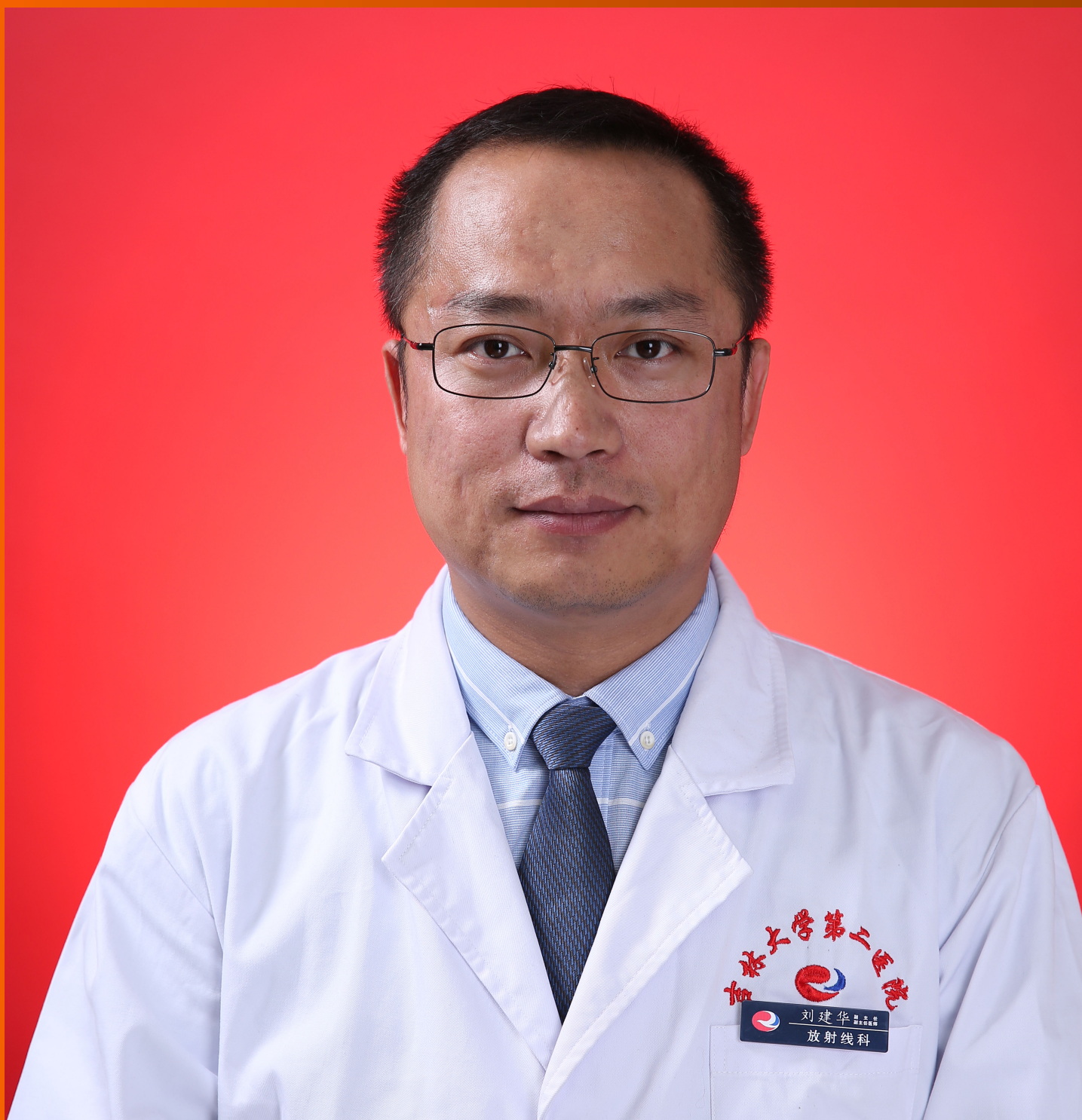


World Journal of *Cardiology*

World J Cardiol 2020 September 26; 12(9): 437-474



REVIEW

- 437 Dispersion of ventricular repolarization: Temporal and spatial
Arteyeva NV

ORIGINAL ARTICLE**Retrospective Cohort Study**

- 450 Clinical significance of prolonged chest pain in vasospastic angina
Teragawa H, Oshita C, Orita Y

CASE REPORT

- 460 Pericardial effusion with tamponade – an uncommon presentation leading to the diagnosis of eosinophilic granulomatosis polyangiitis: A case report
Alam L, Lasam G, Fishberg R
- 468 Diffuse coronary artery vasospasm in a patient with subarachnoid hemorrhage: A case report
Grewal D, Mohammad A, Swamy P, Abudayyeh I, Mamas MA, Parwani P

ABOUT COVER

Editorial board member of *World Journal of Cardiology*, Dr. Jian-Hua Liu obtained his Bachelor of Medicine and Bachelor of Surgery from Beihua University (Jilin, China). He carried out his resident training at the Second Hospital of Jilin University and obtained a Master of Science in Medical Imaging from Kunming Medical University and a PhD from Chemistry College of Jilin University. Dr. Liu then worked as a visiting scholar at Ulm University in Germany before returning to the Second Hospital of Jilin University to serve as Chief Physician and Vice Director of the Department of Radiology, positions he holds currently. His ongoing research interests involve the application of clinical and molecular imaging in cardiovascular diseases, which have led to authorship of more than 60 scientific papers in the medicinal field (H-index = 27). (L-Editor: Filipodia)

AIMS AND SCOPE

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

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

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Jia-Hui Li; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Cardiology

ISSN

ISSN 1949-8462 (online)

LAUNCH DATE

December 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Ramdas G Pai, Dimitrios Tousoulis, Marco Matteo Ciccone

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1949-8462/editorialboard.htm>

PUBLICATION DATE

September 26, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Dispersion of ventricular repolarization: Temporal and spatial

Natalia V Artyeva

ORCID number: Natalia V Artyeva
0000-0002-3421-9452.

Author contributions: Artyeva NV analyzed the literary and own data, and wrote the paper.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: February 28, 2020

Peer-review started: February 28, 2020

First decision: May 28, 2020

Revised: June 11, 2020

Accepted: August 24, 2020

Article in press: August 24, 2020

Published online: September 26, 2020

Natalia V Artyeva, Laboratory of Cardiac Physiology, Institute of Physiology of Komi Science Centre of the Ural Branch of the Russian Academy of Sciences, Syktyvkar 167982, Russia

Corresponding author: Natalia V Artyeva, PhD, Senior Scientist, Laboratory of Cardiac Physiology, Institute of Physiology of Komi Science Centre of the Ural Branch of the Russian Academy of Sciences, 50 Pervomayskaya st, Syktyvkar 167982, Russia.
natalia.arteyeva@gmail.com

Abstract

Repolarization heterogeneity (RH) is an intrinsic property of ventricular myocardium and the reason for T-wave formation on electrocardiogram (ECG). Exceeding the physiologically based RH level is associated with appearance of life-threatening ventricular arrhythmias and sudden cardiac death. In this regard, an accurate and comprehensive evaluation of the degree of RH parameters is of importance for assessment of heart state and arrhythmic risk. This review is devoted to comprehensive consideration of RH phenomena in terms of electrophysiological processes underlying RH, cardiac electric field formation during ventricular repolarization, as well as clinical significance of RH and its reflection on ECG parameters. The formation of transmural, apicobasal, left-to-right and anterior-posterior gradients of action potential durations and end of repolarization times resulting from the heterogenous distribution of repolarizing ion currents and action potential morphology throughout the heart ventricles, and the different sensitivity of myocardial cells in different ventricular regions to the action of pharmacological agents, temperature, frequency of stimulation, *etc.*, are being discussed. The review is focused on the fact that RH has different aspects – temporal and spatial, global and local; ECG reflection of various RH aspects and their clinical significance are being discussed. Strategies for comprehensive assessment of ventricular RH using different ECG indices reflecting various RH aspects are presented.

Key Words: Temporal; Spatial; Global and local dispersion of repolarization; Action potential duration; Tpeak-Tend interval; Tpeak-Tend dispersion; T-vector; Arrhythmogenesis

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: A comprehensive assessment of ventricular repolarization process is an important part of electrocardiogram (ECG) diagnostics. First of all, the increased

P-Reviewer: Iacoviello M**S-Editor:** Yan JP**L-Editor:** A**P-Editor:** Li JH

repolarization heterogeneity is associated with arrhythmogenesis. Besides, repolarization disturbances reflect the degree of electric remodeling of myocardium related to heart failure degree and mortality. We herein discuss the electrophysiological basis for repolarization heterogeneity and the factors that modulate it. We demonstrate that repolarization heterogeneity has various aspects – temporal and spatial, global and local, and there is a need in different ECG-indices to evaluate all the aspects.

Citation: Arteyeva NV. Dispersion of ventricular repolarization: Temporal and spatial. *World J Cardiol* 2020; 12(9): 437-449

URL: <https://www.wjgnet.com/1949-8462/full/v12/i9/437.htm>

DOI: <https://dx.doi.org/10.4330/wjc.v12.i9.437>

INTRODUCTION

Repolarization process is cardinally different from depolarization. During depolarization, the elementary (cellular) electric field generators responsible for QRS complex formation are concentrated in narrow (approximately 0.8-1 mm) regions of space that separates the excited myocardium (cells with peak action potential) from unexcited one (cells with resting potential)^[1]. In contrast, during repolarization the elementary electric generators are dispersed in almost the entire volume of the ventricles, with small gradients in membrane potential between the neighbouring cells. All ventricular cells, the repolarization of which is not yet completed, contribute to cardiac electric field generation.

T-wave is a result of repolarization heterogeneity (RH) – non-simultaneous end-of-repolarization in different ventricular layers and regions. This heterogeneity arises from: (1) Different activation times; and (2) Different action potential duration (APD) of ventricular cells, due to the heterogeneous distribution of repolarizing currents^[2]. The global RH in the heart ventricles is defined by the areas of the earliest and the latest repolarization – the difference in end-of-repolarization times in these areas and in their location (temporal and spatial heterogeneity, correspondingly).

In normal heart, physiological heterogeneities in structure, electrical and mechanical activity are crucial for normal, efficient excitation and pumping^[3]. Due to multiple reasons (impaired function of outward K⁺ currents in cardiac myocytes, which may be caused by genetic defects or result from various acquired pathophysiological conditions, including electrical remodelling in cardiac disease, ion channel modulation by clinically used pharmacological agents, and systemic electrolyte disorders seen in heart failure, such as hypokalaemia), the level of RH could increase^[4].

Exceeding the physiologically reasonable level of RH could lead to the development of life-threatening ventricular arrhythmias^[4-6]. In this regard, an accurate and comprehensive evaluation of RH on the basis of electrocardiogram (ECG) is of importance. This review focuses on various aspects of RH (temporal and spatial, global and local) – their electrophysiological basis, ECG reflection and clinical significance.

ELECTROPHYSIOLOGICAL BASIS FOR RH

The reason for different action potential morphology and different sensitivity of myocardial cells to the action of pharmacological agents, temperature, frequency of stimulation, *etc.* is the heterogenous distribution of repolarizing ion currents throughout the heart ventricles. There are differences in repolarizing currents across ventricular walls^[7,8], between the left and the right ventricles, between the apex and the base of the ventricles, and between anterior and posterior ventricular surface^[9,10].

In transmural plane, *in vitro* studies revealed three types of cells: Epicardial (with the shortest APD), endocardial and M-cells with the longest APD, belonging to the deep layers of the myocardium (Figure 1)^[7,8]. In interventricular septum, M-cells were less pronounced than in the free walls of the ventricles^[11]. In epicardial and M-cells, the morphology of phase 1 is characterized by a prominent transient outward current (I_{to})-mediated notch responsible for the ‘spike and dome’ morphology^[8]. M cells are distinguished from the other cell types in that they display a smaller slowly activating delayed rectifier current (I_{Ks}), but a larger late sodium current (late I_{Na}) and sodium-

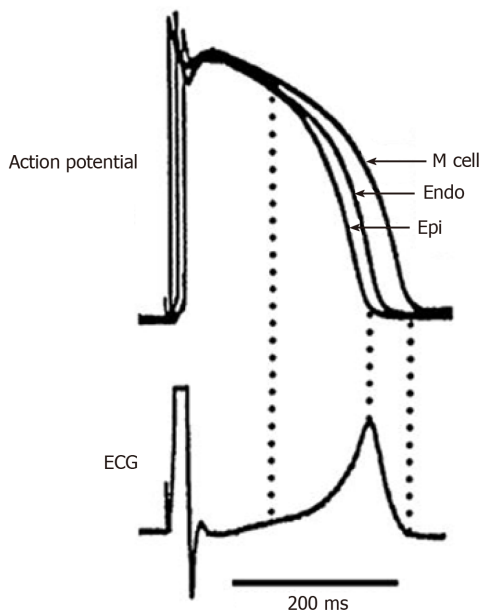


Figure 1 Transmembrane action potential and pseudo electrocardiogram recordings from a canine arterially perfused ventricular wedge preparation reveal the cellular basis for the T wave. Top: Action potentials simultaneously recorded from endocardial, epicardial, and M region sites; Bottom: Electrocardiogram recorded across the wedge; the peak and the end of T-wave correspond to the end-of-repolarization of epicardial and M-cells, correspondingly. Compiled from Figure 2^[8]. ECG: Electrocardiogram.

calcium exchange current (INa-Ca). These ionic distinctions underlie the longer APD and steeper APD-rate relationship of the M-cells, which is more pronounced in the presence of antiarrhythmic agents with class III actions^[8].

In vivo experiments did not confirm the existence of M-cells and a substantial transmural APD gradient^[12-14]. This fact can be explained, firstly, by electrotonic interaction in myocardium *in vivo*, which partially eliminates intrinsic differences in the electrophysiological properties of the cells across ventricular wall^[15,16]. Secondly, M-cells can be functionally detected at a low frequency of stimulation, while at physiological frequencies, transmural electrophysiological differences between the cells are significantly reduced^[17,18]. It should also be noted that APD recorded *in vivo* is always significantly less than those recorded *in vitro*^[14].

At the same time, *in vivo* as well as *in vitro* studies confirm the existence of apicobasal, anteroposterior and left-to-right differences in repolarizing ion currents^[12,19-22]. Apico-basal differences were found in the expression of those channel proteins which are involved in mediation of the transient outward K(+) current and the slow delayed rectifier K(+) current: Expression of Kv1.4, KChIP2, KvLQT1 and MinK was significantly higher in apical than in basal myocardium in both canine and human hearts^[19]. Prominent differences in the magnitude of the I(to) 1-mediated action potential notch were found in cells isolated from the right and the left canine ventricular epicardium; the influence of this current, although small, is more important in the left ventricle^[20-22].

APD GRADIENTS IN THE HEART VENTRICLES

Transmural gradient

Transmural APD gradient is mostly pronounced in isolated myocardial cells and wedge preparations extracted from different ventricular regions – left ventricle^[23-25], right ventricle^[26], interventricular septum^[27,28]; it is resulted from APD differences between epi- and M-cells (*in vitro*), and between epi- and endo cells (*in vivo*). The magnitude of transmural APD gradient recorded *in vitro* reached 100 ms and more^[24], and it depended on the wall thickness (the largest transmural APD gradient was recorded in the interventricular septum, the smallest one - in the right ventricle^[28,29]) and location (transmural APD gradient was different at the apex and at the base of the ventricles^[23]).

The transmural APD gradient is even attributed a key role in T-wave formation and it is assumed as “the symbol of repolarization dispersion”^[30,31]. Although, this is true

only for a ventricular wedge preparation (Figure 1), but in the whole heart dispersion of repolarization (DOR) and T-wave are resulted from several gradients^[32-34]. *In vivo* experiments did not reveal a substantial transmural APD gradient in the heart ventricles^[12-14].

Apicobasal gradient

Apicobasal gradient was detected in almost all animal and humans studies. However, its direction was found to be different in various species and sometimes controversial. APD recorded at the apex were longer than those recorded at the base of the ventricles in human^[35-37], rabbit^[38,39], dog^[12,13], and pig^[40]. In other studies, the apical APD were shorter than the basal ones in rabbit^[41], pig^[42], guinea pig^[43], rats^[44,45], and chicken^[46]. The controversial direction of apicobasal APD gradient in the same species can be explained by the high sensitivity of repolarization to temperature conditions, which could vary in different studies. In some cases, apicobasal gradient was dominating and responsible for cardiac electric field formation^[47,48].

Left-to-right gradient

Along with the transmural and apicobasal gradients, the left-to-right gradient was revealed in human and several animal species. APD in the right ventricle were longer than in the left ventricle in human^[49], rabbit^[50], pig^[40] and guinea pig^[51]. The opposite interventricular gradient was recorded in dog^[52,53] and rat^[44,45].

Anterior-posterior gradient

APD measured on the anterior surface of the heart ventricles were shorter than posterior APD in human^[37], dog^[54,55], and rabbit^[56].

EFFECT OF ACTIVATION SEQUENCE ON REPOLARIZATION

Activation sequence affects RH in two ways. First, it contributes to repolarization sequence, because end of repolarization time of myocardial cell is a sum of activation time and APD, and repolarization gradients are combinations of activation and APD gradients. Second, activation sequence can directly effect on APD magnitude, especially at heart stimulation. APD were longer in the center of stimulation, and decreased towards the periphery^[57]. The transfer of stimulus from endo- to epicardium prolonged epicardial APD and shortened endocardial APD, and, correspondingly, changed the transmural repolarization gradient^[16,58,59]. The reversed activation sequence mostly affected APD of M cells^[58]. Thus, earlier activation was associated with longer APD. Nevertheless, the relationship between early activation and longer APD is ambiguous: In rabbit hearts, repolarization sequence in general corresponded to those of depolarization, *i.e.*, the shorter APD were associated with the earlier activation times^[60].

REPOLARIZATION GRADIENTS IN THE HEART VENTRICLES

Repolarization gradients in the heart ventricles responsible for T-wave genesis are formed as a result of superimposed gradients of activation times and APD. Nevertheless, the magnitudes of APD gradients usually exceed the magnitudes of activation gradients, therefore APD gradients determine the sequence of repolarization to a greater extent, and changes in repolarization occur almost always because of APD changes.

The analysis of contribution of different parts of the canine heart ventricles to dispersion in repolarization times showed that transmural gradient contributed only 13% to the total DOR, while apicobasal, interventricular, and anterior-posterior gradients contributed the remaining 87%^[54]. Simulation studies support that transmural, apicobasal, interventricular and anteroposterior repolarization gradients are all essential to T-wave genesis^[32-34].

FACTORS MODULATING RH

Repolarization is rather sensitive than depolarization to the changes in external and internal conditions such as fluctuations in temperature, concentration of various ions,

heart rate, electrical remodeling associated with various pathologies. Inhomogeneous changes in action potentials' morphology modify and amplify the temporal and/or spatial heterogeneity of repolarization. Exceeding the physiologically based level of RH can lead to the development of life-threatening ventricular arrhythmias^[5,6]. In this regard, the analysis of both temporal and spatial RH parameters is of importance.

In experimental diabetes mellitus, there were substantial changes in spatial but not in temporal repolarization gradients. In mice, there were increased apicobasal and left-to-right gradients^[61]; in rabbit, apicobasal gradient was decreased but a large anteroposteral gradient arised^[62-64].

At electrical heart stimulation, the location of stimulus effected on APD and, correspondingly, on repolarization gradients: APD were longer in the center of stimulation, and decreased towards the periphery^[57,59,65].

In Tako-Tsubo cardiomyopathy, the ischemic-like Wellens' ECG pattern coincides and quantitatively correlates with apicobasal gradient of myocardial edema as evidenced by using cardiovascular magnetic resonance imaging^[66]; dynamic negative T-waves and QTc prolongation are likely to reflect the edema-induced transient inhomogeneity and an increased RH between apical and basal left ventricular regions. An increase in apicobasal repolarization gradient on endo- and epicardium was also found in patients with cardiomyopathy and ventricular arrhythmia vulnerability^[67]. In Brugada syndrome, APD shortening in the right ventricle strengthens the left-to-right repolarization gradient and spatial RH^[68].

In hypertrophic cardiomyopathy, ECG analysis allowed to reveal the mechanism of cardiomyopathy: Ionic remodelling and action potential prolongation in hypertrophied apical and septal areas (T-wave inversion with normal QRS complex), or abnormal Purkinje-myocardial coupling causing abnormal QRS morphology in leads V4-V6^[69].

In hypothermia, which is used for protection of myocardium from hypoxic injury, APD of all myocardial cells, including conducting system and pacemakers, prolong nonuniformly as a result of an increase in repolarizing currents^[70,71]; the nonuniform APD prolongation leads to the increase in both temporal and spatial RH^[5,72,73]. Epicardial APD prolong to the larger extent than endocardial ones, resulting in the inversion of transmural repolarization gradient at hypothermia^[30]. Apicobasal, left-to-right and anteroposteral repolarization gradients were inversed at hypothermia, too^[73]. Earlier, T-wave inversion at hypothermia was associated with the inversion of transmural^[30] or apicobasal^[73] repolarization gradients. The recent *in silico* studies demonstrated that transmural repolarization gradient do not play a crucial role in the cardiac electric field inversion under hypothermia, and the inversion of epicardial repolarization gradients (apicobasal, anterior-posterior and interventricular) causes T-wave inversion regardless of transmural gradient direction^[74].

In hypoxia/ischemia, APD shortening is associated with electrolyte imbalance in conditions of oxygen supply termination/limitation^[75], and increase in extracellular potassium concentration^[76]. Hyperkalemia leads to sodium channels' inactivation and slower conduction velocity^[77], as well as to shorter repolarization, since it enhances potassium currents^[77,78]. In addition, APD shortening at hypoxia may be associated with the release of catecholamines, which enhance the calcium-dependent chlorine current ICl (Ca) and activate the cAMP-dependent chlorine current ICl (cAMP)^[79]. *In vitro* studies showed that subepicardial layers were more sensible to ischemia than subendocardial ones^[80,81], although *in vivo* there were no transmural differences in response to ischemia^[82]. At ischemia, a significant increase in left-to-right repolarization gradient was observed^[83]. In general, ischemia enhanced both temporal and spatial RH^[84].

DOR: TEMPORAL AND SPATIAL, ITS ECG-REFLECTION AND CLINICAL SIGNIFICANCE

Temporal aspect

The quantitative temporal measure of RH is DOR – the time difference between the earliest and the latest end of repolarization in the heart ventricles. A number of experimental studies demonstrated that an increased DOR promotes arrhythmogenic substrate formation^[4-6]. Table 1 summarizing ECG-indices with their ability to evaluate the degree and the nature of ventricular RH and the degree of arrhythmic risk.

The most "traditional", but perhaps the least accurate index of DOR is QT interval dispersion. Because of the low reproducibility of clinical data, almost two decades ago it was concluded that QT dispersion gives a poor assessment of DOR^[85,86]. From

Table 1 Physiological meaning and cut-off values of electrocardiogram -indices of ventricular repolarization

Repolarization heterogeneity aspect	T-wave index	Cut-off values (arrhythmogenesis)
Maximal end of repolarization/ maximal APD values	QT	450 ms (males), 460 ms (females) ^[119]
Maximal end of repolarization/ maximal APD values in conditions of QRS widening	JTend	
The proportion between the minimal and the maximal APD	Tpeak-Tend/QT	0.22 ^[122] ; 0.23 ^[123] ; 0.31 ^[114]
	T-wave symmetry	≤ 1.7 ^[98]
The global repolarization dispersion	Tpeak-Tend	≥ 103.3 ± 17.4 ms ^[86,87] ; ≥ 142 ms ^[114]
	T-wave amplitude and T-wave area, calculated on the basis of T-vector or Root Mean Square ECG	
	Ventricular gradient, or QRS-T integral	
Local differences in repolarization dispersion	Tpeak-Tend dispersion	35 ms ^[113] ; 42 ms ^[114]
	Lead-to-lead differences in Tpeak and Tend instants between adjacent leads	
Local differences in the end of repolarization times	QT dispersion	39 ms ^[114] ; 93 ms ^[124]
Early repolarization (plateau phase)	JTpeak	
The difference in the spatial sequence of depolarization and repolarization	Spatial QRS-T angle	135° ^[89,94-99]
The general direction of repolarization sequence	T-vector projection onto the heart ventricles	
	T-loop complexity	
The relative magnitudes of apicobasal, anterior-posterior and left-to-right repolarization gradients	Ratio between X, Y, Z components of T-vector	
The location or the areas of the shortest and the longest APD	T-vector projection onto the heart ventricles	
Electrical instability of ventricular myocardium at cellular level	Macrovolt and microvolt T-wave alternans	
	Beat-to-beat T-vector variability	

APD: Action potential duration; ECG: Electrocardiogram.

theoretical viewpoint, QT dispersion reflects local differences in the latest (T-wave end), but not the earliest repolarization; thus, it reflects DOR only partially.

The more accurate index of DOR is Tpeak-Tend interval - a useful arrhythmic risk stratification tool in a wide variety of pathologies^[87-89]. It was proven both experimentally and in silico that Tpeak-Tend directly reflects DOR magnitude^[56,90-92]. Although, a serious problem in using Tpeak-Tend for diagnostics is the discrepancy between the cut-off values resulting from different T-end determining method (baseline or tangent) as well as different number of ECG leads involved in calculations. In some studies, Tpeak-Tend was not a predictor of arrhythmia^[93,94]; however, this does not decrease its clinical significance, but suggests that mechanisms of triggering arrhythmias are not necessarily associated with increased DOR, and the search for new arrhythmogenic indices should be continued. The alternative relative assessments of DOR magnitude are T-wave amplitude, width, area and symmetry^[95-99] (Table 1).

Spatial aspect

Traditionally, the term DOR is associated with temporal RH. However, since the regions of early and late repolarization differ both in time and location, DOR is a vectorial parameter, directed from point A (the region of the earliest end of repolarization) to point B (the region of the latest end of repolarization) (Figure 2). The spatial characteristic of RH is T-vector of vectorcardiogram – a three-dimensional total electric vector of ventricular repolarization, which can be calculated on the basis of standard ECG set^[100].

T-vector amplitude is not directly equal to DOR: The first is calculated in mV, and the second in ms. However, from physical viewpoint, T-vector amplitude must be

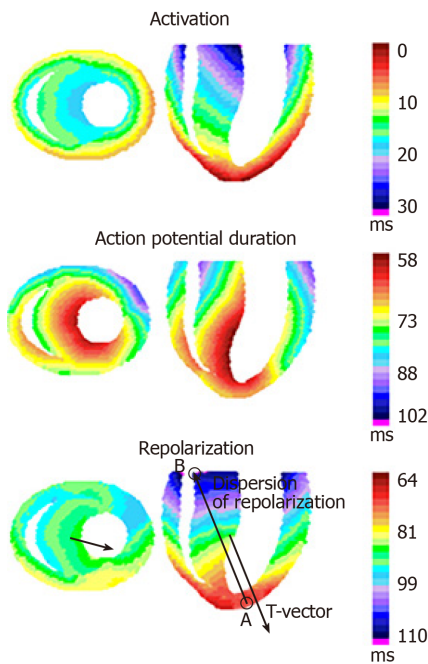


Figure 2 Realistic activation sequence, action potential duration distribution and end-of-repolarization sequence in the rabbit heart ventricles' model, simulated from intramural and epicardial measurements^[56]. The middle transversal and longitudinal cross-sections of the model and the corresponding T-vector projections are shown. Transmural, apicobasal, anterior-posterior and left-to-right gradients in activation times, action potential duration and end-of-repolarization times, reconstructed from experimental data, are presented. A and B – the regions of the earliest and the latest end-of-repolarization, correspondingly. T-vector direction is parallel but opposite to the general direction of repolarization sequence.

proportional to DOR magnitude, and the relationship between T-vector components (Tx, Ty and Tz) must reflect the proportion between ventricular repolarization gradients in corresponding directions.

T-vector direction reflects the general sequence of repolarization, but in the opposite way: T-vector is oriented from the regions of late repolarization towards the regions of early repolarization (Figure 2). Substantial changes in T-vector direction, even if DOR magnitude is within normal range (e.g., experimental Diabetes Mellitus^[61-64]), indicate a large-scale electrical heart remodeling.

T-vector provides important information in addition to “scalar” DOR value^[101]: The amplitudes of cardiac potentials' peaks and the time of their occurrence on ECG depend on lead location, while vectorcardiogram provides objective, “weighted” values; Ventricular gradient (three-dimensional QRS-T integral) reflects the distribution of the action potentials' morphology in the heart ventricles^[102]; ST-vector reflects the presence and peculiarities of ischemia; A distorted, twisted T-loop (the trajectory of T-vector projections on anatomical planes during ventricular repolarization) indicates pathological repolarization, while normal T-loop has a correct smoothed shape^[103-105].

Besides T-vector direction itself, the angle between T-vector and QRS-vector (QRS-T angle) is highly informative regarding spatial RH^[106,107]. In healthy people, repolarization is practically opposite to depolarization, and QRS-T angle is relatively small ($\leq 105^\circ$)^[101,108]. An increased QRS-T angle ($\geq 135^\circ$) indicates the changes in repolarization sequence, and, correspondingly, the changes in repolarization gradients resulted from electrophysiological disturbances in ventricular myocardium – the altered distribution of ion channels and action potentials' durations^[105,109]. An increased QRS-T angle was shown to be the most reliable predictor of the risk of life-threatening arrhythmias and death from heart disease compared with other ECG parameters^[105,109-111].

LOCAL DOR VS GLOBAL DOR

DOR magnitude along with T-vector reflects the total (global) temporal and spatial repolarization pattern in the heart ventricles, but do not reflect the local electrophysiological heterogeneities. At the same time, increase in local RH may be

more relevant for arrhythmia development than increase in global DOR: The regions with the greatest local repolarization time differences often serve as sources for ectopic beats and Torsade de pointes^[111-113].

The same condition (e.g., myocardial ischemia) can lead to the increase in both local and global DOR, and in such a case the global and local repolarization changes are hardly distinguishable, and specific novel markers for local DOR magnitude are needed. Dispersion of Tpeak-Tend interval (the difference between the earliest Tpeak and the latest Tend among 12 standard leads) was proposed as a possible specific marker for the local DOR^[114,115]. Besides, mathematical simulations showed that local increase in DOR can be expressed in increased lead-to-lead differences in Tpeak and Tend instants between adjacent anatomically ordered standard leads [aVL, I, aVR(-), II, aVF, III, and V1-V6], even if global DOR, Tpeak-Tend interval and Tpeak-Tend dispersion are within a normal range^[116].

OTHER REPOLARIZATION PARAMETERS

In some cases, indices characterizing duration and morphology of action potentials (QT, JTpeak and JTend intervals)^[117-120], as well as electrical instability of ventricular myocardium at cellular level (macrovolt and microvolt T-wave alternans, beat-to-beat T-vector variability)^[121,122] may be of clinical importance (Table 1).

CONCLUSION

Both temporal (the time difference between the earliest and the latest end of repolarization in the whole ventricles, and the local differences in end of repolarization times) and spatial (the general direction of ventricular repolarization sequence and the relative magnitudes of repolarization gradients) heterogeneity of ventricular repolarization are of clinical importance. The complex use of different ECG indices (Tpeak-Tend interval and its dispersion, T-vector and T-loop parameters, QRS-T angle, etc.) provides information about temporal and spatial, global and local characteristics of ventricular repolarization for better heart state assessment.

REFERENCES

- 1 **Vander Ark CR**, Reynolds EW Jr. An experimental study of propagated electrical activity in the canine heart. *Circ Res* 1970; **26**: 451-460 [PMID: 5435708 DOI: 10.1161/01.res.26.4.451]
- 2 **Nerbonne JM**, Kass RS. Molecular physiology of cardiac repolarization. *Physiol Rev* 2005; **85**: 1205-1253 [PMID: 16183911 DOI: 10.1152/physrev.00002.2005]
- 3 **Dressler FF**, Brado J, Odening KE. Electromechanical heterogeneity in the heart: A key to long QT syndrome? *Herzschrittmacherther Elektrophysiol* 2018; **29**: 43-47 [PMID: 29234865 DOI: 10.1007/s00399-017-0544-9]
- 4 **Osadchii OE**. Role of abnormal repolarization in the mechanism of cardiac arrhythmia. *Acta Physiol (Oxf)* 2017; **220** Suppl 712: 1-71 [PMID: 28707396 DOI: 10.1111/apha.12902]
- 5 **Han J**, Moe GK. Nonuniform Recovery of Excitability in Ventricular Muscle. *Circ Res* 1964; **14**: 44-60 [PMID: 14104163 DOI: 10.1161/01.res.14.1.44]
- 6 **Nanke T**, Nakazawa K, Arai M, Ryu S, Osada K, Sakurai T, Miyake F. Clinical significance of the dispersion of the activation-recovery interval and recovery time as markers for ventricular fibrillation susceptibility in patients with Brugada syndrome. *Circ J* 2002; **66**: 549-552 [PMID: 12074270 DOI: 10.1253/circj.66.549]
- 7 **Yan GX**, Shimizu W, Antzelevitch C. Characteristics and distribution of M cells in arterially perfused canine left ventricular wedge preparations. *Circulation* 1998; **98**: 1921-1927 [PMID: 9799214 DOI: 10.1161/01.cir.98.18.1921]
- 8 **Antzelevitch C**, Fish J. Electrical heterogeneity within the ventricular wall. *Basic Res Cardiol* 2001; **96**: 517-527 [PMID: 11770069 DOI: 10.1007/s003950170002]
- 9 **Brahmajothi MV**, Morales MJ, Reimer KA, Strauss HC. Regional localization of ERG, the channel protein responsible for the rapid component of the delayed rectifier, K⁺ current in the ferret heart. *Circ Res* 1997; **81**: 128-135 [PMID: 9201036 DOI: 10.1161/01.res.81.1.128]
- 10 **Strom M**, Wan X, Poelzing S, Ficker E, Rosenbaum DS. Gap junction heterogeneity as mechanism for electrophysiologically distinct properties across the ventricular wall. *Am J Physiol Heart Circ Physiol* 2010; **298**: H787-H794 [PMID: 20035026 DOI: 10.1152/ajpheart.00887.2009]
- 11 **Morita ST**, Zipes DP, Morita H, Wu J. Analysis of action potentials in the canine ventricular septum: no phenotypic expression of M cells. *Cardiovasc Res* 2007; **74**: 96-103 [PMID: 17266946 DOI: 10.1016/j.cardiores.2007.01.003]
- 12 **Bauer A**, Becker R, Karle C, Schreiner KD, Senges JC, Voss F, Kraft P, Kuebler W, Schoels W. Effects of the I(Kr)-blocking agent dofetilide and of the I(Ks)-blocking agent chromanol 293b on regional disparity of

- left ventricular repolarization in the intact canine heart. *J Cardiovasc Pharmacol* 2002; **39**: 460-467 [PMID: 11862126 DOI: 10.1097/00005344-200203000-00018]
- 13 **Janse MJ**, Sosunov EA, Coronel R, Opthof T, Anyukhovsky EP, de Bakker JM, Plotnikov AN, Shlapakova IN, Danilo P Jr, Tijssen JG, Rosen MR. Repolarization gradients in the canine left ventricle before and after induction of short-term cardiac memory. *Circulation* 2005; **112**: 1711-1718 [PMID: 16157774 DOI: 10.1161/CIRCULATIONAHA.104.516583]
- 14 **Voss F**, Opthof T, Marker J, Bauer A, Katus HA, Becker R. There is no transmural heterogeneity in an index of action potential duration in the canine left ventricle. *Heart Rhythm* 2009; **6**: 1028-1034 [PMID: 19560091 DOI: 10.1016/j.hrthm.2009.03.028]
- 15 **Joyner RW**. Modulation of repolarization by electrotonic interactions. *Jpn Heart J* 1986; **27** Suppl 1: 167-183 [PMID: 3820585 DOI: 10.1016/0167-5273(86)90151-8]
- 16 **Myles RC**, Bernus O, Burton FL, Cobbe SM, Smith GL. Effect of activation sequence on transmural patterns of repolarization and action potential duration in rabbit ventricular myocardium. *Am J Physiol Heart Circ Physiol* 2010; **299**: H1812-H1822 [PMID: 20889843 DOI: 10.1152/ajpheart.00518.2010]
- 17 **Sicouri S**, Antzelevitch C. A subpopulation of cells with unique electrophysiological properties in the deep subepicardium of the canine ventricle. The M cell. *Circ Res* 1991; **68**: 1729-1741 [PMID: 2036721 DOI: 10.1161/01.res.68.6.1729]
- 18 **Liu DW**, Gintant GA, Antzelevitch C. Ionic bases for electrophysiological distinctions among epicardial, midmyocardial, and endocardial myocytes from the free wall of the canine left ventricle. *Circ Res* 1993; **72**: 671-687 [PMID: 8431990 DOI: 10.1161/01.res.72.3.671]
- 19 **Szentadassy N**, Banyasz T, Biro T, Szabo G, Toth BI, Magyar J, Lazar J, Varro A, Kovacs L, Nanasi PP. Apico-basal inhomogeneity in distribution of ion channels in canine and human ventricular myocardium. *Cardiovasc Res* 2005; **65**: 851-860 [PMID: 15721865 DOI: 10.1016/j.cardiores.2004.11.022]
- 20 **Di Diego JM**, Sun ZQ, Antzelevitch C. I(to) and action potential notch are smaller in left vs. right canine ventricular epicardium. *Am J Physiol* 1996; **271**: H548-H561 [PMID: 8770096 DOI: 10.1152/ajpheart.1996.271.2.H548]
- 21 **Medei E**, Marocolo M, Rodrigues Dde C, Arantes PC, Takiya CM, Silva J, Rondinelli E, Goldenberg RC, de Carvalho AC, Nascimento JH. Chronic treatment with anabolic steroids induces ventricular repolarization disturbances: cellular, ionic and molecular mechanism. *J Mol Cell Cardiol* 2010; **49**: 165-175 [PMID: 20462507 DOI: 10.1016/j.yjmcc.2010.04.014]
- 22 **Martin CA**, Siedlecka U, Kemmerich K, Lawrence J, Cartledge J, Guzadhur L, Brice N, Grace AA, Schwenning C, Terracciano CM, Huang CL. Reduced Na(+) and higher K(+) channel expression and function contribute to right ventricular origin of arrhythmias in Scn5a+/- mice. *Open Biol* 2012; **2**: 120072 [PMID: 22773948 DOI: 10.1098/rsob.120072]
- 23 **Sekiya S**, Ichikawa S, Tsutsumi T, Harumi K. Nonuniform action potential durations at different sites in canine left ventricle. *Jpn Heart J* 1983; **24**: 935-945 [PMID: 6672263 DOI: 10.1536/ihj.24.935]
- 24 **Glukhov AV**, Fedorov VV, Lou Q, Ravikumar VK, Kalish PW, Schuessler RB, Moazami N, Efimov IR. Transmural dispersion of repolarization in failing and nonfailing human ventricle. *Circ Res* 2010; **106**: 981-991 [PMID: 20093630 DOI: 10.1161/CIRCRESAHA.109.204891]
- 25 **Di Diego JM**, Sicouri S, Myles RC, Burton FL, Smith GL, Antzelevitch C. Optical and electrical recordings from isolated coronary-perfused ventricular wedge preparations. *J Mol Cell Cardiol* 2013; **54**: 53-64 [PMID: 23142540 DOI: 10.1016/j.yjmcc.2012.10.017]
- 26 **Li GR**, Feng J, Yue L, Carrier M. Transmural heterogeneity of action potentials and Ito1 in myocytes isolated from the human right ventricle. *Am J Physiol* 1998; **275**: H369-H377 [PMID: 9683422 DOI: 10.1152/ajpheart.1998.275.2.H369]
- 27 **Ramackers C**, Stengl M, Späthjens RL, Moorman AF, Vos MA. Molecular and electrical characterization of the canine cardiac ventricular septum. *J Mol Cell Cardiol* 2005; **38**: 153-161 [PMID: 15623432 DOI: 10.1016/j.yjmcc.2004.10.011]
- 28 **Sicouri S**, Glass A, Ferreira M, Antzelevitch C. Transseptal dispersion of repolarization and its role in the development of Torsade de Pointes arrhythmias. *J Cardiovasc Electrophysiol* 2010; **21**: 441-447 [PMID: 19909385 DOI: 10.1111/j.1540-8167.2009.01641.x]
- 29 **Wan X**, Bryant SM, Hart G. A topographical study of mechanical and electrical properties of single myocytes isolated from normal guinea-pig ventricular muscle. *J Anat* 2003; **202**: 525-536 [PMID: 12846474 DOI: 10.1046/j.1469-7580.2003.00187.x]
- 30 **Higuchi T**, Nakaya Y. T wave polarity related to the repolarization process of epicardial and endocardial ventricular surfaces. *Am Heart J* 1984; **108**: 290-295 [PMID: 6464965 DOI: 10.1016/0002-8703(84)90614-8]
- 31 **Antzelevitch C**. Transmural dispersion of repolarization and the T wave. *Cardiovasc Res* 2001; **50**: 426-431 [PMID: 11376617 DOI: 10.1016/s0008-6363(01)00285-1]
- 32 **Okada J**, Washio T, Maehara A, Momomura S, Sugiura S, Hisada T. Transmural and apicobasal gradients in repolarization contribute to T-wave genesis in human surface ECG. *Am J Physiol Heart Circ Physiol* 2011; **301**: H200-H208 [PMID: 21460196 DOI: 10.1152/ajpheart.01241.2010]
- 33 **Arteyeva NV**, Azarov JE, Vityazev VA, Shmakov DN. Action potential duration gradients in the heart ventricles and the cardiac electric field during ventricular repolarization (a model study). *J Electrocardiol* 2015; **48**: 678-685 [PMID: 25818745 DOI: 10.1016/j.jelectrocard.2015.03.010]
- 34 **Zheng Y**, Wei D, Zhu X, Chen W, Fukuda K, Shimokawa H. Transmural, interventricular, apicobasal and anteroposterior action potential duration gradients are all essential to the genesis of the concordant and realistic T wave: A whole-heart model study. *J Electrocardiol* 2016; **49**: 569-578 [PMID: 27034121 DOI: 10.1016/j.jelectrocard.2016.03.010]
- 35 **Franz MR**, Bargheer K, Rafflenbeul W, Haverich A, Lichtlen PR. Monophasic action potential mapping in human subjects with normal electrocardiograms: direct evidence for the genesis of the T wave. *Circulation* 1987; **75**: 379-386 [PMID: 3802441 DOI: 10.1161/01.cir.75.2.379]
- 36 **Cowan JC**, Hilton CJ, Griffiths CJ, Tansuphaswadikul S, Bourke JP, Murray A, Campbell RW. Sequence of epicardial repolarisation and configuration of the T wave. *Br Heart J* 1988; **60**: 424-433 [PMID: 3203037 DOI: 10.1136/hrt.60.5.424]

- 37 **Meijborg VM**, Conrath CE, Opthof T, Belterman CN, de Bakker JM, Coronel R. Electrocardiographic T wave and its relation with ventricular repolarization along major anatomical axes. *Circ Arrhythm Electrophysiol* 2014; **7**: 524-531 [PMID: [24837645](#) DOI: [10.1161/CIRCEP.113.001622](#)]
- 38 **Cheng J**, Kamiya K, Liu W, Tsuji Y, Toyama J, Kodama I. Heterogeneous distribution of the two components of delayed rectifier K⁺ current: a potential mechanism of the proarrhythmic effects of methanesulfonanilideclass III agents. *Cardiovasc Res* 1999; **43**: 135-147 [PMID: [10536698](#) DOI: [10.1016/s0008-6363\(99\)00061-9](#)]
- 39 **Dressler FF**, Bodi I, Menza M, Moss R, Bugger H, Bode C, Behrends JC, Seemann G, Odening KE. Interregional electro-mechanical heterogeneity in the rabbit myocardium. *Prog Biophys Mol Biol* 2017; **130**: 344-355 [PMID: [28655649](#) DOI: [10.1016/j.pbiomolbio.2017.06.016](#)]
- 40 **Newton JC**, Johnson PL, Justice RK, Smith WM, Ideker RE. Estimated global epicardial distribution of activation rate and conduction block during porcine ventricular fibrillation. *J Cardiovasc Electrophysiol* 2002; **13**: 1035-1041 [PMID: [12435192](#) DOI: [10.1046/j.1540-8167.2002.01035.x](#)]
- 41 **Azarov JE**, Shmakov DN, Vityazev VA, Roshchevskaya IM, Roshchevsky MP. Activation and repolarization patterns in the ventricular epicardium under sinus rhythm in frog and rabbit hearts. *Comp Biochem Physiol A Mol Integr Physiol* 2007; **146**: 310-316 [PMID: [17188010](#) DOI: [10.1016/j.cbpa.2006.10.036](#)]
- 42 **Kongstad O**, Xia Y, Liu Y, Liang Y, Olsson B, Yuan S. Ventricular repolarization sequences on the epicardium and endocardium. Monophasic action potential mapping in healthy pigs. *J Electrocardiol* 2012; **45**: 49-56 [PMID: [21696753](#) DOI: [10.1016/j.jelectrocard.2011.04.009](#)]
- 43 **Kanai A**, Salama G. Optical mapping reveals that repolarization spreads anisotropically and is guided by fiber orientation in guinea pig hearts. *Circ Res* 1995; **77**: 784-802 [PMID: [7554126](#) DOI: [10.1161/01.res.77.4.784](#)]
- 44 **Watanabe T**, Delbridge LM, Bustamante JO, McDonald TF. Heterogeneity of the action potential in isolated rat ventricular myocytes and tissue. *Circ Res* 1983; **52**: 280-290 [PMID: [6825220](#) DOI: [10.1161/01.res.52.3.280](#)]
- 45 **Donohoe P**, Hendry BM, Walgama OV, Bertaso F, Hopster DJ, Shattock MJ, James AF. An altered repolarizing potassium current in rat cardiac myocytes after subtotal nephrectomy. *J Am Soc Nephrol* 2000; **11**: 1589-1599 [PMID: [10966483](#) DOI: [10.1089/08927790050152203](#)]
- 46 **Kharin SN**. Depolarisation and repolarisation sequences of ventricular epicardium in chickens (*Gallus gallus domesticus*). *Comp Biochem Physiol A Mol Integr Physiol* 2004; **137**: 237-244 [PMID: [14720609](#) DOI: [10.1016/j.cbpb.2003.10.007](#)]
- 47 **Noble D**, Cohen I. The interpretation of the T wave of the electrocardiogram. *Cardiovasc Res* 1978; **12**: 13-27 [PMID: [76514](#) DOI: [10.1093/cvr/12.1.13](#)]
- 48 **Kongstad O**, Xia Y, Liang Y, Hertervig E, Ljungström E, Olsson B, Yuan S. Epicardial and endocardial dispersion of ventricular repolarization. A study of monophasic action potential mapping in healthy pigs. *Scand Cardiovasc J* 2005; **39**: 342-347 [PMID: [16352486](#) DOI: [10.1080/14017430500188744](#)]
- 49 **Chen PS**, Moser KM, Dembitsky WP, Auger WR, Daily PO, Calisi CM, Jamieson SW, Feld GK. Epicardial activation and repolarization patterns in patients with right ventricular hypertrophy. *Circulation* 1991; **83**: 104-118 [PMID: [1824619](#) DOI: [10.1161/01.cir.83.1.104](#)]
- 50 **Nishimura M**, Watanabe Y, Toda H. The genesis of bifid T waves: experimental demonstration in isolated perfused rabbit hearts. *Int J Cardiol* 1984; **6**: 1-16 [PMID: [6746131](#) DOI: [10.1016/0167-5273\(84\)90240-7](#)]
- 51 **Poelzing S**, Veeraraghavan R. Heterogeneous ventricular chamber response to hypokalemia and inward rectifier potassium channel blockade underlies bifurcated T wave in guinea pig. *Am J Physiol Heart Circ Physiol* 2007; **292**: H3043-H3051 [PMID: [17307991](#) DOI: [10.1152/ajpheart.01312.2006](#)]
- 52 **Coronel R**, Opthof T, Plotnikov AN, Wilms-Schopman FJ, Shlapakova IN, Danilo P Jr, Sosunov EA, Anyukhovskiy EP, Janse MJ, Rosen MR. Long-term cardiac memory in canine heart is associated with the evolution of a transmural repolarization gradient. *Cardiovasc Res* 2007; **74**: 416-425 [PMID: [17391659](#) DOI: [10.1016/j.cardiores.2007.02.024](#)]
- 53 **Opthof T**, Janse MJ, Meijborg VM, Cinca J, Rosen MR, Coronel R. Dispersion in ventricular repolarization in the human, canine and porcine heart. *Prog Biophys Mol Biol* 2016; **120**: 222-235 [PMID: [26790342](#) DOI: [10.1016/j.pbiomolbio.2016.01.007](#)]
- 54 **Opthof T**, Coronel R, Janse MJ. Is there a significant transmural gradient in repolarization time in the intact heart?: Repolarization Gradients in the Intact Heart. *Circ Arrhythm Electrophysiol* 2009; **2**: 89-96 [PMID: [19808447](#) DOI: [10.1161/CIRCEP.108.825356](#)]
- 55 **Janse MJ**, Coronel R, Opthof T, Sosunov EA, Anyukhovskiy EP, Rosen MR. Repolarization gradients in the intact heart: transmural or apico-basal? *Prog Biophys Mol Biol* 2012; **109**: 6-15 [PMID: [22446189](#) DOI: [10.1016/j.pbiomolbio.2012.03.001](#)]
- 56 **Arteyeva NV**, Goshka SL, Sedova KA, Bernikova OG, Azarov JE. What does the T(peak)-T(end) interval reflect? An experimental and model study. *J Electrocardiol* 2013; **46**: 296.e1-296.e8 [PMID: [23473669](#) DOI: [10.1016/j.jelectrocard.2013.02.001](#)]
- 57 **Osaka T**, Kodama I, Tsuboi N, Toyama J, Yamada K. Effects of activation sequence and anisotropic cellular geometry on the repolarization phase of action potential of dog ventricular muscles. *Circulation* 1987; **76**: 226-236 [PMID: [3594771](#) DOI: [10.1161/01.cir.76.1.226](#)]
- 58 **Fish JM**, Di Diego JM, Nesterenko V, Antzelevitch C. Epicardial activation of left ventricular wall prolongs QT interval and transmural dispersion of repolarization: implications for biventricular pacing. *Circulation* 2004; **109**: 2136-2142 [PMID: [15078801](#) DOI: [10.1161/01.CIR.0000127423.75608.A4](#)]
- 59 **Srinivasan NT**, Orini M, Simon RB, Providência R, Khan FZ, Segal OR, Babu GG, Bradley R, Rowland E, Ahsan S, Chow AW, Lowe MD, Taggart P, Lambiase PD. Ventricular stimulus site influences dynamic dispersion of repolarization in the intact human heart. *Am J Physiol Heart Circ Physiol* 2016; **311**: H545-H554 [PMID: [27371682](#) DOI: [10.1152/ajpheart.00159.2016](#)]
- 60 **Vaykshnorayte MA**, Ovechkin AO, Azarov JE. The effect of diabetes mellitus on the ventricular epicardial activation and repolarization in mice. *Physiol Res* 2012; **61**: 363-370 [PMID: [22670698](#) DOI: [10.3109/10641955.2012.697951](#)]
- 61 **Sedova KA**, Vaykshnorayte MA, Ovechkin AO, Kneppo P, Bernikova OG, Vityazev VA, Azarov JE.

- Ventricular electrical heterogeneity in experimental diabetes mellitus: effect of myocardial ischemia. *Physiol Res* 2016; **65**: 437-445 [PMID: 27070744 DOI: 10.33549/physiolres.933161]
- 62 **Ovechkin AO**, Vaykshnorayte MA, Sedova K, Shumikhin KV, Arteyeva NV, Azarov JE. Functional role of myocardial electrical remodeling in diabetic rabbits. *Can J Physiol Pharmacol* 2015; **93**: 245-252 [PMID: 25666101 DOI: 10.1139/cjpp-2014-0293]
 - 63 **Sedova KA**, Azarov JE, Arteyeva NV, Ovechkin AO, Vaykshnorayte MA, Vityazev VA, Bernikova OG, Shmakov DN, Kneppo P. Mechanism of electrocardiographic T-wave flattening in diabetes mellitus: experimental and simulation study. *Physiol Res* 2017; **66**: 781-789 [PMID: 28730829 DOI: 10.33549/physiolres.933494]
 - 64 **Tsvetkova AS**, Kibler NA, Nuzhny VP, Shmakov DN, Azarov JE. Acute effects of pacing site on repolarization and haemodynamics of the canine ventricles. *Europace* 2011; **13**: 889-896 [PMID: 21421575 DOI: 10.1093/europace/eur053]
 - 65 **Perazzolo Marra M**, Zorzi A, Corbetti F, De Lazzari M, Migliore F, Tona F, Tarantini G, Iliceto S, Corrado D. Apicobasal gradient of left ventricular myocardial edema underlies transient T-wave inversion and QT interval prolongation (Wellens' ECG pattern) in Tako-Tsubo cardiomyopathy. *Heart Rhythm* 2013; **10**: 70-77 [PMID: 22975421 DOI: 10.1016/j.hrthm.2012.09.004]
 - 66 **Chauhan VS**, Downar E, Nanthakumar K, Parker JD, Ross HJ, Chan W, Picton P. Increased ventricular repolarization heterogeneity in patients with ventricular arrhythmia vulnerability and cardiomyopathy: a human in vivo study. *Am J Physiol Heart Circ Physiol* 2006; **290**: H79-H86 [PMID: 16113076 DOI: 10.1152/ajpheart.00648.2005]
 - 67 **Antzelevitch C**. Drug-induced spatial dispersion of repolarization. *Cardiol J* 2008; **15**: 100-121 [PMID: 18651395]
 - 68 **Lyon A**, Bueno-Orovio A, Zacur E, Ariga R, Grau V, Neubauer S, Watkins H, Rodriguez B, Mincholé A. Electrocardiogram phenotypes in hypertrophic cardiomyopathy caused by distinct mechanisms: apico-basal repolarization gradients vs. Purkinje-myocardial coupling abnormalities. *Europace* 2018; **20**: iii102-iii112 [PMID: 30476051 DOI: 10.1093/europace/euy226]
 - 69 **Sperelakis N**, Lehmkuhl D. Effects of temperature and metabolic poisons on membrane potentials of cultured heart cells. *Am J Physiol* 1967; **213**: 719-724 [PMID: 6036790 DOI: 10.1152/ajplegacy.1967.213.3.719]
 - 70 **Kiyosue T**, Arita M, Muramatsu H, Spindler AJ, Noble D. Ionic mechanisms of action potential prolongation at low temperature in guinea-pig ventricular myocytes. *J Physiol* 1993; **468**: 85-106 [PMID: 8254536 DOI: 10.1113/jphysiol.1993.sp019761]
 - 71 **Kuo CS**, Munakata K, Reddy CP, Surawicz B. Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations. *Circulation* 1983; **67**: 1356-1367 [PMID: 6851031 DOI: 10.1161/01.cir.67.6.1356]
 - 72 **Azarov JE**, Shmakov DN, Vityazev VA, Roshchevskaya IM, Arteyeva NV, Kharin SN, Roshchevsky MP. Ventricular repolarization pattern under heart cooling in the rabbit. *Acta Physiol (Oxf)* 2008; **193**: 129-138 [PMID: 18284376 DOI: 10.1111/j.1748-1716.2008.01835.x]
 - 73 **Arteyeva NV**, Azarov JE. The Role of Transmural Repolarization Gradient in the Inversion of Cardiac Electric Field: Model Study of ECG in Hypothermia. *Ann Noninvasive Electrocardiol* 2017; **22**: e12360 [PMID: 27018036 DOI: 10.1111/anec.12360]
 - 74 **Carmeliet E**. Cardiac ionic currents and acute ischemia: from channels to arrhythmias. *Physiol Rev* 1999; **79**: 917-1017 [PMID: 10390520 DOI: 10.1152/physrev.1999.79.3.917]
 - 75 **Hill JL**, Gettes LS. Effect of acute coronary artery occlusion on local myocardial extracellular K⁺ activity in swine. *Circulation* 1980; **61**: 768-778 [PMID: 7357719 DOI: 10.1161/01.cir.61.4.768]
 - 76 **Shaw RM**, Rudy Y. Electrophysiologic effects of acute myocardial ischemia: a theoretical study of altered cell excitability and action potential duration. *Cardiovasc Res* 1997; **35**: 256-272 [PMID: 9349389 DOI: 10.1016/s0008-6363(97)00093-x]
 - 77 **Yan GX**, Yamada KA, Kléber AG, McHowat J, Corr PB. Dissociation between cellular K⁺ loss, reduction in repolarization time, and tissue ATP levels during myocardial hypoxia and ischemia. *Circ Res* 1993; **72**: 560-570 [PMID: 8431984 DOI: 10.1161/01.res.72.3.560]
 - 78 **Ruiz Petrich E**, Schanne OF, Ponce Zumino A. Electrophysiological responses to ischemia and reperfusion. *EXS* 1996; **76**: 115-133 [PMID: 8805792 DOI: 10.1007/978-3-0348-8988-9_8]
 - 79 **Kimura S**, Bassett AL, Kohya T, Kozlovskis PL, Myerburg RJ. Simultaneous recording of action potentials from endocardium and epicardium during ischemia in the isolated cat ventricle: relation of temporal electrophysiologic heterogeneities to arrhythmias. *Circulation* 1986; **74**: 401-409 [PMID: 3731429 DOI: 10.1161/01.cir.74.2.401]
 - 80 **Lukas A**, Antzelevitch C. Differences in the electrophysiological response of canine ventricular epicardium and endocardium to ischemia. Role of the transient outward current. *Circulation* 1993; **88**: 2903-2915 [PMID: 8252704 DOI: 10.1161/01.cir.88.6.2903]
 - 81 **Taggart P**, Sutton PM, Opthof T, Coronel R, Trimlett R, Pugsley W, Kallis P. Transmural repolarisation in the left ventricle in humans during normoxia and ischaemia. *Cardiovasc Res* 2001; **50**: 454-462 [PMID: 11376621 DOI: 10.1016/s0008-6363(01)00223-1]
 - 82 **Pandit SV**, Kaur K, Zlochiver S, Noujaim SF, Furspan P, Mironov S, Shibayama J, Anumonwo J, Jalife J. Left-to-right ventricular differences in I(KATP) underlie epicardial repolarization gradient during global ischemia. *Heart Rhythm* 2011; **8**: 1732-1739 [PMID: 21723845 DOI: 10.1016/j.hrthm.2011.06.028]
 - 83 **Salama G**, Kanai AJ, Huang D, Efimov IR, Girouard SD, Rosenbaum DS. Hypoxia and hypothermia enhance spatial heterogeneities of repolarization in guinea pig hearts: analysis of spatial autocorrelation of optically recorded action potential durations. *J Cardiovasc Electrophysiol* 1998; **9**: 164-183 [PMID: 9511890 DOI: 10.1111/j.1540-8167.1998.tb00897.x]
 - 84 **Malik M**, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *J Am Coll Cardiol* 2000; **36**: 1749-1766 [PMID: 11092641 DOI: 10.1016/s0735-1097(00)00962-1]
 - 85 **Rautaharju PM**, Mason JW, Akiyama T. New age- and sex-specific criteria for QT prolongation based on rate correction formulas that minimize bias at the upper normal limits. *Int J Cardiol* 2014; **174**: 535-540 [PMID: 24825030 DOI: 10.1016/j.ijcard.2014.04.133]

- 86 **Antzelevitch C**, Di Diego JM, Argenziano M. Tpeak-Tend as a predictor of ventricular arrhythmogenesis. *Int J Cardiol* 2017; **249**: 75-76 [PMID: 29121761 DOI: 10.1016/j.ijcard.2017.09.005]
- 87 **Tse G**, Yan BP. Traditional and novel electrocardiographic conduction and repolarization markers of sudden cardiac death. *Europace* 2017; **19**: 712-721 [PMID: 27702850 DOI: 10.1093/europace/euw280]
- 88 **Coronel R**. Complexity and the interpretation of results. *Heart Rhythm* 2009; **6**: 528-529 [PMID: 19246250 DOI: 10.1016/j.hrthm.2008.12.029]
- 89 **Opthof T**, Coronel R, Wilms-Schopman FJ, Plotnikov AN, Shlapakova IN, Danilo P Jr, Rosen MR, Janse MJ. Dispersion of repolarization in canine ventricle and the electrocardiographic T wave: Tp-e interval does not reflect transmural dispersion. *Heart Rhythm* 2007; **4**: 341-348 [PMID: 17341400 DOI: 10.1016/j.hrthm.2006.11.022]
- 90 **Kors JA**, Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. *J Electrocardiol* 2008; **41**: 575-580 [PMID: 18954608 DOI: 10.1016/j.jelectrocard.2008.07.030]
- 91 **Xia Y**, Liang Y, Kongstad O, Holm M, Olsson B, Yuan S. Tpeak-Tend interval as an index of global dispersion of ventricular repolarization: evaluations using monophasic action potential mapping of the epi- and endocardium in swine. *J Interv Card Electrophysiol* 2005; **14**: 79-87 [PMID: 16374554 DOI: 10.1007/s10840-005-4592-4]
- 92 **Porthan K**, Viitasalo M, Toivonen L, Havulinna AS, Jula A, Tikkanen JT, Väänänen H, Nieminen MS, Huikuri HV, Newton-Cheh C, Salomaa V, Oikarinen L. Predictive value of electrocardiographic T-wave morphology parameters and T-wave peak to T-wave end interval for sudden cardiac death in the general population. *Circ Arrhythm Electrophysiol* 2013; **6**: 690-696 [PMID: 23881778 DOI: 10.1161/CIRCEP.113.000356]
- 93 **Smetana P**, Schmidt A, Zabel M, Hnatkova K, Franz M, Huber K, Malik M. Assessment of repolarization heterogeneity for prediction of mortality in cardiovascular disease: peak to the end of the T wave interval and nondipolar repolarization components. *J Electrocardiol* 2011; **44**: 301-308 [PMID: 21511064 DOI: 10.1016/j.jelectrocard.2011.03.004]
- 94 **Arteyeva NV**, Azarov JE. Effect of action potential duration on T_{peak}-T_{end} interval, T-wave area and T-wave amplitude as indices of dispersion of repolarization: Theoretical and simulation study in the rabbit heart. *J Electrocardiol* 2017; **50**: 919-924 [PMID: 28784265 DOI: 10.1016/j.jelectrocard.2017.07.001]
- 95 **Mainardi L**, Sassi R. Some theoretical results on the observability of repolarization heterogeneity on surface ECG. *J Electrocardiol* 2013; **46**: 270-275 [PMID: 23622343 DOI: 10.1016/j.jelectrocard.2013.02.011]
- 96 **Végh EM**, Engels EB, van Deursen CJ, Merkely B, Vernooy K, Singh JP, Prinzen FW. T-wave area as biomarker of clinical response to cardiac resynchronization therapy. *Europace* 2016; **18**: 1077-1085 [PMID: 26462704 DOI: 10.1093/europace/euv259]
- 97 **Fuller MS**, Sándor G, Punske B, Taccardi B, MacLeod RS, Ershler PR, Green LS, Lux RL. Estimates of repolarization dispersion from electrocardiographic measurements. *Circulation* 2000; **102**: 685-691 [PMID: 10931810 DOI: 10.1161/01.cir.102.6.685]
- 98 **Sasaki A**, Takimiya A, Arai T, Song Y, Nakajima S, Muto K, Ibukiyama C. Abnormalities of T waves in effort angina pectoris patients at rest evaluated by spatial velocity electrocardiogram. *Jpn Heart J* 1996; **37**: 879-889 [PMID: 9057682 DOI: 10.1536/ihj.37.879]
- 99 **Kors JA**. Lead transformations and the dipole approximation: Practical applications. *J Electrocardiol* 2015; **48**: 1040-1044 [PMID: 26386499 DOI: 10.1016/j.jelectrocard.2015.08.015]
- 100 **Man S**, Maan AC, Schali MJ, Swenne CA. Vectorcardiographic diagnostic & prognostic information derived from the 12-lead electrocardiogram: Historical review and clinical perspective. *J Electrocardiol* 2015; **48**: 463-475 [PMID: 26027545 DOI: 10.1016/j.jelectrocard.2015.05.002]
- 101 **Draisma HH**, Schali MJ, van der Wall EE, Swenne CA. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. *Heart Rhythm* 2006; **3**: 1092-1099 [PMID: 16945809 DOI: 10.1016/j.hrthm.2006.05.025]
- 102 **Hartl DL**. Genetic dissection of segregation distortion II. Mechanism of suppression of distortion by certain inversions. *Genetics* 1975; 539-547 [PMID: 821814]
- 103 **De Ambroggi L**, Aimè E, Ceriotti C, Rovida M, Negroni S. Mapping of ventricular repolarization potentials in patients with arrhythmogenic right ventricular dysplasia: principal component analysis of the ST-T waves. *Circulation* 1997; **96**: 4314-4318 [PMID: 9416898 DOI: 10.1161/01.cir.96.12.4314]
- 104 **Zabel M**, Malik M. Practical use of T wave morphology assessment. *Card Electrophysiol Rev* 2002; **6**: 316-322 [PMID: 12114858 DOI: 10.1023/a:1016353714372]
- 105 **Dilaveris P**, Gialafos E, Pantazis A, Syntetos A, Triposkiadis F, Gialafos J. The spatial QRS-T angle as a marker of ventricular repolarisation in hypertension. *J Hum Hypertens* 2001; **15**: 63-70 [PMID: 11224004 DOI: 10.1038/sj.jhh.1001129]
- 106 **Voulgari C**, Pagoni S, Tesfaye S, Tentolouris N. The spatial QRS-T angle: implications in clinical practice. *Curr Cardiol Rev* 2013; **9**: 197-210 [PMID: 23909632 DOI: 10.2174/1573403x113099990031]
- 107 **Scherptong RW**, Henkens IR, Man SC, Le Cessie S, Vliegen HW, Draisma HH, Maan AC, Schali MJ, Swenne CA. Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. *J Electrocardiol* 2008; **41**: 648-655 [PMID: 18817923 DOI: 10.1016/j.jelectrocard.2008.07.006]
- 108 **Kors JA**, Kardys I, van der Meer IM, van Herpen G, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS-T angle as a risk indicator of cardiac death in an elderly population. *J Electrocardiol* 2003; **36** Suppl: 113-114 [PMID: 14716610 DOI: 10.1016/j.jelectrocard.2003.09.033]
- 109 **Rautaharju PM**, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic abnormalities that predict coronary heart disease events and mortality in postmenopausal women: the Women's Health Initiative. *Circulation* 2006; **113**: 473-480 [PMID: 16449726 DOI: 10.1161/CIRCULATIONAHA.104.496091]
- 110 **Dunnink A**, Stams TRG, Bossu A, Meijborg VMF, Beekman JDM, Wijers SC, De Bakker JMT, Vos MA. Torsade de pointes arrhythmias arise at the site of maximal heterogeneity of repolarization in the chronic complete atrioventricular block dog. *Europace* 2017; **19**: 858-865 [PMID: 28525920 DOI: 10.1093/europace/euw087]
- 111 **Yoon N**, Patocska B, Antzelevitch C. Epicardial Substrate as a Target for Radiofrequency Ablation in an

- Experimental Model of Early Repolarization Syndrome. *Circ Arrhythm Electrophysiol* 2018; **11**: e006511 [PMID: 30354293 DOI: 10.1161/CIRCEP.118.006511]
- 112 **Verrier RL**, Huikuri H. Tracking interlead heterogeneity of R- and T-wave morphology to disclose latent risk for sudden cardiac death. *Heart Rhythm* 2017; **14**: 1466-1475 [PMID: 28610987 DOI: 10.1016/j.hrthm.2017.06.017]
- 113 **Castro Hevia J**, Antzelevitch C, Tornés Bárzaga F, Dorantes Sánchez M, Dorticos Balea F, Zayas Molina R, Quiñones Pérez MA, Fayad Rodríguez Y. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. *J Am Coll Cardiol* 2006; **47**: 1828-1834 [PMID: 16682308 DOI: 10.1016/j.jacc.2005.12.049]
- 114 **Xianpei W**, Sha W, Chuanyu G, Juanjuan Y, Chong C, Yongen S, Yu F, Zhenhao L. Tpeak-Tend dispersion as a predictor for malignant arrhythmia events in patients with vasospastic angina. *Int J Cardiol* 2017; **249**: 61-65 [PMID: 29121758 DOI: 10.1016/j.ijcard.2017.07.093]
- 115 **Arteyeva NV**, Azarov JE. ECG markers of local but not global increase in dispersion of ventricular repolarization (simulation study). *J Electrocardiol* 2020; **60**: 54-59 [PMID: 32268231 DOI: 10.1016/j.jelectrocard.2020.03.009]
- 116 **Zareba W**, McNitt S, Polonsky S, Couderc JP. JT interval: What does this interval mean? *J Electrocardiol* 2017; **50**: 748-751 [PMID: 28942950 DOI: 10.1016/j.jelectrocard.2017.07.019]
- 117 **Zulqarnain MA**, Qureshi WT, O'Neal WT, Shah AJ, Soliman EZ. Risk of Mortality Associated With QT and JT Intervals at Different Levels of QRS Duration (from the Third National Health and Nutrition Examination Survey). *Am J Cardiol* 2015; **116**: 74-78 [PMID: 25929581 DOI: 10.1016/j.amjcard.2015.03.038]
- 118 **Mazzanti A**, Maragna R, Vacanti G, Monteforte N, Bloise R, Marino M, Braghieri L, Gambelli P, Memmi M, Pagan E, Morini M, Malovini A, Ortiz M, Sacilotto L, Bellazzi R, Monserrat L, Napolitano C, Bagnardi V, Priori SG. Interplay Between Genetic Substrate, QTc Duration, and Arrhythmia Risk in Patients With Long QT Syndrome. *J Am Coll Cardiol* 2018; **71**: 1663-1671 [PMID: 29650123 DOI: 10.1016/j.jacc.2018.01.078]
- 119 **Postema PG**, Wilde AA. The measurement of the QT interval. *Curr Cardiol Rev* 2014; **10**: 287-294 [PMID: 24827793 DOI: 10.2174/1573403x10666140514103612]
- 120 **Aro AL**, Kenttä TV, Huikuri HV. Microvolt T-wave Alternans: Where Are We Now? *Arrhythm Electrophysiol Rev* 2016; **5**: 37-40 [PMID: 27403292 DOI: 10.15420/aer.2015.28.1]
- 121 **Klingenheben T**, Hohnloser SH. Clinical value of T-wave alternans assessment. *Card Electrophysiol Rev* 2002; **6**: 323-328 [PMID: 12114859 DOI: 10.1097/FJC.0b013e3181d6b781]
- 122 **Sucu M**, Ucaman B, Ozer O, Altas Y, Polat E. Novel Ventricular Repolarization Indices in Patients with Coronary Slow Flow. *J Atr Fibrillation* 2016; **9**: 1446 [PMID: 28496926 DOI: 10.4022/jafb.1446]
- 123 **Zhao Z**, Yuan Z, Ji Y, Wu Y, Qi Y. Left ventricular hypertrophy amplifies the QT, and Tp-e intervals and the Tp-e/QT ratio of left chest ECG. *J Biomed Res* 2010; **24**: 69-72 [PMID: 23554614 DOI: 10.1016/S1674-8301(10)60011-5]
- 124 **Magri D**, Santolamazza C, Limite L, Mastromarino V, Casenghi M, Orlando P, Pagannone E, Musumeci MB, Maruotti A, Ricotta A, Oliviero G, Piccirillo G, Volpe M, Autore C. QT spatial dispersion and sudden cardiac death in hypertrophic cardiomyopathy: Time for reappraisal. *J Cardiol* 2017; **70**: 310-315 [PMID: 28341542 DOI: 10.1016/j.jjcc.2017.01.006]

Retrospective Cohort Study

Clinical significance of prolonged chest pain in vasospastic angina

Hiroki Teragawa, Chikage Oshita, Yuichi Orita

ORCID number: Hiroki Teragawa 0000-0002-0183-2541; Chikage Oshita 0000-0003-3471-2543; Yuichi Orita 0000-0002-3448-9233.

Author contributions: Orita Y and Oshita C contributed to the acquisition of data; Teragawa H contributed to the writing and revision of the manuscript.

Institutional review board statement: This study was approved by the Institutional Review Board of Medical Corporation JR Hiroshima Hospital.

Informed consent statement: Informed consent was obtained from all of the patients.

Conflict-of-interest statement: None of the authors have any conflicts of interest to declare.

Data sharing statement: No additional data.

STROBE statement: The guidelines of the STROBE statement have been adopted.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0)

Hiroki Teragawa, Chikage Oshita, Yuichi Orita, Department of Cardiovascular Medicine, JR Hiroshima Hospital, Hiroshima 732-0057, Japan

Corresponding author: Hiroki Teragawa, FACC, FACP, FAHA, MD, PhD, Chief Doctor, Department of Cardiovascular Medicine, JR Hiroshima Hospital, 3-1-36 Futabanosato, Higashi-ku, Hiroshima 732-0057, Japan. hiroki-teragawa@jrhh.or.jp

Abstract

BACKGROUND

Patients with vasospastic angina (VSA) sometimes experience prolonged chest symptoms. The clinical characteristics of these patients have not been clarified.

AIM

To investigate the clinical characteristics of prolonged VSA patients.

METHODS

This study included 167 patients with VSA diagnosed by spasm provocation tests (SPTs) using acetylcholine, which recorded the frequencies of positive reactions to a low dose of acetylcholine (L-ACh), total occlusion due to spasm (TOC), focal spasm, and the unavoidable use of nitroglycerin (unavoidable-NTG) during SPTs. The patients underwent a medical interview that investigated the maximum duration and frequency of chest symptoms as well as the frequencies of variant angina and other serious symptoms. The patients were divided into two groups based on the maximal duration: The short-duration group (< 15 min; $n = 114$) and the long-duration group (≥ 15 min; $n = 53$). They were also divided into two groups based on the frequency of chest symptoms: The low-frequency group (< 4/mo; $n = 88$) and the high-frequency group (≥ 4 /mo; $n = 79$).

RESULTS

The long-duration group showed higher frequencies of other serious symptoms ($P < 0.001$) and variant angina ($P < 0.05$) as well as higher frequencies of spasm induction by L-ACh ($P < 0.05$), TOC ($P < 0.05$), focal spasm ($P < 0.01$), and unavoidable-NTG ($P < 0.01$) than the short-duration group. These parameters did not differ significantly between the low-frequency and high-frequency groups.

CONCLUSION

These findings suggest that patients with VSA who experience prolonged chest symptoms may have more severe characteristics of VSA.

Key Words: Acetylcholine; Prolonged angina attacks; Variant angina; Vasospastic angina;

license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: June 2, 2020

Peer-review started: June 28, 2020

First decision: June 15, 2020

Revised: June 28, 2020

Accepted: September 15, 2020

Article in press: September 15, 2020

Published online: September 17, 2020

P-Reviewer: Sueda S

S-Editor: Gong ZM

L-Editor: A

P-Editor: Li JH



Spasm provocation test; Prognosis

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: We have sometimes experienced patients with vasospastic angina (VSA) who had prolonged chest symptoms (≥ 15 min). We showed that such VSA patients had higher frequencies of other serious symptoms and variant angina as well as higher frequencies of spasm induction by a low dose of acetylcholine, total occlusion due to spasm, focal spasm, and unavoidable use of nitroglycerin in the spasm provocation test (SPT). On the other hand, the frequency of chest symptoms did not influence these findings in the SPT. Prolonged chest symptoms may be related to more severe characteristics of VSA.

Citation: Teragawa H, Oshita C, Orita Y. Clinical significance of prolonged chest pain in vasospastic angina. *World J Cardiol* 2020; 12(9): 450-459

URL: <https://www.wjgnet.com/1949-8462/full/v12/i9/450.htm>

DOI: <https://dx.doi.org/10.4330/wjc.v12.i9.450>

INTRODUCTION

Some patients with vasospastic angina (VSA) experience prolonged chest symptoms^[1]. The guidelines for VSA^[2] note that chest pain in patients with VSA usually occurs at rest, with pain persisting for several minutes up to approximately 15 min. The guidelines also noted that chest pain due to coronary spasms often persisted longer than that during exercise and that these attacks are sometimes accompanied by cold sweats and disturbances of consciousness. However, the clinical characteristics of patients with VSA who experience these prolonged chest symptoms have yet to be clarified. We investigated the clinical characteristics of such patients.

MATERIALS AND METHODS

This observational, retrospective study included patients with VSA diagnosed by spasm provocation tests (SPTs) who attended our institution from 2011 to 2015 ($n = 251$). We applied the following exclusion criteria: Patients without chest symptoms, such as those with only syncope ($n = 8$) or heart failure ($n = 15$), and those with an unclear duration of chest symptoms ($n = 38$). During the study period, spasm provocation at our institution was performed first in the right coronary artery (RCA). We therefore also excluded patients for whom spasm provocation could not be performed in the RCA because of its small size or the inability to place a catheter into the ostium of the RCA ($n = 23$). Finally, 167 patients were enrolled in the present study. The protocol of the study was approved by the ethics committee of our institution. Written informed consent was obtained from all of the patients.

The patients and their families underwent detailed medical interviews that established the maximum duration of chest symptoms and the frequency of chest symptoms per month. The maximum duration of chest symptoms was determined as follows: It was 5 min when the patients and their families answered "several minutes", and it was 20 min when they answered "from 10 to 20 min". In addition, the interviews recorded whether the patients experienced cold sweats or syncope^[3,4], which were considered to be symptoms accompanying VSA. The patients were divided into two sets of two groups according to the maximum duration and frequency of their chest symptoms. The long-duration and short-duration groups comprised patients with maximum durations of symptoms of ≥ 15 min and < 15 min, respectively. The cut-off value of 15 min was in accordance with the guidelines for VSA^[2]. The median frequency of symptoms was four times per month. The high-frequency and low-frequency groups were comprised of patients whose frequencies of symptoms were > 4 times/month and ≤ 4 times/month, respectively.

An SPT was performed using the methods described previously^[5]. In brief, after the initial coronary angiogram (CAG), 20 and 50 μ g doses of acetylcholine (ACh) were injected into the RCA. When coronary spasm was not induced by 50 μ g of ACh, a maximum dose of 80 μ g of ACh was infused into the RCA. CAG was obtained just

after coronary spasms were induced or the maximum ACh infusion was finished. If a coronary spasm was induced but improved spontaneously, an SPT of the left coronary artery (LCA) was then performed without an intracoronary injection of nitroglycerin (NTG) into the RCA. In such cases, once the SPT for the LCA was finished, CAG was repeated following an NTG injection into the RCA. If the coronary spasm provoked by ACh infusion into the RCA was prolonged or severe enough to induce hemodynamic instability, an intracoronary injection of 0.3 mg of NTG was applied to relieve the spasms.

An SPT of the LCA was then performed. The SPT of the LCA was performed by infusing 50 and 100 μ g doses of ACh into the LCA using a similar method. If coronary spasm was not induced by 100 μ g of ACh, a maximum of 200 μ g of ACh was infused into the LCA. CAG was performed just after a coronary spasm was provoked or the maximum ACh infusion was finished. An intracoronary injection of 0.3 mg of NTG was administered, followed by the final CAG for the LCA.

We adopted the use of an autoinjector as described previously^[5]. When unstable hemodynamics continued, small doses of intracoronary or intravenous catecholamines were infused. In this study, low doses of ACh (L-ACh) were considered to be 20 μ g for the RCA and 50 μ g for the LCA. The diameters of the coronary artery were measured as described previously^[5]. Lesions with > 20% stenosis were defined as atherosclerotic lesions. Because an association between myocardial bridges and VSA has been reported^[6,7], we assessed whether a myocardial bridge, which was defined as the systolic narrowing of the coronary artery diameter by > 20% compared to that in diastole, was present.

We defined variant angina (VA) as angina with a recorded spontaneous ST elevation on ECG. VSA was defined as $\geq 90\%$ narrowing of the coronary arteries on angiograms during the provocation accompanied by the presence of usual chest pain and/or the presence of ST-segment deviation on ECG^[2]. A focal spasm was defined as a transient vessel narrowing of > 90% localized to the major coronary arteries. A diffuse spasm was defined as a 90% diffuse vasoconstriction observed in ≥ 2 adjacent coronary segments of the coronary arteries^[8]. Multivessel spasms were defined as coronary spasms that occurred in ≥ 2 major coronary arteries. For multivessel spasms, we could not assess when the subsequent SPT was negative after an unavoidable use of NTG. For the present study, data for each patient were collected based on the frequency of the following test and the other events: Spasm provocation induced by L-ACh, total occlusion of the coronary artery due to spasm (TOC), unavoidable administration of NTG into the RCA, severe complications accompanied by prolonged unstable hemodynamics requiring intravenous catecholamines, ventricular fibrillation, and pulseless ventricular tachycardia. In addition, the use of coronary vasodilators was assessed when the patient attended the hospital before admission for CAG.

The patient was asked about his or her current smoking status, and any family history of coronary artery disease (FH-CAD) was recorded. Hypertension, dyslipidemia, diabetes mellitus and chronic kidney disease were defined based on the standard definitions described in previous papers^[5]. A patient was defined as an alcohol drinker if he or she consumed alcohol one or more times a week.

The left ventricular ejection fraction was measured using cardiac ultrasonography. In the majority of studied patients ($n = 158$), flow-mediated dilation (FMD) as an endothelium-dependent function and NTG-induced dilation (NID) as an endothelium-independent function were measured as previously described^[9].

After discharge, the patients were followed up at our institution as far as possible, and all studied patients visited for at least one follow-up. One hundred twenty-two patients have been followed through the final check-up in 2019. Eight patients died during the follow-up period, and the remaining 37 patients were followed through 2018.

Among the 122 patients with a recent follow-up (73%), the follow-up examinations included information about the patients' medications from their medication notebooks. We assessed the number of coronary vasodilators used and the number of angina attacks (per month) experienced in the previous 3 mo. Cardiac events related to VSA were recorded for each patient, including readmission for angina or other cardiovascular diseases and death from cardiac and noncardiac causes. The major adverse cardiac event (MACE) was defined as death from cardiac causes or readmission for cardiovascular causes.

Data are presented as the mean \pm SD or medians with interquartile ranges for nonnormally distributed data and noncontinuous variables, respectively. Baseline characteristics of the groups were compared using Student's unpaired *t*-tests, Wilcoxon signed-rank tests, or χ^2 analysis, as appropriate. Survival was analyzed by the Kaplan-Meier survival curve method with log-rank tests.

The statistical analyses were performed using JMP Ver. 14 (SAS Institute Inc., United States). A *P* value < 0.05 was considered statistically significant.

RESULTS

There were 114 patients in the short-duration group, 53 patients in the long-duration group, 88 patients in the low-frequency group, and 79 patients in the high-frequency group (Table 1). There were no significant differences in patient characteristics between the short-duration and long-duration groups. The only significant difference between the low-frequency and high-frequency groups was the presence of an FH-CAD, which was higher in the high-frequency group than in the low-frequency group. There was no significant relationship between the maximum duration and the frequency of chest symptoms. There were no significant differences between the groups regarding FMD and NID.

The frequencies of chest symptoms at rest and during exercise did not differ among the four groups (Table 2). The median values of the maximum duration of chest symptoms were 30 min for the long-duration group and 6 min for the short-duration group. The median frequency of chest symptoms did not differ between these two groups (both 4 times/mo). The median frequency of chest symptoms was 12 times/mo for the high-frequency group and 2 times/mo for the low-frequency group. The median values of the maximum duration of chest symptoms did not differ between these two groups (both 10 min). The frequencies of VA and other serious symptoms, including cold sweats and syncope, were higher in the long-duration group than in the short-duration group ($P = 0.0369$ and $P < 0.0001$, respectively). The frequency of VA and other serious symptoms did not differ between the low- and high-frequency groups. The number of patients taking vasodilators before admission was similar across the four groups.

Table 3 summarizes the angiographic and SPT findings. The frequencies of atherosclerotic changes and the presence of a myocardial bridge did not differ significantly among the groups. There were no significant differences in the angiographic and SPT-related parameters between the low- and high-frequency groups. However, spasm induction by L-ACh, TOC, focal spasm, and the unavoidable use of NTG were significantly higher in the long-duration group than in the short-duration group ($P = 0.0444$, $P = 0.0113$, $P = 0.0006$, and $P = 0.0062$, respectively). The frequency of multivessel spasms did not differ significantly between these two groups. Severe complications were experienced by 12 patients (7%), including ventricular fibrillation in one patient and unstable hemodynamics in eleven. The frequency of severe complications did not differ between the long- and short-duration groups.

The numbers of patients taking vasodilators at discharge were similar in the four groups (Table 4). The median period of follow-up was 58 mo. Of the 167 patients, 122 (73%) were followed up at our institution through 2019, with no differences in the numbers and periods of follow-up among the groups. The median numbers of angina attacks and numbers of patients taking vasodilators were not significantly different among the groups. None of the patients experienced cardiac death during follow-up. The frequencies of noncardiac death and cardiac events requiring readmission for angina and heart failure or valvular heart disease did not differ among the four groups. Among all studied patients, the Kaplan-Meier survival curves showed no significant differences in the incidence of MACE among the groups (Figure 1).

DISCUSSION

This study investigated the clinical characteristics of patients with VSA who experienced prolonged chest symptoms lasting ≥ 15 min, including their symptoms, SPT-related parameters, and prognosis, and compared these with those of patients whose chest symptoms lasted < 15 min. The results showed that the VSA patients who experienced longer-duration chest symptoms had more serious symptoms and that they were more likely to have VA. In the SPT, these patients were more likely to experience spasms induced by L-ACh, TOC, focal spasms, and the unavoidable use of NTG. Thus, the maximum duration of episodes of chest symptoms may provide important information regarding higher VSA activity.

We performed a similar comparison in the same patient group between those who experienced chest symptoms fewer than four times per month (the median frequency of symptoms) and those who experienced symptoms more frequently. This did not

Table 1 Patient characteristics

	Short-duration	Long-duration	<i>P</i> value	Low-frequency	High-frequency	<i>P</i> value
No.	114	53		88	79	
Age (yr)	67 ± 10	67 ± 11	0.8401	67 ± 11	68 ± 10	0.6669
Male/female	58/56	28/25	0.8142	40/48	46/33	0.0991
BMI (kg/m ²)	24.3 ± 4.1	24.2 ± 3.6	0.7171	24.2 ± 3.8	24.5 ± 4.1	0.5697
Coronary risk factors (%)						
Current smoker	24 (21)	9 (17)	0.5385	17 (19)	16 (20)	0.8796
Hypertension	81 (71)	38 (72)	0.9316	64 (73)	55 (70)	0.6578
Dyslipidemia	76 (67)	29 (58)	0.1368	56 (64)	49 (62)	0.8297
Diabetes mellitus	31 (27)	9 (17)	0.1501	19 (19)	23 (29)	0.1386
Alcohol consumption (%)	40 (35)	23 (43)	0.3025	34 (39)	29 (37)	0.7995
Family history of CAD (%)	26 (23)	10 (19)	0.5645	13 (15)	23 (29)	0.0244
CKD (%)	34 (30)	16 (30)	0.9619	21 (24)	29 (37)	0.0704
Taking statins (%)	50 (44)	20 (38)	0.4554	34 (39)	36 (46)	0.3646
LVEF on UCG (%)	66 ± 10	67 ± 9	0.5752	66 ± 9	67 ± 10	0.7165
FMD (% _i , <i>n</i>)	3.9 ± 3.1 (107)	3.4 ± 3.2 (51)	0.3200	3.9 ± 2.8 (82)	3.5 ± 3.5 (76)	0.4872
NID (% _i , <i>n</i>)	15.2 ± 7.0 (107)	14.5 ± 6.4 (51)	0.5795	14.8 ± 6.5 (82)	15.1 ± 7.1 (76)	0.8295

BMI: Body mass index; CAD: Coronary artery disease; CKD: Chronic kidney disease; FMD: Flow-mediated dilation; LVEF: Left ventricular ejection fraction; NID: Nitroglycerin-induced dilation; UCG: Cardiac ultrasonography.

Table 2 Vasospastic angina-related symptoms and medications before admission

	Short-duration	Long-duration	<i>P</i> value	Low-frequency	High-frequency	<i>P</i> value
Chest symptoms						
Only at rest (%)	88 (77)	48 (91)	0.0814	75 (85)	61 (77)	0.2360
At rest and exercise (%)	12 (11)	1 (2)		4 (5)	9 (11)	
Only during exercise (%)	14 (12)	4 (8)		9 (14)	9 (11)	
Maximum duration (min)	6 (5, 10)	30 (20, 60)	< 0.0001	10 (6, 20)	10 (5, 10)	0.3633
Frequency (/mo)	4 (2, 12)	4 (2, 10)	0.1833	2 (1, 4)	12 (8, 20)	< 0.0001
Frequency of VA (%)	0 (0)	2 (4)	0.0369	2 (3)	0 (0)	0.1776
Other serious symptoms (%)	3 (3)	13 (25)	< 0.0001	12 (14)	4 (5)	0.0602
No. taking vasodilators before admission	0.5 (0, 1)	0 (0, 1)	0.1786	0 (0, 1)	0 (0, 1)	0.4895

No.: Number; VA: Variant angina.

show any significant differences. In addition, the maximum duration and frequency of chest symptoms had no influence on prognosis or the chest symptoms reported during follow-up.

There has been little investigation into the relationship between the maximum duration of chest symptoms and VSA activity. Myocardial ischemia related to the organic stenosis of a coronary artery is generally induced by an increase in oxygen demand relative to the amount of oxygen that can be supplied^[10]. This mismatch in oxygen demand and supply can be caused by increases in blood pressure and heart rate due to exercise, anger, and low temperatures.

When a patient with organic coronary stenosis experiences chest symptoms, these can usually be controlled by reducing the factor causing the increase in oxygen demand. Thus, chest symptoms in patients with organic coronary stenosis are

Table 3 Coronary angiography and spasm provocation test-related parameters

	Short-duration	Long-duration	P value	Low-frequency	High-frequency	P value
CAG						
Atherosclerotic change (%)	73 (64)	34 (64)	0.9884	53 (60)	54 (68)	0.7747
Myocardial bridge (%)	11 (11)	5 (9)	0.9646	9 (10)	7 (9)	0.7645
SPT						
Low dose of ACh (%)	26 (23)	20 (38)	0.0444	26 (30)	20 (25)	0.5414
Total occlusion (%)	7 (6)	10 (19)	0.0113	6 (7)	11 (14)	0.1295
Multivessel spasm (%)	63 (62)	30 (70)	0.3189	50 (62)	48 (68)	0.4500
(No.)	(n = 102)	(n = 50)		(n = 81)	(n = 71)	
Focal/diffuse spasm	12/102	17/36	0.0006	15/73	14/65	0.9083
RCA spasm (%)	78 (68)	39 (74)	0.4977	61 (69)	56 (71)	0.8252
Unavoidable use of NTG (%)	25 (32)	23 (59)	0.0062	20 (34)	28 (49)	0.096
LAD spasm (%)	96 (94)	49 (98)	0.2833	75 (93)	70 (99)	0.0783
(No.)	(n = 102)	(n = 50)		(n = 81)	(n = 71)	
Severe complications (%)	7 (6)	5 (9)	0.4430	5 (6)	7 (9)	0.4211

ACh: Acetylcholine; CAG: Coronary angiography; LAD: Left anterior descending coronary artery; No.: Number; NTG: Nitroglycerin; RCA: Right coronary artery; SPT: Spasm provocation test.

Table 4 Vasospastic angina status at follow-up and prognosis

	Short-duration	Long-duration	P value	Low-frequency	High-frequency	P value
No. taking vasodilators at discharge	1 (1, 1)	1 (1, 1)	0.9199	1 (1, 1)	1 (1, 1)	0.7862
Median period of follow-up (mo)	58 (36, 75)	56 (34, 67)	0.3505	54 (20, 75)	59 (41, 71)	0.4678
Follow-up						
No. of recent follow-ups (a, %)	82 (71.9)	40 (75.5)	0.7547	60 (68.2)	62 (78.5)	0.2434
No. of deaths during follow-up (b, %)	5 (4.4)	3 (5.6)		4 (4.5)	4 (5.0)	
No. of follow-ups before 2018 (c, %)	27 (23.7)	10 (18.9)		24 (27.3)	13 (16.5)	
No. of anginal attacks (/mo) in patients (a)	0 (0, 1)	0 (0, 1)	0.4574	0 (0, 1)	0 (0, 2.5)	0.1305
No. taking vasodilators among patients (a)						
No. taking vasodilators among patients (a) at follow-up	1 (1, 2)	1 (1, 2)	0.2131	1 (1, 2)	1 (1, 2)	0.7408
Prognosis among patients (a) and (b)						
Cardiac death (%)	0 (0)	0 (0)		0 (0)	0 (0)	
Noncardiac death (%)	5 (6)	3 (7)	0.7837	4 (6)	4 (6)	0.9642
Cardiac events (%)	13 (15)	4 (9)	0.3695	6 (9)	11 (17)	0.2176

No.: Number; NS: Not significant.

typically relieved within 15 min. Regarding VSA, exercise^[11], smoking^[12], hyperventilation^[13], and alcohol consumption^[14] are recognized as specific inducers of VSA. However, for most VSA patients, the onset of a coronary spasm is not triggered by a specific factor. Thus, chest symptoms in VSA patients may persist longer. In this study, we looked for factors that may contribute to longer chest symptoms, but we were unable to identify any.

Peripheral endothelial dysfunction has been shown to be associated with coronary endothelial dysfunction^[15]. We therefore investigated peripheral endothelial function in most of the patients in this study, but the results suggested that this did not account

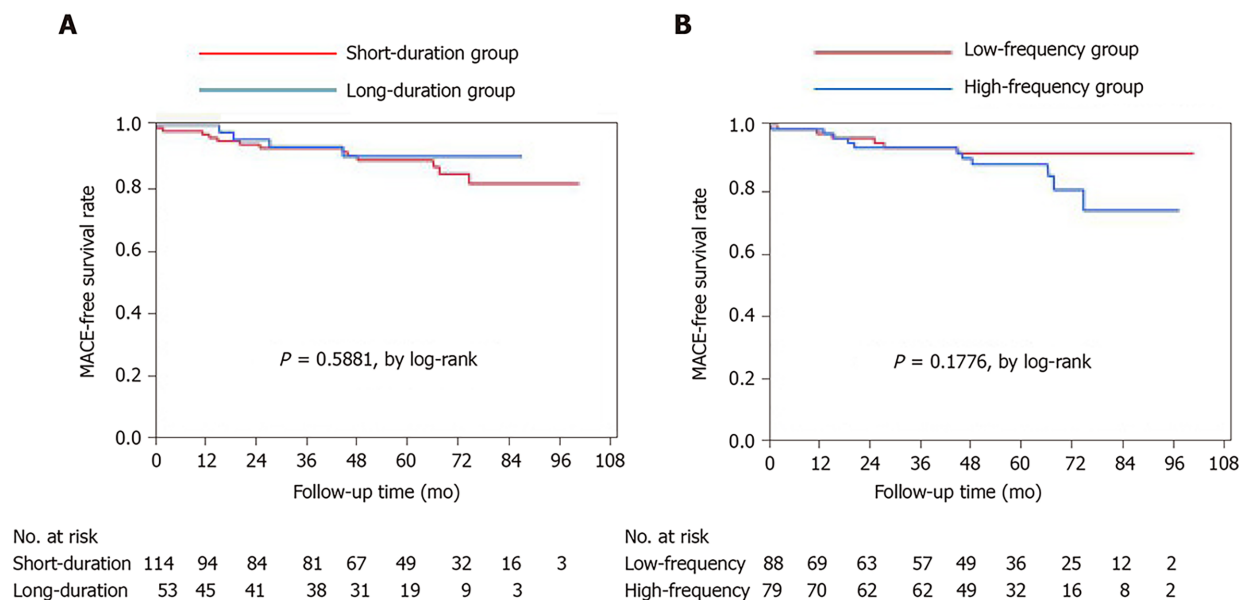


Figure 1 Kaplan–Meier curve for major adverse cardiac event-free survival during the follow-up period for the short-duration and long-duration groups (A) and the low-frequency and high-frequency groups (B). Major adverse cardiac event indicates major adverse cardiovascular events. MACE: Major adverse cardiac event.

for the longer-duration chest symptoms. However, there was a significant finding that a family history of coronary artery disease was more common among the VSA patients who experienced more frequent chest symptoms. We cannot account for this finding, and further investigation is needed.

It has been reported that cold sweating is a serious symptom in VSA^[3,4], and it is widely recognized that VA is a significantly higher activity of VSA^[16,17]. The presence of atherosclerotic changes^[16], spasm induction by L-ACh^[18], TOC^[18], focal spasms^[8,19] and multivessel spasm^[16] in the SPT have been reported as factors associated with higher VSA activity or a poor prognosis. In the present study, the patients who experienced longer-duration chest symptoms had higher frequencies of spasms induced by L-ACh, TOC, and focal spasm. However, the frequencies of atherosclerotic changes and multivessel spasm did not differ from those of the patients who did not experience long-duration symptoms. In addition, the frequency of the unavoidable use of NTG was higher in the VSA patients who experienced longer-duration chest symptoms, although spasm provocation in the RCA was similar between the two groups.

Given the higher frequencies of these serious symptoms and SPT findings, the presence of longer-duration chest symptoms in patients with VSA is undoubtedly an important indicator suggestive of higher VSA activity. Conversely, classifying the patients according to the frequency of their chest symptoms showed no association with higher VSA activity. This may have been because the classification according to the median value of the frequency of chest symptoms may have been insufficient or because the frequency of chest symptoms in patients with VSA may not be a good indicator of VSA activity.

In this study, neither the maximum duration nor the frequency of chest symptoms showed associations with the numbers of patients using vasodilators, frequency of chest symptoms, or cardiac events such as readmission for cardiovascular disease or cardiac death. The low follow-up rate of the patients in this study and our aggressive medication approach may have contributed to these results. These results may also have been affected by the types of vasodilators used, the timing and frequency of their use, and whether they were brand-new or generic types of vasodilator^[18,20]. However, even when these factors are taken into consideration, the severity and/or degree of chest symptoms before SPT may not reflect the long-term prognosis.

The present study has some clinical implications. Longer-duration chest symptoms are undoubtedly a clinically important sign for detecting patients with higher VSA activity. The patients with longer-duration chest symptoms exhibited high frequencies during the SPTs of several findings suggestive of a higher VSA activity; thus, provocation in these patients should be performed carefully, starting with a very low dose of ACh. At our institution, based on the duration of chest symptoms and/or

other serious symptoms, we start the SPTs with a dose of ACh of 10 µg for the RCA and of 20 µg for the LCA.

The present study had several limitations. First, the SPTs started with the RCA. However, the guidelines for VSA^[2] have recommended starting the SPT with the LCA. Thus, some of the results of the present study may not be generalizable to all patients with VSA.

Second, the definitions of duration and frequency of chest symptoms adopted in the present study are not universally accepted or consistently applied. The cutoff duration of 15 min used in this study was based on the VSA guidelines^[2]. Conversely, the cutoff value used for the frequency of chest symptoms was simply the median value of four per month. In addition, the durations and frequencies of the symptoms were determined by questionnaires and thus may not be accurate. In addition, silent myocardial ischemia due to coronary spasm has been reported^[11]; therefore, the symptom-dependent assessment of the degree of VSA activity may not be completely accurate.

Third, the unavoidable use of NTG was not determined by any objective parameters but by the judgment of the CAG operator. Finally, the rate of follow-up was not high, at 73%, and the results of the follow-up should be assessed in light of this low follow-up rate.

CONCLUSION

In conclusion, approximately 30% of the patients with VSA experienced chest symptoms that persisted longer than 15 min. These patients exhibited higher VSA activity. When taking the medical histories of patients with VSA, the cardiologist should record not only the frequency of chest symptoms but also their maximum duration.

ARTICLE HIGHLIGHTS

Research background

Patients with vasospastic angina (VSA) sometimes experience prolonged chest symptoms compared with patients with atherosclerotic coronary sclerosis.

Research motivation

The clinical characteristics of VSA patients who have prolonged chest symptoms have not been clarified.

Research objectives

The objective of the present study was to clarify the clinical characteristics, including the results of the spasm provocation test (SPT) and prognosis, of VSA patients with prolonged chest symptoms.

Research methods

This study included 167 patients with VSA diagnosed by SPT using acetylcholine and recorded the frequencies of positive reactions to a low dose of acetylcholine (L-ACh), total occlusion due to spasm (TOC), focal spasm, and the unavoidable use of nitroglycerin (unavoidable-NTG) during the SPT. The patients underwent a medical interview that investigated the maximum duration and frequency of chest symptoms as well as the frequencies of variant angina and other serious symptoms. The patients were divided into two groups based on the maximal duration: The short-duration group (< 15 min; *n* = 114) and the long-duration group (≥ 15 min; *n* = 53). They were also divided into two groups based on the frequency of chest symptoms: The low-frequency group (< 4/month; *n* = 88) and the high-frequency group (≥ 4/month; *n* = 79). Furthermore, prognosis including major cardiovascular events was investigated in the studied patients.

Research results

The long-duration group showed higher frequencies of other serious symptoms (*P* < 0.001) and variant angina (*P* < 0.05) as well as higher frequencies of spasm induction by L-ACh (*P* < 0.05), TOC (*P* < 0.05), focal spasm (*P* < 0.01), and unavoidable-NTG (*P* <

0.01) than the short-duration group. These parameters did not differ significantly between the low-frequency and high-frequency groups. On the other hand, neither the duration nor frequency of chest symptoms influenced the prognosis in the studied patients.

Research conclusions

These findings suggest that patients with VSA who experience prolonged chest symptoms may have more severe characteristics of VSA. Cardiologists should keep this in mind and be more careful in performing the SPT in such patients.

ACKNOWLEDGEMENTS

We would like to thank Ms. Akemi Seno for her secretarial help.

REFERENCES

- 1 Teragawa H, Oshita C, Ueda T. The Significance of Recognizing Myocardial Bridge in the Coronary Spasm Diagnosis in Myocardial Infarction with Nonobstructive Coronary Arteries. *Intern Med* 2020; **59**: 89-92 [PMID: 31484908 DOI: 10.2169/internalmedicine.3266-19]
- 2 JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (Coronary Spastic Angina) (JCS 2013). *Circ J* 2014; **78**: 2779-2801 [PMID: 25273915 DOI: 10.1253/circj.cj-66-0098]
- 3 Nishiyama C, Iwami T, Kawamura T, Kitamura T, Tanigawa K, Sakai T, Hayashida S, Nishiuchi T, Hayashi Y, Hiraide A. Prodromal symptoms of out-of-hospital cardiac arrests: a report from a large-scale population-based cohort study. *Resuscitation* 2013; **84**: 558-563 [PMID: 23069588 DOI: 10.1016/j.resuscitation.2012.10.006]
- 4 Sueda S, Kohno H. Impact of pharmacological spasm provocation test in patients with a history of syncope. *Heart Vessels* 2018; **33**: 126-133 [PMID: 28905210 DOI: 10.1007/s00380-017-1046-8]
- 5 Teragawa H, Oshita C, Ueda T. History of gastroesophageal reflux disease in patients with suspected coronary artery disease. *Heart Vessels* 2019; **34**: 1631-1638 [PMID: 30993440 DOI: 10.1007/s00380-019-01413-1]
- 6 Teragawa H, Oshita C, Ueda T. The Myocardial Bridge: Potential Influences on the Coronary Artery Vasculature. *Clin Med Insights Cardiol* 2019; **13**: 1179546819846493 [PMID: 31068756 DOI: 10.1177/1179546819846493]
- 7 Teragawa H, Fukuda Y, Matsuda K, Hirao H, Higashi Y, Yamagata T, Oshima T, Matsuura H, Chayama K. Myocardial bridging increases the risk of coronary spasm. *Clin Cardiol* 2003; **26**: 377-383 [PMID: 12918640 DOI: 10.1002/clc.4950260806]
- 8 Sato K, Kaikita K, Nakayama N, Horio E, Yoshimura H, Ono T, Ohba K, Tsujita K, Kojima S, Tayama S, Hokimoto S, Matsui K, Sugiyama S, Yamabe H, Ogawa H. Coronary vasomotor response to intracoronary acetylcholine injection, clinical features, and long-term prognosis in 873 consecutive patients with coronary spasm: analysis of a single-center study over 20 years. *J Am Heart Assoc* 2013; **2**: e000227 [PMID: 23858100 DOI: 10.1161/JAHA.113.000227]
- 9 Teragawa H, Kato M, Kurokawa J, Yamagata T, Matsuura H, Chayama K. Usefulness of flow-mediated dilation of the brachial artery and/or the intima-media thickness of the carotid artery in predicting coronary narrowing in patients suspected of having coronary artery disease. *Am J Cardiol* 2001; **88**: 1147-1151 [PMID: 11703961 DOI: 10.1016/s0002-9149(01)02051-3]
- 10 Sandoval Y, Jaffe AS. Type 2 Myocardial Infarction: JACC Review Topic of the Week. *J Am Coll Cardiol* 2019; **73**: 1846-1860 [PMID: 30975302 DOI: 10.1016/j.jacc.2019.02.018]
- 11 Yasue H, Kugiyama K. Coronary spasm: clinical features and pathogenesis. *Intern Med* 1997; **36**: 760-765 [PMID: 9392345 DOI: 10.2169/internalmedicine.36.760]
- 12 Sugiishi M, Takatsu F. Cigarette smoking is a major risk factor for coronary spasm. *Circulation* 1993; **87**: 76-79 [PMID: 8419026 DOI: 10.1161/01.cir.87.1.76]
- 13 Nakao K, Ohgushi M, Yoshimura M, Morooka K, Okumura K, Ogawa H, Kugiyama K, Oike Y, Fujimoto K, Yasue H. Hyperventilation as a specific test for diagnosis of coronary artery spasm. *Am J Cardiol* 1997; **80**: 545-549 [PMID: 9294979 DOI: 10.1016/s0002-9149(97)00419-0]
- 14 Mizuno Y, Harada E, Morita S, Kinoshita K, Hayashida M, Shono M, Morikawa Y, Murohara T, Nakayama M, Yoshimura M, Yasue H. East asian variant of aldehyde dehydrogenase 2 is associated with coronary spastic angina: possible roles of reactive aldehydes and implications of alcohol flushing syndrome. *Circulation* 2015; **131**: 1665-1673 [PMID: 25759460 DOI: 10.1161/CIRCULATIONAHA.114.013120]
- 15 Teragawa H, Ueda K, Matsuda K, Kimura M, Higashi Y, Oshima T, Yoshizumi M, Chayama K. Relationship between endothelial function in the coronary and brachial arteries. *Clin Cardiol* 2005; **28**: 460-466 [PMID: 16274093 DOI: 10.1002/clc.4960281004]
- 16 Takagi Y, Takahashi J, Yasuda S, Miyata S, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Sato T, Ogawa S, Kubo N, Momomura S, Ogawa H, Shimokawa H; Japanese Coronary Spasm Association. Prognostic stratification of patients with vasospastic angina: a comprehensive clinical risk score developed by the Japanese Coronary Spasm Association. *J Am Coll Cardiol* 2013; **62**: 1144-1153 [PMID: 23916938 DOI: 10.1016/j.jacc.2013.07.018]
- 17 Ahn JM, Lee KH, Yoo SY, Cho YR, Suh J, Shin ES, Lee JH, Shin DI, Kim SH, Baek SH, Seung KB, Nam CW, Jin ES, Lee SW, Oh JH, Jang JH, Park HW, Yoon NS, Cho JG, Lee CH, Park DW, Kang SJ, Lee SW,

- Kim J, Kim YH, Nam KB, Lee CW, Choi KJ, Song JK, Kim YH, Park SW, Park SJ. Prognosis of Variant Angina Manifesting as Aborted Sudden Cardiac Death. *J Am Coll Cardiol* 2016; **68**: 137-145 [PMID: 27386766 DOI: 10.1016/j.jacc.2016.04.050]
- 18 **Teragawa H**, Oshita C, Ueda T. Coronary spasm: It's common, but it's still unsolved. *World J Cardiol* 2018; **10**: 201-209 [PMID: 30510637 DOI: 10.4330/wjc.v10.i11.201]
- 19 **Kim DW**, Her SH, Ahn Y, Shin DI, Han SH, Kim DS, Choi DJ, Kwon HM, Gwon HC, Jo SH, Rha SW, Baek SH. Clinical outcome according to spasm type of single coronary artery provoked by intracoronary ergonovine tests in patients without significant organic stenosis. *Int J Cardiol* 2018; **252**: 6-12 [PMID: 29249438 DOI: 10.1016/j.ijcard.2017.08.052]
- 20 **Goto-Semba R**, Fujii Y, Ueda T, Oshita C, Teragawa H. Increased frequency of angina attacks caused by switching a brand-name vasodilator to a generic vasodilator in patients with vasospastic angina: Two case reports. *World J Cardiol* 2018; **10**: 15-20 [PMID: 29588810 DOI: 10.4330/wjc.v10.i3.15]

Pericardial effusion with tamponade – an uncommon presentation leading to the diagnosis of eosinophilic granulomatosis polyangiitis: A case report

Loba Alam, Glenmore Lasam, Robert Fishberg

ORCID number: Loba Alam 0000-0002-6605-9297; Glenmore Lasam 0000-0002-7066-3374; Robert Fishberg 0000-0002-6605-9297.

Author contributions: Alam L and Lasam G contributed to conception and design of the study, and acquisition of the data; Fishberg R was involved in analysis and interpretation of data and contributed to drafting and revising the article.

Informed consent statement:

Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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

CARE Checklist (2016) statement:

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution

Loba Alam, Department of Medicine, Atlantic Health System-Overlook Medical Center, Summit, NJ 07901, United States

Glenmore Lasam, Department of Cardiology, Icahn School of Medicine, Mount Sinai Heart at Mount Sinai Morningside, New York, NY 10025, United States

Robert Fishberg, Department of Cardiology, Atlantic Health System Overlook, Summit, NJ 07901, United States

Corresponding author: Loba Alam, MD, Doctor, Department of Medicine, Atlantic Health System-Overlook Medical Center, 99 Beauvoir Avenue, Summit, NJ 07901, United States. alamloba@gmail.com

Abstract

BACKGROUND

Eosinophilic granulomatosis polyangiitis (EGPA) is a small vessel necrotizing vasculitis that commonly presents as peripheral eosinophilia and asthma; however, it can rarely manifest with cardiac involvement such as pericarditis and cardiac tamponade. Isolated pericardial tamponade presenting as the initial symptom of EGPA is exceedingly rare. Early diagnosis and appropriate treatment are crucial to prevent life-threatening outcomes.

CASE SUMMARY

52-year-old woman with no past medical history presented with progressive dyspnea and dry cough. On physical exam she had a pericardial friction rub and bilateral rales. Vital signs were notable for tachycardia at 119 beats per minute and hypoxia with 89% oxygen saturation. On laboratory exam, she had 45% peripheral eosinophilia, troponin elevation of 1.1 ng/mL and N-terminal prohormone of brain natriuretic peptide of 2101 pg/mL. TTE confirmed a large pericardial effusion and tamponade physiology. She underwent urgent pericardial window procedure. Pericardial and lung biopsy demonstrated eosinophilic infiltration. Based on the American College of Radiology guidelines, the patient was diagnosed with EGPA which manifested in its rare form of cardiac tamponade. She was treated with steroid taper and mepolizumab.

CONCLUSION

This case highlights that when isolated pericardial involvement occurs in EGPA,

NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: June 6, 2020

Peer-review started: July 2, 2020

First decision: June 20, 2020

Revised: July 2, 2020

Accepted: September 1, 2020

Article in press: September 1, 2020

Published online: September 26, 2020

P-Reviewer: Hamaoka T

S-Editor: Zhang H

L-Editor: A

P-Editor: Li JH



diagnosis is recognized by performing pericardial biopsy demonstrating histopathologic evidence of eosinophilic infiltration.

Key Words: Eosinophilic granulomatosis polyangiitis; Cardiac tamponade; Pericardial effusion; Mepolizumab; Peripheral eosinophilia; Pericardial biopsy; Case report

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: (1) To be able to investigate the etiology of pericardial effusion and cardiac tamponade with eosinophilia which is rarely caused by eosinophilic granulomatosis polyangiitis (EGPA); (2) To be mindful that anti-neutrophil cytoplasmic antibody is negative in EGPA with cardiac involvement rather than pulmonary or renal involvement; (3) To be aware that when isolated pericardial involvement leading to cardiac tamponade occurs, diagnosis is recognized by performing pericardial biopsy demonstrating histopathologic evidence of eosinophilic infiltration; (4) To consider early diagnosis of EGPA with cardiac involvement is crucial because it carries a major burden of morbidity and mortality; (5) To initiate early treatment with corticosteroids when an isolated pericardial involvement is present whereas immunosuppressants are utilized with multiorgan involvement; and (6) To conduct close surveillance in the outpatient setting to monitor the response to treatment and maintenance medications such as steroids and monoclonal antibodies.

Citation: Alam L, Lasam G, Fishberg R. Pericardial effusion with tamponade – an uncommon presentation leading to the diagnosis of eosinophilic granulomatosis polyangiitis: A case report. *World J Cardiol* 2020; 12(9): 460-467

URL: <https://www.wjgnet.com/1949-8462/full/v12/i9/460.htm>

DOI: <https://dx.doi.org/10.4330/wjc.v12.i9.460>

INTRODUCTION

Eosinophilic granulomatosis polyangiitis (EGPA) is a systemic necrotizing vasculitis with eosinophilic infiltrates of the small to medium vessels and extravascular granulomas, first described by Dr. Jacob Churg and Dr. Lotte Strauss in 1951^[1]. EGPA is commonly revealed by late onset asthma and peripheral eosinophilia, however it can rarely present as isolated cardiac tamponade. Owing to the high mortality rate of EGPA presenting as isolated cardiac tamponade, rapid diagnosis and early treatment is critical and lifesaving. Other more common cardiac manifestation of EGPA includes pericarditis, myocarditis, valvulopathies, cardiomyopathy and coronary artery vasculitis.

CASE PRESENTATION

Chief complaints

52-year-old female presented to the hospital with chief complaints of progressive shortness of breath, orthopnea, chest pain, and dry cough.

History of present illness

The symptoms started one month ago and progressively worsened which prompted her to visit the hospital.

History of past illness

She had no significant prior personal or family history.

Physical examination

Vital signs were notable for blood pressure of 124/79 mmHg, sinus tachycardia with heart rate of 119 beats per minute, hypoxia with oxygen saturation of 89%, respiratory rate of 16 breaths per minute and afebrile temperature. On physical examination, she demonstrated sinus tachycardia, a pericardial friction rub, and rales in her bilateral

lower lung fields. She did not demonstrate pulsus paradoxus. Review of system was notable for numbness and tingling of the right hand for the past month.

Laboratory examinations

Initial laboratory findings were notable normal white blood cell count of 11/nL, however with 45% peripheral eosinophilia. Troponin was mildly elevated at 1.1 ng/mL and N-terminal prohormone of brain natriuretic peptide (NT ProBNP) was elevated at 2101 pg/mL. D-Dimer was elevated at 3.66 µg/mL. Electrocardiogram revealed low voltage QRS complex with small ST-T wave changes (Figure 1). A chest radiograph showed cardiomegaly and bilateral opacities (Figure 2). At this stage, given the initial diagnostic information, differentials included congestive heart failure, pulmonary embolism, and/or eosinophilic pneumonia.

Imaging examinations

Computed tomography angiogram revealed a large pericardial effusion, moderate right and small left pleural effusions, and bilateral pulmonary infiltrates (Figure 3). This was followed with a transthoracic echocardiogram which demonstrated normal left ventricular cavity size, wall thickness and systolic function with estimated ejection fraction greater than 55%. No regional wall motion abnormalities were detected. Aortic and mitral valves were normal. There was trace tricuspid regurgitation. The right atrium was normal in size. The right ventricle collapsed in diastole. There was a large pericardial effusion (Figure 4). The diastolic compression of the right ventricle was suggestive of tamponade physiology.

FINAL DIAGNOSIS

Based on the American College of Radiology (ACR) guidelines, the patient was diagnosed with EGPA which manifested in its rare form of cardiac tamponade.

TREATMENT

Cardiothoracic surgery was consulted, and she was taken to the operating room for right video-assisted thoracoscopic surgery pericardial window, right lower lobe lung wedge resection, and drainage of pericardial effusion. Pericardial fluid studies were notable for a cloudy, exudative effusion with white blood cell count of 3092 µL and 25% eosinophilia. Pericardial fluid cytology was negative for malignancy. Aerobic, anaerobic, and fungal cultures were negative for any growth. Pericardial biopsy demonstrated eosinophilic pericarditis (Figure 5). Lung tissue pathology demonstrated findings consistent with eosinophilic pneumonia *vs* EGPA (Figure 6).

Following the drainage of pericardial fluid, the patient demonstrated relief of her presenting symptoms. She denied any chest pain or shortness of breath. Repeat troponin levels were within normal limits. Other laboratory workup including respiratory viral panel, blood cultures, rheumatologic marker including antinuclear antibody, rheumatoid factor and anti-neutrophil cytoplasmic antibody (ANCA) were negative. Hypersensitivity pneumonitis panel was also negative. Repeat echocardiogram the following day showed normal biventricular function, valvular function, and wall motion. It did not demonstrate accumulation of new pericardial effusion. As such coronary catheterization was deferred.

The patient was started on oral prednisone 40 mg daily. A month later, mepolizumab was added to her treatment course and prednisone was concurrently tapered down. Eventually, she has been maintained on oral prednisone 7.5 mg daily as well as mepolizumab monthly with no recurrence of her symptoms.

OUTCOME AND FOLLOW-UP

At one-month interval, transthoracic echocardiogram, CT chest with contrast, and cardiac magnetic resonance imaging (MRI) with and without contrast were performed to monitor disease progression. Echocardiogram showed resolution of pericardial effusion and normal biventricular function. CT chest showed resolution of bilateral infiltrates. Cardiac MRI with and without contrast showed normal biventricular volume and systolic function. There were no areas of focal hyperenhancement,

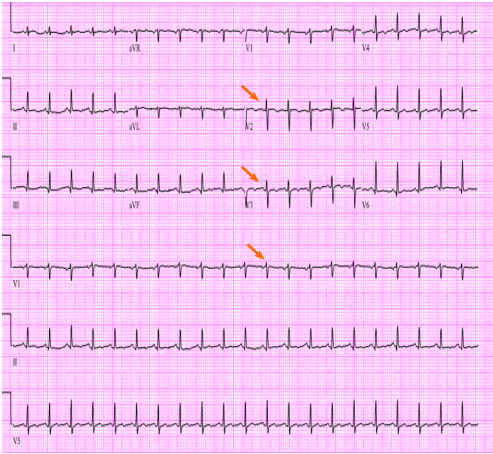


Figure 1 Electrocardiogram showed sinus tachycardia, low voltage QRS (arrows) with small ST-T wave changes.

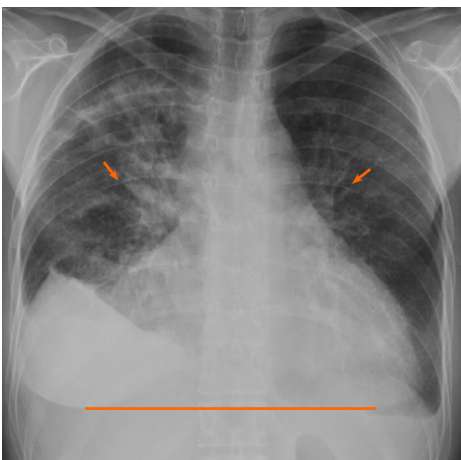


Figure 2 Chest radiograph revealed cardiomegaly (line) and bilateral opacities (arrows).

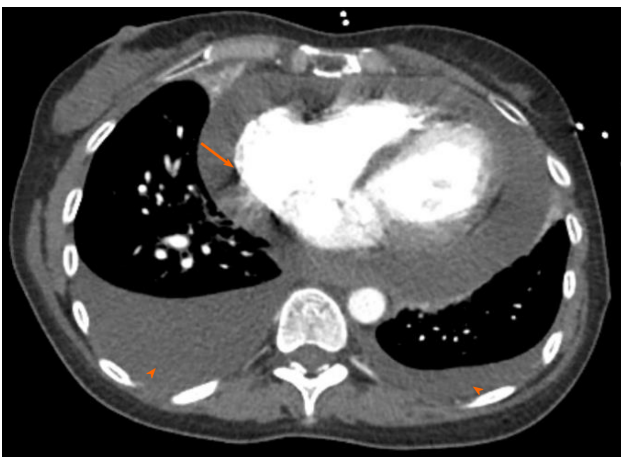


Figure 3 Chest computed tomography angiogram revealed a large pericardial effusion (arrow); moderate right and small left pleural effusion (arrowhead).

consistent with the absence of myocardial scarring or fibrosis. A post gadolinium LAVA sequence was acquired which demonstrated normal measurements of biventricular dimensions, volume and ejection fraction. At follow up office visits, she had no recurrence of cardiopulmonary symptoms, her mononeuritis had resolved, there was no evidence of eosinophilia on hemogram, and she tolerated the medication



Figure 4 Transthoracic echocardiogram showed large pericardial effusion (arrowhead).

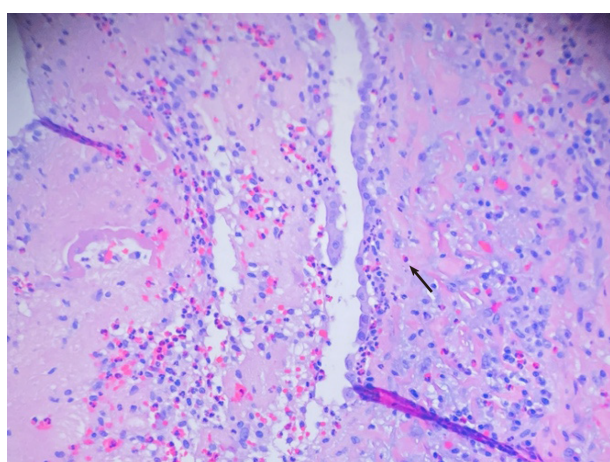


Figure 5 Cardiac biopsy revealed pericardial thickening with eosinophil predominant infiltrate (arrow).

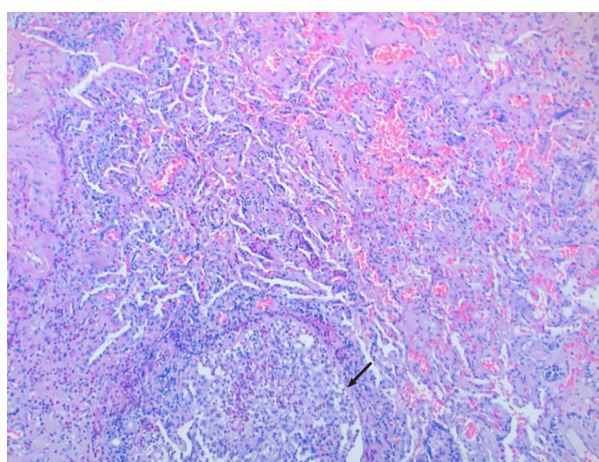


Figure 6 Lung biopsy revealed organizing inflammatory infiltrate, micro abscess (arrow), and eosinophil infiltrate.

well.

DISCUSSION

EGPA is a rare systemic disease characterized by asthma, peripheral and tissue eosinophilia and systemic vasculitis. It is reported to have an annual incidence of 1.0 – 4.2 cases per million^[2]. Cardiac involvement commonly includes eosinophilic endomyocarditis, coronary vasculitis, arrhythmia, cardiomyopathy and pericarditis with small pericardial effusions^[3]. EGPA presenting as cardiac tamponade is exceedingly rare^[3,4]. When cardiac involvement is present, rapid diagnosis is necessary because it is an important predictor of morbidity and mortality.

According to the ACR, the diagnostic criteria for EGPA includes: (1) Asthma; (2) Eosinophilia > 10%; (3) Neuropathy; (4) Non-fixed pulmonary infiltrates; (5) Paranasal sinus abnormality; and (6) Extravascular eosinophils^[5]. The ACR determined that having at least four of the six criteria yields a sensitivity of 85% and a specificity of 99.7% for EGPA^[5]. Our patient met four of the six criteria for the diagnosis of EGPA including: peripheral eosinophilia of 45%, mononeuropathy of right hand, bilateral pulmonary infiltrates on CT angiogram and pericardial/Lung tissue biopsy with extravascular eosinophilia.

The French vasculitis study group demonstrated that EGPA constitutes of two separate clinical patterns which can be distinguished by the ANCA status; patients with cardiac eosinophilic tissue infiltration are usually ANCA negative, whereas patients with pulmonary and renal involvement are ANCA positive^[6,7].

In a literature search on PubMed between January 1960 – March 2020 we found 14 cases of EGPA manifesting as cardiac tamponade (Table 1). Of the total 14 cases reviewed (including ours), age range included 12-73, with 50% male and 50% female patients. Myocardial involvement was detected in five of the fourteen EGPA cases with cardiac tamponade. ANCA status was only positive in one case, thus it is unlikely for ANCA to be related to pericardial involvement leading to cardiac tamponade in EGPA. Cytology from aspirated pericardial fluid did not provide diagnostic value as their presence were variable in the reported cytology results. The diagnosis of seven of the EGPA cases with cardiac tamponade were made from pericardial biopsy.

EGPA manifesting as isolated pericarditis with pericardial effusion may present as mild symptoms of chest pain, cough, and dyspnea to life threatening conditions such as hemodynamic instability. Chest radiograph and electrocardiogram can show initial abnormalities, while urgent echocardiogram confirms the diagnosis of pericardial effusion and tamponade. In such scenarios, pericardiocentesis is performed, and pericardial fluid analysis demonstrates exudative effusion with marked eosinophilia. Histopathology from pericardial biopsy demonstrates vasculitis with eosinophilic infiltration. When patients with EGPA exhibits tamponade without involvement of other visceral organs, the diagnosis is difficult to make without pericardial biopsy. Cardiac MRI is an important noninvasive tool in demonstrating extent of cardiac involvement and following disease progression^[8].

The management and prognosis of EGPA depends on the number of organs involved and their severity. Isolated pericarditis can be treated with high dose steroids alone, whereas pericarditis with myocardial injury and other visceral organ involvement are treated with a combination of high dose steroids and immunosuppressive drugs^[3,4]. Biologics such as mepolizumab, a humanized monoclonal anti-interleukin (IL)-5 antibody has been shown to maintain higher proportion of study participants in remission, as well as reduce glucocorticoid use in patients with EGPA^[9,10]. IL-5 is a cytokine involved in eosinophil proliferation, maturation, and differentiation. IL-5 is found to be at increased levels in patients with EGPA^[10]. Mepolizumab binds to IL-5 and prevents interaction with its receptor on the eosinophil surface, thus providing consistent reduction of peripheral eosinophilia and clinical improvement in patients with eosinophilic disorders such as severe eosinophilic asthma and EGPA^[10].

CONCLUSION

In summary we have presented a patient with pericarditis leading to pericardial effusion and cardiac tamponade which lead to the diagnosis of EGPA. Pericardial fluid analysis revealed eosinophilic infiltrate and pericardial biopsy demonstrated eosinophilic tissue infiltration. Furthermore, cardiac MRI did not show any evidence of inflammation or scarring to indicate myocardial involvement. Thus, this is a rare case of EGPA presenting with isolated pericardial involvement which eventually lead to cardiac tamponade. The patient was initiated on high dose prednisone with good

Table 1 PubMed literature review of case reports of eosinophilic granulomatosis polyangiitis with cardiac tamponade

Patient	Age	Sex	Histological diagnosis	Other cardiac involvement	Other organ involvement	Eosinophil in pericardial fluids	Treatment	ANCA	Ref.
1	66	M	Pericardium	None	Lung	Numerous	Prednisolone	Negative	Agard <i>et al</i> ^[3]
2	73	F	Pericardium	Myocarditis	Nerve	N/A	Prednisolone, cyclophosphamide	Negative	Agard <i>et al</i> ^[3]
3	73	F	Skin	None	Skin, colon, nerve	Numerous	Prednisolone	Negative	Yano <i>et al</i> ^[4]
4	44	F	Skin	Myocarditis	Lung, skin	None	Prednisolone, azathioprine	N/A	Hasley <i>et al</i> ^[11]
5	30	M	Myocardium	Myocarditis	Nerve	Numerous	Prednisolone	Negative	Uren <i>et al</i> ^[12]
6	56	F	Pericardium	None	Skin	N/A	Prednisolone	N/A	Sharma <i>et al</i> ^[13]
7	12	M	Skin	Myocarditis	Lung, skin, nerve	N/A	Prednisolone	Positive	Wang <i>et al</i> ^[14]
8	50	F	Pericardium	None	Lung, eye	77% of white cells	Prednisolone	Negative	Keefe <i>et al</i> ^[15]
9	59	M	Skin	None	Skin, ear, nerve	0.4% of white cells	Prednisolone	Negative	Ovadia <i>et al</i> ^[16]
10	57	M	N/A	None	Eye, nerve	30% of white cells	Prednisolone	Negative	Suganuma <i>et al</i> ^[17]
11	31	F	Pericardium	None	Gall bladder	Numerous	Prednisolone	Negative	Lenders <i>et al</i> ^[18]
12	57	M	N/A	Myocarditis	N/A	Numerous	Prednisolone	N/A	Gerlach <i>et al</i> ^[19]
13	56	M	Pericardium	None	None	N/A	Prednisolone	Negative	David <i>et al</i> ^[20]
14		F	Pericardium, Lung	None	Lung, Nerve	25% of white cells	Prednisone, mepolizumab	Negative	Our Case

ANCA: Anti-neutrophil cytoplasmic antibody.

response over four weeks. Subsequently, the patient was started on a steroid taper and mepolizumab was added as an adjunct to reduce steroid requirement and maintain longer remission rates. On interval follow up the patient had excellent response, which indicates EGPA presenting as cardiac tamponade can be managed with mepolizumab as a steroid sparing agent.

REFERENCES

- 1 **Churg J**, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. *Am J Pathol* 1951; **27**: 277-301 [PMID: [14819261](#)]
- 2 **Watts RA**, Lane S, Scott DG. What is known about the epidemiology of the vasculitides? *Best Pract Res Clin Rheumatol* 2005; **19**: 191-207 [PMID: [15857791](#) DOI: [10.1016/j.berh.2004.11.006](#)]
- 3 **Agard C**, Rendu E, Leguern V, Ponge T, Masseau A, Barrier JH, Trochu JN, Hamidou MA, Guillemin L. Churg-Strauss syndrome revealed by granulomatous acute pericarditis: two case reports and a review of the literature. *Semin Arthritis Rheum* 2007; **36**: 386-391 [PMID: [17303217](#) DOI: [10.1016/j.semarthrit.2006.12.002](#)]
- 4 **Yano T**, Ishimura S, Furukawa T, Koyama M, Tanaka M, Shimoshige S, Hashimoto A, Miura T. Cardiac tamponade leading to the diagnosis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome): a case report and review of the literature. *Heart Vessels* 2015; **30**: 841-844 [PMID: [25070496](#) DOI: [10.1007/s00380-014-0556-x](#)]
- 5 **Masi AT**, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990; **33**: 1094-1100 [PMID: [2202307](#) DOI: [10.1002/art.1780330806](#)]
- 6 **Sablé-Fourtassou R**, Cohen P, Mahr A, Pagnoux C, Mouthon L, Jayne D, Blockmans D, Cordier JF, Delaval P, Puechal X, Lauque D, Viallard JF, Zoulim A, Guillemin L; French Vasculitis Study Group. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med* 2005; **143**: 632-638 [PMID: [16263885](#) DOI: [10.7326/0003-4819-143-9-200511010-00006](#)]
- 7 **Comarmond C**, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, Maurier F, Jouneau S, Bienvu B, Puéchal X, Aumaitre O, Le Guenno G, Le Quellec A, Cevallos R, Fain O, Godeau B, Seror R, Dunogué B, Mahr A, Guilpain P, Cohen P, Aouba A, Mouthon L, Guillemin L; French Vasculitis Study

- Group. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum* 2013; **65**: 270-281 [PMID: [23044708](#) DOI: [10.1002/art.37721](#)]
- 8 **Eyler AE**, Ahmad FA, Jahangir E. Magnetic resonance imaging of the cardiac manifestations of Churg-Strauss. *JRSM Open* 2014; **5**: 2054270414525370 [PMID: [25057389](#) DOI: [10.1177/2054270414525370](#)]
- 9 **Kim S**, Marigowda G, Oren E, Israel E, Wechsler ME. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. *J Allergy Clin Immunol* 2010; **125**: 1336-1343 [PMID: [20513524](#) DOI: [10.1016/j.jaci.2010.03.028](#)]
- 10 **Wechsler ME**, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, Merkel PA, Moosig F, Specks U, Cid MC, Luqmani R, Brown J, Mallett S, Philipson R, Yancey SW, Steinfeld J, Weller PF, Gleich GJ; EGPA Mepolizumab Study Team. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *N Engl J Med* 2017; **376**: 1921-1932 [PMID: [28514601](#) DOI: [10.1056/NEJMoa1702079](#)]
- 11 **Hasley PB**, Follansbee WP, Coulehan JL. Cardiac manifestations of Churg-Strauss syndrome: report of a case and review of the literature. *Am Heart J* 1990; **120**: 996-999 [PMID: [2220558](#) DOI: [10.1016/0002-8703\(90\)90227-o](#)]
- 12 **Uren NG**, Hammond PJ. Myopericarditis in Churg-Strauss syndrome. *Tex Heart Inst J* 1991; **18**: 127-131 [PMID: [15227496](#)]
- 13 **Sharma A**, De Varennes B, Sniderman AD. Churg-Strauss syndrome presenting with marked eosinophilia and pericardial effusion. *Can J Cardiol* 1993; **9**: 329-330 [PMID: [8513426](#)]
- 14 **Wang SJ**, Yang YH, Lin YT, Tsai MJ, Chiang BL. Childhood Churg-Strauss syndrome: report of a case. *J Microbiol Immunol Infect* 2000; **33**: 263-266 [PMID: [11269373](#)]
- 15 **Keefe AC**, Hymas JC, Emerson LL, Ryan JJ. An atypical presentation of cardiac tamponade and periocular swelling in a patient with eosinophilic granulomatosis with polyangiitis: a case report. *J Med Case Rep* 2017; **11**: 271 [PMID: [28941467](#) DOI: [10.1186/s13256-017-1434-9](#)]
- 16 **Ovadia S**, Dror I, Zubkov T, Tanay A, Levy D, Zandman-Goddard G. Churg-Strauss syndrome: a rare presentation with otological and pericardial manifestations: case report and review of the literature. *Clin Rheumatol* 2009; **28** Suppl 1: S35-S38 [PMID: [19225706](#) DOI: [10.1007/s10067-009-1119-x](#)]
- 17 **Suganuma K**, Hashimoto T, Sato H, Suzuki T, Sakurai S. Oculomotor Nerve Palsy following Cardiac Tamponade with Churg-Strauss Syndrome: A Case Report. *Case Rep Neurol* 2011; **3**: 274-277 [PMID: [22125528](#) DOI: [10.1159/000334127](#)]
- 18 **Lenders G**, Goethals M, Verstreken S, Dierckx R, Vanderheyden M. Acalculous cholecystitis and tamponade: an unusual combination? *Acta Cardiol* 2011; **66**: 383-385 [PMID: [21744712](#) DOI: [10.1080/ac.66.3.2114142](#)]
- 19 **Gerlach RM**, Saha TK, Allard RV, Tanzola RC. Unrecognized tamponade diagnosed pre-induction by focused echocardiography. *Can J Anaesth* 2013; **60**: 803-807 [PMID: [23681721](#) DOI: [10.1007/s12630-013-9968-9](#)]
- 20 **David C**, Cazes A, Dossier A, Pasi N, Tadros VX, Papo T, Sacre K. A 56-Year-Old Man With Cardiac Tamponade and Eosinophilia. *Chest* 2018; **154**: e173-e176 [PMID: [30526985](#) DOI: [10.1016/j.chest.2018.06.031](#)]

Diffuse coronary artery vasospasm in a patient with subarachnoid hemorrhage: A case report

Dennis Grewal, Adeba Mohammad, Pooja Swamy, Islam Abudayyeh, Mamas A Mamas, Purvi Parwani

ORCID number: Dennis Grewal

0000000344299721; Adeba

Mohammad 0000-0002-1754-0770;

Pooja Swamy 0000-0002-8223-8738;

Islam Abudayyeh 0000-0002-6366-

4205; Mamas A Mamas 0000-0001-

9241-8890; Purvi Parwani 0000-0002-

4707-992X.

Author contributions: Grewal D provided references for and wrote the majority of the introduction, discussion and conclusion sections and provided the figures; Mohammad A wrote the majority of the case presentation, acquired necessary documentation for submission and completed final formatting of submission documents; Swamy P performed the initial evaluation of the patient and assisted with the coronary catheterization; Abudayyeh I performed the coronary angiogram and provided the coronary catheterization films and still images; Swamy P, Abudayyeh I and Mamas MA contributed towards revising the manuscript critically for important intellectual content; Parwani P handled supervision, made substantial contribution to the conception of the paper, drafted the first manuscript, provided critical edits to the final manuscript in addition to providing the CMRI imaging, and is the senior and corresponding author of the

Dennis Grewal, Adeba Mohammad, Pooja Swamy, Islam Abudayyeh, Purvi Parwani, Division of Cardiology, Department of Cardiology, Loma Linda University Medical Center, Loma Linda, CA 92354, United States

Mamas A Mamas, Keele Cardiovascular Research Group, Centre for Prognosis Research, Institutes of Applied Clinical Science and Primary Care and Health Sciences, Keele University, Stoke on Trent, Manchester M139PT, United Kingdom

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

Abstract

BACKGROUND

Coronary artery vasospasm (CAV) is a reversible, transient form of vasoconstriction with clinical manifestations ranging from stable angina to acute coronary syndromes (ACS). Vasospasm of epicardial coronary arteries or associated micro-vasculature can lead to total or subtotal occlusion and has been demonstrated in nearly 50% of patients undergoing angiography for suspected ACS. The mechanism for CAV has been described in literature, but in a subgroup of patients presenting with intracranial hemorrhage, it appears to be multifactorial. These patients tend to have electrocardiographic changes, elevation of cardiac biomarkers of injury and neurogenic stress cardiomyopathy.

CASE SUMMARY

A 44-year-old woman presented with severe headaches and tonic-clonic seizures. She was found to have diffuse subarachnoid hemorrhage (SAH) requiring ventricular drain placement, coil embolization and induced hypertension. She subsequently developed chest pain with ST elevations in anterior precordial leads, elevated cardiac enzymes and apical ballooning with left ventricular ejection fraction of 35% on transthoracic echocardiogram. Coronary angiogram revealed severe diffuse triple vessel stenoses secondary to CAV seen distally. Subsequent cardiac MRI notable for apical non-viability and scar formation.

CONCLUSION

This case highlights a unique etiology of acute myocardial infarction in a patient with SAH leading to ST elevations, diffuse triple vessel CAV and apical scar.

manuscript.

Informed consent statement:

Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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

CARE Checklist (2016) statement:

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised accordingly.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: June 6, 2020

Peer-review started: June 6, 2020

First decision: June 20, 2020

Revised: July 3, 2020

Accepted: September 15, 2020

Article in press: September 15, 2020

Published online: September 26, 2020

P-Reviewer: Haaf P, Sato A

S-Editor: Gong ZM

L-Editor: A

P-Editor: Li JH



Key Words: ST-elevation myocardial infarction; Acute coronary syndrome; Stress induced cardiomyopathy; Coronary artery vasospasm; Cerebral vasospasm; Subarachnoid hemorrhage; Case report

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Acute coronary syndromes often occur in patients with multiple co-morbidities and treatment plans need to be tailored to each unique presentation. We present a case of ST-elevation myocardial infarction in a patient with aneurysmal subarachnoid hemorrhage complicated by cerebral and coronary vasospasms, leading to apical infarct.

Citation: Grewal D, Mohammad A, Swamy P, Abudayyeh I, Mamas MA, Parwani P. Diffuse coronary artery vasospasm in a patient with subarachnoid hemorrhage: A case report. *World J Cardiol* 2020; 12(9): 468-474

URL: <https://www.wjgnet.com/1949-8462/full/v12/i9/468.htm>

DOI: <https://dx.doi.org/10.4330/wjc.v12.i9.468>

INTRODUCTION

Coronary artery vasospasm (CAV) is a reversible, transient form of vasoconstriction with clinical manifestations ranging from stable angina to acute coronary syndromes (ACS). Vasospasm of epicardial coronary arteries or associated micro-vasculature can lead to total or subtotal occlusion and has been demonstrated in nearly 50% of patients undergoing angiography for suspected ACS. The mechanism for CAV has been described in literature, but in a subgroup of patients presenting with intracranial hemorrhage, it appears to be multifactorial^[1]. These patients tend to have electrocardiographic changes, elevation of cardiac biomarkers of injury and neurogenic stress cardiomyopathy^[2].

CAV was initially described by Prinzmetal *et al*^[3] in 1959 as a form of variant angina different from the heterogeneous group of classical anginal syndromes. A complex interplay of mechanisms including increased sympathetic drive to microvascular dysfunction have been described in the literature^[4]. Here, we present a case of a patient with an aneurysmal subarachnoid hemorrhage (SAH) complicated by cerebral vasospasm and concomitant severe CAV leading to an acute myocardial infarction presenting as ST-elevation myocardial infarction (STEMI) on electrocardiography (ECG). While severe CAV is the underlying pathophysiology for stress induced cardiomyopathy, acute myocardial infarction (AMI) and apical scarring are rare in those cases. There are only a few published case reports in the literature with such findings^[5-7]. Treatment options are challenging in such cases due to diffuse CAV and intracerebral hemorrhage.

CASE PRESENTATION

Chief complaints

Left sided chest pain.

History of present illness

A 44-year-old woman presented to the emergency department with thunderclap headache. She was found to have a ruptured cerebral aneurysm and SAH requiring neurosurgical intervention. This was followed by severe cerebral vasospasm and neurologic deficits treated with induced hypertension using high doses of vasopressors. Subsequently she was noted to develop chest pain associated with elevated cardiac biomarkers, ST elevation in precordial electrocardiogram leads and new apical hypokinesia evident on echocardiogram. This was promptly evaluated with a coronary angiogram that demonstrated tapering of distal small caliber coronary vessels supplying the territory noted to have wall motion abnormality.

History of past illness

Hypertension that is controlled on atenolol and hydrochlorothiazide outpatient.

Physical examination

The patient's heart rate was 97 bpm, respiratory rate was 19 breaths per minute, blood pressure was 121/71 mmHg and oxygen saturation on room air was 100%. Cardiac examination revealed a regular rate and rhythm, and no jugular venous distention. Lung exam revealed clear breath sounds without crackles or wheezing.

Laboratory examinations

Cardiac enzymes with the onset of chest pain showed initial Troponin T at 0.60 ng/mL and peaked at 1.72 ng/mL with normal complete blood count and basic metabolic panel.

ECG during initial onset of chest pain showed sinus rhythm with ST elevations in V3-V5 (Figure 1A). Repeat ECG in the setting of ongoing symptoms showed normal sinus rhythm with ST elevations in V1-V3 with deep T-wave inversions in the anterior-septal leads (Figure 1B).

Imaging examinations

Initial echocardiogram during admission was unremarkable with LVEF 60% and normal wall motion. Repeat echocardiogram during STEMI showed a decrease in LVEF to 35%-40% with apical ballooning (Figure 2).

Coronary angiography showed patent left main artery, but 100% occlusion of the mid to distal left anterior descending artery and distal left circumflex (Figure 3A). There was 100% occlusion of the distal posterior descending artery and posterolateral artery (Figure 3B). We were unable to give nitrates during left heart catheterization to see if the vasospasm would improve as patient was hypotensive and we were instructed to keep permissive hypertension by our neurology colleagues. Three weeks after the initial angiogram, Cardiac MRI revealed intense delayed enhancement in subendocardial fashion involving the apical septum and apical segment suggestive of scarred myocardium due to myocardial infarction with LVEF of 58% (Figure 4). We believe this to have been an acute MI as baseline ECG did not show q-waves nor was there a personal history of MI or symptoms indicative of coronary artery disease (CAD) in the past.

Personal and family history

She has a past surgical history of cholecystectomy. She denies alcohol, tobacco, or recreational drug use. Family history is positive for hypertension in her parents.

FINAL DIAGNOSIS

ST elevation myocardial infarction secondary to severe coronary artery vasospasm causing reduced left ventricular function and apical ballooning.

TREATMENT

After the coronary angiogram, dual antiplatelet therapy and nitrates were added to her regimen to help reduce CAV. Her discharge medications included aspirin 81 mg daily, carvedilol 3.25 mg BID, atorvastatin 40 mg qhs, clopidogrel 75 mg daily, isosorbide mononitrate 30 mg daily and nitroglycerin sublingual as needed.

OUTCOME AND FOLLOW-UP

Patient follows up regularly with our cardiology clinic. She's doing well with good exercise tolerance and remains angina free. Her systolic function remains persistently borderline with 50% EF and apical wall motion suggestive of apical infarct three months after her hospital discharge.

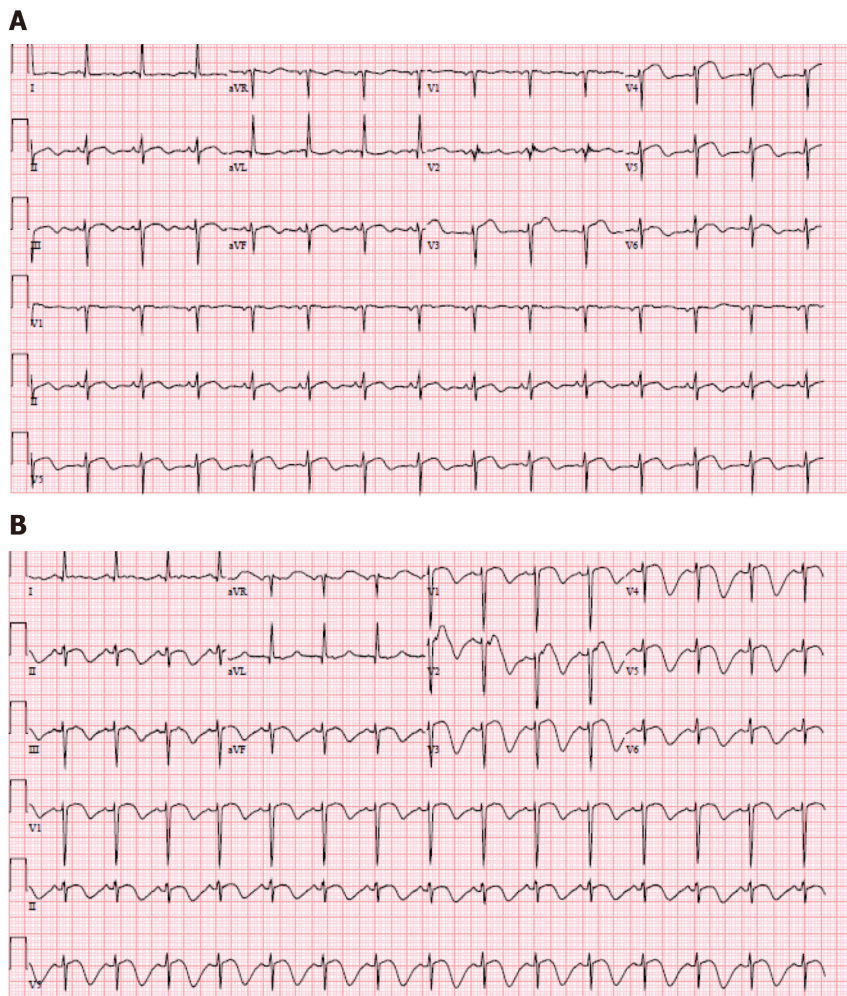


Figure 1 Electrocardiogram. A: Electrocardiogram (ECG) showing ST elevations in leads V3-V5, and evidence of left ventricular hypertrophy with repolarization abnormality and prolonged QTc. B: ECG showing normal sinus rhythm with ST elevations in V1-V3 with deep T-wave inversions in the anterior-septal leads.

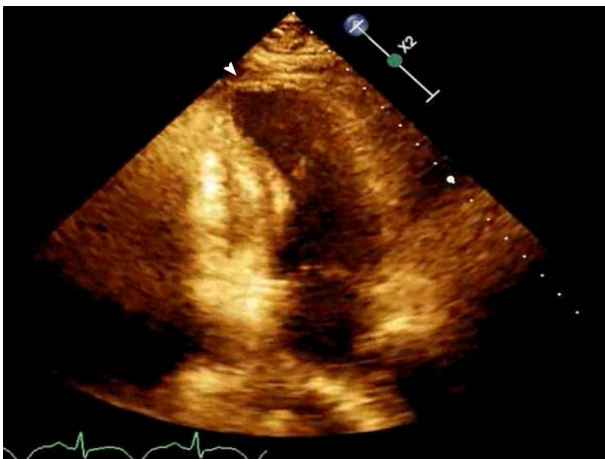


Figure 2 Echocardiogram on HD 16 showing apical ballooning.

DISCUSSION

We present a rare case of severe CAV leading to apical infarct and low-normal EF in setting of SAH and induced hypertension employed for its treatment. To our knowledge, this is the first case describing the coronary findings in a patient with SAH and apical infarct on CMR.

The typical pathogenesis for myocardial ischemia involves coronary artery

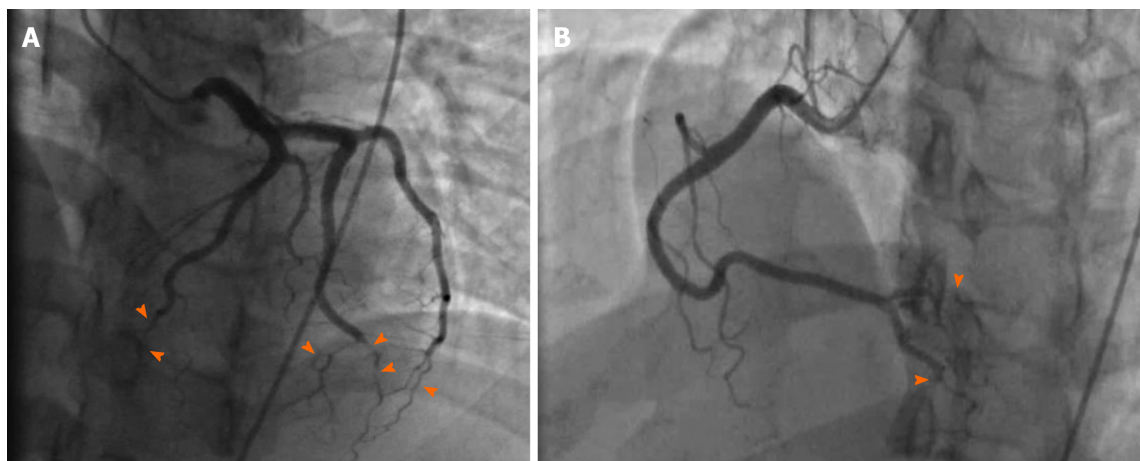


Figure 3 Coronary angiogram. A: Coronary angiogram shows severely atretic distal left anterior descending artery and obtuse marginal coronary arteries; B: The posterolateral and posterior descending artery branches of the right coronary artery are severely narrowed distally.

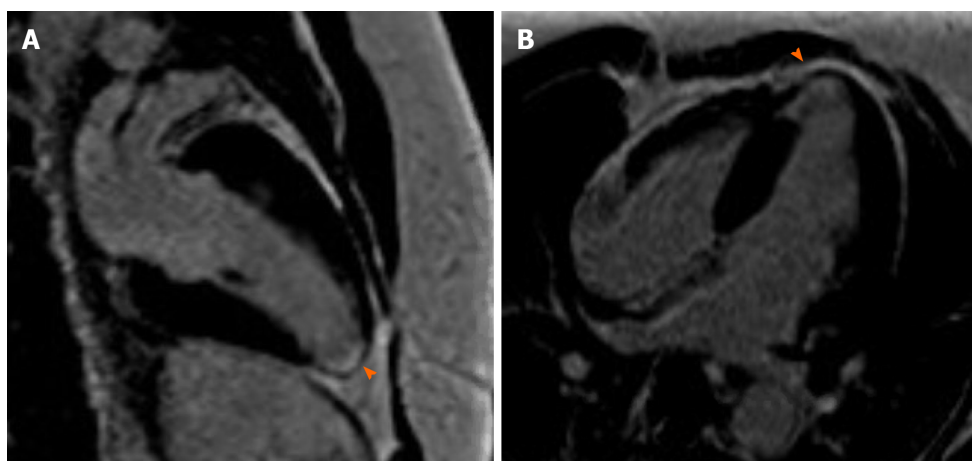


Figure 4 Cardiac magnetic resonance imaging shows delayed gadolinium enhancement suggestive of apical scarring and nonviability.

atherosclerosis and/or plaque rupture^[8]. Our patient had minimal risk factors for CAD and suffered an acute myocardial infarction due to severe CAV which is known to be triggered by high sympathetic drive in patients with SAH. It is believed that excessive sympathetic drive in such cases lead to mismatch in myocardial oxygen demand and supply leading to neurogenic stunned myocardium (NSM)^[9,10].

Neurogenic myocardial stunning has been described frequently in medical literature and is described as a state of reversible left ventricular dysfunction that occurs in up to 30% of patients with SAH. Echocardiographic manifestations of Takotsubo cardiomyopathy can be found in 1% to 6% of SAH patients with CAV being one of the underlying mechanisms^[10,11]. Overall involvement of myocardium and the incidence and description of SAH complicated by cerebral and coronary vasospasm is seldom described in literature^[12]. Animal studies have shown when blood is injected into the subarachnoid space, it is associated with increased amounts of coronary vasospasm in the subjects due to vagal pathway paralysis induced by sympathetic overactivity^[13]. This sympathetic overactivity can also occur as a result of rising intracranial pressures from SAH due to increased secretion of cerebrospinal fluid triggered by hemorrhage^[14,15]. Elevated catecholamine levels can be linked to cerebral vasospasms and have been associated with left ventricular dysfunction^[11]. Therapy for cerebral vasospasm includes hypervolemia and induced hypertension, which may further result in potential cardiopulmonary complications like myocardial ischemia and pulmonary edema^[16]. Proposed interventions like mechanical circulatory-assist devices with intra-aortic balloon pump have been shown to be successful for isolated patients with severe myocardial dysfunction complicated by cerebral vasospasms, but has not been studied thoroughly in this patient population^[17].

Incidence of CAV in the setting of ACS has been studied with varying percentages

of frequency based off populations studied. In a Taiwanese population, patients suspected to have coronary ischemia underwent coronary angiograms with findings of non-obstructive CAD, but ergonovine provocation testing was positive in 41% of patients^[18]. In a French study, Caucasian patients being worked up for acute MI showed CAV positive in only 15.5% of patients^[19]. Diagnosis and treatment of CAV has been well described in literature, but data in SAH remains scarce. Some research has been attempted in this area, in which prophylactic beta-blockers were hypothesized to reduce catecholaminergic surges in order to reduce the incidence and complications that arise from NSM, but a meta-analysis by Luo *et al*^[20] showed no statistical benefit to this therapy. Clinical evidence is widespread for CAV and treatment modalities using nitrates and calcium-channel blockers; however, in the subset of patients complicated by SAH, there is limited data regarding acute cardioprotective strategies^[3].

Our patient was empirically treated with heparin infusion, aspirin therapy and calcium channel blocker (nimodipine) and was not taken to the catheterization lab immediately due to suspicion for coronary vasospasm due to SAH and high doses of vasopressor use. However, in order to attain a definitive cardiac diagnosis, the angiogram was done showing diffuse epicardial CAV resulting in her cardiomyopathy and evidence of myocardial infarction seen on CMR. Her delayed enhancement seen on CMR with wall motion abnormalities was intense and in subendocardial fashion which is indicative of an MI than stress induced cardiomyopathy like Takotsubo, which generally leads to little midmyocardial or patchy delayed enhancement. Due to permissive hypertension requirement from neurology colleagues, her initial management of MI was tricky. Once her symptoms resolved, she was initiated on guidelines directed medical therapy of cardio selective beta-blocker and antiplatelets. Scarcity of medical literature relevant to this specific clinical scenario calls for individualized management approach. As we identify large percentage of patients with SAH and electrocardiographic abnormalities, elevated cardiac biomarkers and wall motion abnormalities, more data on how to carefully proceed with risk stratification, diagnosing and treating acute coronary syndromes in this population is needed^[4].

CONCLUSION

Severe diffuse coronary artery vasospasm can lead to myocardial dysfunction and acute myocardial infarction in patients with SAH. Further research is needed to understand coronary vasospasm happening concomitantly with cerebral vasospasm in order to attenuate consequences of severe CAV and develop cardioprotective strategies to minimize end-organ damage.

REFERENCES

- 1 **Banki NM**, Kopelnik A, Dae MW, Miss J, Tung P, Lawton MT, Drew BJ, Foster E, Smith W, Parmley WW, Zaroff JG. Acute neurocardiogenic injury after subarachnoid hemorrhage. *Circulation* 2005; **112**: 3314-3319 [PMID: 16286583 DOI: 10.1161/CIRCULATIONAHA.105.558239]
- 2 **Mayer SA**, Lin J, Homma S, Solomon RA, Lennihan L, Sherman D, Fink ME, Beckford A, Klebanoff LM. Myocardial injury and left ventricular performance after subarachnoid hemorrhage. *Stroke* 1999; **30**: 780-786 [PMID: 10187879 DOI: 10.1161/01.str.30.4.780]
- 3 **Prinzmetal M**, Kennamer R, Merliss R, Wada T, Bor N. Angina pectoris. I. A variant form of angina pectoris; preliminary report. *Am J Med* 1959; **27**: 375-388 [PMID: 14434946 DOI: 10.1016/0002-9343(59)90003-8]
- 4 **Lee VH**, Oh JK, Mulvagh SL, Wijdicks EF. Mechanisms in neurogenic stress cardiomyopathy after aneurysmal subarachnoid hemorrhage. *Neurocrit Care* 2006; **5**: 243-249 [PMID: 17290097 DOI: 10.1385/ncc.5:3:243]
- 5 **Chen HY**. Angiographic Coronary Spasm in a Case of Spontaneous Subarachnoid Hemorrhage Mimicking Acute Myocardial Infarction. *Cardiol Res* 2013; **4**: 74-77 [PMID: 28352424 DOI: 10.4021/cr269w]
- 6 **Yuki K**, Kodama Y, Onda J, Emoto K, Morimoto T, Uozumi T. Coronary vasospasm following subarachnoid hemorrhage as a cause of stunned myocardium. Case report. *J Neurosurg* 1991; **75**: 308-311 [PMID: 2072171 DOI: 10.3171/jns.1991.75.2.0308]
- 7 **Toyama Y**, Tanaka H, Nuruki K, Shirao T. Prinzmetal's variant angina associated with subarachnoid hemorrhage: A case report. *Angiology* 1979; **30**: 211-218 [PMID: 434581 DOI: 10.1177/000331977903000311]
- 8 **Shah PK**. Pathophysiology of coronary thrombosis: role of plaque rupture and plaque erosion. *Prog Cardiovasc Dis* 2002; **44**: 357-368 [PMID: 12024334 DOI: 10.1053/pcad.2002.123473]
- 9 **Jain R**, Deveikis J, Thompson BG. Management of patients with stunned myocardium associated with subarachnoid hemorrhage. *AJNR Am J Neuroradiol* 2004; **25**: 126-129 [PMID: 14729541]
- 10 **Talahma M**, Alkhachroum AM, Alyahya M, Manjila S, Xiong W. Takotsubo cardiomyopathy in aneurysmal

- subarachnoid hemorrhage: Institutional experience and literature review. *Clin Neurol Neurosurg* 2016; **141**: 65-70 [PMID: 26741878 DOI: 10.1016/j.clineuro.2015.12.005]
- 11 **Kerro A**, Woods T, Chang JJ. Neurogenic stunned myocardium in subarachnoid hemorrhage. *J Crit Care* 2017; **38**: 27-34 [PMID: 27837689 DOI: 10.1016/j.jcrc.2016.10.010]
- 12 **Nguyen H**, Zaroff JG. Neurogenic stunned myocardium. *Curr Neurol Neurosci Rep* 2009; **9**: 486-491 [PMID: 19818236 DOI: 10.1007/s11910-009-0071-0]
- 13 **Yolas C**, Kanat A, Aydin MD, Altas E, Kanat IF, Kazdal H, Duman A, Gundogdu B, Gursan N. Unraveling of the Effect of Nodose Ganglion Degeneration on the Coronary Artery Vasospasm After Subarachnoid Hemorrhage: An Experimental Study. *World Neurosurg* 2016; **86**: 79-87 [PMID: 26365883 DOI: 10.1016/j.wneu.2015.09.004]
- 14 **Kanat A**, Turkmenoglu O, Aydin MD, Yolas C, Aydin N, Gursan N, Tumkaya L, Demir R. Toward changing of the pathophysiologic basis of acute hydrocephalus after subarachnoid hemorrhage: a preliminary experimental study. *World Neurosurg* 2013; **80**: 390-395 [PMID: 23247027 DOI: 10.1016/j.wneu.2012.12.020]
- 15 **Shivalkar B**, Van Loon J, Wieland W, Tjandra-Maga TB, Borgers M, Plets C, Flameng W. Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function. *Circulation* 1993; **87**: 230-239 [PMID: 8419012 DOI: 10.1161/01.cir.87.1.230]
- 16 **Temes RE**, Tessitore E, Schmidt JM, Naidech AM, Fernandez A, Ostapovich ND, Frontera JA, Wartenberg KE, Di Tullio MR, Badjatia N, Connolly ES, Mayer SA, Parra A. Left ventricular dysfunction and cerebral infarction from vasospasm after subarachnoid hemorrhage. *Neurocrit Care* 2010; **13**: 359-365 [PMID: 20945116 DOI: 10.1007/s12028-010-9447-x]
- 17 **Apostolides PJ**, Greene KA, Zabramski JM, Fitzgerald JW, Spetzler RF. Intra-aortic balloon pump counterpulsation in the management of concomitant cerebral vasospasm and cardiac failure after subarachnoid hemorrhage: technical case report. *Neurosurgery* 1996; **38**: 1056-9; discussion 1059-60 [PMID: 8727836 DOI: 10.1097/00006123-199605000-00042]
- 18 **Wang CH**, Kuo LT, Hung MJ, Cherng WJ. Coronary vasospasm as a possible cause of elevated cardiac troponin I in patients with acute coronary syndrome and insignificant coronary artery disease. *Am Heart J* 2002; **144**: 275-281 [PMID: 12177645 DOI: 10.1067/mhj.2002.123843]
- 19 **Da Costa A**, Isaaz K, Faure E, Mourot S, Cerisier A, Lamaud M. Clinical characteristics, aetiological factors and long-term prognosis of myocardial infarction with an absolutely normal coronary angiogram; a 3-year follow-up study of 91 patients. *Eur Heart J* 2001; **22**: 1459-1465 [PMID: 11482919 DOI: 10.1053/euhj.2000.2553]
- 20 **Luo H**, Song WX, Jiang JW, Zhao JL, Rong WL, Li MH. Effects of preadmission beta-blockers on neurogenic stunned myocardium after aneurysmal subarachnoid hemorrhage: A meta-analysis. *Clin Neurol Neurosurg* 2017; **158**: 77-81 [PMID: 28499220 DOI: 10.1016/j.clineuro.2017.04.022]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

