk ratio (RR) = 1.02, 95%CI: 0.94-1.11, I^2 = 0%], hospitalization for heart failure (RR = 1.09, 95%CI: 0.92-1.29, I^2 = 65%) and cardiovascular death (RR = 1.02, 95%CI: 0.93-1.11, I^2 = 0%). DPP-4 inhibitors resulted in a non-significant decrease in the risk for fatal and non-fatal stroke (RR = 0.96, 95%CI: 0.85-1.08, I^2 = 0%) and coronary revascularization (RR = 0.99, 95%CI: 0.90-1.09, I^2 = 0%), Finally, DPP-4 inhibitors demonstrated a neutral effect on the risk for hospitalization due to unstable angina (RR = 1.00, 95%CI: 0.85-1.18, I^2 = 0%). As far as cardiac arrhythmias are concerned, DPP-4 inhibitors did not significantly affect the risk for atrial fibrillation (RR = 0.95, 95%CI: 0.78-1.17, I^2 = 0%), while they were associated with a significant increase in the risk for atrial flutter, equal to 52% (RR = 1.52, 95%CI: 1.03-2.24, I^2 = 0%). DPP-4 inhibitors did not have a significant impact on the risk for any of the rest assessed cardiac arrhythmias.

CONCLUSION

DPP-4 inhibitors do not seem to confer any significant cardiovascular benefit for patients with T2DM, while they do not seem to be associated with a significant risk for any major cardiac arrhythmias, except for atrial flutter. Therefore, this drug class should not be the treatment of choice for patients with established cardiovascular disease or multiple risk factors, except for those cases when newer antidiabetics (glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors) are not tolerated, contraindicated or not affordable for the patient.

Key Words: Dipeptidyl peptidase-4 inhibitors; Cardiovascular outcomes; Atrial fibrillation; Atrial flutter; Type 2 diabetes mellitus

Core Tip: The antidiabetic efficacy of dipeptidyl peptidase-4 (DPP-4) inhibitors has already been proven in recently published large randomized controlled trials. The purpose of the present meta-analysis was to clarify the impact of antidiabetic therapy with DPP-4 inhibitors on surrogate cardiovascular outcomes, and to elucidate the effect of these drugs on major cardiac arrhythmias. According to our analysis, this drug class does not significantly affect the risk for any of the addressed cardiovascular outcomes; however, it increases the risk for atrial flutter compared to placebo.

Citation: Patoulias DI, Boulmpou A, Teperikidis E, Katsimardou A, Siskos F, Doumas M, Papadopoulos CE, Vassilikos V. Cardiovascular efficacy and safety of dipeptidyl peptidase-4 inhibitors: A meta-analysis of cardiovascular outcome trials. *World J Cardiol* 2021; 13(10): 585-592
URL: https://www.wjgnet.com/1949-8462/full/v13/i10/585.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i10.585

INTRODUCTION

It is well-established that type 2 diabetes mellitus (T2DM) represents an independent risk factor for the development of cardiovascular disease, which accounts for half of deaths among diabetic patients[1]. Patients with T2DM experience higher incidence of vascular interventions compared to high-risk patients without T2DM or cardiovascular disease at baseline, underscoring the necessity for targeted therapeutic interventions[2]. In addition, development of cardiovascular complications among patients with T2DM boosts medical costs, leading to an unbearable economic burden [3]. Besides major adverse cardiovascular events, patients with T2DM experience an increased risk of heart rhythm disorders, nevertheless the exact mechanisms of arrhythmogenesis in the context of T2DM are still under investigation[4].

Dipeptidyl peptidase-4 (DPP-4) inhibitors constitute a safe treatment option with adequate glycemic efficacy in T2DM. However, their cardiovascular efficacy has been

doubted over recent years, after the publication of relevant cardiovascular outcome trials. Previous meta-analyses failed to show any cardiovascular benefit with their use in patients with T2DM[5-7]. Since then, additional randomized controlled trials addressing "hard" cardiovascular outcomes with DPP-4 inhibitors have been published. Therefore, we sought to update and extend these meta-analyses, by incorporating all relevant data from published cardiovascular outcome trials until October 2020. In addition, we planned to assess the effect of DPP-4 inhibitors on major cardiac arrhythmias, since there are no relevant studies published in the literature so far.

MATERIALS AND METHODS

Our meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched PubMed database and grey literature sources form inception to October 2020, in order to identify relevant cardiovascular outcome trials assessing the cardiovascular efficacy and safety of DPP-4 inhibitors in patients with T2DM. Our inclusion criteria were: (1) Randomized controlled trials; (2) Enrollment of patients with T2DM; (3) Enrollment of adult patients; and (4) Assessment of at least one cardiovascular outcome of interest. Our exclusion criteria were: (1) Observational studies; (2) Studies enrolling patients with type 1 diabetes mellitus; and (3) Studies enrolling children or adolescents.

We utilized the following search terms: "DPP-4 inhibitor", "dipeptidyl peptidase-4 inhibitor", "vildagliptin", "sitagliptin", "alogliptin", "linagliptin", "saxagliptin", "omarigliptin", "tenegliptin", "evogliptin", "gliptin", "cardiovascular outcome", "cardiac arrhythmia", "atrial fibrillation" combined with the use of Boolean operators "AND" and "OR". We used both free-text words and MeSH terms. We did not imply any filter regarding study setting, study sample, language or publication date. Unfortunately, we did not registered prospectively our protocol in a publicly available repository.

After de-duplication and assessment of eligible studies at title and abstract level for potential inclusion, two independent reviewers (D.P. and E.T.) extracted the data from the eligible reports, by using a pilot tested, data extraction form. We assessed the following cardiovascular efficacy outcomes: fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for heart failure, hospitalization for unstable angina, hospitalization for coronary revascularization and cardiovascular death. We also assessed the risk for the following cardiac arrhythmias with DPP-4 inhibitor treatment compared to placebo or active comparator: atrial fibrillation, atrial flutter, atrial tachycardia, ventricular fibrillation, ventricular tachycardia, ventricular extrasystoles, supraventricular tachycardia, sinus node dysfunction, second degree atrioventricular block, complete atrioventricular block.

As we assessed only dichotomous variables, differences were calculated with the use of risk ratio (RR), with 95% confidence interval (CI), after implementation of the Mantel-Haenszel random effects formula. Statistical heterogeneity among studies was assessed by using I^2 statistics. Heterogeneity was considered to be low if I^2 was between 0% and 25%, moderate if I^2 was between 25% and 50%, or high if I^2 was greater than 75%[8]. All analyses were performed at the 0.05 significance level, while they were undertaken with RevMan 5.3 software.

Two independent reviewers (D.P. and A.B.) assessed the quality of the included RCTs, by using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) for the primary efficacy outcome[9]. Discrepancies between reviewers were solved by discussion, consensus or arbitration by a third senior reviewer (V.V.).

RESULTS

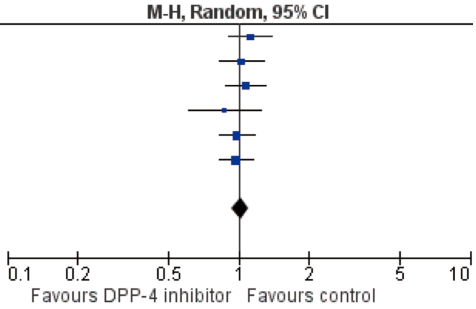
We finally pooled data from six trials in a total of 52520 patients[10-15]. Overall risk of bias was considered as low across all selected trials.

DPP-4 inhibitor treatment did not significantly affect any of the prespecified cardiovascular efficacy outcomes. More specifically, DPP-4 inhibitors compared to control led to a non-significant increase in the risk for fatal and non-fatal myocardial infarction (RR = 1.02, 95%CI: 0.94-1.11, I^2 = 0%), hospitalization for heart failure (RR = 1.09, 95%CI: 0.92-1.29, I^2 = 65%) and cardiovascular death (RR = 1.02, 95%CI: 0.93-1.11, I^2 = 0%), as shown in Figures 1A, 1C and 1F. In addition, DPP-4 inhibitors produced a non-significant decrease in the risk for fatal and non-fatal stroke (RR = 0.96, 95%CI:

A

Study or Subgroup	DPP-4 inhibitor Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CARMELINA	165	3494	146	3485	14.8%	1.13 [0.91, 1.40]
CAROLINA	153	3023	148	3010	14.5%	1.03 [0.83, 1.28]
EXAMINE	187	2701	173	2679	17.6%	1.07 [0.88, 1.31]
NCT01703208	52	2092	60	2100	5.2%	0.87 [0.60, 1.25]
SAVOR-TIMI 53	234	8240	236	8173	22.1%	0.98 [0.82, 1.18]
TECOS	269	7257	276	7266	25.8%	0.98 [0.83, 1.15]
Total (95% CI)		**26807**		**26713**	**100.0%**	**1.02 [0.94, 1.11]**
Total events	1060		1039			

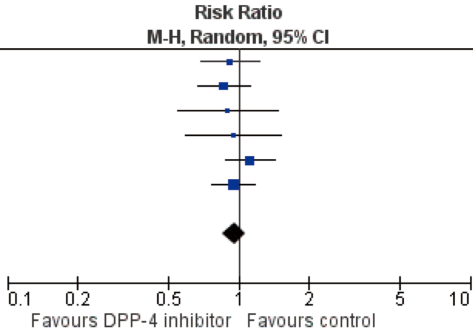
Heterogeneity: Tau² = 0.00; Chi² = 2.21, df = 5 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.69)



B

Study or Subgroup	DPP-4 inhibitor Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CARMELINA	81	3494	88	3485	15.4%	0.92 [0.68, 1.24]
CAROLINA	104	3023	120	3010	20.7%	0.86 [0.67, 1.12]
EXAMINE	29	2701	32	2679	5.5%	0.90 [0.55, 1.48]
NCT01703208	32	2092	34	2100	6.0%	0.94 [0.59, 1.53]
SAVOR-TIMI 53	135	8240	120	8173	23.0%	1.12 [0.87, 1.42]
TECOS	157	7257	165	7266	29.4%	0.95 [0.77, 1.18]
Total (95% CI)		**26807**		**26713**	**100.0%**	**0.96 [0.85, 1.08]**
Total events	538		559			

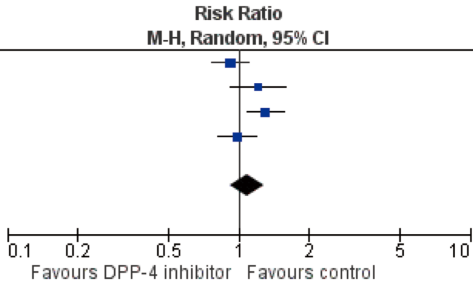
Heterogeneity: Tau² = 0.00; Chi² = 2.28, df = 5 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)



C

Study or Subgroup	DPP-4 inhibitor Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CARMELINA	209	3494	226	3485	27.1%	0.92 [0.77, 1.11]
CAROLINA	112	3023	92	3010	19.8%	1.21 [0.92, 1.59]
SAVOR-TIMI 53	256	8240	194	8173	26.9%	1.31 [1.09, 1.57]
TECOS	200	7257	202	7266	26.2%	0.99 [0.82, 1.20]
Total (95% CI)		**22014**		**21934**	**100.0%**	**1.09 [0.92, 1.29]**
Total events	777		714			

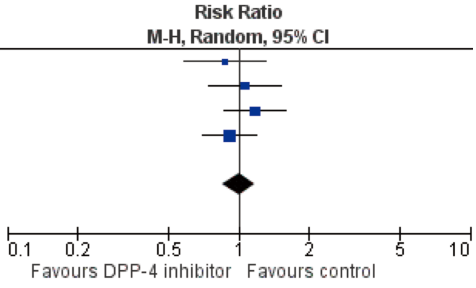
Heterogeneity: Tau² = 0.02; Chi² = 8.53, df = 3 (P = 0.04); I² = 65%
Test for overall effect: Z = 0.99 (P = 0.32)



D

Study or Subgroup	DPP-4 inhibitor Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CARMELINA	42	3494	48	3485	15.3%	0.87 [0.58, 1.32]
CAROLINA	60	3023	56	3010	19.9%	1.07 [0.74, 1.53]
SAVOR-TIMI 53	89	8240	75	8173	27.7%	1.18 [0.87, 1.60]
TECOS	104	7257	114	7266	37.2%	0.91 [0.70, 1.19]
Total (95% CI)		**22014**		**21934**	**100.0%**	**1.00 [0.85, 1.18]**
Total events	295		293			

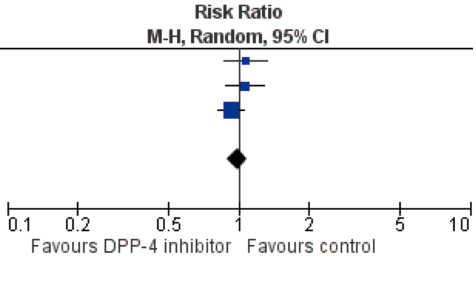
Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)



E

Study or Subgroup	DPP-4 inhibitor Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CARMELINA	160	3494	149	3485	20.2%	1.07 [0.86, 1.33]
CAROLINA	202	3023	189	3010	26.1%	1.06 [0.88, 1.29]
SAVOR-TIMI 53	395	8240	422	8173	53.7%	0.93 [0.81, 1.06]
Total (95% CI)		**14757**		**14668**	**100.0%**	**0.99 [0.90, 1.09]**
Total events	757		760			

Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)



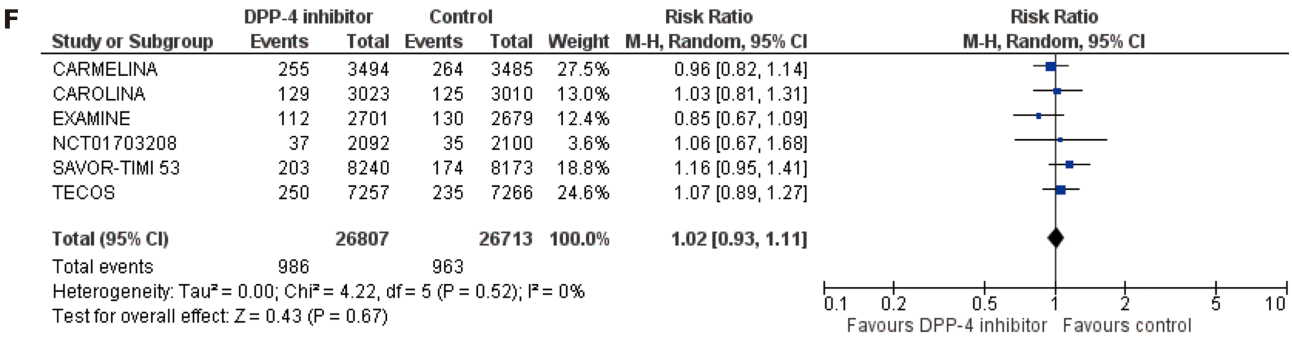


Figure 1 Effect of dipeptidyl peptidase-4 inhibitor treatment compared to control on the risk. A: Fatal and non-fatal myocardial infarction; B: Fatal and non-fatal stroke; C: Hospitalization for heart failure; D: Hospitalization due to unstable angina; E: Hospitalization for coronary revascularization; F: Cardiovascular mortality.

0.85-1.08, I^2 = 0%) and coronary revascularization (RR = 0.99, 95%CI: 0.90-1.09, I^2 = 0%), as depicted in Figures 1B and 1E. Finally, DPP-4 inhibitors demonstrated a neutral effect on the risk for hospitalization due to unstable angina (RR = 1.00, 95%CI: 0.85-1.18, I^2 = 0%), as shown in Figure 1D.

Regarding the risk for major cardiac arrhythmias, DPP-4 inhibitor treatment did not significantly affect the risk for atrial fibrillation (RR = 0.95, 95%CI: 0.78-1.17, I^2 = 0%), as shown in Supplementary Figure 1A. Of note, DPP-4 inhibitors were associated with a significant increase in the risk for atrial flutter, equal to 52% (RR = 1.52, 95%CI: 1.03-2.24, I^2 = 0%), as shown in Supplementary Figure 1B. Finally, DPP-4 inhibitors did not have a significant impact on the risk for any of the rest assessed major cardiac arrhythmias, as depicted in Supplementary Figures 1C-J.

DISCUSSION

To our knowledge, this is the first meta-analysis of recently published, large, placebo-controlled cardiovascular outcome trials broadly assessing the cardiovascular efficacy and safety of DPP-4 inhibitors in T2DM. Our meta-analysis demonstrates a rather neutral effect of DPP-4 inhibitors on the risk for myocardial infarction, hospitalization for heart failure, stroke, urgent coronary revascularization and cardiovascular death; in parallel, we highlighted the absence of a significant effect of DPP-4 inhibitors on different types of cardiac arrhythmias, except for atrial flutter, for which corresponding risk increased by 52% compared to placebo. Our results are in accordance with previous meta-analyses in the field[6,16]; nevertheless, the impact of DPP-4 inhibitors on the arrhythmic burden across patients with T2DM has not been previously evaluated.

To date, a series of previous reports have indicated some cardioprotective effects of antidiabetic treatment with DPP-4 inhibitors; these generally safe and well-tolerated regimens have been associated with a significant reduction in blood pressure and with a rather low risk for hypoglycemia compared to other categories of antidiabetic drugs, while they do not increase body weight[17,18]. It has also been shown that they reduce arterial stiffness, whereas no significant effect on endothelial function was documented[19]. Additionally, in animal models, DPP-4 inhibitors have been shown to stabilize cardiac electrophysiology by decreasing the total number of premature ventricular contractions and demonstrating an antiapoptotic effect, significantly reducing the infarct size in experimental myocardial ischemia[20,21]. However, the above cardioprotective effects were not clearly translated into clinically significant results in relevant cardiovascular outcome trials and in our meta-analysis, as well.

Of particular interest is the finding of our analysis that DPP-4 inhibitors are associated with a significant increase in the risk for atrial flutter. Underlying pathophysiologic mechanisms remain largely unknown, since there are no relevant published data. However, it is well-established that diabetes mellitus increases the odds for atrial flutter development, almost by two times, as derived from epidemiological data two decades before[22]. In addition, it is known that atrial flutter at baseline is strongly associated with a significant increase in the 10-year risk for myocardial infarction, stroke, heart failure and all-cause death among affected subjects, constituting this arrhythmia as a prognostic marker of future adverse

cardiovascular outcomes[23]. Therefore, the observation that DPP-4 inhibitors actually increase the risk for atrial flutter is of utmost importance that may influence decision-making concerning high-risk patients, such as those suffering from T2DM.

The importance of documenting a neutral effect on a surrogate, prespecified endpoint for a drug class is as important as demonstrating a positive or negative effect, since knowledge about the risk to benefit profile of each different class plays a crucial role in decision-making process in daily clinical routine[24]. Furthermore, considering CVOTs demonstrating significant cardiovascular and renal benefits of other classes of glucose-lowering agents, namely sodium glucose cotransporter-2 inhibitors and glucagon-peptide-1 receptor agonists[25,26], in patients with T2DM, it is important that all such information is incorporated into the clinical guidelines, which have already incorporated these results in their latest recommendations[27,28].

CONCLUSION

In conclusion, DPP-4 inhibitors do not confer any significant cardiovascular benefit for patients with T2DM. In addition, they are not associated with a significant risk for any major cardiac arrhythmias, except for atrial flutter. However, this drug class should not be the treatment of choice for patients with established cardiovascular disease or multiple risk factors, except for those cases when newer antidiabetics (glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors) are not tolerated, contraindicated or not affordable for the patient.

ARTICLE HIGHLIGHTS

Research background

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a safe and efficacious treatment option in type 2 diabetes mellitus (T2DM).

Research motivation

Recently, several large, cardiovascular-outcome, randomized controlled trials (RCTs) with DPP-4 inhibitors in patients with T2DM have been published, raising some doubts on the cardiovascular efficacy and safety of this drug class.

Research objectives

Herein the authors provide the most updated and broad relevant meta-analysis by pooling data of interest from the available cardiovascular-outcome RCTs, addressing the cardiovascular efficacy and safety of this drug class.

Research methods

The authors searched PubMed and grey literature sources for all published RCTs assessing cardiovascular outcomes with DPP-4 inhibitors compared to placebo until October 2020.

Research results

Overall, DPP-4 inhibitors seem to have a neutral effect on most surrogate cardiovascular outcome endpoints, such as cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure decompensation, hospitalization for unstable angina or coronary revascularization.

Research conclusions

DPP-4 inhibitors do not provide any clear cardiovascular benefit in patients with T2DM.

Notably, DPP-4 inhibitors are not associated with a significant effect on the risk for major cardiac arrhythmias, except for atrial flutter, increasing the risk by 52% compared to placebo.

Research perspectives

DPP-4 inhibitors do not provide any clear cardiovascular benefit in patients with T2DM.

REFERENCES

1 **Einarson TR**, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc Diabetol* 2018; **17**: 83 [PMID: 29884191 DOI: 10.1186/s12933-018-0728-6]

2 **Engelen SE**, van der Graaf Y, Stam-Slob MC, Grobbee DE, Cramer MJ, Kappelle LJ, de Borst GJ, Visseren FLJ, Westerink J; SMART study group. Incidence of cardiovascular events and vascular interventions in patients with type 2 diabetes. *Int J Cardiol* 2017; **248**: 301-307 [PMID: 28802735 DOI: 10.1016/j.ijcard.2017.07.081]

3 **Einarson TR**, Acs A, Ludwig C, Panton UH. Economic Burden of Cardiovascular Disease in Type 2 Diabetes: A Systematic Review. *Value Health* 2018; **21**: 881-890 [PMID: 30005761 DOI: 10.1016/j.jval.2017.12.019]

4 **Grisanti LA**. Diabetes and Arrhythmias: Pathophysiology, Mechanisms and Therapeutic Outcomes. *Front Physiol* 2018; **9**: 1669 [PMID: 30534081 DOI: 10.3389/fphys.2018.01669]

5 **Fei Y**, Tsoi MF, Cheung BMY. Cardiovascular outcomes in trials of new antidiabetic drug classes: a network meta-analysis. *Cardiovasc Diabetol* 2019; **18**: 112 [PMID: 31462224 DOI: 10.1186/s12933-019-0916-z]

6 **Sinha B**, Ghosal S. Meta-analyses of the effects of DPP-4 inhibitors, SGLT2 inhibitors and GLP1 receptor analogues on cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure. *Diabetes Res Clin Pract* 2019; **150**: 8-16 [PMID: 30794833 DOI: 10.1016/j.diabres.2019.02.014]

7 **Alfayez OM**, Almutairi AR, Aldosari A, Al Yami MS. Update on Cardiovascular Safety of Incretin-Based Therapy in Adults With Type 2 Diabetes Mellitus: A Meta-Analysis of Cardiovascular Outcome Trials. *Can J Diabetes* 2019; **43**: 538-545.e2 [PMID: 31175007 DOI: 10.1016/j.jcjd.2019.04.003]

8 **Higgins JPT GS**, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Collaboration. *Cochrane Database Syst Rev* 2010; **6**: 143-148

9 **Sterne JAC**, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898 [PMID: 31462531 DOI: 10.1136/bmj.l4898]

10 **Green JB**, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; TECOS Study Group. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2015; **373**: 232-242 [PMID: 26052984 DOI: 10.1056/NEJMoa1501352]

11 **Rosenstock J**, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, Pfarr E, Keller A, Mattheus M, Baanstra D, Meinicke T, George JT, von Eynatten M, McGuire DK, Marx N; CAROLINA Investigators. Effect of Linagliptin *vs* Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. *JAMA* 2019; **322**: 1155-1166 [PMID: 31536101 DOI: 10.1001/jama.2019.13772]

12 **Rosenstock J**, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, Alexander JH, Pencina M, Toto RD, Wanner C, Zinman B, Woerle HJ, Baanstra D, Pfarr E, Schnaidt S, Meinicke T, George JT, von Eynatten M, McGuire DK; CARMELINA Investigators. Effect of Linagliptin *vs* Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. *JAMA* 2019; **321**: 69-79 [PMID: 30418475 DOI: 10.1001/jama.2018.18269]

13 **Gantz I**, Chen M, Suryawanshi S, Ntabadde C, Shah S, O'Neill EA, Engel SS, Kaufman KD, Lai E. A randomized, placebo-controlled study of the cardiovascular safety of the once-weekly DPP-4 inhibitor omarigliptin in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol* 2017; **16**: 112 [PMID: 28893244 DOI: 10.1186/s12933-017-0593-8]

14 **Scirica BM**, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013; **369**: 1317-1326 [PMID: 23992601 DOI: 10.1056/NEJMoa1307684]

15 **White WB**, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013; **369**: 1327-1335 [PMID: 23992602 DOI: 10.1056/NEJMoa1305889]

16 **Liu D**, Jin B, Chen W, Yun P. Dipeptidyl peptidase 4 (DPP-4) inhibitors and cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM): a systematic review and meta-analysis. *BMC Pharmacol Toxicol* 2019; **20**: 15 [PMID: 30832701 DOI: 10.1186/s40360-019-0293-y]

17 **Karagiannis T**, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. *BMJ* 2012; **344**: e1369 [PMID: 22411919 DOI: 10.1136/bmj.e1369]

18 **Papagianni M**, Tziomalos K. Cardiovascular effects of dipeptidyl peptidase-4 inhibitors. *Hippokratia* 2015; **19**: 195-199 [PMID: 27418775]

19 **Batzias K**, Antonopoulos AS, Oikonomou E, Siasos G, Bletsa E, Stampouloglou PK, Mistakidi CV, Noutsou M, Katsiki N, Karopoulos P, Charalambous G, Thanopoulou A, Tentolouris N, Tousoulis D. Effects of Newer Antidiabetic Drugs on Endothelial Function and Arterial Stiffness: A Systematic Review and Meta-Analysis. *J Diabetes Res* 2018; **2018**: 1232583 [PMID: 30622967 DOI: 10.1155/2018/1232583]

20 **Chinda K**, Palee S, Surinkaew S, Phornphutkul M, Chattipakorn S, Chattipakorn N. Cardioprotective effect of dipeptidyl peptidase-4 inhibitor during ischemia-reperfusion injury. *Int J Cardiol* 2013; **167**: 451-457 [PMID: 22285447 DOI: 10.1016/j.ijcard.2012.01.011]

21 **Kubota A**, Takano H, Wang H, Hasegawa H, Tadokoro H, Hirose M, Kobara Y, Yamada-Inagawa T, Komuro I, Kobayashi Y. DPP-4 inhibition has beneficial effects on the heart after myocardial infarction. *J Mol Cell Cardiol* 2016; **91**: 72-80 [PMID: 26739213 DOI: 10.1016/j.yjmcc.2015.12.026]

22 **Movahed MR**, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. *Int J Cardiol* 2005; **105**: 315-318 [PMID: 16274775 DOI: 10.1016/j.ijcard.2005.02.050]

23 **Rahman F**, Wang N, Yin X, Ellinor PT, Lubitz SA, LeLorier PA, McManus DD, Sullivan LM, Seshadri S, Vasan RS, Benjamin EJ, Magnani JW. Atrial flutter: Clinical risk factors and adverse outcomes in the Framingham Heart Study. *Heart Rhythm* 2016; **13**: 233-240 [PMID: 26226213 DOI: 10.1016/j.hrthm.2015.07.031]

24 **Chi C**, Snaith J, Gunton JE. Diabetes Medications and Cardiovascular Outcomes in Type 2 Diabetes. *Heart Lung Circ* 2017; **26**: 1133-1141 [PMID: 28473214 DOI: 10.1016/j.hlc.2017.02.030]

25 **Zelniker TA**, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019; **393**: 31-39 [PMID: 30424892 DOI: 10.1016/S0140-6736(18)32590-X]

26 **Giugliano D**, Maiorino MI, Bellastella G, Longo M, Chiodini P, Esposito K. GLP-1 receptor agonists for prevention of cardiorenal outcomes in type 2 diabetes: An updated meta-analysis including the REWIND and PIONEER 6 trials. *Diabetes Obes Metab* 2019; **21**: 2576-2580 [PMID: 31373167 DOI: 10.1111/dom.13847]

27 **American Diabetes Association**. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes-2020*. *Diabetes Care* 2020; **43**: S98-S110 [PMID: 31862752 DOI: 10.2337/dc20-S009]

28 **Buse JB**, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, D'Alessio DA, Davies MJ. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2020; **43**: 487-493 [PMID: 31857443 DOI: 10.2337/dci19-0066]

World Journal of Cardiology

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

World J Cardiol 2021 October 26; 13(10): 593-598

DOI: 10.4330/wjc.v13.i10.593

ISSN 1949-8462 (online)

CASE REPORT

Cardiac involvement in hydrocarbon inhalant toxicity — role of cardiac magnetic resonance imaging: A case report

George Jolly, Shevel Dacosta Davis, Saif Ali, Lauren Bitterman, Ashley Saunders, Hana Kazbour, Purvi Parwani

ORCID number: George Jolly 0000-0003-3128-1848; Shevel Dacosta Davis 0000-0002-2749-4421; Saif Ali 0000-0002-8043-8971; Lauren Bitterman 0000-0002-5799-9367; Ashley Saunders 0000-0001-5039-9062; Hana Kazbour 0000-0001-7019-6721; Purvi Parwani 0000-0002-4707-992X.

Author contributions: Jolly G provided references for and wrote the majority of the introduction, discussion and conclusion sections; Dacosta Davis S, Bitterman L and Saunders A wrote the majority of the case presentation, acquired necessary documentation for submission and completed final formatting of submission documents; Kazbour H supervised the primary medicine team involved in patient care; Kazbour H and Ali S contributed towards revising the manuscript critically for important intellectual content; Parwani P handled supervision, made substantial contribution to the conception of the paper, drafted the first manuscript, provided critical edits to the final manuscript in addition to providing the CMRI imaging, and is the senior and corresponding author of the manuscript.

Informed consent statement: Informed written consent was

George Jolly, Saif Ali, Purvi Parwani, Division of Cardiology, Loma Linda University Medical Center, Loma Linda, CA 92354, United States

Shevel Dacosta Davis, Lauren Bitterman, Ashley Saunders, Hana Kazbour, Department of Internal Medicine, Loma Linda University Medical Center, Loma Linda, CA 92354, United States

Corresponding author: Purvi Parwani, MD, Assistant Professor, Division of Cardiology, Loma Linda University Medical Center, 11234 Anderson St, Loma Linda, CA 92354, United States. pparwani@llu.edu

Abstract

BACKGROUND

We report a patient who was diagnosed with toxic myopericarditis secondary to hydrocarbon abuse using cardiac magnetic resonance imaging (CMR).

CASE SUMMARY

A 25-year-old male presented to emergency department with chest pain for 3 d. Patient also reported sniffing hydrocarbon containing inhalant for the last 1 year. Labs showed elevated troponin and electrocardiography was suggestive of acute pericarditis. Echocardiogram showed left ventricular (LV) ejection fraction (EF) of 40%. Given patient's troponin elevation and reduced EF, cardiac catheterization was performed which showed normal coronaries. CMR was performed for myocardial infarction with non-obstructive coronary arteries evaluation. CMR showed borderline LV function with edema in mid and apical LV suggestive of myocarditis.

CONCLUSION

CMR can be used to diagnose toxic myopericarditis secondary to hydrocarbon abuse.

Key Words: Myocarditis; Cardiac magnetic resonance imaging; Hydrocarbon abuse; Hydrocarbon inhalant toxicity; Case report

obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare no potential financial interests.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Manuscript source: Unsolicited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: United States

Peer-review report's scientific quality classification

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

Received: January 24, 2021
Peer-review started: January 24, 2021
First decision: February 28, 2021
Revised: March 7, 2021
Accepted: September 17, 2021
Article in press: September 17, 2021
Published online: October 26, 2021

P-Reviewer: Najafi M
S-Editor: Gao CC
L-Editor: A

Core Tip: Inhalant abuse has been rampant in the United States population in the last 2 decades. Cardiac manifestations of hydrocarbon inhalant abuse are not well reported. We report a case of myopericarditis in a patient with inhalant abuse. We also describe the role of Cardiac Magnetic Resonance Imaging in diagnosis and treatment of these patients.

Citation: Jolly G, Dacosta Davis S, Ali S, Bitterman L, Saunders A, Kazbour H, Parwani P. Cardiac involvement in hydrocarbon inhalant toxicity — role of cardiac magnetic resonance imaging: A case report. *World J Cardiol* 2021; 13(10): 593-598
URL: https://www.wjgnet.com/1949-8462/full/v13/i10/593.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i10.593

INTRODUCTION

Inhalant abuse has been rampant in the United States population in the last 2 decades [1,2]. Commonly used domestic and industrial items including hair spray, spot remover, PC cleaner and glues have hydrocarbon constituents like dimethyl ether and hydrofluorocarbons. We present our patient who has a longstanding history of huffing dust off, (the propellant cleaner which has difluoroethane as the active hydrocarbon ingredient) who developed myopericarditis with systolic dysfunction. We also discuss the role of Cardiac Magnetic Resonance Imaging in diagnosing and prognosticating in these patients.

CASE PRESENTATION

Chief complaints

Chest pain, nausea and vomiting × 3 d.

History of present illness

A 25-year-old male patient with no prior medical history presented to the emergency department with chest pain, nausea and vomiting × 3 d. He described sharp, intermittent chest pain that is sub sternal, radiating to the back and left arm for last 3 d. His pain is worse upon leaning forward and worse with deep inspiration. He also had multiple episodes of nausea and vomiting with an episode of coffee-ground emesis. Patient reported long-term abuse of hydrocarbon containing inhalant (PC keyboard dust off) for the last 1 year. He used to huff 2 cans of dust off at the same time to achieve a hallucinogenic effect along with marijuana use. One week prior to admission, he reported increased use (10 cans/d).

Personal and family history

History of intracranial aneurysm rupture in father.

Physical examination

The patient's heart rate was 112 bpm, respiratory rate was 15 breaths per minute, blood pressure was 114/73 mmHg and oxygen saturation on room air was 99%. His body mass index (BMI) was 37 kg/m^2. Cardiac examination revealed a regular rate and rhythm, and no jugular venous distention with mild chest wall tenderness. Erythematous, non-scaling lesions were noted on the chest wall, arm and lips. Abdominal examination revealed right upper quadrant and bilateral flank tenderness.

Laboratory examinations

Initial laboratory evaluation showed leukocytosis (WBC-19.6 bil/L), acute kidney injury (Cr-3.4 mg/dL, BUN-54 mg/dL), elevated transaminases (AST-161 U/L, ALT-77 U/L), troponin-1.63 (ng/mL) peaked at 2.06 (ng/mL), CK-3000 ng/mL, CKMB-45 ng/mL. Urine drug screen was positive for cannabinoids. Initial electrocardiography (EKG) showed sinus tachycardia with diffuse inferolateral ST elevation, concerning for acute myopericarditis (Figure 1).

P-Editor: Li JH

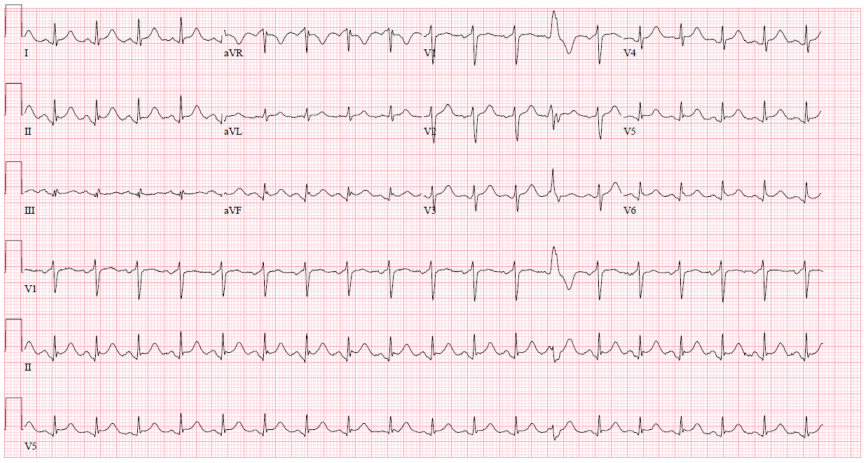


Figure 1 Electrocardiography showing diffuse inferolateral ST elevation without reciprocal ST depression, suggestive of pericarditis.

Imaging examinations

Echocardiogram showed left ventricular (LV) ejection fraction (EF) of 40% to 45% with severe aortic root dilation (5.0 cm) and trivial pericardial effusion. Given patient's elevated troponins, cardiac catheterization was performed. Coronary angiogram showed no evidence of coronary artery disease (Figure 2). Working diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA) was established and cardiac magnetic resonance imaging (CMR) was performed to evaluate the etiology further.

CMR

CMR showed borderline LV function with edema in the mid and apical LV suggestive of myocardial inflammation (Figure 3A and B). No delayed enhancement was seen in the myocardium or in the pericardium (Figure 4A and B). There was no evidence of pericardial effusion.

FINAL DIAGNOSIS

Based on the clinical presentation and imaging findings, patient was diagnosed with acute toxic myopericarditis secondary to hydrocarbon inhalant abuse. NSTEMI and MINOCA was ruled out based on coronary angiogram and CMR respectively.

TREATMENT

Supportive management for pain control was initially initiated. Once renal function improved, colchicine 0.6 mg b.i.d. was initiated for ongoing chest pain and EKG findings.

OUTCOME AND FOLLOW-UP

Repeat echo obtained 6 wk after the index presentation revealed EF of 60%.

DISCUSSION

Hydrocarbon compounds have been previously reported to have multiple cardiotoxic effects. Cates and Cook[3] reported a case of severe cardiomyopathy complicated by significant reduction in EF (25%) and torsades de pointes in the patient with history of huffing dust off. Interestingly, patient in this case report, recovered normal ventricular function prior to discharge. Samson *et al*[4] reported a similar case of inhalant abuse

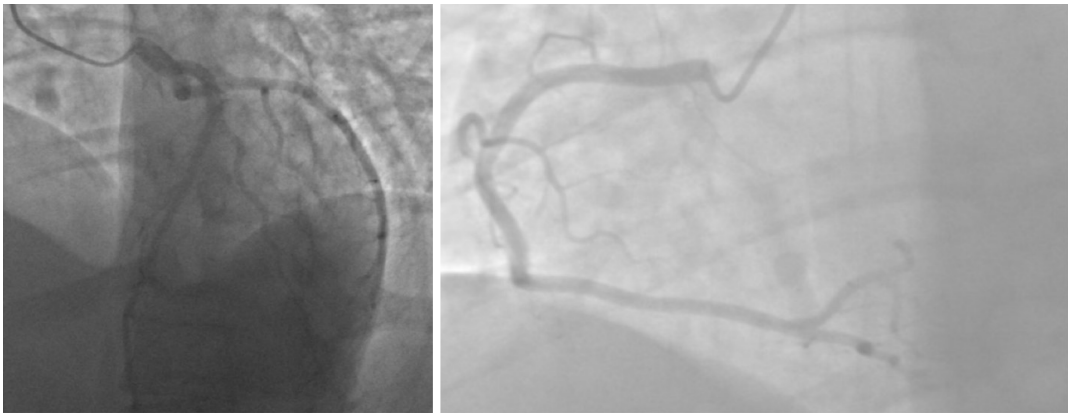


Figure 2 Cardiac catheterization projections showing normal coronaries.

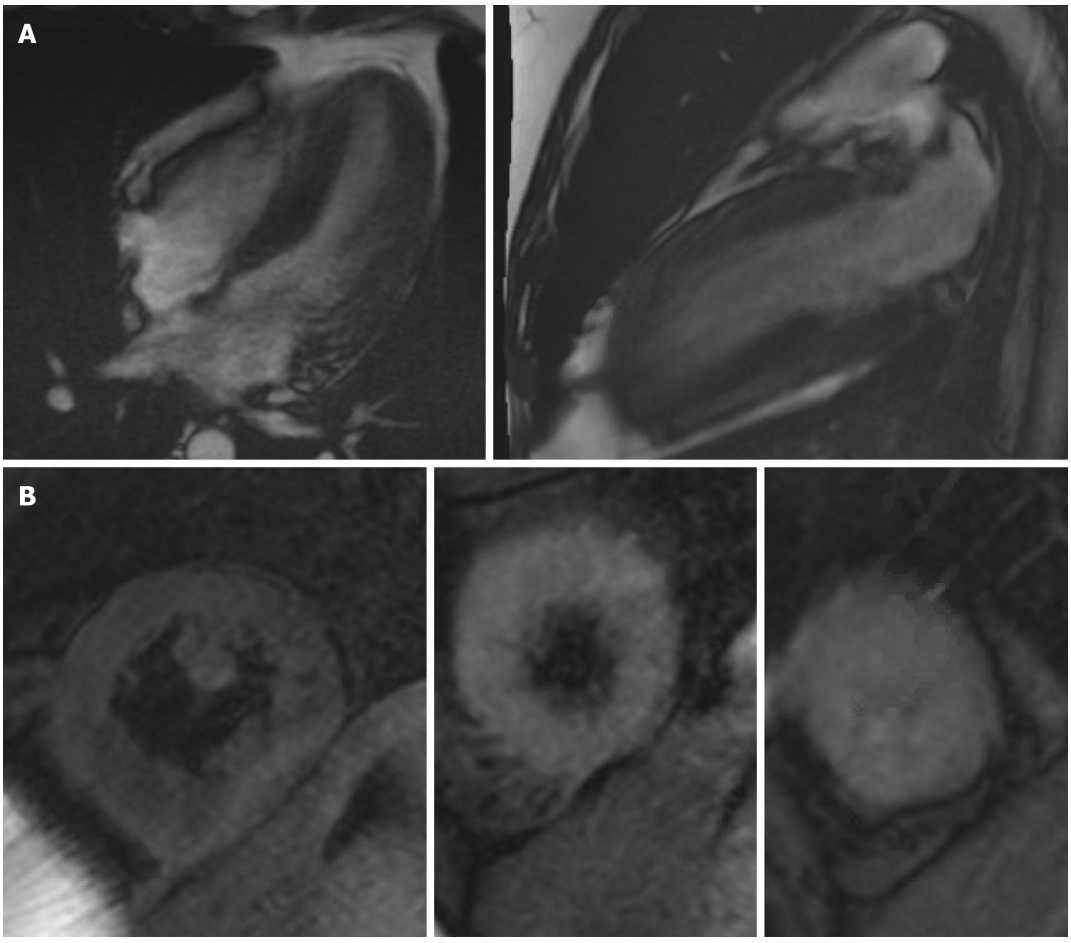


Figure 3 Cardiac magnetic resonance imaging. A: 4 chamber cine, 2 chamber cine showing EF of 40% with global hypokinesis; B: T2 Weighted images showing edema in mid and apical segments.

with severe reduction in EF on presentation, which improved prior to discharge. Cao *et al*[5] reported a case of NSTEMI without significant reduction in EF in a patient with air duster huffing. This patient was noted to have significant hepatic and renal injury, similar to our patient. Life threatening arrhythmias including ventricular fibrillation causing sudden cardiac death has been reported previously[6-8]. Toxic myopericarditis have been previously diagnosed in these patients[2]. Dinsfriend *et al*[2] reported a case of recurrent myopericarditis diagnosed in a patient with inhalant abuse with CMR. CMR showed edema and late gadolinium enhancement (LGE) in base and mid lateral wall and in the mid anterior wall.

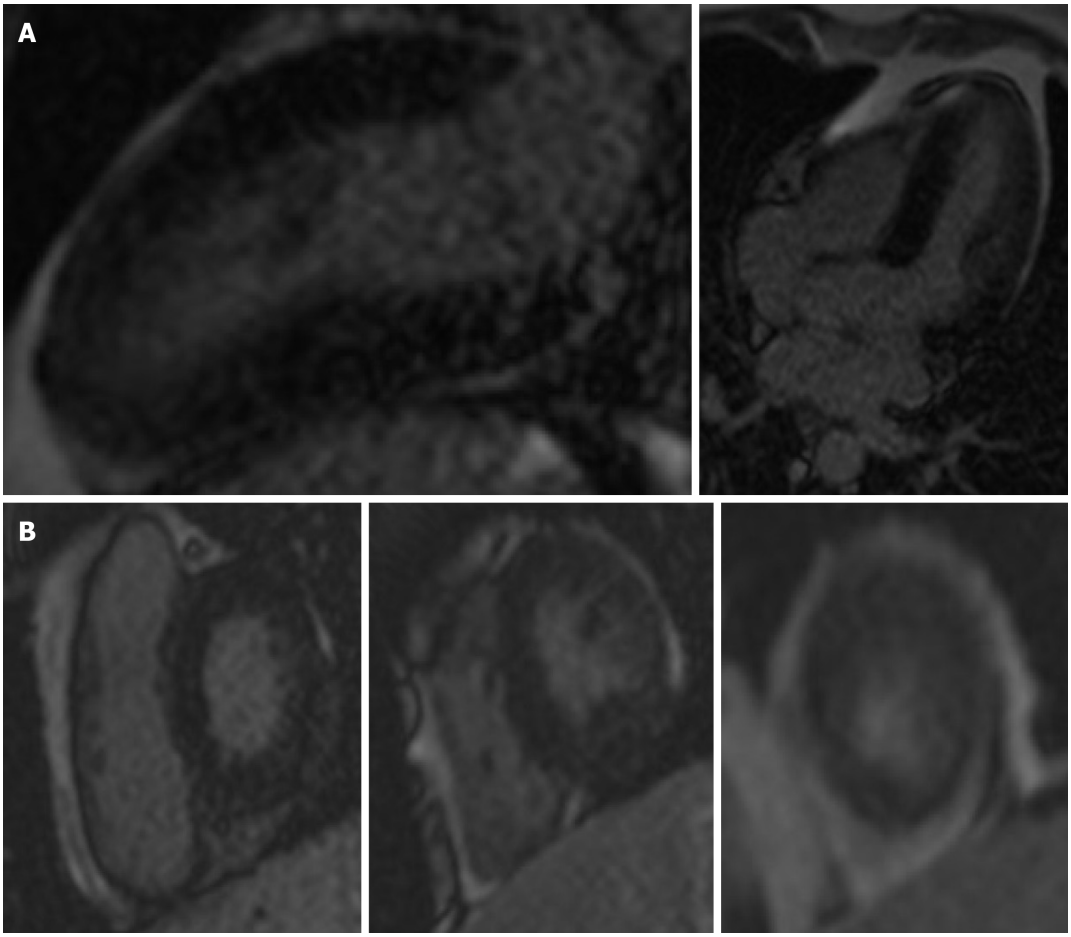


Figure 4 Cardiac magnetic resonance imaging. A: Absence of any late gadolinium enhancement in 4 chamber and 2 chamber; B: Absence of any late gadolinium enhancement in basal, mid and apical left ventricle on short axis.

Myopericarditis refers to an inflammatory process affecting the pericardium and myocardium[9]. Myopericarditis is diagnosed based on clinical features defining pericardial and myocardial involvement. Diagnosis of acute pericarditis involves presence of 2 or more of the 4 criteria: Pleuritic chest pain, pericardial friction rub, suggestive ECG changes (widespread ST segment elevation, PR depression) and new or worsening pericardial effusion[10]. Myocardial involvement is defined by elevated serum cardiac enzymes levels (creatine kinase-MB fraction, or troponin I or T), or new onset of focal or diffuse reduced LV function by echocardiography in the absence of evidence of any other causes[11]. CMR can be utilized to make diagnosis of myopericarditis. CMR diagnosis of myocarditis can be made based on the modified Lake Louise criteria[12]. The three diagnostic targets proposed using this criterion include edema, hyperemia and necrosis or scar. If CMR images indicate 2 out of 3 criteria, there is a high likelihood for acute myocarditis.

We report a case of patient with diffuse ST elevations, chest pain, decreased ejection on CMR in absence of any LGE. Our patient demonstrated early CMR finding in hydrocarbon toxicity manifested predominantly by low EF and edema in absence of LGE. Our patient had BMI of 37 with high low-density lipoprotein and positive family history of CAD. We ruled out coronary artery disease by doing cardiac catheterization however given the modest troponin rise and hydrocarbon toxicity, per recent European Society of Cardiology NSTEMI guidelines and class I recommendation on role of CMR in MINOCA, CMR was performed. CMR was useful in establishing presence of edema without any LGE[13]. This finding although nonspecific, points more towards, myocardial involvement. The absence of LGE provided excellent prognostic information[14]. CMR thus was helpful in diagnosis, prognosis and treatment in this case of inhalant toxicity.

CONCLUSION

Patients with inhalant abuse can have various cardiovascular manifestations. In patients with hydrocarbon toxicity with myocarditis, CMR can provide diagnosis, prognosticate the overall illness and give treatment options.

REFERENCES

1 **Howard MO**, Bowen SE, Garland EL, Perron BE, Vaughn MG. Inhalant use and inhalant use disorders in the United States. *Addict Sci Clin Pract* 2011; **6**: 18-31 [PMID: 22003419]

2 **Dinsfriend W**, Rao K, Matulevicius S. Inhalant-Abuse Myocarditis Diagnosed by Cardiac Magnetic Resonance. *Tex Heart Inst J* 2016; **43**: 246-248 [PMID: 27303242 DOI: 10.14503/THIJ-14-4919]

3 **Cates AL**, Cook MD. Severe Cardiomyopathy after Huffing Dust-Off™. *Case Rep Emerg Med* 2016; **2016**: 9204790 [PMID: 27313914 DOI: 10.1155/2016/9204790]

4 **Samson R**, Kado H, Chapman D. Huffing-induced cardiomyopathy: a case report. *Cardiovasc Toxicol* 2012; **12**: 90-92 [PMID: 21904803 DOI: 10.1007/s12012-011-9143-x]

5 **Cao SA**, Ray M, Klebanov N. Air Duster Inhalant Abuse Causing Non-ST Elevation Myocardial Infarction. *Cureus* 2020; **12**: e8402 [PMID: 32637281 DOI: 10.7759/cureus.8402]

6 **Sakai K**, Maruyama-Maebashi K, Takatsu A, Fukui K, Nagai T, Aoyagi M, Ochiai E, Iwadate K. Sudden death involving inhalation of 1,1-difluoroethane (HFC-152a) with spray cleaner: three case reports. *Forensic Sci Int* 2011; **206**: e58-e61 [PMID: 20875935 DOI: 10.1016/j.forsciint.2010.08.026]

7 **Avella J**, Wilson JC, Lehrer M. Fatal cardiac arrhythmia after repeated exposure to 1,1-difluoroethane (DFE). *Am J Forensic Med Pathol* 2006; **27**: 58-60 [PMID: 16501351 DOI: 10.1097/01.paf.0000202715.71009.0e]

8 **Ouali S**, Guermazi O, Guermazi F, Halima MB, Boudiche S, Khedher N, Meghaieth F, Farhati A, Larbi N, Mourali MS. Drug Abuse-Induced Cardiac Arrhythmias: Mechanisms and Management, Cardiac Arrhythmias, Umashankar Lakshmanadoss, IntechOpen 2018 [DOI: 10.5772/intechopen.76022]

9 **Caforio AL**, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Heliö T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013; **34**: 2636-2648, 2648a [PMID: 23824828 DOI: 10.1093/eurheartj/eht210]

10 **Imazio M**, Spodick DH, Brucato A, Trinchero R, Markel G, Adler Y. Diagnostic issues in the clinical management of pericarditis. *Int J Clin Pract* 2010; **64**: 1384-1392 [PMID: 20487049 DOI: 10.1111/j.1742-1241.2009.02178.x]

11 **Imazio M**, Trinchero R. Myopericarditis: Etiology, management, and prognosis. *Int J Cardiol* 2008; **127**: 17-26 [PMID: 18221804 DOI: 10.1016/j.ijcard.2007.10.053]

12 **Ferreira VM**, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P, Friedrich MG. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. *J Am Coll Cardiol* 2018; **72**: 3158-3176 [PMID: 30545455 DOI: 10.1016/j.jacc.2018.09.072]

13 **Ibanez B**, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; **39**: 119-177 [PMID: 28886621 DOI: 10.1093/eurheartj/ehx393]

14 **Mahrholdt H**, Greulich S. Prognosis in Myocarditis: Better Late Than (N)ever! *J Am Coll Cardiol* 2017; **70**: 1988-1990 [PMID: 29025555 DOI: 10.1016/j.jacc.2017.08.062]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com