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REVIEW

Pericardial decompression syndrome: A comprehensive review

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Abstract

Pericardial decompression syndrome (PDS) is an infrequent, life-threatening complication following pericardial drainage for cardiac tamponade physiology. PDS usually develops after initial clinical improvement following pericardiocentesis and is significantly underreported and may be overlooked in the clinical practice. Although the precise mechanisms resulting in PDS are not well understood, this seems to be highly associated with patients who have some underlying ventricular dysfunction. Physicians performing pericardial drainage should be mindful of the risk factors associated with the procedure including the rare potential for the development of PDS.

Key words: Pericardial decompression syndrome; Cardiac tamponade; Pericardiocentesis; Pericardiostomy; Low cardiac output syndrome

Core tip: Pericardial decompression syndrome (PDS) is an infrequent, life-threatening complication following an uncomplicated pericardial evacuation for cardiac tamponade physiology. Physicians should be familiar with the prevention strategies for PDS and offer vulnerable patients a very close clinical monitoring, especially those undergoing pericardial drainage for large malignant effusions for suspected tamponade.

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INTRODUCTION

Cardiac tamponade is an emergent clinical condition that occurs after a rapid and/or excessive accumulation of fluid in the pericardial space. It restricts appropriate filling of the cardiac chambers and impairs normal hemodynamics which ultimately causes hypotension and cardiac arrest[1-3]. Pericardial drainage either by pericardiocentesis or pericardiotomy is required to make the patients hemodynamically stable, however, it has been associated with many complications including a rare, underreported and potentially fatal complication known as pericardial decompression syndrome (PDS).

PDS was first described in 1983 by Vandyke *et al*[4]and the terminology was first proposed by Angouras *et al*[5] in 2010 and since then, it has been recognized in multiple clinical settings[6-9]. PDS is characterized by a paradoxical hemodynamic instability and/or pulmonary edema following an otherwise non-complicated pericardial drainage. Another terminology used to describe PDS is the post-pericardial drainage low cardiac output syndrome[10-12]. Epidemiological data is limited, however, the incidence of PDS from a few studies is estimated to be around < 5%, following surgical drainage[11]. The exact etiology of PDS remains unclear, but most patients usually have an underlying pathology involving myocardial or ventricular dysfunction. There have been various suggested pathophysiological mechanisms for this phenomenon in the literature.

In this paper, we provide a comprehensive case-based review of the PDS describing the etiology, pathophysiology, clinical presentation and prevention and treatment related strategies.

LITERATURE RESEARCH

We searched MEDLINE/PubMed and google scholar literature database for original articles, reviews, editorials, abstracts and case reports published between 1983 and 2017. The search terms we used, alone or in combination, were "pericardial decompression syndrome", "cardiac tamponade", "pericardial effusion", "pericardiostomy", and "low cardiac output syndrome". All articles were independently reviewed for their appropriateness for data analysis and inclusion for drafting this review. The articles were independently screened to avoid any duplication of reported cases or reports. Also, any books or book chapters were screened for the search term of pericardial decompression syndrome and cardiac tamponade. Subsequently, the data from all studies were carefully selected for inclusion which was found most relevant to the subject of this review. All articles included in the data assessment were English-language, full-text papers and/or abstracts.

PATHOPHYSIOLOGY OF CARDIAC TAMPONADE

In cardiac tamponade, the main abnormality is rapid or slow compression of the cardiac chambers resulting from an increased intrapericardial pressure. Once the pericardial contents reach the limit of the pericardial reserve volume (volume resulting in pericardial distension), the expansion rate increases significantly thus exceeding the pericardial stretch[1-3]. While the pericardium gradually stretches over time, when at any instant it is inextensible, it impairs the cardiac contractility as the heart has to compete with the increased pericardial contents for a fixed intrapericardial volume. As the cardiac chambers become sequentially smaller in size, the myocardial diastolic compliance is reduced leading to a limited cardiac inflow; and ultimately leading to equalization of the mean diastolic pericardial and chamber pressures. The rate of fluid accumulation relative to pericardial stretch is the key element to the effectiveness of compensatory mechanisms[1-3].

Rapidly developing pericardial effusion such as acute intrapericardial hemorrhage or cardiac rupture may lead to a quick development of tamponade physiology as

there is a relatively stiff pericardium with limited stretch capacity and there is less time for adaptation before routine activation of the most of the compensatory mechanisms. On the contrary, in cases of a slow increase in pericardial effusion such as idiopathic or malignant effusions, effusion size of 2 L or even more can occur before critical tamponade physiology may ensue[1-3].

Rising pericardial pressure reduces and ultimately offsets the transmural pressure (intracardiac minus pericardial pressure), first for the right heart and ultimately for all chambers. Usually, during inspiration, the right heart filling increases at the expense of the left, so that its transmural pressure shows transient improvement which then reverses during expiration and this phenomenon is referred to as interventricular dependence in tamponade (Figure 1). When florid tamponade ensues, this mechanism cannot compensate for reduced stroke volumes, as these volumes are dependent on the elements which protect cardiac output and arterial pressures, mainly beta-adrenergic response causing increased heart rate, systemic peripheral resistance and ventricular ejection fraction. Emergent needle decompression of the pericardial fluid or pericardiocentesis is often required in tamponade as it helps in improvement of the transmural pressure, releases the interventricular dependence and thus ultimately restores normal hemodynamics (Figure 2). Rarely, there can be a paradoxical worsening of the hemodynamics after an otherwise successful and uncomplicated pericardial drainage (usually in long-standing large pericardial effusions) causing cardiac tamponade which can result in PDS and its pathophysiology has been discussed in further details below.

PATHOPHYSIOLOGY OF PDS

Various hypotheses have been reported to describe the clinical mechanism of PDS, however, its exact pathophysiology still remains unclear[12-34]. The proposed mechanism of PDS centers around three main hypotheses, namely: Hemodynamic, ischemic and autonomic hypothesis. These mechanisms provide greater insight into the possible pathophysiology of the PDS.

Hemodynamic hypothesis

The simplest explanation of PDS is hemodynamic changes related to the interventricular interdependence. The hemodynamic hypothesis was first proposed in 1983 by Vandyke *et al*[4] when they first reported pulmonary edema in a patient who underwent uncomplicated pericardiocentesis for cardiac tamponade. Vandyke *et al*[4] hypothesized that pulmonary edema was precipitated by preload/afterload mismatch.

Following the rapid removal of the pericardial fluid originally compressing the right sided chambers during tamponade, now may lead to an increased venous return causing significant right ventricular expansion at the expense of the left chamber resulting in the reduced left ventricle volume/output and thus ensuing decompensated left heart failure and/or pulmonary edema. The rapid tamponade release is also followed by a net increase in the pulmonary venous return (left ventricular preload) while adaptive systemic vascular resistance (after-load) being still high (which is usually a compensatory phenomenon in tamponade to counteract hypotension response) may result in preload/afterload mismatch thus precipitating an acute onset heart failure (Figure 3)[10,11,14-16].

Ischemic hypothesis

It is postulated that the coronary artery blood perfusion may be impaired due to compression caused by the pericardial fluid that may augment the risk of myocardial ischemia, leading to transient myocardial stunning that can persist after the removal of pericardial fluid thus causing transient left ventricular dysfunction.

Skalidis *et al*[21] demonstrated the first human-based report on how pericardial pressure can affect the coronary blood flow in humans, while previous reports had been based solely on animal studies. They studied a case of 52-years old patient with lung cancer who developed cardiac tamponade. The patient had successful pericardiocentesis, resulting in the removal of 850 mL of hemorrhagic fluid. The patient underwent a percutaneous balloon pericardiotomy 5 d later due to recurrence of pericardial effusion. During the pericardiotomy, the authors performed calculation of the amount of blood flow to the non-diseased left anterior descending coronary artery while pericardial pressure was gradually increased by infusing warmed normal saline at the rate of 30 mL/min. Coronary vasodilator reserve was computed using intracoronary adenosine. With increase in pericardial pressure, there was a gradual decline in the coronary blood flow, a gradual increase in the coronary vascular resistance, and an unaffected hyperemic response throughout. The maximal

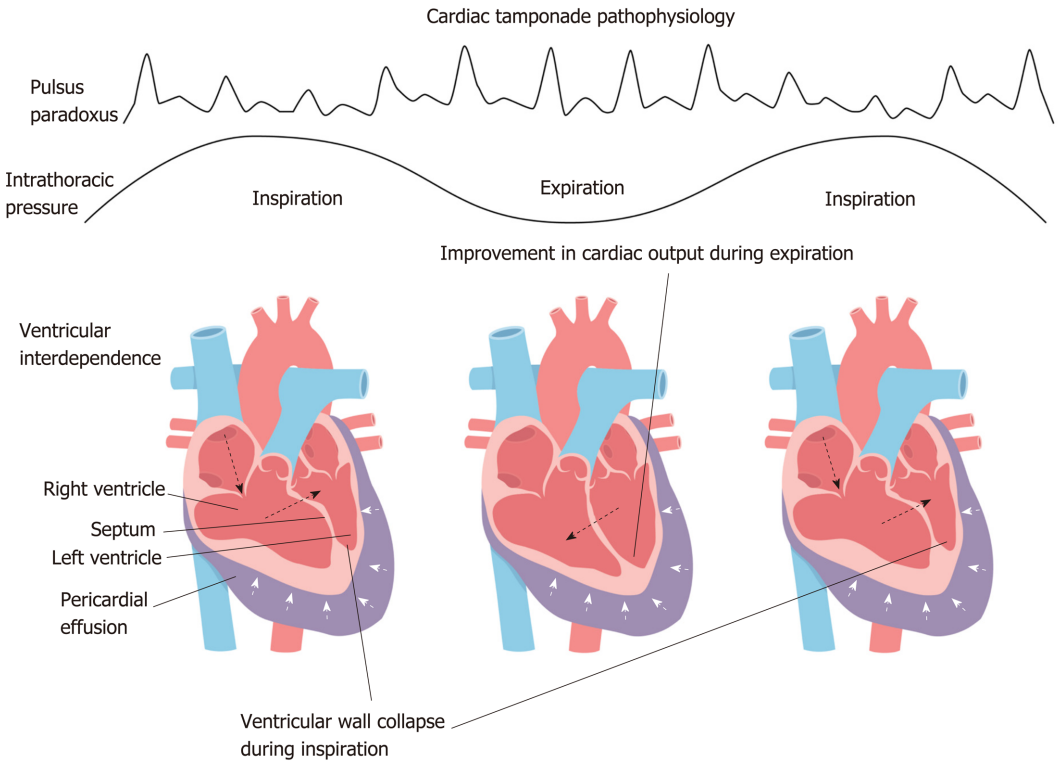

Figure 1 Cardiac tamponade physiology. There is offset of the transmural pressure (intracardiac minus pericardial pressure) in cardiac tamponade. During inspiration, the right heart filling occurs at the expense of the left, so that its transmural pressure transiently improves and then reverts during expiration and this phenomenon is referred to as interventricular dependence.

hyperemic flow was significantly less under the increased pericardial pressure than at normal pericardial pressure, which suggested an increased susceptibility to myocardial ischemia. In conclusion, the increased pericardial pressure during tamponade physiology can impair coronary perfusion leading to myocardial ischemia which can eventually cause left ventricular myocardial stunning that may persist even after pericardial drainage and can result in diastolic dysfunction thereby increasing the risk of PDS.

Autonomic/sympathetic overdrive hypothesis

The imbalance in the autonomic system, specifically acute withdrawal of sympathetic stimulus after removal of pericardial fluid, may also be a precipitating factor for myocardial dysfunction and PDS. The myocardial dysfunction may occur by two ways due to this mechanism: One being the unmasking of underlying/pre-existing myocardial dysfunction and the second being the development of new myocardial dysfunction.

Wolfe and Edelman[14] reported that removal of sympathetic stimulus after pericardiocentesis might lead to unfolding of underlying left ventricular dysfunction that was not previously revealed due to an excessive catecholamine state, producing a markedly positive chronotropic and inotropic effect. Furthermore, Martins and colleagues showed that even though exogenous catecholamine administration improved coronary blood flow in patients with tamponade, filling pressures remained unchanged and there was only a modest increase in the cardiac index[22]. They proposed that since the sympathetic nervous system activation was already present, the elevated endogenous catecholamine levels did not provide any further potential benefit. The removal of the stimulus for an increased sympathetic state (that is, the relief of tamponade by pericardiocentesis) might well lead to the unmasking of left ventricular dysfunction that was previously compensated for by high endogenous catecholamine levels[17,18]. Thus, sympathetic overdrive mechanism might play an important role in the etiology of PDS because left ventricular systolic function abnormalities may occur after pericardiocentesis intervention as described.

Secondly, the patients may develop *de novo* transient systolic dysfunction due to overwhelming autonomic functional variations as a result of the stress from the cardiac tamponade and sudden hemodynamic alterations predisposed by the rapid evacuation of the pericardial space. This hypothesis may share some similar

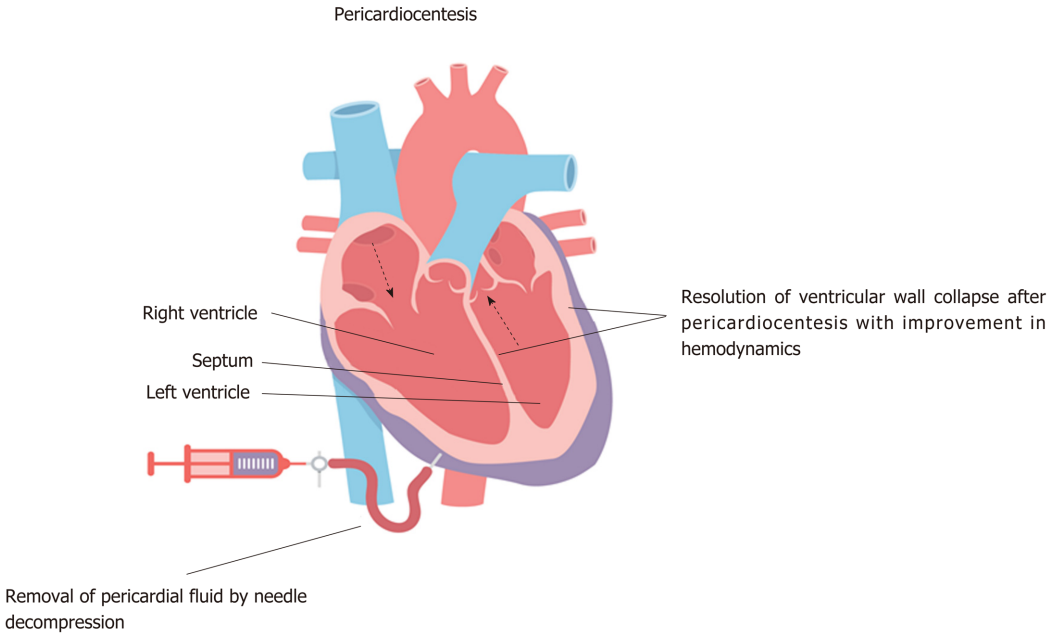

Figure 2 Pericardiocentesis. Emergent needle decompression of the pericardial fluid with pericardiocentesis is often required in tamponade as it helps in restoration of a normal transmural pressure and thus ultimately restores normal hemodynamics. Interventricular dependence has resolved with pericardial decompression.

characteristics to the pathophysiology of patients with Takotsubo syndrome or stress-related cardiomyopathy[23].

AN ILLUSTRATIVE CASE OF PDS

A 58-year-old woman with a history of Hodgkin lymphoma status post radiation therapy ten years ago, hypertension, diabetes mellitus and hypothyroidism presented to the emergency room with increasing dyspnea on exertion over 2 wk duration. Her medications included metformin 500 mg twice daily, aspirin 81 mg daily, levothyroxine 100 mcg daily, and metoprolol 25 mg twice a day. Initial vital signs demonstrated blood pressure of 96/60 mmHg, heart rate of 110 beats per minute (regular) and 96% oxygen saturation on room air. Her lung fields were clear, jugular venous pressure was elevated to the earlobe in an upright position, and the heart sounds were faint and distant. Peripheral pulses were weak bilaterally. 12-lead electrocardiogram showed low voltage and sinus tachycardia. Chest X-ray demonstrated cardiomegaly but otherwise was clear. Transthoracic echocardiogram demonstrated a left ventricular ejection fraction (LVEF) of 60%-65%, a large circumferential pericardial effusion with end diastolic right ventricular compression, and a swing sign (Figure 4A-B). Patient was taken to the cardiac catheterization laboratory for emergent pericardiocentesis. Ultrasound-guided pericardiocentesis resulted in rapid drainage of approximately 2200 mL of serous fluid with minimal improvement in hemodynamics. Patient was then taken to the cardiac catheterization laboratory holding area to be transported to the coronary care unit with the pericardial drain sutured in place. About 1 h later, the patient developed worsening dyspnea, hypotension (blood pressure of 72/40 mmHg), and labored breathing. Emergent chest radiograph showed diffuse bilateral pulmonary edema. She required intubation for hypoxic respiratory failure. Hemodynamic support was initiated with dobutamine and norepinephrine. Repeat emergent limited bedside echocardiogram demonstrated interval resolution of pericardial effusion, low-normal LVEF (50%), and mild to moderately dilated right ventricle with mild right ventricular (RV) hypokinesis and septal shift towards the left ventricle (Figure 4C). Patient was administered an intravenous saline bolus. Subsequently, the patient required hemodynamic support with intravenous vasopressors (norepinephrine) and inotropes (low-dose dopamine). Later, she was diuresed with intravenous lasix and vasopressor-inotropic support was gradually weaned off over the next 48 h. CT-chest angiography showed no evidence of pulmonary embolism with interval improvement in pulmonary edema. On day 3, patient's hemodynamics improved without requirement of vasopressors and she was extubated. A repeat echocardiogram on day

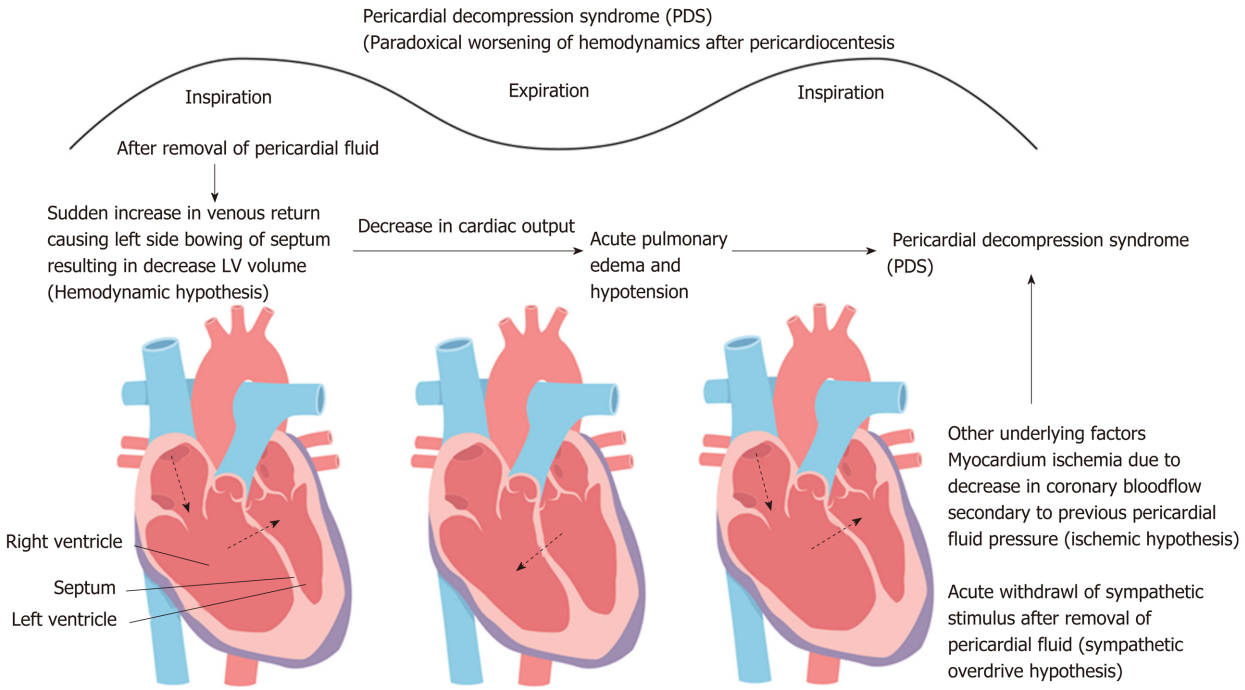

Figure 3 Pericardial decompression syndrome. Following the rapid removal of the pericardial fluid originally compressing the right sided chambers during tamponade, may lead to an increased venous return causing significant right ventricular expansion at the expense of the left chamber resulting in the reduced left ventricle volume/output and thus ensuing decompensated left heart failure and/or pulmonary edema. The rapid tamponade release is also followed by a net increase in the pulmonary venous return (left ventricular preload) while adaptive systemic vascular resistance (after-load) being still high and may result in preload/afterload mismatch thus precipitating an acute onset heart failure.

5 demonstrated normalized ventricular function and trivial/minimal pericardial effusion (Figure 4D). She was discharged to home on day 6. We suspect that this patient developed pericardial decompression syndrome shortly after the pericardial drainage. Rapid pericardial fluid decompression may have resulted in paradoxical worsening of hemodynamics likely secondary to a combination of two factors, the first being a sudden increase in the venous return with still relatively higher systemic vascular resistance posing to a preload-afterload mismatch (hemodynamic hypothesis) and secondly likely due to sympathetic overdrive (as possibly evident from transient mild RV hypokinesis). These factors may have possibly led to the development of pulmonary edema, respiratory failure, and transient ventricular dysfunction. Supportive management resulted in spontaneous gradual improvement of her cardiopulmonary function.

PRESENTATION AND TREATMENT OF PDS

Symptoms of pericardial decompression syndrome usually accompany with the paradoxical worsening of the patient's hemodynamics after a brief initial improvement in hemodynamics. The symptoms may be similar to those of acute heart failure exacerbation such as development of dyspnea, leg swelling, and increasing oxygen requirements, usually associated with rapid clinical deterioration including pulmonary edema and/or shock. Based on the papers by Pradhan *et al*[10] and Imazio[11], the onset of the syndrome ranged from immediate to usually 48 h following the pericardial fluid drainage for cardiac tamponade as an indication. According to an excellent analysis of 35 published cases from 1983 to 2013 by Pradhan *et al*[10], about 40% of patients had shock with left ventricular failure, 29% with pulmonary edema without shock, 20% with shock associated with biventricular failure and 11% with shock associated with RV failure and non-cardiogenic pulmonary edema. Diagnosis of PDS should only be established when other conditions predisposing to a shock-like state such as septic shock, cardiogenic shock resulting from MI and intraprocedural mechanical trauma (such as cardiac puncture, pneumothorax, diaphragmatic injury) have been ruled out. In relevant cases such as those presenting with isolated or significant RV dysfunction, exclusion of new-onset pulmonary embolism should probably be considered. Another important differential diagnosis is Takotsubo cardiomyopathy (TC) or stress-induced cardiomyopathy with cardiac tamponade,

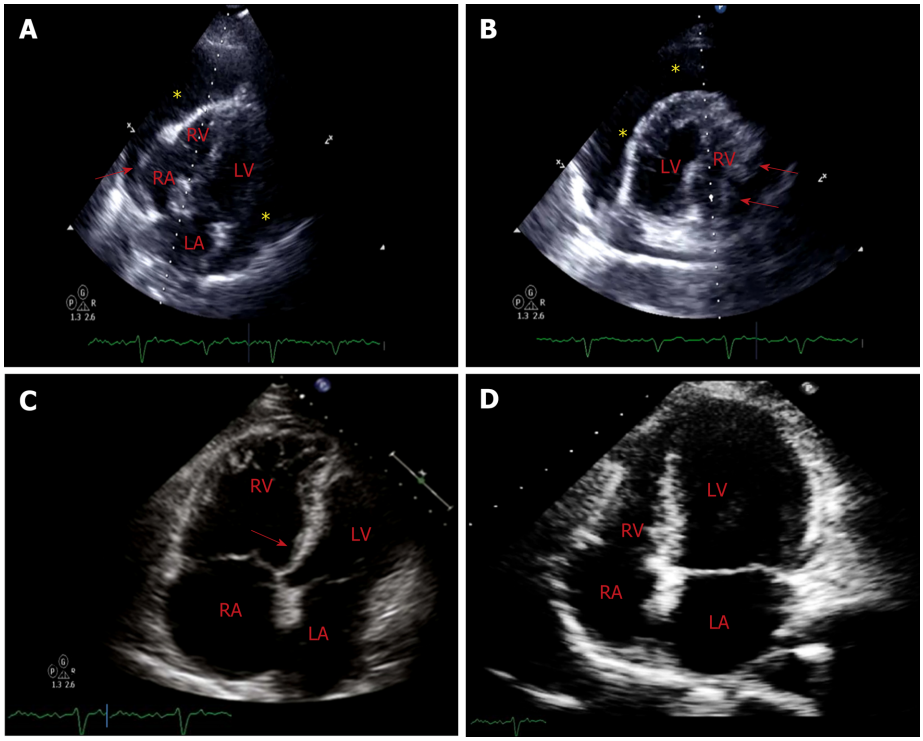

Figure 4 Computed tomography. A: Off-axis 4-chamber view of transthoracic echocardiogram demonstrates a large circumferential pericardial effusion (marked by *) with evidence of end diastolic right chamber compression (marked by red arrow) and normal left ventricular ejection fraction. Swinging heart sign was also noted which is used to describe pendular swinging of the heart inside the pericardial space and is associated with a large pericardial effusion; B: 4-chamber view (mirror-view) demonstrates RA inversion, RV diastolic compression (marked by red arrows) and the swinging heart sign; C: Limited surface echocardiogram after pericardiocentesis demonstrated interval resolution of pericardial effusion and mild to moderately dilated right ventricle with mild RV hypokinesis and septal shift towards the left ventricle(as marked by red arrow). Patient demonstrated paradoxical worsening of blood pressure. Rapid pericardial fluid decompression may have resulted in paradoxical worsening of hemodynamics likely secondary to a combination of two factors: the first being a sudden increase in the venous return with still relatively higher systemic vascular resistance posing to a preload-afterload mismatch (hemodynamic hypothesis) and secondly likely being focal RV hypokinesis, predisposed by an increased sympathetic tone; D: A repeat echocardiogram on day 5 demonstrated normalized ventricular function. RV: Right ventricular; LV: Left ventricular; RA: Right atrial; LA: Left atrial.

emotional stress and stress from significant hemodynamic derangements being the precipitating stressors for the development of TC[20,23]. In fact, transient ventricular (single or biventricular) dysfunction may be one of the driving mechanisms for the development of PDS as reported in some previous reports. The transient cardiac systolic dysfunction may be mechanistically very similar to TC. Most of the cases of primary TC are usually associated with characteristic staged ECG changes (which may include ST-elevations and T-wave inversions), rise in cardiac enzymes with most common presenting symptom being chest pain. In most of the reported cases of PDS (mimicking pathophysiology of TC) however, the patients usually have experienced dyspnea with no rise in cardiac enzymes and characteristic ECG changes only in minority[24,25].

The treatment of PDS is essentially supportive as the improvement of ventricular function is expected in survivors[7,10-12]. Patients undergoing pericardiocentesis or pericardiotomy require very close monitoring for the first 24 h, preferably in the intensive care unit[1,12,26]. In case of development of PDS, patients would require a very critical intensive monitoring, management with inotropic support, aggressive heart failure treatment with pressors and diuretics and as needed hemodynamic device support such as with an intra-aortic balloon pump.

GENERAL DISCUSSION AND PREVENTION STRATEGIES FOR PDS

Till date, there are no clear evidence-based guidelines or recommendations to specifically prevent PDS. A sensible strategy would be not drain large quantities of

pericardial fluid in a single sitting especially in case of large pericardial effusions. The most reasonable approach would be to remove the amount of pericardial fluid just enough to result in the resolution of the cardiac tamponade physiology (which can be easily achieved by hemodynamic or echo-doppler monitoring) and then place a prolonged pericardial drainage to achieve a slow and gradual removal of additional pericardial fluid. Prolonged pericardial drainage may be removed when there is a daily fluid return below 30-50 mL[1,11]. The maximum amount of safely drainable pericardial fluid and rate of drainage has been previously suggested in some studies and guideline documents[1,27,28]. European Society of Cardiology 2004 guidelines generally recommend draining pericardial fluid in steps of less than 1 L at a time to avoid PDS based on case series of 3 patients with echocardiographic evidence of volume overload after pericardiocentesis[27,28]. Although judicious pericardial drainage may be potentially preventative against PDS, PDS may rarely develop even after small amount of pericardial drainage as previously documented in an isolated case report where patient developed PDS with pericardial fluid drainage of as little as 450 mL[29]. In general, the experts recommend stopping the initial drainage following the improvement of symptoms and hemodynamics followed by a slow gradual decompression through an indwelling pericardial catheter[4,27,30]. The slow gradual drainage may potentially allow a myocardial adaptation to the hemodynamic and filling pressure changes.

Cardiac tamponade is a critical clinical condition that results from a sudden and/or excessive accumulation of pericardial fluid. The treatment of cardiac tamponade is pericardiocentesis, preferably by a needle with the use of echocardiography. However, hemodynamically unstable patients warrant the use of pericardiocentesis without imaging following ruling out type A aortic dissection. Surgical drainage is required if the heart cannot be reached by a needle such as loculated effusion or predominant posterior location, clotted hemopericardium or ongoing intrapericardial bleeding where needle drainage is either ineffective or contraindicated[1].

Pericardiocentesis and pericardiostomy has its own procedure-related mechanical complications that include cardiac puncture, arrhythmias, pneumothorax, hemothorax, pneumopericardium, hepatic and diaphragmatic injury[27,35]. PDS is a rare complication that manifests as paradoxical worsening of hemodynamics following pericardial fluid drainage. The actual incidence of PDS is unknown among the general patient population with cardiac tamponade and may be related to its under-reporting and/or low general familiarity to the Cardiologists regarding PDS. Incidence has been estimated to be between 5% to 34% following pericardial drainage from malignant pericardial effusion from a handful of case studies and series[20,24]. The clinical presentation may be variable that may include pulmonary edema, shock and/or reversible ventricular impairment (RV, LV or biventricular dysfunction). Certain clinical variables such as history of malignancy, prior radiotherapy use, pericardial calcification, low ejection fraction, and connective tissue disorders have been known to increase the risk of PDS. Among these, most of the reported cases in literature who developed pericardial effusion leading to cardiac tamponade and PDS were related to malignant effusions. Thus, patients with history of malignancy and suspected malignant pericardial effusion may require more close monitoring for possible development of PDS. Halting the initial pericardial drainage following the improvement of symptoms and hemodynamics followed by gradual slow decompression by using pericardial catheter may be a favored approach in such patients[11]. Some authors also favor pericardiocentesis over pericardiotomy as pericardiotomy was associated with a higher mortality in patients who developed PDS. Although no precise reason known for this observation, it has been argued that surgical drainage may lead to a more rapid expansion of the right ventricle due to a rapid pericardial decompression[10,36].

Supportive therapy is the key for the treatment of PDS that includes intra-aortic balloon pump, inotropic support, and aggressive heart failure treatment as previously discussed. LV dysfunction if present, may usually demonstrate improvement within a few days, accompanied with a solid mid-term prognosis[37].

CONCLUSION

PDS is an uncommon complication of pericardial drainage and has a high mortality and morbidity. Physicians should be familiar with the prevention strategies for PDS and offer vulnerable patients a very close clinical monitoring, especially those undergoing pericardial drainage for large malignant effusions for suspected tamponade.

Further studies are needed to for better understanding of the pathophysiology and

prevention strategies for PDS. Also, establishing a large multicenter registry database may provide further insights about the best choices for the drainage techniques and treatment strategies.

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REVIEW

Red blood cell distribution width: A marker of anisocytosis potentially associated with atrial fibrillation

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Abstract

The incorporation of biomarkers in the actually used risk scores seem to be helpful for early identifying atrial fibrillation (AF) patients at higher risk. The aim of this critical review of the scientific literature is to investigate the potential clinical significance of red blood cell distribution width (RDW) in AF. A systematic electronic search was carried out to identify all articles describing an epidemiological association between RDW and AF in adult human populations. Data abstraction was conducted on a final number of 35 articles (13 cross-sectional, 12 prospective and 10 retrospective studies). The results of these epidemiological investigations were all virtually concordant to emphasize that an enhanced RDW value is not only a predictive factor and a marker of AF but its measurement may also be helpful for predicting the risk of developing many adverse complications in patients with AF, such as recurrence and duration of AF, hospitalization for heart failure, bleeding, left atrial thrombosis and stasis, thromboembolic events and mortality. AF patients with RDW values exceeding the local reference range may be more aggressively investigated and managed, in order to identify and attenuate the impact of possible underlying disorders causing both anisocytosis and AF.

Key words: Atrial fibrillation; Arrhythmia; Erythrocytes; Red blood cell distribution width

Core tip: This critical review of the scientific literature aims to investigate the potential clinical significance of red blood cell distribution width (RDW) in atrial fibrillation (AF). We concluded that an enhanced RDW value is not only a predictive factor and a

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marker of AF but its measurement may also be helpful for predicting the risk of developing many adverse complications in patients with AF, such as recurrence and duration of AF, hospitalization for heart failure, bleeding, left atrial thrombosis and stasis, thromboembolic events and mortality.

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INTRODUCTION

Atrial fibrillation (AF) is the most common heart arrhythmia worldwide[1]. Worryingly, AF is related to higher rates of stroke and mortality[2]. Many risk scores and biological markers have been identified and developed to predict future AF events. Among the most frequently used and validated risk scores based on clinical parameters are CHADS2 [congestive heart failure, hypertension, age ≥ 75 years, diabetes, and stroke or transient ischemic attack (2 points)] and CHA2DS2-VASc [cardiac failure or dysfunction, hypertension, age 65-74 (1 point) or ≥ 75 years (2 points), diabetes mellitus, and stroke, TIA or thromboembolism (2 points) –vascular disease, and sex category (female)][3,4]. In addition, biomarkers may significantly contribute to obtain additional information regarding the risk that could influence the management of AF. Therefore, there is also an increasing interest in determining whether biomarkers themselves or in combination with clinical risk scores enhances prognostic accuracy for thromboembolism and mortality in AF patients[5,6]. A wide range of biomarkers have been evaluated as predictors and/or prognostics, such as cardiac troponin I and T, natriuretic peptides, D-dimer, CRP, galectin-3, growth differentiation factor-15, among others[1,5,7,8].

The incorporation of biomarkers in the actually used risk scores seem to be helpful for early identifying AF patients at higher risk (*i.e.*, enhanced risk for stroke, systemic embolic event or death), determining also their eligibility for anticoagulation and/or individualizing the most appropriate treatment strategy. Biomarkers are dynamic, and for that reason, they are also highly recommended to be included into management of patients with AF. Therefore, knowledge of new biomarkers related to AF may provide clinicians with more potential tools to quickly identify patients at higher risk of AF, attenuate its occurrence, improve its management, and decrease the risk of adverse events in patients with AF.

The search for hematological predictors of AF commenced in 1987 with the publication of a seminal study by Imataka *et al*[9], who demonstrated that plasma volume and erythrocyte biology may be significantly perturbed in patients with AF. Ten years later, Takahashi *et al*[10] first showed that erythrocyte size was altered both before and after the onset of chronic AF, thus leading to way to subsequent research aimed to define whether high heterogeneity of erythrocytes volumes, conventionally known as anisocytosis, may have clinical significance in AF.

Anisocytosis, defined as the presence of red blood cells (RBCs) with a broad heterogeneity of size and volume in peripheral blood, can be reliably estimated by the vast majority of modern hematological analyzers using different techniques, which provide a similar final index called RBC distribution width (RDW)[11]. The RDW, which is not directly measured by the analyzers, but can be calculated as standard deviation (SD) of the mean corpuscular volume (MCV), and is usually expressed in absolute value (*i.e.*, RDW-SD) or as the coefficient of variation [*i.e.*, RDW-CV: (RDW-SD)/(MCV) × 100]. Albeit largely instrument-dependent, the reference range of RDW-CV is usually comprised between 11.5%-14.5%[12]. Increased RDW values, thus reflecting anisocytosis, may be due to many pathological conditions including congenital erythrocyte disorders (*i.e.*, β-thalassemia, sickle cell disease, hereditary spherocytosis), anemia (*e.g.*, due to iron, folate or vitamin B deficiencies), blood transfusions, some forms of hemolytic anemias, oxidative stress, inflammation and impaired renal function[13-15]. Since the measurement of RDW has now become a useful part in diagnostic and prognostic assessment of many cardiovascular disorders such as acute coronary syndrome (ACS), heart failure and venous thromboembolism[16,17], the aim of this critical review of the scientific literature is to investigate the potential

clinical significance of measuring RDW in patients with, or at risk of, AF.

SEARCH STRATEGY

A systematic electronic search was carried out using the three well-recognized and widely accessed scientific databases (*i.e.*, Medline interface PubMed, Web of Science and Scopus/EMBASE)[18], with no date or language limits, to identify all articles which described the association between RDW and AF in epidemiological investigations involving human adult populations (cross-sectional, retrospective and prospective studies). The following keywords were used: "atrial fibrillation" AND "red blood cell distribution width" OR "RDW". The bibliographic references of selected items were also carefully checked for identifying additionally relevant documents. The title, abstract and full text of the articles were accurately reviewed by two authors (Lippi G and Cervellin G), and potential disagreement for inclusion was eventually resolved by the opinion of the third author. Although no meta-analysis was specified before the electronic search, since it was already clear that the studies could not be combined due to large heterogeneity in sample size, setting, and endpoints, it was our aim to explore whether this approach would still be possible after analyzing the data of the included studies.

SEARCH RESULTS

The search strategy retrieved a total number of 70 documents after elimination of replicates among the three scientific search platforms. Thirty five studies ought to be excluded since they did not match our search criteria (Figure 1). Data abstraction was hence conducted on a final number of 35 articles describing an epidemiological association between RDW and atrial fibrillation in adult populations, published between the years 2010 and 2019 (13 cross-sectional, 12 prospective and 10 retrospective studies) (Figure 1). It was finally decided that, as predictable, a meta-analysis was unfeasible due to large heterogeneity of the different studies (difference in nature, clinical settings, and endpoints, sample size from 49 to over 69000, no clear description of comorbidities in all studies, use of rather different RDW thresholds) (Table 1).

DESCRIPTION OF STUDIES OUTCOME

The first epidemiological investigation which could be identified in this critical literature review was published in 2010 by Horne and collaborators[19]. In this prospective investigation, based on the Intermountain Heart Collaborative Study, a total number of 3927 patients undergoing coronary angiography were evaluated after 1 year and 30 d, with the aim of defining the frequency of incident cardiovascular disorders and complications (including AF). When patients were classified according to quintiles of RDW, the frequency of incident AF steadily increased from the lowest up to the highest (*i.e.*, from 2% to 14%) RDW quintiles. A highly significant trend towards increasing frequency of AF was consistently observed across RDW quintiles ($P < 0.001$).

Providência *et al*[20] carried out a cross-sectional study including 247 patients presenting with symptomatic AF to the emergency department, who were then subjected to transesophageal echocardiography for ruling out left atrial appendage thrombus. Overall, eft atrial appendage thrombus was evidenced in 21/247 (8.5%) of all AF patients, and its presence was found to be significantly more frequent in patients with RDW ≥ 15.0% than in those with lower RDW values (14.8% *vs* 5.4%; $P = 0.013$).

Liu *et al*[21] carried out another cross-sectional study including 133 patients with paroxysmal AF and 101 healthy controls. In multivariate logistic regression analysis, a RDW value > 12.55% was associated with a 63% enhanced risk of AF (odds ratio, 1.63; 95%CI: 1.01-2.61).

Ertaş *et al*[22] retrospectively studied 132 patients undergoing nonemergency coronary artery bypass graft (CABG) surgery. A RDW > 13.45% was associated with a nearly 1.5-fold increased risk of new-onset AF (hazard ratio 1.48; 95%CI: 1.07-2.06). The same team of authors published another cross-control study, in which RDW was measured in 126 patients with non-valvular AF (39 with stroke and 87 without) and in 126 healthy controls with no AF[23]. The value of RDW was found to be significantly higher in AF patients with (14.1% ± 1.7%) or without stroke (14.3% ± 1.8%) compared

Table 1 Summary and concise description of the studies

Authors	Study design	Study population	Endpoints	Outcome
Horne *et al*[19], 2010	Prospective	3927 patients undergoing coronary angiography, endpoints collected at 30-d and 1-yr	Risk of developing cardiovascular diseases and complications	RDW positively correlated with the frequency of incident AF
Providência *et al*[20], 2013	Cross-sectional	247 patients presenting with symptomatic AF	Association with outcomes of transesophageal echocardiography	High RDW associated with left atrial appendage thrombosis
Liu *et al*[21], 2014	Cross-sectional	133 patients with paroxysmal AF and 101 healthy controls	Difference between groups	High RDW independently associated with AF
Ertaş *et al*[22], 2013	Retrospective	132 patients undergoing nonemergency CABG	Risk of new-onset AF until hospital discharge	RDW independently predicted the risk of developing AF
Ertaş *et al*[23], 2013	Cross-sectional	126 patients with AF (39 with stroke and 87 without) and 126 healthy controls	Difference among groups	RDW significantly higher in patients with AF than in controls, but non different between AF patients with or without stroke
Kurt *et al*[24], 2014	Cross-sectional	320 patients with AF	Relationship with CHA2DS2-VASc score	High RDW independently associated with higher CHA2DS2-VASc score
Güngör *et al*[25], 2014	Cross-sectional	117 patients with AF and 60 health control subjects	Difference among groups	RDW significantly higher in AF patients than in controls
Adamsson Eryd *et al*[26], 2014	Prospective	27124 subjects free from AF at enrollment, followed-up for 13.6 yr	Risk of developing AF	RDW independently predicted the risk of developing AF
Sarikaya *et al*[27], 2014	Cross-sectional	126 hypertensive patients (63 with AF and 63 without)	Difference among groups	High RDW significantly associated with AF
Gurses *et al*[28], 2015	Prospective	299 AF patients undergoing cryoballoon-based ablation, followed-up for 24 mo	Outcome of cryoballoon-based ablation	RDW independently predicted the risk of recurrence and duration of AF
Korantzopoulos *et al*[29], 2015	Prospective	109 patients undergoing elective cardiac surgery, followed-up throughout hospitalization	Risk of AF lasting > 5 min during hospitalization	RDW independently predicted the risk of postoperative AF
Wan *et al*[30], 2015	Prospective	300 patients with AF followed-up for a median up period of 3.2 yr	Risk of adverse clinical outcomes	RDW independently predicted the risk of major adverse events and death
Lee *et al*[31], 2015	Prospective	567 patients with newly diagnosed paroxysmal AF	Risk of adverse clinical outcomes	RDW independently predicted the risk of new-onset stroke, composite outcome and bleeding
Zhao *et al*[32], 2015	Cross-sectional	90 AF patients, 24 with evidence of left atrial thrombus (n = 11) or left atrial spontaneous echo contrast (n = 13)	Evidence of left atrial thrombus or left atrial spontaneous echo contrast	RDW associated with presence of left atrial thrombus or left atrial spontaneous echo contrast
Aksu *et al*[33], 2015	Prospective	49 patients with AF followed-up for 10 mo	Risk of AF recurrence	RDW predicted the risk of AF recurrence
Korantzopoulos *et al*[34], 2016	Cross-sectional	101 patients with sick sinus syndrome (32 with AF)	Difference between groups	High RDW independently associated with AF
Karataş *et al*[35], 2016	Retrospective	621 patients with myocardial infarction undergoing primary percutaneous coronary intervention	Risk of new-onset AF throughout hospitalization	RDW independently predicted the risk of new-onset AF
Yanagisawa *et al*[36], 2016	Prospective	757 AF patients undergoing radiofrequency catheter ablation followed-up for 22 mo	Risk of adverse clinical outcomes	RDW independently predicted the risk of recurrent AF and major adverse events
Vizzardi *et al*[37], 2016	Retrospective	232 patients with stable heart failure 1 yr after enrolment	Risk of adverse events 1 yr after enrolment	RDW independently predicted the risk of cardiovascular death and/or hospitalization for heart failure

Geçmen *et al*[38], 2016	Prospective	94 patients undergoing isolated on-pump CABG surgery followed-up until discharge from cardiovascular intensive care unit	Risk of postoperative AF	RDW independently predicted the risk postoperative AF
Zhang *et al*[39], 2017	Prospective	172 patients with nonvalvular AF undergoing catheter ablation, followed-up for 3 mo	Risk of bleeding	RDW predicted the risk of bleeding events
Al-Kindi *et al*[40], 2017	Retrospective	46720 patients with a diagnosis of HIV infection followed-up for development of cardiovascular complications	Risk of cardiovascular complications	RDW independently predicted the risk of AF
Liu *et al*[41], 2017	Cross-sectional	99 patients with AF, categorized according to their CHADS2 and CHA2DS2-VASc scores	Association with risk of stroke	High RDW independently associated with higher CHADS2 and CHA2DS2-VASc scores
Saliba *et al*[42], 2017	Retrospective	69412 patients with AF	Risk of death 2 yr after study entry	RDW independently predicted the risk of death; persistently increased RDW values at two time points stronger predictors of death than a single increased RDW value
Kaya *et al*[43], 2017	Cross-sectional	619 patients with AF (325 with left atrial stasis and 294 without)	Association with left atrial stasis	High RDW independently associated with left atrial stasis
Cha *et al*[44], 2017	Retrospective	5082 patients with AF	Risk of thromboembolic events during 5.2 yr	High peak RDW value during follow-up independently associated with the risk of thromboembolic events
Nam *et al*[45], 2017	Cross-sectional	103 healthy control subjects and 117 patients with AF patients, 65 of whom with paroxysmal and 52 with persistent AF	Difference among groups	RDW values non significantly different between controls and all AF cases; RDW values significantly higher in patients with persistent than in those with paroxysmal AF
Wasilewski *et al*[46], 2017	Retrospective	1734 patients with LVEF ≤ 35% and without ACS	Risk of AF after 660 d	High RDW independently predicted the risk of AF
Kilicgedik *et al*[48], 2018	Retrospective	358 patients after who underwent CABG surgery (57 with PSAF and 301 patients with non-PSAF)	Risk of AF after CABG surgery	High RDW was predictive of PSAF
Cerşit *et al*[47], 2018	Retrospective	50 patients with AF and 62 age- and sex- matched controls, who had presented with ACS	Association and predictive value of RDW with AF in patients with ACS.	High RDW was associated with AF and had long-term predictive value
Ozsin *et al*[49], 2018	Retrospective	93 patients who underwent off-pump CABG (24 patients with PSAF and 69 without PSAF)	Association and predictive value of RDW for development PSAF	Elevated RDW levels may be predictive of PSAF
Pilling *et al*[50], 2018	Prospective	240477 healthy UK Biobank study volunteers aged 40 ± 70 yr at baseline (follow-up ≤ 9 yr)	Association of RDW with AF in healthy subjects.	High RDW was associated with AF and had long-term predictive value
Han *et al*[51], 2019	Cross-sectional	303 patients with nonvalvular AF living at low altitude (3.5 m above the sea level) and high altitude (2260 m above the sea level).	Association of RDW with AF in subjects living at low and high altitude.	Elevated RDW levels were an independent risk marker for AF and is affected by type of AF and altitude
Jurin *et al*[52], 2019	Prospective	579 patients with AF (non-permanent and permanent AF), with a median follow-up time of 21 mo	Association of RDW values with progression to permanent AF	RDW was independently associated with AF progression
Li *et al*[53], 2019	Cross-sectional	106998 Chinese individuals	Relationship between RDW and AF	Elevated RDW is significantly related to higher prevalence of AF in a general Chinese population

AF: Atrial fibrillation; RDW: Red blood cell distribution width; LVEF: Left ventricular ejection fraction; CABG: Coronary artery bypass graft; ACS: Acute

coronary syndrome; PSAF: Post-surgery atrial fibrillation.

to the control population (13.2% ± 0.9%), but its value did not differ among AF patients with or without stroke ($P > 0.05$).

Kurt *et al*[24] measured RDW in 320 patients with AF and found that those with a higher CHA2DS2-VASc score had also significantly higher RDW values than those with a lower CHA2DS2-VASc score (14.9% ± 2.7% *vs* 13.6% ± 1.7%; $P < 0.001$). A highly significant correlation could be observed between RDW and CHA2DS2-VASc score ($r = 0.383$; $P < 0.001$). In multivariate analysis, a RDW value > 14.05% was associated with a 25% higher risk (odds ratio, 1.25; 95%CI: 1.11-1.42) of having high CHA2DS2-VASc score (*i.e.*, ≥ 2).

In an ensuing investigation, Güngör *et al*[25] studied 117 patients with AF and 60 healthy control subjects, concluding that RDW values were significantly higher in AF cases than in controls (13.4% *vs* 12.6%; $P = 0.01$). In multivariate regression analysis, a RDW > 12.9% was associated with a nearly 4-fold higher risk (odds ratio, 4.18; 95%CI: 2.15-8.15) of AF.

Adamsson Eryd *et al*[26] carried out a large prospective study including 27124 subjects free from AF at enrollment, who were followed-up for a mean period of 13.6 years. Subjects in the highest quartile of RDW had a 33% enhanced risk (hazard ratio, 1.33; 95%CI: 1.16-1.53) of developing AF on follow-up compared to those in the lowest quartile. Moreover, each 1 SD increase of RDW value was associated with a 8% higher risk (hazard ratio, 1.08; 95%CI: 1.04-1.12) of incident AF.

Sarikaya *et al*[27] studied 126 patients with hypertension (63 with AF and 63 without) and reported that RDW values were significantly higher in patients with AF than in those without (15.1% ± 1.6% *vs* 14.0% ± 1.1%; $P = 0.001$). In multivariate logistic regression analysis, a RDW value > 14.2% was found to be independently associated with 1.8-fold higher risk (odds ratio, 1.85; 95%CI: 1.22-2.79) of AF.

Gurses *et al*[28] measured RDW in 299 patients with paroxysmal or persistent AF undergoing cryoballoon-based ablation, and who were then followed-up for a mean period of 24 mo. A RDW value > 13.75% was independently associated with both early (hazard ratio, 6.39; 95%CI: 3.41-11.97) and late (hazard ratio, 1.88; 95%CI: 1.41-2.50) recurrence of AF, enhanced left atrial diameter (hazard ratio, 3.09; 95%CI: 1.81-5.27), as well as with duration of AF (hazard ratio, 1.04; 95%CI: 1.01-1.07).

Korantzopoulos *et al*[29] studied 109 patients undergoing elective cardiac surgery, who were then prospectively followed-up throughout hospitalization. In multivariate logistic regression analysis, a RDW > 13.35% was independently associated with a 46% higher risk (odds ratio, 1.46; 95%CI: 1.08-1.99) of developing postoperative AF during hospital stay.

Wan *et al*[30] carried out a prospective study including 300 patients with AF who were followed-up at a median period of 3.2 years. Patients in the fourth quartile of RDW values had a 2.7-fold higher risk (hazard ratio, 2.70; 95%CI: 1.35-5.83) of major adverse events (all-cause mortality, ACS, stroke and major hemorrhage) and a 3.8-fold higher risk (hazard ratio, 3.83; 95%CI: 1.53-9.58) of death during follow-up.

Lee *et al*[31] measured RDW values in 567 patients with newly diagnosed paroxysmal AF, who were followed-up for a median period of 4.8 years. In multivariate analysis, an increased RDW value (no indications provided on the cut-off used) was independently associated with 47% higher risk (hazard ratio, 1.47; 95%CI: 1.05-2.05) of new-onset stroke, 26% higher risk (hazard ratio, 1.26; 95%CI: 1.02-1.54) of composite outcome (mortality, new-onset stroke and hospitalization for heart failure), and 74% enhanced risk of bleeding (hazard ratio, 1.74; 95%CI: 1.28-2.36) throughout follow-up.

Zhao *et al*[32] retrospectively analyzed a local echocardiology database for identifying all AF patients who underwent transesophageal echocardiography before catheter ablation or electrical cardioversion. The final study population consisted of 90 AF patients, 24 of whom had evidence of left atrial thrombus ($n = 11$) or left atrial spontaneous echo contrast ($n = 13$). The mean RDW value was found to be significantly higher in patients with these two complications than in those without (13.0% ± 0.9% *vs* 12.6% ± 0.8%; $P = 0.039$).

Aksu *et al*[33] studied 49 patients with symptomatic paroxysmal AF who underwent cryoballoon ablation and were then followed-up for a mean period of 10 mo. Patients with AF recurrence on follow-up had significantly higher RDW values than those without (16.1% ± 1.4% *vs* 14.9% ± 0.5%; $P = 0.033$). Interestingly, the post-ablation RDW value remained almost unchanged in patents without recurrence of AF, but in those with AF recurrence the RDW significantly increased from 16.1% ± 1.4% to 16.3% ± 2.4% ($P < 0.05$).

In another study, Korantzopoulos *et al*[34] measured RDW in 101 patients with sick

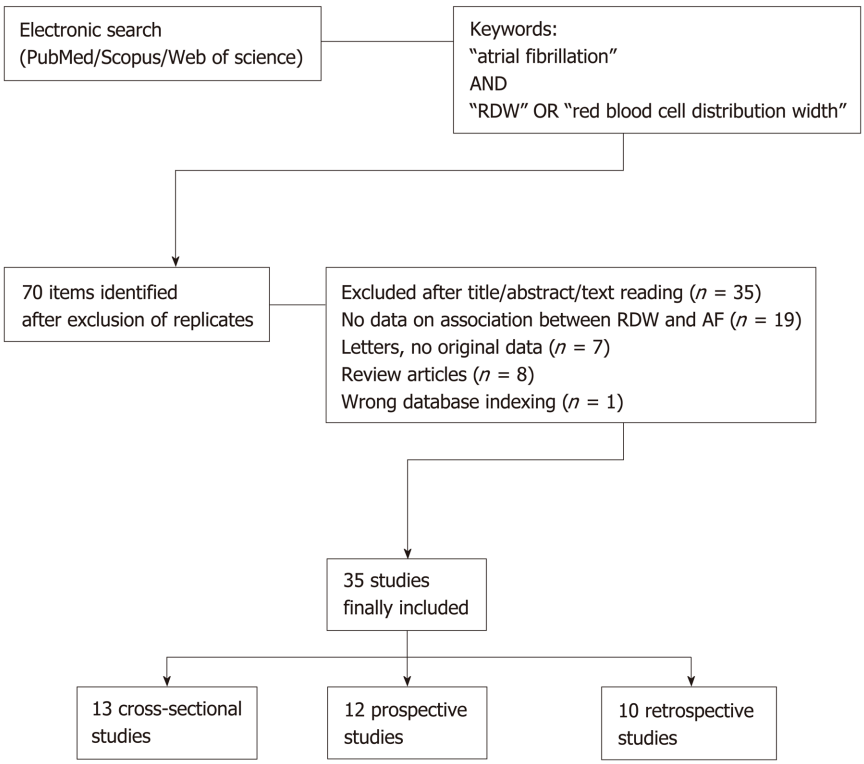

Figure 1 Search strategy and search results.

sinus syndrome (32 with AF), and found that a RDW value > 14.0% was independently associated with AF (odds ratio, 1.58; 95%CI: 1.06-2.85).

Karataş *et al*[35] studied 621 patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention, and who were followed-up throughout hospitalization. Patients with RDW > 13.4% had a 55% higher risk (odds ratio, 1.55; 95%CI: 1.20-2.01) of developing new-onset AF until hospital discharge.

Yanagisawa *et al*[36] measured RDW in 757 patients undergoing radiofrequency catheter ablation for AF, who were then followed-up for a mean period of 22 mo. In multivariate linear regression analysis, a RDW value > 13.9% was associated with 20% higher risk (hazard ratio, 1.20; 95%CI: 1.01-1.40) of recurrent AF in patients with heart failure, whilst no significant association was found in those without heart failure. In patients with heart failure, a RDW value > 14.8% was also associated with 83% higher risk (hazard ratio, 1.83; 95%CI: 1.13-2.72) of developing major adverse events (all-cause mortality, hospitalization for heart failure and cerebral ischemia) during follow-up.

Vizzardi *et al*[37] carried out a retrospective study including 232 patients with stable heart failure, whose clinical outcome was assessed 1 year after enrolment. In multivariate logistic regression analysis, a RDW value > 14.45% was independently associated with 3.9-fold enhanced risk (odds ratio, 3.89; 95%CI: 1.04-14.55) of cardiovascular death and/or hospitalization for heart failure in the first year after enrolment.

Geçmen *et al*[38] carried out a prospective study including 94 patients undergoing isolated on-pump CABG surgery, who were followed-up until discharge from the cardiovascular intensive care unit. In univariate analysis, higher RDW values were associated with a 41% higher risk (odds ratio, 1.41; 95%CI: 1.01-1.96) of postoperative AF during cardiovascular intensive care unit stay. The cut-off value of RDW was unavailable in the publication and the association between RDW and postoperative AF was not tested in multivariate analysis.

Zhang *et al*[39] measured RDW in 172 patients diagnosed with nonvalvular AF, who were followed up for 3 mo after catheter ablation. The overall number of bleeding events was found to be higher in patients with RDW values > 12.8% than in those with lower RDW values (11.8% *vs* 3.4%). Interestingly, the diagnostic efficiency (*i.e.*, area under the receiver operating characteristics curve; AUC) for predicting bleeding occurrence was higher for RDW than for activated partial thromboplastin time (0.737 *vs* 0.558; $P < 0.01$).

Al-Kindi *et al*[40] used a large commercial database including electronic health

records of many participating hospitals, with the aim of identifying patients aged 18 years or older with a diagnosis of HIV and who had at least one available RDW measurement. The search allowed the extraction of a total number of 46720 records (mean or median follow-up period for development of cardiovascular complications is unavailable in the article). In these HIV patients, a RDW value > 14.5% was independently associated with a 96% higher risk (odds ratio, 1.96; 95%CI: 1.64-2.33) of incident AF.

Liu *et al*[41] studied 99 patients with AF, divided into two groups according to their CHADS2 and CHA2DS2-VASc scores. In multivariate logistic regression analysis, a RDW value > 12.55% was found to be significantly associated with higher (≥ 2) CHADS2 score (odds ratio, 2.18; 95CI%: 1.14-3.22), whilst a RDW value > 12.75% was found to be significantly associated with higher (≥ 2) CHA2DS2-VASc score (odds ratio, 5.75; 95%CI: 3.70-7.79).

Saliba *et al*[42] searched the electronic database for a large national health maintenance for identifying all patients diagnosed with AF in whom at least two RDW measurements were performed 1 year before study entry. Mortality data were retrospectively reviewed for up to 2 years after patients inclusion in the database. The electronic search identified a total of 69412 records. A RDW value > 14.5% was independently associated with a 49% increased risk (hazard ratio, 1.49; 95%CI, 1.43-1.55) of all-cause mortality during the follow-up period. More importantly, persistently increased RDW values at the two-time points were independently associated with an even higher risk of death during the same follow-up period (HR, 1.70; 95%CI: 1.61-1.79).

Kaya *et al*[43] analyzed the data of 619 AF patients undergoing transesophageal echocardiography examination before cardioversion or AF ablation. In multivariate regression analysis, a RDW value > 13.7% was associated with a 67% increased risk of left atrial stasis (odds ratio, 1.67; 95%CI: 1.44-1.94).

Cha *et al*[44] carried out a retrospective study including 5082 patients with non-valvular AF, who were followed-up for a mean period of 5.2 years. The RDW was measured several times during follow-up, allowing to identify nadir (*i.e.*, the lowest), peak (*i.e.*, the highest) and mean RDW values. Among the various RDW measures, a peak value ≥ 13.9% was independently associated with a 66% enhanced risk (odds ratio, 1.66; 95%CI: 1.41-1.96) of thromboembolic events, including ischemic stroke and systemic embolism.

Nam *et al*[45] carried out a cross-sectional study including 103 healthy control subjects and 117 patients with AF, 65 of whom with paroxysmal AF and 52 with persistent AF. Overall, no significant difference was found in mean RDW values between controls and AF cases (13.4% ± 1.6% *vs* 13.5% ± 0.8%; $P = 0.343$), whilst patients with persistent AF exhibited significantly higher mean RDW values than those with paroxysmal AF (13.9% ± 0.9% *vs* 13.3% ± 0.6%; $P < 0.05$).

Wasilewski *et al*[46] performed a sub-analysis of the COMMIT-HF (COnteMporary Modalities In Treatment of Heart Failure) registry, including 1734 patients with left ventricular ejection fraction ≤ 35% and without ACS at baseline, who were retrospectively investigated for a median period of 660 d. Patients in the highest RDW tertile had a more than double risk of developing AF on follow-up compared to those in the lowest tertile (44.1% *vs* 20.2%; $P < 0.01$).

Cerşit *et al*[47] investigated the association between RDW and AF in 50 patients with and without AF after an ACS. RDW was significantly higher in patients with AF than the control group (14.5% ± 2% *vs* 12.6% ± 1%, $P < 0.001$). A RDW of > 11.7% also predicted AF (sensitivity 56% and specificity of 64%; AUC = 0.637, $P < 0.001$).

Kılıcgedik *et al*[48] evaluated the RDW values in 358 patients who underwent CABG surgery [57 with post-surgery AF (PSAF) and 301 patients with non-PSAF]. Interestingly, RDW values were significantly higher in PSAF group. In multivariate analysis, RDW [OR:1.16 (95%CI: 1.0-1.36), $P = 0.05$] was found to be predictive for PSAF (68.4% sensitivity and 51.2% specificity; $P = 0.001$). Likewise, Ozsin *et al*[49] analyzed the RDW levels in 93 patients who underwent off-pump CABG surgery. 24 patients developed PSAF while 69 did not. RDW was significantly correlated with PSAF and was also found to be predictive for PSAF (79.2% sensitivity and 65.2% specificity; $P = 0.001$).

Pilling *et al*[50] analyzed the RDW levels in 240477 healthy volunteers (40 ± 70 at baseline) during a follow-up period of ≤ 9 years. Higher RDW levels (≥ 15% variation, $n = 6050$) was associated with AF (sHR 1.37: 1.21 to 1.55). RDW was also predictive of new-onset AF.

Han *et al*[51] investigated the effects of low altitude (3.5 m above the sea level) and high altitude (2260 m above the sea level) on RDW levels of 303 patients with nonvalvular AF. RDW levels were higher in AF than control individuals ($P < 0.05$) and higher in persistent AF than paroxysmal AF ($P < 0.05$) in both low and high altitudes. Moreover, RDW, was independently associated with AF in low altitude

(RDW, OR: 1.687, 95%CI: 1.021–2.789; $P < 0.05$), whereas it was an independent predictor for AF (RDW, OR: 1.755, 95%CI: 1.179–2.613; $P < 0.05$) in high altitude.

Jurin *et al*[52] recruited 579 patients with AF, 412 with non-permanent AF and 167 with permanent AF, and followed-up the patients with non-permanent AF during a median time of 21 mo. The main endpoint was progression of non-permanent AF to permanent AF. 109 patients (26.6%) progressed to permanent AF. Moreover, increased RDW levels showed a significant independent association with the progression to permanent AF (HR 1.19, 95%CI: 1.03–1.39, $P = 0.022$).

Finally, Li *et al*[53] recently examined the relationship between RDW and AF in a general Chinese population (106998 subjects). The authors concluded that RDW was significantly related to a higher prevalence of AF; the OR (95%CI) of AF for increasing tertiles of RDW were 1.00 (reference), 1.08 (0.69, 1.67), and 2.65 (1.75, 4.07) (P for trend < 0.0001), respectively.

Taken together, the results of these epidemiological studies, as well as results from two systematic reviews and meta-analysis recently published[54,55], are all virtually concordant to emphasize that an enhanced RDW value not only is a predictive factor and a marker of AF but its measurement may also be helpful for predicting the risk of developing many adverse complications in patients with AF, such as recurrence and duration of AF, hospitalization for heart failure, bleeding, left atrial thrombosis and stasis, thromboembolic events (including new-onset stroke) and mortality.

ANISOCYTOSIS IN ATRIAL FIBRILLATION: ACTIVE PLAYER OR BYSTANDER?

There are at least two biological explanations which can be brought for justifying the strong epidemiological association observed between anisocytosis and AF, either of which is plausible (Figure 2).

The first and rather predictable scenario is that the same causative factors for AF may also impair erythropoiesis, and thereby the observation of an increased RDW value may only be a coincident epiphenomenon in AF[56]. For example, a high RDW value is commonplace in patients with recent blood transfusions or severe anemia[13], and both RBC transfusion[57] and anemia[58] are associated with an excess incidence of AF, as consequence of onset of heart failure and impairment of renal function. Inflammation is probably the most frequent cause of anisocytosis[59], but its contribution to the pathogenesis of AF is now almost unquestionable, since many inflammatory cytokines are known to impair atrial electrophysiology and structure[60]. Oxidative stress is another important inducer of anisocytosis[61], whilst the oxidation of myofibrillar protein and cardiomyocyte membrane lipids is also a well-recognized mechanism leading to AF[62]. Finally, it is now clearly acknowledged that renal diseases may generate a kaleidoscope of inflammatory, neurohumoral, metabolic and hemodynamic stresses to the heart[63], whilst impaired erythropoiesis and anisocytosis are also commonplace in patients with impaired renal function, mainly due to impaired erythropoietin production[13] (Figure 2).

On the other hand, a support to the thesis that anisocytosis not only may be an innocent bystander in AF, but may also trigger, or contribute to worsening, AF has emerged from a discrete number of studies. Hirayama *et al* showed that the onset of arrhythmias is strongly associated with reduced erythrocyte deformability[64], which is a conventional hallmark of anisocytic erythrocytes[65]. A large variation of erythrocytes volume is also associated with a greater cholesterol content in the RBC membrane, which can then be directly transferred to atherosclerotic plaques enriched in erythrocytes[66,67], thus finally promoting atherogenesis and ultimately predisposing to cardiac arrhythmias, since AF atherosclerosis and AF are now considered two strictly intertwined disorders[68]. Finally, the presence of anisocytic erythrocytes has also been involved in the mechanisms underlying adverse cardiac remodeling[69], thus leading to atrial fibrosis and predisposing the patients to a higher risk of developing AF[70].

CONCLUSION

The value of the RDW can be automatically generated, along with the other parameters of the complete blood cell count, by the majority of modern hematological analyzers. It can therefore be considered an easier, faster and less expensive test compared to other potentially useful biomarkers in AF[1]. Regardless of the fact that anisocytosis may be a simple bystander or an active player in the pathogenesis of AF and of its life-threatening complications, the current epidemiological evidence convincingly suggests that routine measurement of RDW may provide valuable

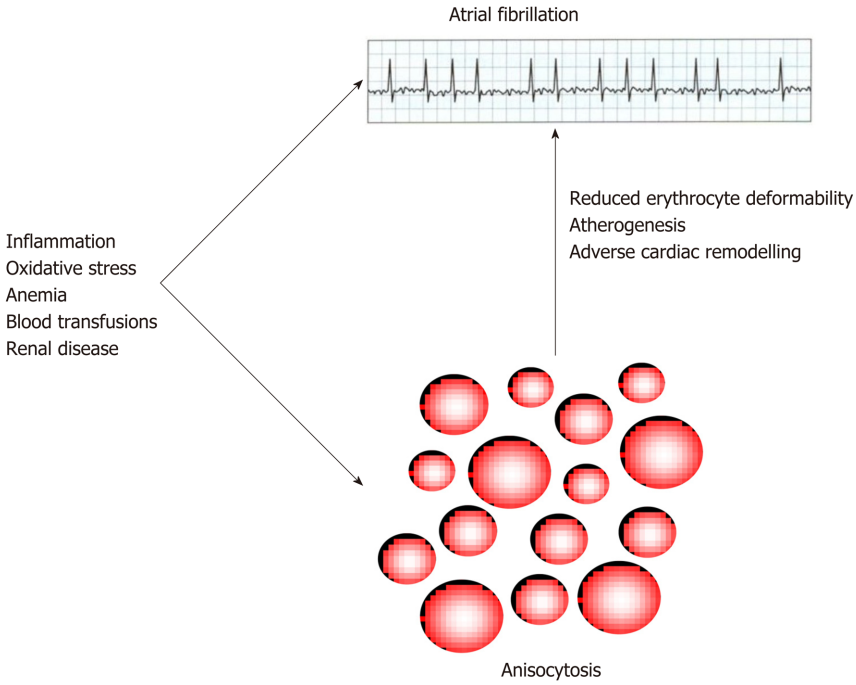

Figure 2 The interplay between atrial fibrillation and anisocytosis.

clinical information for diagnosis and management of AF, alone or combined with traditional risk scores such as CHADS2 and CHA2DS2-VASc[71]. In particular, the strong and often independent association observed between high RDW values and unfavorable outcomes (*e.g.*, recurrence of AF, heart failure, bleeding, thromboembolic events and death) (Table 1), would lead us to conclude that AF patients with RDW values exceeding the local reference range may be more aggressively investigated and managed, in order to identify and reduce the impact of possible underlying disorders causing both anisocytosis and AF (Figure 2), and also for preventing the possible risk of adverse events potentially attributable to anisocytosis. Additional studies are then advised to define whether the inclusion of RDW within conventional risks scores may be effective in providing more accurate risk stratification in AF.

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MINIREVIEWS

Myocardial infarction with non-obstructive coronary arteries: A comprehensive review and future research directions

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Abstract

Acute coronary syndromes constitute a variety of myocardial injury presentations that include a subset of patients presenting with myocardial infarction with non-obstructive coronary arteries (MINOCA). This acute coronary syndrome differs from type 1 myocardial infarction (MI) regarding patient characteristics, presentation, physiopathology, management, treatment, and prognosis. Two-thirds of MINOCA subjects present ST-segment elevation; MINOCA patients are younger, are more often female and tend to have fewer cardiovascular risk factors. Moreover, MINOCA is a working diagnosis, and defining the aetiologic mechanism is relevant because it affects patient care and prognosis. In the absence of relevant coronary artery disease, myocardial ischaemia might be triggered by an acute event in epicardial coronary arteries, coronary microcirculation, or both. Epicardial causes of MINOCA include coronary plaque disruption, coronary dissection, and coronary spasm. Microvascular MINOCA mechanisms involve microvascular coronary spasm, takotsubo syndrome (TTS), myocarditis, and coronary thromboembolism. Coronary angiography with non-significant coronary stenosis and left ventriculography are first-line tests in the differential study of MINOCA patients.

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The diagnostic arsenal includes invasive and non-invasive techniques. Medical history and echocardiography can help indicate vasospasm or thrombosis, if one finite coronary territory is affected, or specify TTS if apical ballooning is present. Intravascular ultrasound, optical coherence tomography, and provocative testing are encouraged. Cardiac magnetic resonance is a cornerstone in myocarditis diagnosis. MINOCA is not a benign diagnosis, and its polymorphic forms differ in prognosis. MINOCA care varies across centres, and future multi-centre clinical trials with standardized criteria may have a positive impact on defining optimal cardiovascular care for MINOCA patients.

Key words: Myocardial infarction; Non-obstructive coronary; Myocardial infarction with non-obstructive coronary arteries; Management; Prognosis

Core tip: Myocardial infarction with non-obstructive coronary arteries (MINOCA) differs from type 1 myocardial infarction regarding patient characteristics, presentation, physiopathology, management, treatment, and prognosis. In the absence of relevant coronary artery disease, myocardial ischaemia might be triggered by an acute event in epicardial coronary arteries, coronary microcirculation, or both. Epicardial causes of MINOCA include coronary plaque disruption, coronary dissection, and coronary spasm. Diagnostic strategies include invasive and non-invasive techniques recently embracing intravascular ultrasound and cardiac magnetic resonance. MINOCA is not a benign diagnosis, and its polymorphic forms differ in prognosis.

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INTRODUCTION

Remarkable progress in medicine regarding the pathogenesis of heart disease has produced lifesaving and life-extending therapies impacting ischaemic patients worldwide. The definition of angina pectoris is over two hundred years old, but the controversy about the aetiologic role of coronary arteries has never ceased to hold interest. Acute myocardial infarction (MI) without significant coronary artery disease (CAD) was initially described almost 80 years ago by Gross and Sternberg, whereas the term myocardial infarction with non-obstructive coronary arteries (MINOCA) is recent[1,2].

The diagnosis of an acute coronary syndrome should be established according to the fourth universal definition of MI, which is when there is evidence of acute myocardial injury accompanied by clinical data suggesting acute myocardial ischaemia such as relevant symptoms, new ischaemic electrocardiogram (ECG) changes, loss of viable myocardium present in imaging, or identification of coronary thrombus. Several diverse definitions of MI have been used, leading to unbalanced criteria and confusion. Thus, a general universal definition of MI was agreed upon for the first time over 50 years ago with the collaboration of multiple groups that were initially created for epidemiological reasons. With the discovery of cardiac biomarkers, the diagnosis of MI has been simplified, but because an increase in cardiac biomarkers is an entity by itself, it is not pathognomonic of an acute coronary syndrome in isolation. Elevation of cardiac biomarkers, such as cardiac troponin I and T, represents injury to myocardial cells, but such increases do not reflect the underlying pathophysiology because they can arise in a variety of situations, including normal hearts. This variability highlights the need for a global uniform definition of MI and myocardial injury[3-5].

There are multiple classifications of MI. Classically, for discrimination of immediate or delayed treatment strategies, patients who develop new ST-segment elevation in two contiguous leads or new bundle branch block with ischaemic alterations are

designated ST-elevation myocardial infarction (STEMI) patients, whereas the subgroup without ST-segment elevation is diagnosed as non-ST elevation MI (NSTEMI). In addition to those two categories, MI can be classified pathophysiologically[4,5]. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis corresponds to type 2 MI; by definition, acute atherothrombotic plaque rupture excludes type 2 MI. Type 1 MI and MINOCA are two separate entities with different underlying mechanisms, management, and prognosis[5,6].

MINOCA is diagnosed in a patient with features of MI with non-obstructive coronary arteries on angiography, is defined as no coronary artery stenosis ≥ 50% in any potential infarct-related artery and is characterized by the absence of a clinically specific cause of the acute presentation. Clinical criteria and biomarker behaviour of MINOCA remain similar to other acute coronary events[3,6].

PREVALENCE AND CLINICAL FEATURES

MINOCA is not an uncommon presentation of acute coronary syndromes. Large MI registries reflect the universal nature of MINOCA with the prevalence ranging between 5% and 25% in different series, with 11% in a recent prospective observational study[7-9]. Throughout the years, MINOCA has remained prevalent with an increasing incidence, as was observed in a Spanish registry[10]. MINOCA patient characteristics differ from those of other Myocardial Infarction and Coronary Artery Disease (MI-CAD) patients because MINOCA subjects are younger, are more often female, and tend to have fewer traditional cardiovascular risk factors. In the VIRGO study, women had 5-fold higher odds of presenting with MINOCA than men; non-white patients also had increased rates of MINOCA than white patients. Pasupathy *et al*[11] reported that MINOCA patients were less likely to have hyperlipidaemia, whereas a similar distribution was observed regarding hypertension, diabetes mellitus, smoking, and family history of premature coronary disease. Electrocardiographic patterns also differ, generally presenting as STEMI or NSTEMI, with two-thirds of patients having the latter. It has also been suggested that hormonal changes, such as the time of menarche and menopause, may also play a role in MINOCA.

CLASSIFICATION ACCORDING TO PATHOPHYSIOLOGY

In the absence of relevant CAD, myocardial ischaemia may be triggered by a disorder of epicardial coronary arteries and/or malfunction in the coronary microcirculation (Table 1). Both have multiple presentations[7,8].

Epicardial causes of MINOCA

Coronary plaque disruption: Many atherosclerotic plaques are positively remodelled, expand outward, and have a lipid-rich body and thin fibrous cap, making them vulnerable to rupture. The transient and partial thrombosis in this type of plaque causes distal thrombus embolization, with possible superimposed vasospasm, and might be responsible for MINOCA; this mechanism resembles type 1 MI. MINOCA represents 5%-20% of all type 1 MI. Since coronary angiography cannot evaluate the vascular lumen, intracoronary imaging modalities such as intravascular ultrasound (IVUS) might play a determinant role in evaluating the lesion. Ouldzein *et al*[12] performed IVUS in MINOCA patients to evaluate the morphological and quantitative characteristics of the culprit lesion and subsequently classified subjects according to the presence or absence of plaque rupture; the frequency of ruptured plaques in MI patients was estimated to be between 20% and 40%, and patients with plaque rupture had increased plaque burden, plaque volume and positive arterial remodelling.

Coronary dissection: Coronary dissection without visible luminal obstruction and coronary artery intramural haematomas constitute 25% of MI in women younger than 50 years of age. IVUS is a cornerstone in the assessment of coronary dissection. The physiology of this entity is unclear; however, fibromuscular dysplasia is thought to be related. This presentation has a high rate of recurrence[8,13].

Coronary artery spasm: Coronary artery spasm (CAS) represents between 3% and 95% of MINOCA cases depending on the registry. Positive provocative tests with intracoronary, adenosine or ergonovine portend a worse prognosis. The diagnosis does not require confirmation of epicardial coronary spasm, and these tests should only be performed by experienced teams because they have a potential risk of

Table 1 Myocardial infarction with non-obstructive coronary arteries classification, management overview, prevalence and suggested therapy

Mechanism	Diagnosis	Prevalence in coronary syndromes	Therapy
Epicardial causes			
Coronary artery disease	IVUS/OCT, FFR/iFR	5%-20% of MI	Antiplatelet therapy, statins, ACEi/ARB, beta-blockers
Coronary dissection	IVUS/OCT	25% of MI in women under 50 yr of age	Beta-blocker and simple antiplatelet therapy
Coronary artery spasm	Intracoronary nitrates, intracoronary Ach or ergonovine test by experienced teams	3%–95% of MI depending on the registry	Calcium antagonists, nitrates
Microvascular causes			
Microvascular coronary spasm	Objective evidence of ischaemia (ECG, LV wall motion abnormalities, PET). Impaired microvascular function (CFR, intracoronary Ach test, abnormal CMR, slow coronary flow)	As high as 25% depending on the registry	Beta-blockers and nitrates, calcium antagonist, possibly ranolazine
Takotsubo syndrome	Ventriculography, echocardiography, troponin, B-natriuretic peptide, CMR	1%-3% of general STEMI, 5%-6% women with STEMI, concomitant CAD 10%-29%	Heart failure treatment, mechanical support in cardiogenic shock
Myocarditis	CMR, EMB, viral serologies, high c-reactive protein	33% of MINOCA when determined by CMR	Heart failure treatment if complication, autoimmune therapy in autoimmune forms
Coronary embolism	History of potential thromboembolic sources, thrombophilia screen, TTE, TOE, bubble contrast echography	2.9% MI	Antiplatelet therapy, anticoagulation, transcatheter closure or surgical repair

MINOCA: Myocardial infarction with non-obstructive coronary arteries; MI: Myocardial infarction; CAD: Coronary artery disease; IVUS: Intravascular ultrasound; OCT: Optical coherence tomography; CMR: Cardiac magnetic resonance; STEMI: ST segment elevation myocardial infarction; PET: Positron emission tomography; FFR: Fractional flow reserve; ECG: Electrocardiogram; iFR: Instantaneous wave-free ratio; EMB: Endomyocardial biopsies; ACEi: Angiotensin-converting-enzyme inhibitors.

arrhythmic complications. Positive testing has been associated with a higher occurrence of death from any cause and cardiac death during follow up, a higher rate of MI readmission and inferior control of angina symptoms; epicardial spasm also showed worse clinical outcomes than microvascular spasm[14].

Microvascular causes of MINOCA

Microvascular coronary spasm: Microcoronary microvascular spasm, also referred to as Syndrome X, can occur in up to 25% of MINOCA patients in some registries and is the cause of persistent angina in up to 36% MINOCA subjects. Catecholamines and endothelin exert transient vasoconstrictive effects primarily in the coronary microvasculature, reducing microvascular blood flow in a transient manner. Objective documentation of myocardial ischaemia should be sought. The presence of four clinical criteria for microvascular angina accomplished a definitive diagnosis: Symptoms of myocardial ischaemia, the absence of obstructive CAD [< 50% diameter reduction in fractional flow reserve (FFR) > 0.80], objective evidence of ischaemia (ECG ischaemic changes, wall motion or perfusion abnormalities), and evidence of impaired coronary microvascular function. This last parameter includes having a coronary flow reserve ≤ 2-2.5, coronary microvascular spasm (reproduction of symptoms, ischaemic ECG shifts) without epicardial spasm in acetylcholine testing, abnormal coronary microvascular resistance indices, or coronary slow flow phenomenon. Diagnostic techniques for the evaluation of microvascular disease include invasive and non-invasive measures. Positron emission tomography (PET) is the most accurate non-invasive outlook of coronary vasomotor function; cardiac magnetic resonance (CMR) can also be applied, although post-processing is technically challenging. Invasive techniques include invasive coronary flow reserve, more recent FFR, and instantaneous wave-free ratio with certain limitations[15]. Plaque burden can be present or absent in MINOCA patients, and a broad spectrum of subtypes have been described, but these usually overlap. The guarded prognosis of these patients justifies an invasive approach[16].

Takotsubo syndrome: This stress cardiomyopathy represents 1%-3% of all STEMI, with 5%-6% prevalence in female subgroups, and is characterized by apical

ballooning of the left ventricle in the absence of occlusive CAD; although concomitant CAD is described in 10%-29% of Takotsubo syndrome (TTS) cases. The proposed Mayo clinical criteria include transient left ventricle mid-segment wall hypokinesis, akinesis or dyskinesis that extends beyond one vascular territory, absence of significant CAD, new electrocardiographic changes or modest elevation in cardiac biomarkers, and exclusion of pheochromocytoma or myocarditis[17,18]. The more recent international TTS diagnostic criteria (interTAK Diagnostic Criteria) vary from the Mayo criteria by recognizing pheochromocytoma as a secondary cause of TTS by stating that the presence of CAD should not be an exclusion and that cases with wall motion abnormalities restricted to one vascular territory should not be excluded (Table 2 and 3)[19]. The causes and aetiologic mechanisms of TTS are complex and still in debate, but reversible coronary microvascular vasoconstriction is a common mechanism in apical ballooning[20]. Diagnostic tools in TTS diagnosis include ventriculography, transthoracic echocardiogram with adenosine and CMR. In the absence of significant CAD, ballooning ventriculography allows a diagnosis. Contrast echocardiography with adenosine may prove microvascular constriction. CMR provides additional findings suggesting takotsubo; the hyperintense signal on T2 sequences, diffuse or transmural oedema, dysfunctional ventricular contraction matching the TTS typical ballooning, and alterations not restricted to a particular vascular territory in the absence of myocardial necrosis[8,21]. Strain echocardiography and F-18 fluorodeoxyglucose positron emission have shown promising results in the diagnosis of TTS and may play a role in the future[22].

Myocarditis: This polymorphic inflammatory disease can mimic many conditions and can have a prevalence of approximately 33% among MINOCA patients when determined by CMR imaging[24]. Young patients and high C-reactive protein findings were associated with myocarditis, while male sex, previously treated hyperlipidaemia and high troponin ratio were correlated with type 1 MI. Myocarditis also accounts for 5%-12% of young athlete sudden cardiovascular death[25]. The most common pathogens identified in patients are human herpesvirus 6 and parvovirus B19. Diagnosis of myocarditis is challenging; thus, given the poor yield of endomyocardial biopsies (EMB) and viral serologies, standard criteria such as the European Society of Cardiology 2013 Myocarditis Task Force criteria were established (Table 4)[7]. Certain diagnoses and aetiologies of myocarditis require EMB (histology, immunohistology, infectious agents by polymerase chain reaction). CMR imaging should be included in the workup of myocarditis; it provides tissue characterization but does not identify the underlying cause. Late gadolinium enhancement is observed in the majority of patients and can have several phenotypes with different prognostic implications[26].

Coronary embolism: Coronary embolism (CE) can affect coronary microcirculation and/or angiographically visible epicardial vessels. Coronary emboli can arise from coronary or systemic arterial thrombi, and coronary thrombosis may be related to thrombotic disorders. The prevalence of de novo CE MINOCA can be 2.9%. Atrial fibrillation is the most common cause of CE. Case definition can be held according to the National Cerebral and Cardiovascular Center criteria for the diagnosis of CE; the 3 major criteria include angiographic evidence of coronary artery embolism and thrombosis without atherosclerotic components, concomitant multivessel CE and concomitant systemic embolization. Minor criteria include CAD with stenosis < 25%, evidence of embolic source detected by imaging, and coexistence of potential thromboembolic disease. Paradoxical embolism due to right-left shunts is a rare cause of MINOCA, and treatment includes trans-catheter device closure or surgical repair. Transthoracic, transoesophageal, and contrast-enhanced echocardiography are the cornerstone methods for uncovering cardiac sources of embolism[8,27].

MINOCA with uncertain etiology

CMR imaging is a cornerstone in determining underlying myocardial tissue pathology. However, 8%-67% of MINOCA patients have no late gadolinium enhancement, myocardial oedema, or wall motion alterations. Vasospastic angina, coronary plaque disease or CE can have normal CMR findings; in these cases, intracoronary imaging may help shed light on the underlying ischaemic trigger. IVUS and CMR provide complementary mechanistic insights into MINOCA patients and may be useful in identifying potential causes and therapies[28].

MINOCA THERAPY ACCORDING TO PATHOPHYSIOLOGY

Epicardial causes of MINOCA

Coronary plaque disruption: Dual antiplatelet treatment for 12 mo is recommended if

Table 2 International takotsubo syndrome diagnostic criteria

Diagnostic criteria
Left ventricular dysfunction usually extending beyond a single coronary territory.
Sometimes triggered by emotional, physical or combined stress.
Acute neurologic disorders, including pheochromocytoma, may become triggers.
New ECG abnormalities. Rare cases can present with without ECG shifts.
Moderate troponin elevation. Usually, significantly high brain natriuretic peptide.
Can have concomitant CAD.
No evidence of infectious myocarditis usually excluded by CMR.
Mostly present in postmenopausal women.

CAD: Coronary artery disease; CMR: Cardiac magnetic resonance; ECG: Electrocardiogram.

allowed by haemorrhage risk, followed by chronic single antiplatelet therapy and statins[8]. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-blocker treatment have the same indication as STEMI and NSTEMI guidelines[4,5].

Coronary dissection: There is no effective treatment to reduce long-term risk. A medical strategy is recommended for coronary interventions, and stenting may cause propagation of the dissection. A conservative strategy along with beta-blockers and single antiplatelet treatment is recommended[8,13].

CAS: Chronic medical treatment includes calcium channel blockers and nitrates. Calcium antagonist dose reduction or discontinuation was associated with worse prognosis regarding mortality, supporting the role of epicardial spasm in the occurrence of adverse events[8].

Microvascular causes of MINOCA

Microvascular coronary spasm: There are no specific therapies for microvascular dysfunction, and management of underlying cardiovascular risk factors is recommended. Traditional anti-ischaemic drugs, such as beta-blockers and nitrates, should be first-line therapy; calcium antagonists can be added to treat refractory angina and are recommended when vasomotor tone is increased. The data on ranolazine for angina relief are controversial in this subset[9,15].

TTS: There are no randomized trials to guide evidence-based treatment. Empiric strategies include cardio-selective beta-blockers, avoidance of inotropes, angiotensin-converting enzyme inhibitors for persistent myocardial dysfunction, mechanical support devices in cardiogenic shock, and antiplatelet treatment with statins if associated with CAD[21].

Myocarditis: Myocarditis treatment differs from that of coronary disease because it does not require anti-ischaemic therapies. Myocarditis generally has a favourable prognosis resolving in 2 to 4 wk, while a minor subgroup develops cardiovascular complications such as heart failure and should be treated correspondingly. Autoimmune forms have negative infection findings on biopsy, and specific autoimmune therapy is required in these cases[7].

CE: Standard treatment of thromboembolic events remains individualized. Multiple factors play a role in this entity, such as the time of presentation and the presence or absence of multiple embolic sites. Patients with paroxysmal embolism in the presence of atrial septal defects require percutaneous or surgical closure. These patients have a high rate of recurrence and major adverse cardiovascular events (MACEs) in the follow-up[8,27].

DETERMINING THE CAUSE

MINOCA patients are a conundrum for clinicians; therefore, a systematic global approach should be pursued, and an attempt must be made to determine the specific aetiologic mechanism as prognosis and management vary. The diagnostic arsenal includes invasive and non-invasive techniques. Medical history can suggest a diagnosis of vasospasm angina if the patient has a chronic pattern of recurrent

Table 3 International takotsubo syndrome diagnostic score

Criteria	Points	Diagnosis probability
Female sex	25 points	≤ 70 points
Emotional stress	24 points	Low/intermediate
Physical stress	13 points	TTS probability
No ST-segment depression	12 points	
Psychiatric disorders	11 points	> 70 points
Neurologic disorders	9 points	High TTS probability
QTc prolongation	6 points	

TTS: Takotsubo syndrome.

episodic angina. Regional LV motion alterations corresponding to a finite vascular territory suggest vasospasm or thrombosis. Apical ballooning suggests TTS. A history of atrial fibrillation, dilated cardiomyopathy, prosthetic heart valves, infective endocarditis, atrial myxoma, and patent foramen oval suggest CE. IVUS or optical coherence tomography are encouraged in non-severe coronary angiography findings with less than 50% luminal reduction; if intracoronary imaging reveals normal findings, provocative functional testing is recommended. Transthoracic or transoesophageal echocardiography, LV ventriculography, and CMR are other well-documented techniques. The test flow-chart does not have a specific order and should be performed according to clinical suspicion[4,7,8]. In Figure 1, we summarize our diagnostic and therapeutic workup for MINOCA management.

MINOCA PROGNOSIS

The prognosis of MINOCA patients is heterogeneous and not benign. Patients should be carefully informed about their condition and must not be inaccurately reassured about a favourable course. Because of the aetiological heterogeneity, the extent of MI damage and different inclusion criteria, registries reporting MINOCA prognosis show diverse data regarding major cardiac adverse events during hospitalization and follow-up[10]. In the VIRGO study, similar proportions of cardiac arrest, reduced ejection fraction, and heart failure were observed in patients with MINOCA and MI-CAD, whereas the mortality rates during follow-up were not significantly different. According to a meta-analysis of eight studies that reported all-cause mortality in patients with MINOCA, both in-hospital and 12-month mortality were comparable to MI-CAD[9].

Moreover, different secondary prevention strategies at discharge have been published with discrepancies regarding medical treatment with proven prognostic value, thus possibly interfering with prognosis. In addition, it may be speculated that within the vast spectrum of MINOCA patients, the multiple categories can have dissimilar prognoses and may be under- or overestimated by grouping them together.

Nordenskjöld *et al*[29] conducted an observational study with 9092 MINOCA subjects and found that 24% of the patients presented a new MACE and 14% died during follow-up. Multiple predictors for MACEs and death among MINOCA patients are similar to those previously shown to predict new events in MI-CAD patients, some of which are older age, diabetes, hypertension, current smoking, previous MI, previous stroke, and reduced LVEF. In this study, a cholesterol paradox was observed, where low levels of total cholesterol were significantly associated with the composite endpoint of MACEs and long-term mortality; this phenomenon was primarily observed in the statin-naive group who received statin treatment after MINOCA.

Nordenskjöld *et al*[30] also studied the possible mechanisms and prognosis for reinfarction in MINOCA patients, describing an average time to readmission of 17 mo. With a median follow-up of 38 mo, mortality was similar whether the reinfarction event was MINOCA or MI-CAD. A progression of coronary stenosis is described in approximately half of the patients, and thus, the performance of another angiography in the MI event following MINOCA was relevant; all-cause mortality and cardiovascular mortality were higher among patients who did not undergo a new coronary angiography than among those who did. Repeated episodes of MINOCA are not harmless.

In a recent study of the Chinese population, MACEs in MINOCA patients at the 1-

Table 4 European Society of Cardiology 2013 Myocarditis Task Force definition of clinically suspected myocarditis

Presence of ≥ 1 clinical presentation and ≥ 1 diagnostic criteria:
Clinical presentation:
Acute coronary-like syndrome
New onset or worsening unexplained heart failure
Chronic unexpected heart failure over 3 mo duration
Life-threatening unexplained conditions (including arrhythmias, aborted sudden death, cardiogenic shock)
Diagnostic criteria:
ECG/Holter/stress test shifts: Any degree atrioventricular block or bundle branch block, ST/T or Q wave changes, sinus arrest, cardiac arrest rhythms, low voltage, frequent premature beat or supraventricular tachycardia
Elevated cardiac troponins
Functional and structural abnormalities on cardiac imaging
Oedema and/or late gadolinium enhancement of myocarditis pattern in CMR

CMR: Cardiac magnetic resonance; ECG: Electrocardiogram.

year follow-up were lower than those in MI-CAD patients. Multi-factorial survival analysis showed that older age (≥ 60 years old), female sex, atrial fibrillation, and reduced LVEF are independent risk factors for MACEs in MINOCA patients within one year[31]. The atherosclerotic burden in MINOCA patients may also have an additional role in their prognosis and represents a promising research target in the following years[23].

TTS is a special subset of MINOCA patients with regard to triggers that can be identified in two-thirds of cases and should be exposed because they can influence prognosis. Generally, long-term outcomes of TTS are comparable to those of age- and sex-matched MI patients. TTS related to emotional stress have a favourable short- and long-term prognosis, whereas those secondary to physical stress or medical conditions such as neurological events are associated with higher mortality in follow up; patients with neurological triggers tend to have higher mortality[23].

KNOWLEDGE GAPS AND FUTURE PERSPECTIVE

The present study shows a knowledge gap and heterogeneous management of MINOCA patients that need attention. MINOCA is a polymorphic aggregate with much more to be uncovered, with special emphasis on the pathophysiology. Standard MI protocols do not apply systematically to all MINOCA patients. Variations in revascularization strategies and the use of proven medical therapies exist[9]. The era of eyeball angiographic quantification is evolving, and measuring only the degree of stenosis is insufficient. The plaque burden is multi-faceted, and different plaque content, volume, and distribution along with luminal stenosis can have a divergent clinical impact and prognosis[29]. There is a demand for the use of standard criteria in MINOCA research for effective worldwide communication, as such criteria may help understand and compare international registries. Standardized criteria may provide an investigative structure for mechanistic, diagnostic, prognostic and clinical trial studies aimed at developing MINOCA evidence-based guidelines.

CONCLUSION

MINOCA should be considered a working diagnosis, and challenges must be overcome to identify its underlying cause because its polymorphic nature has various implications. MINOCA is a prevalent, not benign pathology, and misconceptions regarding this condition must be reviewed. Variable practice patterns and disparities in MINOCA care exist. Future multicentric clinical trials will have a strong impact and refine the optimal cardiovascular care of MINOCA patients.

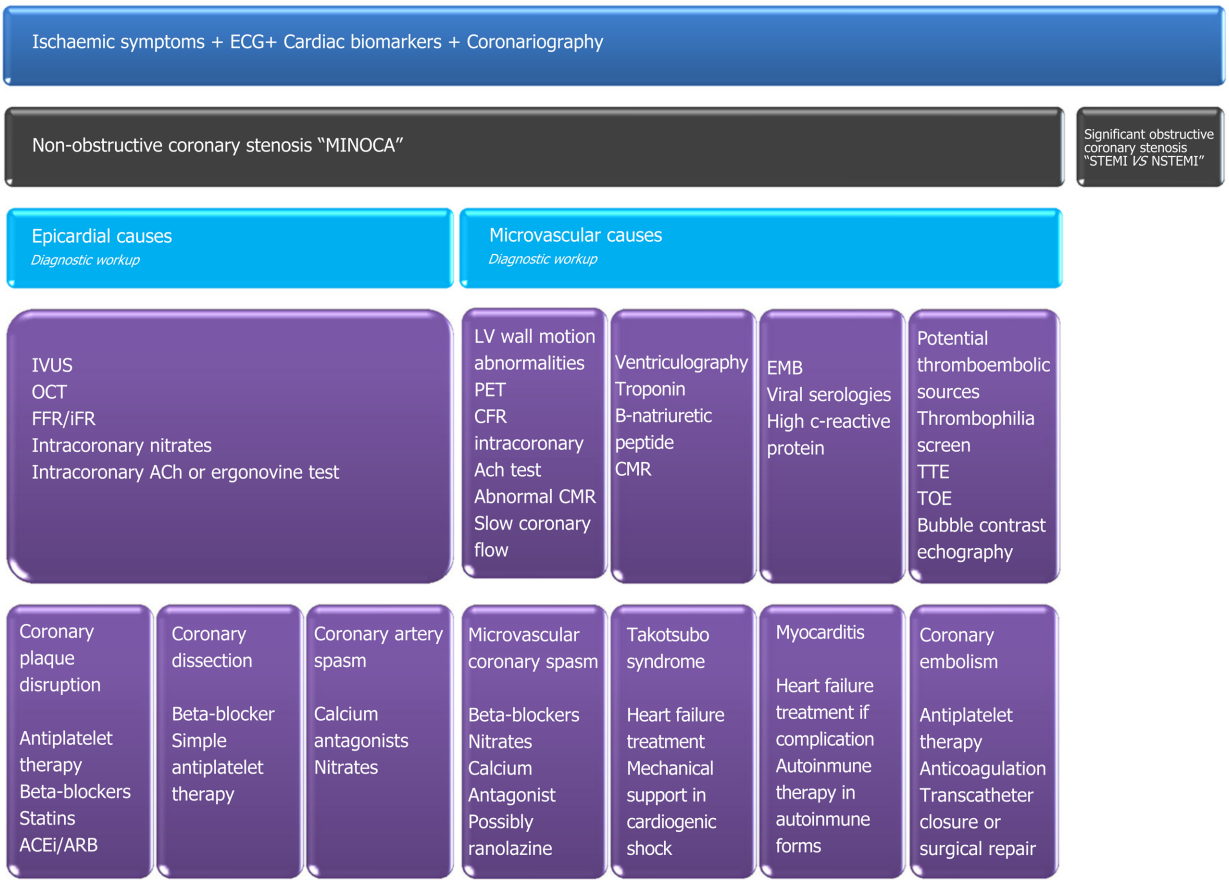

Figure 1 Diagnostic and therapeutic workup for myocardial infarction with non-obstructive coronary arteries. STEMI: ST segment elevation myocardial infarction; NSTEMI: Non-ST segment elevation myocardial infarction; Ach: Acetylcholine; CMR: Cardiac magnetic resonance; EMB: Endomyocardial biopsy; TTE: Transthoracic echocardiography; TOE: Transoesophageal echocardiography; ACEi: Angiotensin-converting-enzyme inhibitors; ARB: Angiotensin II receptor blockers; MINOCA: Myocardial infarction with non-obstructive coronary arteries; ECG: Electrocardiogram; iFR: Instantaneous wave-free ratio; OCT: Optical coherence tomography; FFR: Fractional flow reserve; IVUS: Intravascular ultrasound; PET: Positron emission tomography.

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CASE REPORT

Left recurrent laryngeal nerve palsy following aortic arch stenting: A case report

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Abstract

BACKGROUND

Aortic arch stenting is continuously emerging as a safe and effective option to alleviate aortic arch stenosis and arterial hypertension.

CASE SUMMARY

We present a 15-year-old girl with aortic arch hypoplasia who had undergone implantation of an uncovered 22 mm Cheatham-Platinum stent due to severe (native) aortic arch stenosis. On follow-up seven months later, she presented a significant re-stenosis of the aortic arch. A second stent (LD Max 26 mm) was implanted and both stents were dilated up to 16 mm. After an initially unremarkable post-interventional course, the patient presented with hoarseness five days after the intervention. MRI and CT scans ruled out an intracranial pathology, as well as thoracic hematoma, arterial dissection, and aneurysm around the intervention site. Laryngoscopy confirmed left vocal fold paresis attributable to an injury to the left recurrent laryngeal nerve (LRLN) during aortic arch stenting, as the nerve loops around the aortic arch in close proximity to the area of the implanted stents. Following a non-invasive therapeutic approach entailing regular speech therapy, the patient recovered and demonstrated no residual clinical symptoms of LRLN palsy after six months.

CONCLUSION

Left recurrent laryngeal nerve palsy is a rare complication of aortic arch stenting not previously reported.

Key words: Cardiac catheterization; Congenital heart defects; Hypoplastic aortic arch; Endovascular procedure; Vocal cord paralysis; Case report

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Core tip: This case report demonstrates that endovascular therapy of aortic arch hypoplasia with stent implantation in the stenosed segment may, as a rare complication of the procedure, lead to left recurrent laryngeal nerve palsy with subsequent vocal cord paresis.

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INTRODUCTION

Hypoplasia of the aortic arch may induce arterial hypertension of the right upper body. Alleviation of aortic arch stenosis is indicated to prevent hypertension-related cardiovascular complications. Endovascular therapy including ballooning and stenting has emerged over the last decade as a safe and effective alternative to surgical reconstruction[1-4]. Acute complications of aortic arch stenting almost exclusively involve aortic wall injury, while stent compression of adjacent structures is uncommon[5,6].

CASE PRESENTATION

Chief complaints

We report a 15-year-old girl who presented with recurrent headaches, arterial hypertension, and a systolic murmur.

History of present illness

Echocardiographic examination in a medical practice had revealed a potential coarctation of the aorta.

History of past illness

The patient had no history of serious illness.

Personal and family history

There were no medically relevant aspects from the patient's personal history. Other than arterial hypertension and coronary artery disease in the patient's grandfather, there was no known cardiac disease within the family.

Physical examination upon admission

The patient presented in good general condition. Body weight was 61 kg and height were 172 cm. Her blood pressure in the right arm with 144/86 [MAP (mean arterial pressure) 110 mmHg] was significantly higher than that in the left arm [118/82 (MAP 96) mmHg] and of the right leg [118/72 (MAP 91) mmHg]. We consistently felt an unequal pulse between the right and left radial arteries (right stronger than left). A 2/6 systolic murmur was identified ventrally in the second and third left intercostal space, and, less prominently, dorsally between the shoulder blades. All other aspects of the physical examination were normal.

Laboratory examinations

No laboratory examinations were done in the diagnostic work-up.

Imaging examinations

Echocardiography and cardiac MRI revealed a hypoplastic native aortic arch with a bi-carotid trunk and a segment just proximal of the left subclavian artery which was stenosed by 75% (Supplemental Figure 1A).

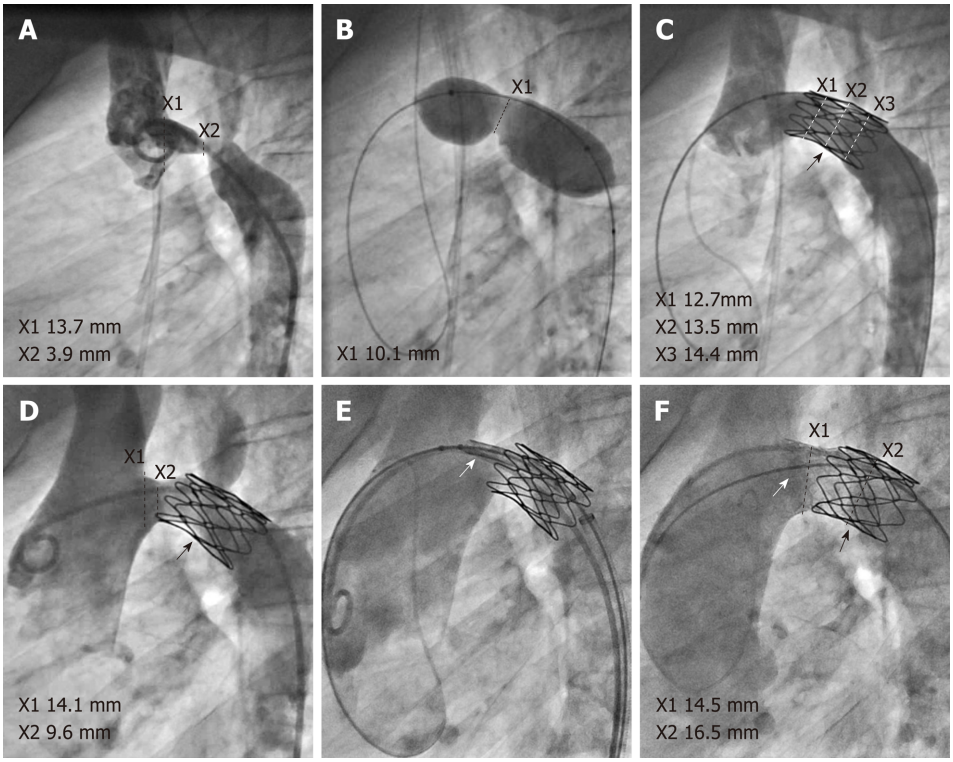

Figure 1 Angiograms in lateral projection (all images, LAO 90°) demonstrating pre-, intra- and post-interventional findings. A: Left aortic arch with bi-carotid trunc and transverse arch hypoplasia with severe native stenosis just proximal to origin of the left subclavian artery; B: Balloon interrogation using an 18 mm Tyshak II that unmasks a relatively high compliance of the stenosis; C: After implantation of a 22 mm Cheatham-Platinum (CP) stent (indicated by black arrow) on 14 mm BiB; D: Re-stenosis proximal of the previously implanted CP stent on follow-up; E: Positioning and implantation of a LD Max 26 mm stent (indicated by white arrow) over the re-stenosis; F: Final result following redilation of both stents with 16 mm Atlas balloon, and proximal stent flaring with 20 mm Cristal balloon.

FINAL DIAGNOSIS

Our final diagnosis was a hypoplastic aortic arch with a bi-carotid trunc and severe coarctation.

TREATMENT

Following discussion with the family and the cardiac surgeons, we opted against surgical treatment in favor of an interventional approach to alleviate the aortic arch stenosis. Cardiac catheterization showed a minimal diameter of 3.8 mm of the stenotic segment (Figure 1A), with a relatively compliant stenosis up to 14 mm on sizing balloon interrogation with a Tyshak II balloon (NuMed, Hopkinton, NY, United States) (Figure 1B). We implanted a short 22-mm uncovered Cheatham-Platinum (CP) stent (NuMed, Hopkinton, NY, United States), which effectively resolved the pressure gradient while preserving good perfusion of the overstented left subclavian artery (Figure 1C). On follow-up seven months later, the patient demonstrated renewed blood-pressure difference between the arms. Re-catheterization revealed re-stenosis with a diameter of 9.5 mm between the brachiocephalic artery's origin and the proximal end of the previously implanted CP stent and a systolic pressure gradient of 18 mmHg under conscious sedation, probably due to slight stent migration towards distal (Figure 1D). The re-stenosis was relieved by implantation of a 26-mm IntraStent LD Max (ev3 - Medtronic, Minneapolis, MN, United States) in telescope technique, proximal flaring of the LD Max stent with a 20-mm Cristal balloon (Balt, Montmorency, France), and (re-)dilation of both stents using a non-compliant 16-mm Atlas balloon (Bard, Tempe, AZ, United States) (Figure 1E and F).

OUTCOME AND FOLLOW-UP

Our interventional result was satisfactory, with a minimum aortic arch diameter of 14.5 mm (Figure 1F) and no relevant residual gradient detectable. Her immediate post-interventional course was unremarkable. However, five days after the

intervention the patient presented with sudden hoarseness and a weakened voice. MRI and CT scans ruled out an aortic aneurysm or dissection, haematoma, thoracic tumour formation, and intracranial pathology such as stroke (Supplemental Figure 1B and C). Otorhinolaryngological examination including laryngoscopy confirmed paresis of the left vocal fold. Due to the anatomically proximity of the left recurrent laryngeal nerve (LRLN) to the implanted stents' region, we attributed the vocal fold palsy to an injury to the LRLN during aortic arch stenting. After careful evaluation, we decided against medical or surgical therapy of the LRLN palsy and took a conservative approach involving regular speech therapy and close otorhinolaryngological monitoring. Fortunately, at follow-up six months later, our patient demonstrated no residual clinical symptoms of LRLN palsy with normal voice sound and speaking volume. For an overview of the time course of this case, see Figure 2.

DISCUSSION

We present a case of LRLN palsy following stent implantation in the transverse aortic arch. Vocal cord paresis is a well-known complication of surgical ligation of patent ductus arteriosus[7], and has also been described secondary to transcatheter closure of patent ductus arteriosus and left pulmonary artery stenting[8-12]. Moreover, LRLN palsy has also occurred after surgical aortic arch reconstruction during the Norwood procedure[13]. However, to our knowledge, LRLN paralysis resulting from transverse arch stenting has not been reported in the MEDLINE database so far. We suggest that, due to the course of the LRLN as is passes underneath the aortic arch in close proximity to the pulmonary artery and the ligamentum arteriosum, stent implantation in a severely hypoplastic aortic arch may either stretch the LRLN as the transverse aortic diameter increases, or compress it between the aortic arch and the pulmonary artery, thereby leading to LRLN damage and left vocal cord paresis. Moreover, after surgical aortic stent-graft placement, additional dilation of the graft is a known independent predictor of LRLN palsy[14]. Therefore, (re-)dilation of the stents in our patient may also have played a significant role in her having developed post-intervention LRLN palsy.

Our patient recovered relatively quickly, most likely due to either nerve growth to accommodate the larger aortic diameter, or due to cessation of an inflammatory reaction or edema following either stretch or compression of the nerve. Contrary to this positive clinical course in our patient, previous reports of LRLN after endovascular therapy of patent ductus arteriosus or left pulmonary artery stenosis have documented persistent vocal cord paralysis after six months in over 50% of patients[8-12]. However, other than the case by Javois and colleagues, who described coughing after their patient drank water[12], there were no previously reported symptoms of LRLN palsy other than hoarseness after transcatheter interventions[8-11]. Presumably due to these relatively mild clinical presentations neither medical therapy nor surgical device removal was performed in any of the cases. Therefore, it remains unclear whether in the case of acute LRLN palsy after aortic arch stent implantation, the administration of medication or decompression of the nerve by surgical stent removal would lead to LRLN recovery. Indeed, further (surgical) manipulation may even aggravate symptoms. Finally, clinicians must carefully assess whether the patient's clinical symptoms justify invasive surgical therapy.

CONCLUSION

LRLN palsy is an extremely rare complication of transverse aortic arch stenting. Interventionalists should be aware of this potential complication and inform their patients accordingly.

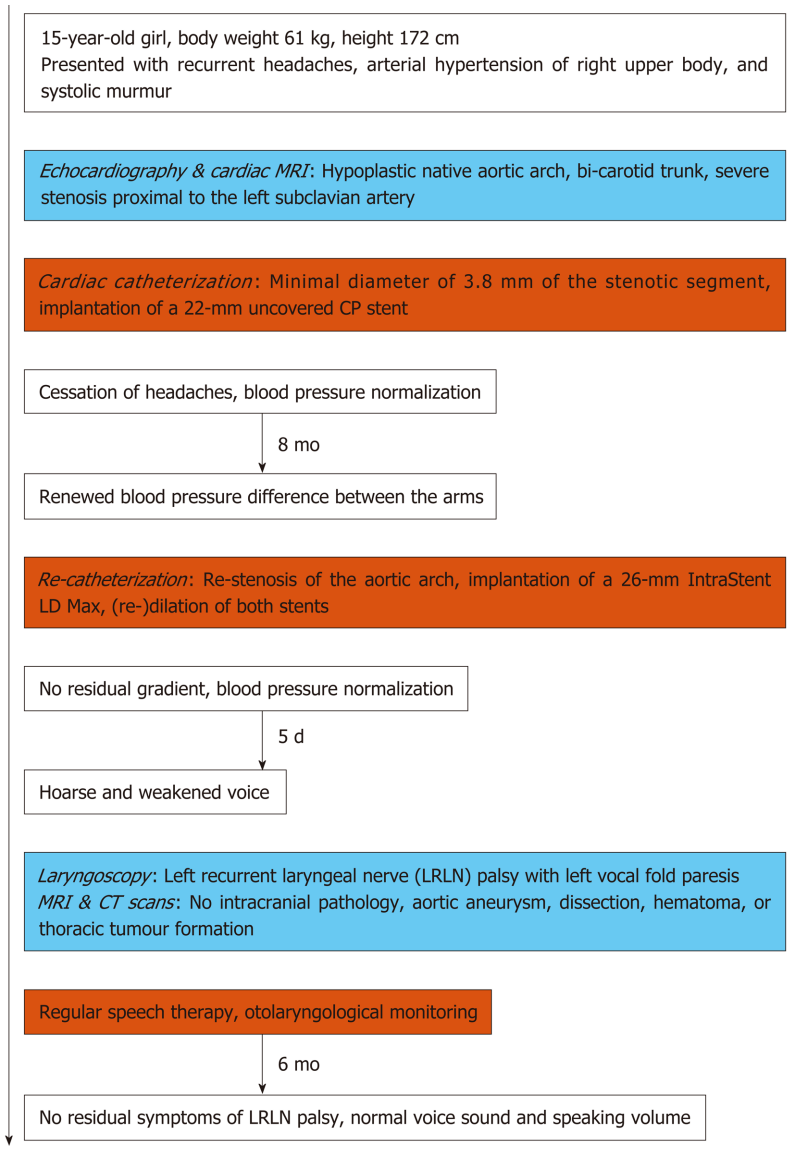

Figure 2 Time line of the case, with clinical findings highlighted in white, diagnostic work-up in blue, and therapeutic procedures in red.

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