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UNIVERSITY OF MEDICINE AND PHARMACY "CAROL DAVILA" BUCURESTI

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MEDICINE

ASPECTS RELATED TO THE ASSESSMENT OF RIGHT VENTRICULAR SYSTOLIC FUNCTION BY TWO- AND THREE-DIMENSIONAL ECHOCARDIOGRAPHIC TECHNIQUES IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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List of abbreviations and symbols

A2C - apical 2-chamber view

A4C – apical 4-chamber view

A4C RV – apical 4-chamber view optimized for right ventricle

2DE – two-dimensional echocardiography

3DE - three-dimensional echocardiography

3D RVEF - three-dimensional right ventricular ejection fraction

ACEI - angiotensin-converting enzyme inhibitors

ACS - acute coronary syndrome

AHA – American Heart Association

AMI - acute myocardial infarction

ARNI - angiotensin/neprilysin receptor inhibitors

ATP - adenosine triphosphate

Bcl-2 - receptor associated with B-cell lymphoma

BMI - body mass index

BSA - body surface area index

Ca 2+ - calcium

CVD - cardiovascular disease

CI - confidence interval

cMRI - cardiac magnetic resonance imaging

cTn - cardiac troponin

DM - diabetes mellitus

ECG - electrocardiogram

EMS - emergency medical service

ESC - European Society of Cardiology

F- female sex

FAC - fractional area change

FMC - first medical contact

GLP1-RAs - glucagon-like peptide type 1 receptor agonist

GLS - global longitudinal strain

GRACE - Global Registry of Acute Coronary Events

HDL - high-density lipoprotein

HORIZONS-AMI - Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction Study

HR – hazard ratio

HTN – arterial hypertension

IHD - ischemic heart disease

INTERHEART - International Study of Myocardial Infarction and the Role of Modifiable Risk Factors

K+ - potassium

LAD – left anterior descending artery

LV – left ventricle

LVEF - left ventricular ejection fraction

LDL - low-density lipoprotein

LOA – limits of agreement

M- male sex

mPTP - mitochondrial membrane permeability pore

Na+ - sodium

NSTEACS - non-ST-segment elevation coronary syndrome

P2Y12 - purine P2Y12 receptor

PCI - percutaneous coronary intervention

PCSK9 - proprotein converting subtilisin/kexin type 9

PLAX - parasternal long axis view

PPCI - primary percutaneous coronary angioplasty

PURE - Prospective Urban Rural Epidemiology

R1 - advanced operator

R2 - intermediate operator

R3 - novice operator

RCA - right coronary artery

RV - right ventricle

RV-EDAi - right ventricular indexed end-diastolic area

RV-EDVi - right ventricular indexed end-diastolic volume

RV-ESAi - right ventricular indexed end-systolic area

RV-ESVi - indexed right ventricular end-systolic volume

RVFWLS - right ventricular free wall longitudinal strain

RVF - right ventricular failure

RV SVi - right ventricular indexed stroke volume

S'_{VD} - systolic wave velocity at the lateral tricuspid annulus

SHOCK - Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock

SGLT2i - sodium-glucose co-transporter type 2 inhibitors

STEMI - ST-segment elevation acute myocardial infarction

TAPSE - systolic excursion of the tricuspid annulus plane

TDI - tissue Doppler imaging

VALIANT - VALsartan In Acute myocardial iNfarcTion study

INTRODUCTION

Although considered a disease of industrialized society, the concern about ischemic heart disease and its main symptom, angina pectoris, are not new. Its first medical description was given by William Heberden in 1772 [1] while, in the inaugural issue of the New England Journal of Medicine, John Warren published a series of cases relating to this mysterious condition [2]. Since then, our knowledge of coronary heart disease has evolved significantly but, despite remarkable progress, cardiovascular disease continues to be the leading cause of death globally. Among these, atherosclerotic coronary artery disease with its acute manifestation of acute myocardial infarction is the main contributor to this mortality, accounting for more than one third of all cardiac deaths. [3]

The current management of myocardial infarction involves, in addition to reperfusion techniques, the correct assessment of cardiac function to facilitate the adoption of treatments with proven impact on survival. Currently, particular attention is given to the assessment of the left ventricle, but right ventricular impairment is known to be a negative prognostic factor in this pathology. [4] Currently, the assessment of right ventricular systolic function is based on two-dimensional echocardiographic methods, but recently the development of three-dimensional echocardiography has added new elements that require increasingly wider integration into current clinical practice.

The present research, "Aspects related to the assessment of right ventricular systolic function by two- and three-dimensional echocardiographic techniques in patients with acute myocardial infarction", presented as a PhD thesis, aimed to analyze the changes in right ventricular systolic function secondary to myocardial infarction by comparing the classical echocardiographic methods of assessing right ventricular systolic function with new parameters derived from three-dimensional echocardiography. The research is descriptive in nature, being entirely original, and aims to improve the knowledge of the usefulness of using new methods of right ventricular assessment by three-dimensional echocardiography to improve the evaluation of patients with acute myocardial infarction.

The paper is structured in two parts: the first is the general part consisting of 3 chapters and the personal contributions part consisting of 5 chapters. The general part of this doctoral thesis aims to present the current state of knowledge by presenting the latest aspects related to the epidemiology, pathophysiology, diagnosis and treatment of acute myocardial infarction as well as the usefulness and importance of the assessment of right ventricular systolic function in the context of this pathology.

In the personal contributions part we have presented the results of research based on a study that analyzed the data of 63 patients with acute myocardial infarction, 43 of them with ST-segment elevation myocardial infarction (STEMI) and 20 with non-ST-segment elevation myocardial infarction (NSTEMI), regarding the parameters of assessment of right ventricular systolic function, correlations between them, reproducibility of these parameters and correlations of these parameters with clinical and paraclinical elements.

The last chapter of the thesis contains the conclusions of the work, highlighting the main results obtained and suggesting new research directions.

The present research is part of a project supported by the Ministry of Research and Innovation, CNCS-UEFISCDI, project number 5/2018 entitled INNATE-IM: Targeting innate immunity mechanisms for better risk stratification and identification of new therapeutic options in acute myocardial infarction, carried out in collaboration with the Institute of Cell Biology and Pathology "Nicolae Simionescu" Bucharest. In conclusion, I would like to thank all those who have been involved in this project and whose hard work has made this PhD thesis possible.

GENERAL PART

1. Acute myocardial infarction

1.1 Definition of myocardial infarction

Type 1 myocardial infarction, the most common type encountered in clinical practice, is the manifestation of complicated atherosclerotic coronary artery disease, caused by rupture of an atherosclerotic plaque. The diagnosis should be established when there is an increase and/or decrease in cardiac troponin (cTn) values - with at least one value above the 99th percentile of reference values, accompanied by at least one of the following criteria:

- Symptoms of acute myocardial ischemia
- New ECG changes suggestive of ischemia
- Onset of pathologic Q waves
- Imaging evidence of loss of myocardial viability or new-onset regional kinetic disturbances suggestive of ischemic etiology
- Identification of an intracoronary thrombus either by coronary angiography or autopsy. [5]

By comparison, myocardial infarction type 2 is caused by an imbalance arising between oxygen supply and demand, unrelated to atherosclerotic plaque rupture or erosion. Type 3 is encountered in patients who suffer a death preceded by symptoms suggestive of myocardial ischemia and with new-onset ECG changes suggestive of acute ischemia or ventricular fibrillation, without evidence of increased levels of biomarkers of myocardial injury. [5]

Myocardial infarction types 4 and 5 refer to the occurrence of myocardial infarction in the context of minimally invasive and surgical cardiac procedures. Type 4a refers to post coronary angioplasty myocardial infarction, type 4b represents stent thrombosis infarction and type 4c is in-stent restenosis infarction. Type 5 myocardial infarction is myocardial infarction occurring after coronary artery bypass grafting. [5]

1.2 Epidemiology of myocardial infarction.

According to the latest data published by the American Heart Association (AHA), cardiovascular disease and stroke accounted for more deaths in 2022 than cancer and lung disease combined. Of these deaths, 39.5% were caused by atherosclerotic coronary artery disease[3] According to data published by the European Society of Cardiology (ESC) cardiovascular mortality has declined by more than 50% over the last 29 years but still accounts for more than 1.6 million deaths among women and 1.5 million deaths among men. Ischemic heart disease has been the largest contributor to cardiovascular death rates, showing inequity in terms of gender distribution (more common in men than women) and socio-economic status (2.5 times higher death rates in middle-income countries compared to high-income countries). [6]

1.3 Pathophysiology of myocardial infarction.

The most common cause of myocardial infarction is atheromatic plaque rupture resulting in exposure of the necrotic core of the plaque to the blood stream followed by a prothrombotic reaction and acute occlusion in an epicardial coronary artery. [7]

Myocyte death secondary to myocardial infarction is achieved by two different mechanisms: (1) cell apoptosis which is a programmed process of cell fragmentation with the formation of apoptotic bodies that are subsequently removed by specialized phagocytes and (2) cell necrosis which is a passive process characterized by the appearance of cell edema and loss of cell membrane integrity. Unlike apoptosis, the onset of necrosis leads to a significant inflammatory response. Recent data suggest that these two processes may be interconnected. [8,9]

Myocyte apoptosis appears to be mediated both by activation of intrinsic pathways related to mitochondrial membrane signaling and extrinsic pathways mediated by the attachment of ligands that signal cell death to cell membrane receptors. The major event that triggers apoptosis is the permeabilization of the mitochondrial outer membrane through interactions with members of the B-cell lymphoma 2 (Bcl-2) family. In comparison, necrosis is caused by the opening of the mitochondrial pore responsible for membrane permeability (mPTP) leading to loss of mitochondrial membrane potential resulting in the cessation of ATP synthesis as well as intramitochondrial influx of water resulting in mitochondrial edema. The consequence is disruption of the mitochondrial outer membrane with activation of apoptogens and the caspase pathway. [8]

The healing process of the infarcted areas consists in replacing cardiomyocytes with non-contractile scar tissue, which has the role of preserving the integrity of the myocardium. This process can be divided into 3 separate but partially overlapping phases: (1) the inflammatory phase in which the activation of innate immune mechanisms and leukocyte recruitment leads to the removal of dead cells; (2) the proliferative phase in which the suppression of proinflammatory signals and the appearance of mesenchymal cells secreting matrix proteins occur; (3) the maturation phase characterized by the removal of cells with repair function and the consolidation of the resulting matrix. [10,11,12]

Secondary to the myocardial infarction and the cellular changes described above resulting in the replacement of myocardial tissue by areas of fibrosis, the decrease in contractile function leads to changes in ventricular geometry with secondary dilatation and increased parietal stress according to Laplace's law. Compensatory mechanisms such as myocardial hypertrophy and neuro-hormonal activation attempt to counterbalance these changes and initially have a beneficial effect but may lead over time to heart failure. [13]

1.4 Right ventricular involvement in myocardial infarction.

A recent study that included 1235 patients with myocardial infarction evaluated by cardiac magnetic resonance imaging (cMRI) revealed the presence of myocardial infarction in 19.6% of cases and identified myocardial ischemia in 12.1% of patients. [14]

The location of myocardial infarction is closely related to coronary anatomy and the distribution of the coronary vasculature. The right coronary artery (RCA) is the main blood supply to the right ventricle via its branches. Right ventricular involvement may also occur with occlusion of the circumflex artery or its branches in patients with left-dominant coronary circulation. [15] Right ventricular (RV) involvement may also occur less frequently with occlusion of the anterior interventricular artery. The results of a series of 107 autopsies performed on patients with coronary artery disease showed right ventricular involvement in 87% of cases, with equal frequency in both anterior and posterior infarcts. [16]

The right ventricle is located retrosternally, being the most anteriorly positioned cardiac structure. A cross-section of the heart shows that the right ventricle has a semilunar shape surrounding the left ventricle. [17] The walls of the right ventricle are composed of only two layers of myocardial fibers: circumferential subepicardial and longitudinal subendocardial fibers [18], causing a predominantly longitudinal contraction. [19] Having a mass up to six times smaller than the left ventricular myocardium [20], the right ventricle acts mainly as a capacitance chamber that is better adapted to volume overload than to pressure overload. [18,21] Thus, impaired right ventricular function in anterior infarcts could be a hemodynamic consequence of increased right ventricular afterload as a result of pulmonary hypertension induced by left ventricular dysfunction [22].

Referring to ventricular interdependence as a cause of right ventricular dysfunction in anterior infarcts, studies have shown that the left ventricle is a major contributor through contraction of the interventricular septum, which generates 20-40% of the volume ejected by the right ventricle into the pulmonary circulation. [17,23] In addition, ventricular interdependence seems to be also related to the presence of circumferential epicardial fibers connecting the two ventricles and the pericardial space. [22]

1.5 Risk factors for myocardial infarction

Modifiable risk factors such as smoking, dyslipidemia, hypertension, diabetes mellitus, abdominal obesity, psychosocial factors, low fruit and vegetable consumption, alcohol consumption and low levels of regular physical activity were identified in the INTERHEART study as being responsible for 90% of the risk of developing myocardial infarction. [23]

Similar data were reported in the PURE study where 79% of the risk of myocardial infarction was attributed to a set of 12 individual and socio-economic risk factors. Of these, elevated non-HDL cholesterol levels, hypertension, smoking, abdominal obesity, diabetes mellitus and low education proved the strongest association with myocardial infarction occurrence. [24]

The Global Cardiovascular Risk Consortium study pooled data from 112 cohort studies in 34 countries and analyzed the prevalence of 5 known risk factors for cardiovascular disease and death from cardiovascular causes. Strict control of these 5 risk factors (body mass index, non-HDL cholesterol, smoking, hypertension, diabetes mellitus) could prevent 57.2% of all cardiovascular deaths among women and 52.6% among men globally. [25]

2. Treatment of acute myocardial infarction

The treatment of acute myocardial infarction focuses on two key aspects:

- reperfusion/revascularization therapy which aims to restore coronary blood flow to the affected myocardial segments as early as possible.
- drug treatment aimed at preventing recurrence of the heart attack and preventing the development of complications such as heart failure.

2.1. Reperfusion/revascularization treatment

The European Society of Cardiology's 2023 Guidelines for Acute Coronary Syndromes proposes a diagnostic algorithm that ultimately leads to the identification of 3 categories of patients: patients with ST-segment elevation myocardial infarction, patients with non-ST-segment elevation myocardial infarction and patients with unstable angina. [26] Patients with persistent ST-segment elevation should be immediately referred for a rapid reperfusion strategy: primary coronary angioplasty or fibrinolysis, with a preference for primary angioplasty when presentation occurs less than 12 hours after symptom onset and time to intervention is less than 120 minutes. [26]

For patients presenting with acute coronary syndrome without persistent ST-segment elevation, further risk stratification guides the optimal timeframe for adopting an invasive strategy. Patients categorized at very high risk according to the ESC 2023 algorithm benefit from immediate invasive strategy according to the ESC guidelines having indication class I, evidence level C. [26] An invasive approach within the first 24 hours is recommended for patients classified as high risk. The recommendation has indication class IIa, evidence level A. [26]

2.2. Symptomatic treatment and management of acute hypoxemia

In addition to revascularization reperfusion therapy, in the acute phase of myocardial infarction, therapeutic measures focus on correcting hypoxemia by administering oxygen to patients with blood oxygen saturation less than 90% (class I indication, evidence level B) and antianginal treatment with nitrates and opioids (class Iia indication, evidence level C) [26].

2.3. Antithrombotic treatment

Antithrombotic treatment consisting of antiplatelet and anticoagulant therapy is an important pillar of therapies for patients with acute myocardial infarction. As regards antiaggregant therapy, aspirin is recommended to be administered to all patients without contraindications in an initial dose of 150-300 mg and a maintenance dose of 75-100 mg/day (class of recommendation I, level of evidence A) [26].

In combination with this, prasugrel is recommended for patients who will benefit from the invasive strategy at a loading dose of 60 mg followed by a maintenance dose of 10 mg/day or alternatively, 5 mg/day for patients over 70 years of age and weighing less than 60 kilograms (indication class I, evidence level B). Ticagrelor is another option of antiplatelet that can be used in combination with aspirin, irrespective of the treatment strategy adopted, with a loading dose of 180 mg followed by a maintenance dose of 90 mg x 2 mg/day (class of indication I, evidence level B). Patients who are contraindicated or intolerant to prasugrel or ticagrelor are recommended to be treated with clopidogrel 300-600 mg loading dose followed by a maintenance dose of 75 mg/day (indication class I, evidence level C) [26].

The standard duration of dual antiplatelet therapy in patients with acute myocardial infarction, in the absence of an increased risk of bleeding, is 12 months (class I indication, evidence level A) but this can be adapted according to the characteristics of each patient by weighing the risk of recurrence of an ischemic event against the risk of a bleeding event. It is not recommended to de-escalate dual antiplatelet therapy in the first 30 days after an acute coronary event (class III indication, evidence level A) [26].

Anticoagulant treatment with unfractionated heparin is recommended for all patients with acute coronary syndromes at the time of diagnosis (class I indication, evidence level A) and during the reperfusion/revascularization procedure (class I indication, evidence level C), alternatively low molecular weight heparins may be used, adapted to the clinical situation. Administration of parenteral anticoagulant therapy is recommended to be discontinued immediately after the revascularization/reperfusion procedure. [26]

For patients with chronic anticoagulation requirements due to the presence of atrial fibrillation, mechanical prostheses or venous thromboembolic disease, a bolus of unfractionated heparin is recommended for patients treated with direct anticoagulants or those with INR < 2.5 on antivitamin K therapy. Thereafter, continuation of oral therapy is recommended with doses adjusted according to the patient's individual bleeding risk. The standard duration of maintenance of the triple antithrombotic combination is 7 days post-angioplasty, followed by continuation of the double combination of oral anticoagulant and clopidogrel for up to one year post-angioplasty (class I indication, level of evidence A). Thereafter, anticoagulant monotherapy is recommended indefinitely (class I indication, level of evidence A) [26].

2.4. Lipid-lowering treatment

According to the latest ESC recommendations, for secondary prevention, the current target is to reduce LDL cholesterol levels to below 55 mg/dl and to achieve at least a 50% reduction from baseline (class I indication, level of evidence A. For patients who experience a second cardiovascular event within two years, further reduction to below 40 mg/dl appears to provide additional benefit (class IIb indication, level of evidence B) [26,27,28].

Given the proven benefits of statins in patients with acute coronary syndromes undergoing coronary angioplasty [29], it is recommended to initiate therapy with a high-intensity statin (atorvastatin 40-80 mg or rosuvastatin 20-40 mg) as soon as possible, regardless of initial LDL cholesterol values. Subsequently, if target values are not reached, treatment can be supplemented by introducing the cholesterol absorption inhibitor ezetimib and PCSK9 inhibitors such as evolocumab, alirocumab [26].

2.5. Beta-blocker treatment

In the initial phase, intravenous beta-blockers are recommended for patients undergoing primary angioplasty who do not show signs of acute heart failure (class IIa indications, evidence level A). Subsequently, chronic beta-blocker therapy is recommended to be given to patients with left ventricular ejection fraction (LVEF) less than 40% irrespective of the presence of heart failure phenomena (class I indication, level of evidence A) but should be considered in all patients who have suffered an acute coronary event, irrespective of LVEF (class IIa indication, level of evidence B) [26].

2.6. Anti-anginal medication

Long-term administration of nitrates and calcium channel blockers has not shown a survival benefit in patients with myocardial infarction. Thus, these drugs can be used for symptomatic control of residual angina in patients with myocardial infarction. [26,30,31]

2.7. Renin-angiotensin-aldosterone axis inhibition medication.

Post-myocardial infarction administration of angiotensin-converting enzyme inhibitors (ACEIs) have been shown to have beneficial effects in patients with heart failure and/or LVEF less than 40%, diabetes mellitus, chronic kidney disease, hypertension, also showing a reduction in 30-day mortality in patients with previous myocardial infarction. (Class I indication, level of evidence A.) ACEI administration should be considered in all post-myocardial infarction patients regardless of LVEF (Class IIa recommendation, level of evidence A). [26]

In the VALIANT trial, the angiotensin receptor blocker valsartan was shown to be non-inferior to the enzyme inhibitor captopril in patients with myocardial infarction and heart failure or LVEF ≤ 40%. [32] Sartan administration is recommended for patients with a history of heart failure of any etiology who do not tolerate treatment with ACEIs or ARNIs. [33]

2.8. Cardio-metabolic medication

In the specific context of patients with acute myocardial infarction, administration of the SGLT2 inhibitor dapagliflozin resulted in improved rates of cardiometabolic events (weight loss and onset of diabetes mellitus) but without improvement in rates of major cardiovascular events. [34] Another study comparing empagliflozin with placebo in patients with ejection fraction ≤ 45% or signs of heart failure showed decreased rates of first hospitalization and total hospitalizations due to heart failure, but no reduction in rates of major cardiovascular events. [35] To date, there are no large randomized trials investigating the effect of GLP1-RAs administration in the setting of acute myocardial infarction.

3. Echocardiographic evaluation of patients with acute myocardial infarction.

3.1. Standard echocardiographic evaluation of patients with acute myocardial infarction.

At the time of presentation, transthoracic echocardiography is recommended to be performed in patients with suspected acute coronary syndrome presenting with cardiogenic shock or suspected mechanical complications (class I indication, evidence level C). It should also be considered in cases where there is uncertainty about the diagnosis but without delaying referral to the catheterization lab when there is a high suspicion of occlusion of an epicardial coronary artery (class IIa indication, evidence level C) [26].

After reperfusion/revascularization treatment, it is recommended to routinely perform transthoracic cardiac ultrasound during hospitalization to assess global and regional left ventricular systolic function, the presence of possible mechanical complications and to visualize the possible presence of intracavitary thrombus (class I indication, evidence level C) [26].

Assessment of global left ventricular systolic function by calculating ejection fraction has prognostic value in STEMI patients who have undergone primary revascularization. The HORIZONS-AMI study showed that at one year post-infarction, patients with severely reduced ejection fraction (≤ 40%) had significantly higher rates of adverse clinical events (27.1 vs 14.2%, $p < 0.0001$), major cardiovascular events (20.7 vs 9.5%, $p < 0.0001$) and cardiac death (20.7 vs 9.5%, $p < 0.0001$) compared to patients with normal ejection fraction. [36]

Echocardiographic assessment of right ventricular function involves obtaining apical 4-chamber views optimized for the right ventricle (RV). The incidence of standard A4C may lead to significant variations in the values obtained due to incomplete right ventricular (RV) sections. The image optimized for right ventricle acquisition is obtained when the LV apex is in the center of the image and the basal diameter of the right ventricle is maximal. RV systolic function is usually assessed by determining the tricuspid annular plane systolic excursion (TAPSE), the fractional area change (FAC) ratio, and the systolic wave velocity at the lateral tricuspid annulus assessed by tissue Doppler (S'_{VD}) [37].

TAPSE is a parameter describing right ventricular longitudinal function. Although it is a one-dimensional parameter, its values have been shown to correlate with other parameters that assess global right ventricular function (FAC, right ventricular ejection fraction determined by radio-isotopic methods). The determination is made in A4C view using M-mode and having the cursor aligned in the direction of the lateral tricuspid annulus with values < 17 mm considered to be abnormal. [37]

FAC is a parameter that estimates global right ventricular function. It is determined by measuring the telesystolic and telediastolic areas using the following formula: $(End - systolic\ area - End - diastolic\ area)/(End - diastolic\ area)\ x\ 100$. It is necessary to optimize the image so that the apex and the free wall of the right ventricle are visible, and the traced margins should also include the trabeculations of the ventricular cavity. Values < 35% are considered to be abnormal. [37]

The systolic wave velocity determined at the lateral tricuspid annulus (S'_{VD}) determined by tissue Doppler imaging (TDI) is another parameter that correlates with the global function of the right ventricle. It is obtained from the same A4C view by keeping the cursor aligned with the lateral annulus and basal segment of the right ventricle. Values < 9.5 cm/sec are representative of right ventricular dysfunction. [37]

3.2. Three-dimensional echocardiographic assessment of right ventricular systolic function

Post-infarction echocardiographic evaluation focuses on assessment of the left ventricle and possible mechanical complications. However, right ventricular involvement is not uncommon in the setting of acute myocardial infarction. Right ventricular dysfunction has been associated with adverse clinical events leading to increased risk of arrhythmias and death at 1 and 6 months post-infarction. [4,38] A recent study evaluating more than 1000 patients with myocardial infarction by cardiac MRI identified right ventricular dysfunction in almost 20% of cases. [14] Results from a series of 107 autopsies identified right ventricle involvement in 87% of cases with an equal proportion in both posterior and anterior infarcts. [16]

The difficulty in assessing right ventricular systolic function by 2D methods arises from the anatomical complexity of the right ventricle shape and its retrosternal localization. As mentioned previously, the right ventricle viewed on a cross-section has a semilunar shape that, enveloping the left ventricle. Thus, 2D assessment underestimates ventricular volumes compared with cardiac magnetic resonance, which is the gold standard in right ventricular quantification. [39]

Three-dimensional assessment of right ventricular systolic function is performed by determining the right ventricular ejection fraction (3D RVEF) by obtaining images from right ventricle-optimized A4C, A2C and parasternal short-axis views. This method is dependent on good visualization of ventricular endocardial delineation. The recorded images are saved and analyzed off-line using dedicated software applications that allow semi-automated image analysis. Recently, software applications based on artificial intelligence have been released, that allow fully automated image analysis. [40]

Three-dimensional assessment of right ventricular ejection fraction is a highly reproducible method, reporting low intra- and inter-observer variability rates (0-0.9% in most studies). RV volumes and ejection fraction values obtained by three-dimensional analysis correlate well with values obtained by cardiac MRI, with a correlation coefficient exceeding 0.75 in most studies. [40]

In a study including 446 patients with various cardiac pathologies, 3D RVEF was identified as an independent prognostic factor for the occurrence of major adverse events. [4] A recent study found that 3D RVEF values determined by automated methods in patients with suboptimal echocardiographic windows correlated significantly with the occurrence of adverse cardiac events. [41]

3.3. Usefulness of assessing right ventricular function by 3D RVEF compared with conventional echocardiographic methods

Analysis by classical two-dimensional methods can provide a truncated picture of right ventricular systolic function. A recently published study analyzing data from over 750 patients with different cardiovascular pathologies (20% with acute myocardial infarction) compared 3D

RVEF with classical 2D parameters such as TAPSE, FAC and right ventricular longitudinal free wall strain of the right ventricle (RVFWLS). Patients who had normal 2D parameter values but who were identified with dysfunction based on 3D RVEF values had up to a 4-fold higher risk of death compared with patients who were not reclassified (TAPSE HR [95% CI], 4.395 [2.127-9.085]; $p < 0.001$; FAC HR [95% CI], 4.186 [1.476-11.880]; $p < 0.001$; RVFWLS HR [95% CI], 4.221 [2.115-8.426]; $p < 0.001$). At the same time, patients identified as having dysfunction on the basis of classical parameters but whose 3D RVEF values were normal had a lower risk of mortality (TAPSE HR [95% CI], 0.326 [0.199-0.532]; $p < 0.001$; FAC HR [95% CI], 0.308 [0.197-0.480]; $p < 0.001$; RVFWLS HR [95%CI], 0.195 [0.102-0.373]; $p = 0.002$) [38,42]

PERSONAL CONTRIBUTIONS

4. Working assumptions and general objectives

Currently, cardiovascular disease and, particularly, ischemic heart disease, remains the leading cause of death globally despite the fact that therapeutic advances have significantly reduced mortality. Given that the current therapeutic arsenal allows the effective treatment of this pathology and its long-term complications, the key directions to be followed are better identification of patients at increased risk of morbidity and mortality secondary to acute myocardial infarction. [3,4,6,26]

Right ventricular assessment in the context of acute myocardial infarction occupies a secondary role in current clinical practice, although existing evidence supports the important negative role that right ventricular damage plays in increasing both short- and long-term adverse event rates [4,38,42]. Three-dimensional echocardiography is a relatively new technique that may provide additional diagnostic features to the two-dimensional methods used in current practice, and evidence from the literature suggests that the application of these methods to identify right ventricular dysfunction by 3D RVEF may be a better predictor for risk stratification of patients with cardiovascular disease. [38]

With these considerations in mind, the objectives of this work were the following:

To compare the correlations between the standard two-dimensional echocardiographic assessment by parameters commonly used in clinical practice such as TAPSE, S'_{VD}, FAC and new parameters such as 3D RVEF, and possible discrepancies resulting from the classification of patients according to current medical practice guidelines based on the values obtained. Such discrepancies may suggest the existence of a category of unidentified patients who are at increased risk of adverse events.

Evaluation of the interobserver reproducibility of the quantification of right ventricular function parameters by both standard 2DE and 3D RVEF methods, analyzing the measurements of echocardiographers with different levels of experience. The usefulness of confirming this hypothesis could be to prove the feasibility of performing these assessments in current practice, independent of the experience level of the operators.

Assessment of associations between impaired right ventricular function and clinical and paraclinical features of patients with acute myocardial infarction. The utility of testing this hypothesis would be to identify categories of patients at higher risk of developing post-infarction right ventricular dysfunction and who would require careful assessment of right ventricular function.

5. Correlations between classical two-dimensional and three-dimensional parameters for the assessment of right ventricular systolic function.

5.1. Introduction

As mentioned previously, despite the fact that cardiovascular disease (CVD) mortality rates have decreased by >50% over the last three decades in European Society of Cardiology (ESC) member countries, CVD remains the most common cause of death, with over 3 million deaths in the most recent calendar year for which data are available. Despite significant advances in the early diagnosis and administration of reperfusion therapies, ischemic heart disease (IHD) remains the most common cause of death from CVD, accounting for 33% and 40% of all CVD deaths in women and men, respectively. [6]

A contemporary series of 1235 patients with acute myocardial infarction (AMI) evaluated by cardiac magnetic resonance imaging (cMRI) identified right ventricular (RV) ischemia and infarction in 19.6% and 12.1% of patients, respectively. [14] RV injury, although more common in inferior infarcts, is also present in a substantial proportion of anterior infarcts. [43] RV dysfunction is associated with poorer outcomes in the setting of various cardiovascular diseases, including myocardial infarction [14,44,45], and impairment of three-dimensional RV ejection fraction (3D RVEF) has been shown to have a significantly higher risk of mortality, independent of left ventricular ejection fraction (LVEF) [45].

Currently, the most commonly used parameters for the assessment of RV systolic function are tricuspid annular plane systolic excursion (TAPSE), right ventricular systolic wave velocity (S'_{RV}) and fractional area change (FAC).

However, these parameters may not be suitable for quantification of global RV function, as they interrogate a limited portion of the right ventricle or a single right ventricular section plane for measurement. [4] Recent data suggests that guideline-recommended cutoff values for standard two-dimensional echocardiographic (2DE) parameters of RV systolic function are only modestly associated with 3D RVEF assessment, and the degree of reclassification of RV function varies with the parameter used and the underlying pathology. [38]

5.2. Objectives of the study

This study aims to evaluate the correlations and concordance between parameters and classification of right ventricular (RV) function obtained by 2D echocardiography (2DE) - tricuspid annulus plane systolic excursion (TAPSE), right ventricular systolic wave velocity (S'_{VD}), fractional area change (FAC) and right ventricular ejection fraction (3D RVEF) obtained by 3D advanced echocardiography (3DE).

5.3. Materials and methods

Study design and patients. The presented study was a single-center, prospective, observational study, which included patients hospitalized with the diagnosis of acute myocardial infarction in the Cardiology Department of the University Emergency Hospital, Bucharest, Romania, between December 2019 and June 2022.

Written informed consent for participation in the study was obtained separately from informed consent for admission within the first 24 hours of hospitalization. The study protocol was approved by the Hospital Ethics Committee.

Inclusion criteria were as follows: patients >18 years of age who signed an informed consent at study enrollment, patients diagnosed with AMI according to the fourth universal definition of acute myocardial infarction, patients with sufficient image quality to perform 2D and 3D echocardiographic analysis.

Exclusion criteria were as follows: patients with a history of heart failure (HF) or any documented LV or RV dysfunction, patients with a history or current atrial fibrillation, patients with a history of significant valvular disease, patients with a history of pulmonary hypertension.

All patients underwent coronary angiography and received standard care according to the recommendations of the European Society of Cardiology Guidelines on the management of ST-segment elevation acute myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndromes (NSTE-ACS) available at the time.[39,40] The topographic localization of the infarct as well as the culprit were recorded for each individual patient.

Clinical examination and medical history. Demographic and clinical data such as: age, weight, height, body surface area, body mass index, type of myocardial infarction, cardiovascular risk factors and significant comorbidities - history of diabetes mellitus, chronic kidney disease, hypertension, peripheral arterial disease, dyslipidemia - were recorded. Records were extracted from patient observation sheets obtained during hospitalization.

Two- and three-dimensional echocardiography. Transthoracic echocardiographic examinations were performed within 48 hours of hospital admission with a state-of-the-art echocardiographic system (Vivid E90 or Vivid E95 - GE Vingmed Ultrasound, GE Healthcare Technologies Inc.) using an M5 S probe for 2DE and a 4Vc-D probe for 3DE acquisition. The acquisition was performed by an advanced echocardiographer with 5 years of experience in 2DE and 3 years of experience in 3DE. The acquired image sets were digitally stored for offline analysis using commercially available dedicated software (EchoPAC version 203, GE Vingmed, GE Healthcare Technologies Inc, Horten, Norway).

The following parameters were analyzed:

Tricuspid annulus plane systolic excursion (TAPSE) that was obtained by analyzing the M-mode acquisition with the cursor placed at the lateral tricuspid annulus in the RV-optimized 4-chamber apical incidence (A4C). TAPSE values ≥17 mm were considered normal as recommended by current guidelines in force. [37]

The fractional area change (FAC) was calculated by determining the right ventricle telediastolic and telesystolic right ventricular area values measured in the RV-optimized A4C window. These values were then used for calculation according to the formula$((End - diastolic\ area) - (End - systolic\ area))/((End - diastolic\ area))\ x\ 100$. Normal values according to current guidelines were considered ≥35%. [37]

The right ventricular systolic wave velocity (S'_{VD}) was measured from tissue Doppler Doppler (TDI) acquisitions obtained by placing the cursor at the lateral tricuspid annulus of the RV-optimized A4C view, representing a parameter of right ventricular longitudinal systolic function. Normal values were considered ≥ 10 mm/s. [37]

3D right ventricular ejection fraction (3D RVEF**).** Three-dimensional (3D) images were obtained using views optimized for the right ventricle. Full-volume 3D datasets were reconstructed using ECG synchronization from sequences of 6 cardiac cycles. Analysis was performed offline using commercially available semi-automated software packages (4D Auto RV Quantification, EchoPAC version 203, GE Vingmed, GE Healthcare Technologies Inc, Horten, Norway). We quantified the 3D right ventricular indexed indexed end-diastolic volume

(3D RV-EDVi), end-systolic volume (3D RV-ESVi), stroke volume (3D RV-SVi), and ejection fraction (3D RVEF). Abnormal values were considered <45%. [37]

Statistical analysis. Was performed using SPSS (ver. 26, IBM Corporation, Armonk, New York, USA). Continuous variables are expressed as mean ± standard deviation (SD), categorical variables are reported as frequencies and percentages. The normal distribution of the variables was checked using statistical tests (Shapiro-Wilk test) and graphical methods (Q-Q charts, standard boxplot plots). The Shapiro-Wilk test is a statistical method used to determine whether a data set is normally distributed. Correlations between continuous echocardiographic variables were assessed using the Pearson correlation test. Patients were then divided into groups describing normal RV function and RV dysfunction based on cutoff values for both each standard 2DE parameter and 3D RVEF. The association between each of the categories derived from categorization based on 2D parameters and the categories derived from categorization based on 3D RVEF was assessed using the Pearson Chi-square test. Sankey diagrams (Python ver. 3.12.4, Wilmington, Delaware, USA) were constructed to visualize the agreements between the classifications derived by standard 2D parameters and 3D RVEF.

5.4. Results

Study population. A total of 63 Caucasian patients were included between December 2019 and June 2022. Analyzing the data demographically, we can observe that the study population consisted mainly of male patients (n = 52, 82.5%) with a mean age of 56.8 (±10.3) years. The patient cohort was characterized by overweight with a mean body mass index (BMI) value of 28.57 ± 3.14. The most commonly observed comorbidities in our cohort were dyslipidemia (n = 61, 96.8%), hypertension (n = 44, 69.8%) and smoking (n = 38, 60.3%).

In terms of hospitalization diagnosis, the majority of patients were admitted with STEMI (n = 43, 68.3%). Access to reperfusion therapy was excellent, with the majority of patients (n = 54, 85.7%) receiving reperfusion or revascularization by percutaneous coronary angioplasty. Analyzing the distribution of the location of the lesions leading to myocardial infarction, they were most frequently located in the left anterior descending (n = 25, 39.68%) and right coronary (n = 24, 38.1%) arteries. Demographic data and characteristics of the study population are shown in Table 2.1

Table 5. 1 Demographic characteristics related to the type of myocardial infarction and risk factors present in the study population.

	Total (n=63)
Demographic characteristics	
Age, years	56.86 ± 10.3
Sex, male, n (%)	52 (82.5)
BMI, kg/ m^2	28.57 ± 3.14
BSA, m^2	1.98 ± 0.21
Type of IMA and revascularization	
ST-segment elevation myocardial infarction, n (%)	43 (68.3)
Myocardial infarction without ST-segment elevation, n (%)	20 (31.7)
Percutaneous coronary intervention, n (%)	54 (85.7)
Culprit lesion localization	
Left anterior descending artery, n (%)	25 (39.68)
Right coronary artery, n (%)	24 (38.1)
Circumflex artery, n (%)	6 (9.52)
Other, n (%)	8 (12.7)
Risk factors and medical history:	
Smoking, n (%)	38 (60.3)
Diabetes mellitus, n (%)	16 (25.4)
Hypertension, n (%)	44 (69.9)
Obesity, n (%)	21 (33.3)
Dyslipidemia, n (%)	61 (96.8)
Peripheral arterial disease, n (%)	1 (1.6)
Chronic kidney disease, n (%)	17 (27.0)

The distribution of the echocardiographic data was verified, given the sample size, using the Shapiro-Wilk test and plotted by histograms and normal Q-Q plots. According to the results of the Shapiro-Wilk test, in the case of TAPSE, the test value (p = 0.016) indicated that the sample studied did not exhibit normal distribution but visual inspection of the histrograms (Figure 5.1) and Q-Q plots (Figure 5.2) showed that the TAPSE values were normally distributed. The result of the test was probably influenced by the presence of a single outlier, which, however, was not excluded from the statistical analysis. The other parameters: S'_{VD} (p = 0.269), FAC (p = 0.369) and 3D RVEF (p = 0.555) had a normal distribution, as can be seen from the histograms and Q-Q plots.

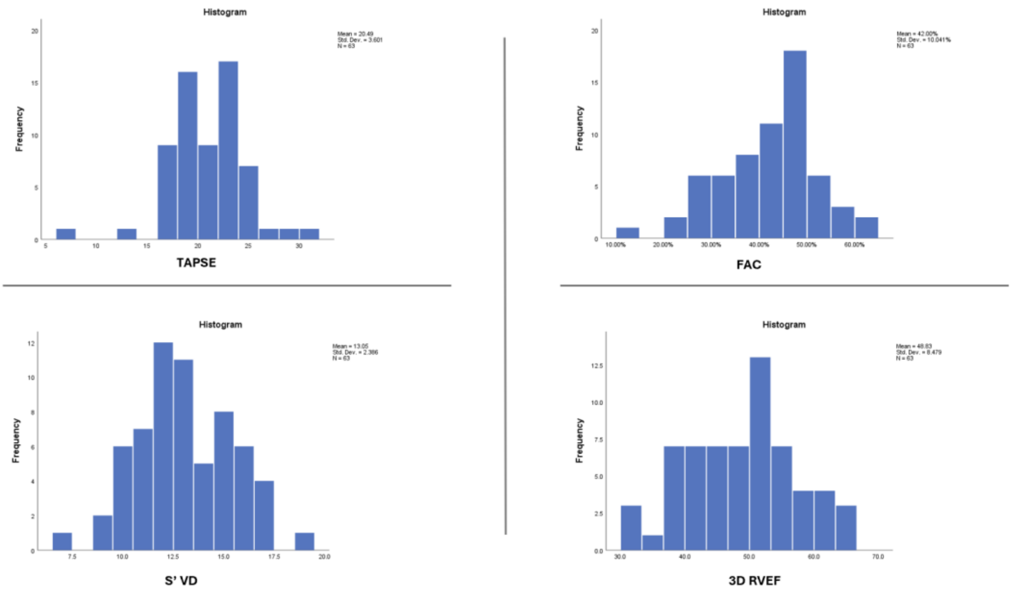

Figure 5.1. Distribution of echocardiographic parameter values in the study population represented by histograms.

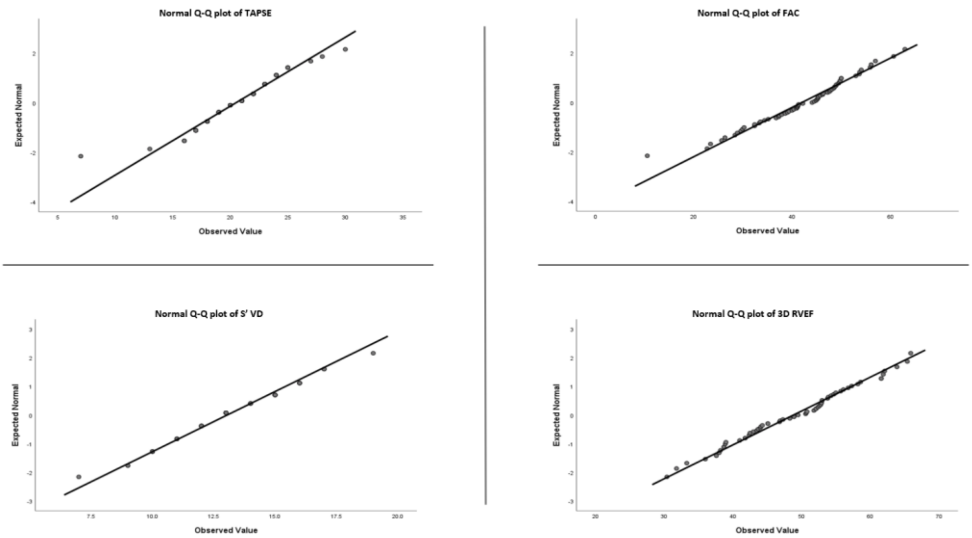

Figure 5.2. Distribution of echocardiographic parameter values in the study population represented by Q-Q plots.

Comparison between 2D and 3D parameters

In the study population, the mean TAPSE value was 20.49 mm with a standard deviation of ± 3.6 mm. The mean value of S'_{VD} was 13.05 cm/s with a standard deviation of 2.38 cm/s. Regarding the mean values of the indexed areas, the mean value of the indexed end-diastolic area was 7.67 $cm^2/m^2$with a standard deviation of 2.01 cm^2/m^2, while the indexed end-systolic area had a mean value of 4.45 $cm^2/m^2$with a standard deviation of 1.34 cm^2/m^2. Thus, the mean FAC was 41.9% with a standard deviation of 10%. Analyzing the mean value of 3D parameters, the mean value of indexed end-diastolic volume was 39.7 $ml/m^2$with a standard deviation of 10.5 ml/m^2, while for indexed end-systolic volume the mean value was 20.38 $ml/m^2$with a standard deviation of 7.7 ml/m^2. The mean value of right ventricular stroke volume was 19.54 $ml/m^2$with a standard deviation of 6.26 ml/m^2, and the mean value of ejection fraction was 48.83% with a standard deviation of 8.48%. The data are presented in Table 5.2

Table 5.2 Mean values and standard deviation for the assessed echocardiographic parameters. Abbreviations: TAPSE - tricuspid annulus plane systolic excursion, RV-EDAi - right ventricular indexed telesystolic right ventricular area, RV-ESAi - right ventricular indexed telesystolic right ventricular area, FAC - fractional area change, S'_{VD}- systolic velocity of the lateral tricuspid annulus, 2D - two-dimensional, 3D - three-dimensional, RV-EDVi - right ventricular indexed telesystolic volume, RV-ESVi - right ventricular indexed telesystolic volume, RV-SVi - right ventricular indexed stroke volume , RVEF - right ventricular ejection fraction.

2D echocardiographic parameters:	
TAPSE, mm	20.49 ± 3.6
RV-EDAi, cm^2/m^2	7.67 ± 2.01
RV-ESAi, cm^2/m^2	4.45 ± 1.34
FAC, %	41.9 ± 10
S'_{VD}, cm/s	13.05 ± 2.38
3D echocardiographic parameters:	
3D RV-EDVi, ml/m^2	39.7 ± 10.5
3D RV-ESVi, ml/m^2	20.38 ± 7.7

3D RV-SVi, ml/m^2	19.54 ± 6.26
3D RVEF, %	48.83 ± 8.48

To assess the degree of correlation between 2D and 3D parameters, scatter plots were generated to visualize the results and the Pearson r test was used (Figure 5.3). When TAPSE and 3D RVEF were compared, no significant correlation was identified between the values of the two parameters ($r = 0.217$, $p = 0.088$). Analyzing S'_{VD} values, it showed a weak, but statistically significant correlation with 3D RVEF values ($r = 0.385$, $p < 0.001$). FAC showed the best, although modest, correlation with statistical significance ($r = 0.482$, $p = 0.002$).

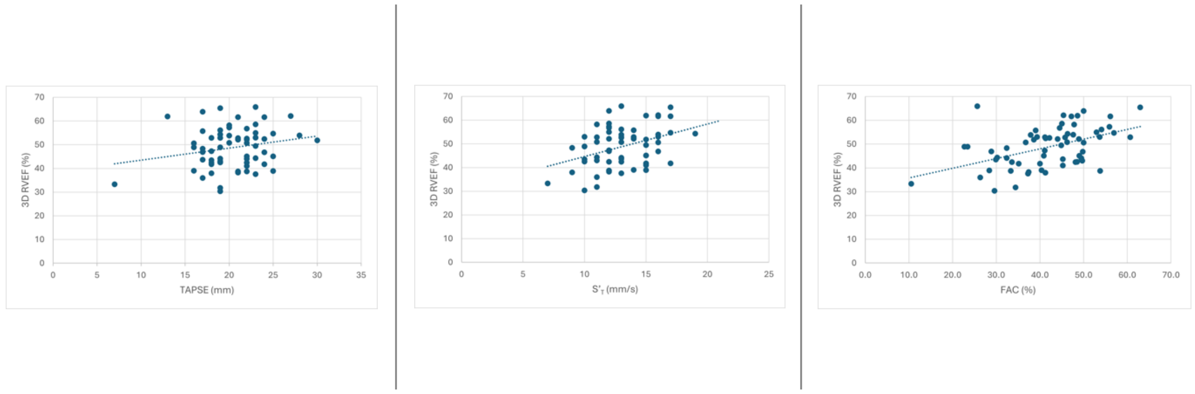

Figure 5.3. Scatter plots of the correlations obtained between the 3D RVEF and the 2D parameters evaluated.

Classification of patients and comparison of categories based on reference values

Patients were dichotomized according to the cutoff values recommended by current guidelines [37], having either normal systolic function or right ventricular systolic dysfunction. When standard 2DE parameters were used, normal RV function was found in 82.5% (n = 52), 85.7% (n = 54) and 76.2% (n = 48) for TAPSE, S'_{VD} and FAC, respectively. 3D RVEF classification identified 63.5% (n = 40) of patients as having normal RV systolic function. The data are represented in Table 5.3.

Table 5.3 Categorization of patients according to reference values recommended by guidelines. Abbreviations: TAPSE - tricuspid annulus plane systolic excursion, FAC - fractional area change, S'_{VD}- lateral tricuspid annulus systolic velocity, 3D RVEF - three-dimensional right ventricular ejection fraction.

Parameter	Normal function	Dysfunction
TAPSE, n (%)	52 (82.5)	11 (17.5)
S'_{VD}, n (%)	54 (85.7)	9 (14.3)
FAC, n (%)	48 (76.2)	15 (23.8)
3D RVEF, n (%)	40 (63.5)	23 (36.5)

Comparison of 2DE and 3DE classifications

Cross comparison was made between the categories obtained by each 2DE parameter individually and 3D RVEF. When TAPSE and 3D RVEF were compared, 41.3% (n = 26) of patients were misclassified, with 30.2% (n = 19) of them initially identified as having normal RV function according to TAPSE despite a 3D RVEF value below the lower reference limit while 11.1% (n = 7) were misidentified as having RV dysfunction despite normal 3D RVEF values. Data are presented in Table 5.4 and illustrated by Sankey diagram (Figure 5.4). There was no statistically significant association between the two classifications using the Chi-square method (x^2 (1, n=63) = 0, p = 0.991). Further analysis using Cohen's k-test showed no significant agreement between the two methods (k = 0.0143, CI [-0.2959,0.3246]).

Table 5. 4 Comparative analysis of patient classification according to TAPSE and 3D RVEF.

			3D RVEF		Total
			Normal	**Dysfunction**	
TAPSE	**Normal**	Number	33	19	52
		% of total	52.4%	30.2%	82.5%
	Dysfunction	Number	7	4	11
		% of total	11.1%	6.3%	17.5%
Total		Number	40	23	63
		% of total	63.5%	36.5%	100.0%

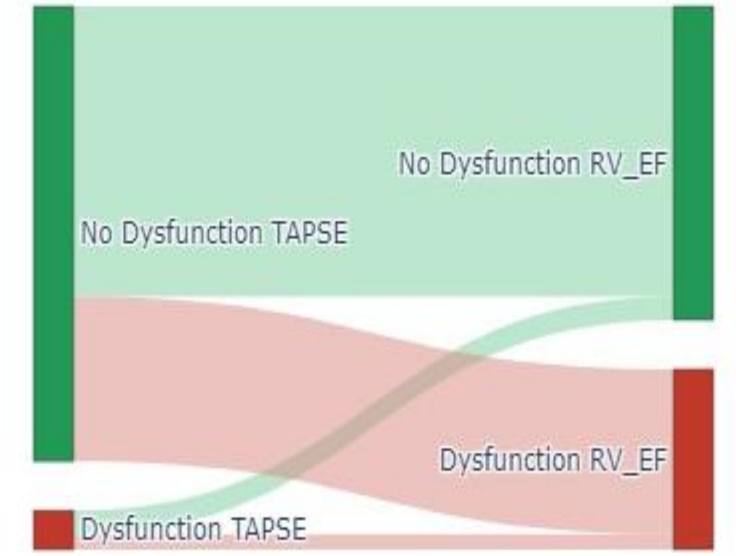

Figure 5.4. Sankey diagram illustrating patient reclassification comparing TAPSE and 3D RVEF classifications.

When S'_{VD} was considered, patients were misclassified in 34.9% (n = 22) of cases, 28.6% (n = 18) were initially classified as having normal VD function according to S'_{VD} despite abnormal 3D RVEF values while 6.3% (n = 4) were misclassified as having dysfunction despite normal 3D RVEF values. Data are illustrated in Table 5.5 and Figure 5.5. There was also no statistically significant association between the two classifications using the Chi-square test (x^2 (1, n=63) = 1.643, p = 0.2). Agreement analysis also did not yield significant results (k = 0.076, CI [-0.2355,0.3875]).

Table 5.5 . Comparative analysis of patient classification according to S'_{VD} and 3D RVEF. Abbreviations: S'_{VD} - systolic lateral tricuspid annular systolic velocity, 3D RVEF - three-dimensional right ventricular ejection fraction.

			3D RVEF		**Total**
			Normal	**Dysfunction**	
S'_{VD}	**Normal**	Number	36	18	54
		% of total	57.1%	28.6%	85.7%
	Dysfunction	Number	4	5	9
		% of total	6.3%	7.9%	14.3%
Total		Number	40	23	63
		% of total	63.5%	36.5%	100.0%

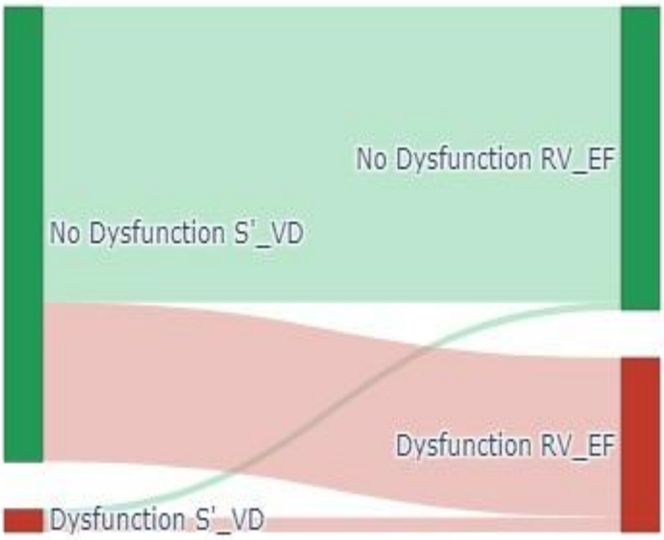

Figure 5.5. Sankey diagram illustrating the reclassification of patients comparing the classifications obtained on the basis of S'_{VD} and 3D RVEF. Abbreviations: S'_{VD} - systolic lateral tricuspid annular systolic velocity, 3D RVEF - three-dimensional right ventricular ejection fraction.

When FAC and 3D RVEF classifications were compared, there was a mismatch in 28.5% (n = 18) of the cases, with 20.6% (n = 13) of them initially classified as having normal RV function according to FAC but dysfunction according to 3D RVEF. Concomitantly, 7.9%

(n = 5) were identified as having dysfunction according to FAC but not after 3D RVEF analysis The data are presented in Table 5.6 and illustrated in Figure 5.6. However, there was a significant association between the two methods (x^2 (1, n = 63) = 7.725, p = 0.005) and also significant concordance (k = 0.3345, CI [-0.0747,0.5943]).

Table 5.6 Comparative analysis of patient classification according to FAC and 3D RVEF. Abbreviations: FAC - fractional RV area change, 3D RVEF - three-dimensional right ventricular ejection fraction.

			3D RVEF		**Total**
			Normal	Dysfunction	
FAC	Normal	Number	35	13	48
		% of total	55.6%	20.6%	76.2%
	Dysfunction	Number	5	10	15
		% of total	7.9%	15.9%	23.8%
Total		Number	40	23	63
		% of Total	63.5%	36.5%	100.0%

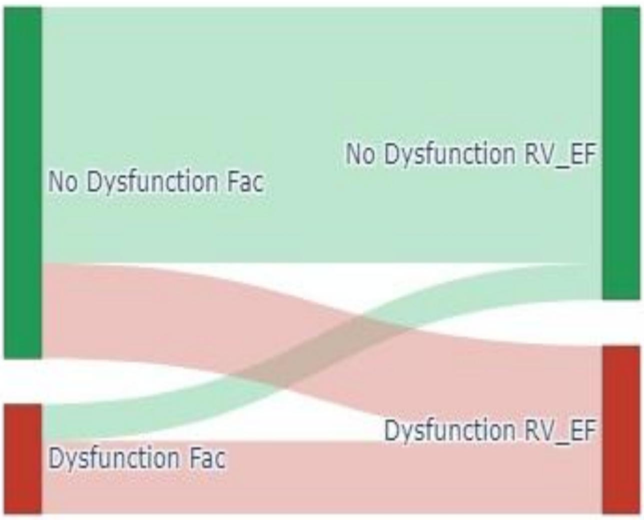

Figure 5.6. Sankey diagram illustrating the reclassification of patients comparing the classifications obtained based on FAC and 3D RVEF. Abbreviations: FAC - fractional RV area change, 3D RVEF - three-dimensional right ventricular ejection fraction.

5.5. Discussion

Routine echocardiographic evaluation after AMI is class I in current clinical practice guidelines [26,46]. In this context, particular attention is paid to quantifying systolic LV function by assessing ejection fraction and highlighting possible complications after AMI. However, right ventricular dysfunction has been shown to be associated with poorer prognosis in various cardiac conditions, including AMI [14,44,45].

Routine assessment of RV systolic function is performed by quantification of TAPSE, S'_{VD} and FAC, whereas three-dimensional determination of RV ejection fraction is considered a time-consuming and operator-experience-dependent method and is currently less widely available.

In our study, when RV function was assessed by 2D echocardiography, the proportion of patients identified with RV dysfunction as quantified by TAPSE, S'_{VD} and FAC was 17.5%, 14.3%, and 23.8%, respectively, which is in agreement with previously reported data in this clinical situation. [42,47,48] RV dysfunction was identified in 36.5% of patients when assessment was performed by 3D RVEF. However, our results show that no correlation or weak to moderate correlation between 2D and 3D RVEF parameters was identified in the studied group.

A possible explanation for our results lies in the complex anatomy of the RV, its crescent shape enveloping the LV. The RV structure contains, in contrast to the three-layered structure of the VS, only two layers of myocardial fibers that produce a peristaltic longitudinal contraction. Furthermore, the VS is an important contributor to RV systolic function, considering that septal contraction provides 20-40% of the RV beat volume. Thus, parameters such as TAPSE and S'_{RV}, which are markers of longitudinal lateral wall function, may be of limited value in assessing global RV function in the context of the IMA, which often leads to regional movement disorders. FAC, although derived by measurements performed in a single cross-sectional plane of the RV, may be better suited to assess global RV function, thus explaining the better correlation of this parameter with 3D RVEF.

A significant proportion of patients in the study group were misclassified as having normal RV function according to the reference values commonly used in 2D assessment, although they were subsequently found to have RV dysfunction when assessed by 3D RVEF. These results are in agreement with data previously reported by Tolvaj et al, who showed a modest correlation between current cut-off values for 2DE parameters and 3D RVEF <45%. [38] This finding has significant implications for two reasons: the presence of RV systolic dysfunction assessed by 3DRVEF is associated with a higher risk of mortality, independent of LVEF [45], and patients with normal standard parameters reclassified as having RV dysfunction based on 3D RVEF had a 4-fold increase in mortality risk. [38]

5.6. Limitations of the study

Some limitations of our study should be mentioned. First, our sample of patients was relatively small, mainly due to limitations regarding the acquisition of good quality images for three-dimensional assessment of the right ventricle. Although the statistical tests used were appropriate for our patient sample size, our findings should be taken as hypothesis-generating, requiring further study of our hypothesis. In addition, our study did not include a cardiac MRI assessment protocol, which is currently the gold standard for RV assessment.

5.7. Conclusions

Our study showed that, in a population with acute myocardial infarction, the assessment of right ventricular systolic function by classical two-dimensional parameters alone may not be sufficient to correctly identify patients with right ventricular dysfunction, with prognostic implications for this category of patients. Three-dimensional assessment of right ventricular function by 3D RVEF, although time-consuming and expertise-dependent, may be a useful tool for better risk stratification in these patients.

6. Comparison of the reproducibility of right ventricular systolic function assessment parameters in patients with acute myocardial infarction.

6.1. Introduction

Echocardiographic evaluation after acute myocardial infarction (AMI) generally focuses on the assessment of left ventricular systolic function, given its prognostic significance and importance in guiding the selection of appropriate therapies in these patients.[26] Despite this, right ventricular impairment is commonly seen in patients with AMI.

Routine assessment of RV systolic function is performed with 2D echocardiography (2DE) by measuring tricuspid annular plane systolic excursion (TAPSE), lateral tricuspid annular systolic wave velocity (S'_{VD}) and right ventricular fractional area change (FAC). [37] Recently, three-dimensional echocardiographic quantification of right ventricular ejection fraction (3D RVEF) has emerged as an alternative method for assessing RV systolic function, although it is not yet widely available and is considered dependent on the quality of image acquisition and operator experience. The presence of RV dysfunction as assessed by 3D RVEF has also been shown to be a predictor of mortality independent of left ventricular ejection fraction (LVEF) [45].

Although all previously mentioned 2D parameters have been shown to have prognostic significance in the context of acute myocardial infarction [48,49,50,51], recently published data have suggested that the current cut-off values for these parameters are only modestly associated with 3D RVEF outcomes, resulting in a significant misclassification of patients according to the parameter used and the underlying pathology. [38] This finding has prognostic significance, as patients who were initially found to have normal values of standard parameters but were subsequently reclassified as having RV dysfunction by 3D RVEF had a 4-fold increased risk of mortality. [38]

6.2. Objectives of the study.

This study aimed to assess the reproducibility of 2D echocardiographic (2DE) parameters of right ventricular systolic function, such as tricuspid annular plane systolic excursion (TAPSE), right ventricular systolic wave velocity (S'_{VD}), fractional area change (FAC) as well as novel 3D parameters such as right ventricular ejection fraction (3D RVEF), measured by operators with different levels of experience in patients with acute myocardial infarction (AMI).

6.3. Materials and methods

Study design and population. The study conducted was a single-center, prospective, observational, prospective study that included patients hospitalized with AMI in the Cardiology Department, University Emergency Hospital, Bucharest, Romania between December 2019 and June 2022. All patients received coronary angiography and standard treatment of myocardial infarction according to the European Society of Cardiology guidelines available at that time. [39,40]

The hospital ethics board approved the study protocol and written informed consent for study participation was obtained prior to inclusion within the first 24 hours of hospitalization. The inclusion and exclusion criteria used have been presented previously.

The measurements were performed by three echocardiographers with different levels of experience: advanced operator - labeled as Reader 1 (R1) - with 5 years of experience in 2DE and 3 years of experience in 3DE - was also the one who performed the image acquisition; intermediate - labeled as Reader 2 (R2) - with 3 years of training in 2DE and 1 year of training in 3DE; beginner - labeled as Reader 3 (R3) - with 1 year of training in 2DE and 3 months of training in 3DE. All measurements were performed independently, without any of the three operators being exposed to each other's results, on the same echocardiographic images. The sequence in which image reading was performed was as follows: the advanced reader (R1) was first, followed by the intermediate (R2) and finally the beginner (R3).

Statistical analysis. Statistical analysis was performed using SPSS (ver. 26, IBM Corporation, Armonk, USA) and Microsoft Excel (ver. 2503, Microsoft Corporation, Redmond, USA). Continuous variables are expressed as mean ± SD, while categorical variables are presented as absolute numbers and percentages.

The Bland-Altman method was used to assess interobserver variability and agreement by quantifying their mean difference (bias). Inter-measurement agreement was assessed by Pearson correlation coefficients, with an r value > 0.80 considered to be a very good correlation and a p value < 0.05 considered to be statistically significant.

6.4. Results

Comparison of TAPSE measurements provided by the three operators with different levels of experience.

The Bland-Altman plots obtained showed a low bias of 0.24 between the advanced (R1) and intermediate (R2) readers, with LOA of -2.2;2.74. The bias between the advanced (R1) and beginner (R3) operator showed a higher value of 0.38 with LOA of -1.9;2.7 (Figure 6.4), while the comparison between the intermediate (R2) and beginner (R3) reader revealed a bias of 0.14 with LOA of -2.4;2.6. (Figure 6.1) The correlations, evaluated by Pearson's method, had excellent values for all three sets of measurements: for the comparison between the advanced and intermediate reader - the R coefficient value was 0.93, highly statistically significant (p<0.001); for the comparison between the advanced and the beginner reader the R coefficient value was 0.94, also highly statistically significant ($p<0.001$); while comparing the intermediate and the advanced reader the correlation coefficient R was 0.93, also with high statistical significance ($p<0.001$) (Figure 6.2).

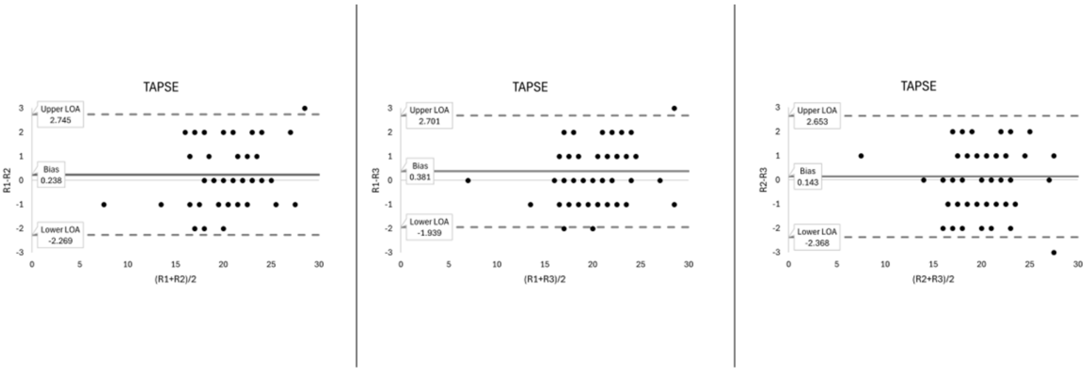

Figure 6.1. Bland-Altman plots representing the variability of the TAPSE measures between the advanced (R1), intermediate (R2) and beginner (R3) operators.

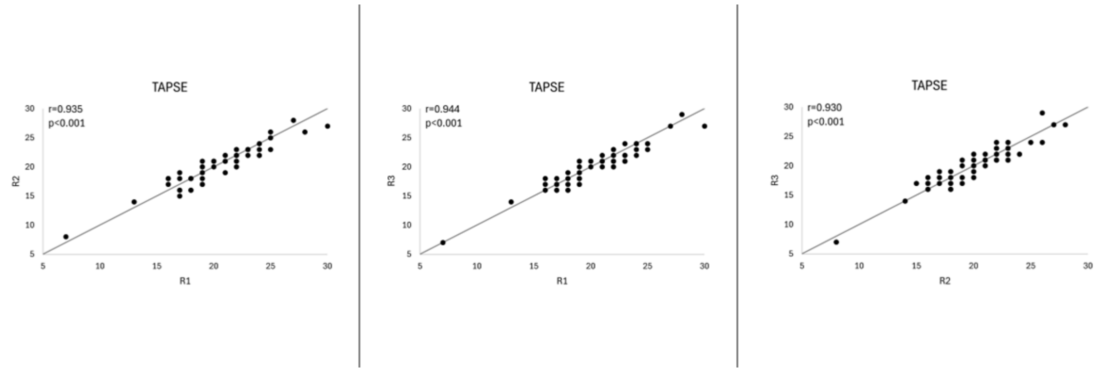

Figure 6.2. Correlations between TAPSE measurements performed by the advanced (R1), intermediate (R2) and beginner (R3) operators.

Comparison of S'_{VD} measurements provided by the three operators with different levels of experience.

Analyzing the measurements made for the determination of S'_{VD}, the statistical analysis and the resulting Bland-Altman plots revealed a bias of 0.19 comparing the measurements made by the advanced operator with those made by the intermediate operator, identifying limits of agreement (LOA) of -1.3;1.7, while the comparison between the advanced and the beginner operator revealed a bias of greater than 0.36, with limits of agreement -1.64;2.37. The comparison between intermediate and novice operators revealed a bias of 0.17, with LOA -2.25;4.85. The results are represented in Figure 6.3. Analyzing the correlations of the measurements made by the three operators, also revealed excellent Pearson R coefficients for this parameter. For the analysis between the advanced and the intermediate operator, the correlation coefficient was R=0.96, highly statistically significant (p<0.001). The comparison between the advanced and the beginner operator also generated a very good correlation coefficient (R=0.90), also statistically significant (p<0.001). The last comparison, the comparison between the intermediate and beginner operator, generated a lower value of the correlation coefficient, but still with an excellent value (R=0.88), also with statistical significance (p<0.001). Results illustrated in Figure 6.4

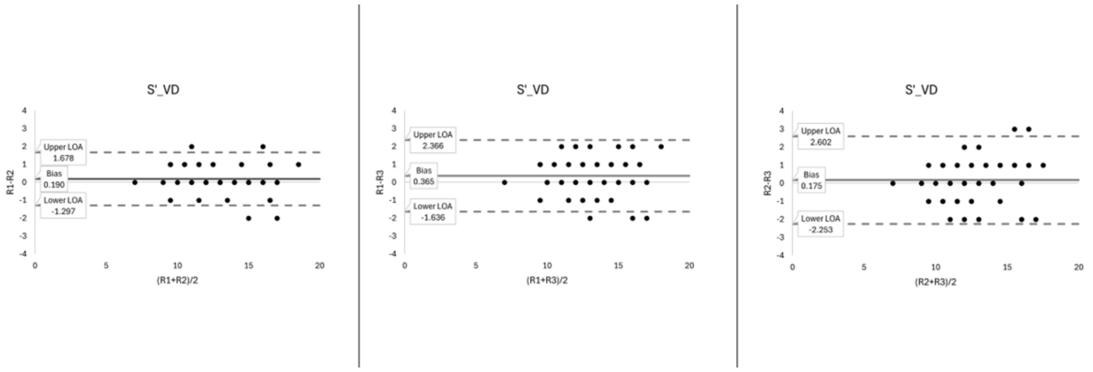

Figure 6.3. Bland-Altman plots representing the variability of the S'_{VD} measures between the advanced (R1), intermediate (R2) and beginner (R3) operators.

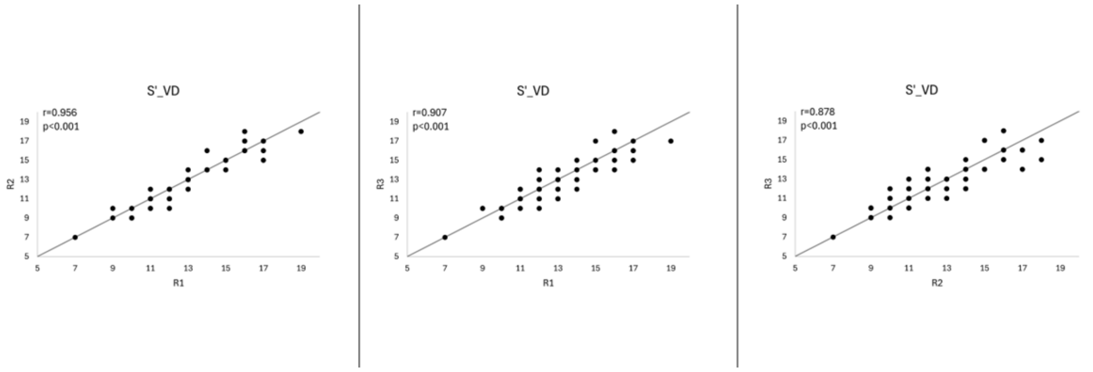

Figure 6.4. Correlations between the S'_{VD} measurements performed by the advanced (R1), intermediate (R2) and beginner (R3) operators.

Comparison of FAC measurements provided by the three operators with different levels of experience.

The third 2D parameter analyzed was the FAC value. The Bland-Altman analysis and the resulting graphs showed a bias of 0.36 when comparing the measurements made by the advanced (R1) and intermediate (R2) operators, with limits of agreement -4.9;5.62. A bias of 0.09 and limits of agreement -6.4;6.6 were found when comparing the measurements of the advanced (R1) versus beginner (R3) operator. Comparison between the intermediate (R2) and beginner (R3) operator revealed a bias of -0.27 with limits of agreement -8.1;7.5. Results are represented in Figure 6.6. When we refer to the degree of correlation between the three sets of measures, the Pearson correlation coefficients had, also in this case, excellent values. The correlation between the measurements made by the advanced and the intermediate operator had a coefficient R=0.96, suggesting an extremely strong correlation, with statistical significance ($p<0.001$). The correlation between the measurements made by the advanced and the beginner operator was almost as strong (R=0.94), also statistically significant ($p<0.001$). Similarly, the correlation performed between the intermediate and beginner level operator also had a coefficient R=0.91, also meeting the significance condition ($p<0.001$). The results are plotted in Figure 6.6.

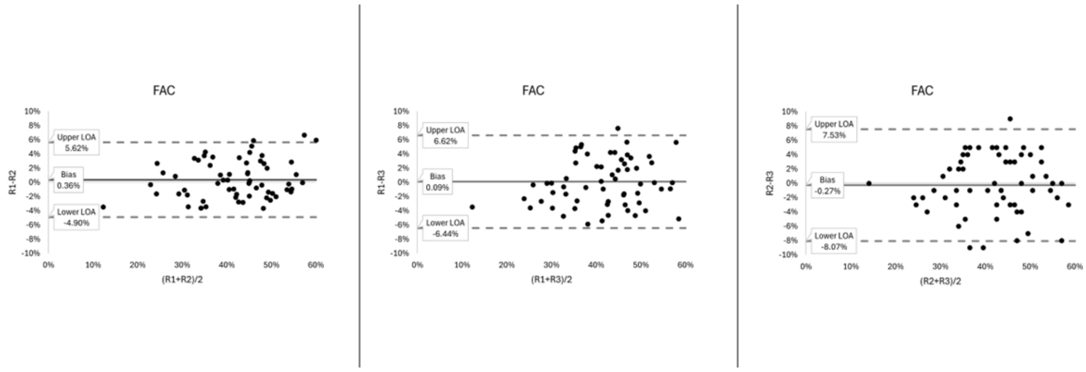

Figure 6.5. Bland-Altman plots representing the variability of the FAC measures between the advanced (R1), intermediate (R2) and beginner (R3) operators.

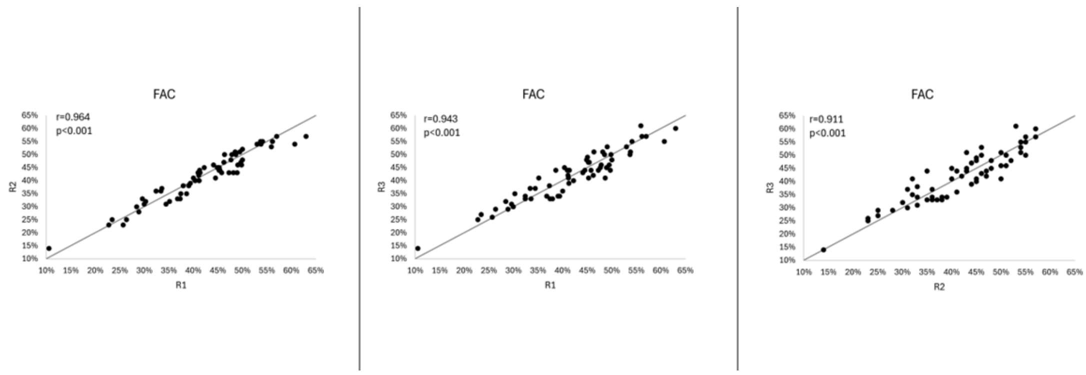

Figure 6.6. Correlations between FAC measurements performed by the advanced (R1), intermediate (R2) and beginner (R3) operators.

Comparison of 3D RVEF measurements provided by the three operators with different levels of experience

The analysis of the 3D RVEF measurements performed by the Bland-Altman method revealed a bias of -0.02 comparing the measurements of the advanced operator (R1) with the intermediate operator (R2) with limits of agreement ranging between -4.96;4.91. When comparing the measurements of the advanced operator (R1) with the intermediate operator (R2) a bias of -0.38 with limits of agreement of -6.48;5.72 was obtained. The comparison between the intermediate (R2) and beginner (R3) operator revealed a bias of -0.36 with limits of agreement -5.57;4.85. The data are represented in Figure 6.7. Next, the correlation analysis, performed using the Pearson method, revealed a value of Pearson's r Pearson's indices indicating very strong correlations between the sets of measures analyzed, accompanied by robust statistical significance. Analyzing the correlation between the measurements of the advanced reader and the intermediate reader, a correlation coefficient R=0.96 ($p<0.001$) was obtained, while comparing the measurements of the advanced and the beginner reader, R=0.93 ($p<0.001$) was obtained. After analyzing the correlation between the intermediate and the beginner reader, a correlation coefficient value R=0.94 ($p<0.001$) was obtained (Figure 6.8).

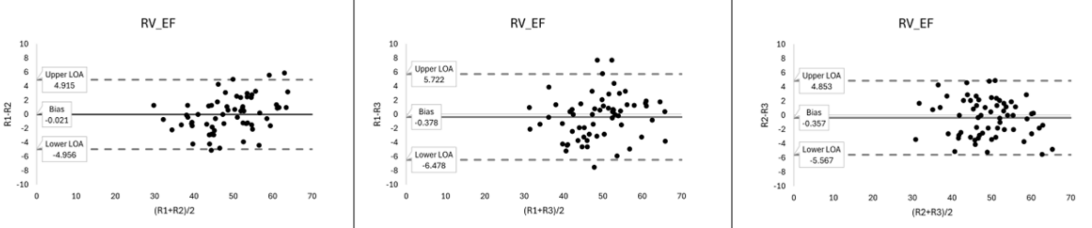

Figure 6.7. Bland-Altman plots representing the variability of the 3D RVEF measures between the advanced (R1), intermediate (R2) and beginner (R3) operators.

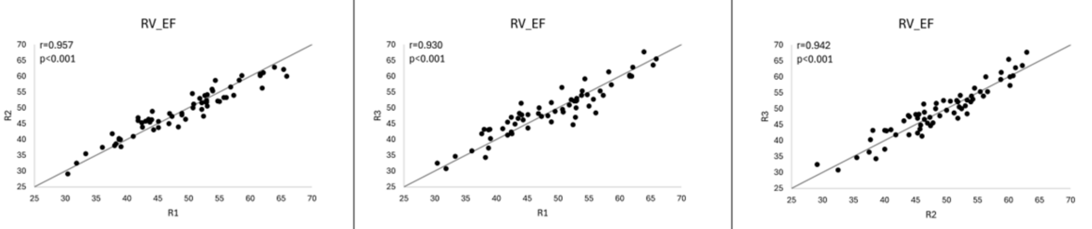

Figure 6.8. Correlations between the 3D RVEF measurements performed by the advanced (R1), intermediate (R2) and beginner (R3) operators.

Comparative inter-observer variability and concordance values are presented in Table 6.1.

Table 6.1 . Interobserver variability and limits of agreement between operators with different levels of experience for TAPSE, S'_{VD}, FAC and 3D RVEF measurements. Abbreviations: 3D RVEF - three-dimensional right ventricular ejection fraction, FAC - fractional change in right ventricular area, LOA - limits of agreement, R1 - advanced level operator, R2 - intermediate level operator, R3 - beginner level operator, TAPSE - tricuspid annulus plane systolic excursion, S'_{VD}- lateral tricuspid annulus systolic wave velocity.

R1 vs R2	**TAPSE**	**S'VD**	**FAC**	**3D RVEF**
Bias	0.24	0.19	0.36	-0.02
LOA	-2.2;2.74	-1.3;1.7	-4.9;5.62	-4.96;4.91
R1 vs R3	**TAPSE**	**S'VD**	**FAC**	**3D RVEF**
Bias	0.38	0.36	0.09	-0.38
LOA	-1.9;2.7	-1.64;2.37	-6.4;6.6	-6.48;5.72
R2 vs R3	**TAPSE**	**S'VD**	**FAC**	**3D RVEF**
Bias	0.14	0.17	0.27	0.36
LOA	-2.4;2.6	-2.25;4.85	-8.1;7.5	-5.57;4.85

6.5. Discussion

Currently, 2DE parameters are the most widely used method of assessing RV systolic function in clinical practice. All three parameters used in this study have previously been shown to correlate well with other imaging methods. TAPSE was found to have a strong correlation with RVEF obtained by radionuclide angiography [52], FAC showed a strong correlation with RVEF values obtained by cMRI [53], while S'_{VD} has been previously validated by both methods. [54,55] We found only one previously published study that analyzed the intra- and inter-observer variability of 2DE measurements, demonstrating that although the reproducibility of TAPSE and S'_{VD} was high, FAC values had low agreement in both intra- and inter-observer analysis. [56] However, we found no studies evaluating interobserver variability between operators with different levels of expertise.

The low bias values and narrow ranges of agreement limits obtained in our study showed that, in a population of patients with AMI, the interobserver reproducibility of TAPSE, S'_{VD} and FAC is excellent and independent of operator experience. It is however noteworthy that, with the exception of FAC, bias values were lower between advanced and intermediate operators, suggesting the existence of a learning curve for these parameters. This is an important message for everyday clinical practice, suggesting that 2DE assessment of the RV can be performed with consistent results even by less experienced clinicians without the risk of misdiagnosis.

3DE assessment of right ventricular function by 3D RVEF has recently emerged as an alternative to classical 2DE methods. The advantages of 3DE are that, given the complex crescent shape of the right ventricle, this method is more appropriate because it does not rely on geometric assumptions. Frequently cited limitations are related to the fact that the method is highly dependent on the quality of image acquisition and operator experience. However, the study by Namisaki et al demonstrated a good correlation (r = 0.83) between 3D RVEF measurements from the 3D RVEF optimized view of the VD (A4C VD) and the standard A4C view. This study also showed that fully automatic 3D RVEF assessment had a significant association with adverse cardiac events, even in patients with poor-quality images (A4C RV: HR, 0.90 [p = .009, n = 44]; A4C: HR, 0.9 [p = .009, n = 68]). [41] Recent studies have also addressed the issue of operator experience, showing that 3DE quantification exhibits good reproducibility even in novice operators. [57-59] Our study also demonstrated very good reproducibility values for 3D RVEF, which are similar to those found for 2DE parameters. Furthermore, the bias between the advanced and intermediate operator was the lowest in the entire study, while the differences in bias when comparing to the beginner-level operator were similar to 2DE parameters. Thus, although 3D RVEF assessment exhibits a learning curve, it is highly reproducible between operators with different levels of experience.

6.6. Limitations

The current study has a number of limitations that should be recognized. First, image acquisition was performed only by the advanced echocardiographer and, given that image quality may influence the measurements, it is not recommended to extend the current results to a scenario in which acquisition is performed by multiple operators with different levels of expertise. Further analysis in this direction is warranted to provide a better understanding of the feasibility and reproducibility of 3D RVEF assessment in everyday clinical practice.

Second, our study did not include patients evaluated by cMRI, which remains the gold standard of RV quantification, and as such cannot be considered a validation study for these methods. Finally, patients with a history of heart failure, documented LV or RV dysfunction, atrial fibrillation, significant valvular disease, and pulmonary hypertension were excluded from our study, so the results cannot be extended to these categories of patients who nevertheless represent a significant proportion of patients encountered in clinical practice.

6.7. Conclusions

Our study demonstrates that both classical 2D and more advanced 3D parameters of right ventricular systolic function are highly reproducible methods that are independent of operator experience. Our results support the use of these methods in current clinical practice in patients with AMI, in whom assessment of RV function has been shown to provide additional prognostic value over and above the standard assessment of left ventricular function.

7. Associations between right ventricular systolic function assessment parameters and clinical and paraclinical characteristics of patients with acute myocardial infarction.

7.1. Introduction

RV damage in the context of acute myocardial infarction has been associated with high morbidity and mortality rates. [60-68] The systemic hypotension that occurs as a result of right ventricular failure post AMI is due to reduced RV systolic function in the context of myocardial ischemia which, due to ventricular interdependece leads to deficient filling of the LV (secondary to the constraints imposed by the lack of distensibility of the pericardium). Direct impairment of LV systolic function may also contribute to the development of this clinical syndrome. The occurrence of right ventricular failure is associated with an increased in-hospital mortality of up to 17%. [69-72] In the context of AMI, approximately 5% of cardiogenic shock cases are primarily due to right ventricular involvement.[12] Data from the analysis of patients included in the SHOCK registry , revealed that shock caused by RV dysfunction was associated with higher mortality than that caused by shock induced by LV dysfunction, despite the fact that patients with RVF (right ventricular failure) were younger and had a lower incidence of multivessel involvement and anterior localization of myocardial infarction. [73] In a study that included 200 patients hospitalized for inferior MI, rates of in-hospital mortality and major complications were higher in patients with RV involvement (defined by ST elevation ≥1 mm in the V4R lead) in patients with AMI compared with other patients [68], results confirmed in another independent study of patients with inferior MI. [74]

Anatomically, proximal occlusion of the RCA with anterolateral wall involvement [74] is the most common localization associated with the occurrence of post-stroke AMI RVF. [73] Occlusion of a dominant circumflex artery or distal segments of the RCA may also lead to right ventricular failure as a result of infarctization of the right ventricular posterior wall. [16,63,75] Irrigation of the left coronary system occurs mainly during diastole and decreases or even reverses during ventricular systole due to large compressive forces resulting from contraction of LV myocardial fibers. By comparison, the flow in the RCA has a less pronounced phasic character because the compressive forces generated by contraction of the RV myocardium are much lower than those generated by the LV. Thus, RV perfusion is achieved throughout the cardiac cycle. Hypotension occurring in the context of acute RCA occlusion further compromises RV perfusion, leading to increased parietal stress. Consequently, the decrease in RV outflow results in a decrease in LV end-diastolic pressure and, consequently, cardiac output, despite preserved systolic LV function. [60,62,76,77] In situations where occlusion of the RCA causes acute ischemic mitral insufficiency, this causes a further increase in RV postsarcsin, leading to further compromise of cardiac output. [78]

With regard to the influence of risk factors and comorbidities on right ventricular function, a recent study demonstrated that the presence of diabetes mellitus was associated with impaired right ventricular diastolic function but without identifying changes in systolic function. [79] The presence of hypertension has also been associated with right ventricular systolic dysfunction - in a study analyzing patients with heart failure secondary to hypertension, right ventricular dysfunction was identified in more than 50% of patients. [80] Chronic kidney disease is also identified as a risk factor for the development of right ventricular dysfunction: in the study by Floccari et al, early right ventricular dysfunction, as assessed by TAPSE and estimated pulmonary artery pressure, was identified in patients with chronic kidney disease without a history of pulmonary hypertension. [81] In a study evaluating the influence of obesity on left ventricular functional parameters, elevated body mass index values were associated with decreased indices of right ventricular function and more severe side effects. [82]

7.2. Objectives of the study

This study aims to evaluate a possible causal relationship between clinical factors (gender, age, body mass index, smoking, diabetes mellitus, hypertension, chronic kidney disease) and anatomic features obtained by coronary angiography on the values of parameters assessing right ventricular systolic function (TAPSE, FAC, S'_{VD}, 3D RVEF) in order to identify possible predictors associated with reduced right ventricular function.

7.3. Materials and methods

Study design and patients. The present study was a single-center, prospective, observational study, which included patients hospitalized with the diagnosis of acute myocardial infarction in the Cardiology Department of the University Emergency Hospital, Bucharest, Romania, between December 2019 and June 2022.

Inclusion and exclusion criteria, research methodology have been previously presented in the previous themes.

Statistical analysis was performed using SPSS (ver. 26, IBM Corporation, Armonk, New York, USA) and Microsoft Excel (ver. 2503, Microsoft Corporation, Redmond, USA). Continuous variables are expressed as mean ± standard deviation (SD), categorical variables are reported as frequencies and percentages. For categorical variables with two variates, causality was assessed using the t-Student test. In the case of categorical variables with more than two variants, the ANOVA (Analysis of Variance) test was used. A positive result is indicated by a high F ratio value and a p-value < 0.05 and is followed by post-hoc analysis to determine exactly which groups differ from each other. Linear regression was used to analyze variables with continuous values, which is a method used to determine the relationship between an independent variable (predictor) and a dependent variable (outcome) and whether it is possible to make predictions about the value of the dependent variable based on the independent variable.

7.4. Results

Association between demographic factors and right ventricular systolic function assessed by two- and three-dimensional parameters.

The analysis performed to assess the association between patients' sex and right ventricular function did not reveal, following the application of the t-Student test in our cohort of patients, any significant difference between male and female patients for any of the four parameters used (TAPSE: t=-1.337, p=0.186; S'_{VD}: t=-0.487, p=0.628; FAC: t=0.935, p=0.353; 3D RVEF: t=0.814, p=0.419). Graphical representations can be found in Figure 7.1.

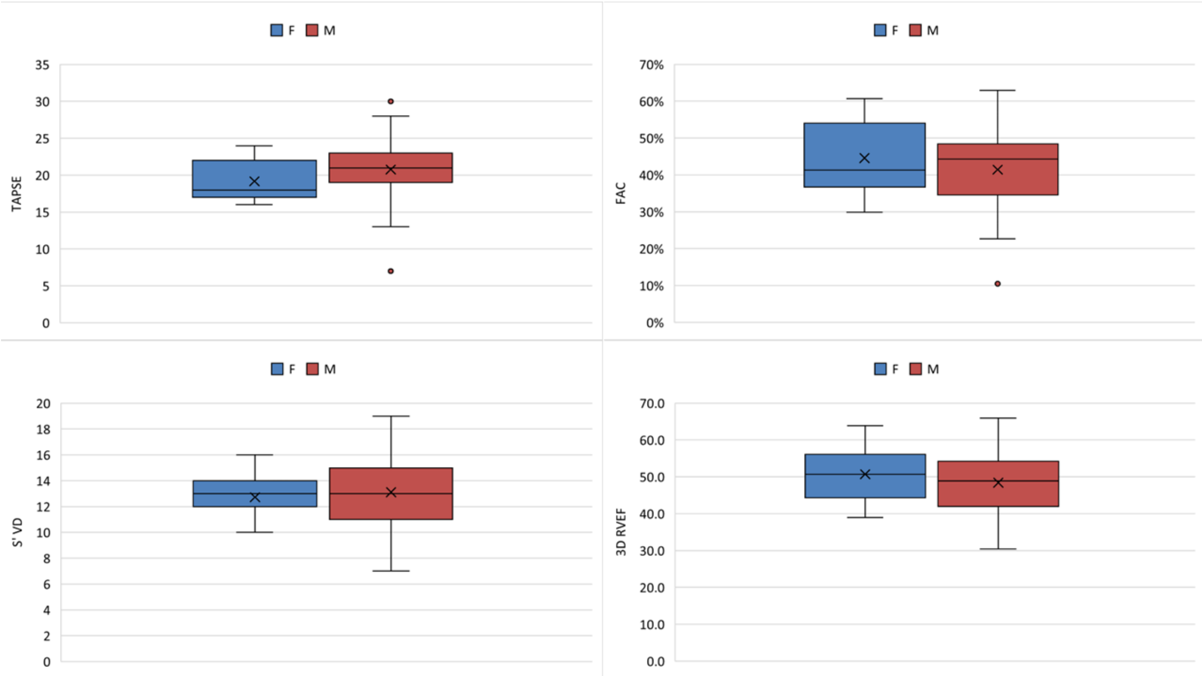

Figure 7.1. Boxplot plot representing the variance of echocardiographic parameters of right ventricular systolic function by sex.

In logistic regression analysis, patient age also did not influence the values of any of the parameters assessing right ventricular systolic function. (TAPSE: B=0.019, p=0.675; S'_{VD}: B=-0.007, p=0.815; FAC: B=-0.156, p=0.212; 3D RVEF: t=-0-07, p=0.512).

Association between clinical factors and right ventricular systolic function assessed by two- and tri-dimensional parameters.

Presence of smoking status was not associated with a lower value of any of the parameters assessing right ventricular function (TAPSE: t=1.199, p=0.235; S'_{VD}: t=0.408, p=0.687; FAC: t=0.289, p=0.774; 3D RVEF: t=0.335, p=0.739) (Figure 7.2).

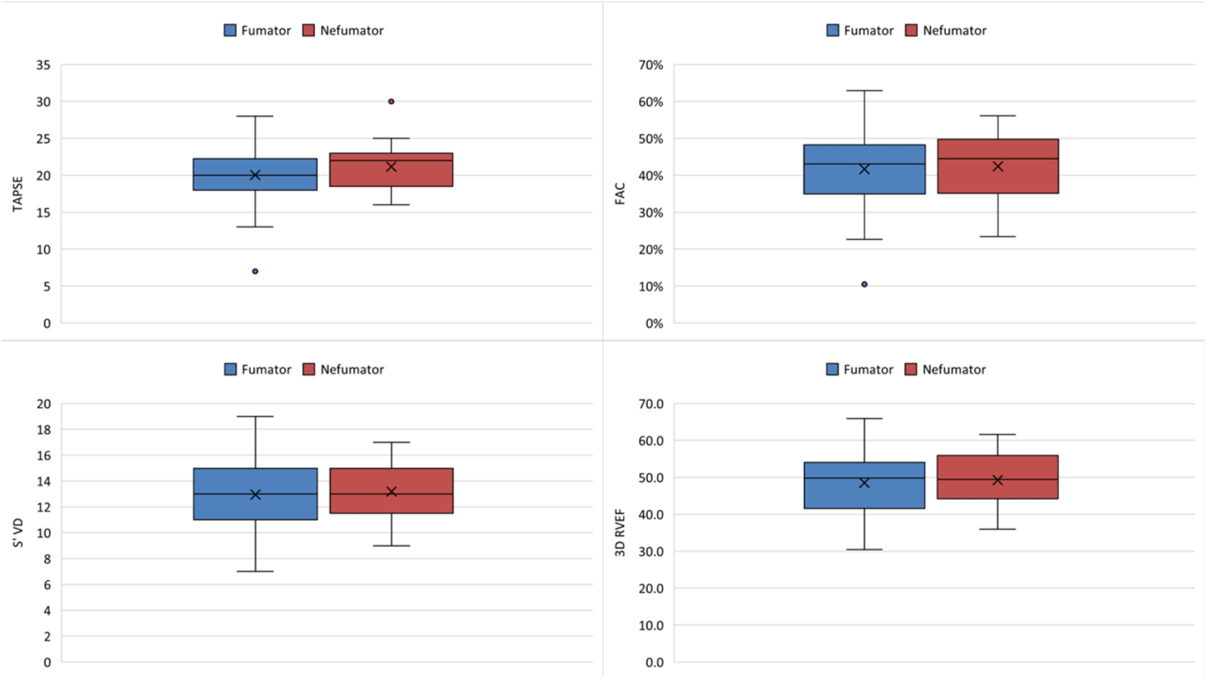

Figure 7.2. Boxplot plot representing the variance of echocardiographic parameters of right ventricular systolic function according to smoking status.

In the cohort, the presence of diabetes mellitus was not identified as a prognostic factor for RV dysfunction. The presence of dysglycemic status did not negatively influence the values of right ventricular systolic right ventricular function parameters, and no significant difference was identified between patients with and without diabetes mellitus. The results of the t-Student test were as follows: TAPSE: t=0.229, p=0.819; S'_{VD}: t=0.212, p=0.833; FAC: t=1.348, p=0.182, 3D RVEF: t=-0.931, p=0.356. The results are represented in Figure 7.3. HbA1c values were also not identified as a negative prognostic factor in linear regression analysis (TAPSE: B=-0.205, p=0.591; S'_{VD}: B=-0.709, p=0.755; FAC: B=-0.852, p=0.0.423; 3D RVEF: t=1.244, p=0.163).

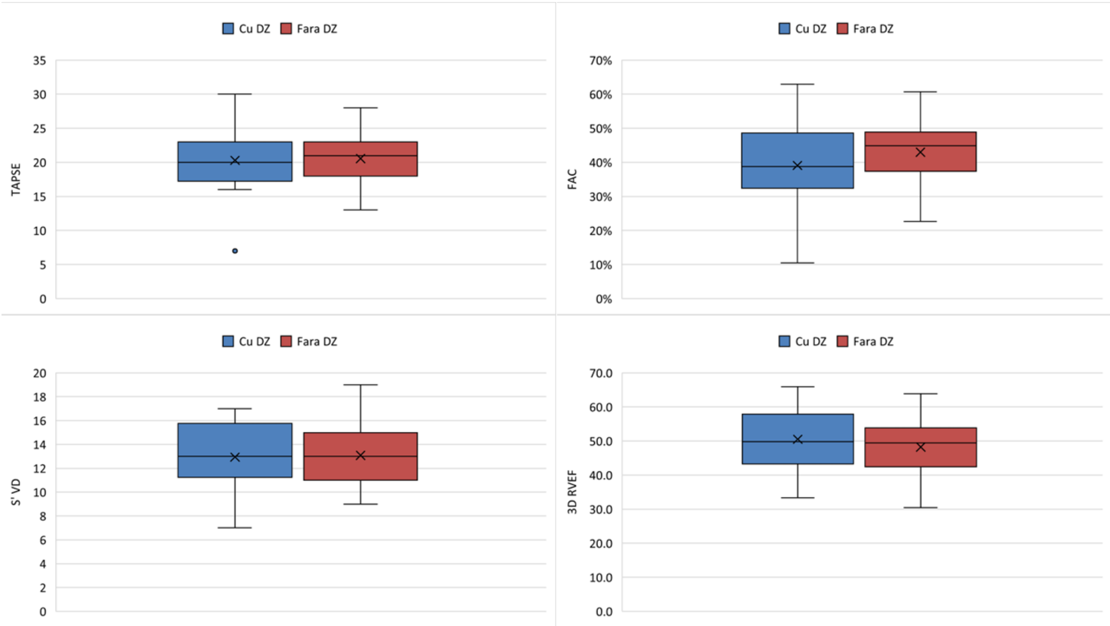

Figure 7.3. Boxplot plot representing the variance of echocardiographic parameters of right ventricular systolic function according to the presence of diabetes mellitus.

The next parameter analyzed for possible causality in terms of lower values of RV systolic parameters was chronic kidney disease. This was also not identified as a negative prognostic factor for impaired right ventricular function. Results of the analysis revealed the following t-Student test values for two-dimensional parameters: TAPSE: t=-1.817, p=0.074; S'_{RV}: t=-0.022, p=0.982. FAC: t=0.624, p=0.535 while for 3D RVEF the values were t=0.604, p=0.548. The results are plotted in Figure 7.4

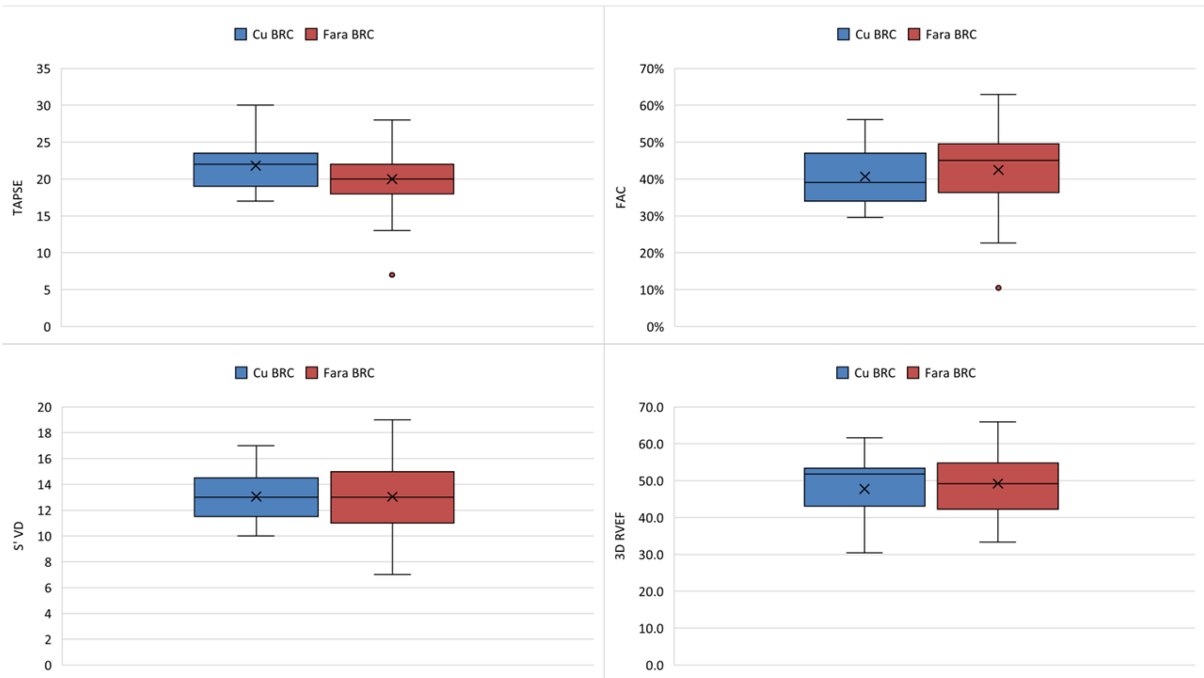

Figure 7.4. Boxplot plot representing the variance of echocardiographic parameters of right ventricular systolic function according to the presence of chronic kidney disease.

When we analyzed the possible causality between the presence of hypertension and right ventricular dysfunction, the results obtained after applying the t-Student test revealed that it was a predictor of a lower value of some of the echocardiographic parameters of right ventricular systolic right ventricular function. Specifically, the presence of HTN was associated with lower values of TAPSE (t=-3.512, p=0.001), FAC (t=-2.521, p=0.014) and 3D RVEF (t=-2.013, p=0.049) but not S'_{VD} (t=-1.5, p=0.139). The results are represented in Figure 7.5.

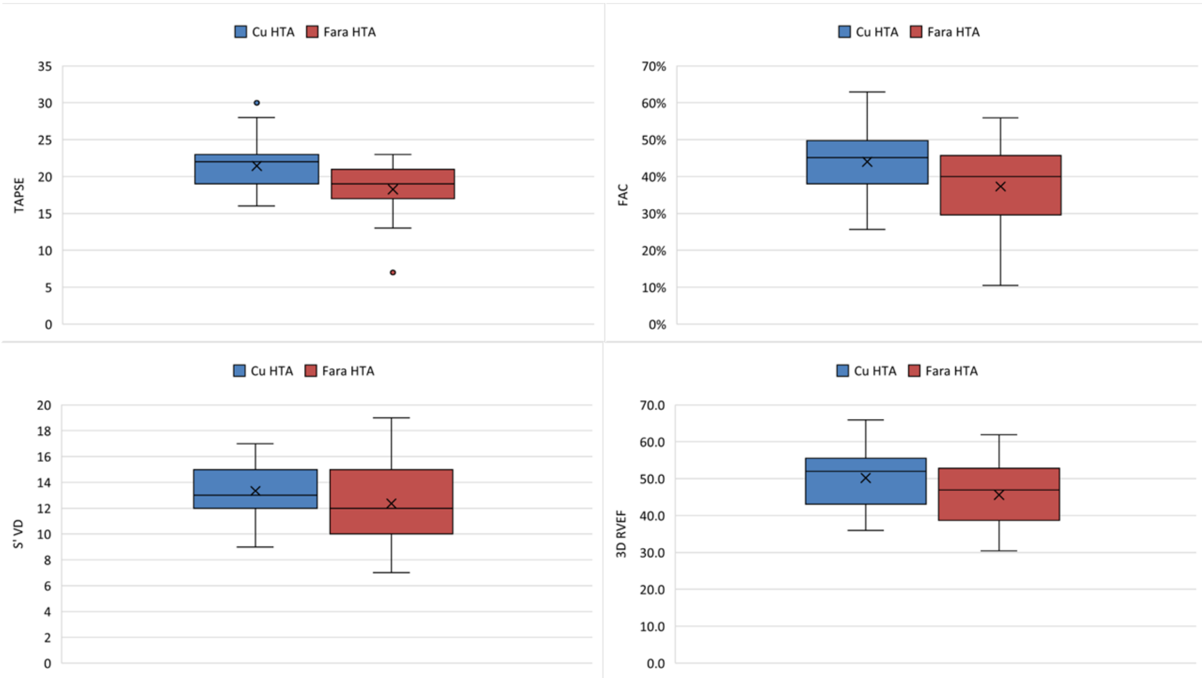

Figure 7.5. Boxplot plot representing the variance of echocardiographic parameters of right ventricular systolic function according to the presence of hypertension.

For the analysis regarding the impact of weight on right ventricular systolic function, the analysis focused in two directions. The first, assessed by t-Student test: whether the presence of obesity represented a prognostic factor for alteration of RV parameters in our cohort, the second, assessed by logistic regression: whether BMI value represented a prognostic factor for RV dysfunction. Regarding the presence of obesity as a diagnosis, this was not associated with lower values of RV parameters (TAPSE: t=-0196, p=0.845 S'_{VD}: t=1.238, p=0.206. FAC: t=1.419, p=0.161; 3D RVEF: t=0.71, p=0.944) (Figure 7.6) but, higher values of BMI were associated with lower values of the RV function assessed by FAC (B= -0.885, p=0.028), a result that was not replicated for the other parameters (TAPSE: B=0.051, p=0.728; S'_{VD}: B=-0.101, p=0.298, 3D RVEF: B=-0.361, p= 0.297).

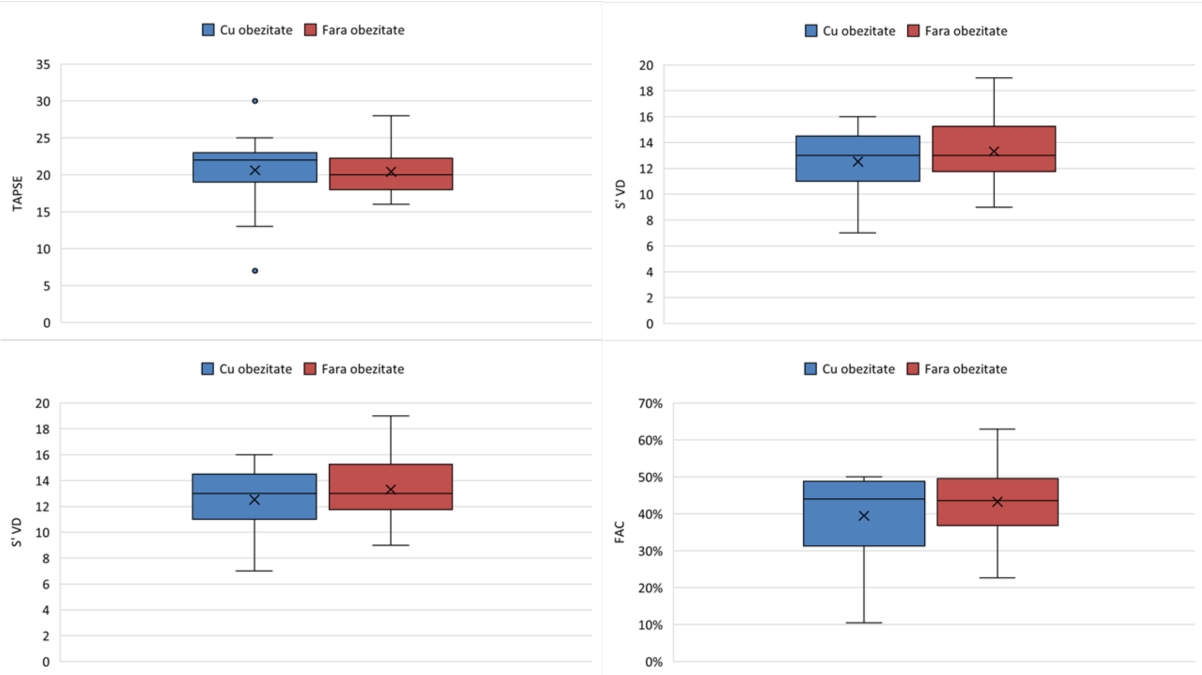

Figure 7.6. Boxplot plot representing the variance of echocardiographic parameters of right ventricular systolic function according to the presence of obesity.

Association between factors related to the localization and severity of coronary lesions, topographic localization of infarct and right ventricular systolic function assessed by two- and three-dimensional parameters.

Analyzing the impact of culprit lesion localization in one of the three coronary arteries, no association between any of the localizations and lower right ventricular systolic systolic function values was identified by ANOVA (TAPSE: F=2.889, p=0.07; S'_{VD}: F=0.42, p=0.659; FAC: F=0.541, p=585, 3D RVEF: F=0.471, p=0.627) The results are represented in Figure 7.7.

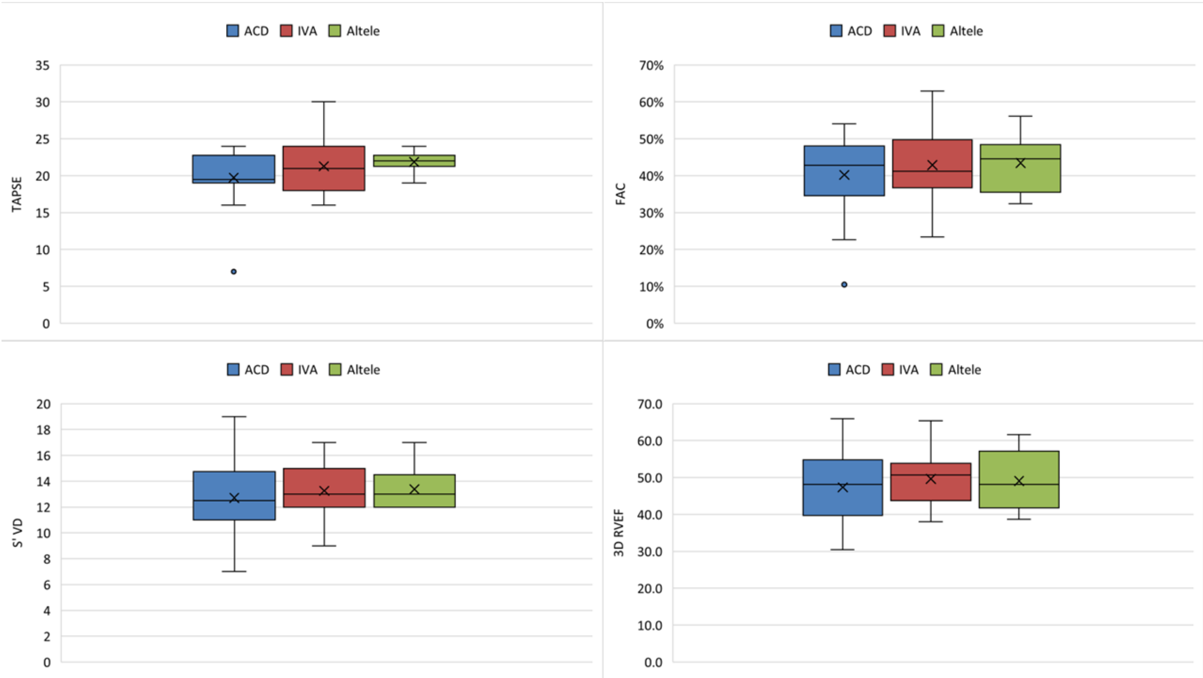

Figure 7.7. Boxplot plot representing the variance of echocardiographic parameters of right ventricular systolic function according to the location of the culprit lesion.

In the studied cohort, the presence of vascular occlusion at the time of diagnostic coronary angiography did not influence the values of right ventricular systolic function parameters (TAPSE: t=0.094, p=0.926; S'_{VD}: t=-0.505, p=0.616; FAC: t=-0.47, p=0.64, 3D RVEF: t=1.433, p=0.158). The results can be seen in Figure 7.8.

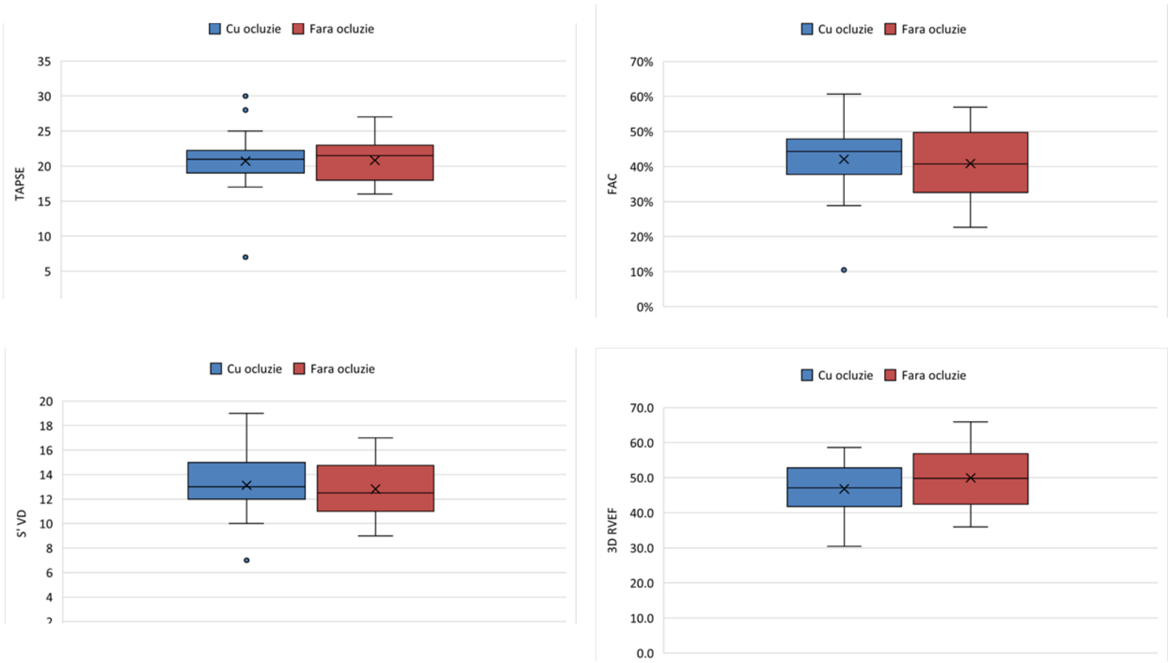

Figure 7.8. Boxplot plot representing the variance of echocardiographic parameters of right ventricular systolic function according to the presence of culprit lesion occlusion.

Nor did the presence of multivessel involvement influence the values of right ventricular function parameters in the study cohort. ANOVA test results were as follows: TAPSE: F=1.064, p=0.352; S'_{VD}: F= 0.006, p=0.994; FAC: F=0.059, p=0.943; 3D RVEF: F=0.102, p=0.903 and were plotted in Figure 7.9.

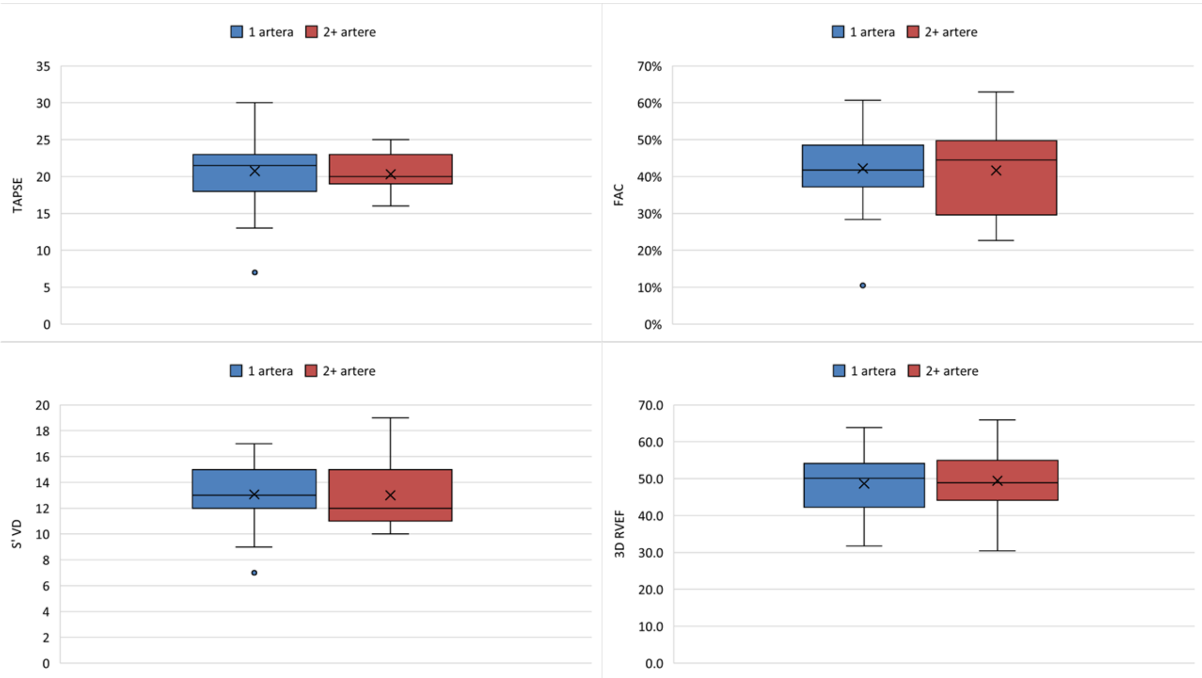

Figure 7.9. Boxplot plot representing the variance of echocardiographic parameters of right ventricular systolic function as a function of the number of affected coronary arteries.

Analyzing whether the localization and type of myocardial infarction were prognostic factors for the values of the parameters assessing right ventricular systolic function, independent of the values of LVEF, we evaluated the cohort of patients by simple linear regression obtaining the following results: the diagnosis of inferior STEMI was a predictor of lower 3D RVEF values (t=-3.259, p=0.002) and S'_{VD} (t=-2.155, p=0.035) , compared to patients with anterior STEMI or NSTEMI. In patients with diagnosis of anterior STEMI, it was a predictor for higher values of FAC (t=2.29, p=0.025) compared to patients with anterior STEMI or NSTEMI. The data are represented in Figure 7.10.

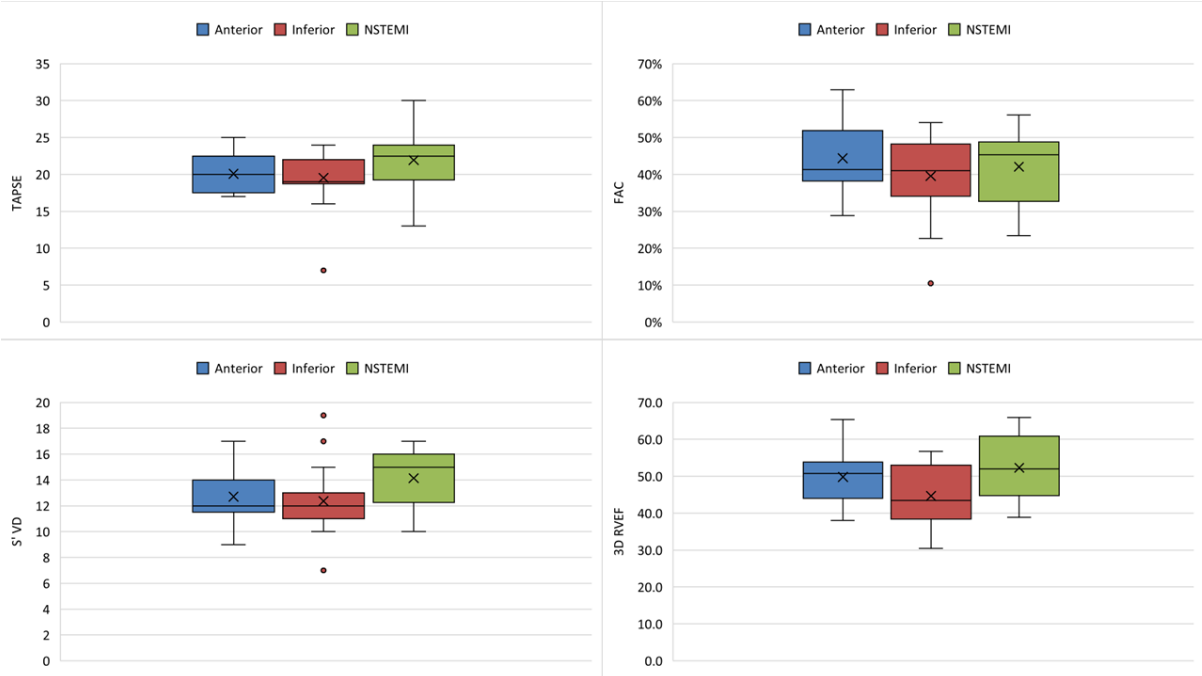

Figure 7.9. Boxplot plot representing the variance of echocardiographic parameters of right ventricular systolic function according to infarct type and location.

7.5. Discussions

Our study attempted to highlight whether certain clinical and paraclinical factors, as well as elements related to coronary anatomy, were predictive of lower values of right ventricular function assessment parameters. Patient gender has not been identified as a prognostic factor for lower right ventricular systolic systolic function. It is known that in both apparently healthy patients and in patients with conditions directly impacting the right ventricle, male sex is associated with lower right ventricular systolic function and a more guarded prognosis. [83-90] Age was also not identified in our cohort as a predictor for lower values of the analyzed parameters. Data from the literature suggest that in apparently healthy subjects, with the aging process, the changes occurring lead to primary alterations in diastolic function and right ventricular morphology. [91-93] To our knowledge, there is currently no study that correlates advancing age with altered right ventricular systolic function.

Regarding the prognostic value of various classical cardiovascular risk factors on right ventricular diastolic function, smoking status and the presence of comorbidities such as diabetes mellitus (nor HbA1c), chronic kidney disease and obesity were not associated with lower values of the analyzed parameters. Hypertension was associated with lower values of right ventricular function assessed by TAPSE, FAC and 3D RVEF. Although obesity was not a prognostic factor for the presence of lower right ventricular function, increased BMI values were prognostic for lower FAC values. Analyzing data from the literature, this is the first study that looked for the existence of prognostic value of these risk factors on RV function in the context of AMI.

Analysis of the prognostic value of elements related to coronary anatomy and the type and localization of myocardial infarction on the right ventricle revealed that the location of the culprit lesion and the presence of vascular occlusion at the time of diagnostic coronary angiography were not predictive factors for lower systolic right ventricular function. In contrast, the diangenosis of inferior STEMI was associated with lower 3DRVEF and S'_{VD} values while the presence of anterior STEMI was a prognostic factor for higher values of FAC, independent of LVEF values. A possible explanation for these results could be that in the context of myocardial infarction detailed aspects such as coronary dominance, localization of occlusion in proximal versus distal segments could be more influential factors.

7.6. Limitations of the study.

Our study has some limitations that are worth mentioning: first of all, the evaluation of right ventricular function was performed at the index time, for the analysis of a possible long-term prognostic value of our results it would have been necessary to evaluate the remote dynamics and the correlation with the possible occurrence of adverse events; cohort size - the analysis of a larger cohort of patients could have increased the statistical power of the study and the identification of associations such as those related to the impact of the location of the infarct-causing lesion in the culprit artery or the impact of coronary dominance.

7.7 Conclusions

Our study revealed that risk factors such as the presence of hypertension and elevated BMI values were prognostic elements for lower right ventricular systolic function. Regarding the impact of myocardial infarction type and localization, our results support the hypothesis that lower localization of ST-segment elevation infarction is associated with lower values of parameters assessing right ventricular systolic function.

Thus, our results suggest that in certain categories of patients such as those with hypertension, elevated BMI values or patients diagnosed with lower STEMI, right ventricular assessment should be comprehensive to allow the identification of those with right ventricular systolic dysfunction.

8. Conclusions and personal contributions

In the following pages I present the conclusions regarding the assessment of right ventricular systolic function performed both by classical two-dimensional echocardiographic methods and by more advanced methods such as three-dimensional right ventricular ejection fraction, which was the main objective of this PhD thesis.

I recall that this was an original study, including 63 patients with a mean age of 56.8 (± 10.3) years diagnosed with acute myocardial infarction, being a prospective, observational study that excluded patients with a history of heart failure or documented ventricular dysfunction, history of atrial fibrillation, pulmonary hypertension or significant valvulopathies.

In this paper, we aimed to highlight the usefulness and feasibility profile of assessing right ventricular systolic function in patients with acute myocardial infarction. We believe that this concern is a justified one since the right ventricle has become a topic of major interest in cardiovascular research in recent years. Its anatomical and structural particularities, the particular manner of its contraction, the importance of interventricular dependence and the impact of right ventricular dysfunction on the long-term prognosis of patients are topical issues. The advent of three-dimensional echocardiographic methods has opened new opportunities in the functional assessment of the right ventricle but their adoption in current practice is hampered by lack of availability and the perception that these techniques are time-consuming and dependent on the experience of the echocardiographer. Thus, we considered it appropriate to compare the results of the assessment of right ventricular function by both classical two-dimensional and more recent methods, namely three-dimensional right ventricular ejection fraction. The reason for selecting these parameters for our analysis is simple: the three selected two-dimensional parameters are the most commonly used parameters in current clinical practice, while 3D RVEF is conceptually equivalent to left ventricular ejection fraction, being an easy to understand parameter, proven to have prognostic impact [41] and which, with the wider adoption of three-dimensional echocardiographic techniques, will become of particular importance in the evaluation of patients.

Our analysis was oriented in three directions that have been extensively discussed in the personal contributions section. Concerning the correlations between classical two-dimensional parameters and three-dimensional parameters assessing right ventricular systolic function, our results show that the classical two-dimensional parameters used in current clinical practice in patients with myocardial infarction showed variable degrees of correlation with right ventricular systolic function assessed by 3D RVEF. Thus, in particular, S'_{VD} and FAC parameters showed a weak and moderate correlation with 3D RVEF values, respectively, both with statistical significance, while no significant correlation was found between TAPSE and 3D RVEF values. These results can be explained by the fact that the classical methods have certain limitations in that TAPSE and S'_{VD} are parameters of right ventricular longitudinal function while FAC, although a two-dimensional parameter, provides a better quantification of global right ventricular systolic function, an important aspect in the context of the possibility of localized kinetic disturbances caused by acute myocardial infarction. These results regarding the correlations between two- and tri-dimensional parameters translated, when patients were categorized based on guideline-recommended cut-off values, into the misclassification of a significant number of patients, mainly by omitting the identification of right ventricular dysfunction, an aspect known to be associated with a more reserved prognosis for patients [38]

In the second research topic, we sought to prove that the new techniques for three-dimensional right ventricular assessment show similar interobserver reproducibility to that of classical two-dimensional parameters. For this purpose we analyzed the results of measurements performed by three echocardiographers with different levels of experience - advanced, intermediate and beginner. Our results confirmed the stated hypothesis as the values obtained in terms of interobserver reproducibility were excellent for both two-dimensional parameters and 3D RVEF assessment. What is novel is that, in the specific context of acute myocardial infarction, our study is the first to address the issue of interobserver reproducibility between echocardiographers with different levels of experience, suggesting that 3D RVEF may be more widely adopted in current clinical practice since the reproducibility of this parameter does not seem to be significantly influenced by the level of operator experience, one of the often cited reasons for the use of this technique.

The final research theme sought to identify prognostic factors for reduced right ventricular systolic function in the context of acute myocardial infarction. We analyzed both demographic, clinical and paraclinical factors known to negatively impact right ventricular function. Based on our results, we concluded that demographic factors such as age and gender were not prognostic for right ventricular function regardless of the parameter used. Among the clinical factors, hypertension was the element that stood out as having prognostic value for lower TAPSE, FAC and 3D RVEF values, while body mass index was identified as a prognostic factor for lower FAC values. We also analyzed the impact of some aspects related to coronary anatomy in patients with infarction - location of culprit lesion, presence of vascular occlusion at the time of angiographic diagnosis, type and location of myocardial infarction. Our results support the fact that the occurrence of inferior ST-segment elevation myocardial infarction is a prognostic factor for lower values of FAC, 3D RVEF and S'_{VD}. These results contribute to current clinical practice in the sense that patients with myocardial infarction presenting with these features should benefit from a comprehensive multiparametric assessment of right ventricular systolic function.

In conclusion, we can say that the present work has succeeded in providing convincing arguments for the usefulness of complex assessment of right ventricular systolic function, not being limited to two-dimensional parameters only, but also by a wider adoption of three-dimensional echocardiographic methods such as 3D RVEF.

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