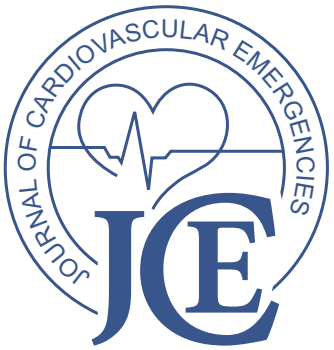

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Atherosclerosis, Hypertension and Acute Coronary Syndromes

Computed Tomography and Acute Cardiac Care

Acute Peri-Myocarditis and Ventricular Function

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Aims and scope

The Journal of Cardiovascular Emergencies is the official journal of the Transylvanian Association of Transvascular Therapy and Transplantation Kardiomed, Tîrgu Mureș, Romania, and is published quarterly.

The Journal of Cardiovascular Emergencies aims to publish top quality papers related to acute conditions in any cardiovascular pathology.

The journal will mainly focus on recent advances in the field of diagnosis and treatment of the most common causes of cardiovascular emergencies, including acute coronary syndromes, acute heart failure, acute aortic diseases, pulmonary embolism, peripheral arterial diseases or cardiac arrhythmia. Interdisciplinary approaches will be extremely welcomed, presenting new advances in the approach of different other pathologies (i.e. stroke) from the cardiovascular perspective.

The Journal of Cardiovascular Emergencies will publish high-quality basic and clinical research related to these topics, in a common approach that will integrate the clinical studies with the pre-clinical work dedicated to discovery of new mechanisms involved in the development and progression of acute cardiovascular conditions.

Especially in the case of acute coronary syndromes, the journal will try to provide the entire cardiology community with the perspective of the regional cardiology networks in Central and Eastern European countries, reflecting the regional model of care in cardiovascular acute conditions.

The journal will primarily focus on publishing original research papers, but also other types of materials (such as review articles, case reports, state-of-the-art papers, comments to editor, etc) will be extremely welcomed.

The Journal of Cardiovascular Emergencies has institutional support from the Transylvanian Association of Transvascular Therapy and Transplantation Kardiomed, Tîrgu Mureș, Romania, the owner of the journal.

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EDITORIAL

Atherosclerosis-Triggered Hypertension or Hypertension-Triggered Atherosclerosis? A Challenging Hypothesis

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Despite the significant progress encountered in recent years in the field of diagnostic techniques, key aspects involved in the development and progression of atherosclerosis are not fully understood. Based on clinical observations of acute coronary syndromes in young patients with angiographically normal coronary arteries, a new premise can be proposed to explain some of the mechanisms involved in atheromatous plaque formation. This hypothesis is that, even in the oscillating phase, hypertension is a trigger for the development of atherosclerotic disease due to mechanical stress.

This premise represents the starting point of a chicken and egg argument: does atherosclerosis lead to hypertension, or do repeated episodes of hypertension lead to atherosclerosis?

ACUTE CORONARY SYNDROMES WITH SLOW-FLOW PATTERN IN NON-OBSTRUCTED CORONARY ARTERIES. CLINICAL OBSERVATIONS GENERATING THE HYPOTHESIS

The hypothesis is based on data recorded in several patients aged between 23 and 44 years, presenting in the emergency department of our institution with typical angina, electrocardiographic (ECG) changes highly suggestive of ischemia, and positive cardiac enzymes.

In these patients, coronary angiography showed the absence of any obstructions or significant stenosis in the coronary arteries and an abnormal non-laminar coronary flow located in the middle segment of the left anterior descending coronary artery (Figure 1A). Optical coherence tomography (OCT) showed the presence of a dissection in the subendothelial layer of the coronary wall at the level of the turbulent flow (Figure 1B). In all these patients, repeated episodes of hypertension preceded an angina attack.

In the proposed hypothesis, the following are proposed as characteristics associated with a new pattern of acute cardiac patient seen in an emergency setting:

- repeated episodes of hypertension;
- presenting with chest pain;
- ECG changes and positive cardiac enzymes;
- coronary angiography indicating slow flow in at least one coronary artery;
- OCT revealing the presence of subendothelial dissection.

FROM HYPERTENSION TO ATHEROGENESIS DUE TO MECHANICAL STRESS

Repeated episodes of a sudden increase in the blood pressure can cause the abrupt dilatation of the coronary wall, which becomes wrinkled on returning to its original shape. This wrinkled surface can lead to the alteration of shear stress and, at the same time, of the circumferential stress inside the coronary lumen, contributing to endothelial dysfunction and the development of turbulent coronary flow at this level.

The endothelium that usually protects the coronary wall is exposed to altered luminal forces caused by the in-

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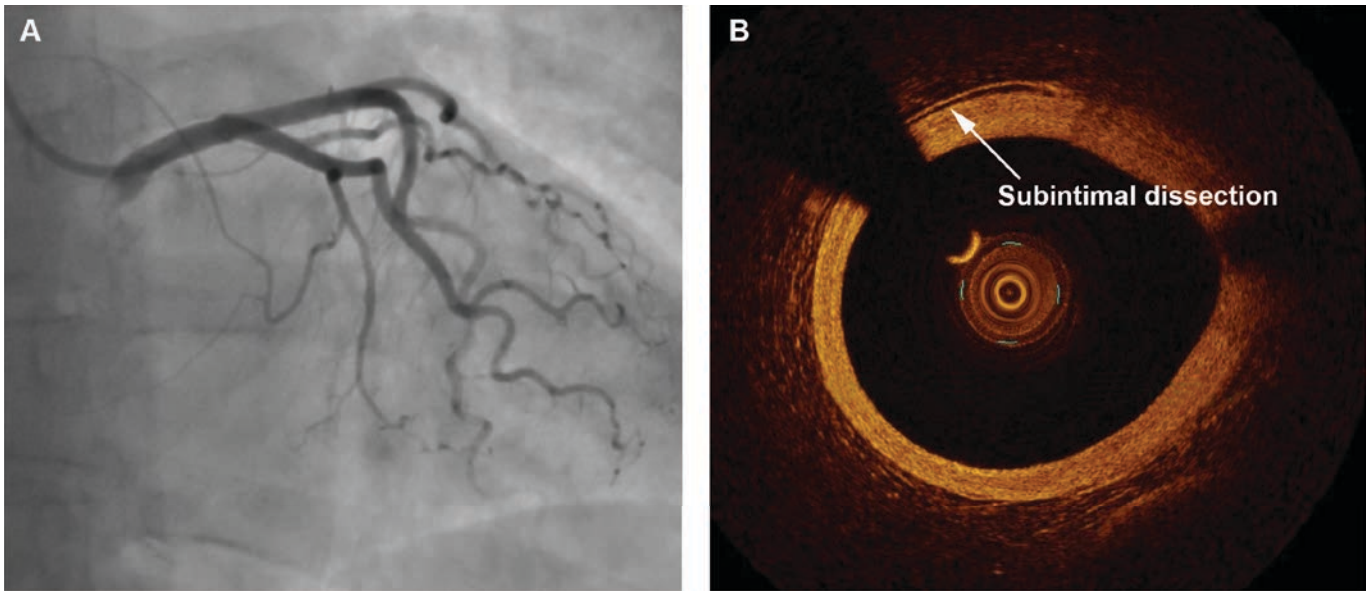

FIGURE 1. Invasive assessment of coronary arteries in a young patient with typical chest pain. A – Coronary angiography indicating absence of any obstructions or any significant stenosis in the coronary arteries and an abnormal non-laminar coronary flow located in the middle segment of the left anterior descending coronary artery. B – Optical coherence tomography (OCT) indicating the presence of a dissection in the sub-endothelial layer of the coronary wall at the level of the turbulent flow.

crease in wall stress during repeated episodes of hypertension, leading to a dilatation of the coronary wall. Once dilated, the coronary wall becomes "wrinkled" when it returns to its original shape, on the return of blood pressure to normal values. This "wrinkled" contour leads to modifications of the typical structure of the arterial wall in the region adjacent to the endothelium, increase in circumferential stress, and alteration of the shear stress. As a result, the endothelium will lose its elastic properties, generating a turbulent laminar coronary flow.

At the same time, during these repeated episodes of coronary wall dilation and contraction the vasa vasorum are compressed, causing alterations of the nutrition of the coronary wall, temporary modifications of the fibroblasts, alteration of endothelial integrity, and dissection. The endothelial structures lose their contact with internal structures, and the process is continued by fibroblast deposition, proliferation, and mastocyte migration. The recurrence of subsequent episodes of hypertension leads to the augmentation of these processes, finally resulting in atherosclerosis (Figure 2).

PATHOPHYSIOLOGICAL SUBSTRATE OF SUBCLINICAL ATHEROSCLEROSIS — A CONTINUING MYSTERY?

In spite of recent progress in understanding the physiopathology of acute coronary syndromes, many key aspects involved in the development of this disease remain unclear. For instance, many patients presenting at an emergency department with typical chest pain, an electrocardiographic pattern characteristic for acute myocardial infarction, and a significant raise in cardiac enzymes have normal coronary arteries as shown by routine coronary angiography. According to reported studies, acute coronary syndromes in patients with normal coronary arteries, as indicated by angiography, have a prevalence of 10 to 20%.[1,2] This distinct pathophysiological entity is termed "acute coronary syndromes with angiographically normal coronary arteries". Different theories have been proposed to explain the cause of this odd clinical presentation, such as coronary vasospasm, coronary embolism, myocardial bridging, or coronary artery dissection.[1–3] When no possible cause can be identified, this clinical presentation is termed "coronary X syndrome", an expression suggestive of the fact that the etiology remains a mistery, and though attempts have been made to associate this atypical presentation with a possible etiological factor, as yet no direct relation has been proven.[3,4]

ENDOTHELIAL DYSFUNCTION — THE PATHWAY FROM HYPERTENSION TO ATHEROSCLEROSIS

The role of endothelial dysfunction (ED) in the pathogenesis of atherosclerosis and in the initiation and progression

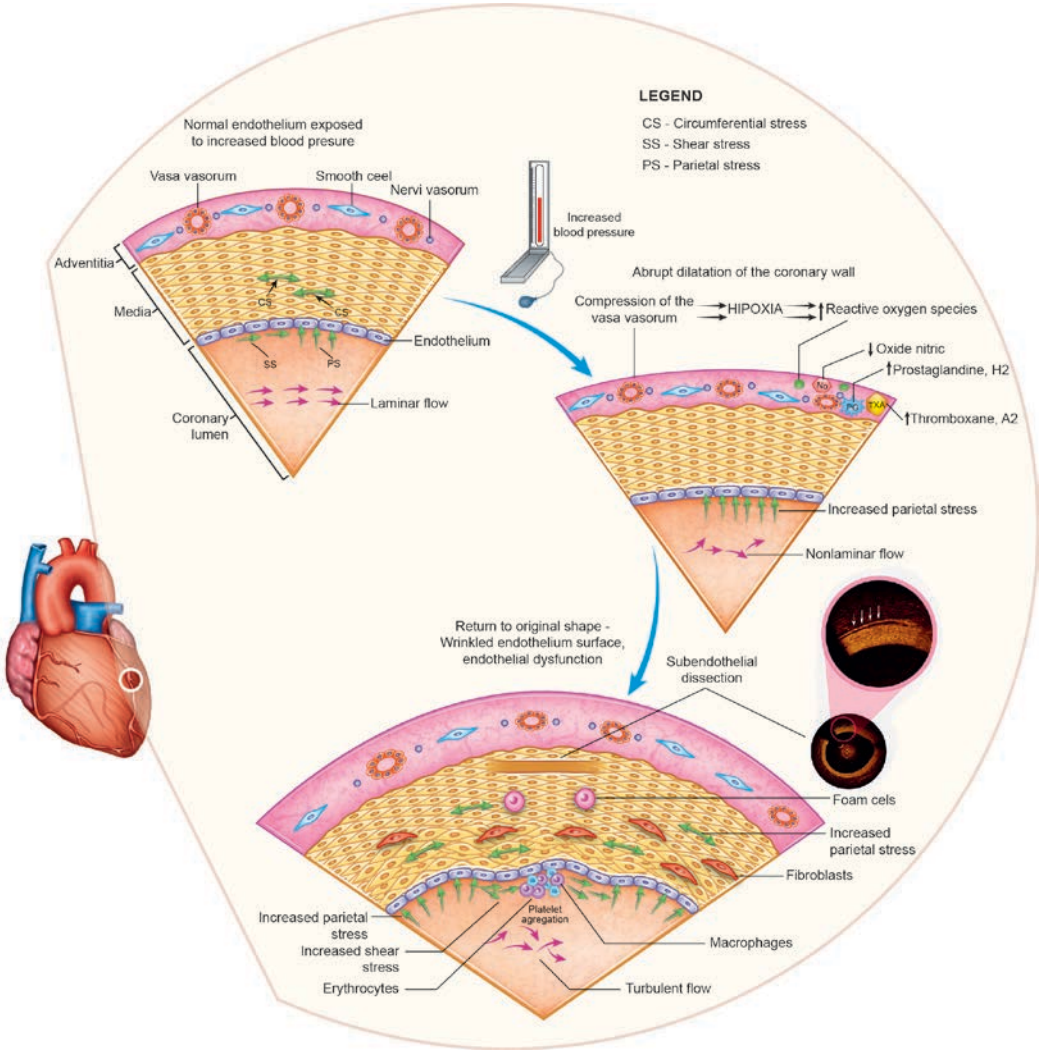

FIGURE 2. From hypertension to atherogenesis via mechanical stress

of coronary artery disease has been described and demonstrated.[5–7] When ED occurs, the endothelium loses its protective role and becomes a pro-atherosclerotic player, releasing pro-atherogen and vasoconstrictor substances and mediators, such as endothelin ET-1, thromboxane A2, prostaglandin H2, and reactive oxygen species.[7]

The increased parietal stress caused by arterial hypertension leads to a reduction in the nitric oxide (NO) production at the level of the vessel intima, and, subsequently, to an increase in the production of free radicals. The augmented oxidative stress associated with ED promotes vascular lesions, platelet aggregation, smooth muscle fiber proliferation, increased macrophage migration, and an overall promotion of inflammation.[4,5,8] This is probably the key pathophysiologic link between hypertension and typical atherosclerosis.

Different types of pressure are exerted on the arterial wall. The normal stress caused by blood pressure acts perpendicularly to the arterial wall, while the so-called "shear stress", or fluid-wall shear stress, acts parallel to the wall. At the same time, cells within the arterial wall are exposed to circumferential wall stress, which varies according to the elastic properties of the vessel.[9]

A low arterial shear stress, below 4 dyne/cm^2, has been demonstrated to be frequently encountered at the level of atherosclerotic plaques, being associated with an atherogenic phenotype and plaque vulnerability.[9]

SUBENDOTHELIAL CORONARY DISSECTION — A NOVEL FINDING IN ACUTE CORONARY SYNDROMES WITH ANGIOGRAPHICALLY NORMAL CORONARY ARTERIES

Vascular remodeling, arterial stiffness, increased and altered parietal, circumferential and shear stress caused by hypertension, along with the inflammatory process, in-

creased oxidative stress, and endothelial dysfunction, may contribute to the development of lesions in the vascular wall.

An increased intracoronary pressure may also lead to rupture of the vasa vasorum, resulting in a subintimal hemorrhage and an intramural hematoma, a condition associated with acute chest pain, though the coronary lumen retains a typical appearance on the coronary angiography.[10]

These alterations of the coronary wall structure are, in most cases, difficult to diagnose using coronary angiography, as this technique allows visualization of the coronary lumen and detection of the luminal narrowing without providing any information about the vessel wall.[11] This can explain the angiographically normal aspect of coronary arteries in patients with acute coronary syndromes and a slow-flow pattern. The assessment of coronary wall structure has become possible in recent years, following the introduction of optical coherence tomography, which has become the golden standard technique for visualization of ruptures in the coronary endothelium.[1] The techniqur allows the identification of zones with even minimal subendothelial dislocation of the coronary vessel layers, the so-called subendothelial dissection, which is another form of separation between the media and adventitia, distinct from the intramural hematoma and the classical endothelial dissection. This subendothelial dissection could be a starting point for the advancement of the atherosclerotic process. Repeated episodes of a sudden raise in blood pressure are present in the history of almost all patients with coronary artery atheromatous plaques and may represent the key element that triggers the destructuration of the endothelium leading to subendothelial dissection. In severe cases, this subendothelial dissection becomes manifest immediately, and the patient presents at an ER with typical chest pain, without any significant luminal narrowing as shown by coronary angiography. In less severe cases this remains clinically silent but may still trigger the future development of an atheromatous process via a complex mechanism involving endothelial dysfunction, alteration of wall nutrition due to compression of vasa vasorum, macrophage accumulation, and increase of the parietal stress leading to non-laminar flow.

CONFLICT OF INTEREST

Nothing to disclose.

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REVIEW

Automatic Segmentation Techniques of the Coronary Artery Using CT Images in Acute Coronary Syndromes

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ABSTRACT

Coronary artery disease represents one of the leading reasons of death worldwide, and acute coronary syndromes are their most devastating consequences. It is extremely important to identify the patients at risk for developing an acute myocardial infarction, and this goal can be achieved using noninvasive imaging techniques. Coronary computed tomography angiography (CCTA) is currently one of the most reliable methods used for assessing the coronary arteries; however, its use in emergency settings is sometimes limited due to time constraints. This paper presents the main characteristics of plaque vulnerability, the role of CCTA in the assessment of vulnerable plaques, and automatic segmentation techniques of the coronary artery tree based on CT angiography images. A detailed inventory of existing methods is given, representing the state-of-the-art of computational methods applied in vascular system segmentation, focusing on the current applications in acute coronary syndromes.

Keywords: image segmentation, computed tomography, pattern recognition coronary artery disease, emergency cases

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ACUTE CORONARY SYNDROMES

Coronary artery disease (CAD) is one of the leading causes of death worldwide, responsible for the death of millions every year.[1] World Health Organization (WHO) statistics show that in 2012, 31% of all deaths were caused by cardiovascular disease, from which 7.4 million were due to coronary heart disease.[2] Acute coronary syndromes (ACS) are among the most severe complications of atherosclerosis, and the majority, although not all, take place due to atheromatous plaque rupture and subsequent thrombosis.[3]

VULNERABLE ATHEROMATOUS PLAQUES

The genesis of the atheroma is triggered by the appearance of a discontinuity in the endothelial layer, followed by an array of complex mechanical, biochemical, and biological mechanisms that will eventually lead to plaque formation.[4–6] The formed atherosclerotic plaque will undergo several pathophysiological changes, including the excessive accumulation of oxidized LDL-cholesterol, enhanced local inflammation, smooth muscle cell proliferation, and extracellular matrix degradation, which will eventually lead to its progression and destabilization.[7]

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In an attempt to define the complications related to atherosclerotic plaques and to find the pathophysiological mechanism of acute coronary syndromes, the concept of "vulnerable plaque" was developed.[8] The definition of the vulnerable coronary plaque comprises an increased propensity towards rupture, erosion, and thrombosis.[9,10]

A vulnerable plaque is described as having a thin fibrous cap and a large necrotic lipid core that initially causes an eccentric vascular remodeling (positive remodeling) followed by luminal stenosis and impaired distal blood flow.[11–13] Other features of unstable coronary lesions include an increased local inflammation,[14] extracellular matrix degradation,[15] neo-vessel formation within the plaque with subsequent hemorrhage,[16,17] as well as calcium formation in the form of spotty calcifications.[18]

Even though the most common fate of an unstable plaque is to rupture, a significant percentage of acute coronary syndromes were shown to be caused by coronary plaque erosion.[19] Lesions that suffer erosions seem to not show the established characteristics of a vulnerable plaque, usually presenting a thick cap, decreased necrotic cores and lower inflammation degree.[20] Thus came the idea that a vulnerable plaque is not as much prone to rupture, but more prone to causing an acute event.[21]

SHEAR STRESS AND VULNERABLE PLAQUES

The complex pathophysiological mechanism of atherosclerosis includes, besides progressive endothelial injury, local inflammation, and vascular remodeling, also hemodynamic alterations.[22] It was shown that there is an increased occurrence of coronary plaques in vascular regions with high shear stress, such as bifurcations or near vascular curvatures.[23] Also, the protrusion of the atheroma in the vessel lumen causes a shift from a normal, laminar flow, with evenly distributed transverse and shear stress, to a turbulent flow.[24] Coronary shear stress (CSS) has been shown to influence the progression of coronary plaques by causing structural and functional changes in the endothelium, enzymatic changes, release of bioactive markers, and gene transcription.[25,26] Low shear stress (LSS) leads to misalignment of the endothelial cells, increased permeability to circulating lipid molecules and inflammatory cytokines, as well as high expression of adhesion molecules, growth factors, and high reactive oxygen species.[22,27–29] In the context of increased systemic cardiovascular risk factors, the dysfunctional endothelium and increased inflammatory status augment the process of plaque growth and cause additional alterations of the endothelial shear stress.[30] High shear stress exposure presents a protective effect on healthy vessels, but if a stenotic lesion is present, it indorses plaque vulnerabilization.[31] High shear stress contributes to plaque destabilization by increased nitric oxide expression and extracellular matrix degradation by stimulating the expression of matrix metalloproteases, increased production of proteolytic enzymes, and apoptosis.[32–34] Furthermore, an increased CSS can stimulate plaque denudation and erosion, which, if associated with an enhanced blood thrombogenicity, lead to acute vessel occlusion and the occurrence of an ACS.[21,35] Shear stress distribution across coronary stenotic lesions appears to be low in the distal region of the plaque, whilst a high stress is mainly present in the proximal part.[36,37] In order to maintain the physiological shear stress, vascular remodeling occurs as an adaptive process,[38] thus a high CSS stimulates an outward remodeling, while a low CSS exposure will lead to an inward remodeling with vessel narrowing.[39]

METHODS FOR THE ASSESSMENT OF VULNERABLE PLAQUE CHARACTERISTICS

There are several established methods for the assessment of biomarkers characteristic for plaque instability, acquired with both invasive and noninvasive techniques.[40] The invasive methods include intravascular ultrasound (IVUS) with its different variations (virtual histology IVUS, iMAP IVUS, and integrated backscatter IVUS), which can assess with high accuracy the total plaque burden, necrotic core, neo-vessel formation, calcifications, as well as the vessel remodeling percentage.[41–43] Optical coherence tomography (OCT), which uses near-infrared light for image acquisition, allows evaluation of the fibrous cap, collagen amount, neoangiogenesis, plaque rupture and thrombus formation; its variant, micro-OCT, is able to offer a histological level of accuracy in the process of plaque component visualization.[21,44,45] Other invasive methods for evaluating unstable coronary plaques include invasive coronary thermography (which measures plaque temperature),[46] near-infrared spectroscopy (NIRS – better visualization of necrotic cores),[47] and also combinations of the above-mentioned methods.[48,49] Coronary computed tomography angiography (CCTA) has emerged as the most used technique for noninvasive plaque evaluation, being able to identify several CT biomarkers for plaque instability.[40] The advantages of this method are that it is noninvasive, it allows the visualization of the complete coronary tree, and it also holds the ability to analyze both the vascular lumen and the wall.[50] Moreover, recent developments have led to an increase in image quality and resolution, by using multiple slice scans with ECG-gat-

ed protocols that allow imaging acquisition in a single heartbeat, during diastole, thus eliminating motion artifacts.[51,52] CCTA displays an increased rule-out capacity for lesion identification and quantification, and studies have shown that its detection accuracy is comparable to invasive methods (IVUS and OCT), even if it does not hold the ability for fibrous cap identification.[21,53,54] Major advantages of the latter are: 3D data collection and visualization, as well as information on arterial calcification and vascular distortion.[55] The markers for plaque vulnerability that are identified by CCTA are the presence and size of the necrotic core (which appears as a hypodense area within the plaque),[56,57] low attenuation plaques,[58] positive remodeling (and calculation of the remodeling index),[59] the presence of the napkin-ring sign,[60] and microcalcification within the plaque (referred to as spotty calcifications).[61,62] CCTA is also able to evaluate the overall degree of calcification of the coronary tree by using the coronary artery calcium score, which has been shown to have a high predictive capacity for major adverse cardiovascular events, being combined with traditional cardiovascular risk factors (c-statistic of 0.93).[63]

Other applications of CCTA include the noninvasive assessment of coronary blood flow and the function significance of coronary lesions, with the use of CT-based fractional flow reserve (CT-FFR),[64,65] as well as the transluminal attenuation gradient through a coronary stenosis.[66] Nevertheless, CCTA has a great potential of being integrated into computational simulation models for coronary flow and fluid dynamics, which will allow the analysis of plaque conduct in physiological and pathological circumstances.[21] Computational models are the sole methods that are currently able to integrate both the external (hemodynamic) and internal (characteristics of plaque) markers for instability in order to achieve a global understanding of the conditions that lead to plaque erosion and rupture with the subsequent occurrence of an acute coronary syndrome.[21,67,68] One of the most important drawbacks of computational simulation models is the increased time needed for image reconstruction, but with recent developments, the time has been reduced from weeks[69] to less than two hours,[70] which will make it possible for computational plaque analysis to be performed as a part of a living vessel.[21]

Accurately identifying coronary plaques is challenging, especially when using noninvasive methods such as CCTA. The problems encountered in the CT analysis of coronary plaques include the presence of non-calcified lesions, small sized vessels, as well as motion artifacts that can be diminished by using ECG-gated CT protocols, multiplanar image acquisition and vessel segmentation, and vascular tree reconstruction techniques.[71,72]

CORONARY TREE SEGMENTATION

The segmentation of vascular trees is a widely researched topic. The literature includes several studies that follow the data-driven approach, namely they treat the notion of the vascular tree in a general way, as a set of interconnected tubular structures, with possible bifurcations and stenoses, but without using any anatomical information. These studies usually concentrate on image quality enhancement for vessel recognition,[73] accurate detection of bifurcations and branches,[74–77] extraction of the most probable centerline,[78,79] vessel diameter estimation,[79,80] and the identification of odd structures.[81,82] Although they are very important in the development of useful medical data processing techniques, these general studies do not take into consideration any anatomical information of a chosen vessel tree.

On the other hand, the literature also includes studies on arterial tree segmentation procedures designed for and tested on specific arterial networks. The major part of such studies focuses on the coronary artery tree (CAT),[83,84] but there are several works developed for the pulmonary arteries,[85–88] cerebral arteries,[89] the carotid artery,[90] and vessels of the retina.[91,92]

SEGMENTATION METHODS FOR CORONARY ARTERIES IN ACUTE CORONARY SYNDROMES

DATA-DRIVEN SEGMENTATION METHODS

Cimen *et al.*[93,94] proposed a method to reconstruct 3D views of the CAT from 2D X-ray images based on a probabilistic mixture model and maximum likelihood estimation. Hu *et al.*[95] proposed a two-step solution for the same problem: in a first stage they extracted artery tree boundaries via minimal path segmentation, then applied maximum a posteriori (MAP) reconstruction using L0-norm and L1-norm priors. Fallavollita and Cheriet[96] provided a 3D coronary artery reconstruction technique from reduced number of 2D X-ray fluoroscopy images that follows the non-rigid movement of arteries, significantly decreasing the reconstruction error.

Gülsün *et al.*[97] employed computed flow fields to eliminate shortcuts in automatically detected blood vessel centerlines, and Kitamura *et al.*[98] used a Markov Random Field framework and AdaBoost classifier for vascular structure segmentation, assisted by topological constraints in order

to avoid inconsistency in the vascular network. Dufour *et al.*[99] combined the Hessian matrix approach and the gray-level hit-or-miss transform to obtain vessel candidate pixels in CTA data, which were later classified using decision trees. Krissian *et al.*[100] established a geodesic level set framework to semi-automatically detect the aorta with its main bifurcations and branches, extract the centerline of each branch, and identify the presence of aortic dissection. Zhou *et al.*[83] introduced the notion of multiscale coronary response, a robust method designed to find coronary arteries via combining 3D multiscale filtering, analysis of the eigenvalues of the Hessian matrices, and expectation maximization (EM) estimation techniques. They also employed a 3D dynamic balloon tracking method to extract complete artery trees. Shang *et al.*[101] defined a vector field based on the eigenanalysis of the Hessian matrix and used it to assist a 3D active contour model in the detection of vascular structures.

MODEL-DRIVEN SEGMENTATION METHODS

The most part of recently developed CAT segmentation methods follows the model-based or the model-driven approach, through involving anatomical models or atlases to improve the segmentation accuracy. Model-based methods start with extracting relevant information from the recorded image data, but in a later processing phase they match the extracted information with predefined atlases or models.

Shin *et al.*[102] employed a manually annotated 2D fluoroscopic X-ray image as reference and proposed a technique to extract coronary vessels from further images via vessel correspondence optimization. Liu *et al.*[103,104] proposed a model-guided centerline extraction method based on ostia detection via directional minimal paths and validated it on the three main branches of the CAT in CTA image data. Sun *et al.*[105] deployed a previously recorded 3D vessel model of the same patient to track the position of various branches within 2D X-ray angiograms, using exploratory shortest paths within the graph model of the vessels. Medrano-Garcia *et al.*[106] built a coronary artery atlas using 122 CTA records of zero calcium score, providing a comprehensive and accurate assessment of the anatomy, including 3D size, geometry, and shape descriptors.

In model-driven methods the identification of vessels and centerlines relies on a priori defined cardiovascular models. For example, the method proposed by Zheng *et al.*[107] automatically segments the heart chambers and then uses an anatomical model to automatically track various branches of the CAT. The model helps the centerline tracing procedure to avoid early termination at severe occlusions and to generate anatomically consistent centerlines.

THE DESIGN OF THE SEGMENTATION METHOD

The main steps of the proposed solution include preprocessing, seed extraction for region growing, data-driven segmentation via robust fuzzy region growing, centerline extraction, model-based validation and vessel identification, and post-processing.[108–112]

THE USE OF CT IN EMERGENCY SETTINGS AND FOR ACUTE CORONARY SYNDROMES

The use of CCTA has been shown to be feasible and useful for patients who present in the emergency department for acute chest pain, but have equivocal laboratory and electrocardiographic (ECG) modifications. The Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT-I) trial included 368 patients with acute chest pain, normal initial troponin values, and no signs of myocardial ischemia on the initial ECG.113 The results showed that emergency CCTA had a high negative predictive value (100% in the absence of CAD, 98% in the presence of significant coronary lesions) in ruling out an acute coronary syndrome.[113]

Another trial on the use of CCTA in the emergency department (ED), which included 1,000 patients with acute chest pain, showed that in comparison to a traditional diagnostic procedure (invasive coronary angiography), the hospitalization index was decreased by 7.6 h (period of stay in the emergency department), and a significantly larger number of patients had been discharged straight from the ED (47% for CCTA vs. 12% for the invasive approach).[114]

As it allows rule-out of acute pulmonary embolism, aortic dissection, and acute coronary syndromes, depiction of the complete coronary anatomy, illustration of the coronary vessel lumen, identification of vulnerable plaque features, as well as the coronary artery calcium score, CCTA is a valuable method for emergency triage and patient management, for the decision-making process and prognosis assessment of patients with coronary artery disease, all in a noninvasive stand-alone procedure.[55,115–117] The noninvasive visualization of plaque characteristics and severity of the coronary artery disease in patients with non-ST elevation acute coronary syndromes at baseline, was shown to predict recurrent adverse events.[118]

CONCLUSIONS

Computational methods can be easily applied in the vascular system for coronary artery tree segmentation using CTA image volumes. This interdisciplinary approach can provide a solid background for a complex assessment of the coronary tree, especially in settings when estimation of the degree of plaque vulnerability can be crucial for the future evolution of the patients.

CONFLICT OF INTEREST

Nothing to declare.

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ORIGINAL RESEARCH

The Assessment of Epicardial Adipose Tissue in Acute Coronary Syndrome Patients. A Systematic Review

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ABSTRACT

Background: This systematic review seeks to evaluate the role of epicardial adipose tissue (EAT), quantified either by thickness, assessed by transthoracic echocardiography, or by volume, assessed by cardiac computed tomography (CT), in the follow-up of patients with acute coronary syndromes (ACS). **Method:** One-hundred forty-four articles were screened, from which 56 were reviewed in full-text. From those, 47 studies were excluded for the following reasons: they did not meet the inclusion criteria; they were either reviews or meta-analyses; the study cohorts included only stable coronary artery disease patients; they did not state a clear and concise study design, endpoints, or follow-up. The final draft included nine studies for systematic evaluation. **Results:** Of the 2,306 patients included in the review, 170 underwent cardiac CT while the remaining 2,136 underwent transthoracic echocardiography for the measurement of EAT. The analysis found that the EAT thickness was significantly associated with major adverse cardiovascular events (MACE) rates during hospitalization (OR: −1.3, 95% CI: 1.05−1.62, p = 0.020) and at three years (HR: 1.524, 95% CI: 1.0−2.2, p = 0.038). The included studies found that EAT was correlated with the following clinical and angiographic risk scores for ACS: GRACE (r = 0.438, p <0.001), TIMI risk score (r = 0.363, p = 0.001), SYNTAX score (r = 0.690, p <0.0001; r = 0.610, p <0.01), and Gensini score (r = 0.438, p = 0.001). There was an inverse correlation between ST-segment resolution of <70% after revascularization and EAT (r = -0.414, p = 0.01), and the myocardial blush grade (r = -0.549, p <0.001). The EF aggregation ranged between 2.65 mm and 4.7 mm within the included studies. **Conclusions:** EAT, evaluated either by echocardiography or cardiac CT, correlates with the severity of coronary lesions, with the clinical and angiographic risk scores for acute coronary syndromes, with indicators for coronary reperfusion, and with short- and long-term MACE rates. Further studies are required to fully elucidate the role of this extensively studied but still novel cardiovascular biomarker as part of a risk prediction tool.

Keywords: epicardial adipose tissue, acute coronary syndromes, echocardiography, cardiac CT

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INTRODUCTION

Acute coronary syndromes remain a leading cause of death worldwide despite the many advances in both preventive strategies and emergency treatment options, including percutaneous coronary interventions.[1]

Several predictors of the severity of coronary artery disease have been established, and, in recent years, attention has been directed towards the role of epicardial adipose tissue (EAT) as a cardiovascular risk factor, as well as the assessment of instability of atherosclerotic coronary plaques.[2]

EAT – ROLE AND PATHOPHYSIOLOGY

Adipose tissue surrounding the heart has several roles, including being an energy provider for myocardial metabolism, thermoregulation, and mechanical protection for both the epicardial coronary vessels and the autonomic innervation of the heart.[3] The metabolic and immunologic effects of EAT remain unclear, although several hypotheses have been suggested, including that of secreting increased quantities of anti- and pro-inflammatory cytokines, regulating the oxidative reactions within the myocardial fibers, as well as influencing the contractility, conductibility, and excitability of the heart.[4]

Furthermore, being a visceral fat and having the same characteristics and behavior as intra-abdominal fat, EAT appears to be one of the extra-vascular culprits associated with the progression and aggravation of atherosclerotic lesions.[5]

The genesis of a coronary atheroma is influenced, in various stages, by the adipose tissue surrounding the heart, from intimal malfunction at an early stage, to plaque erosion and rupture, with subsequent thrombosis and the occurrence of an acute coronary syndrome.[6,7]

Histopathological studies of epicardial fat samples acquired during cardiac surgery have shown that EAT contains several inflammation biomarkers, including tumor necrosis factor-α, interleukins, and chemokines, which might contribute to the development and progression of insulin resistance, and also enhance apoptosis within the coronary plaque and vessel inflammation.[8]

On the other hand, epicardial adipose tissue has beneficial effects by secreting adiponectin — with anti-inflammatory and anti-atherogenic properties and also by stimulating neo-angiogenesis in subjects with chronic coronary occlusions.[8,9]

EAT IN CORONARY ATHEROSCLEROSIS AND ACUTE CORONARY SYNDROMES

EAT has been shown to be linked with the presence and severity of coronary atherosclerotic lesions.[10,11] Subjects with an increased EAT, assessed either by echocardiography or cardiac CT, have a more severe extension of coronary atherosclerosis, and EAT is also linked to the overall plaque burden and cardiovascular risk factors.[12–14] Furthermore, the incidence of myocardial infarction seems to be directly proportional to the increase in epicardial fat, which is also related to a higher rate of major adverse cardiovascular events in subjects with known coronary artery disease (CAD).[15,16] Due to its paracrine properties, by secreting serum inflammatory biomarkers EAT brings a significant contribution to the vulnerability of the coronary atheromatous plaque, either by local inflammation or by stimulating neo-angiogenesis and the development of vasa-vasorum and subsequent intra-plaque hemorrhage, plaque rupture and thrombosis.[15,17,18] Patients without chest pain who present with major adverse cardiovascular events have a bigger epicardial fat volume compared to event-free patients.[19] The coronary artery calcium score, a marker of CAD severity, has a positive correlation with EAT in patients with both obstructive and non-obstructive CAD. An increased EAT volume, together with low attenuation plaques with the presence of a napkin-ring sign, are correlated with a higher risk of future acute coronary events in non-obese subjects.[20,21] Moreover, the thickness of the epicardial fat has been shown to be closely linked to the presence of multi-vessel CAD in patients with acute myocardial infarction.[22]

EAT – METHODS OF ASSESSMENT AND IMAGING TECHNIQUES

The imaging methods for assessing epicardial fat include 2D transthoracic echocardiography (TTE), native cardiac computed tomography and magnetic resonance imaging (MRI).[23] MRI remains the gold-standard technique for measuring not only the adipose tissue surrounding the heart but also the total visceral fat. Despite the fact that MRI allows the acquisition of high-resolution images and the possibility of quantifying EAT volume, it is not feasible in an emergency clinical setting, as it is more costly and less available than other methods.[24]

Transthoracic 2-dimensional echocardiography is a low-cost and easily available, non-invasive method that allows the quantification of epicardial fat. It has been proven to be as useful as more advanced imaging meth-

ods such as CT or MRI.[25] The 2-D TTE measurement of epicardial fat thickness is expressed in millimeters and is performed with the patient in a lateral decubitus position, at the level of the free wall of the right ventricle, from a parasternal long axis view, in three consecutive cardiac cycles, at the end-diastolic period.[26] EAT is illustrated on TTE as a hypoechoic space between the epicardium and pericardium. The consensus of opinion is that a value of >5 mm should be considered suggestive of an increased EAT.[23,26–29] TTE assessment of EAT has several limitations, including inter- and intra-observer variability, as well as the location of epicardial fat on the surface of the heart and the phases of the cardiac cycle in which the measurements are done.[30] Further drawbacks include problems in discriminating between epicardial and pericardial material or fluid in the pericardial sack.[26]

Cardiac computed tomography (CT) examination can accurately assess the volume, total area, and thickness of epicardial adipose tissue, and concomitantly it can evaluate coronary atheromas and their degree of calcification.[23,31] EAT can be measured by CT at the level of the free wall of the right ventricle, in the atrioventricular and interventricular spaces, and also in the proximity of the main coronary vessels, when it is regularly associated with coronary calcium score evaluation.[23] Similarly to TTE assessment, EAT volume measured by CT does not have a precise range considered as normal. A study (2008) stated the average EAT volume was 110 ± 41 ml in females and 137 ± 53 ml in males,[32] and Shmilovich *et al.* (2011) reported that epicardial fat volume indexed to the whole body surface area, at the 95th percentile, was 68.1 ml/m2.[33] The limitations of this technique are represented by the difficulty of achieving standard location limits for the measurements and by the inter-observational variability.[34,35]

MATERIALS AND METHOD

SEARCH STRATEGY

The study was conducted in agreement with the PRISMA methodology (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[36]

The literature search was centered on accessing all published articles related to epicardial adipose tissue evaluation in acute coronary syndrome patients, either by TTE or cardiac CT.

Two investigators searched the PubMed/Medline and Thomson Reuters scientific databases. The comprehensive search strategy comprised the following medical subject headings (MeSH) terms: "epicardial fat AND acute coronary syndromes", "epicardial adipose tissue AND acute coronary syndromes", "epicardial fat thickness", "epicardial fat volume".

DATA EXTRACTION AND ANALYSIS

The two investigators extracted the following data from the selected manuscripts: the number of subjects included in the study, age, gender, type of acute coronary syndrome for which they had been admitted, the follow-up period, the primary and secondary endpoints, the method of assessment of EAT, the mean values (TTE) and volume (cardiac CT) of EAT respectively, as well as the presence of diabetes, smoking, hypertension history, obesity. Furthermore, whenever available, data extraction included the odds ratios (OR) and hazard ratios (HR) when appropriate for the endpoints of each study.

STUDY QUALITY ASSESSMENT AND ELIGIBILITY CONDITIONS

No study was excluded for motives of decreased study quality, but the selected studies presented a concise portrayal of the inclusion and exclusion criteria, the endpoints and the follow-up periods, as well as a precise method for assessing the EAT, irrespective of the non-invasive method that had been used (TTE or cardiac CT). Articles that enrolled only subjects with stable CAD were excluded from the search. Also, we excluded various articles such as case reports, case series, reviews, editorials, letters, as well as manuscripts that were not available in full-text form. The search filter also excluded species other than humans.

RESULTS

One-hundred forty-four manuscripts were screened in total, out of which 56 were identified using the described search strategy and were reviewed in a full-text form. From those, 47 studies were excluded for not meeting the inclusion criteria. These were either reviews or meta-analyses, the study cohorts included only stable coronary artery disease patients, or they did not state a clear and concise study design, endpoints or follow-up (Figure 1). The final draft included nine studies for systematic evaluation: one study that used CT for EAT assessment, and eight manuscripts that assessed EAT with TTE.

In all, 2,306 patients were included, of which 170 subjects underwent cardiac CT for EAT evaluation,[37] while the remaining 2,136 patients underwent TTE measure-

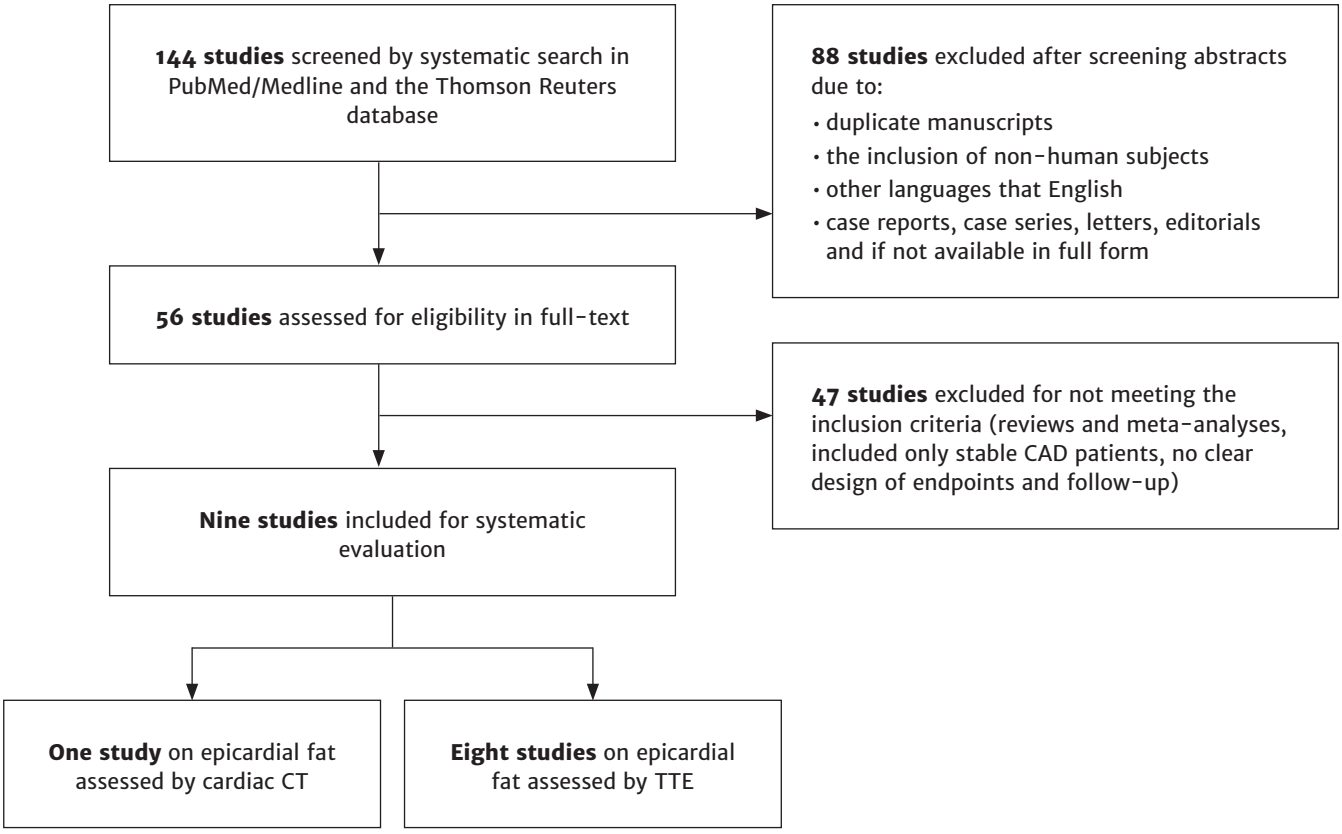

FIGURE 1. Diagram of the search protocol and results of manuscript selection

ment of EAT.[38–45] Table 1 presents a summary of the included manuscripts. All systematized manuscripts contain a concise and clear portrayal of the inclusion and exclusion criteria and the method for assessing EAT, either through cardiac CT or TTE (Table 1). All studies enrolled patients with acute coronary syndromes. Six of the nine studies used, as one of the main exclusion criteria, previous revascularization therapies, either by coronary artery bypass grafting or percutaneous coronary intervention.

CHARACTERISTICS OF THE STUDY POPULATIONS

The overall characteristics of the patients included in the nine study cohorts, including cardiovascular risk factors and gender distribution, are listed in Table 2.

STATISTICAL ANALYSIS AND STUDY DESIGN OF THE SELECTED MANUSCRIPTS

There was a diversity of study methodology and statistical approaches used in the selected manuscripts. Four studies were retrospective and calculated odds ratios based on multivariate logistic regression. From the five prospective observational studies, only one used Cox proportional hazards models for the prediction of major adverse cardiovascular events (MACE) rates during the three-year follow-up.[42] Most researchers (n = 6) used the Receiver Operator Characteristics (ROC) curve and the area under the curve for the determination of the cut-off value for EAT values that predicted the study outcome.[37–41,45] All selected articles used Spearman or Pearson correlation coefficient statistics for evaluating the link between epicardial fat and other clinical and laboratory variables.

STUDY ENDPOINTS AND RESEARCH HYPOTHESES

EAT and MACE

Two manuscripts examined the prognostic value of EAT, and the endpoints included the in-hospital MACE rates.[40] One study42 had a three-year follow-up period, with major adverse cardiovascular events as a primary endpoint. Both survival studies included multivariate adjustments for cardiovascular risk factors (smoking, diabetes, age) as well as medical history (previous cardiovascular and

TABLE 1. Summary of the included studies

Authors (*ref)	Year	Inclusion criteria	Exclusion criteria	Follow-up	Research hypothesis
Studies that assess the EFV (ml) by using cardiac CT					
Harada *et al.*[37]	2011	ACS patients (STEMI and NSTEMI)	• previous revascularization (CABG or PCI)	None	Higher EFV in patients with ACS
Studies that assess EFT (mm) by using transthoracic echocardiography					
Altun *et al.*[38]	2013	ACS patients (STEMI and NSTEMI)	• poor quality images on TTE • history of CABG • CKD • severe valvular disease	None	Correlation of EFT with GRACE and SYNTAX scores
Tanindi *et al.*[39]	2015	• stable angina patients • ACS patients	• previous revascularization (CABG or PCI) • pericardial effusion • more than moderate valvular disease • poor quality images on TTE	None	EFT with impaired coronary perfusion evaluated with MBG and TCF
Wang *et al.*[40]	2014	AMI patients with: • normal thoracic shape • sinus rhythm • no severe respiratory diseases	• previous revascularization (CABG or PCI) • CKD with GFR <30 ml/min • severe hydro-pericardium • poor quality images on TTE	None	Composite of major in-hospital events – cardiac death, acute heart failure, repeated revascularization, recurrent MI or ischemia
Sen *et al.*[41]	2015	STEMI patients undergoing PCI	• recent MI • previous revascularization (CABG or PCI) • presentation after >12h from symptom onset • severe hepatic and kidney disorders • neoplastic diseases	None	Correlation between EFT and IRA patency at presentation evaluated with the TIMI flow grading system
Tscharre *et al.*[42]	2016	ACS patients (STEMI and NSTEMI)	• poor quality images on TTE • the impossibility of obtaining the long parasternal axis view on TTE	3 years	MACE rates (cardiovascular death, non-fatal MI, non-fatal stroke)
Gul *et al.*[43]	2015	Patients with first occurrence of NSTEMI	• chronic pulmonary and hepatic disorders • systemic inflammatory diseases • chronic myopathies • CKD (creatinine >2.5 mg/dl) • myocarditis and cardiomyopathies • congestive heart failure	None	Correlation between EFT and GRACE score
Özcan *et al.*[44]	2013	NSTEMI and USAP patients	• rheumatic diseases • neoplastic disorders • active infections • persistent ST elevation MI • history of HF with low EF <40% • poor quality images on TTE	None	Association between EFT and TMI risk score
Zencirci *et al.*[45]	2014	First acute STEMI patients who underwent primary PCI	• left ventricular hypertrophy (ECG Sokolow-Lyon index of >35 mV) • left bundle branch block • temporary or permanent pacing	None	Relationship between ST-segment resolution after pPCI and EFT

EFV – epicardial fat volume (ml); EFT – epicardial fat thickness; CABG – coronary by-pass grafting; PCI – percutaneous coronary intervention; CAD – coronary artery disease; ACS – acute coronary syndromes; CKD – chronic kidney disease; BMI- body mass index; TTE – transthoracic echocardiography; MBG – myocardial blush grade; TCF – thrombolysis in myocardial infarction frame count; IRA – infarct-related artery; USAP –unstable angina pectoris.

TABLE 2. Patient characteristics of the study population in the included manuscripts

Authors (*ref)	Total number of subjects enrolled	Gender (male) n (%)	Age (years)	BMI (kg/m²)	Diabetes n (%)	Smoking n (%)	Hypertension n (%)	Dyslipidemia n (%)
Studies that assess the EFV (ml) by using cardiac CT								
Harada *et al.*[37]	170	120 (70.5%)	63.5 ± 11.5	24.25 ± 3.25	nr	60 (35.2%)	nr	nr
Studies that assess EFT (mm) by using transthoracic echocardiography								
Altun *et al.*[38]	65	60 (92.3%)	57.4 ± 12.2	26.0 ± 2.07	22 (33.8%)	nr	27 (41.5%)	nr
Tanindi *et al.*[39]	200	160 (72.3%)	60.66 ± 13.33	27.7 ± 3.2	64 (28.9%)	99 (44.7%)	119 (53.8%)	107 (48.4%)
Wang *et al.*[40]	373	310 (83.1%)	66 ± 12	nr	99 (26.5%)	194 (52.0%)	209 (56%)	nr
Sen *et al.*[41]	640	523 (81.7%)	53.9 ± 9.7	26.0 ± 4.5	336 (52.5%)	354 (55.3%)	286 (44.6%)	305 (47.6%)
Tscharre *et al.*[42]	438	293 (66.9%)	nr	nr	nr	nr	nr	nr
Gul *et al.*[43]	162	115 (70.9%)	63.9 ± 12.8	27.6 ± 4.05	54 (33.3%)	85 (52.4%)	84 (51.8%)	nr
Özcan *et al.*[44]	144	101 (70.1%)	62.55 ± 11.4	28.1 ± 4.1	49 (34.0%)	71 (49.3%)	76 (52.7%)	nr
Zencirci *et al.*[45]	114	99 (86.8%)	54 ± 10	27.65 ± 3.55	23 (20.1%)	63 (55.2%)	40 (35.0%)	nr

Values are listed as mean ± standard deviation, or as a median
nr – not reported

TABLE 3. Prognostic value of epicardial fat thickness assessed by transthoracic echocardiography

Authors (*ref)	Time of Endpoint evaluation	Outcome	Events n (%)	EFT aggregation	OR (95% CI)	HR (95% CI)	P value	Multivariate Adjustments
Wang *et al.*[40]	Hospitalization index	In-hospital MACE	55 (14.7%)	4.7 mm	1.3 (1.05–1.62)	–	0.020	Diabetes, smoking, previous myocardial infarction, age
Tscharre *et al.*[42]	3 years	MACE	64 (14.6%)	2.65 mm	–	1.524 (1.0–2.2)	0.038	Statin therapy, age, AF, Previous MI, previous stroke, HF, diabetes

MACE – major adverse cardiovascular events; MI – myocardial infarction; HF – heart failure

TABLE 4. EFT and risk scores for acute coronary syndrome

Study	Risk score	Risk score value	EFT aggregation	Correlation coefficient r/β	P value
Altun *et al.*[38]	GRACE	101.8 ± 33.1	5.5 mm	0.224	0.072
	SYNTAX	11.5 ± 5.6	5.5 mm	0.690	<0.0001
Tanindi *et al.*[39]	MBG	1.7 ± 1.16	>7 mm	-0.549	<0.001
	TFC	35.02 ± 7.7	>7 mm	0.757	<0.001
Sen *et al.*[41]	TIMI flow	0, 1, 2 – impaired coronary flow	5.6 ± 1.84 mm	nr	0.001
Gul *et al.*[43]	GRACE	nr	4.68 mm	0.438	<0.001
Özcan *et al.*[44]	TIMI RS	5.2	8.2 ± 2.1 mm	0.363	0.001
	Gensini	54.3 ± 17.5	8.2 ± 2.1 mm	0.442	0.001
Zencirci *et al.*[45]	ST segment resolution after PCI (ΔSTR)	<70%	5.5 ± 2 mm	-0.414	0.01
Wang *et al.*[40]	SYNTAX	≥33	4.7 mm	0.610	<0.01

GRACE – global registry of acute coronary events risk score; SYNTAX -; MGB – myocardial blush grade; TFC – TIMI frame count; nr – not reported; TIMI RS – thrombolysis in myocardial infarction risk score; PCI – percutaneous coronary intervention; ΔSTR – difference between the sum of ST segment elevations before and after revascularization

cerebrovascular events, heart failure) (Table 3). Wang *et al.* (2014) showed that there is a significantly higher rate of MACE during hospitalization for acute myocardial infarction in patients with an EAT thickness of >4.7 mm (p = 0.02) after multivariate adjustments.[40] The other study on the prognostic value of EAT, on ST-elevation myocardial infarction (STEMI) versus non-ST-elevation myocardial infarction (NSTEMI) patients, revealed that a median EAT thickness of 2.6 mm (interquartile range 2.00–3.00) had a significant predictive capacity for the primary endpoint on both univariate (HR: 1.479, 95% CI: 1.192–1.953, p = 0.006) and multivariate (HR: 1.524, 95% CI: 1.011–2.267, p = 0.038) Cox regression analysis.[42]

EAT and ACS risk scores

Seven manuscripts evaluated the correlation between EAT (measured with TTE) and various ACS risk scores (Table 4).[38–41,43–45] Zencirci *et al.* (2014) hypothesized that there is an inverse association between the EAT and the ST-segment resolution following primary PCI for acute STEMI.[45] Other studied risk scores are the SYNTAX score for coronary atherosclerosis severity, the GRACE and TIMI risk scores for survival following an acute cardiac event, and also indicators for coronary perfusion after PCI (TIMI flow, myocardial blush grade – MBG, and TIMI frame count – TFC) (Table 4).

The overall results of the manuscripts that evaluated risk scores state that there are statistically significant correlations between an increased EAT thickness and enhanced integer values of the calculated risk scores and low perfusion indicators.

EAT and acute coronary syndromes

Of the 2,306 patients, 1,527 presented with STEMI, 378 with NSTEMI, and thirty-four with unstable angina pectoris. Furthermore, two of the manuscripts included, in addition to patients with ACS, stable angina pectoris patients or subjects with suspected CAD, which acted as a control group.[37,39] Harada *et al.* (2011) evaluated EAT using cardiac CT and compared epicardial fat volume (EFV, ml) in subjects with ACS (n = 80) and controls (n = 90). There was no significant coronary artery stenosis, and healthy individuals had a significantly lower EFV compared to the case lot (p <0.001). Tanindi *et al.* (2015) showed that patients with AMI have a significantly higher EAT thickness compared to unstable angina or stable CAD patients (p <0.001)[39] (Table 5).

EAT assessed by TTE was variable among study measurements, the mean ranging from a minimum of 2.65 mm, to a maximum of 8.5 ± 1.4 mm (Table 5).

DISCUSSIONS

Although study design in the available research articles was not constant, the prognostic value of EAT in ACS and the possible correlations between EAT and ACS risk scores and coronary perfusion indicators were appraised. Despite not being consistent, the results indicated that EAT tends to negatively impact the outcome, the risk of further adverse events, and the success of coronary revascularization procedures.

The role of epicardial fatty tissue has been extensively studied, and its pathophysiology is now better known, showing both positive and negative bearings on the development and progression of CAD.[3–9]

TABLE 5. Epicardial fat thickness or volume in acute coronary syndromes

Authors	STEMI		NSTEMI		USAP		Total ACS		Stable SAP/controls*		P value
	n	EF	n	EF	n	EF	n	EF	n	EF	
Harada *et al.*[37]	51	na	29	na	na	-	80	117 ± 47 ml	90	95 ± 33 ml	<0.001 (ACS vs. Controls)
Altun *et al.*[38]	40	na	25	na	na	-	65	5.5 ± 0.5 mm	na	-	na
Tanindi *et al.*[39]	16	8.5 ± 1.4 mm**	17	8.5 ± 1.4 mm**	34	6.3 ± 1.8 mm	67	7.4 ± 1.6 mm	133	5.4 ± 1.9 mm	<0.001 (SAP-USAP vs. SAP-AMI vs. USAP-AMI)***
Wang *et al.*[40]	373	4.5 ± 1.05 mm	na	-	na	-	na	-	na	-	na
Sen *et al.*[41]	640	5.26 ± 1.96 mm	na	-	na	-	na	-	na	-	na
Tscharre *et al.*[42]	293	nr	145	-	na	-	528	2.65 mm	na	-	na
Gul *et al.*[43]	nr	-	162	5.0 ± 1.15 mm	na	-	na	-	na	-	na
Özcan *et al.*[44]	nr	-	na	-	na	-	144	7.2 ± 2.15 mm	na	-	na
Zencirci *et al.*[45]	114	4.65 ± 1.85 mm	na	-	na	-	na	-	na	-	na

na – not available; STEMI – ST-elevation myocardial infarction; NSTEMI – non-ST elevation myocardial infarction; USAP – unstable angina pectoris; ACS – Acute coronary syndrome; SAP – stable angina pectoris; EF – epicardial fat assessed either as volume (ml) or as thickness (mm);
* Controls – patients with no significant coronary artery stenosis, with or without chest pain.
** The study analysed patients with acute myocardial infarction without differentiating between STEMI and NSTEMI patients, the mean EF is expressed for the total AMI patients (STEMI+NSTEM)
*** AMI includes both STEMI and NSTEMI.

There is evidence that EAT is in direct relation with the body mass index and the presence of obesity, and it is also increased in patients with metabolic syndromes.[32,46–48]

Epicardial fat has also been linked to an increased systemic inflammatory status in type 2 diabetes patients with acute myocardial infarction, and in patients with a higher EAT thickness it was associated with an enhanced left ventricular remodeling process and lower ejection fraction at six months.[49]

Further studies are needed to elucidate the effect of a reduction of EAT on risk diminution, although some researchers have proved that the regression of EF can be achieved with weight loss measures, dietary modifications, regular physical exercise, and lipid-lowering therapies with statins and ezetimibe.[28,50–52]

Coronary artery plaque burden was shown to be associated with a higher quantity of epicardial fat.[53] Several studies have stated that there is a relationship between an increased EAT and plaque vulnerability.[54–56] Noninvasive imaging biomarkers, identified by computed tomography coronary angiography, include the coronary artery calcium score, low-density plaques with an increased necrotic core, the presence of spotty calcifications and the napkin-ring sign.[57,58] Biomarkers for plaque instability, detected by advanced imaging methods such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) include the thick fibrous cap atheroma, fibrous cap thickness, the extent of intra-plaque macrophage deposition, vessel extension and rupture.[59–61]

Two of the largest EAT studies included cohorts of patients with no cardiovascular disease. The MESA trial/study showed a positive association between the coronary artery calcium score and the EFV assessed by CT, but the Heinz-Nixdorf Recall study found that EAT predicted an excessive risk for coronary events, independently of the calcium score and classic cardiovascular risk factors.[15,62] The studies analyzed in our systematic review did not include manuscripts that had evaluated coronary calcium or vulnerable plaque biomarkers, as these did not meet the inclusion criteria.

EAT AND ACS RISK SCORES

Ongoing research is being undertaken to identify additional risk markers which could predict future cardiovascular events after an ACS. Several risk scores have been developed for risk assessment in ACS, including GRACE (Global Registry of Acute Coronary Events), SYNTAX, the TIMI risk score, all of which have been validated in predicting MACE rates.[63–65]

Our systematic analysis showed that several investigations have studied the correlation between EAT thickness and established ACS risk scores.[38,43–45] One study[43] found a significant association between EAT and GRACE scores ($p < 0.001$), though this was not corroborated by other studies.[38] The angiographic SYNTAX score for coronary lesion severity and the clinical TIMI risk score for adverse coronary events were also found to be significantly linked with EAT.[38,40,44] Being associated with ACS severity and risk prediction scores and connected with markers that express an increased patient vulnerability for acute coronary syndromes, at the same time being proven as an independent CAD,[53] EAT qualifies as a candidate for inclusion in current ACS risk scores.

One of the included studies hypothesized that an increased thickness of the epicardial fat is linked to impairment in the ST-segment resolution following revascularization in acute MI patients.[45] ST-segment resolution is a surrogate for tissue level reperfusion, illustrating the no-reflow phenomenon after primary PCI, and the lack of ST-segment regression after PCI has been proved to be a predictor for in-hospital mortality rates.[66,67]

EAT AND MAJOR ADVERSE CARDIOVASCULAR EVENTS

Epicardial fat might provide supplementary evidence regarding future cardiac events in patients with acute coronary syndromes. It is well known that an increased systemic inflammatory status leads to a poorer outcome in patients with STEMI.[68,69] Being an active metabolic tissue that secretes inflammatory cytokines and chemokines, epicardial fat could contribute to the overall inflammation, thus negatively impacting the outcome of ACS patients.4 EAT thickness can be used as a predictor of MACE, including MI and cardiovascular death.[70] Furthermore, an increased EF volume was shown to predict MI or cardiovascular death in patients suspected of CAD.[71] In a study that compared MACE individuals with event-free controls, patients with MACE had a significantly higher EF volume, even after multivariate adjustments for age, BMI, coronary calcium score, and Framingham risk score.[72]

The present review included two studies that evaluated the MACE rate with different endpoint evaluation times.[40,42] Wang *et al.* (2014) evaluated the influence of EAT thickness on the rate of major events during hospitalization, and after multivariate adjustments, concluded that the cut-off value for epicardial fat thickness (EFT) was 4.7 mm for predicting the primary endpoint (OR: 0.13, 95% CI: 1.05–1.62).[40] Tscharre *et al.* (2016) concluded that EFT was predictive for MACE rates during a follow-up period of three years (HR: 1.524, 95% CI: 1.0–2.2).[42]

EAT — ECHOCARDIOGRAPHY VERSUS CARDIAC CT

EAT, appraised by echocardiography, was shown to be associated with the EFV assessed by CT.[25,26] While cardiac CT and MRI allow the volumetric assessment of endocardial adipose tissue, echocardiography determines only the regional thickness of EAT. Since a close relationship has been shown to exist between EAT volume and thickness, echocardiographic measurement of EAT is preferable due to low costs, high availability and reproducibility, noninvasiveness, and no exposure to radiation.[73]

STUDY LIMITATIONS

Although initially we sought to conduct a systematic review of studies that assessed EAT using echocardiography in comparison with cardiac CT, in the course of our search we found that there were few studies that used CT in emergency clinical settings for diagnosing and managing acute coronary syndromes.

Secondly, cut-off values for epicardial fat have not been reproduced, due mainly to the fact that there are assorted descriptions of EF aggregation reported in the literature.

The power of this systematic review, in common with similar studies, is limited by the quality of the incorporated manuscripts, the study designs, and the statistical methods that had been used.

Regardless of these limitations, we are of the opinion that the study provides insights into the role of EAT in diagnosing and managing patients with acute coronary syndromes.

CONCLUSIONS

Epicardial adipose tissue, evaluated either by thickness using echocardiography, or by volume using cardiac CT, is associated with the severity of coronary stenosis, with the clinical and angiographic risk scores for acute coronary syndromes, and also with indicators of coronary reperfusion. Information provided by epicardial fat tissue can be used as predictors of major cardiovascular events in patients with acute coronary syndromes, over both short and long term.

CONFLICT OF INTEREST

Nothing to declare.

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ORIGINAL RESEARCH

Regional Wall Motion Abnormalities and Ventricular Function in Acute Peri-Myocarditis

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ABSTRACT

Introduction: Myocardial involvement in pericardial diseases and the effect of pericardial inflammation and effusion on the function of the left ventricle (LV) is still a controversial issue. The present study aimed to evaluate LV regional wall abnormalities in patients with acute peri-myocarditis, using 3D echocardiographic assessment of LV contractility. **Material and methods:** The study included 56 subjects divided into two groups: Group 1 – 28 subjects with acute peri-myocarditis and Group 2 – 28 healthy controls. All subjects underwent a complete clinical examination, including laboratory tests. 3D echocardiography was performed to assess the left ventricular end-diastolic (EDV) and end-systolic volumes (ESV), and to calculate specific indexes for global and regional ventricular contractility, such as the index of contraction amplitude (ICA) and the regional index of contraction amplitude (RICA) for each segment corresponding to the region affected by peri- myocarditis. **Results:** 3D echocardiography showed no differences between the groups regarding the EDV (p = 0.2), the LV ejection fraction (Group 1: 55.82% ± 3.36% vs. Group 2: 57.21% ± 4.69%, p = 0.2). The ESV however, was significantly higher in Group 1 compared to Group 2 (55.78 ± 5.45 ml vs. 52.20 ± 6.43 ml, p = 0.04). ICA was similar between the groups (p = 0.2). However, the RICA was significantly lower in Group 1 compared to Group 2 (2.27 ± 0.63 vs. 5.16 ± 0.54, p <0.0001). **Conclusions:** The extension of the inflammatory process from the pericardium to the adjacent myocardial layer may affect the contractility of the LV. A good association exists between peri-myocarditis and the regional contractility abnormalities of the LV.

Keywords: peri-myocarditis, echocardiography, original index of contraction, amplitude

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INTRODUCTION

Pericardial diseases represent one of the most underdiagnosed cardiovascular conditions in clinical practice due to the absence of well-established diagnostic criteria.[1,2] This condition has been reported in approximately 1% of hospitalized patients and 5% of necropsies performed in general hospitals. The most common causes of acute pericarditis are represented by a viral infection, frequently labeled as idiopathic due to the difficult identification of the involved virus, followed by bacterial or parasitic infections.[3] Systemic inflammatory diseases, neoplasms, and traumas may represent the underlying cause of the acute inflammation of the peri- and myo-

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cardium.[4] Although pericarditis is considered a benign condition, its acute complications, such as cardiac tamponade or involvement of the myocardial layer, may lead to life-threatening conditions such as acute heart failure or death.[5] However, although a vast number of studies have investigated the clinical aspects of pericardial diseases, surprisingly few of them have analyzed the extension of the inflammatory process from the pericardium into the myocardium.[6]

The first-line diagnostic means for the recognition of peri-myocardial diseases are echocardiography and cardiac magnetic resonance (CMR), whereas computed tomography (CT) is considered a second-line option.[7,8] The recent improvement in different diagnostic techniques, notably echocardiography, and longer survival times have led to an increase in the recognition of pericardial diseases in recent years.[9]

The current literature mentions the possible effects of pericardial effusion accumulation on the general function of the heart, however, it does not state its exact influence on the regional wall motion abnormalities of the left ventricle (LV).

Our hypothesis is that the extension of the inflammatory process from the pericardium to the myocardial layer in acute peri-myocarditis may lead to the alteration of ventricular wall motion, involving the regions near to the affected pericardium.

The aim of our study was to evaluate regional ventricular wall motion abnormalities in patients with acute peri-myocarditis using three-dimensional echocardiography.

MATERIAL AND METHODS

STUDY DESIGN

This is a prospective observational study, conducted at the Cardiology Clinic of the County Emergency Clinical Hospital of Tîrgu Mureș, Romania, in which fifty-six subjects were enrolled and divided into two groups: Group 1 – 28 patients diagnosed with acute peri-myocarditis; Group 2 – 28 healthy subjects, without any signs or symptoms of peri-myocarditis. The study protocol was approved by the Ethical Committee of the County Emergency Clinical Hospital of Tîrgu Mureș, Romania, and all patients signed a written informed consent form before enrollment.

INCLUSION CRITERIA

The inclusion criteria were the presence of clinical symptoms of acute chest pain that worsens on breathing or when changing the position of the body, associated with at least one of the following:

- pericardial friction rub;
- PR- or ST-segment modifications on the 12-lead electrocardiogram (ECG), suggestive for pericarditis;
- evidence of pericardial effusion/thickening of the pericardium with at least 5 m on transthoracic ECG.

EXCLUSION CRITERIA

- patients presenting with atherosclerotic or thrombotic coronary lesions;
- unstable angina;
- post-infarction angina;
- recent myocardial infarction;
- congestive heart failure;
- cancers;
- history of heart surgery;
- NYHA functional class 4;
- severe valve disease;
- severe renal, hepatic, hematologic or pulmonary disease;
- age below 18 years.

METHODOLOGY

Clinical data

The history and clinical data of all enrolled subjects were recorded, including age, gender, cardiovascular risk factors (diabetes mellitus, hypertension, dyslipidemia, smoking, family history of cardiovascular diseases), and personal history (stable/unstable angina, myocardial infarction, ischemic heart disease, stroke).

Paraclinical data

Standard 12-lead resting ECG was obtained from all patients, documenting the existence of any abnormality of the repolarization phase.

Echocardiography was performed using an Agilent Sonos 4500 ultrasound imaging system (Philips, Amsterdam, the Netherlands), and the following parameters were recorded:

- pericardial thickening;
- amount and location of pericardial fluid;
- left ventricular volumes;
- left ventricular ejection fraction;
- contraction abnormalities.

Three-dimensional echocardiography was also performed for the assessment of the following:

- total and regional left ventricular ejection fraction;
- detection of regional wall motion abnormalities;
- calculation of the end-diastolic and end-systolic volume;
- evaluation of the regions with wall motion abnormalities (contraction asynchronies);
- measurement of the delay in maximal global systolic contraction amplitude, assessment of the index of contraction amplitude (ICA);
- regional index of contraction amplitude (RICA);
- the volumetric curve for each ventricular region;
- polar mapping of the delay in maximal systolic contraction amplitude.

For patients in Group 2, the contractility index was calculated for each ventricular region corresponding to the region affected by peri-myocarditis compared to the regions without peri-myocarditis.

As the clinical, laboratory, and ECG findings in acute peri-myocarditis may be similar to ischemic coronary disease, invasive coronary angiography was performed in cases when an acute coronary syndrome could not be ruled out by noninvasive examination.

The study has been carried out in accordance with the code of ethics of the World Medical Association's Declaration of Helsinki. All patients gave written informed consent, and the study protocol was approved by the ethics committee of the institution where the study was conducted.

STATISTICAL ANALYSIS

JMP statistical software was used for statistical analysis. The Mann-Whitney test was used for continuous values expressed as means (SD). Fisher's exact test or the Chi-square test was used for the comparison of categorical variables expressed as percentages. The level of significance was set at $\alpha = 0.05$.

RESULTS

BASELINE AND CLINICAL CHARACTERISTICS

There was no significant difference between the two study groups regarding age, with a mean of 55.28 ± 11.28 years in Group 1 vs. 53.6 ± 10.51 years in Group 2 (p = 0.5). There was a preponderance of female subjects in both study groups (p = 0.1). The presence of cardiovascular risk factors and comorbidities was similar in the two study groups in respect of diabetes mellitus (p = 0.7), hypertension (p = 0.5), obesity (p = 0.7), and smoking (p = 0.2) (Table 1).

ECHOCARDIOGRAPHIC FINDINGS

M-mode and two-dimensional echocardiography revealed thickening of the pericardium. The localization of the pericardial effusion was mainly in the lateral region of the left ventricle (n = 12, 42.8%), followed by the inferior region of the left ventricle (n = 10, 35.7%), and the apical region (n = 6, 21.4%). M-mode and two-dimensional echocardiography showed no pathological findings in Group 2.

Three-dimensional echocardiographic analysis of the global and regional contractility showed no significant difference between the two study groups in terms of end-diastolic volume (EDV), with a mean of 123.14 ± 11.87 ml in Group 1 vs. 126.25 ± 7.2 ml in Group 2 (p = 0.2) (Figure 1A).

The end-systolic volume (ESV) was significantly higher in patients from Group 1 with 55.78 ± 5.45 ml (95% CI: 53.67–57.90) vs. 52.50 ± 6.43 ml (95% CI: 50.00–54.99) in Group 2 (p = 0.04) (Figure 1B).

There was no significant difference in respect of the calculated global ejection fraction (EF) between the study

TABLE 1. Baseline characteristics of the study groups

Laboratory findings	Group 1 n = 28	Group 2 n = 28	p value
Age	55.28 ± 11.28	53.60 ± 10.51	0.5
Female gender, n (%)	19 (67.85%)	18 (64.28%)	0.1
Diabetes mellitus, n (%)	9 (32.14%)	7 (25.00%)	0.7
Hypertension, n (%)	10 (35.71%)	7 (25.00%)	0.5
Obesity, n (%)	5 (17.85%)	7 (25.00%)	0.7
Smoking (past or present), n (%)	11 (39.28%)	8 (28.57%)	0.2

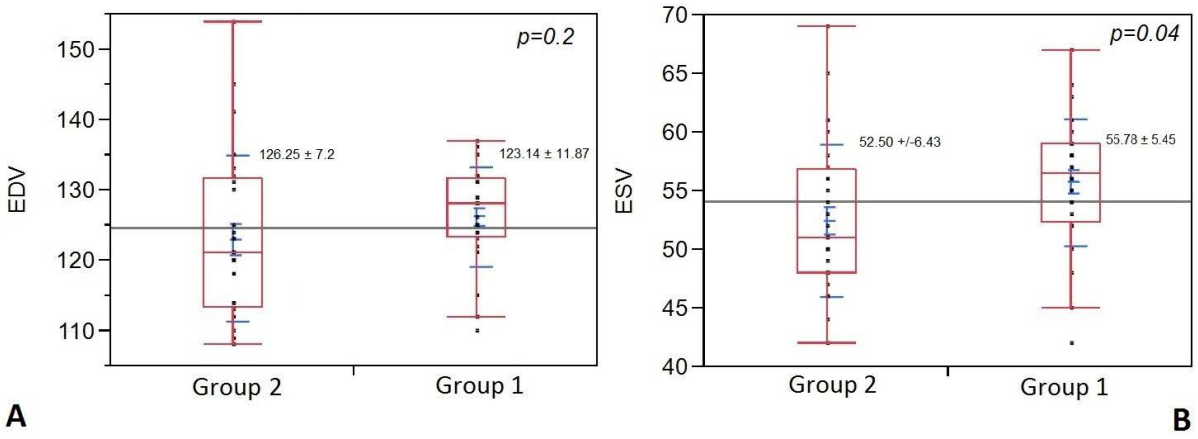

FIGURE 1. A- End-diastolic volume of the study groups. B - End-systolic volume of the study groups

groups, with 55.82 ± 3.36 % (95% CI: 54.52–57.13) in Group 1 vs. 57.21 ± 4.69% (95% CI: 55.39–59.03) in Group 2 (p = 0.2) (Figure 2).

ICA was similar in the two study groups with a value of 3.22 ± 0.68 (95% CI: 2.92–3.53) for patients with acute peri-myocarditis vs. 3.93 ± 0.33 (95% CI: 3.76–4.11) in the control group (p = 0.2).

RICA was significantly lower in the proximity of the affected peri-myocardium in patients with acute peri-myocarditis in Group 1, with a mean of 2.27 ± 0.63 (95% CI: 2.02–2.51) vs. 5.16 ± 0.54 (95% CI: 4.95–5.37) in Group 2 (p <0.0001) (Figure 3).

DISCUSSION

Peri-myocarditis can occur at any age, with peak prevalence middle-aged subjects. The mean age of our study population with acute peri-myocarditis was 55.28 ± 11.28 years. Some authors suggest that there may be a difference in respect of age in patients presenting with acute pericarditis versus those showing associated myocardial affection.[10]

The literature data is conflicting regarding the sex-related risk of developing peri-myocarditis.[11,12] In an experimental study, Frisancho-Kiss *et al.* (2009) reported on the role of testosterone in the development of myocarditis.[13] In the present study female gender was predominant in patients with acute peri-myocarditis (67.85%). These results may be explained by the fact that systemic inflammatory diseases are more common in females, and some authors suggest that progesterone may aggravate myocardial inflammation, though estrogen inhibits the immune response.[14,15]

No significant differences were recorded between the two groups in terms of associated comorbidities such as diabetes mellitus (p = 0.7), hypertension (p = 0.5), obesity (p = 0.7), and smoking (p = 0.2), suggesting that these well-known cardiovascular risk factors do not have an influence on the inflammatory process that is taking place during the acute phase of peri-myocardial disease.[16]

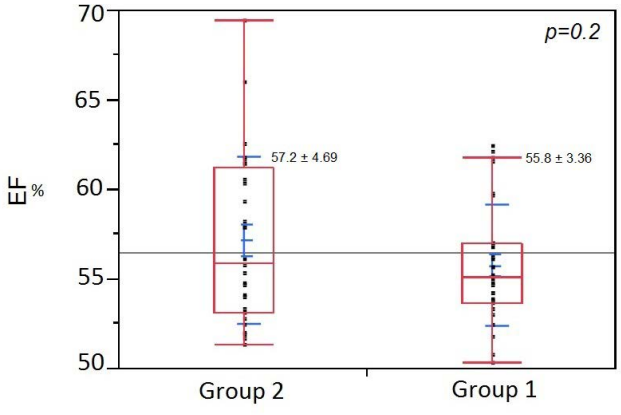

FIGURE 2. Ejection fraction of the study groups

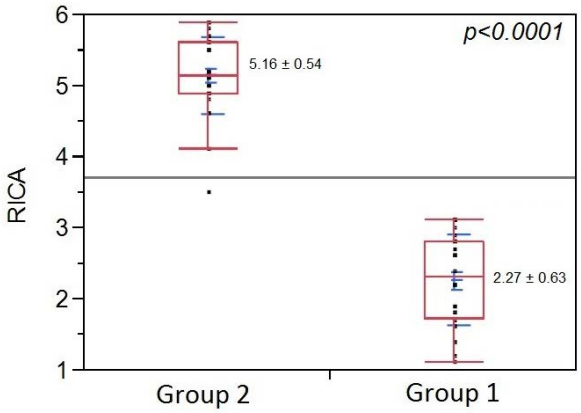

FIGURE 3. Regional index of contraction amplitude (RICA)

Echocardiography is the first-line diagnostic choice for the identification of acute pericarditis, being a non-invasive, commonly available examination. It has a high accuracy in assessing the hemodynamic and physiologic influences on heart function.[8]

Acute heart failure can be caused by the existence of large myocardial inflammation zones resulting in a reduction of left ventricular ejection fraction, characterizing a rare, but severe complication of peri-myocarditis.[17] A significant amount of rapidly accumulated pericardial effusion causing cardiac tamponade represents a life-threatening condition in acute pericarditis, which requires immediate treatment.[18] In the current study, the thickening of the pericardium and the presence of pericardial effusion, identified by echocardiography, did not have a significant bearing on the performance of the left ventricle expressed by the left ventricular ejection fraction, end-diastolic volume, and end-systolic volume in patients with acute peri-myocarditis. The global ICA, determined by three-dimensional echocardiography, was lower for Group 1 patients with acute peri-myocarditis compared with the control group, although the difference was not significant ($p = 0.2$). These results are concordant with literature data, as acute peri-myocarditis rarely has a major effect on the overall function of the heart.[19] In an MRI-controlled study, Goitein *et al.* (2009) reported 23 patients presenting acute myocarditis with a mean left ventricular EF of 57%, without any significant decrease in the global function of the left ventricle.[20]

Pericardial effusion and regional wall motion abnormalities were mainly present on the lateral wall of the left ventricle (42.8%), followed by the inferior wall (35.7%) and the apex (21.4%). In a study of 100 patients with acute peri-myocarditis, Leitman *et al.* (2012) reported a predominance of regional wall abnormalities of the postero-inferolateral wall of the LV in the absence of any effect on LV performance.[21]

In the present study, the RICA was significantly lower in the proximity of the affected myocardial areas in Group 1 patients compared with Group 2 ($p < 0.0001$). This may be explained by the presence of pericardial effusion and the thickening of the pericardium, which has a bearing on the regional wall motion through the extension of the inflammatory process from the pericardium to the adjacent myocardium but does not affect the overall function of the left ventricle. Speckle-tracking imaging may also identify regional wall motion abnormalities in patients with acute peri-myocarditis.[22]

The hemodynamic impact of pericardial effusions varies from mild to life-threatening, depending on the rate of accumulation and the thickness of the pericardium. Adhesions of the pericardial layers and localized liquid build-up may develop an atypical tamponade.10 However, no patient with cardiac tamponade was recorded in the current study.

CONCLUSIONS

Detailed echocardiographic evaluation of patients presenting with a possible acute peri-myocarditis should be considered the basis of clinical differentiation of peri-myocardial syndromes. The extension of the inflammatory process from the pericardium to the myocardium in patients with acute peri-myocarditis may have an influence on the contractility of the left ventricle, evaluated by three-dimensional echocardiography based on objective assessment and quantification of contractility parameters. Statistical analysis of an easily measurable objective echocardiographic parameter such as the regional index of contractility amplitude, demonstrated the existence of an association between the presence of peri-myocarditis and the regional contractility abnormalities of the left ventricle.

CONFLICT OF INTEREST

Nothing to declare.

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CLINICAL UPDATE

Computed Tomography — an Emerging Tool for Triple Rule-Out in the Emergency Department. A Review

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ABSTRACT

New imaging tools have been developed in recent years to rapidly and accurately diagnose life-threatening diseases associated with high mortality rates, such as acute coronary syndromes, acute aortic dissection, or pulmonary embolism. The concept of using computed tomographic (CT) assessment in emergency settings is based on the possibility of excluding multiple acute pathologies within one scan. It can be used for patients complaining of acute chest pain of unclear etiology with the possible association of acute coronary dissection or pulmonary embolism, but only a low to moderate risk of developing an acute coronary syndrome. One of the benefits of this protocol is the possibility of decreasing the number of patients who are hospitalized for further investigations. The technique also allows the rapid triage of patients and the safe discharge of those who show negative results. The aim of this review is to summarize the current medical literature regarding the potential use of CT for the triple rule-out (TRO) of coronary etiologies.

Keywords: CT, triple rule-out, emergency department, chest pain

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INTRODUCTION

The effective triage of patients who are admitted through the emergency department (ED) complaining of chest pain is a common challenge in the field of emergency cardiology. By achieving this goal, the patients would benefit from an accurate diagnosis and also a decreased mortality rate due to an appropriate approach and adequate therapy. Chest pain is a frequent symptom for many visits to the ED. The most recent health statistics published in 2010 by the Centers for Disease Control and Prevention (CDC) emphasized that chest pain is the primary symptom in 9% of patients who present to the ED.[1] Patients with chest pain as a primary complaint can develop acute coronary syndromes (ACS), and it is important for the patient to undergo a specific treatment. Un-

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fortunately, many studies emphasized that patients with ACS are misdiagnosed and discharged unsafely, and their mortality rate reaches 2%.[2–5]

The first evaluation of patients who are admitted through the ED with chest pain as a primary symptom consists of blood tests analysis of the cardiac enzymes and electrocardiogram (ECG), and if these are modified, more specific invasive diagnosing procedures are needed.[6] Currently, along with the development of imaging techniques, patients are further investigated with noninvasive procedures such as computed tomography (CT), which seems to have a good specificity in the triage of patients accusing chest pain in the ED.[7–9] The role of CT in evaluating ACS patients with low to intermediate risk was studied in many trials that concluded that it is a safe investigation, with a sensitivity of 86–100% and a high negative predictive rate of 93–100%.[10–12] In a meta-analysis published in 2002, Safriel *et al*. found that CT has a sensitivity of 71.4% and a specificity of 89.5% in detecting pulmonary embolism.[13] Another life-threatening disease that can be ruled out using CT is acute aortic dissection. Nienaber *et al*. found that CT has a sensitivity of 93.8% in detecting aortic dissection, whereas magnetic resonance imaging (MRI) was associated with a sensitivity of 98.3%.[14] These three diagnoses: ACS, pulmonary embolism, and acute aortic dissection, are considered to lead to a high mortality rate and thus their early diagnose is vital.[15–17] Aortic dissection type A is associated with a mortality rate of 1% per hour initially and almost 80% after 2 weeks, whereas aortic dissection type B has lower death rates, 10% at 30 days.[18] The International Cooperative Pulmonary Embolism Registry reported a mortality higher than 15% in patients with pulmonary embolism.[19] Having such a huge social impact, the need of an imaging modality appeared, that would assess, with a single examination, the pulmonary arteries, the thoracic aorta, and the coronary arteries, in order to rule out these three pathologies. Thus, the idea of triple-rule-out computed tomography (TRO-CT) emerged, which can be used in the ED for patients who present chest pain without ECG changes or high levels of cardiac enzymes, who are suspected of life-threatening diseases such as those mentioned above.

To exclude these three life-threatening diseases with one single scan, CT should be performed using an ECG-gated protocol, as the coronary arteries cannot be analyzed by regular thoracic CT. A clear imaging protocol and appropriate patient preparation are prerequisites for a good quality assessment.

CT is an imaging tool highly suitable for patients who have been evaluated as having a low to intermediate risk of developing an acute coronary syndrome. It is not always easy for the clinician to decide whether a patient with chest pain requires hospitalization or can be safely discharged, especially in cases when ECG changes are not specific.[20–22]

Using the triple rule-out strategy in the evaluation of patients with atypical chest pain, border levels of cardiac enzymes and non-pathognomonic ECG changes can help in deciding on the best therapeutic strategy and the safe discharge of patients.

The aim of this manuscript is to emphasize the benefits of using CT in patients who present with chest pain and have been evaluated as having a low to moderate risk for developing an acute coronary syndrome. At the same time, it aims to illustrate the most recent advances regarding the ability of the scan to rule out three major pathologies associated with high mortality rates: acute coronary syndrome, pulmonary embolism, and aortic dissection.

THE ECONOMIC IMPACT OF USING TRO-CT IN THE ED

It has been proved that the CT-based assessment can significantly reduce the economic impact generated by the unnecessary hospitalizations of patients. Henzler *et al*. (2013) recently demonstrated that integrating the triple rule-out protocol in the evaluation of patients referring at the ED for chest pain reduces the number of hospitalizations and consequently the related costs. They performed a comparative assessment of the expenses related to patients whose treatment was based on standard care and patients who received the triple rule-out CT protocol. They observed that the costs were lower in the group of patients following a triple rule-out protocol, the majority of them being discharged on the same day, compared with the second group in which the patients were hospitalized and underwent further invasive diagnostic procedures.[23]

Khare *et al*. (2009) agreed with these views and concluded that using this protocol the costs were lower than using other stress-based procedures for patients at low to moderate risk. Thus, they reported the costs of care associated with low risk patients who presented in the ED for chest pain as follows: the costs amounted to $2,684 in case of patients who underwent CT compared to the $3,265 associated with stress echocardiography.[24]

Patients admitted with atypical chest pain, without ST-segment elevation on the ECG and exhibiting slightly modified levels of cardiac enzymes, are usually hospitalized and receive invasive coronary angiography to exclude coronary artery disease. In such cases, hospital stays are

longer, with concomitant increases in expenditure. A triple rule-out CT strategy could be helpful in reducing healthcare-related costs.

The benefits of the procedure consist in the evaluation of the three arteries and also the upper level of the chest in a single scan. The TRO-CT protocol results in a speedier examination and a safer triage. Recent studies indicated that, on average, 18% of physicians base the triage on triple rule-out CT for patients with chest pain.[25,26]

WHICH ARE THE ELIGIBLE PATIENTS FOR THE TRIPLE-RULE-OUT CT PROTOCOL?

For a correct application of the triple-rule-out CT protocol, it is crucial to establish the exact inclusion criteria of eligible patients. First, the diagnostic protocol is used in patients with acute chest pain of doubtful etiology. Secondly, it is important to evaluate the stratification risk of developing an acute coronary syndrome. Only patients assessed as having a low to moderate risk gain an advantage from this approach. Patients who attend with acute chest pain with elevated cardiac enzymes and ST-segment elevation should not have CT as a primary strategy. The correct therapeutic approach is usually an invasive one, with time being of the essence. Yoon *et al.* (2001) stated that triple-rule-out CT should not be a routine screening tool used in the ED and should be included in the assessment of patients with suspicion of aortic dissection or pulmonary embolism.[28]

TRIPLE-RULE-OUT PROTOCOL-BASED STUDIES

In 2008, Takakuwa *et al.* published the first large study on triple-rule-out CT protocol in which they enrolled 197 patients who accused chest pain at their visit at the ED. They observed that in 11% of the patients the chest pain was due to coronary disease that required further diagnostic testing.[29]

Gruettner *et al.* (2013) assessed one hundred patients with acute chest pain. They performed the triple-rule-out CT protocol or coronary CT, and all patients were followed for 90 days to evaluate the rate of major adverse cardiac events (MACE). They observed that 60% of patients could be rapidly discharged on the same day, following the exclusion of non-coronary disease and concluded that triple-rule-out CT might contribute to lowering the number of diagnostic angiographies.[30]

An aspect that should not be ignored is the high dose of radiation that is required for triple-rule-out CT. Many studies emphasized that the high-dose radiation exposure is due to long scanning length.[31–34]

A meta-analysis published in 2013 highlighted the radiation aspect of the TRO-CT. Ayaram *et al.* (2013) studied radiation exposure in 2,307 patients, of which 377 were included in the triple-rule-out CT group and 1,930 in the control group. A statistically significant difference was observed between the two groups, patients assessed with TRO-CT being exposed to a significantly higher dose of ionising radiation.[34]

THE TRIPLE-RULE-OUT CT PROTOCOL

The basic technical challenge of this method is to obtain simultaneously an intense, consistent contrast enhancement in all three arterial territories. This can be accomplished only by using a tailored contrast medium administration regimen.[35] Usually biphasic injection is preferred, contsisting of the administration of an undiluted contrast, followed by diluted contrast medium with saline. This type of contrast administration provides a highly homogeneous contrast enhancement in the aorta and coronary arteries and a slightly lower but also homogeneous contrast in the pulmonary arteries. Several variants regarding the volume and rate of contrast and saline are proposed for a scanning time of 15 seconds. A rapid flow rate in both phases is indicated to minimize venous return from the inferior vena cava, and for a good image quality it is also important to adjust the contrast dose not to have bright contrast in the superior vena cava during scanning time.[36] The region of interest for the triple-rule-out technique is in the left atrium, and scanning starts after 5 seconds after the threshold value is reached, in order to get the peak contrast intensity of the aorta and coronary arteries.

Similarly to a coronary computed tomography angiography (CCTA), in order to get a high image quality, triple-rule-out studies use ECG gating to reduce motion artefacts produced by cardiac pulsations, and acquisitions are performed during breath-hold to prevent respiratory movement artefacts.

To reduce radiation doses, a prospective ECG-gated acquisition is preferred, but it is only suitable in patients with a stable heart rate.

The "field of view" is another parameter that is adjusted to reduce radiation exposure. Because the radiation dose is directly proportional to the scan length, in the triple-rule-out technique the acquisition includes only the thoracic aorta and the heart, while lung apices above the aortic arch are not included.[37] Scans are designed to start at the base of the heart, with the superior margin at one

cm above the aortic arch. An important aspect concerning acquisition is the scanning direction, which is caudal-cranial in order to include distal pulmonary arteries at the base of the lungs, which otherwise may be visualized at a low contrast intensity.

CONCLUSION

Triple-rule-out computed tomography angiography is a relatively new technique used in the evaluation of acute chest pain in patients without invasive coronary angiography indication. Using an optimized CT protocol with tailored parameters for decreased radiation exposure concomitant with an efficient contrast medium injection, the triple-rule-out CT protocol is a powerful tool suitable for simultaneously evaluating the thoracic aorta, the coronary arteries, and the pulmonary arteries. Further data is needed to validate this protocol in the assessment of patients with acute chest pain before it can be validated as a routine emergency screening tool.

CONFLICT OF INTEREST

Nothing to declare.

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CASE REPORT

Role of the Methylene Tetrahydrofolate Reductase (MTHFR) Gene Mutation in Acute Myocardial Infarction

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ABSTRACT

This is a case report of a 36-year-old male who was diagnosed with acute inferior and right ventricular myocardial infarction and treated with percutaneous coronary angioplasty with a drug-eluting stent in the right coronary artery. A profile test for thrombophilia was performed for methylene tetrahydrofolate reductase (MTHFR) gene mutation; the test was positive for a heterozygous mutation — C677C and 1298A. The patient received a long-term treatment with folic acid supplements, taken daily. This case report shows that medical doctors should have an outside-the-box approach for the diagnosis and therapeutic management of young patients who present with acute cardiovascular events. If the patient in question does not present clear cardiovascular risk factors for acute myocardial ischemia, the clinician should seek for possible causes, thus leading to several benefits in the management and secondary prevention of such cases.

Keywords: acute myocardial infarction, young patient, MTFR gene mutation, increased homocysteinemia

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INTRODUCTION

Adjustable risk factors for ischemic heart disease consist of elevated arterial blood pressure, hyperlipidemia, chronic tobacco use, increased body weight, sedentary lifestyle, diabetes mellitus, and anxiety.[1] Other aspects, such as gender and age, are unchangeable cardiovascular risk factors.[2] If a patient is admitted to the hospital for typical symptoms of an acute thrombotic event (acute myocardial infarction in the presented case), without any significant cardiovascular risk factors, the clinician is required to exclude genetic disorders as etiology for the acute diagnosis.[3] Genetic causes that have been shown to be independent risk factors for acute thrombotic events include the mutation of several genes that encode the coagulation factors, such as antithrombin, C and S protein, fibrinogen, prothrombin, and factor V from the clotting cascade.[4] The genetic mutation of the methylene tetrahydrofolate reductase (MTHFR) gene, which causes a transitional shift in cytosine to thymidine on the 677 nucleotide, leads to a low enzymatic activity and a modified folic acid state with increased folate necessity. The 677 T mutation of the gene that encodes the MTHFR causes C/C, C/T, and T/T genotypes, leading to an elevated serum level of homocysteine in human subjects.[5,6] Increased levels of homocysteinemia lead to early atherosclerotic lesion formation and venous thromboembolism.[7]

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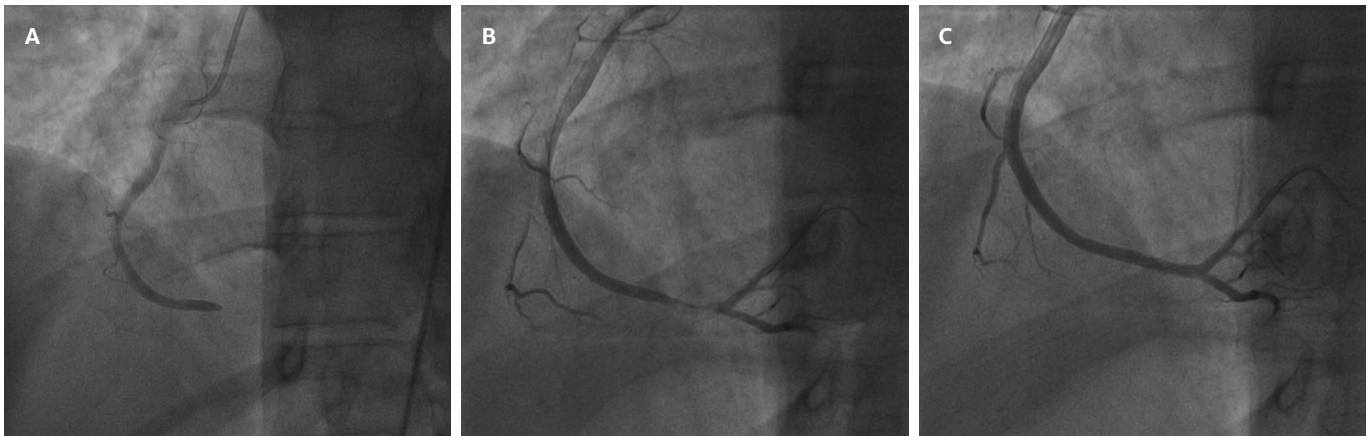

FIGURE 1. Periprocedural coronary angiogram. A – right coronary stenosis, B – after thrombus aspiration, C – postinterventional

This manuscript is a report on a 36-year-old male who was admitted in emergency conditions, with acute chest pain that proved to be an acute right ventricular myocardial infarction (MI). A profile test for thrombophilia was performed for MTHFR gene mutation; the test was positive for a heterozygous mutation — C677C and 1298A.

CASE PRESENTATION

The patient, male, 36 years old, presented to the Emergency Department after 3 hours from the onset of a constrictive, acute chest pain that irradiated down his left arm, with diaphoresis, nausea, and fatigue. The patient's medical history was negative for diabetes, high blood pressure, and chronic tobacco use. The patient did not present any family history of cardiac or cerebrovascular events. The clinical examination on admission revealed a regular heart beat (91/min) and normal blood pressure (137/71 mmHg), with no other pathological modifications. The electrocardiography was illustrative of a postero-inferior and right ventricular ST elevation myocardial infarction (ST-segment elevation in leads D2, D3, aVF, V3R-V5R, ST depression in leads D1, aVL, V1–V2). The patient underwent emergency invasive coronary angiography that showed the acute thrombotic occlusion of the right coronary artery, for which a primary percutaneous coronary angioplasty with a drug-eluting stent was performed (Figure 1). The angiographic aspect of the left coronary artery did not show any atherosclerotic lesions. The laboratory tests were normal for the complete blood cell count, with normal ranges of serum cholesterol triglycerides, kidney and hepatic enzymes.

Following the percutaneous coronary intervention, the patient showed a complete resolution of ST-segment elevation, as well as the disappearance of chest pain and other symptoms. The full hospitalization time was 5 days.

Due to the young age of the subject, screening for thrombophilia was performed, which included testing for MTHFR gene mutation. The screening results showed that the patient was positive for a heterozygous (C677C and 1298A) MTHFR gene mutation. Also, the patient had an increased serum level of homocysteine: 10.5 µmol/L (normal range <10 µmol/L).

A hematology consult was requested, which recommended decreasing the homocysteine level, without long-term oral anticoagulant therapy. The patient has been followed-up in out-patient conditions at regular time periods.

The patient agreed to the publication of his data and the institution where the patient had been admitted approved the publication of the case.

DISCUSSION

Coronary atherosclerotic lesions appear as a result of a complex process that takes place within the vessel wall. Several studies have evaluated the involvement of homocysteine in the process of cell injury at the level of the endothelium.[8,9]

Genetic polymorphism associated with several risk factors leads to increased incidence of ischemic heart disease. Elevated serum levels of homocysteine, caused by MTHFR gene mutation, can be treated with folate supplements. It has been shown that the clinical evolution of arterial or venous thrombotic events in patients with MTHFR gene mutation and increased homocysteine levels improves under supplementation with folic acid, as seen also in this case report.[10] Gene disorders that affect clotting factor V, prothrombin, and homocysteine, increase the risk of developing acute coronary syndromes or stroke, especially at a young age.[11] Nevertheless, the screening protocol applies to a relatively low number of subjects, since the number of

patients who present the association of acute myocardial infarction and these mutations is modest. The tendency for thrombotic events, either arterial or venous, analyzed individually, is influenced by the complex interaction between local and systemic processes.[12]

In the case presented here, screening for MTHFR gene mutation was performed due to the patient's age and lack of cardiovascular risk factors.

We found few cases with acute MI and MTHFR gene mutation in the literature. The first report was published in 1997, on a 35-year-old male patient who presented with acute MI, a homozygous MTHFR gene mutation that led to hyperhomocysteinemia, and a heterozygous mutation of the Leiden V factor gene.[13] The patient also presented several risk factors for ischemic heart disease, including late onset type I diabetes and increased cholesterol level. The other described cases also presented a homozygote mutation (with or without other gene mutations), risk factors such as smoking, use of oral contraceptive medication, obesity, and developed myocardial infarction. The particularity of our case is that a heterozygote MTHFR gene mutation was found in a patient with no significant medical history and no cardiovascular risk factors who has been admitted under emergency conditions for acute myocardial infarction.

Establishing an accurate prognosis and predicting future adverse cardiovascular events in patients with MTHFR gene mutation is far from easy, due to its heterogenous mutation process and various forms of clinical presentation. Nevertheless, medical practitioners should have an outside-the-box approach to such patients, especially when young patients present with acute MI in the lack of any other cardiovascular risk factors.

CONCLUSIONS

When the presentation diagnosis is not explained by established pathophysiological mechanisms and there are no obvious and identifiable etiological explanations, clinicians should seek for rare causes that will eventually lead to a complex therapeutic approach, beneficial for both the patients and their families.

CONFLICT OF INTEREST

Nothing to declare.

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CASE REPORT

Multiple Mediastinal Arteriovenous Fistulas in a Patient with Myocardial Ischemia Symptoms and Tachy-Brady Arrhythmias

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ABSTRACT

Arteriovenous fistulas are abnormal vascular communications between the arterial and venous system and may lead to the development of arteriovenous shunts. These malformations are extremely rare, and their diagnosis can be difficult due to the lack of symptoms or the absence of hemodynamic consequences. In many cases, arteriovenous fistulas are discovered by chance. In this brief report, we present the case of a 31-year-old male with symptoms suggestive of angina pectoris, tachycardia-bradycardia syndrome and multiple episodes of syncope. Multi-slice computed tomography revealed the presence of multiple mediastinal fistulas connecting the aorta, superior vena cava, pulmonary veins and azygos system.

Keywords: arteriovenous fistulas, CT angiography, aorta, superior vena cava, pulmonary veins, azygos system

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INTRODUCTION

Mediastinal vascular fistulas are the consequence of the abnormal variation of blood flow from one vessel to another and might develop between any arterial or venous structure.[1–3] Nowadays, arteriovenous fistulas are more frequently diagnosed, even in asymptomatic patients, during routine investigations, due to the improvement of imaging techniques.[4] Computed tomographic angiography (CTA) and conventional angiography are the gold-standard methods for diagnosing AV fistulas, being able to expose the convoluted pathways arising from abnormally connected vessels.[1]

Congenital and acquired fistulas connecting the arterial and venous systems are exceedingly rare. Clinical status and physical examination may vary from an asymptomatic pattern to audible thoracic murmur, dyspnea, or cardiac insufficiency.[1,5]

The case of a young man presenting with symptoms of myocardial ischemia but with no invasive or noninvasive evidence of any heart disease is discussed in this paper. Thoracic CT angiography showed multiple mediastinal tortuous pathways between the descending aorta and the superior vena cava, the aorta and the left superior pulmonary vein, and the azygos vein and the right superior pulmonary vein.

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CASE REPORT

The case concerns a 31–year–old man, with no history of cardiovascular disease, admitted to the Cardio Med Medical Center in Tîrgu Mureș, Romania.

He complained of anterior constrictive chest pain and tightness and rapid palpitations, followed by episodes of bradycardia associated with dizziness, syncope and shortness of breath.

The patient gave informed consent allowing the publication of his data, and the institution where the patient had been admitted approved the publication of the case.

The patient's clinical signs and symptoms were suggestive of a tachycardia-bradycardia type arrhythmia, but initial investigations — physical examination and laboratory tests — showed no significant findings.

An electrocardiogram (ECG) performed during chest pain showed normal sinus rhythm with a frequency of 70 beats per minute (bpm) and negative T waves in DIII and V1–V4. Resting ECG also showed normal sinus rhythm with a frequency of 75 bpm and normal axis, but the T wave appeared to be flat in DIII and aVF, and negative T waves were seen in V1 and V2.

Echocardiography parameters were within normal ranges. However, the posterior and lateral pericardium appeared to have a higher echodensity than normal.

The patient also underwent cycle ergometer stress testing, which was positive for the alteration of myocardial perfusion. The test was stopped after 2 minutes (100 W) due to the dyspnea and dizziness, though there were no signs of any angina symptoms. During the cycle ergometer stress testing, the ECG showed T wave variations that became negative in DII, DIII, aVF, and V2–V5. After a two-minute resting period, the patient's ECG returned to normal, with positive T waves in these leads.

Taking into consideration the palpitation symptoms, a Holter ECG was performed, which denoted three tachycardia events, with a maximum heart rate of 110 bpm, alternating with bradycardia episodes with a minimum heart rate of 30–40 bpm.

In order to assess the presence of possible coronary lesions, a CTA was performed, starting with the dynamic administration of 100 ml of non-ionic contrast material Iopamiro 370 (Patheon Italy SpA, Italy) at a rate of 5 ml/s, followed by 100 ml saline solution at 5 ml/s, via the right anterior cubital approach, followed by CT scanning using a Somatom Sensation 64 slices CT (Siemens, Erlangen, Germany). The examination was well tolerated, and there were no complications.

Three-dimensional post-processing programs — MPR, MIP, and reconstruction curved VRT — were used, and the examination showed a dominance of the right coronary

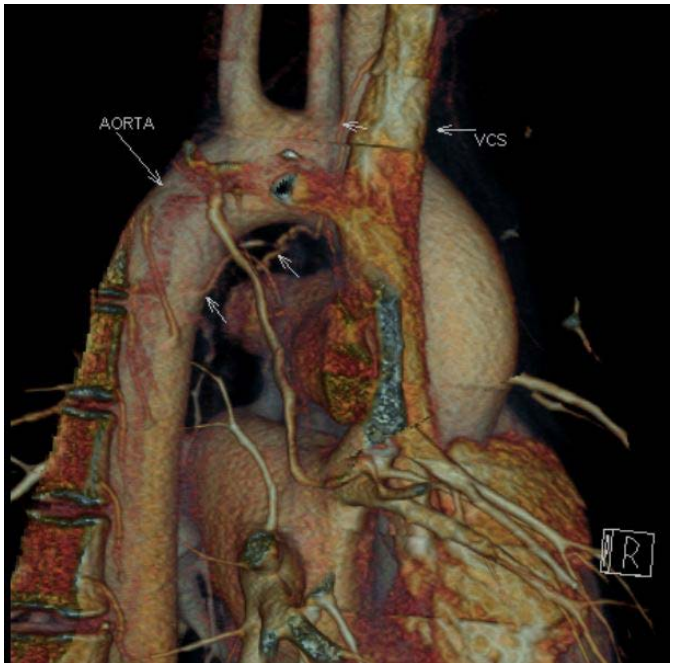

FIGURE 1. CTA showing arterial–venous fistula between azygos vein and right superior pulmonary vein; aorta and superior vena cava; descending aorta and left superior pulmonary vein

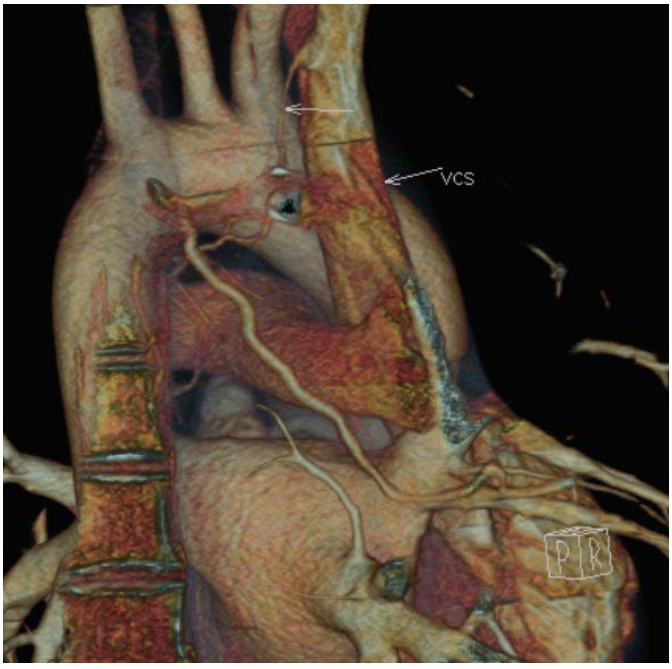

FIGURE 2. CTA showing arterial–venous fistula between descending aorta and left superior pulmonary vein; aorta and superior vena cava

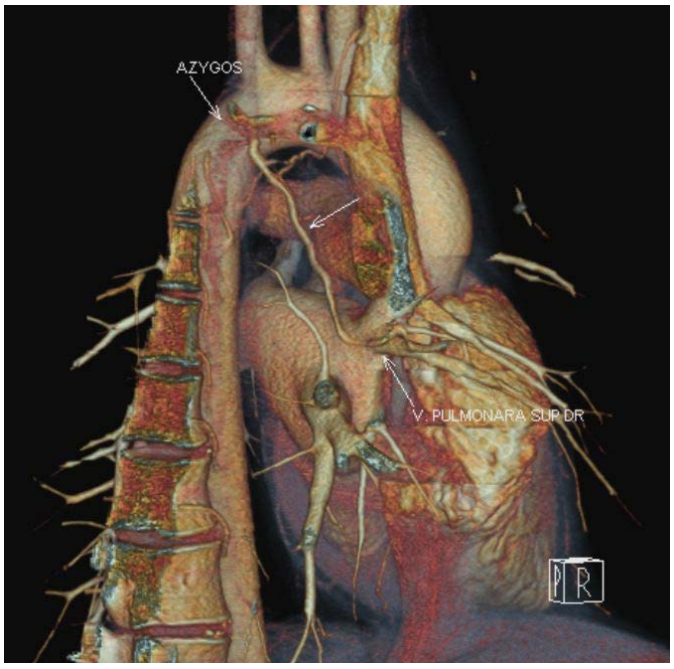

FIGURE 3. CTA showing fistula between azygos vein and superior right pulmonary vein

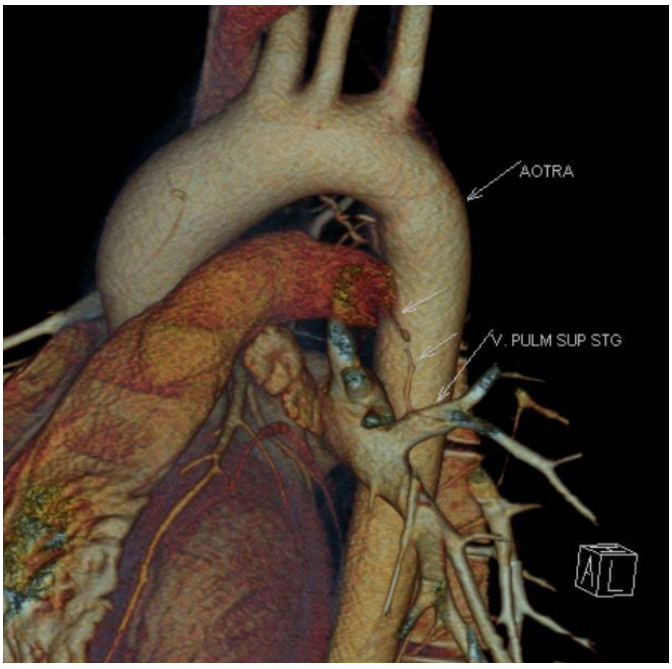

FIGURE 4. CTA showing fistula between the upper aorta and left superior pulmonary vein

artery, with the coronary arteries, pericardium, thoracic aorta, lungs, and pleura showing normal characteristics. Due to these normal results and the patient's subjective complaints of angina and palpitations, the investigation was extended, and the thoracic vessels were investigated in more detail. Following CT angiography, a diagnosis of AV fistulas located in the middle mediastinum was established. Small diameter tortuous vascular pathways interposed between the descending aorta and superior vena cava (Figure 1), the aorta and left superior pulmonary vein (Figures 2 and 3), and between the azygos and right superior pulmonary vein were identified (Figure 4).

The surgical team recommended the ligature of the venous fistulas between the descending aorta and superior vena cava, the aorta and left superior pulmonary vein, and the azygos and right superior pulmonary vein, but the patient refused the intervention.

During hospitalization, the patient was treated with anti-ischemic therapy, 25 mg of beta blocker (metoprolol 25 mg, two times per day, for an indefinite period, but with regular check-ups and re-assessment of treatment), with significant improvement of his symptoms, in the absence of surgical intervention.

DISCUSSION

Arteriovenous fistulas are extremely rare, being described in only a few cases in the literature.[1] Due to the similarity of cardiac and extra-cardiac symptoms associated with this condition, the diagnosis of these cases may be problematic.[6]

Soler *et al*. reported that an AV fistula originating from the descending aorta and draining into the azygos vein is a very rare condition.[6] They attributed this malformation to abnormal connections between embryologic arterial and venous channels. The signs and symptoms associated with the presence of an AV fistula depend largely on the size of the fistula and the degree of resulting left-to-right shunting.[7] Several studies have suggested that the malformations of the great vessels and abnormal drainage can produce arrhythmias in patients with different types of AV fistula.[8]

The noninvasive diagnosis of this disease is based on thoracic multi-slice computed tomography, CT angiography, conventional angiography, magnetic resonance imaging, and radionuclide angiograms.[1,9]

Although in the past open surgical correction was the gold-standard of treatment of this disease, nowadays interventional treatment is preferred, including balloon occlusion, coiling embolization, and other occlusion devices such as the Gianturco coil or, more recently, the Gianturco-Grifka Vascular Occlusion Device (Cook Inc.).[10–12] Despite all new therapeutic techniques, the treatment procedure depends on the origin of the AV fistula. Large congenital fistulas may require surgical intervention. However, small ones may be treated conservatively.[1]

The case reported here is the first documented case of multiple mediastinal arterial-veno-venous fistulas, which was associated with a suggestive ECG pattern including negative T waves and positive cycle ergometer stress test. Moreover, another particularity of this case is that the patient was admitted several times because of his chest pain accompanied by tachy-brady arrhythmia and episodes of syncope, without any precise etiology. On his last admission with these symptoms, the decision was taken to perform a CTA, which revealed no evidence of coronary or pulmonary abnormalities. Additionally, CT angiography investigations revealed multiple small caliber fistulas in the mediastinum, between the descending aorta and the superior vena cava, the aorta and the left superior pulmonary vein, and the azygos vein and the right superior pulmonary vein.

CONCLUSION

Thoracic arteriovenous fistulas are extremely rare malformations that are usually underdiagnosed due to equivalent signs and symptoms of other cardio-pulmonary and mediastinal conditions. Based on the complexity and the type of the shunt, the symptoms can vary from asymptomatic conditions to heart failure. Because of the lack of symptoms, in many cases, the diagnosis is made by chance. Hemodynamic consequences can be absent in small diameter shunts or can be substantial in large ones.

CTA, the gold-standard noninvasive imaging technique used for the assessment of these cases, linked with complex 3D post-processing techniques, can reveal the location of the malformations, assess their complexity and help guide treatment planning.

CONFLICT OF INTEREST

Nothing to declare.

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