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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.

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EDITORIAL

Role of artificial intelligence in cardiology

Rafael Vidal-Perez, Jose Manuel Vazquez-Rodriguez

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Abstract

Artificial intelligence (AI) is the process of having a computational program that can perform tasks of human intelligence by mimicking human thought processes. AI is a rapidly evolving transdisciplinary field which integrates many elements to develop algorithms that aim to simulate human intuition, decision-making, and object recognition. The overarching aims of AI in cardiovascular medicine are threefold: To optimize patient care, improve efficiency, and improve clinical outcomes. In cardiology, there has been a growth in the potential sources of new patient data, as well as advances in investigations and therapies, which position the field well to uniquely benefit from AI. In this editorial, we highlight some of the main research priorities currently and where the next steps are heading us.

Key Words: Artificial intelligence; Machine learning; Deep learning; Electrocardiography; Cardiac imaging

Core Tip: The main aims of artificial intelligence (AI) in cardiovascular medicine are triple: To improve patient care, increase efficiency, and enhance clinical outcomes. In cardiology, there has been a progress in the potential sources of new patient data, along with advances in diagnostic tests and therapies, which position this specialty well to uniquely gain from AI. For the prediction of the future probably, we must focus on the potential gaps and limitations of AI, knowing that elements will guide us on the new advances that we must expect in the years to come.

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INTRODUCTION

Artificial intelligence (AI) is the process of having a computational program that can execute tasks of human intelligence (*e.g.*, pattern recognition) by mirroring human thought processes[1]. AI is a transdisciplinary fast evolving field which puts together statistics, computer science, material science, neuroscience, psychology, computer hardware design, and mechanical engineering to create algorithms that aim to simulate human intuition, object recognition, and decision-making[2].

AI IN CARDIOLOGY

The main aims of AI in cardiovascular medicine are triple: To improve patient care, increase efficiency, and enhance clinical outcomes. In cardiology, there has been a progress in the potential sources of new data from patients, along with innovations in diagnostic tests and therapies, which position this specialty well to distinctively gain from AI[3].

The AI applications in cardiology are showing for instance that uncomplicated instruments like electrocardiography (ECG) might provide us a plenty of useful data, and AI converts the ECG data in a robust tool for prediction[4]. On the same side with more complexity, the use of AI tools in cardiovascular imaging into daily decision-making will improve care provision. AI has influenced every area of cardiovascular imaging in all stages from acquisition to reporting[5-7].

In cardiovascular medicine, the pioneer uses of AI were the creation of self-learning neural networks applied to ECG[8,9]. The next step on research has been the use of enormous sets of digital ECGs connected to detailed clinical data to create AI algorithms for the detection of silent (previously asymptomatic and undocumented) atrial fibrillation, left ventricular dysfunction, and hypertrophic cardiomyopathy, in addition to the ability to determinate a person's age, race, and sex, amongst other phenotypes. The population-level and daily clinical implications of AI-based ECG phenotyping keep up to arise, especially with the fast rise in the disposal of wearable and mobile ECG technologies[4]. These deep learning algorithms, once created, could be used in low-end machines like smartphones or wearables like smartwatches, providing great access to population. The first example has been recently published[10], applying an algorithm that detects the potential presence of left ventricular dysfunction through the ECG signal. This approach for sure is the future to spread this technology.

In the field of imaging, the progress of AI has been enormous in the last years, affecting all the phases of the diagnostic process. The advances have been bigger in the field of computed tomography imaging or magnetic resonance imaging[11], but the next step is echocardiography to generalize the value of AI in imaging[12], as shown in the review of Barry *et al*[11].

For the prediction of the future probably, we must focus on the potential gaps and limitations of AI, knowing that elements will guide us on the new advances that we must expect in the years to come. Currently, nearly all studies of AI in echocardiography for example are constructed with retrospective data and concentrated largely on the performance of AI in concrete diagnostic tasks, and these studies range from small and simple exploratory studies[13] to larger studies[14,15]. There is a need on prospective studies to show the feasibility of the AI algorithms in the cardiovascular field[15]. One more preoccupation is what to make when machine and man differ. The value of outstanding validation of the algorithms must, consequently, be emphasised. Clinical judgment by the physician will be crucial, with a dose of humbleness additionally, to guarantee that AI will be employed to assist and not substitute clinical decision-making.

CONCLUSION

A possible future lies in having this AI software implemented in low-end machines, and it would certainly help in the early detection and prevention of some cardiovascular diseases. We could affirm that for sure it will be essential that cardiovascular medicine specialists should keep the final step in the handling of the system, take care for the decisions, and have the power to modify algorithms in the situations that get mistaken.

FOOTNOTES

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REVIEW

Arrhythmic syncope: From diagnosis to management

Jaume Francisco Pascual, Pablo Jordan Marchite, Jesús Rodríguez Silva, Nuria Rivas Gándara

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Abstract

Syncope is a concerning symptom that affects a large proportion of patients. It can be related to a heterogeneous group of pathologies ranging from trivial causes to diseases with a high risk of sudden death. However, benign causes are the most frequent, and identifying high-risk patients with potentially severe etiologies is crucial to establish an accurate diagnosis, initiate effective therapy, and alter the prognosis. The term cardiac syncope refers to those episodes where the cause of the cerebral hypoperfusion is directly related to a cardiac disorder, while arrhythmic syncope is cardiac syncope specifically due to rhythm disorders. Indeed, arrhythmias are the most common cause of cardiac syncope. Both bradyarrhythmia and tachyarrhythmia can cause a sudden decrease in cardiac output and produce syncope. In this review, we summarized the main guidelines in the management of patients with syncope of presumed arrhythmic origin. Therefore, we presented a thorough approach to syncope work-up through different tests depending on the clinical characteristics of the patients, risk stratification, and the management of syncope in different scenarios such as structural heart disease and channelopathies.

Key Words: Syncope; Arrhythmia; Electrophysiological study; Loop recorder; Myocardiopathy; Atrioventricular conduction block

Core Tip: In this review, we summarized the most important and novel data on arrhythmic syncope, the value of the different diagnostic tests, the management, and the specific characteristics in some particular populations such as patients with cardiomyopathies or channelopathies. The review emphasized the importance of an appropriate stepwise approach work-up and intervention.

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INTRODUCTION

Definition and causes

Syncope is a total loss of consciousness (T-LOC) secondary to cerebral hypoperfusion, characterized by rapid onset, short duration, and complete spontaneous recovery[1]. It must be differentiated from other T-LOC that do not meet these characteristics, such as T-LOC of traumatic origin, some types of epilepsy, or certain psychiatric disorders. It should be noted that syncope is a symptom that encompasses a heterogeneous group of pathologies ranging from trivial causes to diseases with a high risk of sudden death. Therefore, it should not constitute a final diagnosis. It is of great importance to stratify the risk and try to determine the cause.

The term cardiac syncope refers to those episodes where the cause of the cerebral hypoperfusion is directly related to a cardiac disorder, while arrhythmic syncope refers to cardiac syncope specifically due to rhythm disorders. Indeed, arrhythmias are the most common cause of cardiac syncope (Table 1). Both bradyarrhythmia and tachyarrhythmia can cause a sudden decrease in cardiac output, causing the syncope. Non-arrhythmic causes of cardiac syncope are usually related to structural heart diseases with obstruction of outflow and/or inflow of blood. These obstructions can restrict increases in cardiac output on exercise rendering this insufficient to maintain the circulation. Severe aortic stenosis (AoS), hypertrophic cardiomyopathy (HCM), mitral stenosis, atrial myxoma, or severe pulmonary hypertension are some examples of conditions that can cause cardiac syncope *via* this mechanism.

Furthermore, myocardial ischemia and acute ischemic syndromes may also precipitate syncope through multiple mechanisms. It is important to highlight that most of these heart diseases can also be associated with arrhythmias or reflex syncope, and therefore it is often challenging to determine the main cause of syncope in structural cardiac syncope[1-5]. In other words, the mere presence of structural heart disease associated with obstruction does not allow us to conclude that the syncope is due to this mechanism. In many cases, it will be necessary to rule out other possible causes, especially arrhythmic ones.

Epidemiology

It is estimated that almost one in two people will suffer at least one syncopal episode in their lifetime[1,6]. It is a front-line health problem with a high impact on the health system, even though it is known that only a small proportion of patients with syncope seek medical attention. An epidemiological study carried out in the United States showed that the prevalence of patients with syncope in the community requiring medical attention is 9.5 per 100 inhabitants, and that 1 in 10 required hospital admission[7].

The incidence of the first syncopal episode is distributed with a bimodal curve, with a first peak in youth (between 10-30 years of age) and a second peak over 65 years of age. Cardiac syncope is the third most common cause of syncope after reflex and orthostatic hypotension (OH)[1,8,9]. In the emergency department (ED), cardiac syncope accounts for 5%-21% of syncope. In the Framingham cohort, the prevalence of syncope and long-term prognosis were analyzed[10]. The incidence of a first report of syncope was 6.2 per 1000 person-years. Reflex or vasovagal syncope is the most common cause in the general population. In the Framingham cohort it represented 21.0% of the cases, while cardiac syncope made up only 9.5%[10]. It is remarkable that the prevalence of cardiac syncope increases with advancing age[1,9-11]. Cardiac syncope causes less than 1% of syncope in youth (< 40 years)[12] and up to one-third in those over 60 years of age[10,12].

Prognosis

The prognosis of syncope is mostly related to the underlying cause and the presence of structural heart disease. While reflex syncope has an excellent prognosis in terms of survival, cardiac syncope is associated with an increased risk of mortality, especially if it is not identified and treated properly. Patients with reflex syncope have similar survival to patients without syncope[10], with a mortality rate between 4%-12% after 1 year (depending on the patient's age and comorbidities)[10,13-15]. By contrast, the 1-year mortality rate for cardiac syncope rises to 20%-30%[10,13-15]. In the Framingham cohort,

Table 1 Main cardiac causes of syncope

Cardiac syncope			
Arrhythmic causes	Bradyarrhythmia	Sick sinus syndrome/sinus node disfunction	
		Atrioventricular block	
	Tachyarrhythmia	Supraventricular tachycardia (AVNRT, AVRT, AT, fast AF, *etc.*)	
		Ventricular arrhythmias	Related to structural heart disease
			Channelopathies and inherited arrhythmia syndromes
Non-arrhythmic causes	Mechanical causes	Valvulopathies (aortic stenosis, mitral stenosis, *etc.*)	
		HCM	
		Atrial myxoma	
		Pulmonary emboli	
		Tamponade	
		Severe pulmonary hypertension	
Acute coronary syndrome			

AVNRT: Atrioventricular nodal re-entrant tachycardia; AVRT: Atrioventricular re-entrant tachycardia; HCM: Hypertrophic cardiomyopathy; AF: Atrial fibrillation; AT: Atrial tachycardia.

cardiac syncope was associated with a two-fold increase in the risk of death compared with those without a history of syncope, with an approximately 50% 5-year survival[10]. In this study, patients with syncope of unknown origin also had an increased risk of all-cause mortality compared with the general population [hazard ratio = 1.32, 95% confidence interval (CI): 1.09-1.60]. This observation was also made in other studies focused on specific populations[5]. This may be due to the fact that there are potentially serious causes for syncope left untreated due to a lack of diagnosis.

Importantly, in patients with syncope of unknown origin, the mere presence of structural cardiac abnormalities or the evidence of a conduction system disorder is associated with a poor prognosis, increasing the risk of death by a factor of more than five[1,9,16-19]. On the other hand, a structurally normal heart with a normal electrocardiogram (ECG) is usually associated with a benign etiology for syncope and a favorable prognosis[1,20-22].

DIAGNOSTIC APPROACH AND TEST

Initial evaluation, clinical history, physical examination, and ECG

T-LOC is a relatively common cause of presentation to the ED, and half of these episodes can be attributed to syncope[23]. However, it is important to distinguish it from other causes of T-LOC, to avoid unnecessary investigations in patients with benign causes, and to correctly detect and treat patients with cardiac syncope, which can lead to serious outcomes. The most common condition that can be confused with syncope is probably epilepsy. This confusion is an important phenomenon leading to misdiagnosis with rates ranging from 6%-67%[24]. This misdiagnosis contributes significantly to the numbers of patients with a questionable diagnosis of epilepsy and to those with apparently drug-resistant epilepsy. Syncope can be accompanied with urinary incontinence and/or muscular contractions that can resemble epileptic seizures, making it difficult to differentiate between the diagnoses. While in epilepsy muscular movements are generalized and appear from the beginning of the T-LOC and continue for a few minutes, syncope can also be associated with muscular contractions, which often tend to appear a few seconds after the collapse. They tend to be pleiomorphic and last only a short period of time. Some clinical findings have been suggested to differentiate seizures from convulsive syncope. Tongue biting and confusion on awakening are the most useful in predicting an epileptic origin[25]. In addition, clinical clues that should raise the suspicion for psychogenic pseudo-syncope include prolonged duration, eye closure during the episode, unusual triggers, no recognizable prodromes, and a high frequency of attacks[26].

Another common source of confusion in the ED is represented by falls, especially in the elderly population with non-witnessed T-LOC. On the one hand, elderly people with cognitive impairment and muscular weakness can present with falls as a manifestation of another illness, such as infections or

metabolic disorders[27]. On the other hand, these populations are usually treated with medications that can lower blood pressure (BP) and heart rate (HR) and tend to be dehydrated due to reduced water consumption. This combination of factors can promote orthostatic syncope. Additionally, in the elderly, there is a high prevalence of sinus node dysfunction, conduction disturbances, and structural heart disease, putting these patients at high risk of presenting with cardiac syncope[2]. For all these reasons, current guidelines recommend that repeated falls in elderly people without a reasonable explanation should be approached like unexplained syncope[1].

Once the syncope diagnosis has been established, special attention should be paid to determining the underlying cause. Syncope can be caused by three main different etiologies: Reflex mechanism (also known as neural-mediated syncope); OH; or cardiac syncope, which can be due to arrythmia or structural heart disease. The diagnostic approach should focus on detecting potential cardiac syncope, as it could be clinical manifestation of a primary cardiac disease with high risk of events.

Initial evaluation of any patient presenting with syncope should include three basic elements: (1) Careful history taking regarding the current and previous episodes (including eyewitness accounts); (2) Physical examination; and (3) ECG. Clinical history is probably the most important one, and it should be focused on past medical history, especially previous cardiac conditions, and symptoms related to the episode. Syncope during exertion or in a supine position accompanied by chest pain or palpitations have been described as high-risk factors and should raise the suspicion of cardiac syncope[28,29]. In addition, a family history of sudden cardiac death (SCD) at a young age or personal history of structural heart disease or coronary artery disease (CAD) have been considered high-risk factors. Physical examination does not usually show relevant findings, but it could reveal signs of heart failure or a systolic murmur suggesting structural heart disease. Performing an ECG is crucial, as it can show conduction disturbances, pathological Q waves, or repolarization abnormalities reflecting an underlying cardiac disease[15,30-32] (Figure 1). It is important to mention that every patient with syncope should have an ECG even if there is clear evidence that is a reflex syncope since there are some channelopathies such as long QT syndrome (LQTS) that can present with ventricular arrhythmias after emotional stimulus that can be confused with reflex syncope. Additionally, it has been described that patients with Brugada syndrome (BrS) are more prone to vasovagal syncope[33].

There are several scores developed for risk stratification according to clinical and ECG findings[34]. However, some of them have been tested with external validation cohorts showing poor sensitivity and specificity for detecting cardiac syncope, and they perform no better than clinician judgement at predicting short-term serious outcomes. Therefore, current guidelines do not recommend using them alone to make decisions in the ED. Most items included on these scales are those suggesting cardiac syncope, such as ECG abnormalities or signs or symptoms of structural heart disease.

Carotid sinus massage

Carotid sinus massage (CSM) consists of applying external pressure to the area of the neck where the carotid sinus is located and is indicated in patients over 40 with syncope. According to current clinical guidelines, carotid sinus hypersensitivity is defined by a sinus pause longer than 3 s or a drop in systolic BP (SBP) higher than 50 mmHg[1,9]. However, this condition is very common among older individuals with cardiovascular disease, even in the absence of syncope. To avoid misdiagnoses, it has been proposed that the diagnosis of carotid sinus syndrome requires reproduction of patient's symptoms and a sinus pause longer than 6 s or more or a drop in mean arterial pressure of 60 mmHg or more[35]. Patients fulfilling these criteria have been shown to have recurrent long pauses on monitoring and to respond well to cardiac pacing[36,37]. The worst complication of CSM is stroke, which is extremely uncommon.

Orthostatic challenge

Orthostatic challenge consists of measuring HR and BP changes between supine and upright positions. It is recommended to measure them during the first 3 min, but it can be extended to the first 10 min if there is a high suspicion of OH since retarded responses have been described[38]. OH is defined by a drop of more than 20 mmHg in SBP, or a drop of more than 10 mmHg of diastolic BP, or if SBP becomes lower than 90 mmHg, and always accompanied by symptoms[39]. OH is very common among elderly people, especially in patients taking anti-hypertensive medications and/or with autonomous nervous system diseases like Parkinson's disease or diabetes, and it represents an important cause of syncope in this population[2,40].

Tilt testing

Tilt testing is recommended in patients with suspected reflex syncope or autonomic failure, including delayed forms of OH or postural orthostatic tachycardia syndrome. The most frequently used protocol is the so called "Italian protocol," which includes a 20-min stabilization phase, followed by administration of sublingual nitroglycerin[41]. It is useful in patients with true reflex syncope, as it has been demonstrated that a positive cardioinhibitory response is highly predictive of asystolic spontaneous syncope[42]. However, it can also be positive in a high percentage of patients with unexplained syncope and even in patients with cardiac arrhythmic syncope. Therefore, it offers little diagnostic value in these

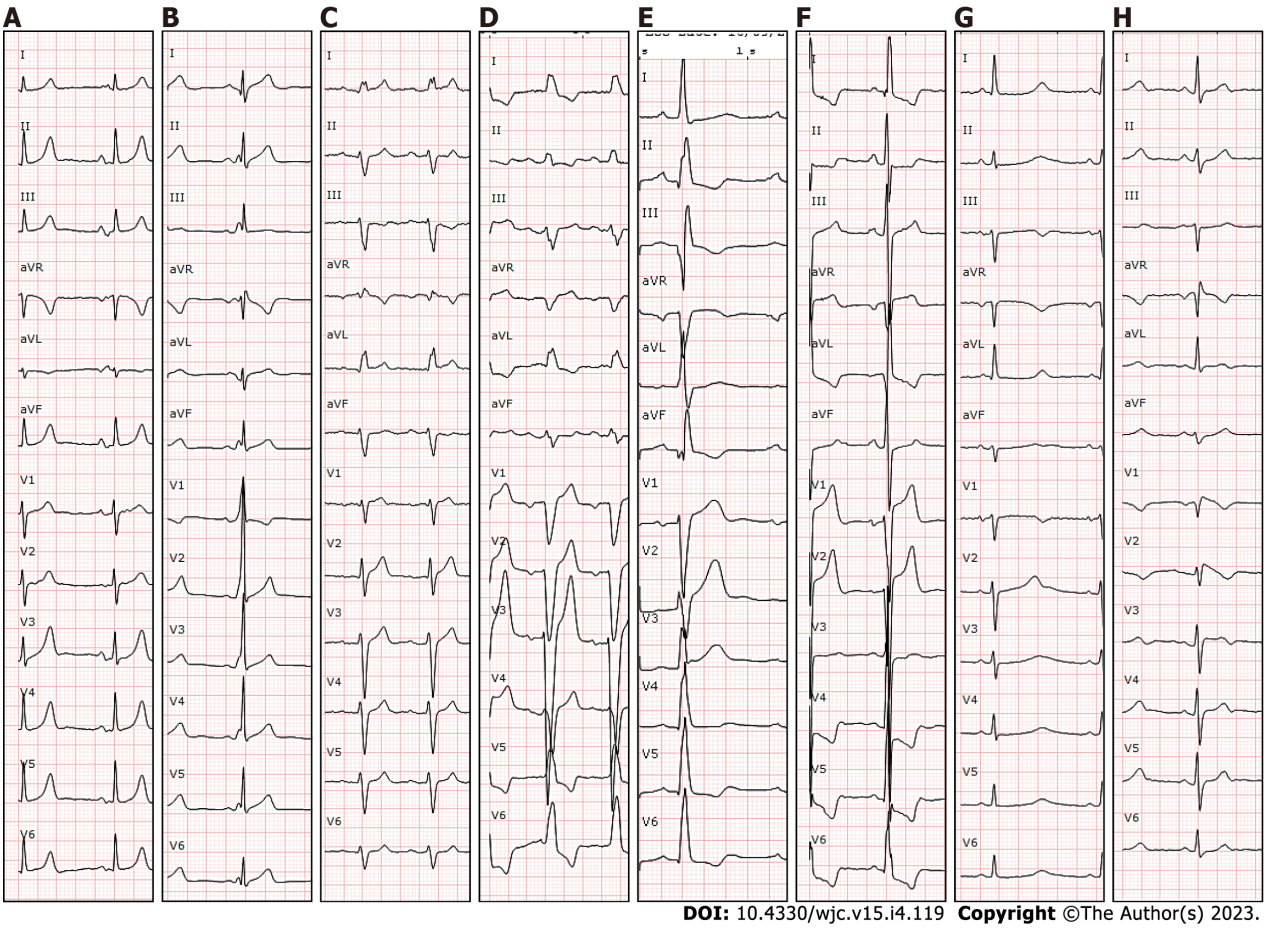

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Figure 1 Examples of pathological electrocardiogram that should lead to suspicion of an arrhythmic origin of the syncope. A: Bayes Syndrome (biphasic p wave in inferior leads compatible with interatrial block, which is related with atrial arrhythmias); B: Pre-excitation syndrome; C: Long PR interval and left anterior fascicular hemiblock; D: Left bundle branch block; E: Inferior necrosis (Q waves); F: Hypertrophic cardiomyopathy; G: Long QT syndrome; H: Brugada syndrome. Suspected supraventricular tachycardia (A and B), suspected atrioventricular block (C and D), suspected ventricular tachycardia (E and F), and suspected polymorphic ventricular tachycardia (G and H).

populations and should not be performed routinely[1]. It has also been tested to evaluate treatment effectiveness, showing little value in this aspect. Finally, in recent years it has been demonstrated that cardiac denervation of parasympathetic ganglia can be highly effective in reducing cardioinhibitory reflex syncope, a technique known as cardioneuroablation[43]. Tilt test might play a crucial role in detecting suitable patients for this promising procedure[44].

Electrophysiological study

According to current European Guidelines[1], electrophysiological study (EPS) is indicated in patients with syncope and bifascicular block (BFB) or previous myocardial infarction or other scar-related conditions, when the etiology remains unexplained after non-invasive evaluation. It could also be considered when syncope is preceded by palpitations or in patients with sinus bradycardia, when the rest of the study has been negative. However, in patients with normal ECG and no structural heart disease, EPS is of poor diagnostic value, and other options like home monitoring are more appropriate. Additionally, a positive EPS is strongly predictive of the origin of the previous syncope, but a negative result cannot exclude arrhythmic events in the future. Therefore, it has a low negative predictive value [45,46].

Sick sinus syndrome is a heterogenous disease where sinus node does not function normally and includes some different kinds of bradycardia such as sinus pauses or junctional rhythm. However, these conditions are relatively common in elderly people, and it is crucial to correlate the bradycardia episodes with the patient's symptoms. A sinus node recovery time (SNRT) longer than 1600 ms is considered abnormal [or corrected SNRT (cSNRT) longer than 525 ms] and has been correlated with sick sinus syndrome[45], but its prognostic value remains unclear. There are few data supporting the benefit of pacing in patients with an abnormal SNRT.

Patients with intraventricular conduction disturbances like BFB or nonspecific conduction disturbance with a QRS greater than 120 ms are at higher risk of arrhythmic events due to His-Purkinje system disease, and in this population paroxysmal atrioventricular block (AVB) is the most common

cause of syncope[46-48]. In these patients with syncope suspected to be related to bradycardia, an HV interval longer than 70 ms or the development of second or third-degree AVB during incremental atrial pacing or pharmacological stress identifies a group with a high risk of developing AVB in the future [49], and pacing is recommended. In addition, some studies have evaluated the relationship between ECG conduction disturbance and the results of EPS, showing that PR interval prolongation and/or BFB patterns make a positive result in EPS more likely rather than a right bundle branch block (RBBB) pattern alone[50] (Figure 2).

Another important part of the EPS in the syncope work-up is programmed ventricular stimulation. In patients with previous myocardial infarction and syncope, the induction of monomorphic sustained ventricular tachycardia (MSVT) is strongly predictive of the cause of syncope and should be managed as spontaneous MSVT[51,52]. In contrast, the induction of polymorphic ventricular tachycardia (PVT) or ventricular fibrillation (VF) is considered a less specific finding, especially with aggressive stimulation protocols[53]. However, induction of PVT or VF may play a role in risk stratification of specific populations such as patients with repaired tetralogy of fallot[19,54-56] or BrS[57,58].

Electrocardiographic cardiac monitoring

ECG cardiac monitoring is one of the cornerstones of the etiological diagnosis of arrhythmic syncope. In addition, there are several areas of interest other than unexplained syncope in which monitoring devices have been investigated[54,59-72]. The objective of ECG monitoring is to correlate the patient's symptoms with the electrocardiographic recordings to reach an objective diagnosis. For this reason, the diagnostic yield of ECG monitoring is primarily related to the duration of monitoring and the frequency of symptoms. Since syncope is often an infrequent event, a long-term monitoring device is usually needed to have a chance of recording a syncopal episode. Moreover, the identification of significant asymptomatic arrhythmias (such as advanced AV block) can be important for the diagnosis. Therefore, as a general rule, ECG monitoring is indicated when there is a high pre-test probability of identifying an arrhythmia associated with syncope and after appropriate risk stratification. The choice of monitoring modality depends on the frequency of events.

In recent years, ECG monitoring systems have incorporated many technical upgrades allowing for improvement in several of the limitations presented by the 24-hr Holter monitor. This evolution of the ECG recording systems include, among other aspects, smaller devices, greater memory capacity for long-term monitoring, better quality of records, or remote monitoring capacity[70] (Table 2).

The main current ECG monitoring devices available are the following:

(1) In-hospital telemetry. In-hospital monitoring should be mandatory in patients with high-risk clinical features, especially if the monitoring is applied immediately after syncope. A recent study that evaluates the optimal ECG monitoring duration of ED patients with syncope found that a serious underlying arrhythmia was often identified within the first 2 h of ED arrival for low-risk patients and within 6 h for medium-risk and high-risk patients[73]. The diagnostic yield of ECG monitoring varies from 2%-20% depending on the patients' characteristics[1,9,69,73-75].

(2) 24/48-hr Holter monitoring. Despite likely being the most frequently used device, the diagnostic yield is as low as 1%-2% in unselected patients due to its short monitoring time[69,70]. Even the newest devices with a longer recording capacity (7-14 d) offer a very limited diagnostic yield. In the opinion of the authors of this review, at the present time, the 24/48-hr Holter should only be considered in patients with daily or very frequent symptoms[69,70]. In different circumstances, other modalities offer not only a greater diagnostic yield but also better cost efficiency per diagnosis.

(3) Loop recorders. These allow for more prolonged monitoring since they do not store a continuous recording. Even though they continuously monitor the ECG, the device just stores a few minutes, which is subsequently overwritten with a newer recording. Only when the device is activated (be it *via* manual activation or through an automatic arrhythmia detection algorithm), it stores from a few minutes before the start of the event until its end in another part of the memory. These stored episodes are protected from overwriting and available for review. In this way, several minutes before activation are stored in the device memory, and the likelihood of recording the trace at the time of the syncope episode is relatively high. Within this category, we have differentiated between external and implantable devices.

External loop recorders. The device uses cutaneous electrodes to record, like the 24 hr Holter monitor. The patients themselves position the electrodes daily. Due to the characteristics of these devices, these systems tend to be worn by patients for no more than a few weeks (usually 3-4 wk, although there are reports of more prolonged periods of time[70,76]). For this reason, in the setting of syncope, the diagnostic yield is no greater than 10%. They are especially useful for the investigation of symptoms that occur every 2-3 wk. Significantly, it has been found in various studies that early recorder use increased the likelihood of diagnostic events during external ECG monitoring[73,77].

Implantable loop recorders (ILR). These are small devices that are implanted subcutaneously, usually in the left parasternal region. They have the disadvantage of being minimally invasive since the latest models have been made significantly smaller. However, these devices allow for a more prolonged continuous monitoring of up to 3 to 4 years, making them especially useful in patients with syncope. Numerous studies have evaluated the diagnostic value and the usefulness of ILRs for the work-up and the diagnostic yield increases up to 30%-50%[5,48,59,62,78-82]. In a meta-analysis of five randomized controlled trials, it was found that initial implantation of an ILR in the work-up provided a 3.7-fold

Table 2 Main advantages, limitations, and indications of the most commonly used devices for electrocardiogram cardiac monitoring in patients with syncope

	Advantages	Disadvantages	Main indications
24-hr holter	Continuous recording: 12 leads with good correlation with surface ECG; low economic cost per study	Discomfort for the patient; artifacts; maximum recording of 24-48 h (low diagnostic yield); high economic cost per diagnosis	Very frequent (daily) symptoms; in-hospital monitoring (if ECG-telemetry not available)
Skin patches	Continuous recording of 7-14 d; good tolerability for patients	Single-use and greater economic cost; only one lead[1]; low diagnostic yield	Frequent (weekly) symptoms
External loop recorders	Loop recording (includes beginning and end of arrhythmic event); monitoring for 4 wk; low economic cost per study	Patient discomfort; requires education from healthcare professional on how to correctly place the electrodes; relatively low diagnostic yield	Frequent (weekly-monthly) symptoms
Implantable loop recorders	Loop recording; up to 3-yr monitoring (good diagnostic yield); patient does not have to do anything; remote monitoring	Invasiveness and associated complications (infection, bleeding, *etc.*); individual economic cost; single lead	Infrequent symptoms; most useful in syncope

[1]There are devices with more leads.
ECG: Electrocardiogram.

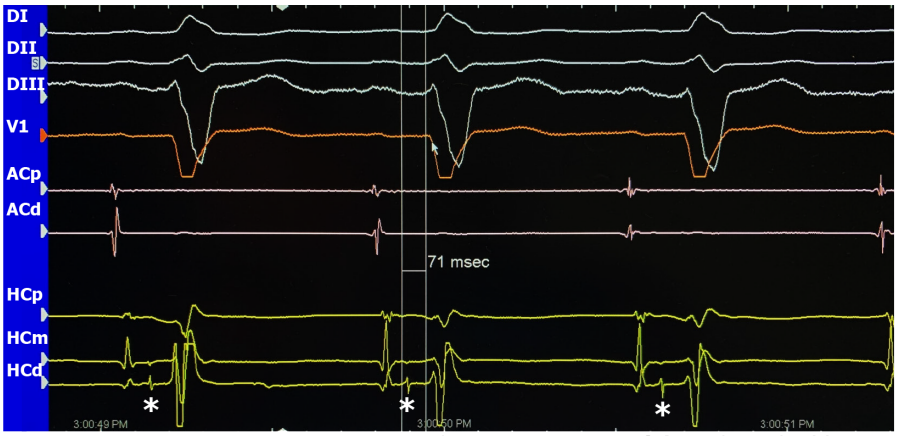

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Figure 2 Electrophysiological study of a patient with syncope and left bundle branch blocked. Surface electrocardiogram (DI, DII, DIII, V1) (top) and intracardiac electrograms at 100 mm/seg of an electrophysiological study to evaluate infra-Hisian conduction. A diagnostic catheter was placed in the right atrium (pink register: ACp and Acd) and in the His bundle zone (yellow register: HCp, HCm and HCd). *Indicates the His deflection. HV interval, from the onset of the His deflection to the onset of the QRS, is measured with the caliper (71 milliseconds in this case).

(95%CI: 2.7-5.0) increase in the relative probability of a diagnosis compared with the conventional strategy[1,71,83,84]. Different studies have also demonstrated that ILR was more cost-effective than the conventional strategy[69,81,83-85].

(4) Skin patches. They consist of patches of different materials, which adhere to the skin and contain electrodes to obtain one (the most common) or two ECG leads that allow for a continuous ECG recording for 7-30 d of monitoring. Diagnostic yield and limitations are similar to external loop recorders. It should be noted that some new wearable devices like intelligent watches or other ECG prospective intermittent event recorders, which are quite popular nowadays, are generally not useful for syncope workup. These devices start recording only when the patient activates them. They have the limitation of not allowing for the recording of the onset of the episodes, which is often important for diagnosis. Furthermore, if the patient activates the device after recovering from the syncopal episode, in most cases the possible rhythm disorder would have resolved.

Other tests

Autonomic function tests like the Valsalva maneuver or deep breathing test can be considered to diagnose autonomic disfunction, but there is weak evidence that these tests may be useful in patients with syncope. Echocardiography should be performed in all patients with suspected valvular or structural heart disease, as it can detect some conditions that could present with cardiac obstructive syncope (*i.e.*, AoS or cardiac tamponade). Exercise testing is especially useful in patients that have experienced syncope during or shortly after exertion. The main purpose of these tests is to rule out ventricular arrythmias related to CAD or exercise-induced advanced AVB, which is usually located distally to the AV node. Cardiac biomarkers such as high sensitivity troponin and natriuretic peptides

can be elevated in patients with syncope and have been associated with worse outcomes in some case series[86,87]. However, such determinations are highly non-specific and rarely contribute to a certain diagnosis, and they may indicate serious illness rather than myocardial ischemia or heart failure. Therefore, it remains unclear whether they should be determined on a routine basis[88].

RISK STRATIFICATION

Cardiac syncope is a life-threatening condition. By consequence, the main goal of risk stratification is to identify those low-risk patients with benign causes that can be discharged home and only require medical education from those high-risk patients with syncope likely related with cardiac arrythmias or structural heart disease who require hospital admission for further investigation. This initial evaluation is especially necessary in the ED, where most patients with syncope first consult (Table 3).

For this purpose, several risk scores have been developed. In 2016, the Canadian Syncope Risk Score [34] was published. They included 4030 patients who presented to EDs of three centers in Canada for syncope and analyzed the occurrence of serious events including death, myocardial infarction, arrythmia, structural heart disease, pulmonary embolism, serious bleeding, and procedural intervention within 30 d from admission. Finally, they included nine predictors: (1) Predisposition to vasovagal syncope; (2) Heart disease; (3) Any systolic pressure reading in the ED < 90 or > 180 mmHg; (4) Troponin level above 99th percentile for the normal population; (5) Abnormal QRS axis (< -30° or > 100°); (6) QRS duration longer than 130 ms; (7) QTc interval longer than 480 ms; (8) ED diagnosis of cardiac syncope; and (9) ED diagnosis of vasovagal syncope. Those items suggesting reflex syncope conferred negative points, and those suggesting cardiac syncope conferred positive points. Each patient obtained a final score, with higher scores representing a greater risk of serious events (-3-0 points are considered low risk, while 0-3 points and 4-11 points are considered high and very high risk, respectively).

Recently, the same authors have validated this risk score in another large cohort of 3819 patients, showing very good correlation. Setting a threshold score of -1 point, they achieved very good sensitivity (97.8%) but poor specificity (44.3%) for serious events[89]. In addition, another group of researchers validated the same score in a cohort of 2283 patients from three continents also showing good correlation and better performance when compared with another European risk score[90]. However, they also observed that a simplified model including only the clinical classification (vasovagal, cardiac, or other), also achieved a similar degree of discrimination with regard to the primary outcome, showing that some of the predictors included may have a secondary role.

There are some other scales previously developed, such as the San Francisco Syncope Rule[91] or the EGSY score[29]. Both have shown similar results with good sensitivity but poor specificity. However, lack of reproducibility and remarkable heterogeneity in study design, variables, and outcome definitions of primary studies have prevented widespread use of these tools in clinical practice[92]. Moreover, recently some authors compared the EGSY score with clinical judgement, both alone and in addition to cardiac biomarkers, showing that clinical judgement has the highest diagnostic accuracy[93].

In summary, multiple risk scores have shown good sensitivity but poor specificity for predicting short-term serious outcomes, and they performed no better than clinical judgement. Therefore, they should not be used in isolation for the purposes of decision-making. It is also worth mentioning that, apart from risk scores, some other tests such as EPS, cardiac magnetic resonance (CMR), or stress test may be useful for risk stratification in selected groups of patients, as is discussed above in other sections of this article.

ARRHYTHMIC SYNCOPE IN SPECIFIC POPULATIONS

As previously mentioned, syncope could be the presenting symptom of an impending sudden cardiac arrest or can be related to more benign conditions such as neuro-mediated syncope or OH. Thus, it is important to correctly stratify the risk of each patient. For this reason, we need to understand the clinical scenario in which syncope takes place. Patients without overt structural heart diseases are at a lower risk of subsequent cardiac complications. Nonetheless, we must also consider some inherited heart diseases, which are primarily electrical, known as channelopathies and that can take place themselves in the absence of structural heart disease. In the following paragraphs we summarized some of those heart conditions that are associated with a higher risk of ventricular arrhythmias and sudden cardiac arrest.

Structural heart disease

Ischemic heart disease: Patients with ischemic heart disease (IHD) are at a higher risk of ventricular arrhythmias. It is necessary to differentiate between three stages in the ischemic evolution: (1) Acute ongoing ischemia. A patient suffering from an acute myocardial infarction might have VF and ventricular tachycardia related to the ischemic myocardium[1,19,94,95]. The acute ischemia induces a dispersion of the repolarization that may produce polymorphic ventricular arrhythmias and VF in the

Table 3 High-risk features suggesting cardiac syncope

High-risk features
Past medical history
Previous myocardial infarction
Previous cardiovascular condition (*i.e.*, BrS, hypertrophic cardiomyopathy, Long QT syndrome, *etc.*)
Syncopal event
Syncope during exertion or in supine position
Syncope associated with chest pain, palpitations, breathless, or abdominal pain
Physical examination
Signs of heart failure
Cardiac murmur suggesting specific condition (*i.e.*, aortic stenosis)
Signs of shock
Electrocardiogram
Conduction disturbance (AV block, bundle branch block)
Pathological Q waves
Long QT interval
Pre-excitation syndrome
Negative T waves

BrS: Brugada syndrome; AV: Atrio-ventricular.

acute setting. In the same way, some patients might present with monomorphic ventricular arrhythmias during acute myocardial infarction, in which a macro re-entrant circuit involving the ischemic tissue is a more probable mechanism. This latter mechanism is much less frequent than the former[94]; (2) In the subacute phase of ischemia, comprising hours to days after the ischemic event, Purkinje-related ectopia is a frequent mechanism for VF and acute cardiac arrest. The premature ventricular complexes are characterized by their very short coupling intervals and by the presence of a normal QT interval. It is believed that the ischemia induces an abnormal calcium release to the cytosol of Purkinje cells, which causes such early post depolarization[94]; and (3) In the chronic setting, which accounts for most patients with syncope and IHD, a frequent mechanism is a ventricular arrhythmia due to macro re-entry in well-established ventricular scars[1,19]. The risk of ventricular arrhythmias is much higher among those patients with IHD with low ventricular ejection fraction[1,19,96].

Ventricular arrhythmias should be suspected in patients with syncope and IHD[1,6,9,97]. If the patient has a left ventricle ejection fraction (LVEF) of < 35% despite optimal medical treatment, an implantable cardiac defibrillator (ICD) is indicated[18,19,98]. These patients have solid evidence of high arrhythmic risk independently of the invasive risk stratification, and an ICD implantation is strongly indicated even if the etiology of the syncope is treated subsequently. This recommendation is strongly supported by large randomized clinical trials (SCD-HeFT, MADIT-II)[99,100] and class 1A recommendation in the 2022 European Society of Cardiology (ESC) guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD, the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[101], and the 2019 Guidelines on Chronic Coronary Syndromes[102].

When the cause of the syncope remains unknown after an initial evaluation, and there is no apparent direct indication for ICD, an EPS with programmed ventricular stimulation should be performed. If MSVT are induced, the implantation of an ICD should be considered. The induction of polymorphic ventricular arrhythmias or VF has not been consistently related with ventricular arrhythmias or sudden cardiac arrest and no recommendation about ICD implantation can be made in this scenario. Despite the absence of solid evidence, the 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[19] recommends performing an EPS in patients with syncope and previous ST elevation myocardial infarction with a class IC recommendation. It is not clear if this recommendation is applicable to patients with a history of coronary revascularization without infarction or in the absence of late gadolinium enhancement in the CMR, and further studies are needed.

As we previously mentioned, the induction of a monomorphic VT in a patient with previous myocardial infarction presenting with syncope is an indication for an ICD implantation. On the other hand, the induction of VF has been traditionally considered as a non-specific result as these patients

appear to have a similar prognosis as patients without any ventricular arrhythmia induction. Brugada *et al*[103] demonstrated that non-sustained PVT and VF are nonspecific responses to an aggressive stimulation protocol including three to four extra stimuli. Brodsky *et al*[104], presenting the results of the AVID trial, were not able to demonstrate that the induction of VF or fast VT (rate > 200 bpm) is related with death or ventricular arrhythmia recurrence (P = 0.07), but the induction of slow VTs (HR < 200 bpm) was independently related with recurrences as monomorphic VT.

Mittal *et al*[53] also evaluated the prognosis of ventricular arrhythmia induction in a cohort of 118 consecutive patients with CAD presenting with syncope. The mean LVEF of their cohort was 42% ± 13%. VF was the only arrhythmia induced in 20 patients (17% of the cohort). There was a survival rate of 89% and 81% at 1 year and 2 years consecutively in the entire cohort, and there were no differences between patients with VF induction or no induced arrhythmia (P = 0.39). By contrast, Link *et al*[105] found contradictory results in their cohort where they followed 274 consecutive patients with CAD and syncope or presyncope. The risk of arrhythmia occurrence was evaluated at the time of presentation with syncope by an EPS. VF was induced in 23 patients (8%) and ventricular flutter (monomorphic tachycardia with CL < 230 ms) in 24 patients (9%). Overall, 41 patients (15% of the cohort) were inducible for monomorphic ventricular tachycardias. After a follow-up of 37 ± 25 mo, 34 patients had ventricular arrhythmias. VF was induced in the initial EPS in 3 out of 23 patients (13% of this group) and in ventricular flutter in 7 out of 24 patients (30% of this group). Considering these results together, the induction of VF/ventricular flutter was predictive of ventricular arrhythmias during follow-up ($P \leq$ 0.001 *vs* non-inducible patients)[105].

Nonetheless, the 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[19] only have clear recommendations for the induction of sustained monomorphic ventricular tachycardia. Thus, an ICD is recommended in patients with CAD and unexplained syncope with MSVT induced during EPS with a IIa B level of recommendation. The induction of polymorphic VT, VF, or non-sustained ventricular arrhythmias are considered non-specific responses, and considering the absence of solid evidence, no specific recommendations can be made.

Despite the fact that VT should be ruled out in patients with IHD, many other causes may be present in this set of patients[3,9,106,107]. In fact, VT is not the most common cause of syncope. Patients with IHD have some factors that predispose them to other causes. For example, they are often on different hypotensive drugs that predispose to OH or reflex syncope[2]. Also, some conduction disturbances are more frequent in patients with IHD[30,48,50]. In the presence of conduction disturbances on the ECG, advanced AV block is a common cause of syncope[46,50,108]. Importantly, if the EPS is negative, VT is unlikely to be the cause of syncope, with reflex and OH syncope being the most probable etiologies[3,107].

Mid-range left ventricular dysfunction

Patients with left ventricular disfunction are at high risk of cardiac and arrhythmic syncope[6]. In observational studies, unexplained syncope in this population has been associated with an increased risk of sudden death[1,9,79,109,110], although the evidence for the benefit of an ICD is limited. In general, the direct implantation of an ICD is indicated in those patients who fulfil the primary prevention criteria (NYHA class II-III heart failure, with LVEF < 35% on optimized pharmacological therapy). The evidence regarding the management of syncope in patients with mid-range LVEF is even more scant. Current ESC syncope clinical practice guidelines[1], which are similar to ACC/AHA/HRS [9] guidelines, suggest a work-up in line with general recommendations and state that the implantation of an ICD should be considered in patients with systolic dysfunction and unexplained syncope. The implantation of a cardiac monitor (ICM) is an alternative that may be considered in patients with recurrent episodes. Newly published ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[19] suggest a conservative strategy based on risk stratification and ICM implantation in patients with no other direct indication for an ICD.

Our group has recently investigated a similar strategy based on a stepwise protocol[79]. In summary, the diagnostic work-up for syncope in this population is based on three steps. Step 1 consists of the initial assessment in the ED. In a systematic manner, a clinical history and physical examination are performed, including testing for OH and CSM (if not contraindicated), general bloodwork, chest x-ray, and 12-lead ECG, as well as 12-24-h telemetry monitoring and a transthoracic echocardiogram. In cases where no certain or highly probable diagnosis is reached, it is considered unexplained syncope, and the patient is admitted to the hospital. Step 2 involves the hospital admission with continuous ECG monitoring and carrying out an invasive EPS if the following criteria are fulfilled: (1) Presence of conduction disorder on baseline ECG [1st degree AV block, Mobitz type 1 s degree AV block, complete RBBB or left bundle branch block (LBBB), BFB, left anterior or posterior fascicular block]; (2) Clinical, electrocardiographic, and/or imaging evidence of myocardial scar (history of myocardial infarction, presence of Q waves on surface ECG, presence of late enhancement on cardiac magnetic resonance imaging, and/or presence of necrosis on myocardial perfusion single-photon emission computed tomography scan); and (3) History of palpitations prior to the syncopal episode. If these criteria are not fulfilled, the EPS is not carried out, and the patient moves on to Step 3. Step 3 involves implanting an implantable cardiac monitor with subsequent clinical monitoring (Figure 3).

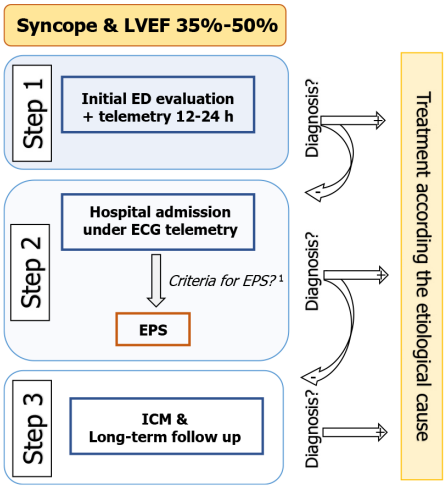

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Figure 3 Proposed algorithm for the management of syncope in patients with mid-range left ventricular dysfunction. [1]Criteria for electrophysiological study: (1) Presence of conduction disorder on baseline electrocardiogram (1st degree atrioventricular block or Mobitz 1 s degree block, complete right or left bundle branch block, left anterior or posterior hemiblock); (2) Evidence of myocardial scar; and (3) Palpitations prior to the syncopal episode. ECG: Electrocardiogram; ED: Emergency department; LVEF: Left ventricle ejection fraction; EPS: Electrophysiological study; ICM: Implantable cardiac monitor.

In a recent published study that evaluated patients with unexplained syncope (excluding patients diagnosed in step 1), it was found that the application of this systematic protocol had a high diagnostic yield with a low rate of sudden death[79]. The overall diagnostic yield with both steps was 68.3%. Of note, the most common cause was arrhythmia. In 60 patients (57.7% of the total patients and 84.5% of the total diagnoses), a rhythm disorder was identified as the cause of the syncopal episode, with a high proportion of bradycardias, mostly due to AV block (47 patients, 45.2%). VT was the second most frequent cause, although it was significantly less common (9.6%). Most of the arrhythmias, be they AV block or VT, were able to be diagnosed in step 2. Another key finding of the study was that the diagnoses reached allowed treatment to be effectively guided. The sudden or unknown cause mortality rate of 0.9 per 100 person-years was comparable with general mortality rates published in the literature in patients with mid-range left ventricular dysfunction without syncope[106,111-113]. The findings of this study, in line with others on patients with structural heart disease[3,107,114], suggest that a stepwise diagnostic strategy and prolonged monitoring may be a safe and effective management alternative, reducing the number of patients requiring an ICD.

HCM

The hallmark of HCM is the abnormal increase of left ventricular wall thickness unrelated to abnormal loading conditions such as high BP, valvular heart diseases, or congenital heart disease. At the histopathological level, HCM is characterized by an increase in the size of myocardial cells and disordered myocardial cell organization with interstitial fibrosis that may predispose patients to suffer from ventricular arrhythmias. HCM carries a mortality rate that ranges from 1%-2%. New data from cohorts of patients with ICDs suggest that the mortality rate might be even lower (about 0.8%) and that it is related with several risk factors summarized in the HCM-SCD score[115]. The eight variables included in the risk score are: Age, LV wall thickness, left atrial size, left ventricular outflow tract (LVOT) gradient, nonsustained ventricular tachycardia, unexplained syncope, and family history of SCD.

HCM patients may have different syncope etiologies such as: Hypovolemia, conduction system disorders, sustained ventricular tachycardia, LVOT obstruction, and abnormal vascular reflexes, *etc*[116-118]. After ruling out non-cardiogenic and neural-mediated causes, arrhythmic syncope is one of the more worrisome causes for syncope in those patients. Patients with unexplained syncope should be tested with at least 24-hr Holter recording and exercise time-to-exhaustion to rule out LVOT obstruction on exertion. After an extensive evaluation of causes of syncope in those patients without clear diagnosis, an ILR should be implanted[1,117]. Routine tilt table testing in patients with HCM may be associated with an unacceptable number of false positives, and its use should be limited to selected cases[117].

Syncope of unknown origin is included in the risk score with an independent hazard ratio of 2.05 (1.48, 2.82; $P < 0.001$)[115]. Patients with intermediate-risk and low-risk clinical profiles should be evaluated for additional risk factors not included in the score, following 2022 ESC guidelines[19]. LV systolic dysfunction, apical aneurysm, > 15% of LV mass with late gadolinium enhancement on CMR, and several sarcomeric mutations have demonstrated a higher risk of ventricular arrhythmias in different studies and should be considered when evaluating the risk profile of a given patient[117,118]. The risk of ventricular arrhythmias is nonetheless dynamic and needs to be reassessed at every clinical

visit. Those patients with syncope and a high-risk clinical profile (SCD HCM risk score > 6%) or intermediate risk and other risk factors should be considered for ICD implantation (IIa B level of recommendation)[116], and those with intermediate risk (SCD HCM risk score 4%-6%) may be considered for ICD implantation (IIb B level of recommendation)[19].

Valvulopathies

A hemodynamic origin of syncope should be suspected in patients with valvular heart disease. However, other causes are possible[1,5,9,119-123]. The valvular heart disease with the highest risk of syncope is AoS[5,124,125]. Syncope is more frequent in severe stages of AoS but can occur in patients with moderate severity when suffering from other hemodynamic disturbances. Pharmacologic hypotension and atrial arrhythmias are also a frequent cause of syncope in patients with moderate and severe AoS[5,72,121,126]. In a recent study performed by our group in a cohort of patients with severe AoS and syncope, we observed that in 65% of the patients, the stenosis per se was initially identified as the likely cause of syncope, but later only 17.5% of the total cohort of patients was confirmed as having AoS as their final diagnosis. Conduction system disease and vasovagal etiologies were a more frequent cause of syncope in this population[5]. Importantly, syncope in the setting of a severe AoS has been suggested as having prognostic implications.

In a study published in 2019, these patients had a greater risk of mortality after aortic valve replacement in both the short-term (hazard ratio = 2.27; 95%CI: 1.04-4.95) and the long-term (hazard ratio = 2.11; 95%CI: 1.39-3.21) compared with patients who did not have syncope[127]. Although patients with syncope had somewhat different characteristics on echocardiography (smaller aortic valve area, smaller cardiac chambers, and lower ejection volumes), we believe that this rise in mortality was also partially due to the presence of other causes for the syncope such as underdiagnosed arrhythmias. In the cohort studied by Francisco-Pascual *et al*[5], those patients in whom it was not possible to precisely determine the cause of the syncope had more than triple short-term and medium-term mortality.

Furthermore, several studies have observed a high incidence of syncope and SCD after transcatheter aortic valve replacement (TAVR)[66,67,72,126,128]. It is theorized that induced conduction system delays after TAVR may predispose patients to suffer from electrical re-entry within the His-Purkinje system favoring a rare type of cardiac arrhythmia called bundle-branch re-entry in which the electrical impulse circulates between both branches of the conduction system with a slight delay often happening in the left bundle in the retrograde arm of the tachycardia. This arrhythmia is very rapid and frequently compromises the patient hemodynamically producing syncope or sudden cardiac arrest. The real incidence of this problem is unknown, but it needs to be kept in mind when evaluating a patient after a TAVR with some degree of conduction system delay.

Another significant but infrequent cause of syncope in patients with valvular heart disease is the presence of VF in patients with mitral valve prolapse, which has been named "the malignant mitral valve prolapse syndrome". In a recent meta-analysis carried out by Nalliah *et al*[129], they reported the population prevalence of mitral valve prolapse (MVP) of 1.2% and the prevalence of MVP in SCD autopsies of 11.7%. Nonetheless an incidence of 0.14 SCD events per 100 patient-years in the community MVP cohort, deserves an in-depth investigation of other risk factors for ventricular arrhythmias such as the presence of myocardial fibrosis or frequent complex ventricular ectopy, as has been proposed.

Conduction disturbances

In patients with conduction disturbances and syncope, the presence of bradyarrhythmia is always a concern although other causes may also be present. For example, in a recent cohort of 503 patients with unexplained syncope and BBB, arrhythmic syncope was identified in 57.9% patients, mostly secondary to AV block (51.3%). However, 12% were due to reflex syncope or an OH mechanism, 1.4% were due to ventricular tachycardia, and 10% were secondary to other causes[108].

The optimal management of patients with unexplained syncope and BBB is still controversial[1,9,46-48,130,131]. In fact, the 2017 ACC/AHA Guidelines[9] suggest empirical direct pacemaker implantation after exclusion of other syncope etiologies, while ESC guidelines[1] recommend opting for a stepwise approach. The systematic stepwise approach (that includes an EPS and long-term follow-up with an ICM) was initially evaluated in the B4 study[47]. This study found that the diagnostic approach is safe and achieves a high rate of etiological diagnosis allowing for the selection of specific treatment and avoiding the implantation of unnecessary pacemakers. The results of the B4 study have been confirmed by several subsequent studies, some of them with a relatively high number of patients and long-term follow-up[80,108,132-134].

On the other hand, the strategy of direct pacemaker implantation was recently evaluated in the SPRITELY trial. This study randomized 105 patients older than 50 years with BFB (41 LBBB and 74 RBBB plus left fascicular block) and at least one syncope in the previous year to receive ICM or empirical pacemaker implantation. In the 33-mo follow-up period, the 57 patients randomized to the pacemaker arm showed a lower primary composite endpoint (cardiovascular death, syncope, bradycardia resulting in an intervention, and device complications) than the ILR arm; [20 (35%) *vs* 44 (76%); $P < 0.0001$]. However, the presence of syncope during follow-up was similar in both groups (29% *vs* 26%; $P = 0.95$)[135].

It must be highlighted that in the SPRITELY trial, EPS was not systematically carried out before ICM implantation, and therefore it cannot be considered as a direct comparison with the stepwise approach. Similar findings were previously found in the PRESS study[136], where patients were randomized to pacemaker in pacing mode (DDD at 60 bpm) or backup pacing mode (drug-drug interaction at 30 bpm). The primary endpoint of this study was a composite endpoint of syncope, presyncope with device intervention, or documented bradycardia and AVB, and patients allocated to active pacing had a significant reduction of this composite endpoint. However, when only syncope recurrences were analyzed separately, there were no differences between the two groups. Furthermore, there are some studies that have analyzed the recurrence rate in patients with syncope and BBB, in whom a pacemaker has been implanted, showing that syncope recurrence is higher in those patients in whom a pacemaker was implanted empirically than in those in whom a pacemaker was implanted after a positive EPS or a documented AVB[137,138].

With the available evidence, the authors of this review continue to support the stepwise approach to manage these patients. Nevertheless, direct pacemaker implantation should be considered in some patients, especially in elderly or frail patients after an individual risk/benefit assessment (Figure 4). According to the newest 2021 ESC guidelines for cardiac pacing and resynchronization[18], in patients with sinus bradycardia and syncope of unclear origin after a thorough work-up, an exercise test to evaluate chronotropic competence and an EPS to evaluate for sinus node overdrive suppression pathologic responses might be indicated. cSNRT (basal cycle length; normal value 525 ms) has demonstrated good predictive value in patients with sinus bradycardia despite the presence of symptoms (overall accuracy of cSNRT in predicting serious sinus node disease regardless of the presence of symptoms: 90%, 100% in the presence of symptoms; sensitivity of the test: 66%). Patients presenting with a ventricular rate below 40 bpm have a 70% probability of having an abnormal cSNRT. In patients with a basal HR of 50 to 55 bpm, the probability of finding an abnormal response in cSNRT test is 24%[139]. However, it should be noted that pacing patients with sinus node dysfunction has not demonstrated improved survival so far[18,131].

EPS diagnostic yield is higher in patients with sinus bradycardia or BFB and structural heart disease and is lower in patients with a normal ECG and no structural heart disease[46,50]. Thus, it is preferable to perform EPS in patients with higher pretest probability and implant a loop recorder in those with lower pretest probability. Patients with first degree AV block and second degree type I (Wenckebach) block presenting with syncope without a firm diagnosis after extensive study should be offered an EPS. The presence of second degree type II block or third degree AVB constitutes a clear indication for cardiac pacing. Patients with 2:1 AV block can be evaluated by increasing the sinus node rate (atropine 1 mg or exercise test). If the degree of block increases by increasing of the sinus rate, an infra-Hisian origin must be suspected, and pacemaker implantation should be considered. Patients with syncope and BFB represent a group whose risk of syncope is especially difficult to stratify. Therefore, in patients with BFB and syncope of unknown origin an EPS should be performed.

In the presence of an HV interval longer than 70 ms (basal) or > 100 ms after infusion of 2 mg/kg of flecainide (or other Vaughan Williams class I antiarrhythmic drugs), cardiac pacing should be considered[140]. The absence of high-risk characteristics in the EPS of patients with syncope and BBB or BFB does not preclude the development of paroxysmal AV block, and an ILR needs to be considered. Roca-Luque *et al*[50] demonstrated that the most predictive combination of conduction disorders were LBBB or RBBB + long PR interval + left fascicular block [odds ratio = 4.5 (1.06-20.01); $P < 0.042$], LBBB + prolonged PR interval [5.2 (1.52-17.74); $P < 0.001$], and RBBB + prolonged PR interval [3.8 (1.7-8.7); $P < 0.001$] in their 271 patient cohort in 2018.

Channelopathies and inherited arrhythmia syndromes

Cardiac channelopathies are a group of diseases in which a mutation of different regulatory proteins of the action potential may predispose a patient to suffer from ventricular arrhythmias and SCD. Syncopal episodes in these patients might be due to non-sustained polymorphic VT or VF. In this section, we discussed the implications of the presence of syncope in patients with BrS, LQTS, and catecholaminergic PVT.

BrS

BrS was first described by the Brugada *et al*[141] in their elegant paper published in JACC in 1992. In their first publication of this syndrome, they described a cohort of 8 patients with RBBB and ST elevation in leads V1-V2-3 that suffered from aborted episodes of SCD[142].

Even though the mechanism of the electrical dysfunction leading to VF is not completely understood, it is believed that an increase in early repolarizing currents (Ito current) or a reduction in depolarizing currents (INaT) may lead to a phase II dispersion of repolarization and early post-depolarizations, which might generate phase II re-entries, possibly triggering VF. This electrical disorder seems to be more accentuated in the anterior part of the right ventricular outflow tract obstruction, where Ito current has been shown to be higher than in other heart sites. This latter observation might explain the isolated ST elevation in precordial leads and the effectiveness of ablation on the right ventricular outflow tract in patients with BrS and arrhythmic storm[143].

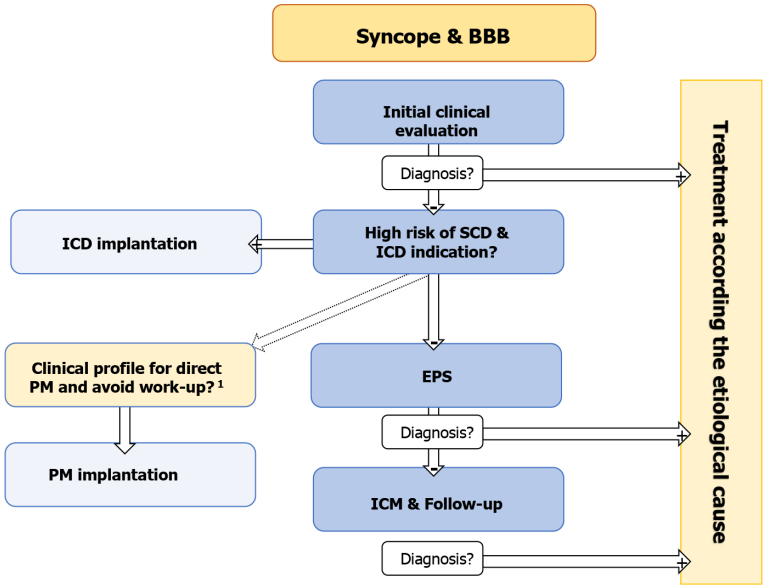

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Figure 4 Proposed algorithm for the management of syncope in patients with bundle branch block. [1]Direct pacemaker implantation should be considered in some patients, especially in elderly or frail patients after an individual risk/benefit assessment. SCD: Sudden cardiac death; BBB: Bundle branch block; EPS: Electrophysiological study; ICD: Implantable cardiac defibrillator; PM: Pacemaker; ICM: Implantable cardiac monitor.

Patients with BrS pattern on ECG and syncope have a four-fold risk of sudden cardiac arrest, representing a 1.5% annual risk of sudden cardiac arrest. When the syncope cannot be classified as neuromediated or a cardiac origin is a possibility, ICD implantation should be considered[19]. Therefore, it is usually not necessary to perform an EPS to stratify the risk in the presence of unexplained syncope, as it is assumed to be high risk.

However, patients with sodium channel dysfunction may exhibit conduction system dysfunction as well. It is not infrequent for patients with those specific mutations to exhibit sinus bradycardia and/or BBB. Furthermore, reflex syncope is also frequent in young patients with BrS[144]. For these reasons, some authors have also suggested a more conservative approach, where implantation of a loop recorder can be considered in BrS patients with an unexplained syncope (not clearly cardiac) and without other indications for an ICD[19,145].

LQTS

The hallmark of the LQTS is an inadequately prolonged corrected QT interval, measured from the beginning of the QRS complex to the point at which the descending limb of the T wave crosses the isoelectric baseline of the ECG. The measure is frequently performed in leads II or V5-6 where the T wave and the isoelectric baseline are often well demarcated. The diagnosis of LQTS is made in the presence of a cQT interval of ≥ 480 ms or a Schwartz score (including several clinical and electrocardiographic parameters) of > 3. In the presence of a cardiogenic syncope, the presence of a cQT ≥ 460 ms is sufficient to reach the diagnosis.

The mechanism of arrhythmogenicity in patients with LQTS seems to be related with dispersion of the repolarization. The prolongation of the repolarization is not homogeneous among the different layers of myocardium. Therefore, early post depolarization occurring over the T wave may generate functional re-entry patterns of conduction ultimately generating fibrillatory conduction.

Up to 17 different mutations leading to LQTS have been described. The majority of them are produced by three specific mutations. LQTS1 is produced by mutation in the α subunit of the delayed rectifier potassium channel with slow opening kinetics. This mutation comprises 40%-55% of cases. LQTS1 patients are prone to suffering from ventricular arrhythmias during sports or physical activity (especially during swimming). LQTS2 is caused by a mutation in the α subunit of the delayed rectifier potassium channel with rapid opening kinetics. This mutation is present in up to 30%-45% of cases, and ventricular arrhythmias are frequent during loud noises and in the postpartum period in females. The activating mutation in the α subunit of the sodium channel (INaT) keeps the channel opened beyond phase 0, increasing late sodium currents (INaL), thus prolonging repolarization and therefore the QT interval. This mutation is present in 5%-10% of patients and is related to fatal events during rest or sleep [146].

It has been observed that LQTS patients respond favorably to beta-blockers; thus every patient with a diagnosis of LQTS should be treated with beta-blockers. Apparently, non-specific beta-blockers, such as propranolol or nadolol, have shown better results with a lower incidence of ventricular arrhythmias. If patients suffer from syncope despite the use of beta-blockers, an ICD must be implanted for the

prevention of SCD[147].

Catecholaminergic PVT

Catecholaminergic PVT (CPVT) is an inherited channelopathy in which several mutations may affect the intracellular handling of calcium release-uptake. The overload of cytoplasmatic calcium leads to cell membrane voltage instability leading to delayed depolarizations that lead to the characteristic arrhythmia of this disorder, bidirectional ventricular tachycardia (also seen in digitalis toxicity), or VF.

The mutation in the ryanodine receptor gene, inherited in an autosomal dominant manner, is the cause of 50%-55% of cases. A new mutation in the calsequestrin gene has been described and has an autosomal recessive inheritance pattern. The ryanodine receptor gene mutation generates an aberrant ryanodine channel that permeabilizes the channel to calcium release. The calsequestrin proteins work close to the ryanodine channel, regulating its function.

Patients with CPVT are prone to ventricular arrhythmias related to exercise. Ventricular arrhythmias usually occur with HR over 130 bpm. With increasing levels of exercise, patients may exhibit monomorphic ectopy, polymorphic ectopy, non-sustained VT, bidirectional VT, and finally, if the exercise continues, VF. CPVT is a highly arrhythmogenic condition with a cardiac event rate of up to 80% at 40 years. Therefore, a low threshold for ICD implantation is advised. The use of non-selective beta-blockers has been shown to reduce the incidence of ventricular arrhythmias from 25% to 11% at 8 years[148].

Probably due to small cohorts, no single risk factor has demonstrated sufficient prognostic value to be used routinely. The 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD recommend implantation in patients with CPVT who have survived a cardiac arrest (class I C) and should be considered in patients with CPVT and either arrhythmic syncope or presence of polymorphic VT or bidirectional VT on maximal tolerated doses of beta-blockers (class IIa C)[19].

CONCLUSION

Syncope is a symptom that involves a heterogeneous group of pathologies ranging from trivial causes to diseases with a high risk of sudden death. The highest mortality and SCD risk occur when syncope is associated with underlying cardiac disease, in particular when the main cause of syncope is not well established and treated properly. Arrhythmia is the most common cause of cardiac syncope. Appropriate risk stratification and work-up to determine the main cause of the event is warranted to improve the prognosis of patients. This review provided an update on the important and novel data about arrhythmic syncope, the value of the different diagnostic tests, and the specific characteristics in some particular populations such as patients with cardiomyopathies or channelopathies. This review emphasized the importance of an appropriate stepwise approach work-up and interventions.

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MINIREVIEWS

Optimization of the pharmacological therapy in patients with poly-vascular disease: A multidisciplinary approach

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Abstract

The recent shift of the concept of cardiovascular disease as a chronic progressive condition, potentially involving multiple districts, has driven attention to the optimal management of patients with concomitant coronary and peripheral artery disease, representing a subset of patients with an increased risk of events and impaired survival. Recent pharmacological achievements in terms of antithrombotic therapy and lipid-lowering drugs allow multiple therapeutical combinations, thus requiring optimizing the treatment in a tailored fashion according to patients' risk profiles. Nevertheless, data dedicated to this specific subset of patients are still modest. We summarize currently available strategies and indications for the management of antithrombotic and lipid-lowering drugs in patients with the poly-vascular disease.

Key Words: Poly-vascular disease; Coronary artery disease; Atherosclerosis; Antitrombotic therapy; Cholesterol; Statins; PCSK9

Core Tip: Patients with concomitant coronary and peripheral artery disease, *i.e.* poly-vascular disease, represent a subset of patients with higher risk and worse prognosis. In these patients antithrombotic and antilipidemic drugs should be tailored in order to achieve the most aggressive combination tolerated for each patient. Multidisciplinary approach, involving both a cardiologist and vascular surgeon, combining different therapeutic goals and perspectives, could provide additional benefits in the correct management of poly-vascular patients.

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INTRODUCTION

The large efforts dedicated in the last decades to reducing the burden of cardiovascular disease (CVD) worldwide have allowed a better identification of causal risk factors and pathophysiological mechanisms, thus leading to progressive shift in the concept of CVD as a chronic progressive condition [1].

In the 2019 European Society of Cardiology (ESC) guidelines[2], the term stable coronary artery disease (CAD) has been replaced with "chronic coronary syndrome", focusing on CAD as a dynamic evolutive process, resulting from a myriad of interactions, both environmental and genetic.

A subsequent development has led to consider CAD as part of a wider spectrum of disease, sharing the same atherosclerotic pathogenesis, thus leading to the most recent concept of "cardio-cerebro-vascular continuum"[3,4], representing a condition with a high potential of progression to death or major acute ischemic events, in absence of interventions interrupting this pathological loop.

Recent advances in terms of more potent antithrombotic and lipid-lowering therapies, allowing prevention of a large proportion of acute ischemic events and the progression of the disease[5,6], have significantly modified the prognosis of these patients, therefore promoting attentive research of multidistrict involvement.

However, despite the rising attention, and especially in secondary prevention, among patients with an established diagnosis of CAD or peripheral arterial disease (PAD), still the indications for systematic pan-vascular screening and the appropriate management of the newly available therapies is debated, leading to the risk of underestimation of the risk and undertreatment[7].

Moreover, increasing evidence has emerged on the advantages of an earlier establishment of pharmacological anti-atherosclerotic measures, remarking the importance to identify the instruments for adequate assessment of the cardiovascular risk profile. The present review will aim to provide an overview of the management of patients with poly-vascular disease, with a particular focus on recent updates in the management of antithrombotic and lipid-lowering therapies.

DEFINITION AND RISK STRATIFICATION OF PATIENTS WITH POLY-VASCULAR DISEASE

PAD is defined, according to the European Society of Cardiology guidelines[8], as a blood circulation disorder of the arteries that supply all the districts excluding coronary circulation and aorta.

However, CAD and PAD or multidistrict PAD often tend to co-exist, representing different presentations of the same pathogenetic process, atherosclerosis, an inflammatory disease leading to the progressive occlusion of the vessel lumen[9]. Atherosclerosis within 2 or more arterial beds has been termed a poly-vascular disease and recent studies have documented that its prevalence could be even more common than previously considered[10].

In the Reduction of Atherothrombosis for Continued Health Registry (REACH)[11], an international registry including patients ≥ 45 years of age with established CAD, CVD, PAD, or ≥ 3 risk factors for atherosclerotic disease; 24.7% of patients with CAD and up to 61.5% of patients with PAD had the concomitant disease in other vascular beds, being associated with a severely worsened prognosis. In fact, in the same study, the strongest predictor for future ischemic events was a poly-vascular disease, which was associated with a 99% increased risk of major cardiovascular ischemic events (MACE) at 4-year follow-up, an almost doubled mortality (4.6% *vs* 2.4%) and markedly increased morbidity. A similar negative prognostic impact was also confirmed in several registries and trials[12,13]. However, routine screening for poly-vascular involvement in patients with disease in one arterial bed has not been recommended, so far, in guidelines, in consideration of multiple factors.

Indeed, the modest awareness of patients and physicians, being generally more focused on the prognostic weight of CAD, rather than PAD, and the more delayed presentation of the latter, remaining often symptomatic until the occurrence of critical or acute ischemia, certainly have represented a limitation for many years[14].

Moreover, whereas an early establishment of lifestyle counseling and medications was able to reduce the risk of cardiovascular events in primary prevention, no differential pharmacological management was advised, so far, among patients with CAD, PAD or both, due to the lack of evidence of potential additional benefits with more aggressive therapy[1,8].

Nevertheless, the recently introduced antithrombotic and antilipidemic drugs have provided greater benefits among patients with more severe multidistrict vascular disease, thus raising the need to better define risk models and shared protocols.

In particular, the role of indirect indexes of vascular disease, which are widely validated in primary prevention, still needs to be defined among patients with an established diagnosis of CAD or PAD.

Among them, the ankle-brachial index (ABI) represents an easy-to-measure and widely available tool for objectifying CAD. Several studies have shown that patients with an ABI < 0.9 have more severe coronary artery disease[15].

Moreover, among patients with PAD, ABI has emerged as a strong predictor of mortality and major acute cardiovascular and limb-related ischemic events (MACE and MALE)[16].

A similar prognostic role of ABI, however, was also confirmed among asymptomatic patients undergoing screening for PAD, where an ABI < 0.85 increased the relative risk for total mortality to 2.36 (95%CI: 1.60, 3.48), being even enhanced with decreasing ABI (P < 0.0001). Specific causes of death, directly related to the magnitude of ABI were mainly due to myocardial infarctions, further reinforcing the importance of poly-vascular disease identification[17].

Similarly, pulse wave velocity (PWV), the most widely used measure of arterial stiffness, has emerged as a useful tool for risk stratification in CVD. Various studies and meta-analyses have shown the association between PWV and PAD or CAD. Moreover, PWV emerged as an independent risk factor for future cardiovascular events[18].

Other indirect markers of an ongoing atherosclerotic process, such as carotid intima-media thickness, as well as vasculogenic erectile dysfunction or coronary calcium score, have been addressed for the estimation of cardiovascular risk, although their exact predictive role and prognostic impact is still under debate. Recent studies suggested that carotid intima-media thickness (cIMT) evolution, and in particular cIMT reduction, rather than the baseline value, could predict the degree of CVD risk reduction[19].

Indeed, future dedicated studies are certainly deserved to define the most appropriate tools and criteria for the assessment of cardiovascular risk and for establishing the most appropriate preventive measures for the management of higher-risk patients.

ANTITHROMBOTIC THERAPY IN POLY-VASCULAR DISEASE

The cardiological approach in acute and chronic coronary syndromes

Antiplatelet therapy is the cornerstone of the treatment of patients with acute and chronic coronary syndrome. Dual antiplatelet therapy (DAPT) consisting of aspirin (ASA) and an adenosine diphosphate inhibitor, such as clopidogrel, prasugrel or ticagrelor is currently indicated for the prevention of cardiovascular events in patients presenting with the acute coronary syndrome (ACS), after percutaneous coronary intervention for any indication and in particular subsets of higher-risk stable CAD patients.

Clinical practical guidelines in the United States and Europe recommend more potent P2Y12 inhibitors in ACS, such as ticagrelor and prasugrel, given that head-to-head comparison clinical trials have shown the superiority of these inhibitors over clopidogrel in reducing ischemic events[20,21].

In the acute setting, clopidogrel should be used only if these potent inhibitors are contraindicated or unavailable, while still representing the first choice in patients undergoing elective percutaneous coronary interventions[1].

The recommended duration of DAPT is 12 mo after an acute coronary syndrome, unless there are contraindications, and 6 mo in CCS. In specific clinical scenarios, DAPT duration can be shortened (< 12 mo), extended (> 12 mo) or modified (switching DAPT, DAPT de-escalation) and these decisions depend on individual clinical judgment being driven by the patient's ischemic and bleeding risk[1,22].

Patients are defined as having "high ischemic risk" if presenting multivessel CAD and at least one additional risk factor, including diabetes, recurrent acute myocardial infarction (AMI), renal failure or PAD. On the other hand, patients with at least one criterion between multivessel CAD, diabetes, recurrent AMI, PAD, renal failure or heart failure are considered to be at "moderate" risk[23].

In these patients, the potential advantage of extending DAPT duration beyond the routine period of 6-12 mo was first suggested in the DAPT trial[24]. In this study dual antiplatelet therapy beyond 1 year and up to 30 mo after placement of a drug-eluting stent, as compared with aspirin alone, significantly reduced the risk of stent thrombosis and major adverse cardiovascular and cerebral events, but was associated with an increased rate of bleeding.

Subsequently, the PEGASUS-TIMI 54 trial documented the reduction of MACE with ASA+ ticagrelor 60 mg × 2 among moderate-high risk patients with a previous AMI who had tolerated DAPT for 1 year, with no difference in severe bleedings[25].

Among the patients at higher risk included in the study, patients with PAD are at heightened risk of MACE, including myocardial infarction (MI) and stroke. In a sub-analysis of the PEGASUS-TIMI 54 trial dedicated to this specific setting, it was observed that the benefit of ticagrelor for relative risk reduction of MACE was consistent, regardless of the presence or absence of known PAD; however, patients with

PAD had a particularly robust risk reduction, due to the higher rate of events, furthermore, producing advantages on MALE. However, the low number of patients (only 5% of the overall study population) and the lack of any impact on mortality did not translate into a particular indication for ticagrelor in patients with previous MI and PAD[26].

More recently the COMPASS Trial compared rivaroxaban (2.5 mg bid) plus ASA 100 mg/d or rivaroxaban 5 mg bid alone *vs* ASA 100 mg/die in patients with stable CAD and/ or PAD. Rivaroxaban 2.5 mg bid plus ASA showed a significant reduction of stroke, total and cardiovascular mortality, in addition to reducing MACE and MALE[27]. This regimen was associated with an increase in major bleeding events primarily from gastrointestinal sites, but there was no increase in critical organ bleeding, non-fatal intracranial bleeding or fatal bleeding. The net clinical benefit analysis (inclusive of MACE, MALE and severe bleeding events) maintained significant benefits in favor of the rivaroxaban plus aspirin arm[28,29].

Therefore, given this evidence, the cardiological approach to antiplatelet therapy, should be to pursue the extension of antithrombotic therapy for the longest tolerated period (> 1 year after ACS; > 6 mo after CCS), balancing with the hemorrhagic risk and tailoring the different strategies according to the patient's characteristics. Our proposed strategy is depicted in Figure 1. In patients with poly-vascular disease in whom the ischemic risk outweighs the risk of bleeding, the combination of antiplatelet therapy and low-dose anticoagulation currently appears supported by the most robust evidence and by the larger prescribing criteria, being allowed both in ACS and CCS patients and even in those who have discontinued DAPT at distance from an event.

Surgical approach in a patient with and without revascularization

Peripheral artery disease (PAD) is one of the manifestations of atherosclerosis, which is known to involve many different vascular districts. Indeed, PAD shares with CAD a common etiology and therefore therapeutical approaches are often similar. In this context, the management of antithrombotic therapy is the milestone of pharmacological strategy in vascular surgery, both in primary and secondary prevention after revascularization. Historically, PAD patients have often represented a subgroup in large RCTs assessing generic antithrombotic therapies in poly-vascular populations. These trials then led to more specific studies dedicated to vascular patients in the last years, both in the chronic and postoperative settings. MACE is often the pivotal outcome of these studies; however, in PAD patients, also MALE becomes a crucial parameter to assess the efficacy of antithrombotic therapy. Therefore, in all RCTs and metanalysis these two outcomes are usually evaluated, balanced with the bleeding risk of different antithrombotic approaches.

The benefit of aspirin in atherosclerotic disease is well established. In 2002, the Antithrombotic Trialists' Collaboration established a general benefit of aspirin in terms of prevention of death and different cardiovascular events, but many antiplatelet drugs and regimens were tested[30]. However, use of aspirin was afterward re-assessed in asymptomatic diabetic patients with ABI < 0.9[31].

Clopidogrel, a second-generation thienopyridine, showed better results in terms of MACE *vs* aspirin in the CAPRIE trial, mostly in a subgroup of patients with PAD; however, no benefit for MALE was found.

Ticagrelor is another thienopyridine often used in CAD. The EUCLID trial[13] compared clopidogrel with ticagrelor in PAD patients and showed no difference in MACE or bleeding events.

Nevertheless, the use of these two antiplatelet agents in monotherapy for PAD patients is limited, with only clopidogrel often being considered as an alternative in case of aspirin intolerance.

Aspirin has also been evaluated in combination with both clopidogrel and ticagrelor. The CHARISMA trial[32] compared a heterogeneous population with different cardiovascular diseases receiving aspirin *vs* aspirin plus clopidogrel. In the PAD subgroup no difference in MACE was found between the two groups, with a slightly higher risk of moderate/severe bleeding with the dual antiplatelet regimen.

The PEGASUS-TIMI 54 trial[25] was similar, but ticagrelor was used instead of clopidogrel. The study found a higher benefit of the dual therapy in patients with PAD, both for MACE and MALE.

In the past decades, the combination of antiplatelets and anticoagulants did not show favorable outcomes in PAD patients[33]. The advent of NOACs recently changed the scenario also in vascular surgery. In 2017 the COMPASS trial highlighted the effectiveness of low dose of rivaroxaban (*i.e.* 2.5 mg bid) in a large population of atherosclerotic patients[27]. This benefit was found to be even clearer in PAD patients. In a COMPASS subgroup analysis of PAD patients[28], both MACE and MALE were significantly lower in those assigned to rivaroxaban plus aspirin *vs* aspirin alone and this evidence was directly proportional to the Rutherford class and cardiovascular risk profile at baseline. Furthermore, critical bleedings were not significantly higher in patients with combined therapy.

The role of antithrombotic therapies is even more important after lower extremity revascularization [34]. While single antiplatelet therapy is essential after any kind of bypass, it is unclear whether the addition of warfarin is useful in venous grafts, due to a higher risk of bleeding.

Similarly, there is strong evidence to support single antiplatelet therapy after prosthetic bypass, while the role of DAPT is less clear. Indeed, the CASPAR trial[35] evidenced a benefit of aspirin plus clopidogrel only in a subgroup of patients after below-the-knee prosthetic bypasses (typically at risk of low patency), without significant increasing major bleeding.

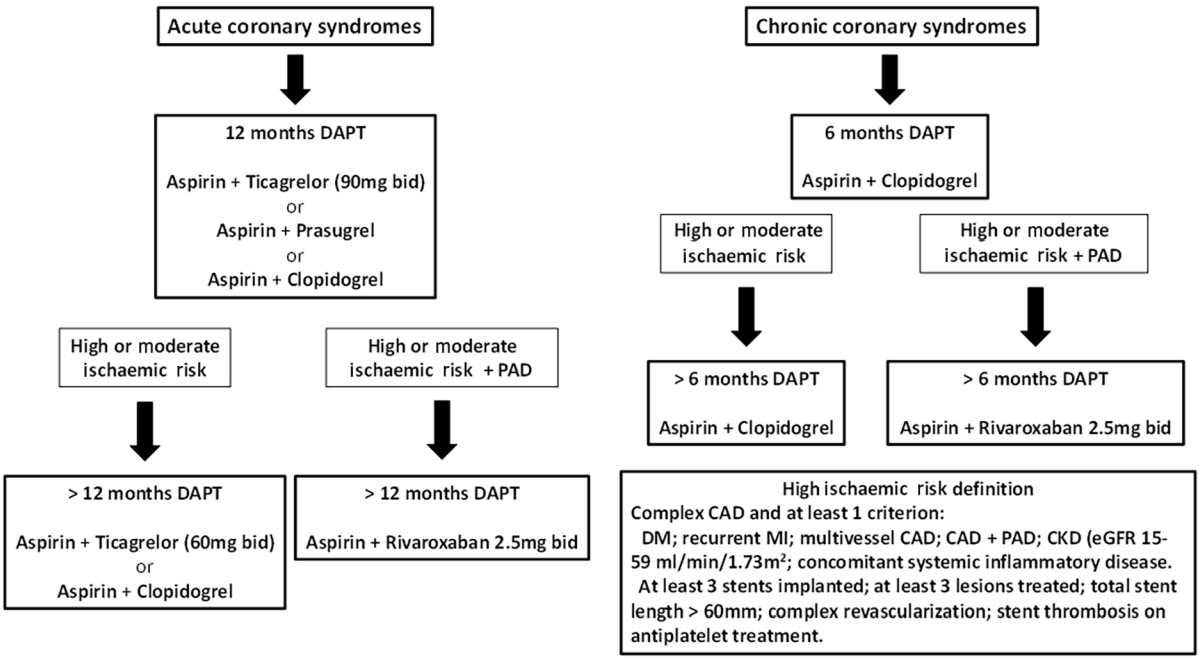

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Figure 1 Flow-chart for the management of antithrombotic therapy in patients with coronary artery disease. CAD: Coronary artery disease; DAPT: Dual antiplatelet therapy; DM: Disease management; eGRF: Glomerular Filtration Rate; PAD: Peripheral arterial disease; MI: Myocardial infarction.

More recently, based on the COMPASS trial findings[28], a randomized controlled trial was designed to assess the efficacy of aspirin plus a low dose of rivaroxaban in patients who underwent lower extremity revascularization[36]. Those assigned to the dual therapy had better outcomes in terms of both MACE and MALE, balanced by an acceptable risk of bleeding. A subgroup analysis that referred to only open-surgical patients confirmed these findings[37]. Recently, Bonaca *et al*[38] tried to compare a "CASPAR-like" population derived from a post hoc analysis of the VOYAGER PAD trial to assess whether aspirin plus rivaroxaban performed better than aspirin plus clopidogrel after LER. No trials so far directly compared these two postoperative antithrombotic regimens. Their findings confirmed that aspirin combined with rivaroxaban led to better postoperative outcomes compared with clopidogrel as adjunctive therapy. Furthermore, Hiatt *et al*[34] found that the addition of rivaroxaban to aspirin after LER was effective and safe even if concomitant clopidogrel was prescribed, suggesting the potential role of a triple antithrombotic therapy, which however should be further evaluated in a dedicated trial.

In the wake of all the aforementioned trials[28,34,36-38], four major guidelines have been published in the last years regarding PAD[8,39-41].

In 2016 the ACC/AHA reported their recommendations for PAD[39]. Single antiplatelet therapy was strongly recommended in symptomatic PAD patients and after revascularization, while its routine use in asymptomatic patients was uncertain, as well as the role of DAPT. Indeed, these guidelines were released before the COMPASS trial, therefore not considering anticoagulant drugs.

The European guidelines[8] were published one year later by the ESC in collaboration with the European Society for Vascular and endovascular Surgery. They recommended antiplatelet therapy for asymptomatic patients, while a single drug is mandatory for symptomatic patients. Of note, deferring from the American guidelines, the latter suggested clopidogrel as the preferred molecule over aspirin [40]. Regarding postoperative schemes, DAPT was recommended after percutaneous procedures for 1 mo (or longer if concomitant CAD), while single antiplatelet was deemed adequate after open surgery. According to these guidelines, standard anticoagulants (*i.e.* warfarin) could be associated with antiplatelet therapy only after endovascular procedures and in patients at low risk of bleeding who were preoperatively on this regimen for other reasons (*i.e.* atrial fibrillation, mechanical heart valve, *etc.*). The European guidelines only cited the COMPASS trial as a potential landmark for future updates, as no published data were available yet.

The Global vascular guidelines on critical limb ischemia (CLI)[41] have been published in 2019. They gave weak recommendations for DAPT after infrainguinal bypasses for a period of 6 to 24 mo postoperatively and at least 1 mo after endovascular procedures (or a longer period in case of multiple reinterventions). Of note, these are the first guidelines that recommend the association between aspirin and a low dose of rivaroxaban to reduce MACE and MALE in patients with CLI (having the COMPASS trial been published 1 year before, while the VOYAGER PAD trial was ongoing at the time of publication).

The Canadian guidelines[42] are the most recently published guidelines for PAD. They confirm most of the recommendations given by the previous ones, except for more precise indications for rivaroxaban

associated with aspirin. Indeed, this represents the preferred antithrombotic strategy in symptomatic patients with high-risk comorbidities and higher stages of limb ischemia ("high-risk patients" and "high-risk limb"). Furthermore, they suggest the same approach after both open and endovascular interventions, with a restricted indication for DAPT only in patients unable to receive rivaroxaban. These conclusions, which are outlined in Figure 2, may represent a paradigm shift in the treatment of PAD patients, regardless of the need for surgical procedures. Of course, these statements have to be confirmed by further trials, but we can affirm that this new antithrombotic strategy represents one of the most interesting fields of research in vascular surgery for the next years.

ANTILIPIDEMIC THERAPY IN POLY-VASCULAR DISEASE

Cardiological perspectives

Low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor for cardiovascular disease, as evidenced by epidemiological and Mendelian randomization studies. LDL-C lowering is associated with a reduction of MACE in a linear way, without any plateau for lower LDL-C levels[43].

Therefore, a progressive lowering of the target of LDL-C has been observed in guidelines and consensus documents. The 2018 AHA/ACC/multisociety cholesterol guidelines[44], are more conservative in the definition of the LDL-C threshold to < 70 mg/dL and in the identification of very-high risk patients (not enclosing patients without established atherosclerotic cardiovascular disease, as those with diabetes or chronic kidney disease). On the contrary 2019 ESC/EAS Guidelines on the management of dyslipidemias[45] recommend, for very-high-risk patients, LDL-C target to be lower than 1.4 mmol/L (55 mg/dL), in addition to the goal of achieving a 50% reduction from baseline. Patients with any documented atherosclerotic cardiovascular disease, involving one or more districts are already considered at "very high" risk, whereas patients with repeated acute coronary syndrome events within 2 years should be considered at "extremely" high risk and pursue a lower threshold of 1.03 mmol/L. Patients with post-acute coronary syndrome and presence of peripheral artery disease or poly-vascular disease; post-acute coronary syndrome and coexistent multivessel coronary artery disease; and post-acute coronary syndrome and familial hypercholesterolemia have been recently paired in the latter category, according to certain European cardiological societies[46].

Lipid-lowering therapies modify the risk in patients with atherosclerosis and have been shown to exert larger absolute risk reductions in patients with the poly-vascular disease[47].

New evidence has raised the opportunity to start with a combination of statin therapy plus ezetimibe for very high-risk patients. If patients do not achieve the 2019 Guideline-recommend LDL-C goal, a third lipid-lowering therapy, such as bempedoic acid or proprotein convertase subtilisinkexin type 9 inhibitor (PCSK9-i) targeted therapies should be added. Furthermore, in extremely high-risk patients triple therapy (statin plus ezetimibe plus PCSK9-inhibitors) could be administered at the beginning[48].

As observed in a sub-analysis of the FOURIER Trial, Evolocumab significantly reduced the risk of MACE in symptomatic PAD, including those without prior MI or stroke. Furthermore, LDL-C lowering with evolocumab reduced the risk of MALE including acute limb ischemia and major amputation. Akin to what has been observed for MACE, there was a consistently lower risk of MALE with lower levels of achieved LDL-C, down to 10 mg/dL[49].

Similar results were found in an analysis of the ODISSEY-OUTCOME trial. In patients with recent ACS and dyslipidemia, the poly-vascular disease is associated with a high risk of MACE and death. The large absolute benefit of PCSK9 inhibition with alirocumab, when added to high-intensity statin therapy, is a potential benefit for this group of patients[50].

A new therapeutic weapon is represented by inclisiran, a small interfering RNA (siRNA) therapeutic agent which reduces hepatic synthesis of PCSK9. Inclisiran was approved in the European Union in 2020 for use in adults with primary hypercholesterolemia or mixed dyslipidemia based on the results of the ORION Trials. Inclisiran, administered subcutaneously every 6 mo, reduces LDL-C levels by approximately 50%[51].

In a post-hoc analysis of the Orion Trials, focused on patients with the polyvascular disease (PVD), two-yearly dosing with inclisiran provided an effective and sustained LDL-C lowering, irrespective of PVD status, with no relevant side effect[52].

Targets and objectives in peripheral artery disease

The relationship between statins and PAD has been seldom investigated. As well as for antithrombotic therapies, the literature focused more on pleiotropic effects rather than limb-related benefits of statins in PAD patients. Moreover, PAD patients often represented a subgroup in large RCTs of atherosclerotic patients, with few dedicated studies published so far. In a meta-analysis by Antoniou[53], statins proved to significantly reduce mortality and stroke in symptomatic PAD patients when compared to placebo. These trends have been recently confirmed by Kokkinidis[54] in another meta-analysis, which summarized some observational studies regarding the impact of statin therapy in CLI patients. Of note, this study investigated almost 27000 patients with CLI, but only half of them were statin users; these patients had better patency rates and a lower risk of amputations after revascularization, besides better

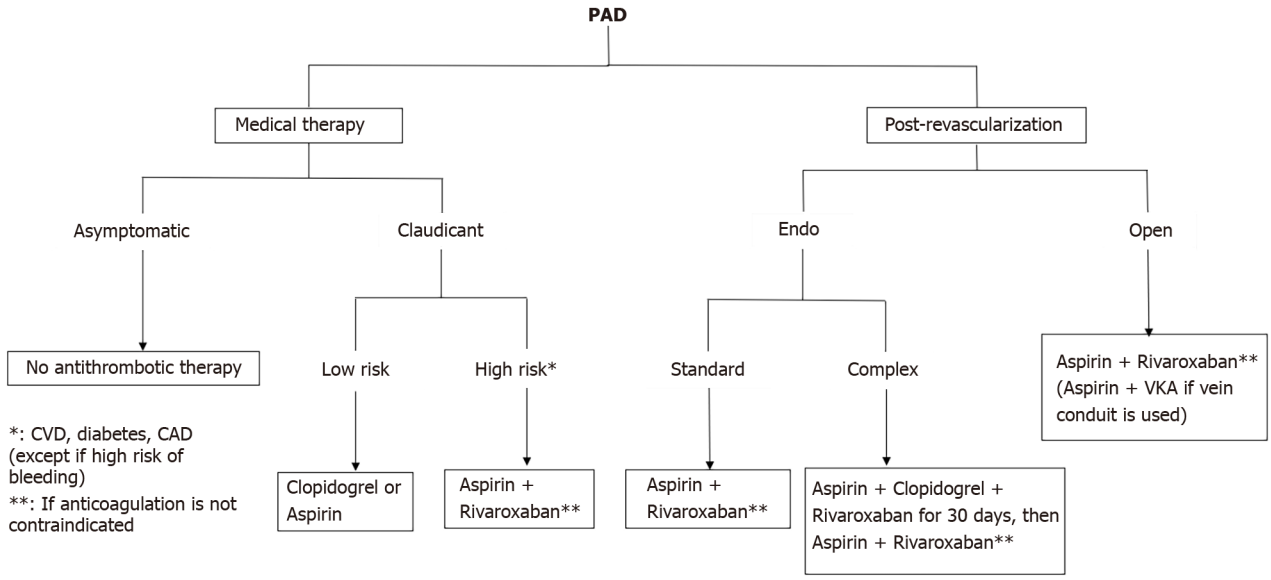

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Figure 2 Antithrombotic strategies in patients with peripheral artery disease according to vascular guidelines. PAD: Peripheral artery disease; CVD: Cardiovascular disease; CAD: Coronary artery disease.

outcomes in terms of MACE and mortality. The issue of under-prescription of statins in PAD patients has also been raised by Parmar[55], in a population of 488 patients who underwent LER. These authors found that statins were the most impactful factor on MACE and MALE after revascularization, even more than all the antithrombotic strategies globally compared. Nevertheless, only 41% of patients in this study were on statin therapy. Furthermore, statins may induce muscle pain, which could affect the adherence to this therapy in PAD patients. In this scenario, the Global guidelines suggest to lower statins to the maximum tolerated dose, adding a non-statin molecule to reduce cholesterol blood levels to the optimum[42].

Recently, PCSK9-i and other new lipid-lowering therapies have been tested in large atherosclerotic populations, with only a small portion of them affected by PAD. The FOURIER trial[47] evaluated evolocumab, a PCSK9-I, in a large cohort of patients, while a PAD subgroup has been subsequently analyzed. The adjunct of evolocumab to statins significantly reduced MACE by 27% and MALE by 37% in this subgroup, regardless of the Rutherford class. On the other hand, the ODYSSEY OUTCOMES trial [50] provided different results with alirocumab. Once again, this was a RCT of patients with acute coronary syndrome (ACS) receiving either the placebo or alirocumab. This drug provided significantly fewer PAD events (*i.e.*: CLI, unplanned amputations, need for limb revascularization) in patients with ACS. Conversely, in a subanalysis of this trial by Jukema[50], patients with concomitant PAD had no benefit in terms of MACE, while the main trial showed positive results in the overall population. This confirms the need for studies specifically designed for PAD patients.

The aforementioned vascular guidelines[8,39-42] give fewer recommendations for lipid-lowering drugs than for antithrombotic therapies in PAD. Both the American and European guidelines generically recommend the use of statins in all PAD patients, with the latter specifying an optimal cut-off of 1.8 mmol/L (*i.e.*: < 70 mg/dL) for LDL-c levels. More specific indications are given by the Global guidelines in patients with CLI[39]. These guidelines suggest the use of moderate or high-intensity statin therapy with rosuvastatin 20-40 mg or atorvastatin 40-80 mg daily, with the same LDL-c target of 1.8 mmol/L. The Canadian guidelines[41] give more detailed indications for aggressive lipid-lowering therapies. All PAD patients should receive the higher tolerated dose of statins; the addition of PCSK9-i or ezetimibe should be considered if the cut-off of 1.8 mmol/L is not reached at the higher dose of statin. Furthermore, triglycerides levels are also mentioned, where the use of icosapent ethyl is suggested when statin therapy alone does not lead to a level of 1.8-5.6 mmol/L. Eventually, while all the previous guidelines give their recommendations for statins to reduce all-cause and CV mortality and morbidity (*i.e.*: Nonfatal MI, nonfatal stroke), these guidelines[41] are the only ones underlying the benefit of a more strict control of lipid levels also on MALEs.

Similarly, the recently released 2022 ACC Expert Consensus Decision Pathway[56] on nonstatin therapies firstly integrated the results of the trials with bempedoic acid, alone or in association with ezetimibe, in order to achieve the target of LDL-C in patients with ASCVD or extremely high cholesterol levels.

Therefore, as summarized in Figure 3, LDL-C reduction should be aimed at any vascular patient. However, the achievement of very low levels should be pursued in patients with CAD+PAD, by establishing an aggressive management, with the combination of all the available strategies,

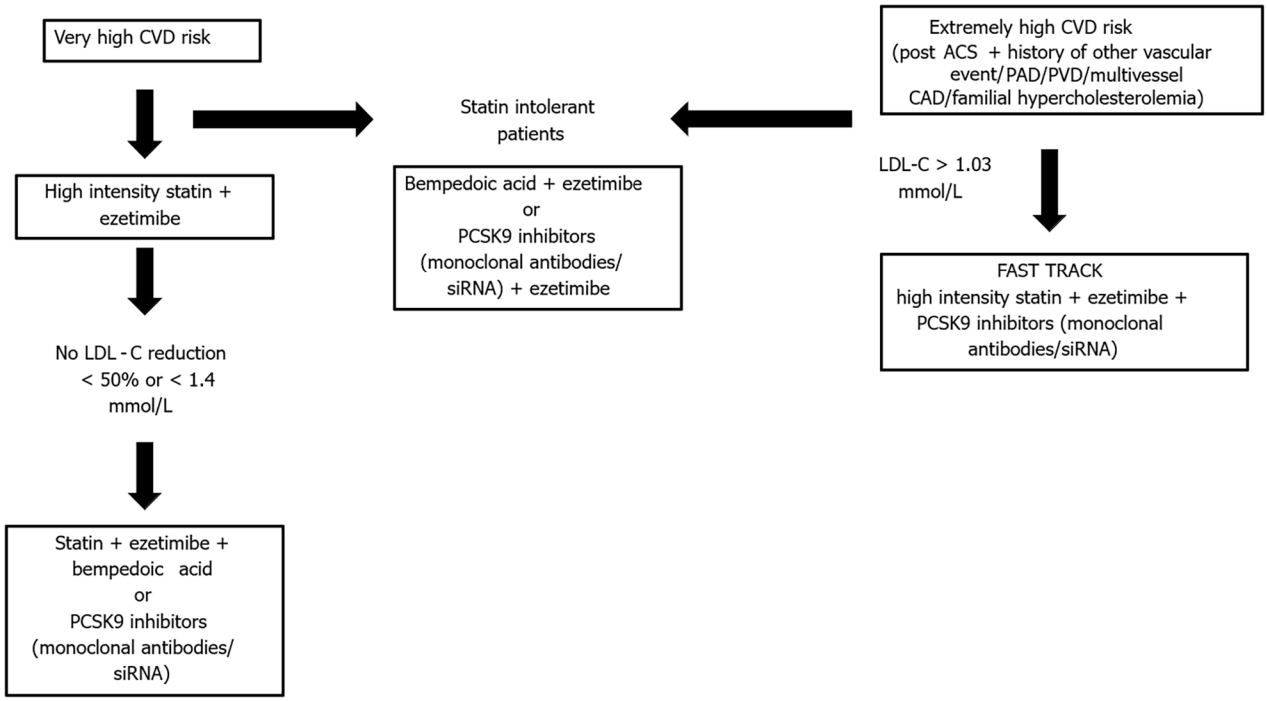

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Figure 3 Current indications to lipid-lowering drugs in patients with coronary and peripheral artery disease. CVD: Cardiovascular disease; LDL-C: Low-density Lipoprotein Cholesterol; PCSK9: Proprotein convertase subtilisinkexin type 9; siRNA: Small interfering RNA.

immediately after the evidence of the poly-vascular disease, seeking an earlier achievement of the required goal.

CONCLUSION

Patients with concomitant multidistrict artery disease, *i.e.* poly-vascular disease, represent a higher risk subset of patients with worse prognosis. In these patients, the most aggressive tolerated antithrombotic and antilipidemic therapy should be attempted, although accounting for the interindividual differences. Multidisciplinary approach, involving both a cardiologist and vascular surgeon, combining different therapeutic goals and perspectives, could provide additional benefits in the correct tailoring of pharmacological therapy among poly-vascular patients.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Vasospastic angina in women: Clinical backgrounds and prognoses of patients younger than and older than 60 years

Hiroki Teragawa, Chikage Oshita, Yuko Uchimura

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Abstract

BACKGROUND

We frequently encounter cases of women with vasospastic angina (VSA). Additionally, some women with VSA are younger than 60 years old. However, it is unknown whether the characteristics of VSA in women aged < 60 years are different from those in women aged ≥ 60 years.

AIM

To investigate and compare the clinical characteristics and prognosis of VSA in women aged < 60 years from those in women aged ≥ 60 years.

METHODS

We enrolled 94 women with VSA who were diagnosed using the spasm provocation test. According to the age at diagnosis, the patients were divided into two groups: Group Y (age < 60 years, n = 17) and Group O (age ≥ 60 years, n = 77). Flow-mediated dilation (FMD) and nitroglycerin (NTG)-induced dilation (NID) of the brachial artery were performed and assessed using brachial ultrasonography. Moreover, conventional coronary risk factors, such as atherosclerotic lesions (stenosis > 20%) detected using coronary angiography and focal spasms (coronary spasm within one segment of one coronary artery), and major cardiovascular adverse events (MACE) were assessed in both groups.

RESULTS

Smoking was more prevalent in Group Y than in Group O (P = 0.04). FMD was similar in both groups (Group O: 4.3% ± 3.2%, Group Y: 4.5% ± 3.3%; P = 0.75), whereas NID was higher in Group Y (20.5% ± 8.6%) than in Group O (13.6% ± 5.3%, P < 0.01). Atherosclerosis was not detected in Group Y but was detected in Group O (61%, P < 0.01). Focal spasms were less frequent in Group Y (12%) than in Group O (38%, P = 0.04). The incidence of major adverse cardiac events did not differ between the two groups (P = 0.40).

CONCLUSION
Women aged < 60 years with VSA have less atherosclerotic lesions and focal spasms. These characteristics may be affected by smoking habits and vascular smooth muscle dysfunction.

Key Words: Acetylcholine; Young female; Smoking; Vasospastic angina; Vascular smooth muscle dysfunction

Core Tip: We investigated whether the clinical background and prognosis of women aged < 60 years with vasospastic angina (VSA) differ from those of women aged ≥ 60 years with VSA. We showed that smoking was more frequent in women aged < 60 years with VSA. We found a significantly greater peripheral vascular response to nitroglycerin in such patients. Coronary angiography revealed fewer atherosclerotic lesions and focal spasms in such patients. Smoking status and vascular dysfunction may have influenced the above clinical characteristics in women aged < 60 years with VSA.

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INTRODUCTION

Vasospastic angina (VSA) is a condition characterized by transient hypercontraction of the epicardial coronary arteries, leading to myocardial ischemia[1,2]. Although the incidence of coronary artery disease is higher in men[3], the incidence of VSA is relatively higher in women[4,5]. Therefore, several reports have investigated gender differences among patients with VSA[5-9], concluding that women have a lower positivity rate than men during the spasm provocation test (SPT)[5-9], and that focal spasms occur more frequently in men than in women[8,10].

Among women with VSA, we have encountered cases of patients younger than 60 years old. In a paper by Kawana *et al*[6] that evaluated the characteristics of women with VSA by age, smoking was more prevalent in younger women with VSA, but the prevalence of hypertension was lower in this population. Additionally, women aged < 50 years with VSA had a worse prognosis. Aside from this study, few reports have examined the characteristics of women with VSA at an early age.

Therefore, in the present study, we retrospectively investigated the differences in clinical characteristics and prognosis between women aged < 60 years and ≥ 60 years with VSA.

MATERIALS AND METHODS

Study patients

This observational retrospective study included female patients with VSA who were diagnosed using SPT at our institution between August 2010 and March 2017 (n = 107). The exclusion criteria were as follows: significant coronary stenosis (stenosis > 50%, n = 3), or a previous medical history of percutaneous coronary intervention (n = 3), heart failure (n = 4), and hypertrophic cardiomyopathy (n = 3). Ultimately, 94 women VSA were enrolled in the study. The mean and median ages of the patients at diagnosis were 69 ± 10 years and 71 (63, 76) years, respectively; the 25th percentile was 63 years. However, the cut-off age for this study was set at 60 years. Hence, the patients were classified into two groups based on the cut-off age: Group Y (age < 60 years, n = 17) and Group O (age ≥ 60 years, n = 77, Figure 1). The study protocol was approved by the ethics committee of our institution. Written informed consent was obtained from all participants.

Coronary angiography and SPT

SPT was carried out in accordance with our prior description[4,11,12]. At our institution, SPT of the right coronary artery (RCA) was carried out continuously. Acetylcholine (ACh) dosages of 20 and 50 mg were injected into the RCA following initial coronary angiography (CAG). When coronary spasm was not induced by 50 mg of ACh, ACh was continuously administered until the maximum dose of 80 mg. CAG was then performed after administration of the maximum dose of ACh or induction of coronary spasms, whichever came first. SPT of the left coronary artery (LCA) was carried out without

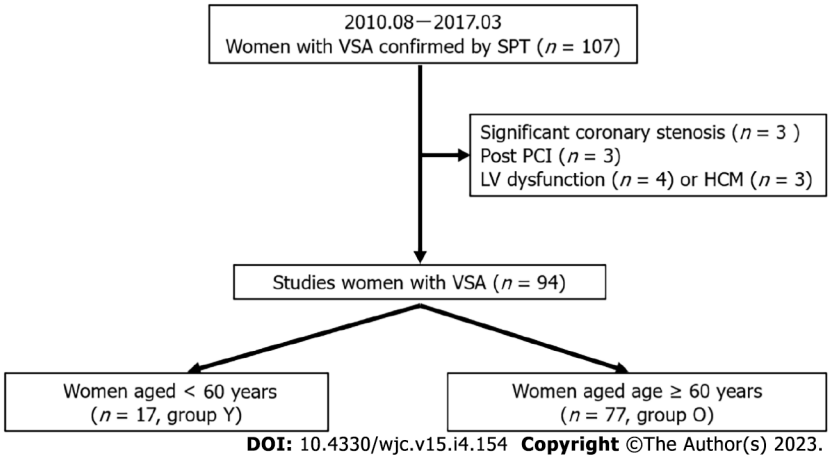

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Figure 1 The flowchart of the study. HCM: Hypertrophic cardiomyopathy; PCI: Percutaneous coronary intervention; VSA: Vasospastic angina; Group O: Older than 60 years of age; Group Y: Younger than 60 years of age.

intracoronary injection of nitroglycerin (NTG) into the RCA if the coronary spasms spontaneously resolved. In such circumstances, NTG injection into the RCA was performed after performing the SPT for the LCA. An intracoronary injection of 0.3 mg NTG was administered to ease spasms if the Ach-induced coronary spasms were severe enough to cause hemodynamic instability; this was referred to as the unavoidable use of NTG[13]. SPT of the LCA was then carried out using 50 and 100 mg of ACh. When coronary spasm was not induced by 100 mg of ACh, ACh was continuously administered until the maximum dose of 200 mg. CAG was then performed after administration of the maximum dose of ACh or the induction of coronary spasms, whichever came first. The final CAG for the LCA was performed after an intracoronary injection of 0.3 mg of NTG.

As previously shown[4], we employed an autoinjector. The coronary artery diameter was measured in accordance with the previous methods[4]. Atherosclerotic lesions were defined as those with a stenosis > 20%. We also explored the likelihood of myocardial bridging (MB), which was defined as systolic reduction > 20% in the coronary artery diameter[14].

Definitions of VSA-related parameters

Angina pectoris was classified into three patterns: resting, exertion, and both resting and exertion. For anginal symptoms, the number of attacks per month, maximum attack duration (minutes), and estimated duration of disease (months) were also calculated. VSA was defined as > 90% narrowing of coronary arteries on angiograms when provoked and accompanied by the presence of usual chest pain and/or the presence of an ST-segment deviation on electrocardiogram (ECG)[15]. Focal spasm was defined as transient vessel narrowing of > 90% within the borders of one isolated coronary segment, as defined by the American Heart Association. Diffuse spasm was defined as 90% diffuse vasoconstriction observed in ≥ 2 adjacent coronary segments of the coronary arteries[10]. Multivessel spasms (MVS) were defined as coronary spasms that occurred in ≥ 2 major coronary arteries. For multivessel spasms, we could not assess when the subsequent SPT was negative after an unavoidable use of NTG[16]. Regarding the presence of coronary spasm per vessel, the frequency of coronary spasms in the left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), and RCA were reviewed.

Other clinical characteristics measured in the present study

Patients were asked about their smoking status and family history of coronary artery disease. Smoking status was classified as active smokers, former smokers (had stopped smoking for at least 1 mo), or never smokers. In the logistic analysis, smoking was defined as the combined number of active and former smokers. Hypertension, dyslipidemia, diabetes mellitus, metabolic syndrome (MtS), and chronic kidney disease (CKD) were defined based on the standard definitions described in previous papers[4]. Patients or family members were asked about their alcohol consumption, and those who drank at least once a week were defined as having alcohol consumption[17]. Blood chemical parameters, including the estimated glomerular filtration ratio (eGFR, mL/min/1.73 m^2) and brain natriuretic peptide level (BNP, pg/mL), were routinely investigated on the same day of CAG. The left ventricular ejection fraction was measured using cardiac ultrasonography. On brachial echosonography, flow-mediated dilation (FMD), as an endothelium-dependent function, and NTG-induced dilation (NID), as an endothelium-independent function, were measured as previously described[18].

All study participants made at least one follow-up visit at our facility, and patients were followed-up as closely as was practical after discharge. The last date of data collection was in October 2022. Information from the medication diaries of patients who had recently made a follow-up visit was

included in the follow-up assessments. We recorded the number of consumed coronary vasodilators monthly and angina events over the past 3 mo. These evaluations were performed on patients who could be assessed at least 6 mo after discharge (n = 85). The number of coronary vasodilators used was also evaluated during hospital admission, discharge, and final follow-up. For each patient, cardiac events, including readmission for angina or other cardiovascular conditions, were recorded. Readmission due to cardiovascular conditions or death from cardiac causes were considered as major adverse cardiac events (MACEs).

Statistical analyses

Data are presented as mean ± standard deviation or median with interquartile ranges for non-normally distributed data and non-continuous variables. Baseline characteristics of the groups were compared using Student's unpaired t-tests, Wilcoxon signed-rank tests, or χ^2 analysis, as appropriate. Logistic regression analysis was used to determine the presence of VAS in Group Y. MACEs were analyzed using the Kaplan–Meier survival curve and the logrank test. JMP Ver. 16 (SAS Institute Inc., Cary, NC, United States) was used to perform all statistical analyses. A P value < 0.05 was considered statistically significant.

RESULTS

Patients' characteristics

There were 17 patients (18%) in Group Y and 77 (82%) in Group O. The patients' characteristics are shown in Table 1. Group Y had a mean age of 54 ± 5 years and Group O had a mean age of 72 ± 7 years; the mean age was significantly lower in Group Y (P < 0.01). Although smoking was more prevalent in Group Y (P < 0.01), hypertension (P < 0.01) and CKD (P = 0.02) were less prevalent. A trend toward more frequent alcohol consumption was observed in Group Y (P = 0.09).

Regarding the blood chemical parameters, eGFR was higher in Group Y than in Group O (P = 0.05), and BNP levels tended to be lower in Group Y (P = 0.09, Table 2). Regarding the brachial ultrasonographic parameters (Table 3), the brachial artery diameter at baseline (P = 0.83) and FMD (P = 0.75) were not different between the two groups, but NID was significantly higher in Group Y (20.6% ± 8.6%) than in Group O (13.6% ± 5.3%, P < 0.01). Brachial ultrasonography was performed after at least 48 h from withdrawal of coronary dilators. The results were similar in patients who had not been taking coronary dilators to rule out the effects of these drugs.

Logistic regression analysis showed that NID [odds ratio (OR): 5.1, P = 0.02] and absence of CKD (OR: 7.5, P < 0.01) and hypertension (OR: 4.5, P = 0.03) were factors responsible for the presence of women aged < 60 years (R^2 = 0.32), while smoking tended to be associated with it (OR: 3.7, P = 0.06).

VSA-related parameters and the results of CAG-SPT

There were no differences between the two groups on whether angina occurred at rest or with exertion nor in the number of attacks, maximum attack duration, or estimated duration of illness (Table 4). The frequency of coronary dilator intake (P = 0.02) and number of coronary dilators taken before admission (P = 0.01) were significantly lower in Group Y.

Regarding CAG (Table 5), the prevalence of atherosclerosis was significantly lower in Group Y (P < 0.01), but that of MB did not differ between the two groups (P = 0.94). Regarding SPT (Table 5), the frequency of focal spasms was significantly lower in Group Y (P = 0.04), while the frequency of MVS was not significantly different among those that underwent evaluation (P = 0.56). The frequency of coronary spasms in the LAD and RCA was not different between the two groups; however, the frequency of coronary spasms in the LCX was significantly higher in Group Y (P < 0.01). The frequency of unavoidable use of NTG was also significantly higher in Group Y (P = 0.01). The incidence of ST-segment elevation on ECG during coronary spasms tended to be higher in Group Y (P = 0.09).

Prognosis

The number of prescribed coronary dilators at discharge was significantly lower in Group Y (P = 0.01). The median follow-up period was 6.4 (3.9, 8.4) years, with no difference between the two groups (Group Y: 4.3 years, Group O: 6.8 years, P = 0.12). There was no difference in the number of coronary dilators taken at the time of the last follow-up in patients who had been followed for more than 6 mo (P = 0.52), but the number of chest symptoms per month was significantly higher in Group Y (P < 0.01). There was no significant difference in the number of MACEs between the two groups (Figure 2, Logrank P = 0.40).

DISCUSSION

The present study investigated the clinical characteristics and prognosis of women aged < 60 years with VSA compared to those in women aged ≥ 60 years with VSA. Our results showed that women aged < 60

Table 1 Patients' characteristics

	Group O	Group Y	*P* value
No. (%)	77 (82)	17 (18)	
Age (yr)	72 ± 7	54 ± 5	< 0.01
Body mass index	23.7 ± 4.5	24.5 ± 5.3	0.50
Coronary risk factors (%)			
Smoking (active/former/never)	3/5/69	3/4/10	< 0.01
Hypertension	58 (75)	7 (41)	< 0.01
Dyslipidemia	55 (77)	10 (59)	0.31
Diabetes mellitus	12 (16)	2 (12)	0.68
Alcohol consumer (%)	10 (13)	5 (29)	0.09
Family history of CAD (%)	18 (23)	5 (29)	0.60
MtS (%)	13 (17)	4 (24)	0.52
CKD (%)	27 (35)	1 (6)	0.02

CAD: Coronary artery disease; CKD: Chronic kidney disease; MtS: Metabolic syndrome; No.: Number; Group O: Older than 60 years of age; Group Y: Younger than 60 years of age.

Table 2 Blood chemical parameters in the two groups

	Group O	Group Y	*P* value
Total cholesterol (mg/dL)	202 ± 33	196 ± 37	0.53
Triglyceride (mg/dL)	131 ± 73	119 ± 46	0.54
HDL-cholesterol (mg/dL)	63 ± 17	62 ± 18	0.82
LDL-cholesterol (md/dL)	113 ± 29	111 ± 32	0.82
Fasting blood sugar (md/dL)	100 ± 16	101 ± 17	0.93
Hemoglobin A1C (%)	6.0 ± 0.7	5.7 ± 0.6	0.10
C-reactive protein (mg/dL)	0.05 (0.02, 0.13)	0.07 (0.02, 0.15)	0.81
eGFR (mL/min/1.73 m^2)	68.8 ± 16.8	77.5 ± 13.2	0.05
BNP (pg/mL)	22 (14, 54)	15 (10, 29)	0.09

BNP: Brain natriuretic peptide; eGFR: Estimated glomerular filtration ratio; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Group O: Older than 60 years of age; Group Y: Younger than 60 years of age.

years with VSA were more likely to be smokers and less likely to have hypertension and CKD. Additionally, they had very good peripheral vascular function as indicated by their response to NTG. The results of CAG and SPT showed that there was less atherosclerosis and less focal spasm in women aged < 60 years with VSA. However, the frequency of coronary spasms in the LCX was high, and NTG was unavoidably used in this population. Additionally, the prognosis of women aged < 60 years with VSA was favorable as long as coronary dilators were strictly administered, although their chest symptoms persisted. These clinical characteristics should be considered in the treatment and follow-up of such patients.

Although there have been several reports on the characteristics of women with VSA[5-10], few reports have explored the characteristics of VSA by age[6]. Kawana *et al*[6] classified patients with VSA based on age: Under 50 years, 50–64 years, and over 65 years, and they found that although the prevalence of hypertension and dyslipidemia was lower in younger patients, the prevalence of smoking was higher. In the present study, the prevalence of hypertension and CKD, which was possibly induced by hypertension itself, was also significantly lower in women aged < 60 years, but these findings appear to be age-related and not limited to the presence of VSA or gender[19,20]. Meanwhile, the same was true for the prevalence of smoking in the present study, confirming that smoking is more frequent in younger age groups. Smoking is a risk factor for coronary spasms even in young women[21], and it was

Table 3 Echographic parameters in the two groups

	Group O	Group Y	*P* value
UCG			
LVEF (%)	68 ± 9	66 ± 6	0.46
Brachial ultrasonography			
All studied patients			
No.	77	17	
Heart rate (/min)	66 ± 10	67 ± 13	0.85
Mean blood pressure	100 ± 14	94 ± 14	0.16
Brachial blood flow			
Baseline (mL/min)	61 ± 44	59 ± 52	0.87
% increase	384 ± 490	327 ± 265	0.59
Brachial artery diameter (mm)			
Baseline	3.5 ± 0.5	3.5 ± 0.5	0.83
Hyperemia	3.7 ± 0.5	3.6 ± 0.5	0.88
After NTG	4.0 ± 0.5	4.2 ± 0.4	0.25
FMD (%)	4.3 ± 3.2	4.5 ± 3.3	0.75
NID (%)	13.6 ± 5.4	20.5 ± 8.6	< 0.01
Patients who did not take any coronary vasodilators			
No.	39	14	
Brachial artery diameter (mm)			
Baseline	3.5 ± 0.5	3.6 ± 0.4	0.68
Hyperemia	3.6 ± 0.6	3.7 ± 0.4	0.60
After NTG	4.0 ± 0.5	4.2 ± 0.4	0.21
FMD (%)	4.1 ± 3.1	4.3 ± 3.5	0.82
NID (%)	14.6 ± 5.7	18.5 ± 6.5	0.04

FMD: Flow-mediated dilation; LVEF: Left ventricular ejection fraction; NID: Nitroglycerin-induced dilation; NTG: Nitroglycerin; No.: Number; UCG: Echocardiography; Group O: Older than 60 years of age; Group Y: Younger than 60 years of age.

reported that smoking causes hypercontraction of vascular smooth muscles through the activation of Rho kinase[22] and/or vascular endothelial dysfunction through increased production of reactive oxygen species[23]. Thus, smoking may be an etiologic factor of VSA in women aged < 60 years.

On the other hand, NID of the brachial artery was higher in women aged < 60 years with VSA and was still a significant and influential factor even when smoking was included in the logistic regression analysis. Meanwhile, FMD did not differ between the two groups. These findings cannot be fully explained but may indicate relative vascular endothelial dysfunction and/or vascular smooth muscle hypercontraction. Smoking may have caused these vascular dysfunctions, but it is also possible that the relative decline in sex hormones during menopause may cause these changes[24]. Furthermore, it is also possible that there is a genetic problem with eNOS that may have caused vascular dysfunction[25], although we have not found significant differences in the family history of CAD between the two groups. Future large studies or registries should carefully evaluate age-specific vascular dysfunction in women with VSA.

Regarding CAD and SPT, women aged < 60 years with VSA had less atherosclerosis, which could be explained by age-related changes regardless of the presence of VSA or gender. Focal spasms were also less frequent in women aged < 60 years, which may also be related to fewer atherosclerotic lesions. Several studies have shown that focal spasm is more likely to occur at sites with atherosclerotic lesions [26,27]. However, the frequency of coronary spasm in the LCX was significantly higher in women aged < 60 years. Sueda *et al*[28] showed that coronary spasms in the LCX was significantly less than those in the RCA or LAD (28%), suggesting that the distribution of muscarinic receptors may differ according to the coronary artery vessel. Furthermore, Sueda *et al*[7] did not report any differences in terms of sex

Table 4 Vasospastic angina-related parameters in the two groups

	Group O	Group Y	*P* value
Chest symptoms			
Rest/Exercise/Both	60/9/9	14/1/2	0.78
Maximum duration of attack (min)	20 ± 27	16 ± 28	0.10
Diseased duration (M)	5 (1, 48)	12 (3, 42)	0.78
No. of anginal attacks (/M)			
At admission	4 (1, 10)	4 (1, 10)	0.43
At follow-up	0 (0, 1)	2 (0.1, 2.8)	< 0.01
No.	69	16	
Medications			
Taking statins at admission (%)	36 (47)	7 (46)	0.68
Taking antiplatelet drugs at admission (%)	20 (26)	1 (6)	0.07
Taking vasodilators at admission (%)	38 (49)	3 (18)	0.02
No. coronary vasodilators			
At admission	0 (0,1)	0 (0, 0)	0.01
	0.6 ± 0.7	0.2 ± 0.4	0.01
At discharge	1 (1, 1)	1 (1, 1)	0.01
	1.2 ± 0.5	0.9 ± 0.3	0.02
At follow-up	1 (1, 2)	1.5 (1, 2)	0.52
	1.5 ± 0.9	1.6 ± 0.9	0.53

M: Months; No.: Number; VSA: Vasospastic angina; Group O: Older than 60 years of age; Group Y: Younger than 60 years of age.

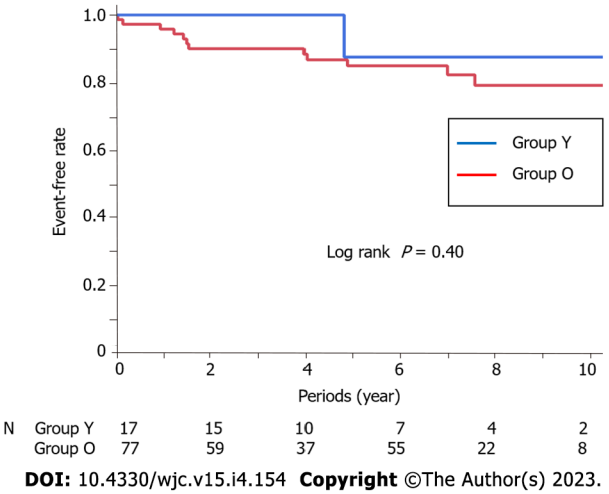

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Figure 2 The Kaplan–Meier curve for MACE-free survival during the follow-up period in the two groups. O group: Older than 60 years of age; MACE: Major adverse cardiac events; N: Number; Y group: Younger than 60 years of age.

regarding the frequency of coronary spasms in the LCX. In the present study, SPT was initiated in the RCA and shifted to the LCA; it is possible that the frequency of coronary spasms in the LCX may differ depending on where SPT is initiated. In any case, the fact that coronary spasms in the LCX were more frequent in women aged < 60 years suggests that muscarinic receptor distribution may change with age in women with VSA. The unavoidable use of NTG was reported to be associated with more active coronary spasms[13], which may suggest that women aged < 60 years with VSA have more active coronary spasms.

Table 5 Coronary angiography spasm provocation test parameters in the two groups

	Group O	Group Y	*P* value
CAG			
Atherosclerotic change (%)	47 (61)	0 (0)	< 0.01
Myocardial bridging (%)	13 (17)	3 (18)	0.94
SPT			
Focal/diffuse/focal and diffuse	16/48/33	0/15/2	0.08
Presence of focal spasm (%)	29 (38)	2 (12)	0.04
Multi-vessels spasm (%, No.)	39 (57, 68)	8 (67, 12)	0.56
Vessels of spasm			
RCA (%, No.)	44 (62, 71)	10 (67, 15)	0.72
LAD (%, No.)	70 (96, 73)	13 (93, 14)	0.62
LCX (%, No.)	5 (7, 72)	5 (38, 13)	< 0.01
An unavoidable use of NTG (%)	14 (18)	8 (47)	0.01
ST deviation during SPT (%)	10 (13)	5 (29)	0.09

CAG: Coronary angiography; LAD: Left anterior descending coronary artery; LCX: Left circumflex coronary artery; No.: Number; NTG: Nitroglycerin; RCA: Right coronary artery; SPT: Spasm provocation test; Group O: Older than 60 years of age; Group Y: Younger than 60 years of age.

Regarding the prognosis, Kawana *et al*[6] reported that women aged < 50 years with VSA had poorer prognoses than those aged ≥ 50 years. In the present study, the prognoses of patients aged < 60 years and ≥ 60 years were similar. This may be due to the small number of cases and the cut-off age of 60 years in this study rather than 50 years. Nevertheless, the fact that focal spasm, a marker of poor prognosis[10,27], was less frequent in patients younger than 60 years and that younger women with VSA have a poorer prognosis[6] and required more coronary dilators may explain the similar prognosis in the two groups. Chest symptoms were significantly more frequent at follow-up in younger patients with VSA, possibly indicating that these patients had more active coronary spasms.

The implications of the present study are as follows: vascular dysfunction is present in relatively young patients with VSA, and since smoking may be a risk factor, it may be important to encourage women to quit smoking immediately. Additionally, because these patients may have more active coronary spasms, it is important to monitor and maintain them with increasing doses of coronary dilators to improve chest symptoms.

This study had several limitations. First, it was a single-center study with a small number of patients, and the distribution of patients was unequal in the studied groups. Thus, the results may not be applicable to all patients experiencing coronary spasms. Furthermore, due to the small number of cases, it was not possible to classify the patients into three groups as in the study of Kawana *et al*[6]. More studies with considerable sample size are needed to support the findings in this study. Second, this study was conducted on women with VSA, and we do not have data from our institution regarding vascular function in men with VSA or in healthy women. Therefore, it is difficult to conclude whether the findings in this study are truly characteristic of women aged < 60 years with VSA. Future large studies and multicenter registries should clarify this issue. Finally, brachial artery echocardiography was performed on the day before SPT and after discontinuation of coronary dilators. We concluded that these findings were true because the results were similar in patients who were not taking coronary dilators. Nevertheless, we cannot rule out the possibility that the results of brachial artery echocardiography may have been influenced by the residual effects of withdrawal of coronary vasodilators.

CONCLUSION

In conclusion, we examined the clinical characteristics and prognosis of women aged < 60 years with VSA and compared them to women aged ≥ 60 years with VSA, revealing that these patients were more likely to be smokers and have vascular dysfunction. The frequency of atherosclerosis and focal spasms was low, but the frequency of coronary spasms in the LCX was high. They were also more likely to unavoidably use NTG, suggesting that they may have more active coronary spasms. Such patients should be carefully monitored by increasing the use of coronary dilators and encouraged to quit smoking, if they smoke. Cardiologists need to be reminded that young women with VSA have high

coronary spasm activity.

ARTICLE HIGHLIGHTS

Research background

We frequently encounter cases of women with vasospastic angina (VSA). Additionally, some women with VSA are younger than 60 years old.

Research motivation

However, it is unknown whether the characteristics of VSA in women aged <60 years are different from those in women aged ≥ 60 years.

Research objectives

The objective of the present study was to investigate and compare the clinical characteristics and prognosis of VSA in women aged < 60 years from those in women aged ≥ 60 years.

Research methods

We enrolled 94 women with VSA who were diagnosed using the spasm provocation test (SPT). According to the age at diagnosis, the patients were divided into two groups: Group Y (age < 60 years, n = 17) and Group O (age ≥ 60 years, n = 77). Flow-mediated dilation (FMD) and nitroglycerin (NTG)-induced dilation (NID) of the brachial artery were performed and assessed using brachial ultrasonography. Moreover, conventional coronary risk factors, such as atherosclerotic lesions (stenosis > 20%) detected using coronary angiography and focal spasms (coronary spasm within one segment of one coronary artery), and major cardiovascular adverse events (MACE) were assessed in both groups.

Research results

Smoking was more prevalent in Group Y than in Group O (P = 0.04). FMD was similar in both groups (Group O: 4.3% ± 3.2%, Group Y: 4.5% ± 3.3%; P = 0.75), whereas NID was higher in Group Y (20.5% ± 8.6%) than in Group O (13.6% ± 5.3%, P < 0.01). Atherosclerosis was not detected in Group Y but was detected in Group O (61%, P < 0.01). Focal spasms were less frequent in Group Y (12%) than in Group O (38%, P = 0.04). The incidence of MACEs did not differ between the two groups (P = 0.40).

Research conclusions

Women aged < 60 years with VSA have less atherosclerotic lesions and focal spasms. These characteristics may be affected by smoking habits and vascular smooth muscle dysfunction.

Research perspectives

Vascular dysfunction is present in relatively young patients with VSA, and since smoking may be a risk factor, it may be important to encourage women to quit smoking immediately. Additionally, because these patients may have more active coronary spasms, it is important to monitor and maintain them with increasing doses of coronary dilators to improve chest symptoms.

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FOOTNOTES

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

Institutional review board statement: The study was reviewed and approved by the JR Hiroshima Hospital Institutional Review Board (Approval No. 2022-38).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. Furthermore, in the retrospective cohort study, we have shown the information about the present study, on our web site (http://www.jrhh.sakura.ne.jp/annnai/torikumi.html), as an opt-out method.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Observational Study

Right ventricle dysfunction does not predict mortality in patients with SARS-CoV-2-related acute respiratory distress syndrome on extracorporeal membrane oxygenation support

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Abstract

BACKGROUND

The prognostic role of right ventricle dilatation and dysfunction (RVDD) has not been elucidated in patients with coronavirus disease (COVID)-related respiratory failure refractory to standard treatment needing extracorporeal membrane oxygenation (ECMO) support.

AIM

To assess whether pre veno-venous (VV) ECMO RVDD were related to in-intensive care unit (ICU) mortality.

METHODS

We enrolled 61 patients with COVID-related acute respiratory distress syndrome refractory to conventional treatment submitted to VV ECMO and consecutively admitted to our ICU (an ECMO referral center) from 31th March 2020 to 31th August 2021. An echocardiographic exam was performed immediately before VV ECMO implantation.

RESULTS

Males were prevalent (73.8%) and patients with a body mass index > 30 kg/m^2 were the majority (46/61, 75%). The overall in-ICU mortality rate was 54.1% (33/61). RVDD was detectable in more than half of the population (34/61, 55.7%) and associated with higher simplified organ functional assessment (SOFA) values (P = 0.029) and a longer mechanical ventilation duration prior to ECMO support (P = 0.046). Renal replacement therapy was more frequently needed in RVDD patients (P = 0.002). A higher in-ICU mortality (P = 0.024) was observed in RVDD patients. No echo variables were independent predictors of in-ICU death.

CONCLUSION

In patients with COVID-related respiratory failure on ECMO support, RVDD (dilatation and dysfunction) is a common finding and identifies a subset of patients characterized by a more severe disease (as indicated by higher SOFA values and need of renal replacement therapy) and by a higher in-ICU mortality. RVDD (also when considered separately) did not result independently associated with in-ICU mortality in these patients.

Key Words: Right ventricle; Echocardiography; Mortality; COVID; Acute respiratory distress syndrome; Right ventricle-pulmonary circulation coupling

Core Tip: In coronavirus disease-related respiratory failure on extracorporeal membrane oxygenation support right ventricle dilatation and dysfunction (defined as the coexistence of dilatation and dysfunction) is a common finding and identifies a subset of patients characterized by a more severe disease (as indicated by higher Sequential Organ Failure Assessment values and need of renal replacement therapy) and by a higher in-intensive care unit (ICU) mortality. However, at logistic regression analysis, right ventricle dilatation and dysfunction (even when considered separately) did not result independently associated with in-ICU mortality in these patients.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease can evolve in some cases in severe respiratory failure, refractory to conventional therapies, which requires veno-venous extracorporeal membrane oxygenation (VV ECMO) support, possibly in experienced centers[1-3]. In coronavirus disease (COVID) respiratory disease, right ventricular (RV) dilatation is frequently encountered especially in severe disease[4,5], but, to date, the prognostic role of RV dilatation has not completed elucidated. In acute respiratory distress syndrome (ARDS) from different etiologies on ECMO support[3] RV dilatation and dysfunction (RVDD) were negatively associated with early outcome, while the prognostic role of RVDD has not been elucidated in patients with COVID-related respiratory failure refractory to standard treatment needing ECMO. We hypothesize that pre ECMO RVDD is related to in-intensive care unit (ICU) mortality, and we tested this hypothesis in 61 consecutive patients with COVID-related ARDS on ECMO support.

MATERIALS AND METHODS

In our prospective observational study, we enrolled 61 patients with COVID-related ARDS refractory to conventional treatment submitted to VV ECMO and consecutively admitted to our ICU (an ECMO referral center) from 31th March 2020 to 31th August 2021. No exclusion criteria. The study protocol was approved by our Ethical Committee ("Comitato Etico Area Vasta Centro" n.17024, approved on March 31th 2020) ("Florence COVID ICU Registry"). The written inform consent for each patient was waived for emerging infectious disease. The need for ECMO support was communicated to the patient's relatives by phone before implantation.

On ICU admission we measured: Troponin (pg/mL), N-terminal-pro brain natriuretic peptide (NT-BNP, pg/mL), C-reactive protein (mg/dL) creatinine (mg/dL), lactose dehydrogenase (UI/L), D-dimer (ng/mL), and interleukin 6 (pg/mL). According to our echocardiography protocol[3,5], an echocardiographic exam was performed immediately before ECMO implantation. Systolic pulmonary artery pressure (sPAP) is obtained using the simplified Bernouilli's equation. RVDD was defined in presence of RVEDA/LVEDA > 0.6 and tricuspid annular plane systolic excursion (TAPSE) < 15 mm (M-mode). Coupling of RV function to the pulmonary circulation was evaluated as the TAPSE to sPAP ratio. Each echo measure is performed three times, and the mean value was recorded[4,6].

All ultrasound cardiac procedures were performed using the necessary protective equipment for professionals. Dedicated machines (Ge HealthCare machine) were used in the COVID ICU and transducers are wrapped in single-use plastic covers. We considered VV ECMO in COVID when respiratory failure persisted despite optimum management including controlled ventilation with tidal volume 6 mL/kg, plateau pressure < 30 cm H_2O, use of neuromuscular blockers, high-positive end-expiratory pressure, and repeated prone positioning sessions[1-3,7,8]. All patients were encouraged to mobilize early[3]. Outcome was death in the ICU.

Statistical analysis

Data have been stored in a dedicated database and analyzed with SPSS for Windows 20.0 (SPSS Inc., Chicago, IL). *P* value less than 0.05 was considered statistically significant. Categorical variables are reported as frequencies and percentages; continuous variables are reported as mean ± standard deviation (SD) or median (range), as needed. Comparisons between the groups were performed using Chi square for categorical data, and student's *t* test and Kruskal-Wallis test for continuous data. Logistic regression backwards models have been developed to detect predictor(s) for ICU-death. Variables were selected based on univariate analysis and on clinical criteria. To avoid overfitting, each model included three variables. Receiver operating curve (ROC) was constructed to identify the cut-off for age and duration of pre-ECMO mechanical ventilation in relation to ICU-death.

RESULTS

Our population comprised 61 consecutive patients with COVID-related respiratory failure on ECMO support (Table 1). Patients transferred from peripheral hospitals accounted for the 62% of our population. Males were prevalent (73.8%) and patients with a body mass index > 30 kg/m^2 were the majority (46/61, 75%). Renal replacement therapy was needed in almost half of the entire population (48%). Renal replacement therapy was started on ICU admission in five patients (17%) and after ECMO start in the remaining 24 patients (83%). The overall in-ICU mortality rate was 54.1% (33/61). At echocardiography left ventricular ejection fraction (LVEF) was normal in all but three patients who had LVEF < 45% because of previously known heart disease.

RVDD vs no RVDD

Table 1 shows the comparison between patients with RVDD and those without. In the entire population, RVDD was detectable in more than half of the population (34/61, 55.7%). In the comparison between the two subgroups, patients with RVDD showed higher values of simplified organ functional assessment (SOFA) (P = 0.029) and a longer mechanical ventilation duration prior to ECMO support (P = 0.046). Renal replacement therapy was more frequently needed in RVDD patients (P = 0.002). A higher in-ICU mortality (P = 0.024) was shown in RVDD patients. Higher values of NT-pro BNP were observed in RVDD patients (P = 0.014). At echocardiography, RVDD patients exhibited higher values of sPAP (P = 0.015), E/e1 (P = 0.0003) and lower TAPSE/sPAP (P = 0.001). Higher doses of norepinephrine were needed in patients with RVDD (P = 0.011) when compared with those without. No differences were detectable in ventilatory parameters between the two subgroups.

Survivors vs no survivors

Table 2 shows the comparison between survivors and no survivors. No survivors were older (P = 0.003) and showed a higher SOFA (P = 0.010) and a longer mechanical ventilation duration before ECMO implantation (P = 0.006). Among biohumoral data, creatinine values were significantly higher in no survivors (P = 0.030), with no other significant difference between the two subgroups. Echocardiography, performed before ECMO implantation, did not show any significant difference between survivors and no survivors.

Multivariate logistic regression analysis

Different models were calculated (Table 3). The following parameters resulted independent predictors of in-ICU death: Age, SOFA, time from symptoms' onset, mechanical ventilation preECMO ≥ 10 d and creatinine. RV dilatation, RV dysfunction and RVDD (dilatation and dysfunction) were not independently associated with in-ICU mortality. At ROC analysis, the age cut-off was ≥ 57 years [area under the curve: 70.5% (95% confidence interval: 57.3- 83.7%), P = 0.006, sensitivity 72.7%, specificity 58.0%].

DISCUSSION

The main finding of the present investigation is that, in COVID-related respiratory failure on ECMO support, RVDD (defined as the coexistence of dilatation and dysfunction) is a common finding. The

Table 1 Comparison between patients with right ventricle dilatation and dysfunction and those without, *n* %

Variable	All patients	RVDD (No. 34)	No RVDD (No. 27)	*P* value
Clinical data				
Age (yr), mean ± SD	54.3 ± 10.3	53.8 ± 9.7	52.9 ± 11	0.735
Gender, M/F	45/16 (74/26)	28/6 (82/18)	17/10 (63/37)	0.087
BMI (kg/m^2), mean ± SD	32.9 ± 5.3	32.4 ± 5.6	32.7 ± 4.9	0.836
Charlson index, median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.772
Transferred from peripheral hospitals	38 (62)	18 (52)	20 (74)	0.9
Time from symptoms' onset to ICU (d), median (IQR)	13 (10-13)	9 (8-12)	12 (10-14)	0.075
SOFA, median (IQR)	8.0 (7.0-10.0)	10 (8-10)	7 (6-10)	0.029
Mechanical ventilation length to ECMO support (d), median (IQR)	6.0 (8.0-11.0)	8.5 (6-12)	7 (4-10)	0.046
ECMO duration (d), median (IQR)	22 (13-42)	24.5 (9-44)	21 (15-35)	0.765
Renal replacement therapy	29 (48)	22 (65)	7 (26)	0.002
ICU death	33 (54.1)	21 (62)	12 (44)	0.024
Biohumoral data				
Creatinine (mg/dL), median (IQR)	1.00 (0.72-1.86)	0.83 (0.61-1.34)	1.65 (0.78-2.00)	0.025
D-dimer (ng/mL), median (IQR)	3594 (2252-7214)	3748 (1740-12085)	3550 (2368-5007)	0.425
CRP (mg/dL), median (IQR)	142 (88-144)	121 (87-174)	165 (98-212)	0.55
IL-6 (pg/mL), median (IQR)	34 (7.4-70.0)	45 (6.9-105.0)	34 (21-58.0)	0.772
Troponin (pg/mL), median (IQR)	21 (14.0-38.0)	33.0 (14.0-112.0)	21.0 (8.5-48.0)	0.253
NT-pro BNP (pg/mL), median (IQR)	874 (345-1654)	735 (252-1467)	1273 (585-1868)	0.058
LDH IU/L, median (IQR)	465 (375-538)	421 (363-510)	473 (424-542)	0.078
Echocardiographic data				
LVEF (%), mean ± SD	63.9 ± 7.6	64.3 ± 7.9	64.5 ± 7.5	0.113
RV/LV, mean ± SD	0.58 ± 0.17	0.69 ± 0.08	0.45 ± 0.14	0.0001
TAPSE (mm), mean ± SD	18.0 (10.0-21.0)	13.9 (10.0 ± 14.5)	17.4 (16.0-22.5)	0.015
sPAP (mmHg), mean ± SD	58.4 ± 9.4	64 ± 11	59.1 ± 7.7	0.015
e/e1	11 ± 3	12 ± 3	9 ± 3	0.0003
TAPSE/sPAP (mm/mmHg), mean ± SD	0.28 ± 0.13	0.19 ± 0.10	0.28 ± 0.11	0.001
Ventilatory parameters				
PEEP (cm H_2O), mean ± SD	12.2 ± 2.3	12.4 ± -2.4	12.1 ± 2.6	0.64
PO_2/FiO_2, mean ± SD	62 (50-88)	66 (54-88)	60 (50-88)	0.442
Norepinephrine, mean ± SD	0.34 ± 0.22	0.39 ± 0.26	0.24 ± 0.10	0.011

IQR: Interquartile range; RVDD: Right ventricle dilatation and dysfunction; BMI: Body mass index; ICU: Intensive care unit; LOS: Length of stay; CRP: C-reactive protein; IL-6: Interleukin 6, SOFA: Simplified organ functional assessment; ECMO: Extracorporeal membrane oxygenation; NT pro BNP: N terminal pro brain natriuretic peptide; RV: Right ventricle; LV: Left ventricle; EF: Ejection fraction; TAPSE: Tricuspid annular plane systolic excursion; sPAP: Systolic pulmonary arterial pressure; LDH: Lactate dehydrogenase; LVEF: Left ventricular ejection fraction; PEEP: Positive end-expiratory pressure.

presence of RVDD identifies a subset of patients characterized by a more severe disease (as indicated by higher SOFA values and need of renal replacement therapy) and by a higher in-ICU mortality. However, at logistic regression analysis, RVDD (even when considered separately) did not result independently associated with in-ICU mortality in these patients.

Growing evidence suggests that, in COVID respiratory failure, varEchoious echocardiographic patterns may be observed across disease severity progression, ranging from isolated systolic pulmonary hypertension to RVDD. Studies are quite often heterogeneous, especially in respect to selected echo parameters and definition of RV dysfunction and dilatation. In a small series of mechanically ventilated

Table 2 Comparison between survivors and no survivors, *n* %

Variable	All patients	Survivors (No. 28)	No survivors (No. 33)	*P* value
Clinical data				
Age (yr), mean ± SD	54.3 ± 10.3	50.1 ± 11.6	58.0 ± 7.3	0.003
Gender, M/F	45/16 (73.8/26.2)	18/10 (40.0/62.5)	6/27 (60.0/37.5)	0.121
BMI (kg/m^2), mean ± SD	32.9 ± 5.3	31.8 ± 4.0	33.8 ± 6.1	0.138
Charlson index, median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.772
Time from symptoms' onset to ICU (d), median (IQR)	13 (10-13)	10 (8-13)	13 (10-15)	0.066
SOFA, median (IQR)	8.0 (7.0-10.0)	7.5 (5.5-9.0)	10.0 (8.0-10.0)	0.01
Mechanical ventilation length to ECMO support (d), median (IQR)	6.0 (8.0-11.0)	6.5 (4.5-9.5)	10.0 (7.0-12.0)	0.006
ECMO duration (d), median (IQR)	22 (13-42)	35 (19-48)	18 (10-30)	0.015
ICU death	33 (54.1)	-	-	-
Biohumoral data				
Creatinine (mg/dL), median (IQR)	1.00 (0.70-1.88)	0.82 (0.60-1.35)	1.60 (0.77-2.00)	0.03
D-dimer (ng/mL), median (IQR)	3694 (2153-7326)	3948 (1740-13095)	3600 (2378-5007)	0.418
CRP (mg/dL), median (IQR)	140 (86-143)	120 (85-172)	164 (97-215)	0.553
IL-6 (pg/mL), median (IQR)	35.5 (7.9-71.0)	46.5 (6.8-107.0)	35.5 (20.5-59.0)	0.851
Troponin (pg/mL), median (IQR)	20.5 (15.0-39.0)	34.0 (15.0-115.0)	22.0 (9.0-50.0)	0.281
NT-pro BNP (pg/mL), median (IQR)	875 (355-1754)	734 (254-1542)	1272 (586-1870)	0.064
LDH IU/L, median (IQR)	466 (378-540)	423 (367-513)	475 (426-543)	0.089
Echocardiographic data				
LVEF (%)	63.9 ± 7.6	65.6 ± 8.1	62.5 ± 6.9	0.113
RV/LV	0.58 ± 0.17	0.58 ± 0.19	0.58 ± 0.16	0.945
TAPSE (mm)	18.0 (10.0-21.0)	19.0 (10.0 ± 22.5)	18.0 (10.0-21.0)	0.375
RVDD	34 (55.7)	13	21	0.275
sPAP (mmHg)	58.4 ± 9.4	60.2 ± 7.6	61.3 ± 10.7	0.638
E/e1	11 ± 3	10.7 ± 2.9	11.6 ± 3.7	0.34
TAPSE/sPAP (mm/mmHg)	0.28 ± 0.13	0.29 ± 0.13	0.27 ± 0.13	0.692
Ventilatory parameters				
PEEP (cm H_2O)	12.2 ± 2.3	12.3 ± 2.3	12.2 ± 2.4	0.91
PO_2/FiO_2	62 (50-88)	66 (54-88)	60 (50-88)	0.442
Norepinephrine (μg/kg/min), mean ± SD	0.34 ± 0.22	0.30 ± 0.20	0.35 ± 0.24	0.388

IQR: Interquartile range; RVDD: Right ventricle dilatation and dysfunction; BMI: Body mass index; ICU: Intensive care unit; LOS: Length of stay; CRP: C-reactive protein; IL-6: Interleukin 6; SOFA: Simplified organ functional assessment; ECMO: Extracorporeal membrane oxygenation; NT pro BNP: N terminal pro brain natriuretic peptide; RV: Right ventricle; LV: Left ventricle; EF: Ejection fraction; TAPSE: Tricuspid annular plane systolic excursion; sPAP: Systolic pulmonary arterial pressure; LDH: Lactate dehydrogenase; LVEF: Left ventricular ejection fraction; PEEP: Positive end-expiratory pressure.

COVID patients, acute pulmonary hypertension (observed in the 39%) was associated with higher 30-d mortality[9]. Likewise, in a retrospective investigation including 214 patients, RV dysfunction, pulmonary hypertension, and moderate to severe tricuspid regurgitation were associated with increased odds for 30-d mortality[10]. In 98 consecutive COVID-related respiratory failure, three different subgroups were identified at serial echocardiograms according to the presence/occurrence and timing of RVDD (defined as the association of RVDD), that is admission RVDD, new onset RVDD, no RV changes. Admission and newly developed RVDD subgroups identified severe COVID respiratory disease which in a high percentage of cases needed ECMO support[11]. In the present investigation, the

Table 3 Multivariate logistic regression analysis (intensive care unit death outcome)

Model	OR	95%CI	*P* value
Model 1			
Age (yr)	1.09	1.02-1.16	0.015
SOFA	1.26	0.99-1.62	0.062
Admission RV/LV	0.64	0.02-21.42	0.805
Model 2			
SOFA	1.24	0.98-1.56	0.062
RV DYS	0.98	0.31-3.84	0.985
Creatinine (mg/dL)	1.78	0.82-3.11	0.14
Model 3			
Age (yr)	1.1	1.03-1.18	0.005
BMI (kg/m^2)	1.09	0.97-1.22	0.138
TAPSE (mm)	0.97	0.89-1.06	0.544
Model 4			
SOFA	1.29	1.03-1.61	0.026
BMI (kg/m^2)	1.06	0.95-1.19	0.278
TAPSE/SPAP (mm/mmHg)	2.53	0.03-20.92	0.68
Model 5			
BMI (kg/m^2)	1.1	0.98-1.24	0.107
Charlson index	0.59	0.29-1.18	0.133
Time from symptom's onset (d)	1.26	1.02-1.56	0.032
Model 6			
NT pro BNP (pg/mL)	0.99	0.97-1.02	0.517
Mechanical ventilation to ECMO ≥ 10 (d)	4.64	1.42-15.12	0.011
Creatinine (mg/dL)	2.56	1.16-5.67	0.02

BMI: Body mass index; SOFA: Symplified organ functional assessment; RV: Right ventricle; TAPSE: Tricuspid annular plane systolic excursion; sPAP: Systolic pulmonary arterial pressure; ECMO: Extracorporeal membrane oxygenation; NT-pro BNP: N terminal pro brain natriuretic peptide; OR: Odd ratio; CI: Confidence index.

study population comprises the most severe state of COVID-related respiratory failure, refractory to standard treatment and requiring ECMO support in whom RVDD (dilatation and dysfunction) is quite common being detectable in more than a half of the entire population. Few data are available on echocardiographic data in patients with COVID-related respiratory failure on ECMO support.

In the series by Bleakley *et al*[11] quite a large proportion of enrolled patients (38/90, 42%) were on ECMO support, but they were not analysed separately. Kopanczyk *et al*[12] performed echocardiography in 11 consecutive patients on ECMO and observed that RV dysfunction (as indicated by abnormal free wall longitudinal strain and fractional area change) was present in the majority (9/11 patients). RV dysfunction was defined as RV dilatation (visual assessment) and abnormal septal motion in the study by Ortiz *et al*[13] who documented that no echo variable was predictor of outcomes (survival to discharge and survival to decannulation) in 64 COVID patients on ECMO (echocardiography performed post cannulation). In a small series of COVID patients on ECMO, we observed, by means of serial echocardiographic exams, that RVDD (defined as the coexistence of dilatation and dysfunction) may be reversible, especially in survivors[13]. We confirm and extend previous findings in a larger series, focusing on the prognostic role (if any) of RVDD for in-ICU death. According to our data, patients with RVDD showed a more severe disease (as indicated by SOFA) and a higher incidence of renal impairment (as inferred by the higher use of renal replacement therapy). Higher values of systolic pulmonary arterial pressure and of NT-pro BNP, observed in RVDD patients, suggest increased RV pressure which might contribute to renal impairment. The lack of differences in creatinine serum values between patients with RVDD and those without can be due to renal replacement therapy itself which does affect creatinine levels. Despite the higher in-ICU mortality observed in patients with RVDD,

RVDD (even when considered separately) are not independent predictor of early death in our population. This might be due to several factors. Firstly, the high incidence of RVDD in these patients, in agreement with previous investigations[3,12,13]. Secondly, at serial echocardiographic assessments, RVDD may be reversible in COVID-related respiratory failure on ECMO support, though a percentage of critically ill COVID patients has been reported to develop RVDD during ICU course[13].

Finally, factors other than RV echo variables can independently predict in-ICU death in COVID-related refractory respiratory failure on ECMO support, such as age and duration of mechanical ventilation. The high frequency of RVDD may be responsible for the lack of association between echocardiographic data and mortality in our patients. Our results are in keeping with those reported by investigations enrolling only critically ill COVID patients who, similarly, were not able to detect a relation between mortality and RV dilatation[13].

In our series, multivariate logistic regression analysis identified the following predictors of in-ICU analysis: Age, severity of disease (as inferred by SOFA and creatinine values) and COVID-disease duration (indicated by time from symptoms' onset) and mechanical ventilation pre-ECMO. A longer time from symptoms' onset to ICU suggests more severe forms of disease, characterized by more pronounced pulmonary derangements, often unresponsive to therapy. Age is a well-known strong predictor in COVID respiratory failure, in line with recent evidence[1] and, though we enrolled patients aged < 65 years according to guidelines, the ROC-determined cut-off was 57 years in our series. Regarding the duration of pre-ECMO mechanical ventilation to date there is no clear indication on the optimal duration of mechanical ventilation before ECMO implantation in COVID disease. Extracorporeal Life Support Organization guidelines report that a period of more than 10 d of mechanical ventilation should be considered a contraindication for ECMO support, while a period of 7 d is reported as a cut-off by other studies[1,2].

Limitations of the study

This is a single centre investigation, including a limited number of patients. On the other hand, ours is a high-volume ECMO centre. Indeed 61 COVID patients on ECMO support were managed at our center in a 15-mo period, treated by the same intensive care team.

CONCLUSION

In patients with COVID-related respiratory failure on ECMO support RVDD (dilatation and dysfunction) is a common finding and identifies a subset of patients characterized by a more severe disease (as indicated by higher SOFA values and need of renal replacement therapy) by a higher in-ICU mortality. RVDD (also when considered separately) did not result independently associated with in-ICU mortality in these patients.

ARTICLE HIGHLIGHTS

Research background

Echocardiography is recognized as a clinical tool in coronavirus disease (COVID)-related respiratory failure needing veno-venous extracorporeal membrane oxygenation (VV ECMO).

Research motivation

The assessment of the prognostic role of right ventricle dilatation and dysfunction (RVDD) in COVID-related respiratory failure refractory to standard treatment requesting ECMO.

Research objectives

In COVID-related respiratory failure on ECMO RVDD is a common finding and identifies a subset of patients characterized by a more severe disease (as indicated by higher sequential organ failure assessment values and need of renal replacement therapy) by a higher in-intensive care unit (ICU) mortality. RVDD (also when considered separately) did not result independently associated with in-ICU mortality in these patients.

Research methods

Observational single center study.

Research results

An echocardiographic examination was performed before ECMO implantation.

Research conclusions

In patients with COVID-related respiratory failure on ECMO support, RVDD is a common finding and identifies a subset of patients characterized by a more severe disease and by a higher in-ICU mortality. RVDD (also when considered separately) did not result independently associated with in-ICU mortality in these patients.

Research perspectives

Risk stratification in COVID-related refractory respiratory failure.

FOOTNOTES

Author contributions: Lazzeri C was the guarantor and designed the study; Batacchi S, Cianchi G, Franci A and Socci F participated in the acquisition, analysis, and interpretation of data; Bonizzoli M, Chiostri M and Peris A drafted the initial manuscript; and all authors revised the article critically for important intellectual content.

Institutional review board statement: The study protocol was approved by our Ethical Committee ("Comitato Etico Area Vasta Centro" n.17024, approved on March 31th 2020) ("Florence COVID ICU Registry").

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ORIGINAL ARTICLE

Observational Study

Perioperative coagulation activation after permanent pacemaker placement

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Abstract

BACKGROUND

Bradyarrhythmias are typically treated with permanent pacemakers (PM). The elimination of bradyarrhythmia by PM implantation improves the patient's quality of life and prognosis, but it can also result in a number of sequalae. It is still unclear how PM implantation affects the hemostasis system's parameters and how such parameters relate to different consequences after PM placement.

AIM

To assess the blood coagulation factor activity in PM patients throughout the perioperative period.

METHODS

Patients treated in the Department of Surgical Therapy of Cardiac Arrhythmias and Pacing at the Ryazan State "Regional Clinical Cardiology Dispensary" from April 2020 to December 2021 were included in the study. Before surgery, 7 and 30 d after PM placement, peripheral venous blood samples were withdrawn to measure the level of blood coagulation factor I (FI) and the activity of blood coagulation factors II (FII), V (FV), VII (FVII), VIII (FVIII), IX (FIX), X (FX), XI (FXI), XII (FXII). We used an automatic coagulometer Sysmex CA 660 (Sysmex Europe, Germany) and reagents from Siemens (Siemens Healthcare Diagnostics Products GmbH, Germany).

RESULTS

The study included 146 patients. The activity of factors FV [147.7 (102.1-247.55)% *vs* 103.85 (60-161.6)% *vs* 81.8 (67.15-130.65)%, $P = 0.002$], FVIII [80.4 (60.15-106.25)% *vs* 70.3 (48.5-89.1)% *vs* 63.7 (41.6-88.25)%, $P = 0.039$], FIX [86.2 (70.75-102.95)% *vs* 75.4 (59.2-88.3)% *vs* 73.9 (56.45-93.05)%, $P = 0.014$], FX [188.9 (99.3-308.18)% *vs* 158.9 (83.3-230)% *vs* 127.2 (95.25-209.35)%, $P = 0.022$], FXI [82.6 (63.9-103.6)% *vs* 69.75 (53.8-97.6)% *vs* 67.3 (54.25-98.05)%, $P = 0.002$], FXII [87.6 (67.15-102.3)% *vs* 78.9 (63.4-97.05)% *vs* 81.2 (62.15-97.4)%, $P < 0.001$] decreased at 7 and 30 d after surgery; FII activity [157.9 (109.7-245.25)% *vs* 130 (86.8-192.5)% *vs* 144.8 (103.31-185.6)%, $P = 0.021$] decreased at 7 d and increased at 30 d postoperatively. There were no statistically significant changes in the FVII activity within 30 d after PM placement [182.2 (85.1-344.8)% *vs* 157.2 (99.1-259)% *vs* 108.9 (74.9-219.8)%, $P = 0.128$]. Subgroup analysis revealed similar changes only in patients on anticoagulant therapy. FXII activity decreased in patients on antiplatelet therapy [82 (65.8-101.9)% *vs* 79.9 (63.3-97.1)% *vs* 89.7 (75.7-102.5)%, $P = 0.01$] 7 d after surgery, returning to baseline values at 30 d postoperatively.

CONCLUSION

PM placement and anticoagulant therapy were associated with decreased activity of clotting factors FV, FVIII, FIX, FX, FXI, FXII in the postoperative period. FVII activity did not decrease within 30 d after PM placement, which may indicate endothelial injury caused by lead placement.

Key Words: Hemostasis; Blood coagulation; Cardiac pacemaker; Anticoagulants; Postoperative complications

Core Tip: Permanent pacemaker placement and anticoagulant therapy are associated with decreased activity of factors V (FV), FVIII, FIX, FX, FXI, FXII in the postoperative period. FVII activity does not decrease within 30 d after PM placement, which may be suggestive of ongoing endothelial injury.

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INTRODUCTION

Cardiac implantable electronic devices (CIED), which include pacemakers (PM), are widely used to treat patients with arrhythmias and chronic heart failure[1,2]. Bradyarrhythmias are typically treated with permanent PM. The elimination of bradyarrhythmia by PM implantation improves the patient's quality of life and prognosis, but it can also result in a number of sequalae[1,3,4]. It is still unclear how PM implantation affects the hemostasis system's parameters and how those parameters relate to different problems and other consequences. The aim of our study was to assess the blood coagulation factor activity in PM patients throughout the perioperative period.

MATERIALS AND METHODS

Study population and data collection

The study included patients treated in the Department of Surgical Treatment of Cardiac Arrhythmias and Cardiac Pacing at the Ryazan State "Regional Clinical Cardiology Dispensary" from April 2020 to December 2021. Inclusion criteria for the study were indications for pacemaker implantation and age over 40 years; non-inclusion criteria were presence of a previously implanted pacemaker, contraindications to antithrombotic therapy, pregnancy or breastfeeding, and active cancer or remission for less than 5 years. After the patient consented to participate in the study and signed the informed consent form, the following data were collected: Age, sex, height, weight, underlying disease, comorbidities, history of surgical interventions, the type of antithrombotic therapy used. Peripheral venous blood samples were taken to analyze the activity of the studied blood coagulation factors on the day of surgery.

Operative techniques

PM placement was carried out in accordance with the "European Heart Rhythm Association expert consensus statement and practical guide on optimal implantation technique for conventional PM and implantable cardioverter-defibrillators"[1]. Endocardial leads were implanted *via* cephalic vein; subclavian vein was used as vascular access only when the cephalic vein was not suitable. All patients had the same PM models, single- and dual-chamber, and leads. Atrial leads with active-fixation systems were implanted in the right atrial appendage, whereas all ventricular leads with passive-fixation systems were placed in the right ventricle's apex. The PM was placed either in the pectoralis major muscle or in the subcutaneous tissues above the fascia of the muscle.

Postoperative follow-up period

After the PM placement, the patients were allowed to stay in bed for 12 h. Moreover, an ice load was administered to the surgical site for 2 h in order to prevent PM pocket hematoma. The patients spent an average of 6 d at the hospital. Venous blood sampling was repeated on the 7th and 30th days after PM placement.

Coagulation factors assessment

Venous blood samples were centrifuged; the resulting plasma was used to assess the studied parameters: The level of blood coagulation factor I (FI) and the activity of blood coagulation factors II (FII), V (FV), VII (FVII), VIII (FVIII), IX (FIX), X (FX), XI (FXI), XII (FXII). We used an automatic coagulometer Sysmex CA 660 (Sysmex Europe, Germany) and reagents from Siemens (Siemens Healthcare Diagnostics Products GmbH, Germany).

Biostatistics

Statistical analysis was performed using IBM SPSS Statistics 26.0 for Windows (SPSS Inc. Chicago, IL, United States). Numbers and percentages were used to express categorical data. The χ^2 test and Fisher exact test were used to analyze categorical data. Shapiro-Wilk test was used to assess normality. Most data were expressed as medians since they were not normally distributed. Wilcoxon test, Mann-Whitney test, Friedman test, Kruskal-Wallis test, and post-hoc tests were used as non-parametric tests for data comparison between two groups. Several cases with normal distribution were analyzed using parametric statistical analysis techniques. *P* values less than 0.05 were considered to indicate statistical significance.

RESULTS

Patients' characteristics

A total of 213 patients were screened to participate in the study. At the screening stage, 57 (26.7%) patients were withdrawn from the study: 38 (17.8%) refused to participate in the study, 19 (8.9%) had indications for placement of the other types CIED rather than a PM. As a result, 156 patients were included in the study, and 146 patients successfully completed the trial. Among 10 patients who dropped out of the study, 6 died and 4 withdrew their consent (Figure 1).

All patients signed an informed consent. This study was approved by the Local Ethics Committee of the Ryazan State Medical University. The clinical characteristics of the patients are shown in Table 1.

Antithrombotic therapy

All patients in the study received antithrombotic therapy (Table 1). All patients with atrial fibrillation received anticoagulants in accordance with clinical guidelines. Dabigatran etexilate was provided at a dose of 150 (110) mg twice day, apixaban at a dose of 5 (2.5) mg twice daily, and rivaroxaban at a dose of 20 (15) mg once daily. Warfarin was provided once daily; warfarin dosage was adjusted to achieve international normalized ratio of 2 to 3. The rest of the patients received acetylsalicylic acid at a dose of 100 mg once daily due to ischemic heart disease. None of the patients received anticoagulants and antiplatelets simultaneously. Antithrombotic therapy was not canceled or changed during the perioperative period.

Perioperative assessment of coagulation parameters

There was a decrease in the activity of factors FV, FVIII, FIX, FX, FXI, and FXII at 7 and 30 d after the procedure, while the activity of FII decreased after 7 d and increased after 30 d. During the observation period, changes in FI levels and FVII activity were not statistically significant (Table 2).

Subgroup analysis

A subgroup analysis was conducted in order to identify the variables impacting the investigated parameters. The type of antithrombotic medication the patient received had the greatest impact on the variables in this study (Table 3).

Table 1 Baseline characteristics of patients included in the study, *n* (%)

Variable (*n* = 146)	Data
Age, years	73 (67-81)
Body mass index, kg/m^2	27.5 (25-31)
Gender	
Male	77 (52.7)
Female	69 (47.3)
Pacemaker placement indication	
Atrioventricular block	49 (33.6)
Sick sinus syndrome	47 (32.2)
Atrial fibrillation with impaired atrioventricular conduction	50 (34.2)
Comorbidity	
Ischemic heart disease	146 (100)
Exertional angina	44 (30.1)
Arterial hypertension	143 (97.9)
Atrial fibrillation	96 (65.8)
Congestive heart failure	146 (100)
NYHA Class I	7 (4.8)
NYHA Class II	60 (41.1)
NYHA Class III	79 (54.1)
NYHA Class IV	0 (0)
History of myocardial infarction	28 (19.2)
History of stroke	12 (8.2)
Atherosclerotic peripheral arterial disease	4 (2.7)
Varicose veins	31 (21.2)
History of venous thromboembolism	8 (5.5)
Type 2 diabetes mellitus	39 (21.2)
History of coronavirus disease	4 (2.7)
Antithrombotic therapy	
Antiplatelet therapy (aspirin)	55 (37.7)
Oral anticoagulants	91 (62.3)
Rivaroxaban	57 (39)
Apixaban	20 (13.7)
Dabigatran etexilate	7 (4.8)
Warfarin	7 (4.8)
Surgery features	
Pacemaker	
Single-chamber	50 (34.2)
Dual-chamber	96 (65.8)
Pacemaker placement side	
Left side	142 (97.3)
Right side	4 (2.7)
Vascular access	

	Cephalic vein (section)	132 (90.4)
	Subclavian vein (puncture)	14 (9.6)
Pacemaker pocket localization		
	Above the pectoral fascia	133 (91.1)
	Inside the pectoralis major muscle	13 (8.9)
Mean surgery time, min		54 (41-60)

NYHA: New York Heart Association.

Table 2 Perioperative coagulation parameters (*n* = 146)

Variable	Before implantation	7 d after implantation	30 d after implantation	*P* value
FI	2.61 (2.05-3.11)	2.76 (2.08-3.42)	2.54 (2.16-2.91)	0.669
FII	157.9 (109.7-245.25)[a]	130 (86.8-192.5)	144.8 (103.31-185.6)	0.021
FV	147.7 (102.1-247.55)[a,b]	103.85 (60-161.6)	81.8 (67.15-130.65)	0.002
FVII	182.2 (85.1-344.8)	157.2 (99.1-259)	108.9 (74.9-219.8)	0.128
FVIII	80.4 (60.15-106.25)[a,b]	70.3 (48.5-89.1)	63.7 (41.6-88.25)	0.039
FIX	86.2 (70.75-102.95)[a,b]	75.4 (59.2-88.3)	73.9 (56.45-93.05)	0.014
FX	188.9 (99.3-308.18)[a,b]	158.9 (83.3-230)	127.2 (95.25-209.35)	0.022
FXI	82.6 (63.9-103.6)[a,b]	69.75 (53.8-97.6)	67.3 (54.25-98.05)	0.002
FXII	87.6 (67.15-102.3)[a,b]	78.9 (63.4-97.05)	81.2 (62.15-97.4)	< 0.001

[a]*P* < 0.05 *vs* 7 d after pacemaker implantation.
[b]*P* < 0.05 *vs* 30 d after pacemaker implantation.
FI: Factor I; FII: Factor II; FV: Factor V; FVII: Factor VII; FVIII: Factor VIII; FIX: Factor IX; FX: Factor X; FXI: Factor XI; FXII: Factor XII.

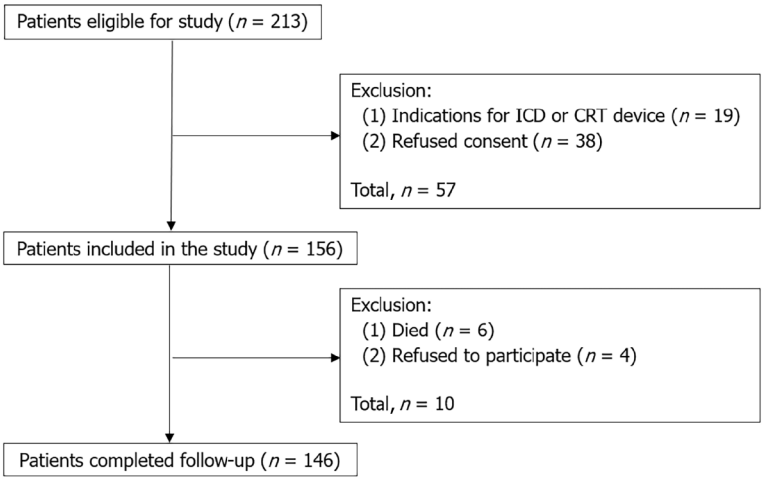

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Figure 1 Flowchart diagram providing patients included in the study. ICD: Implanted cardioverter-defibrillator; CRT: Cardiac resynchronization therapy.

Patients with dual-chamber PMs on anticoagulant therapy 7 d after surgery had lower values of FI (*P* = 0.033), and lower activity of FV (*P* = 0.045), FVIII (*P* < 0.001), FIX (*P* < 0.001), FXI (*P* = 0.004); lower activity of FVIII (*P* = 0.049), FIX (*P* < 0.001), FXI (*P* = 0.003) was seen at 30 d after surgery as compared with patients on antiplatelet therapy. There were no differences in the studied parameters between patients receiving anticoagulant therapy with single-chamber and dual-chamber PM as well as different indications for PM placement (*P* > 0.05).

Table 3 Perioperative coagulation parameters in patients on antiplatelet (*n* = 55) and anticoagulant (*n* = 91) therapy

Variable	Antithrombotic therapy	Before implantation	7 d after implantation	30 d after implantation	*P* value
FI	Antiplatelet	2.66 (2.13-2.99)	2.85 (2.47-3.3)	2.56 (2.19-3.16)	0.513
	Anticoagulant	2.55 (1.9-3.19)	2.58 (1.93-3.44)	2.49 (2.16-2.85)	0.957
	P value	0.675	0.092	0.599	-
FII	Antiplatelet	156.9 (94.5-237.3)	139 (86.8-192.5)	163.5 (112.4-203)	0.289
	Anticoagulant	186.2 (113.8-256.8)	118.5 (86.8 -173)	128.4 (99.6-170.5)	0.067
	P value	0.458	0.609	0.263	-
FV	Antiplatelet	164.9 (103.4-267.5)	115.5 (92.8-198.9)	98.6 (82.6-155.3)	0.245
	Anticoagulant	133.3 (96.6-187.9)[a,b]	80.1 (45.9-152.8)	73.4 (55.4-84.3)	0.005
	P value	0.196	0.033	0.004	-
FVII	Antiplatelet	203.4 (113-352.1)	200 (116.4-438.3)	223 (107.9-376.6)	0.683
	Anticoagulant	182.1 (87.3-384.6)	122.3 (80.3-209.9)	83.7 (64.6-154.8)	0.153
	P value	0.691	0.024	0.002	-
FVIII	Antiplatelet	82.1 (62.5-114.3)	81.6 (63.8-97.5)	75.5 (59.1-100.5)	0.104
	Anticoagulant	78.5 (58.7-99.7)[a,b]	59.6 (41.7-82)	55.1 (40.8-84.4)	0.001
	P value	0.21	0.001	0.033	-
FIX	Antiplatelet	85.4 (74.8-106.9)	84.2 (78-105.8)	96.7 (87.2-104)	0.438
	Anticoagulant	87 (68.4-99.6)[a,b]	69.6 (55.6-81.8)	63.2 (45.5-76.8)	0.004
	P value	0.331	<0.001	<0.001	-
FX	Antiplatelet	200 (105.8-308.2)	163.8 (81.7-228.4)	171.6 (120.2-240)	0.708
	Anticoagulant	187.8 (98.6-286.1)[a,b]	152.6 (89-248.2)	109.8 (82-163.5)	0.007
	P value	0.837	0.983	0.03	-
FXI	Antiplatelet	87.2 (69.8-100.8)	93.8 (63.1-108.2)	96.7 (84.2-108)	0.957
	Anticoagulant	74.8 (62.5-106.9)[a,b]	61 (49.9-82.6)	59.5 (47.5-86.5)	< 0.001
	P value	0.377	0.001	< 0.001	-
FXII	Antiplatelet	82 (65.8-101.9)[a]	79.9 (63.3-97.1)	89.7 (75.7-102.5)	0.01
	Anticoagulant	80.7 (69.4-110.2)[a,b]	78.9 (63.4-97)	73.8 (69.8-90.3)	0.001
	P value	0.989	0.629	0.027	-

[a]*P* < 0.05 *vs* 7 d after pacemaker implantation.
[b]*P* < 0.05 *vs* 30 d after pacemaker implantation.
FI: Factor I; FII: Factor II; FV: Factor V; FVII: Factor VII; FVIII: Factor VIII; FIX: Factor IX; FX: Factor X; FXI: Factor XI; FXII: Factor XII.

When evaluating the effect of each individual anticoagulant on the studied parameters, we found that patients who took apixaban had lower FIX (*P* = 0.049) activity at 7 d after surgery, and lower activity of FV (*P* = 0.046), FIX (*P* = 0.015), and FXI (*P* = 0.014) at 30 d after surgery as compared with patients who received acetylsalicylic acid. Patients who took rivaroxaban had lower activity of FIX (*P* = 0.004), FXI (*P* = 0.02) at 7 d after surgery, and lower activity of FIX (*P* = 0.006), FXI (*P* = 0.004) at 30 d after surgery as compared with patients who took acetylsalicylic acid. Patients who took dabigatran etexilate had lower FIX activity at 7 d (*P* = 0.023) and 30 d (*P* = 0.024) after surgery as compared with patients who took acetylsalicylic acid. Patients who took warfarin had lower FIX activity at 7 d (*P* = 0.023) and 30 d (*P* = 0.001) after surgery as compared to patients who received acetylsalicylic acid.

Female patients had higher baseline FVII (*P* = 0.001) and FIX (*P* = 0.003) activity, regardless of antithrombotic therapy type as compared with males.

DISCUSSION

Our aim was to study coagulation in patients with PM in the perioperative period. As a result, we discovered that at 7 and 30 d following surgery, the activity of coagulation factors V, VIII, IX, X, XI, and XII diminished. A more extensive statistical analysis revealed that patients on anticoagulant therapy experienced such changes more frequently. FXII activity in individuals who received acetylsalicylic acid decreased at 7 d after surgery before returning to baseline levels at 30 d after surgery. Patients undergoing antiplatelet and anticoagulant therapy did not show statistically significant changes in FVII activity or FI levels within 30 d of PM implantation.

Coagulation is one of the components of the human hemostasis system. Blood coagulation factors such as transglutaminases, glycoproteins, and serine proteases are part of the coagulation system[5]. The cascade model was once regarded as the primary coagulation model. This paradigm distinguishes between intrinsic and extrinsic coagulation pathways, which include the successive activation of blood coagulation components. Both pathways merge into a common coagulation pathway, which results in the formation of fibrin, which strengthens the thrombus[6,7].

The modern concept of coagulation is a cell-based model that describes the close relationship between the blood coagulation factors, platelets and endothelial cells. The coagulation process is broken down into three parts by the cell model: initiation, amplification, and propagation. When the vascular endothelium is injured during the initiation phase, cells that express tissue factor (such as smooth muscle cells) interact with FVII (initiation phase). This complex triggers the activation of FII, FIX, and FX. In the amplification phase, FII interfaces with the platelet membrane, where FXI, FVIII, and FV activation start. The propagation phase starts when activated FVIII and FIX combine to generate a complex capable of activating a significant amount of FX. Afterwards, FII and FI are activated, much like in the cascade model. Other interactions of blood coagulation factors in the cell-based model of hemostasis are also described, in addition to those described above. Coagulation is controlled by the anticoagulant system of blood. A cell-based model of hemostasis shifts our understanding of the blood clotting process to a different level, not excluding the cascade model[5,6,8].

The majority of PM patients are elderly people who frequently have a variety of comorbidities and illnesses linked to a hypercoagulable state of the hemostasis system. Atrial fibrillation, arterial hypertension, coronary heart disease, chronic heart failure, obesity, and other disorders fall under this category. Prior to PM implantation, bradyarrhythmia significantly influences the development of chronic heart failure and hypercoagulability in such patients[9,10]. Participants in the study who received anticoagulants displayed a decrease in the activity of intrinsic pathway factors such as FV, FVIII, FIX, FX, FXI, or amplification and propagation phases factors (according to the cell-based model). The baseline values of the examined parameters in these patients would likewise be lower than in patients receiving antiplatelet medications, but this was not the case in our study. In this instance, the use of anticoagulants and the elimination of bradyarrhythmia by PM implantation both likely contributed to the decline in the activity of the examined parameters. Elimination of bradyarrhythmia in patients receiving antiplatelets only temporarily reduced FXII activity.

Vascular access to the right ventricle of the heart is necessary for PM implantation operation. The lead is passed through the venous system after the subclavian vein is punctured or the cephalic vein is sectioned during surgery. Conditions are produced at the damaged area to enable the hemostasis system to function. A rise in tissue factor and von Willebrand factor in patients following pacemaker implantation supports this idea[3,9,11]. The second place of activation of the hemostasis system is the area of contact of the lead with endocardium. Gjesdal *et al*[12] showed high platelet activity *in vitro* when stimulated with PM bipolar leads. Palatianos *et al*[13] in an experiment on pigs noted that the largest accumulation of platelets was detected at the distal end of the PM lead. Although it is thought that lead has a low thrombogenicity, blood clots could still form for a variety of reasons, including a disruption of the laminar blood flow through the vein[13,14]. In our work, FVII activity does not decline in patients throughout the course of the 30-d observation period. This might be because tissue factor continues to activate FVII at the locations where the electrode caused endothelium damage. The persistence of FII activity shows that this coagulation route (extrinsic pathway of the cascade model, initiation phase of the cell-based model) is active during the entire observation time.

Our study did not aim to assess each individual anticoagulant medication's effect on the coagulation hemostasis measures. Amplification phase factors FV, FIX, and FXI's activity was shown to be decreased by apixaban and rivaroxaban when compared to acetylsalicylic acid due to FX's inhibition. Patients taking dabigatran etexilate had lower FIX activity because FII was inhibited as compared to patients receiving acetylsalicylic acid[4,5,15].

Many studies on the topic of coagulation in PM patients have been published in the international literature. The majority of these studies focus on how these patients' coagulation patterns relate to deep vein thrombosis (DVT) of the upper extremities and venous thromboembolism in general[3,11,14,16,17]. Zhang *et al*[3] noted an increase in FVIII activity 7 d after surgery. Lelakowski *et al*[11] observed an increase in FVII activity at the same period. The findings of our previous studies have demonstrated the predictive value of D-dimer levels in relation to the occurrence of DVT in the upper extremities following the initial implantation of the PM and the association between a high level of D-dimer and impaired patency of the veins in the upper extremities in patients with already implanted PM[16,18].

One of the limitations of our study was inability to assess the changes of the studied parameters in patients with single-chamber PM who require antiplatelet therapy. Currently, single-chamber PMs in the vast majority of cases are implanted in patients with permanent atrial fibrillation who require anticoagulant therapy. Placement of a single-chamber PM in the atrial position in patients with sick sinus syndrome, who could potentially receive antiplatelet agents and be investigated in this regard, is not common these days[1,19]. The study was also characterized by a limited number of postoperative visits and a certain choice of antiplatelet therapy (acetylsalicylic acid), non-inclusion of certain categories of patients such as younger patients, children, patients with leadless PM, *etc.*

CONCLUSION

PM placement and anticoagulant therapy were associated with decreased activity of clotting factors FV, FVIII, FIX, FX, FXI, FXII in the postoperative period. FVII activity did not decrease within 30 d after PM placement, which may indicate endothelial injury caused by lead placement. We think that further investigation of hemostasis system will contribute to the creation of newer approaches to the detection, prognosis, management, and prevention of numerous hemorrhagic and thromboembolic complications in patients requiring PM implantation.

ARTICLE HIGHLIGHTS

Research background

Bradyarrhythmias are typically treated with permanent pacemakers (PM). The elimination of bradyarrhythmia by PM implantation improves the patient's quality of life and prognosis, but it can also result in a number of sequalae.

Research motivation

It is still unclear how PM implantation affects the hemostasis system's parameters and how such parameters relate to different complications after PM placement.

Research objectives

To assess the blood coagulation factor activity in PM patients throughout the perioperative period.

Research methods

Patients treated in the Department of Surgical Therapy of Cardiac Arrhythmias and Pacing at the Ryazan State "Regional Clinical Cardiology Dispensary" from April 2020 to December 2021 were included in the study. Before surgery, 7 and 30 d after PM placement, peripheral venous blood samples were withdrawn to measure the level of blood coagulation factor I (FI) and the activity of blood coagulation factors II (FII), V (FV), VII (FVII), VIII (FVIII), IX (FIX), X (FX), XI (FXI), XII (FXII). We used an automatic coagulometer Sysmex CA 660 (Sysmex Europe, Germany) and reagents from Siemens (Siemens Healthcare Diagnostics Products GmbH, Germany).

Research results

The study included 146 patients. The activity of factors FV [147.7 (102.1-247.55)% *vs* 103.85 (60-161.6)% *vs* 81.8 (67.15-130.65)%, $P = 0.002$], FVIII [80.4 (60.15-106.25)% *vs* 70.3 (48.5-89.1)% *vs* 63.7 (41.6-88.25)%, $P = 0.039$], FIX [86.2 (70.75-102.95)% *vs* 75.4 (59.2-88.3)% *vs* 73.9 (56.45-93.05)%, $P = 0.014$], FX [188.9 (99.3-308.18)% *vs* 158.9 (83.3-230)% *vs* 127.2 (95.25-209.35)%, $P = 0.022$], FXI [82.6 (63.9-103.6)% *vs* 69.75 (53.8-97.6)% *vs* 67.3 (54.25-98.05)%, $P = 0.002$], FXII [87.6 (67.15-102.3)% *vs* 78.9 (63.4-97.05)% *vs* 81.2 (62.15-97.4)%, $P < 0.001$] decreased at 7 and 30 d after surgery; FII activity [157.9 (109.7-245.25)% *vs* 130 (86.8-192.5)% *vs* 144.8 (103.31-185.6)%, $P = 0.021$] decreased at 7 d and increased at 30 d postoperatively. There were no statistically significant changes in the FVII activity within 30 d after PM placement [182.2 (85.1-344.8)% *vs* 157.2 (99.1-259)% *vs* 108.9 (74.9-219.8)%, $P = 0.128$]. Subgroup analysis revealed similar changes only in patients on anticoagulant therapy. FXII activity decreased in patients on antiplatelet therapy [82 (65.8-101.9)% *vs* 79.9 (63.3-97.1)% *vs* 89.7 (75.7-102.5)%, $P = 0.01$] 7 d after surgery, returning to baseline values at 30 d postoperatively.

Research conclusions

PM placement and anticoagulant therapy were associated with decreased activity of clotting factors FV, FVIII, FIX, FX, FXI, FXII in the postoperative period. FVII activity did not decrease within 30 d after PM placement, which may indicate endothelial injury caused by lead placement.

Research perspectives

We think that further investigation of hemostasis system will contribute to the creation of newer approaches to the detection, prognosis, management, and prevention of numerous hemorrhagic and thromboembolic complications in patients requiring PM implantation.

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FOOTNOTES

Author contributions: Kalinin R and Suchkov I were the guarantors and designed the study; Povarov V, Mzhavanadze N and Zhurina O participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript.

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SYSTEMATIC REVIEWS

Effectiveness of high intensity interval training on cardiorespiratory fitness and endothelial function in type 2 diabetes: A systematic review

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Abstract

BACKGROUND

Type 2 diabetes mellitus (T2DM) is a chronic metabolic syndrome characterized by insulin resistance and hyperglycemia that may lead to endothelial dysfunction, reduced functional capacity and exercise intolerance. Regular aerobic exercise has been promoted as the most beneficial non-pharmacological treatment of cardiovascular diseases. High intensity interval training (HIIT) seems to be superior than moderate-intensity continuous training (MICT) in cardiovascular diseases by improving brachial artery flow-mediated dilation (FMD) and cardiorespiratory fitness to a greater extent. However, the beneficial effects of HIIT in patients with T2DM still remain under investigation and number of studies is limited.

AIM
To evaluate the effectiveness of high intensity interval training on cardiorespiratory fitness and endothelial function in patients with T2DM.

METHODS
We performed a search on PubMed, PEDro and CINAHL databases, selecting papers published between December 2012 and December 2022 and identified published randomized controlled trials (RCTs) in the English language that included community or outpatient exercise training programs in patients with T2DM. RCTs were assessed for methodological rigor and risk of bias *via* the Physiotherapy Evidence Database (PEDro). The primary outcome was peak VO_2 and the secondary outcome was endothelial function assessed either by FMD or other indices of microcirculation.

RESULTS
Twelve studies were included in our systematic review. The 12 RCTs resulted in 661 participants in total. HIIT was performed in 310 patients (46.8%), MICT to 271 and the rest 80 belonged to the control group. Peak VO_2 increased in 10 out of 12 studies after HIIT. Ten studies compared HIIT with other exercise regimens (MICT or strength endurance) and 4 of them demonstrated additional beneficial effects of HIIT over MICT or other exercise regimens. Moreover, 4 studies explored the effects of HIIT on endothelial function and FMD in T2DM patients. In 2 of them, HIIT further improved endothelial function compared to MICT and/or the control group while in the rest 2 studies no differences between HIIT and MICT were observed.

CONCLUSION
Regular aerobic exercise training has beneficial effects on cardiorespiratory fitness and endothelial function in T2DM patients. HIIT may be superior by improving these parameters to a greater extent than MICT.

Key Words: Type 2 diabetes mellitus; Exercise; High intensity interval training; Cardiorespiratory fitness; Peak VO_2; Endothelial function

Core Tip: Beneficial effects of high intensity interval training (HIIT) in patients with type 2 diabetes mellitus (T2DM) still remain under investigation and number of studies is limited. We investigated the effectiveness of HIIT on cardiorespiratory fitness and endothelial function in patients with T2DM. We observed that regular aerobic exercise training has beneficial effects on peak VO_2 and flow-mediated dilation in type 2 diabetic patients. Moreover, HIIT may be superior by improving these parameters to a greater extent than moderate-intensity continuous training.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic syndrome characterized by persistent hyperglycemia due to low production from the pancreas or/and abnormal response of cells to insulin that may lead to disorders of the circulatory, nervous and immune system. T2DM is a usual comorbidity worldwide, corresponding to 462 million people or to 6.28% of the world's population affecting not only the elderly, but also younger adults[1]. Especially in developed countries, prevalence is even higher compared to the global prevalence. Unhealthy lifestyle, junk food consumption, obesity and lack of exercise are major factors, responsible for developing T2DM. In Europe, there are 8529 patients per 100000 cases while in the US the number is 8911 per 100000 cases[1]. Based on mathematical models, scientists predicted the future prevalence of T2DM among youth aged < 20 years in the United States population and the potential trends in incidence. Specifically, number of youths aged < 20 with T2DM will increase from 28000 in 2017 to 48000 in 2060 under the condition that incidence will remain constant

as observed in 2017[2]. Moreover, corresponding relative increases may raise to 673% (95%CI: 362%; 1341%) for T2DM[2].

Endothelium is a significant modulator of the vascular tone and structure, endothelial progenitor cells proliferation and migration, fibrinolysis and coagulation, inflammation, platelet and leukocyte adherence resulting, thus, in vascular homeostasis[3]. T2DM, and specifically insulin resistance and hyperglycemia, may lead to endothelial dysfunction throughout a number of mechanisms, including disturbances of sub cellular signaling pathways common to both insulin action and nitric oxide (NO) production, oxidative stress, endothelin, imbalance of the renin angiotensin system, as well as the secretion of hormones and cytokines by the adipose tissue[4]. Decreased endothelium-dependent vasodilation in diabetic patients is associated with the impaired action of NO secondary to its inactivation resulting from increased oxidative stress[5]. As a result, T2DM patients usually present endothelial dysfunction causing impaired vasodilation, exercise intolerance and significantly reduced aerobic capacity[6-9].

Regular aerobic exercise has been promoted as the most beneficial non-pharmacological treatment of cardiovascular diseases resulting in improvements in body composition, physical capacity, arterial hypertension, insulin resistance, vascular tone, antioxidant status, quality of life, and, most important, endothelial function and exercise tolerance[10-13]. As far as endothelial function is concerned, exercise training has been shown to improve both basal endothelial NO formation and agonist-mediated endothelium-dependent vasodilation of the skeletal muscle vasculature in patients with cardiovascular diseases[14]. The improvement of endothelium dysfunction is associated with a significant increase in exercise capacity[14]. High intensity interval training (HIIT) seems to be superior than moderate-intensity continuous training (MICT) in cardiovascular diseases by improving brachial artery flow-mediated dilation (FMD)[15,16] and cardiorespiratory fitness[17,18] to a greater extent. However, most studies focus on the effectiveness of HIIT in patients with cardiovascular diseases and metabolic syndrome. The beneficial effects of HIIT in patients with T2DM still remain under investigation and number of studies is limited.

The aim of this systematic review is to evaluate the effectiveness of high intensity interval training on cardiorespiratory fitness and endothelial function in patients with type 2 diabetes and present the most updated knowledge in literature.

MATERIALS AND METHODS

Search strategy

The search was conducted within 1-month time period, from December 20, 2022 until January 20, 2023 in 3 Large databases; PubMed, PEDro and CINAHL. The aim of the investigators was to identify published studies that included community or outpatient exercise training programs in patients with T2DM. Specific terms were used for the search including ("type 2 diabetes mellitus" OR "diabetes" OR "T2DM" OR "DM") AND ("rehabilitation" OR "exercise" OR "exercise training" OR "aerobic exercise" OR "high intensity interval exercise" OR "HIIT" OR "sprint interval training" OR "high intensity intermittent training"). Studies that occurred from this search were selected according to the PRISMA and the PRISMA checklist. Duplicates were removed from the initial number of studies and the rest were evaluated twice. Firstly, they were screened using only the title and the abstract and then, the full text of the articles was reviewed for eligibility by 2 independent reviewers of different Institutions. Moreover, we performed manual searching of references of all eligible studies, so that to include all potential randomized trials that may not have been identified in the original search. The final evaluation of the process was performed by a university professor.

Study selection criteria

Studies were included in the systematic review only if the necessary eligible criteria were met. Inclusion criteria were: (1) Studies available as full texts in English; (2) published randomized controlled trials (RCTs) in peer-reviewed journals; (3) study groups including patients with diagnosed T2DM under stable medication during the last 3 mo or in the initial stages without medication; (4) aged ≥ 18 years, v. exercise training programs using HIIT with duration of ≥ 2 wk compared to either MICT or controls and; and (5) outcome measures focused on either cardiorespiratory fitness assessed by peak oxygen uptake (peak VO_2) and/or endothelial function through FMD or other indices of microcirculation (leg blood flow during knee-extensions, muscle fractional O_2 extraction through near-infrared spectroscopy, *etc*.). HIIT was defined as exercise sessions performing intervals of exercise at a high intensity (according to the initial VO_2 max or HR max) mixed with brief intervals at a lower intensity or even breaks.

Exclusion criteria were: (1) Non RCTs, reviews, guidelines, commentaries, case reports, editorials or conference abstracts; (2) additional interventions in study groups except for exercise training; (3) studies including patients with other comorbidities except for DM (cardiovascular diseases, obesity, metabolic syndrome); (4) studies including patients with other types of DM such as type 1 DM and prediabetes, v. studies including patients aged < 18 years; (5) exercise training including acute exercise bouts or programs with duration < 2 wk and; and (6) studies including HIIT and other exercise modalities that

were unable to be quantified.

All patients were considered to have controlled type 2 diabetes under medication and normal eating habits that did not cause severe hypoglycemic events.

Quality assessment

All RCTs that were included in the systematic review were assessed for methodological rigor and risk of bias by 2 independent reviewers, using similar methods with a recently published study[19], *via* the Physiotherapy Evidence Database (PEDro). PEDro is an 11-point scale for assessing RCTs for internal validity and control of bias. Maximum score is 10 as the first question does not contribute to total score. A study with a score of 6-10 is considered of excellent quality, a study with 4-5 of fair quality, and a score of 3 or less gives a poor-quality study. If the 2 reviewers did not agree for their quality score, then an independent third reviewer made the final decision.

Outcome measures

The primary outcome measure assessing cardiorespiratory fitness was peak VO_2 index after cardiopulmonary exercise testing. The secondary outcome measure of our systematic review was endothelial function assessed either by FMD or other indices of microcirculation. FMD was calculated as the percent change in diameter following reactive hyperemia compared with the baseline diameters at rest. Both outcomes were evaluated at baseline and post-intervention.

RESULTS

Search results

Search and screening results are demonstrated in the PRISMA flowchart (Figure 1). The initial search strategy identified 5219 articles from PubMed, PEDro and CINAHL databases. The removal of duplicate publications, and title and abstract screening excluded 4966 articles. After a full-text review by the investigators, 241 articles were further excluded. Specifically, 140 articles either did not present HIIT as the main intervention or included acute exercise regimens, 35 articles measured different outcomes than those we defined, 7 articles included patients with other types of DM such as type 1 DM and prediabetes, 12 articles were RCT protocols without results, 39 articles included patients with other comorbidities than T2DM, and 8 articles were not RCTs. After the evaluation, 12 studies were finally included in our systematic review[20-31].

Assessment of the methodological quality of the studies

We assessed methodological quality of the included RCTs using PEDro scale. PEDro scores ranged from 4 to 7. None of the studies scored 3 points or less. Eight out of 12 studies scored 4-5 points, being assessed as fair-quality studies while 4 out of 12 scores 6 points or more being assessed as high-quality studies (Table 1). The weakest field of scoring was blindness of therapists and participants.

Characteristics of participants

The 12 RCTs resulted in 661 participants in total with the majority of them being males (406 *vs* 255 females). HIIT was performed in 310 patients (46.8%), MICT to 271 and the rest 80 belonged to the control group. The mean age of the participants ranged from 38 to 65 years, while the mean time since the diagnosis of DM ranged from 1.79 to 21.1 years. Mean HbA_{1c} ranged from 6.4 to 7.5% while BMI was from 26.5 to 33.9 kg/m^2. Studies were mainly conducted in Italy[20], Canada[21], Denmark[22,25,28,29], Thailand[23], Norway[24], the United States[26], the United Kingdom[27], Ireland[30] and China[31]. The main baseline characteristics of patients from the included studies are described in Table 2.

Exercise training protocols

Populations, intervention, comparison, outcomes and study design of the included RCTs are reported in detail in Table 3. Exercise training protocols of the intervention group included HIIT in all studies with small differences in intensity, sets and sessions duration among studies. Eleven out of 12 studies included a second group of T2DM patients with MICT as an exercise regimen[20-26,28-31] while a control group including patients with usual care only was included in 7 studies[22,23,25-27,30,31]. The main HIIT program ranged in duration from 8 wk to 12 mo (12 mo in 1 study, 16 wk in 1 study, 12 wk in 6 studies, 11 wk in 2 studies, 10 wk in 1 study, and 8 wk in 1 study) and sessions were performed from 2 to 5 times weekly. A comprehensive analysis of the characteristics of exercise training programs is demonstrated in Table 3.

Effect of exercise training on cardiorespiratory fitness

The effectiveness of high intensity interval training on cardiorespiratory fitness was assessed by peak VO_2. Peak VO_2 increased in 10 out of 12 studies[20,22-26,28-31] whereas in 2 studies no difference was observed[21,27]. Moreover, 10 studies[20-26,29-31] compared HIIT with other exercise regimens (MICT

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

	Balducci *et al* [20], 2012	Terada *et al* [21], 2013	Karstoft *et al* [22], 2013	Mitranun *et al* [23], 2014	Hollekim-Strand *et al*[24], 2014	Winding *et al* [25], 2018	Hwang *et al* [26], 2019	Suryanegara *et al* [27], 2019	Mortensen *et al* [28], 2019	Baasch-Skytte *et al*[29], 2020	Gildea *et al* [30], 2021	Li *et al* [31], 2022
Eligibility criteria[a]	√	√	√	√		√	√			√	√	√
Random allocation	√	√	√	√	√	√	√	√	√	√	√	√
Concealed allocation									√		√	
Baseline comparability	√	√	√	√	√	√	√	√	√	√	√	√
Blinded subjects												
Blinded therapists												
Blinded assessors		√	√									√
Adequate follow-up	√	√	√	√			√			√		√
Intention-to-treat analysis		√					√					
Between-group comparisons	√	√	√	√	√	√	√	√	√	√	√	√
Point estimates and variability	√	√	√	√	√	√	√	√	√	√	√	√
Total score	5/10	7/10	6/10	5/10	4/10	4/10	6/10	4/10	5/10	5/10	5/10	6/10

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

and/or strength endurance) while 6 studies compared HIIT with patients of the control group who received usual care[22,23,25,27,30,31]. Four studies[22,23,24,31] demonstrated additional beneficial effects of HIIT over MICT or other exercise regimens, while 6 studies[20,21,25,26,29,30] did not observe statistically significant difference between HIIT and MICT. One single study[27] that compared HIIT to usual care only, failed to show superiority of HIIT in peak VO_2.

Specifically, Balducci *et al*[20] found an increase in peak VO_2 from 26.5 ± 5.3 to 31.1 ± 5.9 mL/min/kg ($P < 0.001$) in the high intensity (HI) group, an increase from 25.1 ± 5.4 to 29.6 ± 5.6 mL/min/kg ($P < 0.001$) in the low intensity (LI) group while no difference was observed between HI and LI groups [mean dif (95%CI): 0.14 (20.65,0.92) $P = 0.866$]. In Karstoft *et al* study[22] patients of the HIIT group increased peak VO_2 from 27.1 ± 1.5 to 31.5 ± 2.2 mL/min/kg ($P < 0.001$), but there was no difference within MICT (from 26.1 ± 1.4 to 26.8 ± 1.9 mL/min/kg, $P > 0.05$) and CON groups (from 24.8 ± 1.8 to

Table 2 Main baseline characteristics among patients with type 2 diabetes mellitus of each study included in the systematic review

Ref.	Groups	Males/Females (*n*)	Year after diagnosis	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m^2)	HbA_{1c} (%)
Balducci *et al*[20], 2012	HI (*n* = 152); LI (*n* = 136)	91/61; 83/53	7.8 ± 6.2; 5.9 ± 4.0	59.5 ± 8.3; 58.4 ± 8.9	NA	NA	31.2 ± 4.6; 31.9 ± 4.7	7.24 ± 1.39; 6.99 ± 1.39
Terada *et al*[21], 2013	HIIT (*n* = 7); MICT (*n* = 8)	4/4; 4/3	6 ± 4; 8 ± 4	62 ± 3; 63 ± 5	80.5 ± 9.9; 93.9 ± 18.3	NA	28.4 ± 4.1; 33.1 ± 4.5	6.6 ± 0.6; 6.7 ± 0.6
Karstoft *et al*[22], 2013	HIIT (*n* = 12); MICT (*n* = 12); CON (*n* = 8)	7/5; 8/4; 5/3	3.5 ± 0.7; 6.2 ± 1.5; 4.5 ± 1.5	57.5 ± 2.4; 60.8 ± 2.2; 57.1 ± 3	84.9 ± 4.9; 88.2 ± 4.7; 88.5 ± 4.7	NA	29.0 ± 1.3; 29.9 ± 1.6; 29.7 ± 1.9	6.9 ± 0.2; 6.6 ± 0.2; 6.4 ± 0.2
Mitranun *et al*[23], 2014	HIIT (*n* = 14); MICT (*n* = 14); CON (*n* = 15)	5/9; 5/9; 5/10	19.5 ± 0.4; 20.5 ± 0.4; 21.1 ± 0.6	61.2 ± 2.8; 61.7 ± 2.7; 60.9 ± 2.4	66.5 ± 3.7; 65.8 ± 3.1; 67.7 ± 3.2	149 ± 4; 149 ± 5; 152 ± 5	29.6 ± 0.5; 29.4 ± 0.7; 29.7 ± 0.4	60 ± 2[a]; 61 ± 2[a]; 62 ± 2[a]
Hollekim-Strand *et al*[24], 2014	HIIT (*n* = 20); MICT (*n* = 17)	12/8; 11/6	4.2 ± 2.3; 3 ± 2.6	58.6 ± 5; 54.7 ± 5.3	NA	NA	30.2 ± 2.8; 29.7 ± 3.7	7.0 ± 1.2; 6.7 ± 0.7
Winding *et al*[25], 2018	HIIT (*n* = 13); END (*n* = 12); CON (*n* = 7)	7/6; 7/5; 5/2	8 ± 4; 6 ± 4;7 ± 5	54 ± 6; 58 ± 8; 57 ± 7	84.2 ± 11.1; 82.1 ± 13.7; 87.7 ± 11.3	NA	28.1 ± 3.5; 27.4 ± 3.1; 28.0 ± 3.5	6.8 ± 0.8; 6.9 ± 0.9; 7.0 ± 1.2
Hwang *et al*[26], 2019	HIIT (*n* = 23); MICT (*n* = 19); CON (*n* = 16)	11/12; 11/8; 8/8	7.8 ± 1.3; 8.3 ± 1.5; 8.2 ± 1.5	65 ± 2; 62 ± 2; 61 ± 2	92.0 ± 4.7; 92.6 ± 4.5; 91.5 ± 3.9	170 ± 3; 170 ± 3; 164 ± 2	31.7 ± 1.3; 31.8 ± 1.4; 33.9 ± 1.4	7.1 ± 0.3; 7.2 ± 0.3; 7.4 ± 0.4
Suryanegara *et al*[27], 2019	HIIT (*n* = 13); CON (*n* = 13)	3/10; 3/10	4.8 ± 1.2; 4.3 ± 1.4	61.1 ± 8.6; 59.8 ± 8.6	90.5 ± 15.0; 91.0 ± 9.8	170.4 ± 7.6; 169.8 ± 8.6	31.3 ± 5.4; 31.9 ± 5.3	53.6 ± 10.5[a]; 55.5 ± 6.0[a]
Mortensen *et al*[28], 2019	HIIT (*n* = 11); END (*n* = 10)	6/5; 7/3	7 ± 4; 5 ± 4	53 ± 7; 57 ± 9	85 ± 12; 86 ± 11	NA	NA	6.8 ± 0.9; 6.9 ± 0.9
Baasch-Skytte *et al*[29], 2020	10-20-30 (*n* = 23); MICT (*n* = 21)	23/0; 21/0	8.0 ± 5.9; 7.0 ± 5.7	61.0 ± 6.2; 61.2 ± 7.1	101.9 ± 22.8; 100.3 ± 13.8	181.5 ± 6.5; 180.4 ± 7.2	30.6 ± 5.4; 30.7 ± 4.4	7.5 ± 1.6; 7.3 ± 1.1
Gildea *et al*[30], 2021	HIIT (*n* = 9); MICT (*n* = 10); CON (*n* = 9)	6/3; 7/3; 4/5	6.6 ± 3.5; 6.4 ± 3.8; 6.6 ± 3.3	52 ± 10; 53 ± 10; 54 ± 9	92.0 ± 4.7; 92.6 ± 4.5; 91.5 ± 3.9	NA	28.7 ± 3.0; 30.0 ± 5.7; 30.5 ± 3.6	7.3 ± 0.5; 6.9 ± 0.5; 6.8 ± 1.0
Li *et al*[31], 2022	HIIT (*n* = 13); MICT (*n* = 12); CON (*n* = 12)	13/0; 12/0; 12/0	1.95 ± 0.55; 1.79 ± 0.52; 1.84 ± 0.49	38 ± 6; 39 ± 5; 40 ± 7	75 ± 9.98; 73.1 ± 7.8; 71.76 ± 9.7	166.9 ± 6.25; 165.8 ± 5.56; 166.7 ± 6.86	27.4 ± 5.5; 26.8 ± 4.2; 26.5 ± 5.0	7.2 ± 0.5; 7.02 ± 0.44; 7.06 ± 0.38

[a]Expressed in mmol/moL. CON: Control group; NA: Not available; HIIT: High-intensity interval training; HI: Moderate-to-high intensity; MICT: Moderate intensity continuous training; END: Endurance training; LI: Low-to-moderate intensity.

25.2 ± 2.0 mL/min/kg, $P > 0.05$). In addition, increase in peak VO_2 was higher in the HIIT compared to the MICT and the control group ($P < 0.05$). In another study by Mitranun *et al*[23], HIIT group increased peak VO_2 from 24.2 ± 1.6 to 30.3 ± 1.2 mL/min/kg ($P < 0.05$), MICT group from 23.8 ± 1.0 to 27.1 ± 1.2 mL/min/kg ($P < 0.05$) while no difference was observed in CON group (from 24.4 ± 1.3 to 23.9 ± 1.0 mL/min/kg, $P > 0.05$). Increase was greater in the HIIT group compared to the MICT and the control group ($P < 0.05$). Similar results were demonstrated in 2 other RCTs, the first performed by Hollekim-Strand *et al*[24] in 2014 and the other more recent by Li *et al*[31] in 2022. In the first study[24], HIIT group increased peak VO_2 from 31.5 ± 6.1 to 35.6 ± 6.3 mL/min/kg ($P < 0.001$) and MICT from 33.2 ± 7.4 to 34.4 ± 7.7 mL/min/kg ($P = 0.04$), while HIIT group showed better improvement compared to MICT

Table 3 Population, Intervention, Comparison, Outcomes and Study (PICOS) design of each study included in the systematic review

Ref.	Interventions by group	Frequency	Session duration	Intervention duration	Outcomes	Main results
Balducci *et al* [20], 2012	Both groups performed mixed aerobic *(treadmill, step, elliptical, arm or cycle-ergometer)* and resistance exercise *[4 resistance exercises, i.e. thrust movement on the transverse plane (chest press or equivalent), traction movement on the frontal plane (lateral pull down or equivalent), squat movement (leg press or equivalent), and trunk flexion for the abdominals, plus three stretching positions]*. **HI**: Aerobic training at 70% of predicted VO_2 max and resistance training at 60% of predicted 1-RM. **LI:** Aerobic training at 55% of predicted VO_2 max and resistance training at 60% of predicted 1-RM	2 times/wk	Varied to obtain the same caloric expenditure per kg body weight in the two groups, independent of intensity	12 mo	Peak VO_2	↑ peak VO_2 within HI (from 26.5 ± 5.3 to 31.1 ± 5.9 mL/min/kg, $P < 0.001$) and LI group (from 25.1 ± 5.4 to 29.6 ± 5.6 mL/min/kg, $P < 0.001$). No difference in peak VO_2 between HI and LI groups [mean dif (95%CI): 0.14 (20.65, 0.92) $P = 0.866$]
Terada *et al* [21], 2013	**HIIT**: Treadmill training or cycling intervals 1′ (100% VO_2 max). And 3′ (20% VO_2 max). **MICT**: continuous treadmill training or cycling (40% VO_2 max)	5 times/wk	30-60 min	12 wk	Peak VO_2	No difference in peak VO_2 within HIIT (from 22.8 ± 5.4 to 24.3 ± 7.4 mL/min/kg, $P > 0.05$) and MICT (from 18.1 ± 2.7 to 18.9 ± 4.1 mL/min/kg, $P > 0.05$) groups. No difference in peak VO_2 between HIIT and MICT groups ($P > 0.05$)
Karstoft *et al* [22], 2013	**HIIT**: Interval walking training with 3-min repetitions at low (< 70% peak energy-expenditure rate) and high (> 70%) intensity. **MICT**: Continuous - walking training (< 55%). **CON**: No intervention	5 times/wk	60 min	16 wk	Peak VO_2	↑ peak VO_2 in HIIT group (from 27.1 ± 1.5 to 31.5 ± 2.2 mL/min/kg, $P < 0.001$). No difference in peak VO_2 in MICT (from 26.1 ± 1.4 to 26.8 ± 1.9 mL/min/kg, $P > 0.05$) and CON groups (from 24.8 ± 1.8 to 25.2 ± 2.0 mL/min/kg, $P > 0.05$). Increase was higher in the HIIT compared to the MICT group ($P < 0.05$)
Mitranun *et al* [23], 2014	**HIIT**: 4-6 intervals (85% VO_2 max) during 1 min following 4 min of active rest (50% VO_2 max.). **MICT**: 50%-65% VO_2 max. **CON**: No intervention	3 times/wk	30-40 min	12 wk	Peak VO_2. FMD	**Peak VO_2**: ↑ in HIIT (from 24.2 ± 1.6 to 30.3 ± 1.2 mL/min/kg, $P < 0.05$) and MICT groups (from 23.8 ± 1.0 to 27.1 ± 1.2 mL/min/kg, $P < 0.05$), no difference in CON group (from 24.4 ± 1.3 to 23.9 ± 1.0 mL/min/kg, $P > 0.05$). Increase was greater in the HIIT group compared to the MICT and the control group ($P < 0.05$). **FMD**: ↑ in HIIT (from 5.4 ± 1.1 to 7.4 ± 0.9%, $P < 0.05$) and MICT groups (from 4.8 ± 1.6 to 6.1 ± 1.8%, $P < 0.05$), no difference in CON group (from 5.1 ± 1.3 to 5.6 ± 1.8%, $P > 0.05$). Increase was higher in the MICT group compared to the control group ($P < 0.05$). Increase was higher in the HIIT group compared to the MICT and the control group ($P < 0.05$)
Hollekim-Strand *et al* [24], 2014	**HIIT**: 4 × 4′ (90%-95% HR max). **MICT**: according to guidelines	**HIIT**: 3 times/wk. **MICT**: 210 min/wk	**HIIT**: 40 min. **MICT**: ≥ 10 min	12 wk	Peak VO_2; FMD	**Peak VO_2**: ↑ in HIIT (from 31.5 ± 6.1 to 35.6 ± 6.3 mL/min/kg, $P < 0.001$) and MICT groups (from 33.2 ± 7.4 to 34.4 ± 7.7 mL/min/kg, $P = 0.04$). Increase was greater in the HIIT group compared to the MICT group (difference: 4.1 ± 2.9 *vs* 1.2 ± 2.2 mL/min/kg, respectively; $P = 0.002$). **FMD**: ↑ in HIIT group (from 9.2 ± 9.6 to 18.5 ± 9.6%, $P = 0.004$), no difference in MICT group (from 13.0 ± 9.8 to 13.0 ± 9.9%, $P = 0.99$). Increase was higher in the HIIT group compared to the MICT group (difference: 9.2 ± 11.2 *vs* 0.0 ± 6.2%, respectively; $P = 0.03$)
Winding *et al* [25], 2018	**HIIT**: 10 × 1 min intervals cycling at 95% of peak workload interspersed by 1 min active recovery. **END**: 40 min cycling at 50% of peak workload. **CON**: No intervention	3 times/wk	**HIIT**: 20 min. **END**: 40 min	11 wk	Peak VO_2	↑ in HIIT (from 28.4 ± 6.1 to 34.2 ± 6.3 mL/min/kg, $P < 0.05$) and END groups (from 27.8 ± 5.5 to 30.3 ± 7.5 mL/min/kg, $P < 0.05$), no difference in CON group (from 27.2 ± 9.1 to 26.3 ± 6.8 mL/min/kg, $P > 0.05$). Increase was greater in the HIIT group compared to the control group ($P < 0.05$), but no significant difference between HIIT and END groups ($P > 0.05$)
Hwang *et al*	**HIIT**: 10-min warm-up and a 5-min cooldown at 70% of HR	4 times/wk	**HIIT**: 40 min. **MICT**	8 wk	Peak VO_2	↑ in HIIT group (from 22.3 ± 1.0 to 24.6 ± 1.3 mL/min/kg, $P < 0.0001$) and

[26], 2019	peak, 4 × 4-min intervals at 90% of HR peak interspersed by 3 × 3-min active recovery at 70% of HR peak. **MICT**: 10-min warm-up and a 5-min cooldown at 70% of HR peak, 32 min at 70% HR peak. **CON**: No intervention		: 47 min			MICT group (from 21.6 ± 1.2 to 23.3 ± 1.2 mL/min/kg, $P < 0.005$), no difference in CON group (from 21.4 ± 1.3 to 20.9 ± 1.2 mL/min/kg, $P = 0.4$). No difference between HIIT and MICT groups (increase by 10% in HIIT and 8% in MICT, $P > 0.99$)
Suryanegara *et al*[27], 2019	**HIIT**: Cycle ergometry sessions, exercise intensity with scale ranging from 6 to 20 (5 min of warm up of increasing intensity from 9 to 13, then intensity 16-17 with pedal rate > 80 rev/min for five intervals of 2 min for the first week. It inclined 10s for every week until it reached 3 min and 50s of interval after 12 weeks of training. Each interval was followed with 3 min recovery cycle including 90s of passive recovery. **CON**: No intervention	3 times/wk	40-60 min	12 wk	Peak VO_2	No difference in peak VO_2 within HIIT (from 15.4 ± 2.9 to 15.2 ± 2.2 mL/min/kg, $P = 0.52$) and within CON group (from 15.5 ± 3.1 to 15.0 ± 2.4 mL/min/kg, $P = 0.37$). No difference in peak VO_2 between HIIT and the control group ($P = 0.71$)
Mortensen *et al*[28], 2019	**HIIT**: 20 min of cycling consisting of 10 times 1 min at 95% Wpeak and 1 min of active recovery 20% Wpeak). **END**: 40 minutes of cycling at 50% of Wpeak	3 times/wk	**HIIT**: 20 min. **END**: 40 min	11 wk	Peak VO_2. Leg blood flow	**Peak VO_2**: ↑ in HIIT (from 29 ± 6 to 35 ± 7 mL/min/kg, $P < 0.01$) and END groups (from 28 ± 6 to 31 ± 8 mL/min/kg, $P < 0.05$). **Leg blood flow**: No difference within HIIT (from 1.56 ± 0.09 to 1.44 ± 0.09 L/min, $P > 0.05$) and END group (from 1.42 ± 0.13 to 1.26 ± 0.18 L/min, $P > 0.01$)
Baasch-Skytte *et al*[29], 2020	**10-20-30**: 10-min low-intensity warmup before completing three 5-min sessions of 10-20-30 training interspersed by 2 min of passive recovery. 5 consecutive 1-min exercise periods divided into 30, 20 and 10 s at low (approximately 30–100 W), moderate (approximately 60–180 W) and maximal (≥ 400 W) intensity. **MICT**: 50 minutes of moderate-intensity continuous cycling at an intensity of 60%–75% of HR reserve	3 times/wk	**10-20-30**: 31 min. **MICT**: 50 min	10 wk	Peak VO_2	Peak VO_2 increased within 10-20-30 and MICT groups after exercise training by 1.8 ± 2.9 and 2.2 ± 3.2 mL/min/kg, respectively ($P < 0.01$). No difference in peak VO_2 between 10-20-30 and MICT groups ($P = 0.86$)
Gildea *et al* [30], 2021	5 min warm up and 5 min cool down before and after each session on an aerobic machine (elliptical, treadmill, rowing, or cycle ergometer) in both groups. **HIIT**: 10 × 60-s bouts of high-intensity cycling interspersed with 60 sec of light cycling at a power output equivalent to 70% of the difference between participant's peak power output (PO peak) and the power output at ventilatory threshold (VT). Target heart rate of 90% HR max. **MICT**: 50 min of cycling at a power output equivalent to 80%-90% of ventilatory threshold. **CON**: No intervention	3 times/wk	**HIIT**: 30 min. **MICT**: 60 min	12 wk	Peak VO_2. Muscle fractional O_2 extraction [% Δ (HHb+Mb]) versus %PO slope of the first linear segment (slope1)]	**Peak VO_2**: ↑ in HIIT (from 26.4 ± 4.0 to 30.0 ± 4.0 mL/min/kg, $P < 0.05$) and MICT groups (from 22.1 ± 4.4 to 27.6 ± 5.1 mL/min/kg, $P < 0.05$). It remained unchanged in the control group (from 21.5 ± 3.6 to 22.0 ± 3.4 mL/min/kg, $P > 0.05$). Increase was greater in the HIIT group compared to the control group ($P < 0.05$), but no significant difference between HIIT and MICT groups ($P > 0.05$). **Muscle fractional O2 extraction**: Improvement within HIIT (from 1.89 ± 0.63 to 1.31 ± 0.12, $P < 0.05$) and MICT groups (from 1.96 ± 0.60 to 1.37 ± 0.22, $P < 0.05$). No difference in the control group (from 1.80 ± 0.49 to 1.85 ± 0.25, $P > 0.05$). Improvement was higher in the HIIT and MICT groups compared to the control group ($P < 0.05$), but no significant difference between HIIT and MICT groups ($P > 0.05$)
Li *et al*[31], 2022	5 min warm-up and 5 min to complete the relaxation and finishing process in both groups. **HIIT**: 1 min power cycling (80%–95% maximal oxygen uptake (VO_2 max), 1 min passive or active rest (25%–30% VO_2 max), and 2 min rounds of eight groups. **MICT**: Power bike for 30 min of continuous training (50%–70% VO_2 max). **CON**: Relevant medicine, exercise, and nutrition knowledge	5 times/wk	**HIIT**: 25 min. **MICT**: 40 min	12 wk	Peak VO_2 (L/min)	HIIT (from 3.4 ± 0.4 to 3.9 ± 0.4 L/min, $P = 0.001$) and MICT groups (from 3.5 ± 0.4 to 3.7 ± 0.5 L/min, $P = 0.001$). It remained unchanged in the control group (from 3.5 ± 0.4 to 3.5 ± 0.5 L/min, $P > 0.05$). Increase was higher in the HIIT group compared to the MICT group (difference: 0.52 ± 0.06 *vs* 0.31 ± 0.13, $P < 0.001$)

CON: Control group; END: Endurance training; HI: Moderate-to-high intensity; HIIT: High-intensity interval training; HR: Heart rate; HHb: Hemoglobin; MICT: Moderate intensity continuous training; Mb: Myoglobin; LI: low-to-moderate intensity; PO: Power output; NA: Not available.

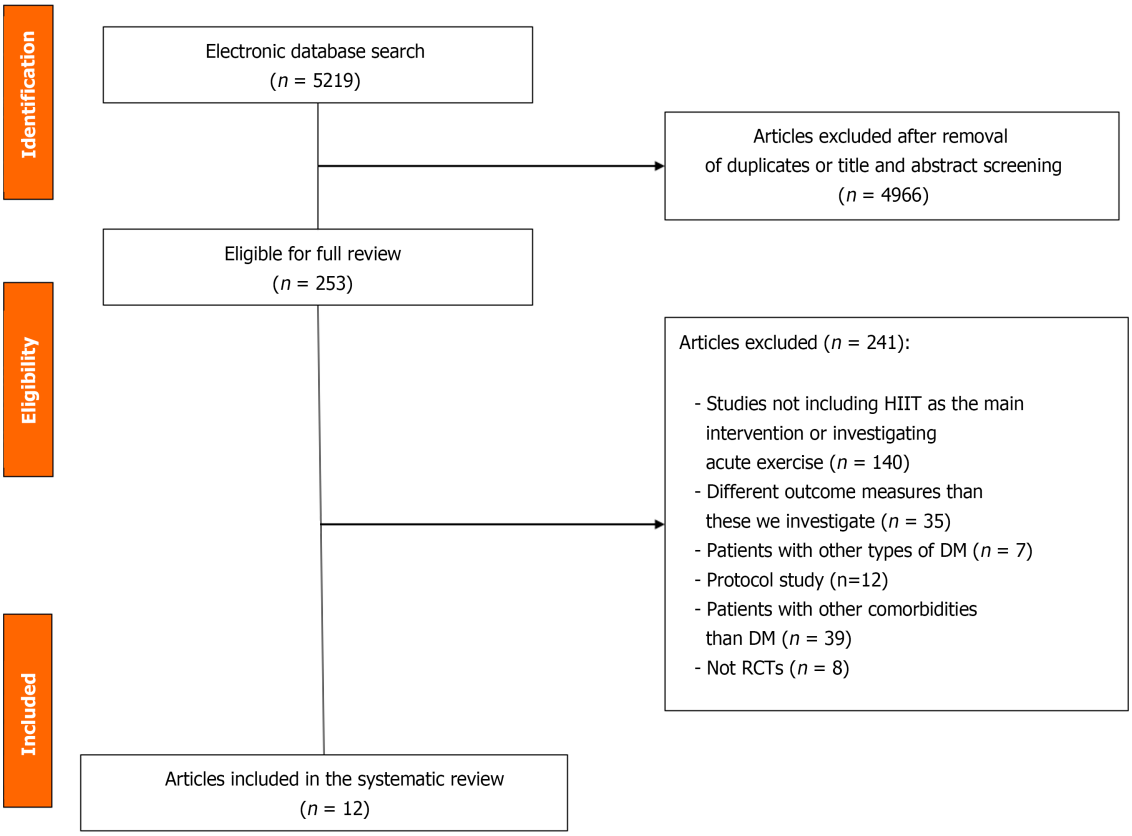

Figure 1 PRISMA flowchart regarding the screening results of the systematic review. DM: Diabetes mellitus; HIIT: High-intensity interval training; RCTs: Randomized controlled trials.

(difference: 4.1 ± 2.9 *vs* 1.2 ± 2.2 mL/min/kg, respectively; P = 0.002). In the second study[31], HIIT group increased peak VO_2 from 3.4 ± 0.4 to 3.9 ± 0.4 L/min (P = 0.001) and MICT group from 3.5 ± 0.4 to 3.7 ± 0.5 L/min (P = 0.001) while it remained unchanged in the control group (from 3.5 ± 0.4 to 3.5 ± 0.5 L/min, P > 0.05). Increase was higher in the HIIT group compared to the MICT group (difference: 0.52 ± 0.06 *vs* 0.31 ± 0.13, P < 0.001).

On the other hand, Terada *et al*[21] did not observe any differences either within (HIIT: From 22.8 ± 5.4 to 24.3 ± 7.4 mL/min/kg, P > 0.05; MICT: From 18.1 ± 2.7 to 18.9 ± 4.1 mL/min/kg, P > 0.05) or between the 2 groups (P > 0.05). More recent studies performed the last 5 years[25,26,29,30], did not manage to show additional benefits of HIIT over MICT, although peak VO_2 improved after exercise training within each group. Finally, a single study[27] which compared HIIT to usual care did not manage to show differences in peak VO_2 within (HIIT: from 15.4 ± 2.9 to 15.2 ± 2.2 mL/min/kg, P = 0.52; control: From 15.5 ± 3.1 to 15.0 ± 2.4 mL/min/kg, P = 0.37) or between the 2 groups (P = 0.71).

Effect of exercise training on endothelial function

Four studies[23,24,28,30] explored the effects of HIIT on endothelial function in type 2 diabetes patients. Two of them assessed the influence of HIIT in FMD[23,24], 1 study assessed leg blood flow during knee-extensions[28] and the last one assessed muscle fractional O2 extraction[30]. In both studies assessing FMD[23,24], FMD further improved in HIIT compared to MICT and/or the control group (P < 0.05). In the study of Mitranun *et al*[23], FMD increased from 5.4 ± 1.1 to 7.4 ± 0.9% (P < 0.05) in HIIT and from 4.8 ± 1.6 to 6.1 ± 1.8% (P < 0.05) in MICT group. Control group did not show any difference (from 5.1 ± 1.3 to 5.6 ± 1.8 %, P > 0.05). Similarly, in the study of Hollekim-Strand *et al*[24] FMD increased from 9.2 ± 9.6 to 18.5 ± 9.6% (P = 0.004) in the HIIT group, but it remained unchanged in the MICT group (from 13.0 ± 9.8 to 13.0 ± 9.9 %, P = 0.99).

A more recent study by Mortensen *et al*[28] that investigated leg blood flow during knee-extension did not observe any differences within HIIT (from 1.56 ± 0.09 to 1.44 ± 0.09 L/min, P > 0.05) and END group (from 1.42 ± 0.13 to 1.26 ± 0.18 L/min, P > 0.01) after exercise training. Finally, Gildea *et al*[30] investigated muscle deoxygenation [deoxygenated hemoglobin and myoglobin, (HHb + Mb)] by near-infrared spectroscopy at the vastus lateralis muscle in adults with T2DM after HIIT, MICT and usual care. They observed that there was improvement within HIIT (from 1.89 ± 0.63 to 1.31 ± 0.12, P < 0.05) and MICT groups (from 1.96 ± 0.60 to 1.37 ± 0.22, P < 0.05), but no difference was found in the control group (from 1.80 ± 0.49 to 1.85 ± 0.25, P > 0.05). Beneficial effects of HIIT and MICT were superior compared to usual care (P < 0.05), but there was no significant difference between HIIT and MICT

groups ($P > 0.05$).

DISCUSSION

The present systematic review investigated the effectiveness of HIIT on cardiorespiratory fitness and endothelial function in type 2 diabetic patients and compared HIIT with other exercise training regimens including MICT, as well as usual care. Through our systematic review, we demonstrated a significant improvement in peak VO_2 and FMD after HIIT in T2DM. By the findings of the present systematic review we also emerged that HIIT may be superior to MICT in functional capacity indices and endothelial function.

Peak VO_2 is considered the best available index for assessment of exercise capacity[32] and is also a strong predictor of outcomes in many cardiopulmonary diseases[33-35]. Reduced peak VO_2 bears a solid negative prognostic value both in the general population[36] and in high risk patients with cardiovascular diseases[37-39]. Moreover, in T2DM subjects, reduced exercise capacity appears to be a predictor of all-cause mortality[40]. Asymptomatic T2DM patients, with no clinically evident cardiovascular disease or overt diabetic complications, usually present reduced exercise tolerance and reduced maximal aerobic capacity, measured by peak VO_2, compared to normal subjects as shown through a big number of studies the last years[41-46]. This reduction corresponds to 20%–30% in peak VO_2 in both adults and adolescents[47-49]. Sustained hyperglycemia leading to poor metabolic control and microvascular complications, could clearly indicate a potential pathophysiological mechanism and a relationship between reduced peak VO_2 and diabetes[47,50,51]. Vice versa, low cardiorespiratory fitness seems to be associated with an increased risk for impaired glycemic control[52]. Therefore, improvement on functional capacity may also improve HbA1c in T2DM.

Aerobic exercise intensity seems to be the primary stimulus for improved peak VO_2 in patients with T2DM[53]. In our study, we showed that HIIT is probably superior to other exercise training regimens, and especially MICT, on peak VO_2 and endothelial function in these patients. These findings are in agreement with the findings of previous meta-analyses not only in T2DM, but also in cardiovascular diseases. A recent meta-analysis by Liu *et al*[54] showed that HIIT presents a great improvement in relative peak VO_2 (mean difference: 3.37 mL/kg/min, 95%CI: 1.88 to 4.87, $P < 0.0001$) and absolute peak VO_2 (mean difference: 0.37 L/min, 95%CI: 0.28 to 0.45, $P < 0.00001$) compared to MICT. Another meta-analysis by Xie *et al*[55], included 21 studies involving 736 participants with cardiac diseases and showed that HIIT was associated with greater improvement in peak VO_2 (mean difference 1.76 mL/kg/min, 95%CI: 1.06 to 2.46 mL/kg/min, $P < 0.001$) and VO_2 at anaerobic threshold (mean difference 0.90 mL/kg/min, 95%CI: 0.0 to 1.72 mL/kg/min, $P = 0.03$). Finally, another recent meta-analysis by Gomes-Neto *et al*[56] investigated the effects of HIIT *vs* MICT in coronary artery disease patients. Authors included 12 studies with 609 patients and showed that HIIT resulted in improvement in peak VO_2 weighted mean difference (1.3 mL/kg/min, 95%CI: 0.6-1.9, $n = 594$) compared with MICT.

As far as endothelial function is concerned, our study showed that HIIT results in greater improvement in FMD and other indices of microcirculation compared to MICT and usual care in T2DM. A recent meta-analyses by Qiu *et al*[57] investigated different types of exercise on endothelial function in T2DM. Authors included 16 datasets and, although they found that exercise training resulted in an overall improvement in FMD by 1.77% (95%CI: 0.94%-2.59%), however, HIIT did not significantly improve FMD over MICT. The relationship between FMD and endothelial function is quite significant, as it has been shown that every 1% increase in FMD is correlated with an estimated 13% risk reduction of cardiovascular events[58]. Moreover, this increase in FMD from a non-pharmacological therapy is even larger than those from pharmacological interventions like statins[59] or phosphodiesterase inhibitors[60], which result in an improvement in FMD by 0.94% (95%CI: 0.38%–1.5%) and 2.19% (95%CI: 0.48%–3.90%), respectively.

Potential pathophysiological mechanisms regarding the beneficial effects of exercise training on endothelial function have been proposed over the years. Three of them seem to be the most prevailing. The first one supports that the increase in blood flow caused by exercise training augments shear stresses on the endothelium, leading to increased nitric oxide synthesis and bioavailability[61]. The second one describes reduction in oxidative stress and the expression of pro-inflammatory molecules after exercise training, which are considered as initiating factors for endothelial dysfunction[62]. Finally, the last one suggests the promotion of endothelial repair and the facilitation of vascular angiogenesis, as a result of the restoration of the function of endothelial progenitor cells after exercise training[63,64].

Arterial stiffness in another characteristic dysfunction in T2DM patients, being recognized as an important predictor for hypertension. Pulse wave velocity (PWV) and augmentation index (Alx) are both criteria for clinical assessment of arterial stiffness[65]. Previous studies have shown that aerobic exercise significantly reduces both PWV[66,67] and Aix[66], increases systemic arterial compliance and, indeed, there is an inverse relationship between exercise intensity and reductions in arterial stiffness, which may suggest that HIIT could be a more effective modality than MICT[66,67]. HIIT is thought to induce a greater amount of shear stress on arterial/vascular walls, particularly in exercising muscles, through utilizing small periods of higher intensity activity, which may explain the larger benefits seen

in vascular function outcomes[68,69]. The well-established beneficial effects of HIIT on endothelial indices in T2DM patients result in improvement in arterial stiffness, as arterial stiffness is mainly influenced by vascular endothelial function[70]. HIIT has been reported to increase endothelial eNOS protein content and NO availability and cause significant improvements in brachial artery endothelial-dependent dilatation and aortic stiffness in patients with elevated CVD risk[15]. Finally, arterial stiffness-associated indices such as arterial velocity pulse index and arterial pressure volume index seem to significantly improve after HIIT, lowering close to the normal ranges[71].

Clinical perspectives

Patients with T2DM may present endothelial dysfunction, impaired functional capacity, exercise intolerance and poor prognosis after a few years since the diagnosis due to complications. The present systematic review aims to evaluate the additional beneficial effects of HIIT programs on prognostic cardiorespiratory fitness indices such as peak VO_2, as well as endothelial function in type 2 diabetic patients in comparison to other aerobic exercise regimens. Moreover, it tries to present all the potential pathophysiological mechanisms of diabetes on endothelial dysfunction and, thus, exercise intolerance. Exercise has been proven to be safe and efficient. Initial screening assessment and appropriate exercise training protocols based on HIIT should be implemented in outpatient settings under supervision in patients with T2DM. A multidisciplinary team approach is necessary prior to participation at these programs. The importance of HIIT does not limit only to cardiorespiratory or endothelial indices, but there are also practical benefits in T2DM patients' performance by improving their duration and strength in daily activities and reducing their fatigue and dyspnea, indicating thus, improvement in their quality of life. Other additional benefits of aerobic exercise are better glycemic control, improvement in arterial stiffness, as well as improvement in their lipidemic and inflammatory profile.

Limitations

Randomized controlled studies regarding the effectiveness of HIIT in patients with T2DM are limited in literature and, therefore, this field still remains under investigation. A potential limitation of the systematic review is that the included studies may present heterogeneity of the study samples, due to different mean age, different duration since diagnosis, and different functional capacity at baseline. As a result, the effects of HIIT on cardiorespiratory fitness indices in patients of different age (for instance between 18y and 70y) may be different due to different arterial stiffness levels.

Our hypothesis of heterogeneity is based on observed differences among means of age, duration since diagnosis, *etc.* among samples of the included RCTs and cannot be confirmed by statistical methods. The reason that we did not perform a meta-analysis was that we did not have access to data of all the included RCTs. Another limitation is that there were studies without adjustment for multiple comparisons and potential confounders in their results. However, the results were consistent and clear in all studies supporting final conclusions. Finally, patients who undertook an exercise intervention may have been more motivated with better functional status than those who did not participate in training programs and, thus, we could not exclude a potential inclusion bias.

CONCLUSION

Regular aerobic exercise training has been shown to have beneficial effects on cardiorespiratory fitness and endothelial function in patients with type 2 diabetes mellitus. HIIT seems to be superior by improving these parameters to a greater extent than MICT. This type of exercise training regimen should be established as significant part of the non-pharmacological therapeutic strategy of this metabolic syndrome. Larger multicenter RCTs are required in order to better understand the potential mechanisms of exercise in T2DM and its therapeutic targets, and define its main characteristics including type, duration, frequency and intensity.

ARTICLE HIGHLIGHTS

Research background

Type 2 diabetes mellitus (T2DM) is a chronic metabolic syndrome characterized by insulin resistance and hyperglycemia that may lead to endothelial dysfunction, reduced functional capacity and exercise intolerance. The improvement of endothelial dysfunction is associated with a significant increase in exercise capacity.

Research motivation

High intensity interval training (HIIT) seems to be superior than moderate-intensity continuous training (MICT) in cardiovascular diseases by improving endothelial indices and cardiorespiratory fitness to a

greater extent. However, the beneficial effects of HIIT in patients with T2DM still remain under investigation and number of studies is limited.

Research objectives

The aim of this systematic review is to evaluate the effectiveness of high intensity interval training on cardiorespiratory fitness and endothelial function in patients with type 2 diabetes and present updated knowledge in literature.

Research methods

A search on three large databases was performed, selecting randomized controlled trials (RCTs) published between 2012 and 2022 regarding exercise training programs in patients with T2DM. The primary outcome was peak VO_2 and the secondary outcome was endothelial function assessed either by FMD or other indices of microcirculation.

Research results

Twelve RCTs resulted in 661 participants in total. Peak VO_2 increased in 10 out of 12 studies after HIIT. Four out of 10 studies demonstrated additional beneficial effects of HIIT over MICT or other exercise regimens. In 2 out of 4 studies, HIIT further improved endothelial function compared to MICT and/or the control group.

Research conclusions

Regular aerobic exercise has been proven to be safe and efficient and presents beneficial effects on cardiorespiratory fitness and endothelial function in T2DM patients. HIIT may be superior by improving these parameters to a greater extent than MICT.

Research perspectives

Initial screening assessment and appropriate exercise training protocols based on HIIT should be implemented in outpatient settings under supervision in patients with T2DM. A multidisciplinary team approach is necessary prior to participation at these programs.

FOOTNOTES

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LETTER TO THE EDITOR

New scoring system for acute chest pain risk stratification: Is it worth SVEAT-ing it?

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Abstract

The emergency room is a very potent environment in the hospital. With the growing demands of the population, improved accessibility to health resources, and the onslaught of the triple pandemic, it is extremely crucial to triage patients at presentation. In the spectrum of complaints, chest pain is the commonest. Despite it being a daily ailment, chest pain brings concern to every physician at first. Chest pain could span from acute coronary syndrome, pulmonary embolism, and aortic dissection (all potentially fatal) to reflux, zoster, or musculoskeletal causes that do not need rapid interventions. We often employ scoring systems such as GRACE/PURSUIT/TIMI to assist in clinical decision-making. Over the years, the HEART score became a popular and effective tool for predicting the risk of 30-d major adverse cardiovascular events. Recently, a new scoring system called SVEAT was developed and compared to the HEART score. We have attempted to summarize how these scoring systems differ and their generalizability. With an increasing number of scoring systems being introduced, one must also prevent anchorage bias; *i.e.*, tools such as these are only diagnosis-specific and not organ-specific, and other emergent differential diagnoses must also be kept in mind before discharging the patient home without additional workup.

Key Words: Chest pain; Acute coronary syndrome; SVEAT score; HEART score; TIMI score; Risk stratification scores

Core Tip: Despite several studies, scoring systems, and artificial intelligence -guided tools available to triage symptoms of chest pain, physicians are often struck with the dilemma before discharging patients from the endoplasmic reticulum. The reason is that chest pain etiologies such as acute coronary syndromes (ACS) can present atypically and, when misdiagnosed, can lead to catastrophic consequences. Tools such as the HEART score and recently published SVEAT score are robustly validated methods of triaging this conundrum. However, while we delineate how they differ, one must be mindful that most patients with ACS could present with chest pain, but not every chest pain is due to ACS.

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TO THE EDITOR

We read with great interest the retrospective cohort study by Antwi-Amoabeng *et al*[1] entitled "SVEAT score outperforms HEART score in patients admitted to a chest pain observation unit." It is a well-written study that validated that the performance of the Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin (SVEAT) score is superior as compared to History, Electrocardiography, Age, Risk factors, and Troponin (HEART) score in stratifying acute chest pain in low to intermediate risk patients for 30-d major adverse cardiovascular events (MACE). The study assessed the potential usefulness of the SVEAT score developed by Roongsritong *et al*[2] in a prospective observational study by comparing it with HEART and TIMI (Thrombolysis In Myocardial Infarction) risk scores.

Acute chest pain is the second most common reason for adults presenting to the emergency department after trauma, of which only 5.1% of cases are caused by acute coronary syndrome (ACS)[3,4]. Patients with ACS symptoms with less than a 1% probability of 30-d MACE or death are classified as low-risk chest pain[5]. High-sensitivity troponins are used to diagnose myocardial infarction and detect myocardial injury[6].

Before 2008, widely used risk scores for ACS like GRACE, PURSUIT, and TIMI mainly focused on high-risk patients[7-10]. In 2008, Six *et al*[11] developed the HEART score in a single-centric study to better guide ER physicians to triage acute chest pain in low-risk patients aiding in safe early discharge, which was further validated by Backus *et al*[12] in a multicentric study stating that low HEART scores had a low likelihood of an ACS and high HEART score predicted higher MACE in 6 wk. Of the currently available risk stratification scores commonly used, the HEART score clinical decision pathway is the most widely employed[13]. Head-to-head comparison studies between GRACE, TIMI, and HEART scores showed that HEART scores had better predictability of MACE in low-risk patients[14]. It is also proven to reduce objective cardiac testing in 30 d, reduce the length of hospital stay and increase early discharges compared to usual care as per ACC/AHA[15].

However, the HEART score includes traditional cardiac risks factors, such as hypertension, diabetes, smoking, and obesity, which have limited value in diagnosing ACS, especially in patients older than 40 [16]; hence, these have been eliminated from the SVEAT score. Instead, the history of vascular events was included in the SVEAT score, as shown in Table 1[2]. Using more objective data in the SVEAT score reduces uncertainty and inter-rater variability inherent to other scores caused by arbitrary, subjective criteria. In addition, as stated by the authors, the SVEAT score incorporates more points for factors with higher risk association and negative points for factors with a lower risk associated with acute coronary events, ranging from +5 to -2. This, in turn, provides a broader range of cumulative scores, helping achieve superior stratifications between subgroups.

The HEART score has a threshold of 3 for stratifying as low risk, while the SVEAT score of 4 was chosen as a cut-off for low risk to achieve a 30-d MACE of 0.8%, calculated retrospectively in the index article. The HEART score identified less than 60% of the low-risk patients, whereas an additional 28% of low-risk patients were identified using the SVEAT score as compared to the HEART score[2,11,12]. Moreover, the HEART score allocates the highest score of '2' for troponins, while the cut-off for low-risk stratification is 3. Hence, with the HEART score, there is a disclaimer that if there is positive high sensitivity troponin despite the score being less than or equal to 3, *i.e.*, low-risk score, experts recommend further workup and admission[13]. However, a score of '5' with the SVEAT score system is allocated if the troponin level is over 0.7 ng/mL. This, by default, ensures that the patient is not in the low-risk group if troponin is significantly elevated. Also, vascular disease has one of the most quantifiable associations with cardiac mortality, which was given a higher individual score in the SVEAT score system[17].

Table 1 Summarizing differences between the HEART and SVEAT scores

Scoring variables	HEART score	SVEAT score
Symptom-Chest pain	Stratifies symptoms subjectively, *i.e.*, based on level suspicion. (This is open to bias based on the provider)	Stratifies symptoms more objectively by using well-defined terminologies for chest pain, hence being less open to bias
Risk factor	Includes hyperlipidemia, hypertension, diabetes mellitus, smoking, and a family history of obesity, and scoring is based on their frequency. Does not take recent coronary disease into account	Includes recent myocardial infarction, PCI/CABG, or any prior vascular event
EKG	Positively scores any EKG changes. If none are present, score 0. No negative scores	Gives a score of 3 for dynamic ST or T wave changes, higher than HEART (2). It also assigns a negative score when there are no EKG changes in the presence of ongoing chest pain
Age	Assigns a score of 2 for all patients over 65 yr	Assigns a score of 2 for all patients over 75 yr. It also assigns a negative score when the patient is < 30 yr
Troponin	Is applicable for both Troponin I and T assays. No negative scores for a normal Troponin	Validated for the 4th generation ultra-sensitive Troponin I assay only. Assigns negative scores for normal Troponin levels after > 4 h of chest pain

CABG: Coronary artery bypass grafting; EKG: Electrocardiographic; PCI: Percutaneous interventions; ST: Subthemes; SVEAT: Symptoms, history of Vascular disease, Electrocardiography, Age, and Troponin; HEART: History, Electrocardiography, Age, Risk factors and Troponin.

Both scores examine the risk stratifying of patients presenting with chest pain due to coronary artery disease. They do not consider other life-threatening illnesses in patients with chest pain, such as aortic dissection, pulmonary embolism, or esophageal rupture. This is important to note since chest pain can cause anchorage bias, and a low score can create a false sense of security, leading to premature discharge. While promising, the SVEAT score has several limitations, as mentioned by the authors, including the need for further validation in multicentric studies with diverse populations. Additionally, we need comprehensive follow-up data regarding prognostication for a longer duration. As the authors state, the individual scores are assigned rather arbitrarily than using a more formally weighted logistic regression model. Further studies could also be performed to validate if a combination of scores can increase reliability and precision in identifying low-risk patients with acute chest pain.

Acute chest pain etiology also differs in a gender-specific manner, with conditions such as coronary artery spasm, subacute coronary artery dissection, and takotsubo being significantly more prevalent in women, unlike obstructive CAD, which is more prevalent in men[18-21]. However, given the absence of conventional risk factors and ECG changes in the conditions mentioned above, screening and specific stratification remain challenging with any available scoring system, including the SVEAT system.

In conclusion, we would like to reiterate that using a well-validated scoring system is crucial to educate patients about chest pain, its implications, and key management measures. Before discharging someone with a low HEART or SVEAT score, patients must be asked if they live alone, have access to phones, are ambulatory, and how far they are from a tertiary medical facility. If these resources are unavailable, the patient should be considered a non-low risk and admitted to the hospital for further workup.

FOOTNOTES

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