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JIM Journal of Interdisciplinary Medicine

Aims and scope

The Journal of Interdisciplinary Medicine aims to publish top quality papers related to any fields of medicine that present an interdisciplinary dimension.

The journal will mainly focus on recent advances in the field of diagnosis and treatment of the most common situations encountered in the clinical or research practice. Interdisciplinary approaches will be extremely welcomed, presenting new advances in the approach of different pathologies from the perspective of various clinical fields.

The Journal of Interdisciplinary Medicine will publish high-quality basic and clinical research related to interdisciplinary medical fields, in a common approach that will integrate the clinical studies with the pre-clinical work dedicated to the discovery of new mechanisms involved in the development and progression of a large spectrum of diseases.

The journal will try to provide the entire medical community with the perspective of the regional specifics of Central and Eastern European countries. 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.

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EDITORIAL

The Multifaceted Role of Epicardial Fat in Cardiovascular Diseases

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Epicardial fat continues to fascinate the imagination of many researchers after the recent discovery of its multifaceted role in various cardiovascular diseases. The inflammatory cytokines released by the fat depots surrounding the heart have been recognized to play an important role in the determination of coronary artery disease, being associated with a higher incidence and severity of coronary artery stenosis.[1] At the same time, this metabolically active tissue has been associated with a higher recurrence of atrial fibrillation after catheter ablation and with worse outcomes in heart failure patients.[2] However, it is currently not known whether epicardial fat represents just a surrogate marker associated with atherosclerosis, or is rather one of its main determinants.

The link between epicardial fat and inflammation, as well as the link between inflammation and cardiovascular diseases, is well-known and largely accepted. However, few studies succeeded so far to demonstrate any link between epicardial fat and coronary plaque vulnerabilization, while the role of inflammation in acute coronary syndromes is also well-known.

Three articles published in this number of JIM address the issue of epicardial fat from the cardiovascular perspective.

In the first one, Nyulas *et al.* demonstrate that epicardial fat volumes are significantly higher in patients with acute coronary syndromes as compared to stable patients, identifying the presence of vulnerability features in coronary plaques of hearts surrounded by large epicardial depots.[3]

In the second one, Rat *et al.* prove that rather than the global epicardial fat, the local accumulation of fat around a coronary lesion, named periplaque adipose tissue, could serve as a more reliable marker associated with plaque vulnerability, being associated with CT features that characterize unstable plaques in a significantly higher extent that the global epicardial fat or the total intrathoracic fat.[4]

In the third article, Rat *et al.* prove that besides its role as marker of plaque vulnerability, epicardial fat could also serve as a marker of increased risk in other diseases such as pulmonary hypertension associated with various conditions: congenital heart diseases and coronary artery diseases, or secondary to sclerodermia.[5]

All three articles have in common the focus on epicardial fat as an inflammation-related marker easily identified by imaging techniques, from classical echocardiography to modern cardiac computed tomography. However, they underline the need for further investigation in this direction, as they only open new hypotheses. These hypothesis-generating studies have been tested by the authors on a low number of patients, with promising results; however, they need validation on larger cohorts in order to offer a clear answer to many open questions related to the role of epicardial fat in cardiovascular diseases.

CONFLICT OF INTEREST

Nothing to declare.

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Journal of Interdisciplinary Medicine

ORIGINAL RESEARCH

CARDIOLOGY // MEDICAL IMAGING

The Effect of Periplaque Fat on Coronary Plaque Vulnerability in Patients with Stable Coronary Artery Disease – a 128-multislice CT-based Study

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ABSTRACT

Background: The role of periplaque fat (PPF), as a fragment of the total epicardial adipose tissue, measured in the vicinity of a target coronary lesion, more specifically within the close proximity of a vulnerable plaque, has yet to be evaluated. **The study aimed to** evaluate the interrelation between PPF and coronary plaque vulnerability in patients with stable coronary artery disease (CAD). Secondary objective: evaluation of the relationship between the total pericardial fat and markers for plaque vulnerability. **Materials and methods:** We prospectively enrolled 77 patients with stable CAD, who underwent 128-multislice computed tomography coronary angiography (CTCA), and who presented minimum one lesion with >50% stenosis. CTCA analysis included measurements of: total pericardial fat and PPF volumes, coronary plaque characteristics, markers for plaque vulnerability – positive remodeling (PR), low attenuation plaque (LAP), spotty calcifications (SC,) napkin ring sign (NRS). Study subjects were divided into two categories: Group 1 – 1 marker of plaque vulnerability (n = 36, 46.75%) and Group 2 – ≥1 marker of vulnerability (n = 41, 53.25%). **Results:** The mean age of the population was 61.77 ± 11.28 years, and 41 (53.24%) were males. The analysis of plaque characteristics showed that Group 2 presented significantly longer plaques (16.26 ± 4.605 mm vs. 19.09 ± 5.227 mm, p = 0.02), remodeling index (0.96 ± 0.20 vs. 1.18 ± 0.33, p = 0.0009), and vessel volume (p = 0.027), and more voluminous plaques (147.5 ± 71.74 mm^3 vs. 207.7 ± 108.9 mm^3, p = 0.006) compared to Group 1. Group 2 presented larger volumes of PPF (512.2 ± 289.9 mm^3 vs. 710.9 ± 361.9 mm^3, p = 0.01) and of thoracic fat volume (1,616 ± 614.8 mm^3 vs. 2,000 ± 850.9 mm^3, p = 0.02), compared to Group 1, but no differences were found regarding the total pericardial fat (p = 0.49). Patients with 3 or 4 vulnerability markers (VM) presented significantly larges PPF volumes compared to those with 1 or 2 VM, respectively (p = 0.008). There was a significant positive correlation between PPF volume and the non-calcified (r = 0.474, 95% CI 0.2797–0.6311, p <0.0001), lipid-rich (r = 0.316, 95% CI 0.099–0.504, p = 0.005), and fibro-fatty (r = 0.452, 95% CI 0.2541–0.6142, p <0.0001) volumes. The total pericardial fat was significantly correlated only with the volume of lipid-rich plaques (p = 0.02). **Conclusions:** Periplaque fat volume was associated with a higher degree of coronary plaque vulnerability. PPF was correlated with lipid-rich, fibro-fatty, and non-calcified plaque-related volumes, as markers for enhanced plaque vulnerability. PPF volume, assessed with native cardiac computed tomography, could become a novel marker for coronary plaque vulnerability.

Keywords: periplaque fat volume, vulnerable coronary plaques, coronary artery disease, pericardial fat volume, CT coronary angiography

BACKGROUND

Vulnerable coronary plaques

Unstable coronary atheromas present increased risk for rupture, erosion, and thrombosis, with the consequent development of an acute coronary syndrome. The concept of "plaque vulnerability" refers to lesions that are prone to cause an acute event, which have been described as presenting a thin fibrous cap and underlying large lipid core, that leads to eccentric vascular remodeling followed by luminal narrowing and distal myocardial ischemia.[1–3] Several invasive and noninvasive imaging methods have been described for the assessment of high-risk vulnerable coronary lesions.[4–7] Invasive imaging techniques used for the identification of vulnerability markers (VM) for coronary atherosclerosis include intravascular ultrasound (with description of plaque burden, remodeling index, cross sectional area, and necrotic core,), and optical coherence tomography (which measures the thickness of the fibrous arch, lipid arch, intracoronary thrombi, or macrophages).[8,9] Computed tomography coronary angiography (CTCA) is a noninvasive method that provides visualization of the entire coronary tree, as well as the vessel lumen and wall characteristics, while offering similar accuracy in detecting coronary vulnerability as the intracoronary imaging techniques.[10–12] VM for coronary plaques assessed via CTCA include the presence and size of the lipid necrotic core, low attenuation plaques (LAP, density of <30 Hounsfield units), positive vessel remodeling (PR), the napkin ring sign (NRS) and spotty calcifications (SC).[13–17]

Epicardial fat on severity of CAD and plaque vulnerability

The total epicardial fat (EF) has been shown to be associated with the total coronary atherosclerotic burden, with the severity of coronary stenoses, and with cardiovascular risk factors. Moreover, EF is directly proportional with the rate of major adverse cardiac events in patients with known coronary artery disease.[18–22] The epicardial adipose tissue is measured with either transthoracic echocardiography as linear thickness, or with volumetric assessment via cardiac computed tomography or magnetic resonance imaging.[23] Recent studies connected the epicardial adipose tissue with the presence of high-risk coronary plaques, defined as presenting one of the following features: low attenuation, positive remodeling, napkin ring sign, spotty calcifications; studies have also shown that patients with high-risk plaques present a larger volume of epicardial fat, compared to those with no high-risk plaques.[24,25]

Pericoronary and periplaque fat

Pericoronary adipose tissue, as a fragment of the total epicardial fat, is located in direct contact to the coronary artery wall and has pro-inflammatory properties through its paracrine effect and local release of inflammatory cytokines, which can trigger plaque formation, progression, vulnerabilization, and even rupture.[26] Pericoronary fat (PF) has also been associated with the presence of vulnerable coronary plaques, even after adjustment for obesity and smoking.[27] The ratio between PF and overall EF has been linked with a higher coronary plaque volume and an increased volume of mixed and non-calcified plaques.[28,29] The role of periplaque fat (PPF), measured in the vicinity of a target coronary lesion, more specifically within the close proximity of a vulnerable plaque, has yet to be evaluated. The alternative hypothesis of the present study is that an increased volume of periplaque adipose tissue, measured adjacent to a hemodynamically significant coronary lesion, is associated with a more extensive plaque vulnerability (presence of plaque vulnerability features), as assessed with the use of CTCA.

The aim of the study was to evaluate the interrelation between the periplaque adipose tissue, measured in the vicinity of a significant coronary lesion, and the degree of plaque vulnerability in patients with stable coronary artery disease, who undergo noninvasive CTCA. Secondary objectives include the evaluation of the relationship between total pericardial fat and markers for plaque vulnerability.

MATERIALS AND METHODS

We conducted a prospective observational cohort study, which included 77 subjects who presented in outpatient settings, at the Cardio Med Medical Center, for symptoms indicative for coronary artery disease (chest pain, dyspnea, fatigue). All subjects underwent a complete clinical examination, 12-lead ECG tracing, two-dimensional transthoracic echocardiography, followed by 128-multislice CTCA. All patients who presented minimum one lesion with ≥50% stenosis were enrolled in the study.

Study procedures were conducted according to the ethical principles stated in the Declaration of Helsinki, and all subjects signed a written informed consent prior to being enrolled in the study.

Subjects with high clinical probability for presenting an acute coronary syndrome (unstable angina, acute ST- or non-ST-segment elevation myocardial infarction)

TABLE 1. Patient characteristics

	Group 1	Group 2	p value
Age (years)	62.14 ± 10.97	61.41 ± 11.59	0.7791
Male gender, n (%)	26 (72.22%)	15 (34.09%)	0.0007
Risk factors			
Hypertension (n, %)	28 (68.09%)	35 (83.72%)	0.13
Hypertension, n (%)	29 (80.56%)	29 (70.73%)	0.4637
Diabetes, n (%)	8 (23.53%)	14 (34.15%)	0.4529
Peripheral arterial disease, n (%)	6 (17.65%)	5 (12.20%)	0.7364
Acute myocardial infarction, n (%)	11 (32.35%)	12 (29.27%)	0.7730
Smoker, n (%)	21 (61.76%)	23 (56.10%)	0.6198

were excluded, as they were referred for emergency invasive coronary angiography. Other exclusion criteria were acute renal failure or terminal-stage chronic kidney disease, pregnancy or lactation, allergy to iodine contrast substance, active malignancy, or refusal to provide written informed consent for study enrollment.

CTCAs were performed with a Somatom Definition 128-Slice CT equipment (Siemens Healthcare GmbH, Ernlagen, Germany), and image acquisitions were analyzed for the following parameters: the overall epicardial adipose tissue volume, the adipose tissue located in the vicinity of the target coronary lesion (from herein referred to as periplaque fat – PPF), plaque-related features (markers for plaque vulnerability, length, degree of stenosis, volume, plaque components – necrotic core, fibro-fatty, fibrotic, and densely calcified volumes), vascular indices (remodeling index, eccentricity index).

The study population was divided into two groups, based on the presence of CT markers for plaque vulnerability (low attenuation plaque, positive remodeling, spotty calcification, napkin ring sign), as follows: Group 1 – patients with 1 marker of plaque instability (n = 36); Group 2 – patients with ≥1 marker of instability (n = 41).

Statistical analysis was performed using GraphPad Prism 7 software (GraphPad Software, Inc., San Diego, USA), with the application of two-tailed statistical comparative testing for unpaired continuous data, or Chi square test for categorical variables, at a statistical significance of alpha 0.05. Spearman or Pearson coefficient when appropriate, was used to describe correlation analysis.

RESULTS

From the 77 study subjects, 36 (46.75%) presented only 1 marker (Group 1), and 41 (53.24%) presented more than 1 CT marker for plaque instability. The mean age of the overall study population was 61.77 ± 11.28 years, and 41 (53.24%) subjects were males.

There were no significant differences between groups in relation to age (p = 0.779), or cardiovascular risk factors including arterial hypertension (p = 0.463), diabetes (p = 0.452), peripheral artery disease (p = 0.736), previous myocardial infarction (p = 0.773), or chronic tobacco use (p = 0.619) (Table 1). However, patients in Group 1 presented a significantly higher number of male subjects, compared to Group 2 (p = 0.0007).

The distribution of CT markers for coronary plaque vulnerability is listed in Table 2. In the first group, while there were no napkin ring signs found in the analyzed plaques, the most frequent vulnerability marker was the presence of spotty calcifications (52.78% of cases). In the second group however, the most encountered vulnerability feature was positive vascular remodeling (in 73.81% of analyzed plaques) (Table 2).

TABLE 2. Presence of vulnerability features in the study groups

	Group 1 n = 36	Group 2 n = 41	p value
Positive remodeling, n (%)	11 (30.55%)	31 (75.60%)	0.0001
Spotty calcification, n (%)	19 (52.78%)	30 (73.17%)	0.3102
Napkin ring sign, n (%)	0 (0%)	10 (24.39%)	0.0013
Low attenuation, n (%)	6 (16.67%)	19 (46.64%)	0.0114

TABLE 3. CT analysis of plaque characteristics in the study groups

Parameter	All n = 77	Group 1 1 vulnerability marker n = 36	Group 2 >1 vulnerability marker n = 41	p value
Plaque length, mm	17.76 ± 5.115	16.26 ± 4.605	19.09 ± 5.227	0.0214
Stenosis, %	56.57 ± 11.25	54.03 ± 10.06	58.8 ± 11.88	0.0575
Minimum luminal area, mm^2	0.041 ± 0.026	0.047 ± 0.025	0.036 ± 0.026	0.0543
Eccentricity index	0.36 ± 0.22	0.374 ± 0.239	0.347 ± 0.219	0.6604
Remodeling index	1.079 ± 0.298	0.9619 ± 0.200	1.182 ± 0.333	0.0009
Vessel volume, mm^3	297 ± 139.1	256.2 ± 115.9	332.8 ± 148.9	0.0272
Lumen volume, mm^3	117.4 ± 64.97	108.6 ± 57.06	125 ± 70.61	0.4250
Plaque volume, mm^3	179.6 ± 97.6	147.5 ± 71.74	207.7 ± 108.9	0.0061
Calcified volume, mm^3	30.92 ± 37.69	34.2 ± 44.57	28.05 ± 30.7	0.9091
Calcified, %	18.52 ± 21.98	21.1 ± 24.67	16.26 ± 19.35	0.3377
Non-calcified volume, mm^3	148.7 ± 95.02	113.3 ± 64.2	179.8 ± 106.9	0.0017
Non-calcified, %	81.49 ± 21.97	78.91 ± 24.64	83.75 ± 19.35	0.4032
Lipid-rich volume, mm^3	11.49 ± 17.66	5.494 ± 6.352	16.75 ± 22.28	0.0128
Lipid-rich, %	5.71 ± 7.33	3.781 ± 3.887	7.405 ± 9.093	0.0661
Fibrotic volume, mm^3	137.2 ± 87.22	107.8 ± 60.67	163 ± 98.87	0.0049
Fibrotic, %	75.77 ± 20.91	75.13 ± 23.6	76.34 ± 18.52	0.7472

CT analysis of plaque-related features

When analyzing the CT characteristics of the target coronary plaques, we found no statistically significant differences between the two groups regarding the degree of vascular stenosis (p = 0.057), minimum lumen area (p = 0.054), eccentricity index (p = 0.660), lumen volume (p = 0.425), or other plaque related volumes (Table 3). However, the results showed significantly longer plaques in patients from Group 2, with more than one vulnerability feature (p = 0.021), a significantly higher remodeling index (0.96 ± 0.20 vs. 1.18 ± 0.33, p = 0.0009) and vessel volume (p = 0.027), as well as significantly more voluminous plaques (147.5 ± 71.74 mm^3 vs. 207.7 ± 108.9 mm^3, p = 0.006). The analysis of plaque-related volumes revealed that patients in Group 2 presented significantly larger non-calcified volumes (p = 0.001), larger lipid-rich volumes (p = 0.012), and larger fibrotic volumes (p = 0.004) in the analyzed coronary plaques (Table 3).

Periplaque fat, total pericardial fat, and thoracic fat in coronary vulnerability

Patients with more than one marker for coronary vulnerability (Group 2), presented a significantly larger volume

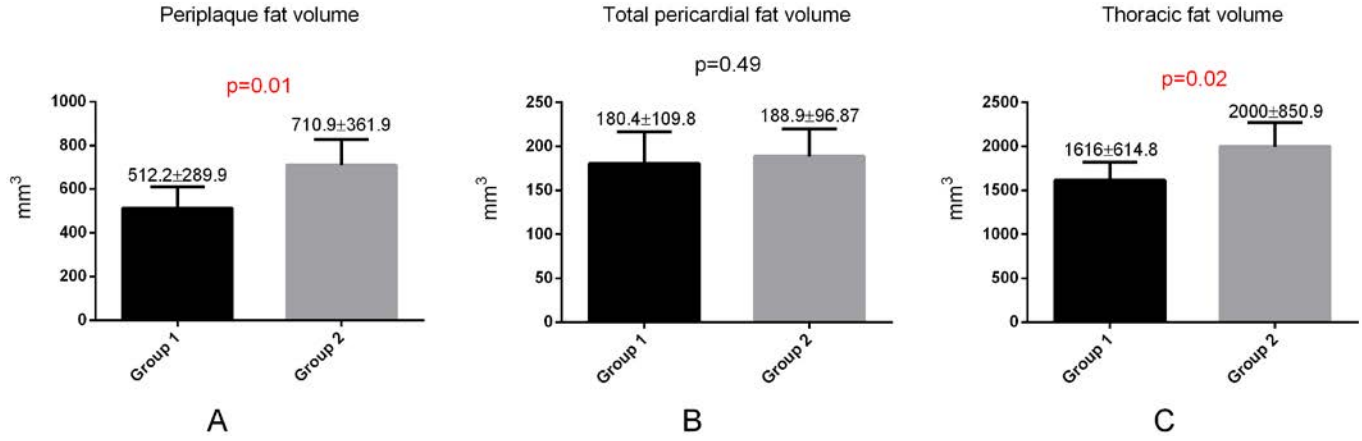

FIGURE 1. Comparative analysis between the two coronary vulnerability groups. **A** – Periplaque fat volume; **B** – Total Pericardial fat volume; **C** – Thoracic fat volume

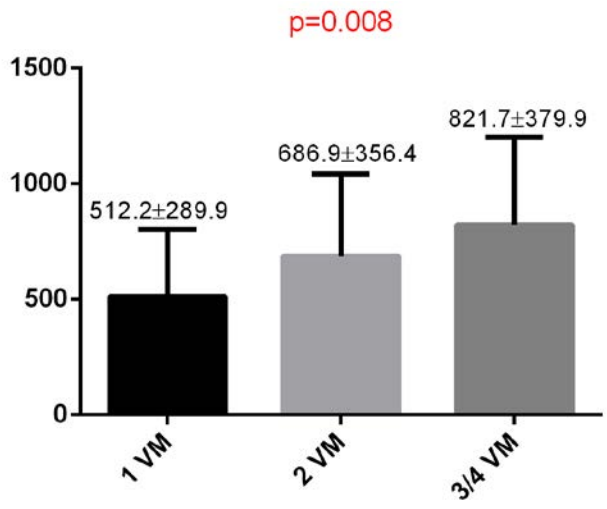

FIGURE 2. Periplaque fat (mm³) and vulnerability degree of coronary plaques. VM – vulnerability markers

of periplaque fat (PPF) compared to Group 1 (Figure 1A). No significant differences were recorded between the two groups regarding the total pericardial fat volume (Figure 1B), but the thoracic fat volume was significantly larger in Group 2 (p = 0.02) (Figure 1C).

The analysis of periplaque volume based on the vulnerability degree of the coronary plaques showed that patients with 3/4 CT markers for plaque instability presented a significantly higher volume of PPF compared to those presenting one or two markers, respectively (p = 0.008) (Figure 2).

Correlations between periplaque fat, total pericardial fat and plaque related volumes

Linear regression analysis revealed significant positive correlations between the volume of adipose tissue located around the analyzed plaque and the following plaque-related volumes: non-calcified volume (r = 0.474, 95% CI 0.2797–0.6311, p <0.0001), lipid-rich volume (r = 0.316, 95% CI 0.099–0.504, p = 0.005), and fibro-fatty volume (r = 0.452, 95% CI 0.2541–0.6142, p <0.0001) (Figure 3). However, there was no significant correlation between the periplaque volume and the total plaque volume (r = –0.12, 95% CI –0.3475–0.1063, p = 0.27) or the calcified volume (p = 0.6) (Figure 3).

The total pericardial fat was not significantly correlated with the plaque volume (p = 0.4), calcified volume

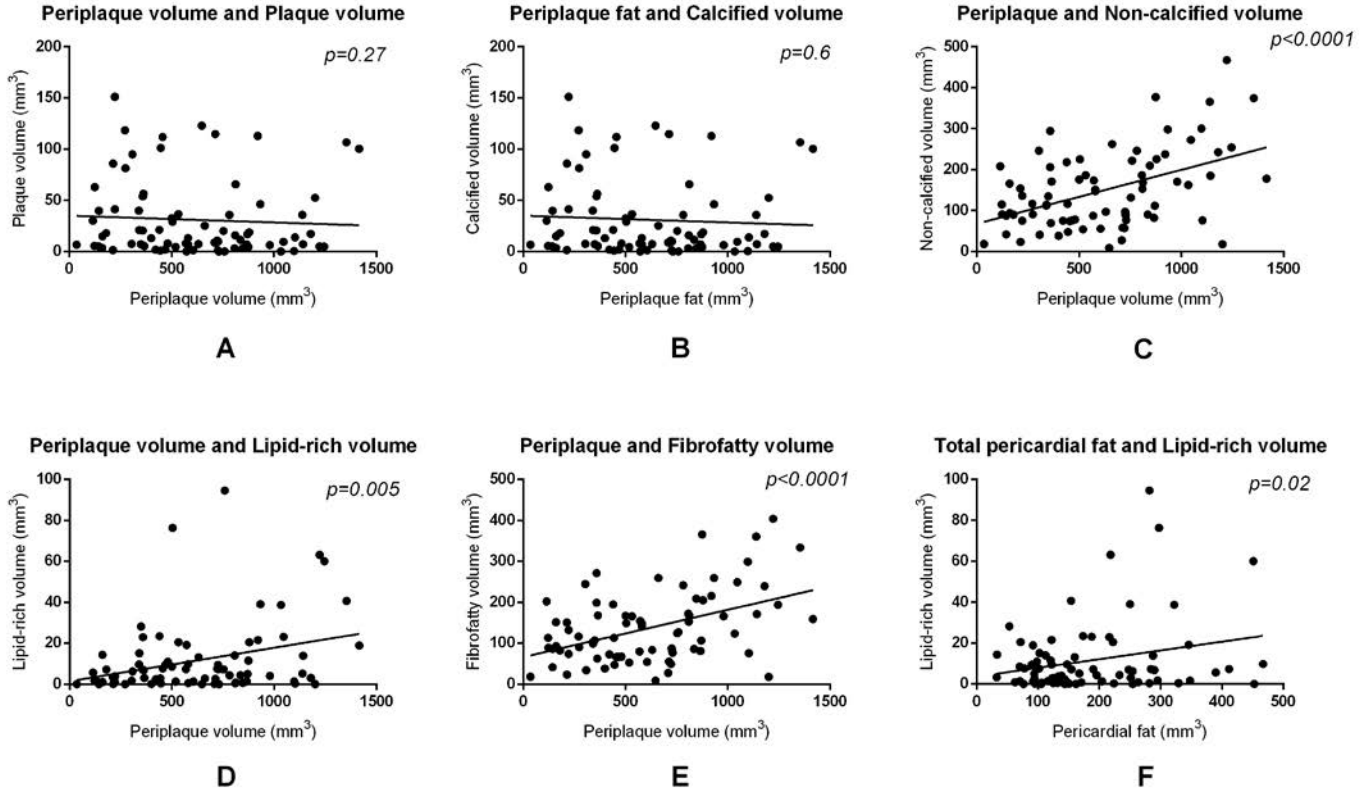

FIGURE 3. Correlations between periplaque fat volume and plaque volume (**A**), calcified plaque volume (**B**), non-calcified plaque volume (**C**), lipid-rich volume (**D**), fibro-fatty volume (**E**), and total pericardial fat and lipid-rich volume (**F**).

(p = 0.6), non-calcified plaque volume (p = 0.2), or fibro-fatty volume (p = 0.4). However, the lipid-rich volume plaques were significantly correlated with the total volume of the pericardial fat (p = 0.02) (Figure 3F).

DISCUSSIONS

The present study aimed to evaluate the relationship between the periplaque fat volume and the presence of CT vulnerability markers for coronary plaques. The adipose tissue surrounding the heart, more specifically the epicardial and pericardial fat, has been the subject of numerous studies that included coronary artery disease patients.[18,30] Epicardial fat represents the visceral adipose tissue between the myocardial cells and the visceral layer of the pericardial membrane, while the pericoronary or perivascular adipose tissue is observed in the vicinity of the coronary vessels. Moreover, the pericardial fat, which is similar to the subcutaneous adipose tissue, having also a common embryological origin, is located between the two layers of the pericardial membrane.[31]

Noninvasive evaluation of epicardial adipose tissue is performed with the help of 2D transthoracic echocardiography as a hypoechoic space at the level of the free wall of the right ventricle during diastole, with non-contrast multidetector computed tomography, which can assess either thickness or volume of the overall EF or in various segments, such as pericoronary or periplaque, as performed in the present study. The gold-standard imaging technique for epicardial fat evaluation is, however, cardiac magnetic resonance imaging, which presents higher costs and low availability, therefore having limited use.[32–34]

Both the pericardial and epicardial adipose tissue have been shown to be correlated with the overall increased cardiovascular risk, as well as with the presence of high-risk coronary plaques.[35,36] Pericoronary adipose tissue has recently emerged as a subject of interest in studies on novel cardiovascular risk factors and on promotors for coronary atherosclerosis and vulnerability.[37] Several studies on histopathological samples of epicardial adipose tissue have revealed that EF contains several pro-inflammatory mediators, which can contribute to the extravascular causes of atherosclerosis progression.[38–40]

The present study found that patients with significant coronary atherosclerosis, who presented high-risk coronary plaques, with more than one CT plaque vulnerability marker, presented significantly higher volumes of periplaque fat and thoracic fat volume compared to patients with one CT vulnerability marker (either positive remodeling, spotty calcifications, low attenuation plaque, or napkin ring sign). Despite the previously mentioned findings, we found no significant association between a higher degree of plaque vulnerability and the total volume of the pericardial adipose tissue. A subanalysis from the Framingham heart study showed that pericardial fat and visceral abdominal fat were independently associated with measures of obesity (waist circumference, body mass index) as cardiovascular risk factors, but the association was not valid after adjustments for traditional risk factors.[35]

In addition, when evaluating the volume of epicardial adipose tissue measured at the level of the target coronary plaque based on an increasing degree of coronary plaque vulnerability, we found that subjects with three or four CT vulnerability markers presented a significantly higher PPF volume compared to those with two or one vulnerability marker, respectively.

Although periplaque fat has not been studied, Hassan *et al.* sought to evaluate the relationship between the segmental epicardial fat volume, evaluated with the use of cardiac magnetic resonance (CMR), and the underlying coronary plaque characteristics in patients with stable angina. Their study included the evaluation of each coronary artery segment (n = 8) with the assessment of segmental adipose tissue volume (with CMR) and the evaluation of coronary plaque features via multidetector computed tomography. Their results revealed a significant correlation between segmental epicardial fat volume and increasing luminal stenosis (p <0.001), and lesions with mixed plaques and low-attenuation non-calcified plaques presented significantly greater volumes of segmental epicardial fat volumes compared to lesions with calcified or CT attenuation plaques.[25]

Our study found significant linear correlations between periplaque fat volume and several plaque-related volumes, which indicate a propensity towards higher vulnerability, including the non-calcified, lipid-rich, and fibro-fatty volumes. This finding suggests that a larger adipose tissue located near a hemodynamically significant coronary lesion is correlated with increased volumes of soft plaque components, which offers a higher degree of lesion instability. On the other hand, no significant correlations were found between the total plaque volume and the volume of calcified components within the analyzed plaque, and a higher extension of periplaque adipose tissue.

CONCLUSIONS

Epicardial adipose tissue located in the vicinity of hemodynamically significant coronary stenosis was associated with a higher degree of plaque vulnerability, as assessed

with cardiac computed tomography. Periplaque fat volume was significantly correlated with lipid-rich, fibro-fatty, and non-calcified plaque-related volumes, as markers for enhanced plaque vulnerability.

Pericardial fat volume was not significantly associated with a higher vulnerability degree of the analyzed coronary plaque, but it was significantly correlated with the lipid-rich volume.

Periplaque fat volume, assessed with native cardiac computed tomography, could become a novel marker for coronary plaque vulnerability, but further larger studies on obstructive coronary artery disease are required.

CONFLICT OF INTEREST

Nothing to declare.

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Epicardial Adipose Tissue Role as a Marker of Higher Vulnerability in Patients with Coronary Artery Disease

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ABSTRACT

Background: Epicardial adipose tissue (EAT) has been recently identified as a major player in the development of the atherosclerotic process. This study aimed to investigate the role of EAT as a marker associated with a higher vulnerability of atheromatous coronary plaques in patients with acute myocardial infarction (AMI) as compared to patients with stable angina. **Material and methods:** This analysis enrolled a total of 89 patients, 47 with stable angina (SA) and 42 with AMI, who underwent echocardiographic investigations and epicardial fat measurement in 2D-parasternal long axis view. The study lot was divided as follows: Group 1 included patients with prior AMI, and Group 2 included patients with SA. **Results:** There were no significant differences between the two groups regarding cardiovascular risk factors, excepting smoking status, which was recorded more frequently in Group 1 as compared to Group 2 (36.17% vs. 11.63%, p = 0.02). The mean epicardial fat diameter was 9.12 ± 2.28 mm (95% CI: 8.45–9.79 mm) in Group 1 and 6.30 ± 2.03 mm (95% CI: 5.675–6.93 mm) in Group 2, the difference being highly significant statistically (p <0.0001). The mean value of left ventricular ejection fraction was significantly lower in patients with AMI (Group 1 – 47.60% ± 7.96 vs. Group 2 – 51.23% ± 9.05, p = 0.04). EAT thickness values showed a weak but significant positive correlation with the level of total cholesterol (r = –0.22, p = 0.03) and with the value of end-systolic left ventricle diameter (r = 0.33, = 0.001). **Conclusions:** The increased thickness of EAT was associated with other serum- or image-based biomarkers of disease severity, such as the left ventricular ejection fraction, end-systolic diameter of the left ventricle, and total cholesterol. Our results indicate that EAT is significantly higher in patients with acute coronary syndrome, proving that EAT could serve as a marker of vulnerability in cardiovascular diseases.

Keywords: atheromatous plaque, epicardial fat, vulnerability marker, acute coronary syndrome

INTRODUCTION

Epicardial adipose tissue (EAT) represents an active organ with a high metabolic activity, releasing various bioactive molecules in the local and systemic circulation. The fat depots surrounding the heart represent a relevant repository of various biomolecules, such as adiponectin, resistin, and inflammatory cytokines, all being significantly involved in the development and progression of atherosclerosis.[1] This process is also related to an increased inflammatory response at the level of the coronary arteries, leading to plaque vulnerabilization and plaque rupture or erosion, and finally resulting in an acute coronary syndrome.

EAT has been significantly correlated to the risk of future cardiovascular diseases, also being associated with the frequency and severity of other diseases such as diabetes mellitus, renal failure, or various conditions characterized by an increased inflammatory status.[2] The amount of pericoronary epicardial fat was also associated with the presence of coronary plaques inside the coronary tree, in a significantly higher extent than other fat deposits such as periaortic or extracardiac fat.[3] At the same time, the association between EAT volume and the incidence of coronary artery disease (CAD) has been demonstrated by several studies that indicated a higher risk of cardiovascular death in patients with larger EAT volumes.[4]

As a result of various studies that demonstrated a significant relationship between EAT and pro-inflammatory biomarkers, EAT is nowadays considered to represent a significant source of pro-inflammatory cytokines acting at systemic and local levels as well.[5]

While inflammation plays a significant role in the atherosclerotic process, there is no conclusive study yet to demonstrate the association between EAT and the vulnerability of coronary lesions in cardiovascular patients. A strong link has been demonstrated between increased EAT and major adverse cardiovascular event (MACE) rates in CAD patients, revealing the role of EAT as a predictor of cardiovascular events.[6] It has been shown that EAT increase is associated with an increased risk of developing plaque in the coronary arteries, indicating that EAT could be a new marker of vulnerability. Thus, an increased EAT could indicate the risk of an acute coronary event, perhaps through an inflammatory mechanism, because it is well documented that inflammation plays a significant role in platelet formation, progression, and rupture. EAT has been shown to be closely and directly related to the severity of coronary lesions, while being an independent risk factor for CAD,[7] even though the EAT volume did not provide relevant information on the functional significance of a coronary artery stenosis.[8]

Various imaging techniques have been proposed for the evaluation of EAT. The most useful and reliable one is computerized tomography (CT), a technique that allows accurate quantification not only of the EAT volume but also of the amount of pericoronary EAT, as well as the density determination of this tissue.

Despite the advantages offered by these top techniques, echocardiography remains an easily accessible method that can be used for routine examination of patients with CAD, including EAT assessment. In a recent study, an initial EAT value of over 7 mm was shown to be a significant predictor for MACE, death, revascularization, and myocardial infarction.[9] However, echocardiography can only determine the EAT diameter, while CT offers the benefit of more reliable quantification and, at the same time, an assessment of plaque vulnerability.

The aim of this study was to evaluate the role of EAT as a marker of vulnerability in establishing clinical cardiovascular prognosis in a group of patients diagnosed with stable angina (SA) and myocardial infarction (MI).

MATERIAL AND METHODS

A total of 89 patients (47 with SA and 42 with MI) were enrolled to perform this assessment; all patients were admitted in the Cardio Med Medical Center in Tîrgu Mureș, Romania.

All patients underwent echocardiographic investigations using a Philips Sonos 7500 echocardiograph (Eindhoven, Netherlands), which included the determination of EAT thickness (EATT), left ventricular end-diastolic (EDLVD) and end-systolic (ESLVD) diameters, and left ventricular ejection fraction (LVEF). In addition, demographic data, medical history, routine biochemistry results, cardiovascular antecedents, and risk factors were also recorded upon admission.

The patients were divided into two groups, as follows: Group 1 comprised patients with non-anterior MI (lower MI, posterior IM, VDD) and anterior MI (antero-lateral MI, anteroseptal IM, lateral MI) and Group 2 comprised patients with SA.

The study was approved by the Ethics Committee of the institution, and all patients agreed with the investigations and signed an informed consent form. All study procedures were conducted in accordance with the World Medical Association's Declaration of Helsinki code of ethics.

Statistical analysis of the collected data was performed using the GraphPad Prim 3.1 software (GraphPad Software, Inc., San Diego, USA). Continuous variables are presented as mean ± standard deviation, while categorical

TABLE 1. Patient baseline characteristics and cardiovascular risk factors

	Total (n = 89)	Group 1 (n = 47)	Group 2 (n = 42)	p value
		Mean ± SD (95%CI)		
Age (years)	63.49 ± 11.37 (61.11–65.87)	61.83 ± 11.60 (58.42–65.23)	65.30 ± 10.96 (61.93–68.67)	0.71
Male gender (n, %)	59 (66.29%)	35 (74.46%)	24 (57.14%)	0.08
Hypertension (n, %)	63 (70.78%)	28 (68.09%)	35 (83.72%)	0.13
Dyslipidemia (n, %)	21 (23.59%)	15 (31.91%)	6 (13.95%)	0.07
Smoking status * (n, %)	22 (24.71%)	17 (36.17%)	5 (11.63%)	0.02
Diabetes mellitus (n, %)	35(39.32%)	17 (36.17%)	18 (41.86%)	0.58
History of atherosclerosis (n, %)	25 (46.06%)	10 (21.28%)	15 (34.88%)	0.15

* Past or present

variables are expressed as numbers and percent values (%). Student's t test was used for normally distributed continuous variables and the Mann-Whitney test for non-normally distributed continuous variables. Logistic regression analysis was performed in order to investigate the association between EATT and echocardiographic parameters. All statistical tests were two-sided, and a p value lower than the threshold $\alpha = 0.05$ was considered statistically significant.

RESULTS

A total of 89 patients were included in the study, of which n = 47 (52.80%) presented stable angina (Group 2) and n = 42 (47.20%) presented MI (Group 1). The patients' baseline characteristics, cardiovascular risk factors assessment, and the differences between the two groups are summarized in Table 1. The male population was larger in patients presenting MI: 74.46% of cases in Group 1 and 57.14% of patients from Group 2, though the difference was not statistically significant (p = 0.08). There were no significant differences between the two groups regarding history of atherosclerosis (p = 0.15), hypertension (p = 0.13), diabetes mellitus (p = 0.58), dyslipidemia (p = 0.07), excepting smoking status, in Group 1 smoking being more frequent than in Group 2 (36.17% vs. 11.63%, p = 0.02).

The biochemical laboratory data analysis of the two groups showed that patients from Group 1 had significantly greater values than patients from Group 2 for the following biochemical parameters: hematocrit (43.13% ± 4.69 vs. 40.48% ± 4.564, p = 0.004), total cholesterol (202.5 ± 36.78 mg/dL vs. 175.9 ± 48.80 mg/dL, p = 0.003), liver enzymes ASAT (185.6 ± 156.0 U/L vs. 34.14 ± 32.06 U/L, p < 0.0001) and ALAT (52.30 ± 26.46 U/L vs. 29.68 ± 17.97 U/L, p < 0.0001) (Table 2).

The main echocardiographic structural and functional parameters according to group diagnosis classification are presented in Table 3. There were no significant differences between the two studied groups in terms of clinical characteristics such as NYHA class (p = 1.00), presence of tricuspid insufficiency (p = 0.48), mitral insufficiency (0.73), aortic insufficiency (p = 0.45), and pulse rate (p = 0.31) (Table 3).

TABLE 2. Biochemical laboratory data characteristics of the two groups

	Total (n = 89)	Group 1 (n = 47)	Group 2 (n = 42)	p value
		Mean ± SD (95%CI)		
Hematocrit (%)	41.86 ± 4.79 (40.86–42.87)	43.13 ± 4.69 (41.75–44.51)	40.48 ± 4.56 (39.07–41.88)	0.004
Triglycerides (mg/dL)	159.4 ± 76.63 (143.3–175.4)	167.0 ± 93.83 (139.5–194.6)	151.0 ± 51.61 (135.1–166.9)	0.75
Total cholesterol (mg/dL)	189.8 ± 44.74 (180.4–199.2)	202.5 ± 36.78 (191.7–213.3)	175.9 ± 48.80 (160.9–198.0)	0.003
Glycemia (mg/dL)	150.5 ± 93.02 (130.9–170.0)	156.0 ± 81.51 (131.8–180.2)	144.5 ± 104.6 (112.3–176.7)	0.10
Creatinine (mg/dL)	1.12 ± 0.52 (1.0–1.23)	1.04 ± 0.45 (0.91–1.17)	1.20 ± 0.59 (1.02–1.38)	0.06
Urea (mg/dL)	44.61 ± 26.88 (38.98–50.24)	43.57 ± 24.97 (36.24–50.90)	45.75 ± 29.09 (36.80–54.70)	0.75
Uric acid (mg/dL)	5.73 ± 1.93 (5.33–6.14)	5.56 ± 2.12 (4.93–6.18)	5.93 ± 1.70 (5.40–6.45)	0.15
ASAT (U/L)	114.1 ± 137.8 (85.08–143.1)	185.6 ± 156.0 (139.7–231.4)	34.14 ± 32.06 (24.15–44.13)	< 0.0001
ALAT (U/L)	41.49 ± 25.36 (36.18–46.81)	52.30 ± 26.46 (44.53–60.07)	29.68 ± 17.97 (24.15–35.21)	< 0.0001

TABLE 3. Clinical and echocardiographic characteristics

	Total (n = 89)	Group 1 (n = 47)	Group 2 (n = 42)	p value
		Mean ± SD (95%CI)		
MI type, anterior (n,%)	17 (19.10%)	8 (17.02%)	–	ns
MI type, non-anterior (n,%)		9 (19.14%)	–	
NYHA class 0	20 (22.47%)	10 (21.28%)	10 (23.26%)	1.00
NYHA class > II	67 (75.28%)	37 (78.72%)	30 (70.21%)	
Tricuspid insufficiency (n,%)	65 (73.03%)	33 (70.21%)	32 (76.74%)	0.48
Mitral insufficiency (n,%)	9 (10.11%)	4 (8.51%0	5 (11.63%)	0.73
Aortic insufficiency (n,%)	58 (65.16%)	32 (68.09%)	26 (60.47%)	0.45
Puls rate (bpm)	71.33 ± 8.99 (69.42–73.25)	72.26 ± 8.085 (69.88–74.63)	70.25 ± 9.948 (67.07–73.43)	0.31
LVEF (%)	49.33 ± 8.64 (47.52–51.14)	47.60 ± 7.96 (45.26–49.93)	51.23 ± 9.05 (48.45–54.02)	0.04
ESLVD (mm)	54.23 ± 5.99 (52.98–55.49)	39.32 ± 6.96 (37.28–41.36)	36.40 ± 7.15 (34.18–38.60)	0.05
EDLVD (mm)	37.92 ± 7.16 (36.42–39.42)	54.79 ± 5.52 (53.17–56.41)	53.63 ± 6.48 (51.63–55.62)	0.18
DsT (ms)	234.1 ± 63.21 (220.8–247.3)	239.6 ± 69.55 (219.2–260.0)	228.0 ± 55.64 (210.9–245.1)	0.6
Epicardial fat tissue diameter (mm)	7.77 ± 2.58 (7.23–8.31)	9.12 ± 2.28 (8.45–9.79)	6.30 ± 2.03 (5.675–6.93)	< 0.0001
Systolic blood pressure (mmHg)	127.8 ± 12.80 (123.4–132.3)	128.9 ± 14.40 (121.5–136.3)	126.8 ± 11.31 120.9–132.6	0.02
Diastolic blood pressure (mmHg)	74.24 ± 11.25 (70.25–78.23)	76.56 ± 14.32 (68.93–84.20)	72.06 ± 7.08 (68.42–75.70)	0.40

LVEF – left ventricle ejection fraction; ESLVD – end-systolic left ventricle diameter; EDLVD – end-diastolic left ventricle diameter; DsT – deceleration time

The mean epicardial fat diameter was 9.12 ± 2.28 mm (95% CI: 8.45–9.79 mm) for Group 1 and 6.30 ± 2.03 mm (95% CI: 5.675–6.93 mm) for Group 2, the difference being highly statistically significant (p <0.0001) (Figure 1). The mean value of LVEF measured by echocardiography was significantly lower in patients presenting MI (Group 1 – 47.60% ± 7.96 vs. Group 2 – 51.23% ± 9.05, p = 0.04) (Figure 2).

The analysis of structural echocardiographic parameters showed no statistically significant differences between the two groups in regard to the ESLVD (p = 0.05), EDLVD (p = 0.18), and deceleration time (p = 0.6) (Figure 2).

EATT values showed a weak but significant positive correlation with the level of total cholesterol (r = –0.22, p = 0.03) (Figure 3) and with the value of ESLVD (r = 0.33, p = 0.001) (Figure 4).

The simple linear regression analysis demonstrated that the EAT volume was negatively correlated with the level of LVEF (r = –0.34, p = 0.0009) (Figure 5).

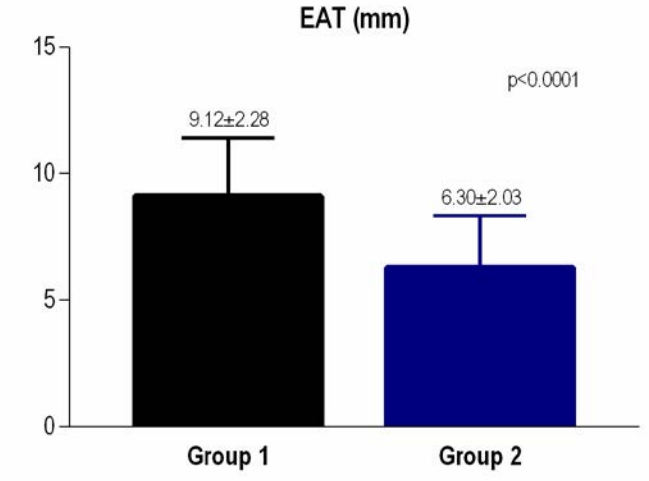

FIGURE 1. Epicardial adipose tissue diameter in the two studied groups

DISCUSSION

In recent years, several studies have investigated a potential correlation between EAT and coronary artery plaque load, represented by different biomarkers, considering the biochemical properties of EAT and its role as a possible cardiovascular risk and vulnerability factor.[10] An estimate of EAT volume would be important, so several methods have been applied as a surrogate for its assessment. The noninvasive quantitative assessment of EAT volume on CT is feasible and could play an important role in assessing cardiovascular risk and vulnerability. Its correlation with the presence of CAD, severity, and prognosis have been demonstrated in various studies.[11]

EAT has been shown to be related to the presence and severity of coronary atherosclerotic lesions.[12,13] Studies revealed that subjects with an increased EAT value evaluated either by CT or cardiac echocardiography exhibit a more

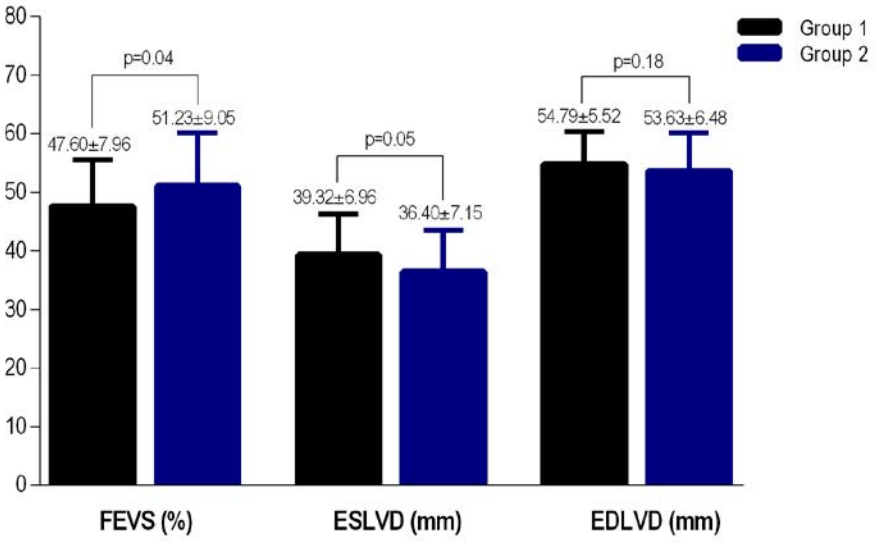

FIGURE 2. Comparison between structural echocardiographic parameters of the study groups

severe extension of coronary atherosclerosis, and EAT is also related to total plaque load and cardiovascular risk factors,[14–16] results confirmed by the present study where patients with MI showed significantly higher volumes of total cholesterol and presented dyslipidemia more frequently than patients with stable angina.

In addition, the incidence of MI appears to be directly proportional to the increase in epicardial fat, which is also related to a higher rate of MACE in subjects with known CAD.[11,17,18]

Furthermore, it has been shown that the thickness of epicardial fat is closely linked to the presence of multivascular CAD in patients with acute myocardial infarction.[19]

Wang *et al.* showed that there was a significantly higher rate of MACE during hospitalization for AMI in patients with an EAT thickness of >4.7 mm (p = 0.02) after multivariate adjustments.[20] Another study of the prognostic value of EAT in STEMI compared with NSTEMI showed that an average 2.6 mm of EAT had a significant predictive

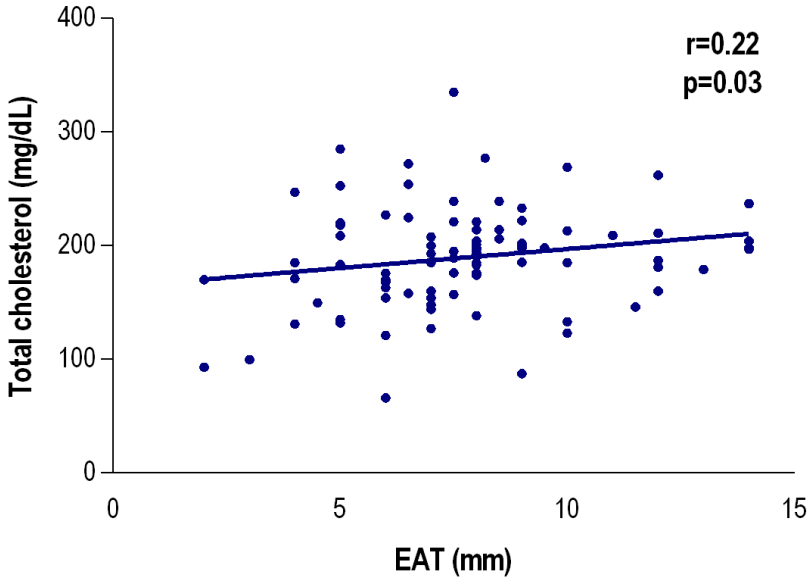

FIGURE 3. Correlation between the thickness of the epicardial adipose tissue and the levels of total cholesterol

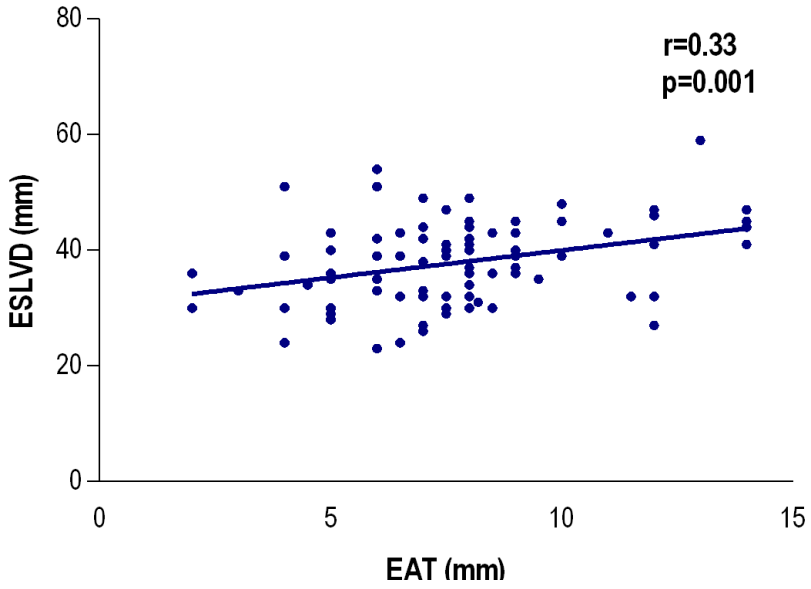

FIGURE 4. Correlation between the thickness of the epicardial adipose tissue and the diameter of end-systolic left ventricle

capacity for the primary endpoint of both univariate and multivariate regression.[21]

Tanindi *et al.* showed that patients with AMI had a significantly higher EAT compared to unstable angina or stable CAD patients (p <0.001). Similarly, the present investigation revealed that patients from Group 1, presenting MI, had significantly higher EATT values than patients from Group 2, diagnosed with stable angina (p <0.0001).[22]

Also, epicardial fat was associated with an increase in systemic inflammatory status in patients with type 2 diabetes mellitus with AMI, and a higher EAT thickness was associated with an improved left ventricular remodeling process and a lower ejection fraction at six months.[23] Also, Tanindi *et al.* demonstrated that EAT thickness measured by echocardiography is independently associated with MI.[24]

Epicardial fat could provide additional evidence of future cardiac events in patients with acute coronary syndromes (ACS). It is well known that an increase in systemic inflammatory status leads to a lower prognosis in

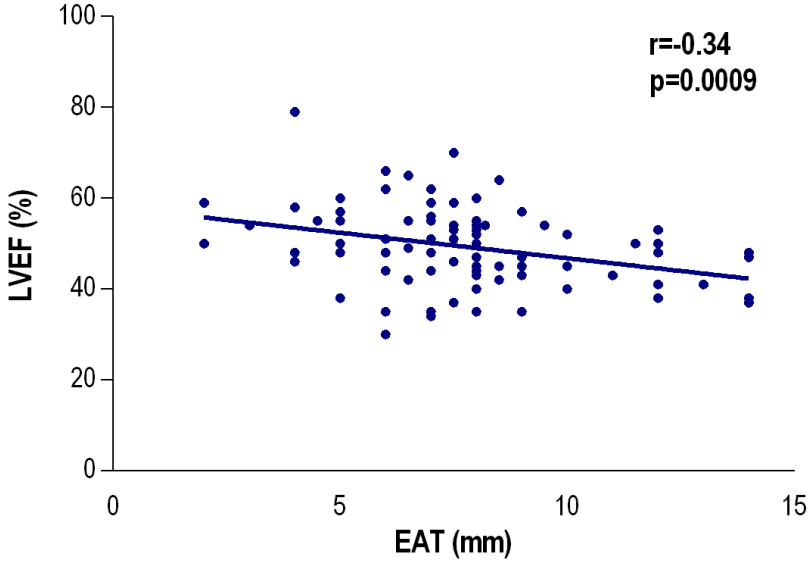

FIGURE 5. Correlation between the thickness of the epicardial adipose tissue and LVEF

patients with STEMI.[25,26] As an active metabolic tissue that secretes inflammatory cytokines and chemokines, epicardial fat may contribute to global inflammation, adversely affecting the outcome and prognosis of patients with ACS. EAT thickness can be used as a predictor of MACE, including MI and sudden death.[24] In addition, it has been shown that an increased volume of epicardial adipose tissue predicted MI or cardiovascular death in patients suspected of CAD.[27]

CONCLUSIONS

In conclusion, there is a relationship between EATT and coronary atherosclerotic burden in CAD patients. The increased thickness of EAT was associated with other biomarkers of disease severity such as LVEF, ESLVD, and total cholesterol. Therefore, the EAT volume could represent a new imaging-derived biomarker, useful to characterize the severity of CAD. Information provided by EAT can be used as a predictor of MACE in patients with ACS, both in the short and long term. Our results indicate that EAT is significantly higher in patients with ACS; thus, we can state that EAT could play a role of marker of vulnerability in establishing cardiovascular prognosis.

CONFLICT OF INTEREST

None to declare.

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ORIGINAL RESEARCH

CARDIOLOGY // RHEUMATOLOGY

The Effect of Epicardial Fat on the Right and Left Ventricular Function in Subjects with Various Etiological Types of Pulmonary Arterial Hypertension

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ABSTRACT

Background: Little is known on the effect of epicardial fat in pulmonary arterial hypertension (PAH). Therefore, the present study sought to perform a comparative analysis on the influence of epicardial fat thickness (EFT) on the right and left ventricular function, between three different etiological varieties of pulmonary arterial hypertension: caused by congenital heart defects (atrial septum defects with left to right shunt), by systemic sclerosis, and by myocardial ischemia. **Materials and Methods:** This is a prospective observational study on 50 patients with documented PAH (systolic pulmonary artery pressure – PASP of >35 mmHg). The thickness of the epicardial adipose tissue was evaluated by 2D cardiac ultrasound, on the free wall of the right ventricle, during end-diastole, in the long parasternal axis view. The patients were divided into three study groups: Group 1 – PAH determined by congenital heart defects with left to right shunts (atrial septum defects, n = 25); Group 2 – PAH induced by systemic sclerosis (n = 12); Group 3 – PAH induced by myocardial ischemia (n = 13). **Results:** The average age was 54.48 ± 10.78 years, 30% (n = 15) of subjects were males, with a mean body mass index of 24.65 ± 4.40 kg/m^2, EFT was 9.15 ± 2.24 mm, and the PASP was 41.33 ± 5.11 mmHg. Patients in Group 3 were more likely to smoke (p = 0.025) and presented a significantly lower LVEF, compared to the other groups (Group 1: 60% ± 6 vs. Group 2: 60% ± 7 vs. Group 3: 48% ± 7, p <0.0001). The largest EFT was found in Group 3 (11.08 ± 2.39 mm), followed by Group 2 (9.14 ± 2.03 mm), and Group 1 (8.16 ± 1.57 mm) (p = 0.0003). The linear regression analysis found no significant correlations between EFT and other echocardiographic parameters: PASP (r = –0.228, p = 0.118), LVEF (r = –0.265, p = 0.06), TAPSW (r = 0.015, p = 0.912), TEI (r = 0.085, p = 0.552), RVEDD (r = –0.195, p = 0.173), RA area (r = –178, p = 0.214), and LA diameter (r = 0.065, p = 0.650). **Conclusions:** Epicardial fat thickness was found to be significantly higher in patients with PAH induced by myocardial ischemia, followed by those with systemic sclerosis and congenital heart defects, respectively. EFT did not influence the echocardiographic parameters for left and right ventricular function in patients with pulmonary arterial hypertension of different etiologies.

Keywords: pulmonary arterial hypertension, epicardial fat thickness, systemic sclerosis, atrial septum defects, myocardial ischemia

INTRODUCTION

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) represents an increase in the pulmonary arterial pressure above 25 mmHg, triggered by a progressive rise in pulmonary vascular resistance due to vasoconstriction, vascular remodeling, fibrosis, and inflammation.[1] Several studies have identified the presence of proinflammatory cytokines as promoters of PAH, including interleukins, tumor necrosis factor, and autoantibodies, which advocate for the autoimmune inflammatory pathogenesis of the disease.[2,3] Vessel remodeling and increased vascular resistance in the pulmonary arterial circulation leads to overload of the right cardiac chambers, with right ventricular hypertrophy, tricuspid regurgitation, and subsequent right atrial remodeling, and in case of associated right ventricle ischemia or fibrosis, the evolution is towards right cardiac failure. The clinical presentation of PAH includes shortness of breath, syncope during physical exertion, fatigue, chest pain, or even death due to right ventricular failure, while the clinical examination reveals signs of increased pressure in the right heart, jugular distension, hepatojugular reflex, peripheral edema, and hepatomegaly.[4,5]

PAH is categorized in 5 subgroups, according to its etiology, as follows: subgroup 1 – idiopathic or familial PAH; subgroup 2 – PAH caused by left heart failure (systolic, diastolic, or valvular); subgroup 3 – PAH caused by respiratory disorders with pulmonary fibrosis, including bronchial asthma, emphysema, interstitial lung disease, or chronic obstructive pulmonary disease; subgroup 4 – PAH caused by chronic pulmonary embolism; subgroup 5 – unclear or multifactorial pathomechanisms.[6]

Although the most cited causes for PAH include pulmonary and left-sided heart disease, congenital cardiac diseases with systemic to pulmonary shunt are associated with pulmonary arterial hypertension.[7] PAH has been reported in around 9–35% of cases with open or closed atrial septum defect, but the pulmonary vascular disease can be prevented if the left to right shunt is corrected before the development of Eisenmenger syndrome or shunt reversal occurs.[8]

Left ventricular failure caused by myocardial ischemia is characterized by increased filling pressures, either due to diastolic dysfunction or mitral regurgitation, which in turn triggers pulmonary venous hypertension and postcapillary pulmonary hypertension. This complex mechanism will lead to endothelial dysfunction and pulmonary vascular remodeling, which in time, will resemble the changes that are present in patients with primary pulmonary hypertension.[9,10]

Autoimmune diseases, such as systemic sclerosis, often present PAH as a complication, and studies have shown that approximately 8–12% of patients with systemic sclerosis present different stages of PAH.[11,12] Moreover, PAH occurring as a complication of systemic connective tissue disorders is associated with significantly higher mortality rates in comparison to patients with other forms of PAH, including the idiopathic form.[13]

Epicardial fat in various clinical settings

Epicardial adipose tissue has been widely researched for its impact on several cardiovascular disorders including ischemic heart disease, acute coronary syndromes, heart failure, and metabolic syndromes.[14,15] Furthermore, epicardial fat was found to be increased in several autoimmune disorders such as systemic sclerosis, psoriasis, or polyarthritis. Epicardial fat volume, measured by cardiac computed tomography, has been shown to be larger in patients with systemic sclerosis compared to controls, and patients with associated PAH present larger epicardial fat volumes compared to those with systemic sclerosis without PAH.[16–18] Also, epicardial fat thickness (EFT) has been associated with the severity of pulmonary disorders that are known for being associated with pulmonary hypertension, and EFT is associated with a higher extent of right ventricular remodeling in patients with chronic obstructive pulmonary disorders.[19]

Little is known on the effect of epicardial fat in pulmonary arterial hypertension. Therefore, the present study sought to perform a comparative analysis on the influence of EFT on the right and left ventricular function, between three different etiological varieties of pulmonary arterial hypertension: caused by congenital heart defects (atrial septum defects with left to right shunt), by systemic sclerosis, and by myocardial ischemia, with the help of 2D transthoracic echocardiography.

MATERIALS AND METHODS

This is a prospective observational study that included 50 patients with documented PAH, with a systolic pulmonary artery pressure of >35 mmHg, as measured with Doppler echocardiography. All patients underwent a complete 2D transthoracic echocardiography examination with assessment of the following parameters: (a) for left cardiac chambers: left ventricular ejection fraction (LVEF), left atrium diameter, tissue Doppler (septal and lateral e'); and

(b) for right cardiac chambers: pulmonary arterial systolic pressure (PASP), right ventricular end-diastolic diameter (RVEDD), tricuspid annular plane systolic excursion (TAPSE), right atrium area, right ventricular myocardial performance index (Tei index).

The thickness of epicardial adipose tissue was evaluated by 2D cardiac ultrasound, on the free wall of the right ventricle, during end-diastole, in the long parasternal axis view, with the ultrasound beam perpendicular to the aortic annulus. Epicardial fat was viewed as a hypoechoic space between the free wall of the right ventricle and the visceral epicardial membrane.

All echocardiography evaluations were performed with a Vivid E9 Ultrasound system (General Electric Vingmed Ultrasound, Horten, Norway). All patients signed a written informed consent before being included in the study, and the research was approved by the Ethics Committee for Scientific Research of the University of Medicine and Pharmacy of Tîrgu Mureș, Romania.

All patients underwent complete evaluation of cardiovascular risk factors, comorbidities, and demographic characteristics.

The total number of patients included 3 different etiological types of PAH: Group 1 – PAH determined by congenital heart defects with left to right shunts, more specifically with various types of atrial septum defects (n = 25); Group 2 – PAH induced by connective tissue disorders, more specifically by systemic sclerosis (n = 12); Group 3 – PAH induced by myocardial ischemia (n = 13).

Statistical analysis was performed with GraphPad Prism 6 statistical software (GraphPad Software, Inc., San Diego, USA), and a two-tailed p value of <0.05 was considered statistically significant. To test the normality of distribution for numerical data, D'Agostino Pearson normality test was used, continuous data was shown as mean ± standard deviation and median respectively, and categorical variables were expressed as percentages and integer values. Pearson and Spearman coefficients were used for correlation analysis.

RESULTS

The average age of the study population was 54.48 ± 10.78 years, and 30% (n = 15) of the subjects were males. The mean body mass index was 24.65 ± 4.40 kg/m2, epicardial fat thickness was 9.15 ± 2.24 mm, and the PASP was 41.33 ± 5.11 mmHg.

The echocardiographic parameters for the total study population and patient comorbidities are listed in Table 1.

The comparative analysis between the three PAH etiological categories showed that there was a significantly higher percentage of smokers in the ischemic PAH group (p = 0.025), but no other significant difference was observed, more specifically with regard to age (p = 0.267), gender (p = 0.09), body mass index (p = 0.679), or cardiovascular risk factors (Table 2).

Analysis of the echocardiographic parameters showed that patients in Group 3 (PAH induced by myocardial ischemia) presented a significantly lower LVEF compared to the other groups, as both groups had a mean LVEF above 60% (Figure 1). No significant difference was found between the three patient categories in relation to the RVEDD (Group 1: 31.34 ± 2.69 mm vs. Group 2: 31.92 ± 1.73 mm vs. Group 3: 30.92 ± 2.25 mm, p = 0.584), the TAPSE value (Group 1: 25.04 ± 5.94 mm vs. Group 2: 25.75 ± 2.30 mm vs. Group 3: 24 ± 4.41 mm, p = 0.670), the TEI index (Group 1: 0.46 ± 0.41 vs. Group 2: 0.59 ± 0.38 vs. Group 3: 0.39 ± 0.64, p = 0.393), left atrium diameter (Group 1: 38.12 ± 6.26 mm vs. Group 2: 37.58 ± 5.97 mm vs. Group 3: 39.85 ± 3.84 mm, p = 0.566), or the PASP value (Group 1: 41.84 ± 5.28 vs. Group 2: 41.83 ± 5.52 vs. Group 3: 39.88 ± 4.47, p = 0.502).

The largest EFT was found in Group 3 – myocardial ischemia PAH (11.08 ± 2.39 mm), followed by Group 2 – systemic sclerosis PAH (9.14 ± 2.03 mm) and Group 1 – congenital heart defects PAH (8.16 ± 1.57 mm), the difference being statistically significant (p = 0.0003) (Figure 2).

Linear regression analysis showed that there were no statistically significant correlations between epicardial fat

TABLE 1. Clinical and echocardiographic characteristics of the total study population

Echocardiographic parameters	Mean ± SD
LVEF (%)	57.12 ± 7
RVEDD (mm)	31.37 ± 2.36
TAPSE (mm)	24.94 ± 4.86
TEI	0.54 ± 0.40
LA diameter (mm)	38.44 ± 5.62
RA area (mm2)	14.78 ± 3.5
T1 (ms)	455.7 ± 110.9
T2 (ms)	317 ± 84.64
LVEDD (mm)	47.96 ± 4.18
LVESD (mm)	31.32 ± 3.92
Septal e' (cm/s)	14.66 ± 2.69
Lateral e' (cm/s)	12.32 ± 2.38
Cardiovascular risk factors	**n (%)**
Hypertension	15 (30%)
Dyslipidemia	9 (18%)
Obesity	7 (14%)
Smoking	11 (22%)
Previous stroke	9 (18%)

TABLE 2. Comparative analysis of clinical characteristics and cardiovascular risk factors between the three etiological PAH groups

	Group 1 (congenital heart defects) n = 25	Group 2 (systemic sclerosis) n = 12	Group 3 (myocardial ischemia) n = 13	p value
Age (years)	52.12 ± 12.23	55.67 ± 9.792	57.92 ± 7.815	0.267
Male gender, n (%)	11 (44%)	2 (16.6%)	2 (15.3%)	0.09
BMI (kg/m^2)	24.03 ± 3.94	24.97 ± 4.43	25.55 ± 5.30	0.672
Hypertension, n (%)	5 (20%)	3 (25%)	7 (53.8%)	0.053
Dyslipidemia, n (%)	2 (8%)	2 (16.6%)	4 (30.7%)	0.191
Obesity, n (%)	1 (4%)	2 (16.6%)	3 (23%)	0.194
Smoke, n (%)	2 (8%)	3 (25%)	6 (46.1%)	0.025
Stroke, n (%)	2 (8%)	3 (25%)	4 (30.7%)	0.171

thickness, measured by 2D echocardiography, and other echocardiographic parameters (Figure 3).

DISCUSSIONS

The present study aimed to evaluate the role of epicardial fat thickness, measured with the help of transthoracic cardiac ultrasound, on the right and left ventricular function in patients with 3 etiological varieties of PAH, more precisely PAH induced by atrial septum defect with right to left shunt, PAH induced by left ventricular myocardial ischemia, and PAH induced by systemic sclerosis.

The main findings of the study were: (1) the largest EFT was found in patients from the myocardial ischemia group, followed by those with systemic sclerosis and with congenital heart defects; (2) there were no statistically significant correlations between any of the measured echocardiographic parameters for left or right ventricular function and the thickness of the epicardial adipose tissue; (3) subjects with myocardial ischemia were more likely to smoke, and they presented, as expected, a significantly lower left ventricular ejection fraction compared to the rest of the groups.

Epicardial adipose tissue has been proved to be a reliable predictor for myocardial ischemia, the severity of coronary artery disease, as well as the rates of major adverse cardiovascular events in patients with acute coronary syndromes. Likewise, many researchers have connected epicardial fat with established risk prediction tools for acute coronary syndromes such as GRACE (Global Registry for Acute Coronary Events), TIMI (Thrombolysis In Myocardial Infarction) or the angiographic SYNTAX score.[14,20–22]

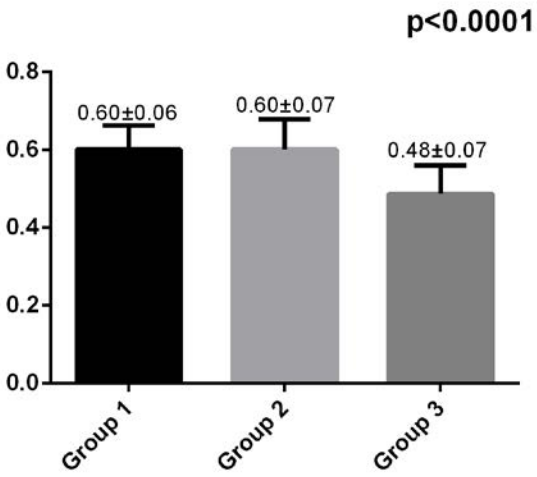

FIGURE 1. Left ventricular ejection fraction between the three etiological PAH groups

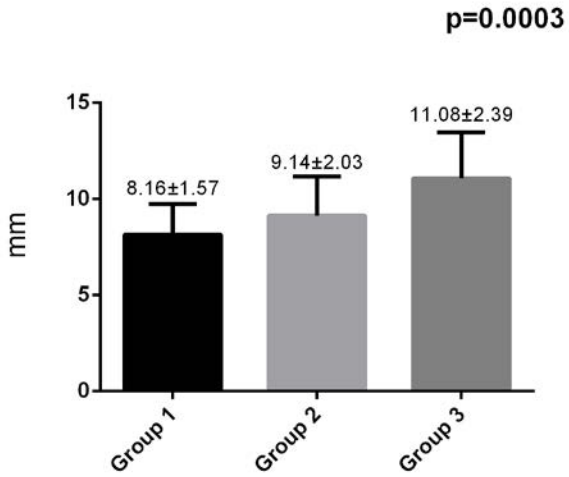

FIGURE 2. Epicardial fat thickness between the three etiological PAH groups

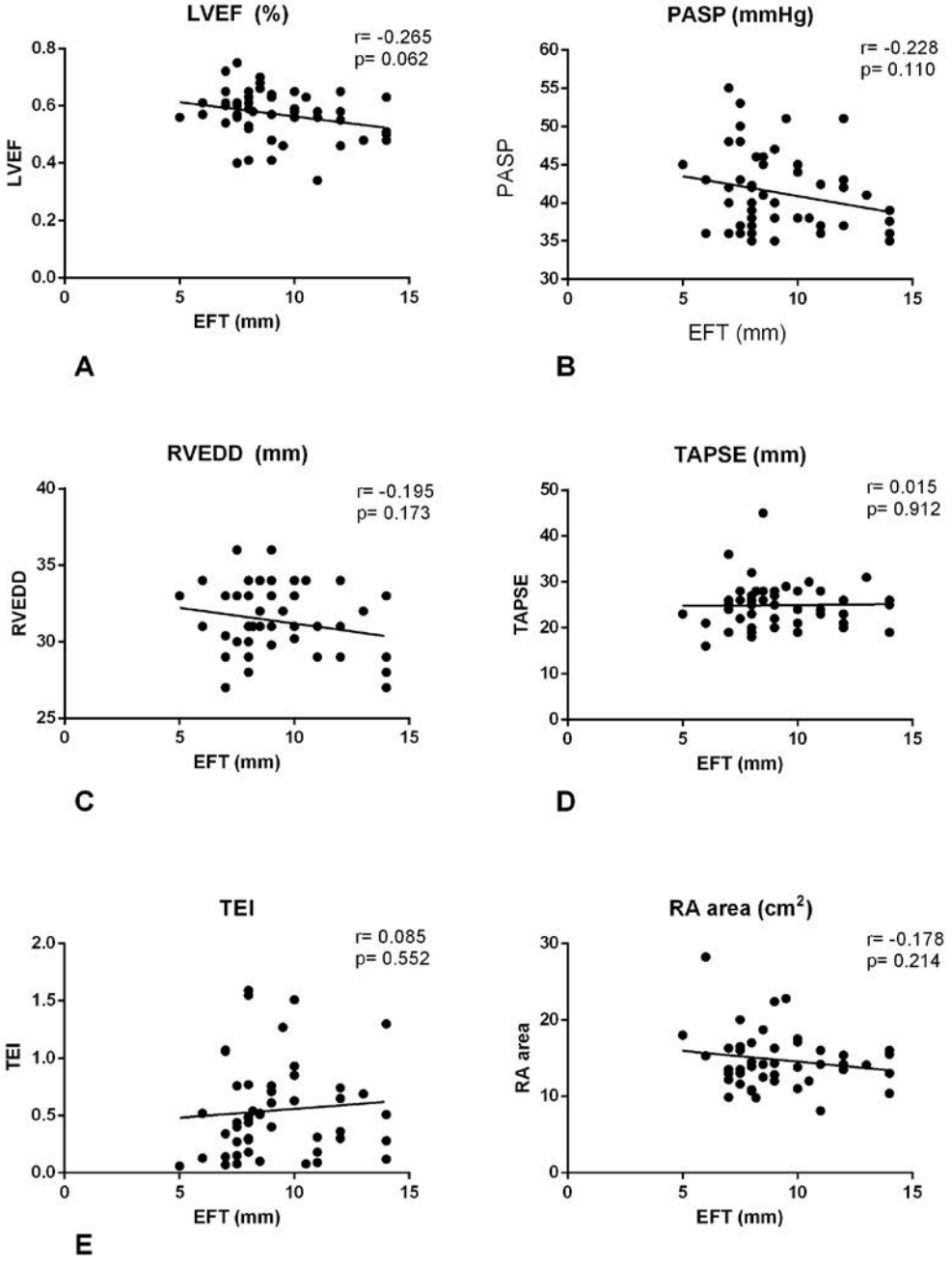

FIGURE 3. Correlations between the EFT and echocardiographic parameters for right and left ventricular function, in the overall study population

In addition, the LVEF was significantly lower in patients with PAH induced by ischemic cardiomyopathy, while the other two patient categories both presented a preserved ejection fraction of over 60%. While the lower ejection fraction, illustrative for left ventricular systolic dysfunction, was to be expected, regarding the larger epicardial fat, remains the age-old chicken-egg conundrum as to which came first: are patients at a higher risk for developing myocardial ischemia due to a larger epicardial adipose tissue, or is it that the epicardial fat thickness develops more because of the already established ischemia?

Being a type of visceral adipose tissue, epicardial fat is believed to influence insulin resistance, to enhance the overall cardiometabolic risk, and to promote a pro-inflammatory status.[23] Several studies have evaluated the impact of an increased epicardial adipose tissue on the clinical

outcomes of patients with autoimmune disorders such as rheumatoid arthritis, psoriasis, or systemic sclerosis.[16–18,22] Fatma *et al*. aimed to study the epicardial adipose tissue in patients with rheumatoid arthritis, as well as its effect on the cardiovascular involvement of the systemic disease. Their study found that EFT was higher in patients with polyarthritis (6.6 ± 2.0 mm vs. 5.4 ± 1.8 mm, p = 0.003) and that EFT was linked to left ventricular diastolic dysfunction, hypertension, or duration of the disease.[24] Long *et al*. sought to determine if the intrathoracic and epicardial fat volumes, assessed with thoracic CT, are linked to the presence of PAH as a marker for clinical severity of systemic sclerosis. Their results revealed that EF volume was significantly associated with the severity of systemic sclerosis, illustrated by the presence of PAH, independent of other cardiovascular risk factors or interstitial pulmonary disease (adjusted OR: 1.010, 95% CI: 1.003–1.018, p = 0.007).[18]

Within our study population, the measured pulmonary arterial systolic pressure did not differ between the three groups, although patients with myocardial ischemia presented slightly lower values compared to those with congenital heart defects or with systemic sclerosis, which is known to stimulate pulmonary fibrosis inflammation and vascular remodeling.

CONCLUSIONS

Epicardial fat thickness was found to be significantly higher in patients with PAH induced by myocardial ischemia, followed by those with systemic sclerosis and congenital heart defects, respectively. In our study, EFT did not influence the echocardiographic parameters for left and right ventricular function in patients with PAH of different etiologies. The largest EFT was found among patients with myocardial ischemia, thus proving, once again, the deleterious effects of the adipose tissue surrounding the heart on coronary artery disease.

CONFLICT OF INTEREST

Nothing to declare.

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ORIGINAL RESEARCH

CRITICAL CARE // CARDIOLOGY

Reduction of Intra-abdominal Hypertension Is Associated with Increase of Cardiac Output in Critically Ill Patients Undergoing Mechanical Ventilation

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ABSTRACT

Objective: To demonstrate the relationship between intra-abdominal hypertension (IAH) and cardiac output (CO) in mechanically ventilated (MV), critically ill patients. **Material and methods:** This was a single-center, prospective study performed between January and April 2016, on 30 mechanically ventilated patients (mean age 67.3 ± 11.9 years), admitted in the Intensive Care Unit (ICU) of the Emergency County Hospital of Tîrgu Mureș, Romania, who underwent measurements of intra-abdominal pressure (IAP). Patients were divided into two groups: group 1 – IAP <12 mmHg (n = 21) and group 2 – IAP >12 mmHg (n = 9). In 23 patients who survived at least 3 days post inclusion, the variation of CO and IAP between baseline and day 3 was calculated, in order to assess the variation of IAP in relation to the hemodynamic status. **Results:** IAP was 8.52 ± 1.59 mmHg in group 1 and 19.88 ± 8.05 mmHg in group 2 (p <0.0001). CO was significantly higher in group 1 than in the group with IAH: 6.96 ± 2.07 mmHg (95% CI 6.01–7.9) vs. 4.57 ± 1.23 mmHg (95% CI 3.62–5.52) (p = 0.003). Linear regression demonstrated an inverse correlation between CO and IAP (r = 0.48, p = 0.007). Serial measurements of CO and IAP proved that whenever accomplished, the decrease of IAP was associated with a significant increase in CO (p = 0.02). **Conclusions:** CO is significantly correlated with IAP in mechanically ventilated patients, and IAH reduction is associated with increase of CO in these critically ill cases.

Keywords: stroke volume, cardiac output, intra-abdominal hypertension, intra-abdominal pressure, mechanical ventilation

INTRODUCTION

Intra-abdominal hypertension (IAH), defined as an increase of the intra-abdominal pressure (IAP) above 12 mmHg, is frequently encountered in critically ill patients who are subjected to mechanical ventilation.[1] According to the World Society of Abdominal Compartment Syndrome, the normal values for IAP

range between 10 and 12 mmHg, while IAH is defined as an increase of the IAP above 12 mmHg.[2]

IAP is frequently elevated in critically ill patients, and it has been proved that IAH in mechanically ventilated patients is associated with a significantly higher length of stay in intensive care units (ICU) and ICU mortality, a higher incidence of organ dysfunction, and a longer duration of mechanical ventilation.[3]

The most severe form of IAH is represented by abdominal compartment syndrome, which is a devastating condition that occurs when intra-abdominal pressure exceeds 20 mmHg, being encountered in 20–30% of critically ill patients.[4] Prospective epidemiological studies reported the presence of IAH in 50.5% of mechanically ventilated patients admitted in ICUs and the presence of abdominal compartment syndrome in 8% of the same population.[5]

Abdominal compartment syndrome represents the final stage of a severe condition characterized by an increase in IAP to a degree that compromises the regional blood flow in vital abdominal organs.[6] Abdominal compartment syndrome is considered nowadays a life-threatening condition, being associated with significant deterioration in cardiac, renal, and respiratory function.[4] Therefore, in mechanically ventilated patients, all the necessary therapeutic measures should be undertaken in order to prevent the progression of IAH to more severe stages and abdominal compartment syndrome.

Cardiac output (CO) is the most reliable expression of cardiac performance, and an appropriate CO is essential for maintaining organ perfusion in critically ill patients. However, in many ventilated patients, CO is decreased due to inappropriate fluid therapy, hypovolemia, or cardiogenic shock, and the development of IAH can lead to further progressive deterioration of the clinical condition in these critical cases.

Mechanical ventilation leads to significant changes in the intra-thoracic pressure and consequently alters the left ventricular preload. The interrelation between intra-thoracic pressure, ventricular preload, and IAP is extremely complex, being demonstrated that the respiratory variation of stroke volume is able to predict fluid responsiveness in patients with increased IAP.[7]

It has been proved that in hypovolemic patients, IAH is associated with a significant increase in the parameters reflecting ventricular preload.[8,9] At the same time, ventricular preload is highly susceptible to the variations of intrathoracic pressures resulting from mechanical ventilation.[7] As ventricular preload in one of the major determinants of CO, at the same time being influenced by the parameters related to mechanical ventilation, a direct correlation should exist between CO and mechanical ventilation parameters.[7] However, the correlation between IAP and CO in mechanically ventilated severely ill patients has not been elucidated so far.

The role of functional hemodynamic monitoring in critically ill patients has been well established, and the relation between functional hemodynamic parameters and IAH has been demonstrated.[7–9] Such a functional hemodynamic monitoring includes the assessment of variable hemodynamic parameters such as stroke volume variation and pulse pressure variation. It has been clearly demonstrated that these parameters can predict fluid responsiveness in mechanically ventilated patients, based on the complex relationship between intra-thoracic pressure and intra-abdominal pressure.[7] However, while the relationship between the variation of stroke volume and intra-abdominal pressure has been well documented, little is known about the correlation between IAP and parameters reflecting the global hemodynamic status, such as CO.

The aim of this study was to demonstrate the relationship between CO and IAP in mechanically ventilated critically ill patients and at the same time to demonstrate that the reduction of IAP is associated with the increase of CO in these critical cases.

PATIENTS AND METHODS

Study population

The study enrolled 30 mechanically ventilated and sedated patients (76.19% males, mean age 67.3 ± 11.9 years, 95% CI 62.9–71.8) admitted in the Intensive Care Unit of the Emergency Clinical County Hospital of Tîrgu Mureș, Romania, between January 2016 and April 2016 for severe abdominal pathology. There were no cases of sepsis in the study lot, and none of the patients required vasopressor support. All patients had comparable ventilator settings.

Clinical, biological, and hemodynamic parameters were compared in 21 patients with normal values of intra-abdominal pressure (IAP <12 mmHg, group 1) and 9 patients with increased values of IAP (IAP >12 mmHg, group 2). The cut-off value of 12 mmHg for defining the IAH was selected according to the value established in the definition released by the World Society of Abdominal Compartment Syndrome.[2]

The study was approved by the ethics committee of the Emergency Clinical County Hospital of Tîrgu Mureș, Romania, and all the investigations were in accordance with the Declaration of Helsinki.

Data collection

In all patients, clinical and laboratory data were collected at enrollment and analyzed (including age, weight, height, gender, blood pressure, urea, creatinine and creatinine clearance, glomerular filtration rate, neutrophil gelatinase-associated lipocalin (NGAL), blood count, central venous pressure, pH). The severity scores APACHE II (Acute Physiology and Chronic Health Evaluation Score), SOFA (Sequential Organ Failure Assessment Score), and SAPS (Simplified Acute Physiology Score) were calculated based on clinical and laboratory data. Parameters reflecting hemodynamic and volemic status such as global end-diastolic blood volume (GEDV), extra-vascular lung water index (EVLWi), and stroke volume variation (SVV) were also collected and analyzed.

Measurements

Determination of IAP was performed daily, on three consecutive days, with the patient on semi-recumbent position, using the AbViser device (ConvaTec, Salt Lake City, USA) and an urethro-vesical catheter (Nelaton type, Shanghai Med SRL, Shangai, China). Measurements were performed after the injection of 20 mL of saline solution in the urethro-vesical catheter, followed by catheter occlusion with a dedicated valve, and were displayed on the device monitor.

CO was determined using the thermodilution method, with a 3 F arterial Piccocatheter inserted percutaneously in the femoral artery and a central venous catheter inserted in the internal jugular vein. The calculation of CO was done using a Pico Plus device (Pulsion, Feldkirchen, Germany), according to the PICCO technique which is based on two physical principles: transpulmonary thermodilution and pulse contour analysis. A cold saline solution (15 mL) was injected by central venous catheter and passed through the right heart, lung, and left heart, being detected by the Picco thermodilution catheter placed in the femoral artery. Upon this thermodilution phase, the monitor was calibrated to perform a continuous hemodynamic monitoring, based on pulse contour analysis. A new calibration was performed just before each IAP measurement to ensure the reliability of CO estimation.

Central venous pressure (CVP) was determined using a 7 F central venous catheterization set, introduced via the internal jugular vein, connected with a standard transducer that measured the CVP, the values being displayed on a monitor.

Hemodynamic parameters (GEDV, EVLWi, and SVV) were determined with the use of the Picco Plus device (Pulsion, Feldkirchen, Germany).

In order to avoid circadian variation, all the measurements were performed in the morning, between 9:00 a.m. and 10:00 a.m. at baseline, and were repeated daily, at the same hour, in 23 patients who survived at least 3 days post inclusion in the study. The variation of CO and IAP between baseline and day 3 was calculated in this subgroup, in order to assess the interrelation between IAP variation and hemodynamic status.

Statistical analysis

All the statistical analyses were performed using the InStat Graph Pad software. Fisher's exact test (or the Student t-test for age) was used to compare the baseline characteristics of patients in group 1 and group 2. Continuous values were expressed as the mean and standard deviation, and statistical significance was determined using the Mann-Whitney test. Linear regression was used for assessing the correlation between CO and IAP. The statistical significance level was set at an alpha of less than 0.05.

RESULTS

Baseline clinical characteristics

The mean age of the population was 66.5 ± 13.4 years in group 1 and 69.3 ± 7.5 years in group 2 (p = 0.4). The clinical baseline characteristics of the study population showed no significant differences between the groups with respect

TABLE 1. Baseline characteristics of the study population

		Group 1 IAP <12 mmHg n = 21 (70.0%)	Group 2 IAP >12 mmHg n = 9 (30.0%)	P value
Age, years	*Mean ± SD*	66.5 ± 13.4	69.3 ± 7.5	0.4
Gender, male	*n (%)*	16 (76.2)	6 (66.5)	0.6
Weight (kg)	*Mean ± SD*	89.9 ± 17.0	85.8 ± 10.1	0.5
Height (cm)	*Mean ± SD*	173.2 ± 5.6	170.2 ± 5.6	0.2

TABLE 2. Clinical and biological characteristics of the study population

	Group 1 IAP <12 mmHg n = 21 (70.0%)	Group 2 IAP >12 mmHg n = 9 (30.0%)	P value
Systolic arterial pressure (mmHg)			0.7
Mean ± SD	110.9 ± 29.6	115.2 ± 31.7	
95% confidence interval	97.4–124.4	89.0–141.1	
Diastolic arterial pressure (mmHg)			0.9
Mean ± SD	54.5 ± 16.8	55.1 ± 18.3	
95% confidence interval	46.8–62.6	41.0–69.2	
Central venous pressure (mmHg)			0.3
Mean ± SD	9.9 ± 3.7	11.3 ± 4.0	
95% confidence interval	8.1–11.6	8.2–14.4	
Urea (mg/dL)			0.4
Mean ± SD	86.3 ± 38.4	72.6 ± 45.11	
95% confidence interval	68.8–103.9	37.9–107.3	
Creatinine (mg/dL)			0.2
Mean ± SD	1.4 ± 0.85	1.1 ± 0.6	
95% confidence interval	1.0–1.8	0.6–1.6	
Creatinine clearance (mL/min)			0.4
Mean ± SD	76.5 ± 37.4	87.6 ± 35.9	
95% confidence interval	58.5–94.6	60.6–115.2	
Glomerular filtration rate (mL/min/1.73 m^2)			0.2
Mean ± SD	59.4 ± 29.5	78.0 ± 39.67	
95% confidence interval	45.8–72.8	47.5–108.5	
NGAL (ng/mL)			0.02
Mean ± SD	324.1 ± 299.0	571.7 ± 411.6	
95% confidence interval	203.3–444.9	373.3–770.1	
Leucocyte count (*10^3/mm^3)			0.5
Mean ± SD	12.548 ± 6.074	14.944 ± 11.099	
95% confidence interval	9.873 - 15.313	6.411 - 23.476	
pH			0.1
Mean ± SD	7.3 ± 0.1	7.2 ± 0.1	
95% confidence interval	7.2–7.3	7.1–7.3	

to age (p = 0.4), gender (p = 0.6), weight (p = 0.5), height (p = 0.2), blood pressure (p = 0.7 for systolic blood pressure, 0.9 for diastolic blood pressure, and 0.3 for mean blood pressure), and central venous pressure (p = 0.4) (Table 1 and Table 2).

IAP was 8.52 ± 1.59 mmHg in group 1 and 19.88 ± 8.05 mmHg in group 2 (p <0.0001).

Biomarkers of organ dysfunction and IAP

Biomarkers expressing renal function, such as urea, creatinine, and GFR, showed no statistically significant differences between the study groups (p = 0.4 for urea, 0.2 for creatinine, and 0.2 for GFR). However, NGAL, a reliable biomarker expressing acute kidney injury, showed significantly higher values in the group with IAH as compared to the group with normal IAP (Table 2).

Cardiac output and IAP

There were no statistically significant differences between the study groups in respect to hemodynamic parameters expressing global volemic status (p = 0.07 for GEDV, p = 0.3 for EVLWI, and p = 0.1 for SVV) (Table 3).

However, mean values of CO were significantly higher in the group with normal values of IAP than in the group with IAH (Figure 1). Furthermore, linear regression demonstrated an inverse correlation between CO and IAP (r = 0.48, p = 0.007) (Figure 2), proving that higher values of IAP are associated with lower values of CO.

Serial measurements of CO proved that each decrease in IAP (from day 1 to day 2 and from day 2 to day 3) was associated with a significant increase in CO, the correlation between IAP decrease and CO increase being statistically significant (p = 0.02) (Figure 3).

TABLE 3. Hemodynamic parameters and intra-abdominal pressure

	Group 1 IAP <12 mmHg n = 21 (70.0%)	Group 2 IAP >12 mmHg n = 9 (30.0%)	P value
Intra-abdominal pressure (mmHg)			<0.0001
Mean ± SD	8.5 ± 1.6	19.8 ± 8.0	
95% confidence interval	7.8–9.2	13.6–26.0	
Cardiac output (L/min)			0.003
Mean ± SD	6.9 ± 2.0	4.5 ± 1.2	
95% confidence interval	6.0–7.9	3.6–5.5	
GEDV (mL)			0.1
Mean ± SD	1455.3 ± 601.2	1073.4 ± 339.7	
95% confidence interval	1092.0–1818.8	812.3–1334.6	
EVLWi (mL/kg)			0.4
Mean ± SD	12.0 ± 4.1	10.4 ± 3.7	
95% confidence interval	9.5–14.4	7.0–13.8	
SVV (%)			0.1
Mean ± SD	15.0 ± 7.5	19.5 ± 7.36	
95% confidence interval	11.1–18.8	13.3–25.6	

GEDV – global end-diastolic blood volume, EVLWi – extra-vascular lung water index, SVV – stroke volume variation

IAP and severity scores

There were no statistically significant differences between the study groups in respect to severity scores. Significantly elevated APACHE II, SOPHA, and SAPS scores were recorded in similar percentages in both groups on day 1, without any major difference between the groups regarding the severity of the condition at baseline (p = 0.4 for APACHE scores >25, p = 0.4 for SOFA scores >10, and p = 1 for SAPS scores >30) (Table 4).

DISCUSSIONS

IAH remains a severe clinical condition with potentially devastating impact on patient outcomes.4,10 In ICU units, mechanical ventilation represents one of the major factors predisposing to the development of IAH, which usually results from a complex interaction between multiple factors. Besides the ventilation settings, other factors involved in the pathophysiology of this syndrome could be related to the biological condition of the patient or to the complex

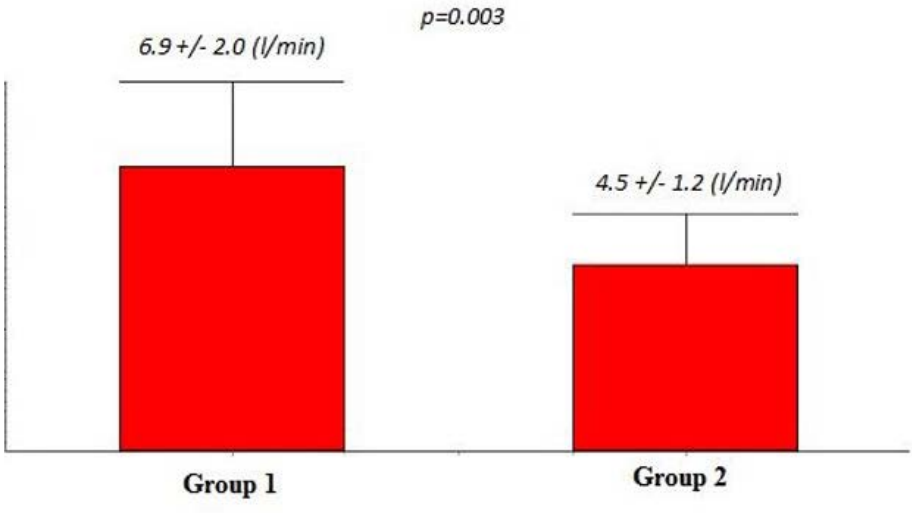

FIGURE 1. Cardiac output in the study groups. CO is significantly higher in the group 1, with no IAH, as compared to group 2, with elevated IAP

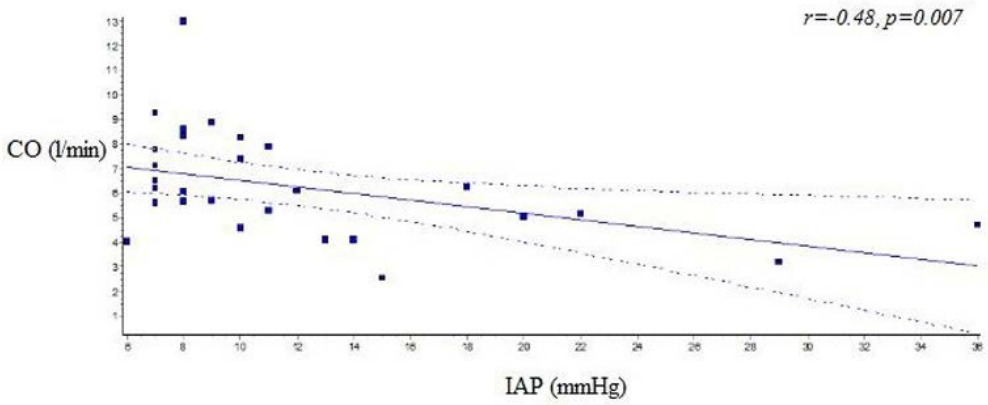

FIGURE 2. Linear regression analysis demonstrating the inverse correlation between CO and IAP

interaction between intra-thoracic and intra-abdominal pressures, interaction in which the volemic status and the cardiac output play a significant role.

IAH, intra-thoracic pressures, and ventricular preload

While the etiological factors for IAH are well defined, including obesity, insufflation of carbon dioxide during abdominal laparoscopic surgery, excessive fluid accumulation in the abdominal cavity or the presence of ascites, the factors that could be associated with the variation of IAP in different clinical scenarios are less clarified. It has been proved that a high tidal volume and the application of positive end-expiratory pressure during mechanical ventilation are associated with elevation of IAP.[11–13]

The elevated IAP pushes the diaphragm upward, decreasing the compliance of the respiratory system, and leads to increase in the intra-thoracic pressures. At the same time, IAH decreases the venous return from the lower extremities and therefore reduces the cardiac preload and the left ventricular end-diastolic volumes.[14–16] This is the most probable mechanism via which IAH alters the preload conditions and, as a direct consequence, reduces the CO. In line with these observations, our study demonstrated significantly lower values of CO in the group with IAH (4.57 ± 1.23 L/min vs. 6.96 ± 2.07 L/min, p = 0.003), proving that an increased IAP is directly associated with the alteration of hemodynamic status. In this study, the interrelation between CO and IAP was also demonstrated by the inverse correlation between them at linear regression analysis (r = 0.48, p = 0.007).

Fluid balance, preload, and IAP

One of the factors that could be associated with the progression of IAH is represented by fluid accumulation in the abdominal cavity, resulting either from excessive fluid administration or from a pathological process in the abdominal cavity (e.g., ascites).

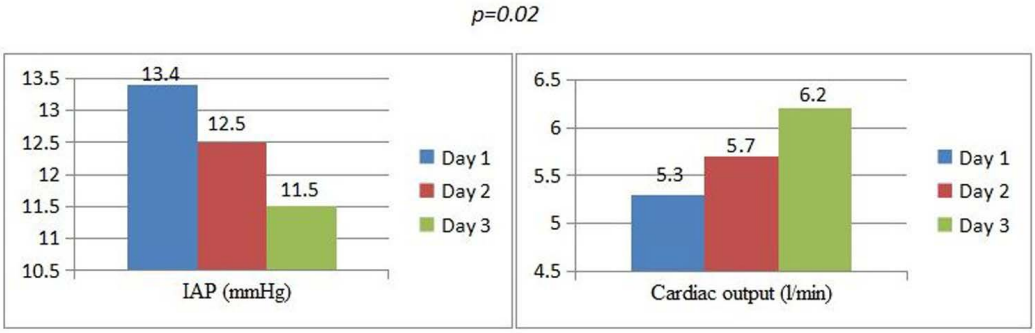

FIGURE 3. Decrease of intra-abdominal pressure is associated with increase of cardiac output – results of serial measurements during 3 consecutive days

TABLE 4. Severity scores and intra-abdominal hypertension

Severe condition according to severity scores	Group 1 IAP <12 mmHg n = 21 (70.0%)	Group 2 IAP >12 mmHg n = 9 (30.0%)	P value
APACHE score >25	13 (61.9%)	4 (44.4%)	0.4
SOFA score >10	9 (42.8%)	2 (22.2%)	0.4
SAPS score >30	8 (38.0%)	4 (44.4%)	1

APACHE – Acute Physiology and Chronic Health Evaluation Score, SOFA – Sequential Organ Failure Assessment Score, SAPS – Simplified Acute Physiology Score

It has been demonstrated that the interaction between IAP and intra-abdominal volume leads to a significant increase in IAP after a relatively small accumulation of fluid or blood in the abdominal cavity.[1,5] Intra-peritoneal fluid collection, obesity, large amount of intravenous fluid received, and abdominal distention have been identified as significant independent predictors of IAH in patients admitted to the ICU.[3]

IAH frequently appears in patients who develop an inflammatory process inside the abdominal cavity and can be further exacerbated by the excessive fluid therapy in these cases.[6] An increase of IAP has been proved to be associated with a significant reduction of the splanchnic blood flow.[16,17] Intraoperative and postoperative optimization of fluid administration has been proved to be strongly associated with a reduction in mortality in critically ill patients; however, in a study by Liu *et al.*, static preload variables represented by central venous pressure and pulmonary capillary wedge pressure were not able to predict the cardiac response to fluid therapy in patients with IAH.[7]

Fluid therapy is considered a predisposing factor for IAP increase, as excessive intravenous fluid administration can worsen IAH. At the same time, volemic status is one of the key determinants of cardiac output and is a directly influencing variable of hemodynamic parameters such as the respiratory variation of stroke volume (SVV) or of pulse pressure (PPV).

It has been shown that elevated IAP increases the preload parameters in patients with hypovolemia.[18,19] At the same time, Diaz *et al.* proved that IAH induction in non-hypovolemic patients significantly increases hemodynamic variables such as SVV and PPV, proving that a direct relation exists between IAP and hemodynamic parameters characterizing cardiac function.[7] In line with these observations, the present study proves that a direct interaction exists between IAH and CO variation in critically ill patients undergoing mechanical ventilation. However, in the present study we did not record any significant difference of SVV between the study groups (15.0 ± 7.5 vs. 19.5 ± 7.36, p = 0.1), probably because SVV increases especially in hypovolemic conditions, while there were no cases of hypovolemia in the study groups.

IAH and CO variation

In an experimental study, Diaz *et al.* proved that induction of IAH leads to a reduction in cardiac index, in the absence of any significant changes in the blood pressure.[7] Similarly, our study demonstrates that an inverse correlation exists between IAH and CO in critically ill patients undergoing mechanical ventilation. Furthermore, we also proved that an increase in CO is achievable after correction of IAP. Reduction of IAP from 13.4 mmHg to 11.5 mmHg resulted in a significant increase in CO, from 5.3 L/min to 6.2 L/min (p = 0.02). According to the authors' knowledge, this is the first study demonstrating that a reduction in IAP could lead to an improvement of CO in critically ill subjects.

The cause-effect interaction between CO to IAP

The results of our study could lead to a challenging debate related to the possible cause-effect mechanism between CO and IAP: is the regression of IAP that leads to the improvement of CO via a complex mechanism that involves the amelioration of left ventricular preload conditions following the re-equilibration of the balance between intra-thoracic and intra-abdominal pressures, or is it rather the increase in CO, consecutive to proper fluid administration and hemodynamic improvement, the factor that leads to regression of IAP? While the effect of IAP on CO has been addressed by many studies, the potential effect of CO on IAP determination has not been studied so far. This new hypothesis launched by our study is not clearly answered in the present, and further studies are required in order to elucidate the potential influence of CO on IAP.

IAH, biomarkers, and severity scores

At the same time, it was demonstrated that in mechanically

ventilated patients with IAH, the application of an increasing positive end-expiratory pressure is associated with an increased release of inflammatory biomarkers such as interleukin-9 and type III procollagen expression and type II epithelial cell damage.[20,21] Other studies demonstrated that IAH is associated with the development of acute renal failure in critically ill patients.[22,23] In line with these results and with our previous experience, we also proved that the levels of NGAL, a biomarker associated with acute renal failure, are increased in patients with IAH compared to the patients with normal IAP. Interestingly, we recorded significantly higher levels of NGAL in patients with IAH (571.7 ± 411.6 vs. 324.1 ± 299.0, p = 0.02), without any significant difference in other serum biomarkers characterizing renal function such as creatinine clearance, GRF, or urea. This could be explained by the fact that NGAL, a complex biomarker, reflects not only the acute renal injury, but also the acute deterioration in cardiac status.[24,25] In a study by Kirbis *et al*., a urine NGAL level of 50 ng/mL had a 90% specificity for the diagnosis of acute heart failure, proving that NGAL is a reliable biomarker for predicting the deterioration of cardiac function.[24] Therefore, the elevated levels of NGAL in patients with IAH in the present study could be also attributed to the deterioration of CO, NGAL being more sensitive to the alteration of CO than the other measured parameters.

Interestingly, in this study there was no association between severity scores and IAH, probably because we did not analyze separately the subgroup of patients with severe IAH (>20 mmHg) or with abdominal compartment syndrome, while the high values for severity scores would be expected in this subcategory of severe IAH patients.

CONCLUSIONS

This study demonstrates a complex interaction between CO and IAP in mechanically ventilated critically ill patients. Patients with increased IAP present lower values of CO, and whenever accomplished, the reduction of IAH was associated with a significant increase in CO in this patient population.

CONFLICT OF INTEREST

None declared.

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ORIGINAL RESEARCH

SURGERY // ONCOLOGY

Laparoscopic Versus Conventional Open Rectum Amputation: a Clinical, Intraoperative, and Short-term Outcome Comparative Study

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ABSTRACT

Objective: To evaluate and compare laparoscopic and conventional open rectum amputation procedures using clinical, intraoperative, postoperative, and oncological criteria. **Methods:** Fifty-nine patients with lower rectal and anorectal cancer were included in a retrospective study, conducted between 2014 and 2017. Patients underwent open or laparoscopic rectum amputation surgery and were divided into two groups: group 1 – laparoscopic amputation group (LAG) and group 2 – open amputation group (OAG). The clinical, intraoperative, and postoperative outcomes and oncological results were compared between the two groups. **Results:** We found a significantly smaller intraoperative blood loss (325 mL vs. 538.29 mL, p = 0.0002), earlier return of bowel motility (2.41 days vs. 3.10 days, p = 0.036), shorter hospital stays (10.08 days vs. 12.66 days, p = 0.03), and a higher number of lymph nodes removed during surgery (12.33 nodes for LAG vs. 9.98 nodes for OAG, p = 0.049). In the open surgery group we found shorter durations of surgery (199.58 minutes for LAG vs. 157.87 minutes for OAG, p = 0.0046). **Conclusion:** Laparoscopic rectum amputation is a technically demanding procedure. The present study demonstrates the benefits and disadvantages of this surgery, with comparable clinical, intraoperative, postoperative, and oncological results compared to the conventional open rectum amputation procedure.

Keywords: rectal tumor, laparoscopic, open, rectum amputation, oncologic

INTRODUCTION

Minimally invasive surgical techniques have revolutionized colorectal surgery in the last years, though it is still a rarely performed intervention. In addition, laparoscopic surgery for lower rectal and anorectal cancer is much more challenging compared to colon cancer, the main reason being the narrow space within the pelvis. Concerns about oncological radicality and long-term outcomes have limited the use of this type of operation. However, recent results of randomized

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controlled trials conducted on large numbers of patients have proven that laparoscopic surgery in the treatment of colorectal malignant diseases is safe from an oncological standpoint, and it also presents favorable short-term outcomes.[1–4]

MATERIALS AND METHODS

We conducted a retrospective study between 2014 and 2017, which included 59 patients with lower rectum and anorectal malignant tumors. For all patients included in this study, rectum amputation surgery was performed. Patients were selected and divided into two groups based on the surgical approach, as follows: group 1 – laparoscopic rectum amputation group (LAG), which included 12 patients, and group 2 – open rectum amputation group (OAG), with 47 patients. In order to compare the two types of procedures, clinical, intraoperative, postoperative, and oncological characteristics were evaluated.

The analyzed clinical characteristics included patient gender, age, tumor location, preoperative irradiation and/or chemotherapy, severity of anemia at admission. The analyzed intraoperative characteristics comprised the duration of surgery, conversion rate, inoperability, presence of hepatic and/or pulmonary metastasis, local tumor invasion (prostatic, bladder, vaginal, sacral, perineal), intraoperative blood loss. Postoperative data compared between the two groups included the return of bowel motility, use of painkillers, length of hospital admission, death during hospital stay, and complications. Oncological outcomes were analyzed by comparing histopathological results, stadialization, removed lymph nodes, recurrence, and survival rates at 6, 12, and 18 months. Furthermore, the study investigates possible associations between anemia at admission and tumor stage in patients with and without preoperative oncological treatment, local invasion severity score, and operation time/hospital stay/complications. The local invasion of the tumor was estimated with the local invasion severity score, using points from 1 to 3 as follows: patients with one local invasion area – 1 point; patients with two invasion areas – 2 points; and patients with at least three local invasion areas – 3 points. To assess the preoperative oncological treatment, the following scoring scale was applied: patients who underwent preoperative chemotherapy – 1 point; those who underwent preoperative irradiation – 2 points; and patients who underwent both chemo- and radiotherapy – 3 points. For tumor staging (Dukes staging system), we used the following numbering scale: A = 0, B1 = 1, B2 = 2, B3 = 3, C1 = 4, C2 = 5, C3 = 6. Patient data was statistically processed and analyzed using the GraphPad InStat software (GraphPad Software, California, USA), and the statistical significance was set at a value of $p < 0.05$.

RESULTS

Between 2014 and 2017, 59 patients diagnosed with lower rectal and anorectal cancer underwent open or laparoscopic rectum amputation surgery.

Table 1 presents the clinical characteristics of the patients. Most patients included in this study were diagnosed with lower rectal cancer (66%). Fifteen patients underwent preoperative radiotherapy and 5 patients underwent preoperative chemotherapy. Only 5 patients benefited from both preoperative chemo- and radiotherapy.

Aspects regarding intraoperative and postoperative outcomes are presented in Table 2. In total, 47 patients underwent open rectum amputation and 12 patients underwent laparoscopic surgery. The duration of surgery was significantly longer for patients undergoing the laparoscopic procedure ($p = 0.0046$). Conversion from laparoscopic to open surgery was considered necessary for one patient

TABLE 1. Clinical assessment

	Group 1 Laparoscopic rectum amputation n = 12	Group 2 Open rectum amputation n = 47
Median age (years)	65.29	63.92
Gender ratio (F:M)	9:3	18:29
Tumor location (1/3 inferior:anorectal)	9:3	36:11
Median hemoglobin levels (g/dL)	12.02	12.48
Median hematocrit (%)	35.6	37.09
Preoperative chemotherapy (yes: no)	0:12	5:42
Preoperative radiotherapy (yes: no)	1:11	14:33

TABLE 2. Intraoperative and postoperative outcomes

	Group 1 Laparoscopic rectum amputation n = 12	Group 2 Open rectum amputation n = 47	p value
Mean duration of surgery (minutes)	199.58	157.87	0.0046
Conversion (to open surgery)	1	0	–
Inoperability	0	2	–
Mean volume of blood loss (mL)	325	538.29	0.0002
Hepatic metastasis	0	2	–
Prostatic invasion	2	8	–
Bladder invasion	0	5	–
Vaginal invasion	1	9	–
Sacral invasion	1	10	–
Perineal invasion	2	6	–
Return of bowel motility (days)	2.41	3.10	0.036
Mean hospital stay (days)	10.08	12.66	0.03
Use of painkillers (days)	7.66	8.02	NS
Complications	3	9	NS
Death during hospital stay	1	1	–

NS: non-significant p value (>0.05)

(8.33%); the reason of conversion was non-surgical; there were serious alterations of vital functions caused by the Trendelenburg position during laparoscopic surgery. Inoperability was found in 2 patients (3.38%); both presented pulmonary and hepatic metastases and advanced local invasion of the tumor. Intraoperative blood loss was significantly lower for patients in the LAG (p = 0.0002). The OAG included a higher number of patients with hepatic metastasis and more advanced local invasion of the tumor. The return of bowel motility was shorter for patients who underwent laparoscopic rectum amputation surgery (p = 0.036). The average hospital stay was 11 days for the overall study population. A significantly shorter hospital stay was registered in case of patients in the LAG (p = 0.03). Painkillers were used for an average period of 7.84 days. Postoperative complications occurred in 3 cases from the LAG (bowel obstruction, parastomal hernia) and in 9 cases from the OAG (bowel obstruction, bladder fistula, ventral hernia, pelvic hematoma, perineal abscess). Death during hospital stay occurred in two cases, one for each type of procedure.

Data regarding oncologic outcomes and survival are presented in Table 3. There was a significant difference regarding the number of removed lymph nodes between the two surgical procedures. Patients in the LAG had more lymph nodes removed (p = 0.049) compared to those in the OAG. Recurrence was present in one case in the LAG and 6 cases in the OAG. The average survival rate was 12 months. Furthermore, the statistical analysis of the tumor staging in patients with and without preoperative oncologic treatment resulted in an extremely significant moderate negative association for the OAG (p = 0.0001).

TABLE 3. Oncological outcomes and prognosis

	Laparoscopic rectum amputation group (LAG)	Open rectum amputation group (OAG)	p value
Histopatology (malignant : benign)	12 : 0	46 : 1	–
Dukes staging	2.08	2.80	NS
Outtaken lymphondes (n)	12.33	9.98	0.049
Recurrence	1 (8.33%)	6 (12.76%)	NS
Average survival rate (12 months)	11 (91.66%)	44 (93.61%)	NS

NS: not significant p value (>0.05)
Dukes stadialization: A = 0, B1 = 1, B2 = 2, B3 = 3, C1 = 4, C2 = 5, C3 = 6

DISCUSSIONS

In this study, patients were diagnosed with tumors situated in the lower rectum or anorectal region, the surgical procedure in this kind of tumors being extremely demanding.[5] Being on the ascending part of the learning curve of laparoscopic rectum amputation surgery, we focused on case selection. Thus, the LAG had only 12 patients, while the OAG had 47 patients. Furthermore, the OAG presented more patients with hepatic metastasis, more advanced local invasion, more advanced tumor stages (Dukes B, C), and severe comorbidities in comparison with patients from the LAG. Preoperative oncologic treatment was performed in 25 patients (42.37%). Preoperative radiotherapy reduces the rate of local recurrence, downstages and downsizes the tumor, consequently increasing the possibility of radical surgery.[6,7] The duration of surgery was longer for patients who underwent laparoscopic rectum amputation surgery. Other authors reported similar results.[8–10] Intraoperative blood loss was significantly lower in case of patients who had undergone LAG compared to patients who underwent open surgical procedure, similar results being reported by other authors.[8,10,12] Patients with laparoscopic rectum amputation surgery presented a significantly higher number of removed lymph nodes in comparison to patients from the OAG, and a recent study registered similar results.[10,13] The return of bowel motility was significantly faster in case of patients from the LAG. Similar results were found in the current literature.[8,12] The average hospital stay was 11 days for the overall study population. A significantly shorter hospital stay was registered in case of patients who underwent laparoscopic surgery, these data being in accordance with other reported results.[9,10,16] Conversion to open surgery was required in only one patient (8.33%). Recent studies registered similar results regarding conversion from a laparoscopic to an open approach.[11,13,15] The overall postoperative complication rate was 20.33% in this study, other authors reporting similar results.[3,14]

CONCLUSIONS

Although laparoscopic rectum amputation is a technically demanding procedure, according to our study, a laparoscopic procedure for the treatment of lower rectum and anorectal malignant tumors is a feasible choice, resulting in less intraoperative blood loss, more excised lymph nodes, earlier return of bowel motility, and shorter periods of hospital admission. In addition, the laparoscopic procedure has shown similar results with the conventional open procedure regarding the postoperative use of painkillers, number of complications, recurrence, and survival. Our study confirms that the laparoscopic procedure can be a safe choice for the treatment of lower rectum and anorectal malignant tumors, offering better or at least equivalent results in comparison to the conventional open procedure.

CONFLICT OF INTEREST

None to declare.

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CASE REPORT

SURGERY // HISTOPATHOLOGY

Left Para-Renal Castleman Disease: Case Report

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ABSTRACT

Castleman disease represents a rare lymphoproliferative disorder of unknown etiology. It is usually located in the mediastinum and in very few cases in the retroperitoneal space. We present the case of a 43-year-old male patient with a retroperitoneal tumor that was incidentally diagnosed during an abdominal computed tomography scan. The patient underwent surgery by open approach, and the tumor, which was adherent to the superior pole of the left kidney, was entirely removed. The histology examination revealed a vascular-hyaline-type Castleman disease. The postoperative evolution was uneventful, with no signs of tumor recurrence at the 4-month check-up. The surgeon should be aware of the possible retroperitoneal location of Castleman disease, even if it is a rare occurrence, and a complete removal of the tumor is followed by a favorable long-term prognosis.

Keywords: Castleman disease, hyaline vascular type, retroperitoneum, pararenal

INTRODUCTION

Angiofollicular hyperplasia, also known as Castleman disease, represents a rare lymphoproliferative disorder with unknown etiology, which usually develops in the mediastinum (70% of cases), in 7% of cases in the retroperitoneum, and only in 2% of patients in the pararenal space.[1]

CASE REPORT

A 43-year-old patient was admitted to the Department of Occupational Medicine for osteoarticular pains of professional etiology (physical overload). Among other investigations, an abdominal and pelvic computed tomography (CT) scan with oral and intravenous contrast agent was performed. The examination highlighted a solid, iodophilic tumor with microcalcifications located posteriorly to the pancreas tail, adjacent to the upper pole of the left kidney, with well-defined edges and a cleavage plane (Figure 1). The vertical extension of the tumor was of 67 mm, with the maximum axial diameters of 64/51 mm. The patient was referred to the surgical department.

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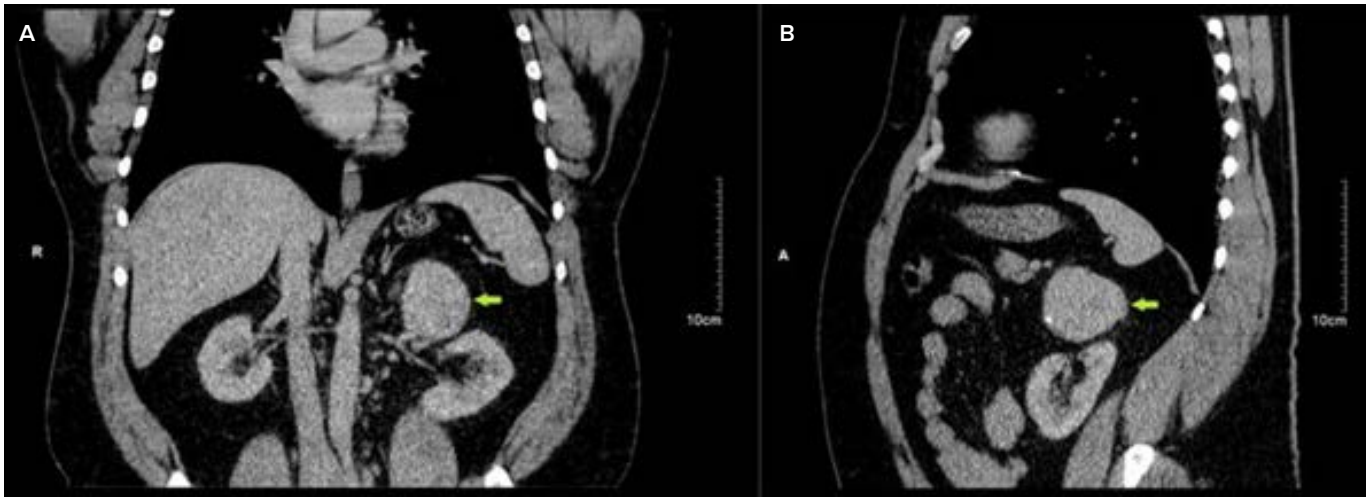

FIGURE 1. CT imaging showing a well-defined retroperitoneal tumor adjacent to the upper pole of the left kidney. **A** – Coronal reconstruction (arrow); **B** – Axial reconstruction (arrow).

The patient underwent surgery by a classical open approach. The intraoperative findings were that of a well-defined, mobile tumor, of soft consistency, located between the upper left renal pole, the spleen, and the posterior aspect of the stomach. A complete removal of the tumor was carried out. The postoperative evolution was uneventful, with complete recovery and discharge on the 9th day after surgery.

The anatomical gross aspect of the tumor on sections was that of a well-defined, 6 cm diameter node, with a whitish aspect, of elastic consistency, not exceeding the edges of the excision.

The histopathological findings were that of a lymph node with unaltered follicular structure; follicles with diminished germinal centers penetrated by vascular structures and some hyalinization (Figure 2). In the interfollicular space, there was an expansion of the mantle area and capillary venous hyperplasia associated with hyalinization. The immunohistochemical profile was the following: CD20 and BCL-2 normal follicles, interfollicular T/

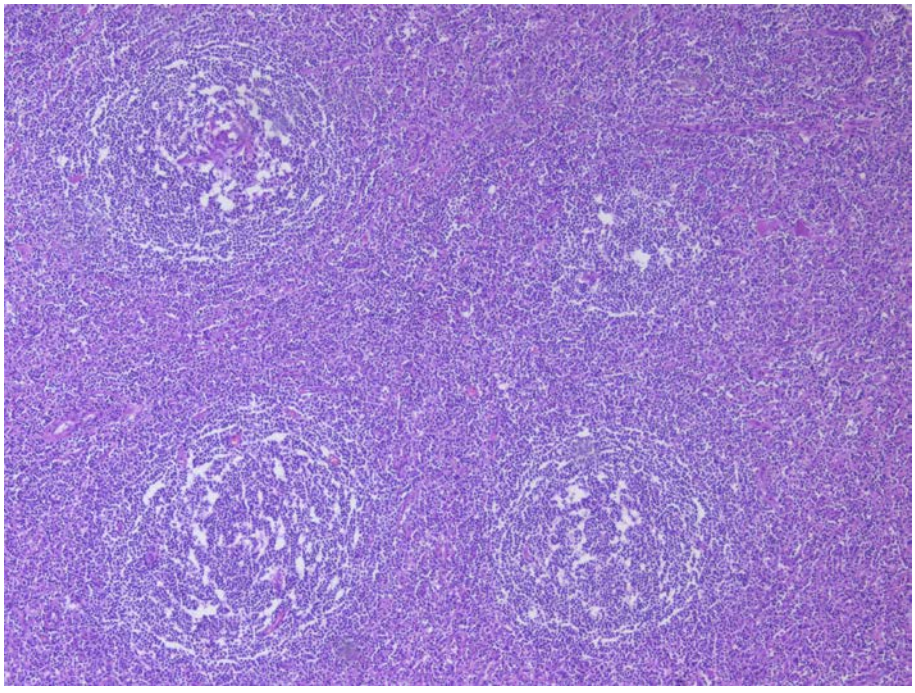

FIGURE 2. Histopathological aspect, Hematoxylin-Eosin, 40x

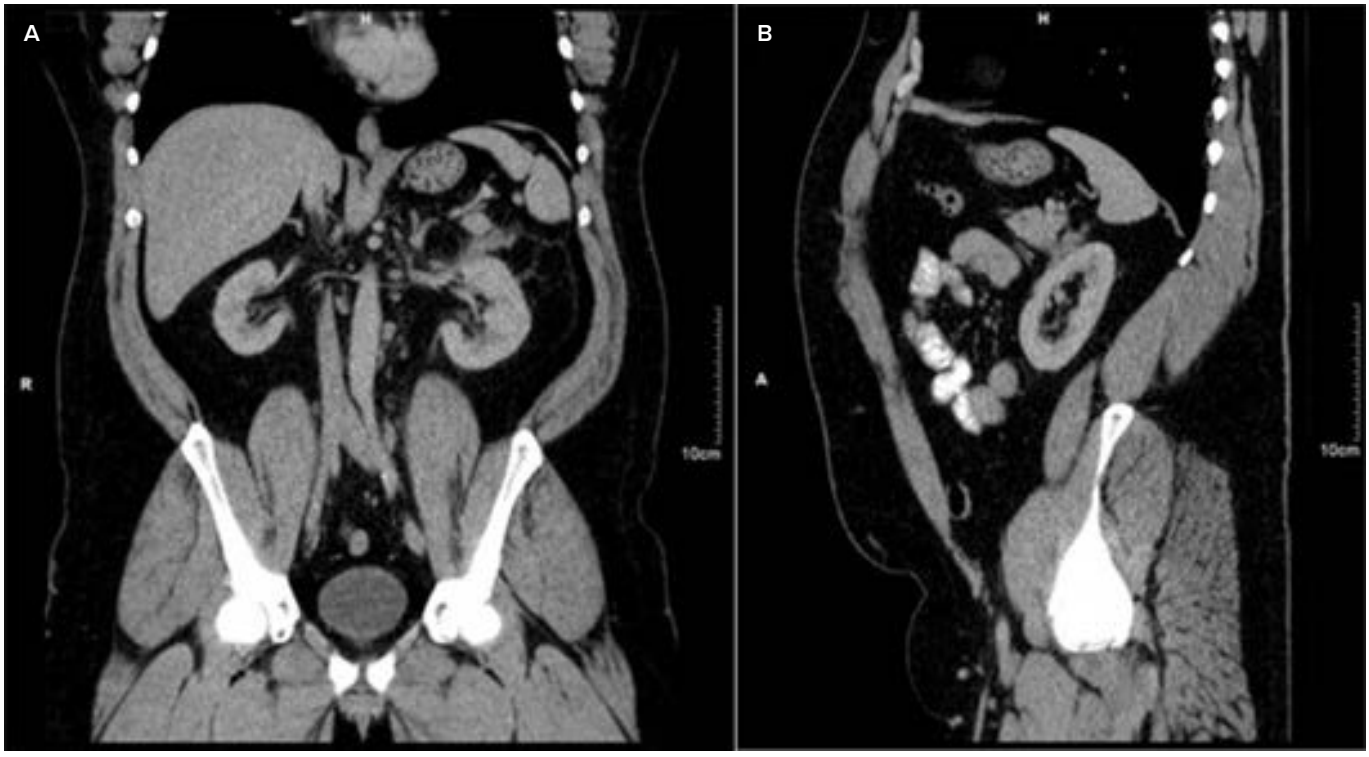

FIGURE 3. CT scan showing the postoperative aspect at the four-month follow-up. **A** – Coronal reconstruction; **B** – Sagittal view.

CD4 and CD8 positive lymphocytes, few B lymphocytes and plasma cells. There was no restriction of light kappa and light lambda chains.

Based on these examinations, the final diagnosis of vascular-hyaline-type Castleman disease was established.

At the four-month follow-up, the CT scan did not find any signs of tumor recurrence (Figure 3).

The patient agreed to the publication of his data, and the manuscript was written according with the ethical principles stated in the Declaration of Helsinki.

DISCUSSIONS

Castleman disease was first described by Benjamin Castleman in 1956.[2] The most frequent location (about 70% of cases) reported by authors was the mediastinum and, in much more rare cases, the retroperitoneum (7%) and the pararenal space (2%).[1,3] The case presented herein falls into the more rare group of cases with pararenal location.

From a clinical point of view, Castleman disease can be classified into a unicentric or multicentric disease, depending on the number of affected lymph nodes.[1] Three histopathological types have been described: vascular-hyaline, plasma-cell, and mixed forms.[4] In the presented case, there was a unicentric, retroperitoneal, vascular-hyaline-type tumor.

In 90% of cases, the vascular-hyaline type is unicentric, represented by an asymptomatic tumor with a benign evolution.[5] In some cases, depending on the size of the tumor and its relationship to the adjacent organs, various symptoms may arise, from abdominal or lumbar pain to vomiting and weight loss.[6] In our case, there were no tumor-related symptoms, the tumor being incidentally discovered by a CT scan, performed in a patient with joint complaints.

The treatment of Castleman disease, whether vascular-hyaline or plasma-cell, consists in surgical resection of the entire tumor, with a favorable long-term prognosis.[7,8] Depending on tumor size and location, the laparoscopic approach should be considered with a faster recovery of the patient compared to the open, classical approach.[9]

Radiotherapy is an alternative treatment, with a response rate up to 72% in cases where surgery is not applicable.[7]

The long-term prognosis for unicentric Castleman disease after complete resection of the tumor is very good, with 95% survival in 10 years.[10]

CONCLUSION

Although in rare cases, retroperitoneal tumors may be represented by Castleman disease. The surgeon should con-

sider this possibility because the complete removal of the tumor is followed by a very good long-term prognosis.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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CASE REPORT

OPHTALMOLOGY // HEMATOLOGY

Dacryocystitis Caused by Lymphoproliferative Infiltration in the Course of Lymphocytic Lymphoma: Case Report

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ABSTRACT

Background: Lacrimal drainage system lymphomas are rare, accounting for less than 10% of lacrimal sac tumors. They often appear as a secondary involvement within the confines of systemic lymphoproliferative disorders, therefore detailed ophthalmological examination and auxiliary testing is necessary to have an accurate diagnosis. **Case report:** We present the case of a 72-year-old woman with a medical history of chronic lymphocytic leukemia and small lymphocytic lymphoma. She presented to the ophthalmology clinic with a painful, discharging swelling in the right lacrimal sac area. Magnetic resonance imaging revealed a mass in the right nasolacrimal duct. A right external dacryocystorhinostomy was performed. The histological findings led to a diagnosis of small lymphocytic lymphoma. **Conclusions:** Special attention is required in cases of known systemic hematological disorders that associate with nasolacrimal duct obstruction or epiphora. Quick recognition and a full history with multidisciplinary clinical and diagnostic workup are fundamental to plan the treatment.

Keywords: dacryocystitis, lymphoproliferative disease, lymphoma, lacrimal sac

INTRODUCTION

Lacrimal drainage system (LDS) pathologies, especially chronic dacryocystitis, represent 3% of cases that present to ophthalmologic clinic consults.[1]

The cardinal symptoms that draw the patients' attention are: epiphora, lacrimal duct obstruction, accumulation of mucous secretion and desquamated cells, leading to a subsequent infection caused by the spread of microorganisms from the surrounding areas (conjunctiva, nasal cavity).[1,2]

Chronic dacryocystitis can be caused by specific inflammation, traumatic damage, mechanical obstruction, and neoplasms. However, in the majority of

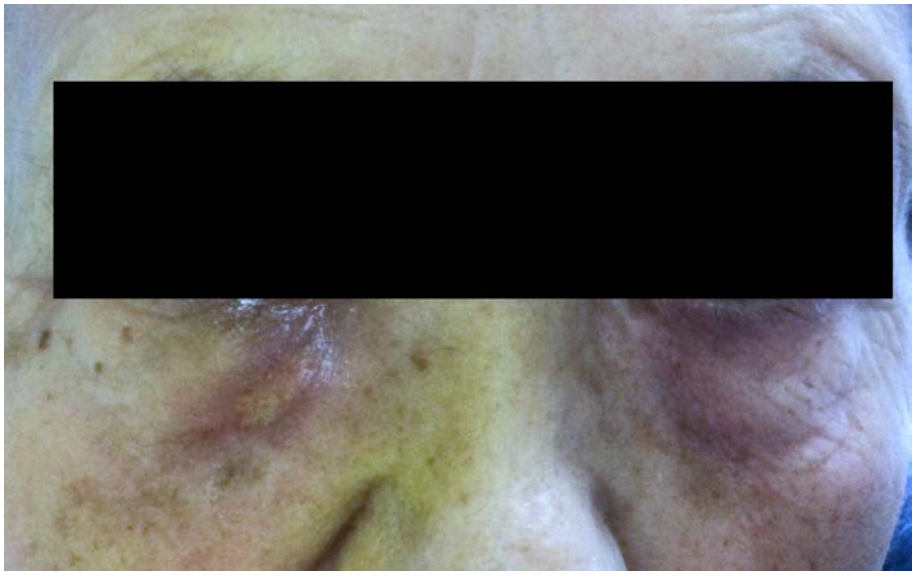

FIGURE 1. The patient's appearance at admission

cases, the etiology of dacryostenosis is idiopathic. It supposedly develops secondarily to an ascending inflammation from the nasal cavity and adjacent sinuses.[3]

Even though uncommon, malignancies can appear as obstructive neoplasms; therefore, a detailed ophthalmological examination and imaging are essential for a correct diagnosis. Lacrimal sac neoplasms appear on computed tomography as orbital tumor masses with or without local bone invasion.[4,5] Dacryocystorhinostomy is fundamental for confirming the diagnosis and planning the adjuvant therapy.[6]

Based on histopathological examination, 90% of lacrimal sac tumors are of epithelial origin, while lymphomas are very uncommon, representing less than 10% of lacrimal sac tumors.

LDS lymphomas usually appear as a secondary involvement within a systemic lymphoproliferative disorder.[5]

CASE REPORT

A 72-year-old woman, with a medical history of chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) since July 2015, presented to the ophthalmology clinic with a painful, discharging swelling in the right lacrimal sac area.

The initial diagnosis was established after the histopathological examination of an enlarged laterocervical lymph node, in which the immunohistochemistry revealed cells positive for CD20, CD79a, CD23, CD5, and BCL-2.

At admission, her ophthalmologic status was:

- best-corrected visual acuity: right eye (RE) 5/9, left eye (LE) 5/12;
- intraocular pressure (Goldmann tonometry): both eyes (BE) 19 mmHg;
- anterior segment evaluation: cortical cataract in BE, and the LE presented with a painful hard mass over the right lacrimal sac, edema, and erythema with nasolacrimal duct obstruction (Figure 1).

Differential diagnoses that were taken into account included acute blepharitis, bacterial conjunctivitis, basal cell carcinoma, chalazion, dermoid cyst, sinus tumors, obstruction of the nasolacrimal duct, and orbital cellulitis, which were all excluded by the patient's history of acute dacryocystitis. She was previously treated for acute dacryocystitis with systemic antibiotics that led to the subsiding symptoms.

She was diagnosed with recurrent right-sided dacryocystitis and cortical cataract in both eyes, and underwent systemic and topical antibiotic, as well as non-steroid anti-inflammatory treatment.

The patient was referred for additional ancillary testing and was later listed for a right external dacryocystorhinostomy.

Magnetic resonance imaging (MRI) revealed a 36/19 mm mass in the right nasolacrimal duct, without bone erosion and multiple laterocervical adenopathies.

Preoperatively, the lacrimal sac was noted to be inflamed and a biopsy was collected.

The histopathological examination revealed diffuse infiltration of small round lymphocytes, with round nucleus. On immunohistochemistry, the tumor cells were positive for CD20, CD5, CD23, and BCL-2, and negative for CD10 and cyclin-D1. In some areas, the cells were positive for

CD68. The proliferation index Ki-67 was 20%; thus, the histological findings led to a diagnosis of small lymphocytic lymphoma.

Taking into account the histological findings of the right-side nasolacrimal tumor, it was considered that there was a transformation of chronic lymphocytic leukemia into small lymphocytic lymphoma, hence leading to initiation of a treatment with vincristine, cyclophosphamide, and epirubicin, together with anti-inflammatory drugs.

All tissue and data collection complied with the guidelines of the Helsinki Declaration, and the patient signed an informed consent form before the admission and surgery (which specified our right to use her personal data and picture).

DISCUSSIONS

Non-Hodgkin lymphomas, such as CLL and SLL, are characterized by the presence of small B-lymphocytes that express CD5 and CD23 as cell surface antigens.[4] The difference between the two is that CLL is associated with a leukemic phase, while SLL with a nodal or solid phase. Because of their similarities, the World Health Organization classified the two malignancies as manifestations of the same disease and combined the two into one category.[7]

Obstruction of the LDS caused by neoplasms are classified into: primary LDS tumors (papilloma/squamous cell carcinoma); primary tumors of tissues surrounding the lacrimal system that invade this system (commonly eyelid carcinoma, capillary hemangioma, osteoma, and lymphoma); and tumors that metastasize in the nasolacrimal region.[8]

The lacrimal duct tissue is rich in mucosa-associated lymph tissue (MALT) and plays a significant role in lymphocyte recirculation, forming a functional unit with the cornea, the lacrimal gland, and the nasal mucosa. Therefore, unsurprisingly, it gives place for the development of primary or secondary hematologic malignancies.[5] However, according to Krishna *et al.*, less than 70 cases were described of secondary involvement.[6,9,10]

In Romania, during a sixteen-year period (between 1999 and 2015), 18 cases of chronic dacryocystitis were described by Costea *et al.*, from which 11.11% presented nodular lymphocytic inflammation.[2]

Despite the fact that it is an uncommon disease, considering that our patient had CLL in her medical history, and her dacryocystitis was recurrent, particular attention was required.

Consistent inflammation can mask pathologic processes; thus, biopsy and histopathological examination of the nasolacrimal tumor are essential in revealing the lacrimal sac pathology.[11,12]

Chronic dacryocystitis should be differentiated from MALT lymphoma of the lacrimal sac. While the chronic inflammation presents a diffuse infiltration pattern, lymphomas of the nasolacrimal duct show small to medium-sized round lymphocytes with round nuclei. Furthermore, if the immunohistochemical examination shows positivity of tumor cells for CD20, CD5, CD23, and BCL-2 antibodies (like in our case), lymphoma diagnosis can be established.[13,14] All lymphoproliferative lesions require an open biopsy for obtaining an adequate tissue specimen, essential in establishing the diagnosis.

Because of its locally invasive and poten¬tially life-threatening nature, quick recognition and a multi¬disciplinary treatment plan is urgent to cure and diminish the metastatic risk.

Lacrimal duct obstruction does not disappear permanently in most described cases, despite the regression of lymphomas due to therapy.[9] The same way, metastases can still appear years after remission, thus long-term follow-up is needed.[4,8,15,16]

CONCLUSIONS

Taking into account what was mentioned above, we have to pay special attention to cases of known systemic hematological disorders that associate with nasolacrimal duct obstruction or epiphora. Biopsy during surgery provides further instructions in diagnosing clinically suspected or unexpected neoplasms. Histopathological examination is undoubtedly fundamental for an adequate treatment. Dacryocystorhinostomy and adjuvant chemotherapy is not enough for a successful remedy. Long-term follow-up and routinely asking for symptoms of epiphora is required to identify recurrences or metastases.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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CASE REPORT

CARDIOLOGY // PEDIATRICS

Favorable Postoperative Evolution after Late Surgical Repair of Truncus Arteriosus Type 1: A Case Report

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ABSTRACT

Truncus arteriosus communis (TA) is a rare cyanotic congenital heart defect, in which the aorta and the pulmonary artery have not been separated during the normal development of the fetal heart, so a single truncal artery is arising from the base of the heart. Most patients with TA present within the first weeks of life with heart failure. This anomaly is an important cause of pulmonary arterial hypertension. Corrective surgery is indicated in the first 3 months of life, to avoid the development of severe pulmonary arterial hypertension. We report the case of a 12-month-old male infant diagnosed by echocardiography with truncus arteriosus type 1 in whom, based on hemodynamic data, surgical treatment could be performed at the age of 1 year.

Keywords: truncus arteriosus, pulmonary arterial hypertension, children

INTRODUCTION

Truncus arteriosus (TA) is a rare cyanotic congenital cardiac malformation characterized by a single common artery, which emerges from the heart through a single semilunar truncal valve and delivers blood to the systemic, pulmonary, and coronary circulation. Pulmonary arteries emerge from the common arterial trunk, after the origin of the coronary arteries and proximal to the first brachiocephalic branch of the aortic arch.[1–3] Characteristically, there is a misalignment over a large ventricular septal defect. This anomaly is often associated with various disorders such as truncal valve stenosis or regurgitation, coronary artery anomalies, atrial septal defect, aberrant subclavian arteries, persistent superior vena cava and a patent ductus arteriosus.

There are several clinical classifications that describe the various forms of TA; the most commonly used are the Collett and Edward classification and the Van Praagh classification.[2]

Truncus arteriosus is a life-threatening condition, as its natural history bears a mortality rate of 80% in the first year of life and especially during infancy.[2] The

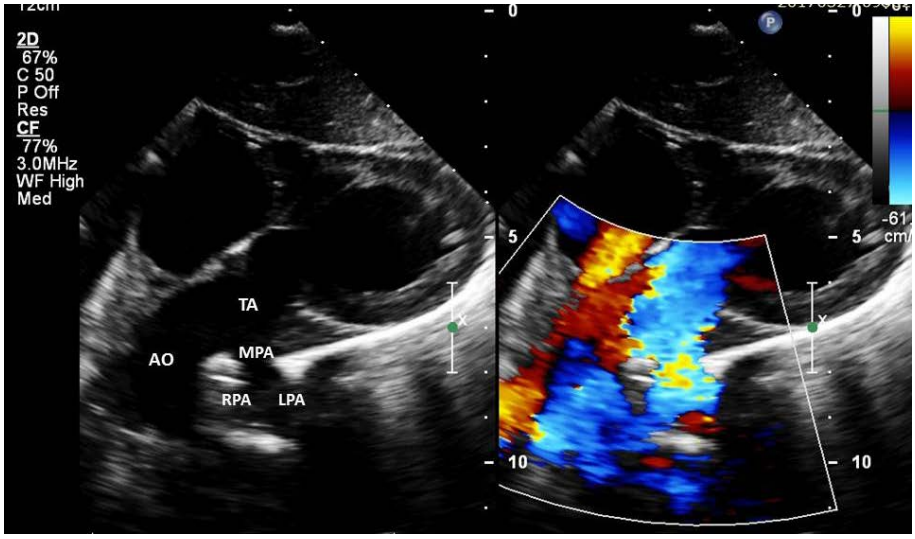

FIGURE 1. Echocardiography (2D and color Doppler) – subcostal view, showing a single overriding great vessel arising from the heart and the truncus of pulmonary artery emerging from the common arterial trunk. MPA – main pulmonary artery, LPA – left pulmonary artery, RPA – left pulmonary artery, AO – aorta

pathophysiology and the clinical manifestations of TA are particularly dependent on the volume of pulmonary blood flow, assessed by the pulmonary vascular resistance (PVR) and the degree of truncal valve regurgitation. There is mixing of systemic and pulmonary blood at the intracardiac level, resulting in mild or moderate cyanosis. In the first weeks of life, PVR decreases to normal values, leading to pulmonary fluid overload and heart failure. The severity of heart failure is increased in cases with significant truncal valve regurgitation. Corrective cardiac surgery is recommended in the first 3 months of life. In surgically uncorrected cases, pulmonary vascular obstructive disease may develop after the age of 6 months.

CASE REPORT

We report the case of a 12-month-old male infant who was referred to our department with a history of respiratory distress, difficulty in breathing, tachypnea, poor feeding, and failure to thrive. On admission, the clinical examination revealed mild cyanosis, peripheral oxygen saturation was 94%, respiratory rate was 70 respirations per minute, heart rate was 150 beats/minute, blood pressure was 90/48 mmHg, and there was a loud and single second heart sound on auscultation and a harsh systolic murmur (3/6) at the lower left sternal border. The liver was enlarged, approximately 2 cm below the right costal margin. His weight was 6.5 kg (80% of the expected weight). The hemoglobin concentration was 12.2 g/dL, and the hematocrit value was 34%.

The electrocardiogram showed peaked P wave and biventricular hypertrophy, and the chest X-ray showed cardiomegaly with prominent right cardiac cavities and increased pulmonary vascular markings.

The echocardiography demonstrated the typical findings of TA: a single arterial stem giving rise to the pulmonary trunk with normal-sized pulmonary arteries arising from the main pulmonary artery segment (Figure 1). A large ventricular septal defect with bidirectional shunt was present. The echocardiographic examination revealed also a quadricuspid truncal valve with mild regurgitation, a normal origin of the coronary arteries, and a normal aortic arch.

The computed tomography (CT) examination confirmed the diagnosis of TA type I (Figure 2A, 2B).

Considering the pathophysiology of this complex congenital heart disease and that the diagnosis was made at the age of 12 months, a hemodynamic investigation was indicated to evaluate the pulmonary pressure and the PVR. The cardiac catheterization revealed quasi-systemic pressures in the pulmonary circulation with a mean pulmonary artery pressure of 47 mmHg, with reactive PVR (3.82 UW/m^2 in atmospheric air and 2.25 W/m^2 after administration of nitric oxide). These findings indicated the need for surgical correction.

A standard method of TA repair was performed with the termination of the ventricular septum defect, separation of the pulmonary arteries from the primitive truncus, and restoration of the right ventricle and pulmonary artery continuity using a 15 mm Contegra conduit. The

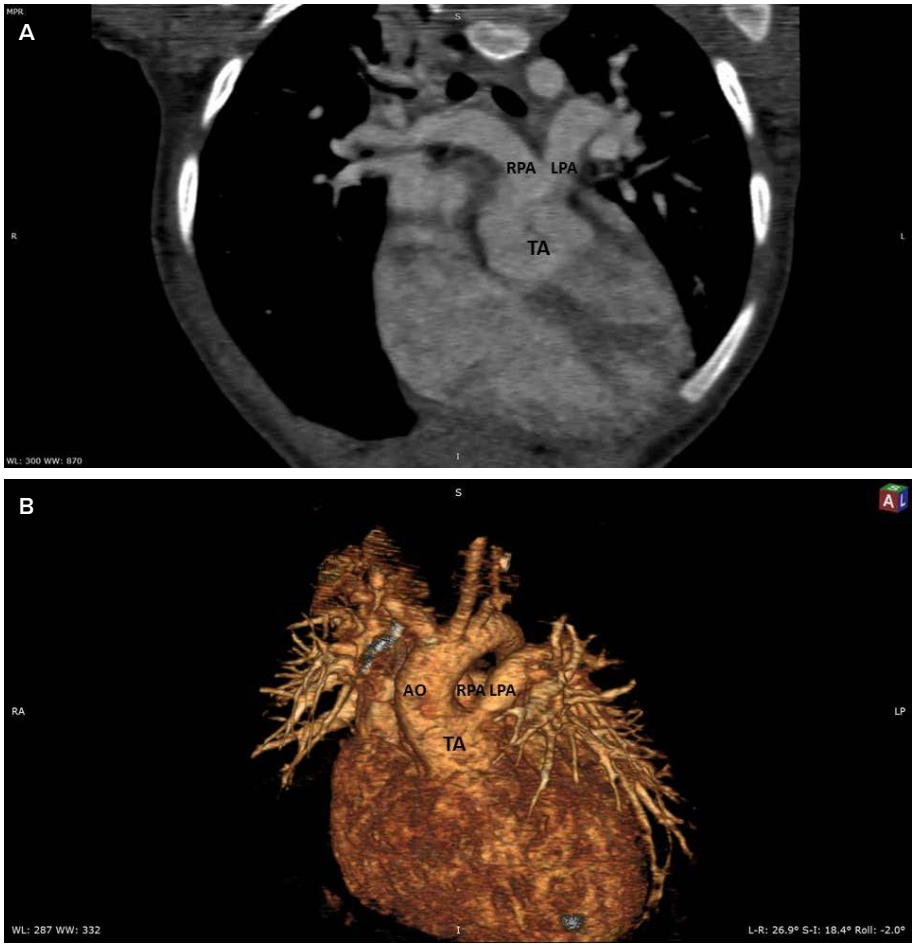

FIGURE 2. Computed tomography (**A** – sagittal image; **B** – 3 D reconstruction) showing a truncus arteriosus communis type I image with a single arterial trunk (TA) giving rise to pulmonary trunk which in turn gave rise to right (RPA) and left pulmonary artery (LPA). AO – aorta

surgery was uneventful. Postoperatively, the patient presented symptoms that indicated a low cardiac output due to biventricular dysfunction, requiring the administration of inotrope agents, and pulmonary arterial hypertension (PAH) crises, requiring pulmonary vasodilator therapy consisting of nitric oxide and sildenafil, a phosphodiesterase type 5 inhibitor.

The patient was discharged 20 days after cardiac surgery in optimal condition. The echocardiogram at the time of hospital discharge showed the pulmonary bioprosthesis with a gradient of 12 mmHg and mean regurgitation, mild aortic regurgitation, a ventricular septal defect patch with a small residual left-to-right shunt, and mild tricuspid regurgitation with a gradient of 40 mmHg, with recovery of biventricular function.

The echocardiographic examination performed at 1 year after the corrective cardiac surgery showed good function and no signs of residual pulmonary arterial hypertension.

DISCUSSIONS

TA is an uncommon lesion, with a prevalence of 0.056 to 0.03 in every 1000 births, described as a single arterial stem emerging from the heart, which in turn gives rise to the pulmonary trunk in various ways.[4–8] TA belongs to the group of ectomesenchymal tissue migration anomalies caused by the aberrant migration of neural crest cells through the branchial arch vessels during cardiogenesis.[9,10]

Chromosomal abnormalities are detectable in 8.7% of cases of TA. Di George syndrome and 22q11 chromosome microdeletion were reported in more than 30–50% of cases.[4,11–13] In our report, there was no chromosomal disorder present.

Several cases of prenatal diagnosis have been reported, but in most cases the diagnosis is made during the neonatal period,[14–16] when it is important to differentiate TA from other cardiac disorders that cause early heart failure and

neonatal sepsis. Failure to thrive, respiratory infections, dyspnea, cyanosis, and clinical signs of congestive cardiac failure are the common features. The electrocardiogram usually shows right axis deviation and right ventricular preponderance, and the chest radiography typically shows cardiac enlargement with an increase in the pulmonary vascular markings.

Diagnosis is achieved by echocardiography, which can identify the type of truncus, the morphology and functionality of the truncal valve, and the physiologic consequences of the cardiac disease.[8]

Due to the advantages of echocardiography, cardiac catheterization with angiography is indicated when pulmonary vascular disease is suspected and to evaluate associated lesions.

The hemodynamic consequences of a common TA may predispose to the development of pulmonary arterial hypertension; for this reason, the corrective operation is indicated before the age of 3 months in order to avoid the development of severe pulmonary vascular obstructive disease.[3,17] Niwa *et al*. reported a one-year survival rate of over 80% in patients who received surgical correction during the neonatal period.[18–23] A delay in the surgical treatment is associated with the risk of postoperative PAH crisis and cardiac failure.[22,24,25] Porter *et al*., in a case series of uncorrected patients, reported a mean period of survival of 5 weeks and a survival rate of only 15% at the age of 1 year.[26] Marcelletti *et al*. concluded that all patients who survive beyond the first year of life, will develop pulmonary vascular obstructive disease.[18,27]

During the postoperative assessment, a careful follow-up for pulmonary hypertension and truncal conduit patency is needed.

The reported case is one of the few cases diagnosed with TA reported in the literature, in which surgical correction could be performed at the age of 1 year because hemodynamic data did not document the presence of pulmonary vascular obstructive disease. Pulmonary arterial hypertension could seriously complicate the postoperative course of pediatric patients. Although the PAH crises complicated the immediate postoperative evolution, the subsequent evolution of the patient was favorable, and the echocardiography performed at 1 year after surgery indicated no significant residual lesions.

ETHICAL CONSIDERATIONS

The manuscript is coherent with the ideologies stated within the Declaration of Helsinki. The patient's legal guardian signed an informed agreement and agreed to the publication of his data. The study has been approved by the ethics committee of the University of Medicine and Pharmacy of Tîrgu Mureș, Romania.

CONCLUSIONS

Truncus arteriosus is a complex cardiac disease, in which primary surgical repair should be performed during the neonatal period in order to avoid the development of severe PAH. The diagnosis is generally confirmed by echocardiography. The management should to be individualized according to the age of the patient, the anatomical type of the TA, the associated lesions, and the hemodynamic consequences.

CONFLICT OF INTEREST

None declared.

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IMAGE FOCUS

DERMATOLOGY // PSYCHIATRY

Hand-biting Lesions in a Child — a Challenging Diagnosis

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ABSTRACT

Background: Self-induced skin lesions, especially in young children, can create confusion within pediatricians, dermatologists, or other medical care providers, leading to different diagnoses, unnecessary investigations, and delaying the correct therapeutic psychiatric evaluation. **Case report:** We report the case of a 4-year-old boy who was referred to Dermatology after being hospitalized in the Allergy Department for a chronic allergic contact dermatitis. He had been previously diagnosed with chronic hand dermatitis, atopic dermatitis, and psoriasis, and treated with no favorable outcome. Scaly erythematous plaques were noticed on the dorsal aspects of both hands and on the lateral folds of the fingers. The skin lesions were distributed in a non-symmetrical way. A diagnosis of self-injurious behavior was presumed, and psychiatric evaluation was asked. The child was transferred to the Psychiatry Department, and a diagnosis of schizophrenia was concluded.

Keywords: allergic contact dermatitis, risk assessment, treatment

INTRODUCTION

Self-induced skin lesions, especially in young children, can create confusion within pediatricians, dermatologists, or other medical care providers, leading to different diagnoses, unnecessary investigations, and delaying the correct therapeutic psychiatric evaluation. The mainstay of the diagnosis is to think about it.

CASE REPORT

A 4-year-old boy was referred to Dermatology after being hospitalized several days in the Allergy Department for a chronic allergic contact dermatitis. He had been previously diagnosed with chronic hand dermatitis, atopic dermatitis, and

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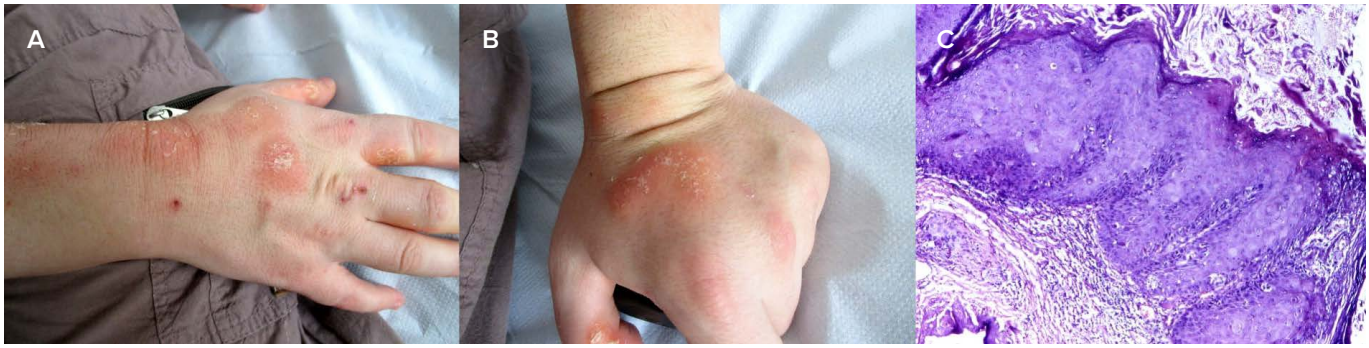

FIGURE 1. Eczematous, excoriated, crusted plaques on the right (**A**) and left (**B**) hand. Hyperkeratosis, acanthosis, and mild inflammatory infiltrate in the superficial dermis (Hematoxylin-Eosin, 10x) (**C**).

psoriasis, and treated with oral antihistamines, topical steroids, and emollients, with no favorable outcome.

The dermatological examination discovered non-symmetrical scaly erythematous plaques on the dorsal aspects of both hands and on the lateral folds of the fingers (Figure 1A, 1B). Pruritus, pain, or any other complains were denied by the mother. During clinical examination, the child seemed relaxed, non-communicative at the beginning, but with compulsive acts of self-biting and sucking of the hands. A detailed family history search for dermatological and/or psychiatric disorders was undertaken and ruled out any medical issues.

Exhaustive laboratory investigations were carried out, including patch tests, prick tests, and direct mycological examinations, and were all negative. A punch biopsy revealed hyperkeratosis, acanthosis, and mild inflammatory infiltrate in the superficial dermis (Figure 1C).

A diagnosis of self-injurious behavior was presumed, and psychiatric evaluation was asked. The child was transferred to the Psychiatry Department, and a diagnosis of schizophrenia was concluded, which required psychiatric hospitalization. The skin lesions were treated with emollients, and the patient received psychiatric treatment, with a good response to treatment as assessed during follow-up.

The Declaration of Helsinki protocols were followed during our study and the patient's family gave their written, informed consent.

DISCUSSIONS

Self-injurious behavior is a syndrome characterized by self-induced physical damage such as nail and finger biting, head banging, oral and genital mutilation.[1]

Dermatitis artefacta covers a large spectrum of self-inflicted but involuntarily induced skin lesions, unlike neurotic excoriations, Munchausen syndrome, and true malingering.[2]

Self-mutilation could be considered as a "cry for attention" or a behavior that reduces anxiety, coexisting with psychiatric disorders; 66.12% of persons with severe self-induced skin lesions were diagnosed with schizophrenia.[3]

Usually, such patients, regardless of their age, are seen first by dermatologists, without psychiatric examination, inducing an important delay in a correct diagnosis and treatment. Moreover, antipsychotic treatment improves cutaneous lesions along with the psychiatric illness.[4]

There is a close correlation between schizophrenia and dermatitis. A recently published study indicates an association between atopic disorders and schizophrenia.[5] Contact dermatitis and other types of eczema have been found in a higher incidence in patients diagnosed previously with schizophrenia.[6]

CONCLUSIONS

Although the diagnosis of self-induced lesions in young children is a challenge for pediatric physicians and dermatologists, a high awareness of a psychiatric disorder must be maintained.

CONFLICT OF INTEREST

None for all authors.

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ERRATUM

Erratum

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