UNIVERSITY OF MEDICINE AND PHARMACY
"CAROL DAVILA", BUCHAREST
DOCTORAL SCHOOL
GENERAL MEDICINE

Prognostic parameters in heart failure with reduced ejection fraction and moderately-reduced ejection fraction- a study in 3D echocardiography

THESIS SUMMARY

Doctoral tutor:
PROF. VINEREANU DRAGOȘ

Doctoral student:
VELCEA ANDREEA-ELENA

2022

Table of contents

Introduction

Heart failure (HF) has a high socio-economic impact on a global scale, because of its high morbidity and mortality. There have been important advances in the therapeutic and diagnostic tools involved in HF, with consequent improvement of survival and quality of life in this patient population. One of the main diagnostic tools in HF is echocardiography. Echocardiography helps classify HF patients into three main categories: HF with preserved ejection fraction (HFpEF), HF with moderately-reduced ejection fraction (HFmrEF) and HF with reduced ejection fraction (HFrEF). HFmrEF is a recent addition to the HF guidelines and has been previously included in the HFrEF category. HFrEF has received the most attention in the past decades, with important therapeutic advances, both pharmacologic and interventional. Most therapeutic decisions in HF patients are based on the measurement of the left ventricular ejection fraction (LVEF). The decision to implant cardiac devices, such as internal cardiac defibrillators (ICD) and cardiac resynchronisation therapy (CRT), is dependent of LVEF assessment. Bidimensional echocardiography (2DE) is the main method used for the assessment of LVEF in current clinical practice. The chamber quantification guidelines recommend the use of the Simpson biplane method for the calculation of LVEF by 2DE, a method which uses geometric assumptions. The use of geometric assumptions for the calculation of LV volumes (LVV) is conducive to important errors in patients with LV remodelling, which is the case of many of those with an ischemic substrate.

The “gold standard” for the measurement of LVEF and LVV is cardiac magnetic resonance (CMR). However, this method is not widely available and is associated with high costs and contraindications.

The present work is focused on the evaluation of the feasibility and reproducibility of three-dimensional echocardiography (3DE), a novel imaging technique, which combines the three-dimensional nature of CMR and wide availability of 2DE. Furthermore, we aimed to evaluate whether 3DE could improve the risk stratification in a population of patients with HFrEF and HFmrEF, when compared to 2DE.

I. CURRENT KNOWLEDGE

1. General notions on heart failure

1.1 The definition of heart failure

Heart failure is a syndrome with specific symptoms, caused by structural or functional cardiac changes with consequent reduction of cardiac pump or filling properties.

The main symptoms involved in HF are fatigue and dyspnoea on physical exertion which, later in the disease course, can manifest during rest. These symptoms are often associated with clinical signs such as jugular distension, inspiratory crackles on pulmonary auscultation and pitting oedema.

The definition of HF from the current guidelines [1,2] is based on the symptomatic phase of the disease. However, some patients do not exhibit any symptoms, but have demonstrable structural or functional cardiac changes on cardiac imaging, which precede the symptoms.

1.2 The classification if heart failure

The widely known HF classifications are based on different aspects of the disease and can be used in a complementary manner. The "American College of Cardiology Foundation/American Heart Association" (ACCF/AHA) classification describes the stages of HF according to their natural progression – firstly, according to structural changes and secondly, according to symptoms. On the other hand, the other widely used HF classification, the "New York Heart Association" (NYHA) classification, uses the severity of the HF symptoms for stratification, without considering the structural changes.

Another essential HF classification is based on LVEF. According to the 2016 HF Guidelines [1], HF is classified as : HFrEF – LVEF<40%, HFmrEF – LVEF 40-49% and HFpEF - LVEF≥50%. HFmrEF is a recent addition to the HF classification and includes patients with LVEF which have been frequently excluded from the fundamental HF clinical studies, previously classified as HFrEF. The classification according to LVEF allows for a separation in the overall risk profile and response to treatment, as has been shown for HFrEF [3] and HFpEF [4]. HFmrEF is a category which warrants further studies, as the current information on its characteristic is limited.

1.3 The aetiology if heart failure

Heart failure with reduced EF and HFpEF have entirely different epidemiologic and etiologic characteristics. Patients with HFpEF are more frequently elderly, predominantly female, with a history of hypertension (HT) and atrial fibrillation (AF), compared to patients with HFrEF. In opposition to HFpEF patients, those with HFrEF have a high prevalence of cardiac ischemic disease.

Patients who fit in the HFmrEF category have characteristics which are found in the risk profile of both HFrEF and HFpEF, so further studies are warranted. The data emerging from the latest trials suggests that HFmrEF patients are frequently elderly, female, with high prevalence of HT, diabetes mellitus (DM), which are commonly associated with HFpEF, as previously mentioned [5]. However, they also have a higher prevalence of cardiac ischemic disease compared to HFpEF patients, which is a trait they share with HFrEF [6]. Given these finding, it is hypothesised that HFmrEF could be an intermediary step between HFpEF and HFrEF in those with ischemic substrate before the occurrence of cardiac remodelling.

The etiology of HF varies in different populations, with multiple causes contributing to HF in one individual. As previously mentioned, the most frequent cause for HFrEF is cardiac ischemic disease, however dilated cardiomyopathy is also prevalent in some populations. Other causes of HF with structural changes of the myocardium are cardiotoxicity from alcohol overuse or chemotherapy, infiltrative diseases and various genetic cardiomyopathies (hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy, laminopathies). Other important and frequent causes of HF involve cardiac filling changes, in valvular heart disease and pericardial diseases.

2. Heart failure diagnosis

The diagnosis of HF is based on a combination of symptoms and signs and is completed by a thorough patient history, cardiac markers and cardiac imaging, in order to establish the severity of the disease, the etilogy and prognosis.

2.1 Evaluation using bidimensional echocardiography – general data, advantages and disadvantages compared to cardiac magnetic resonance

Transthoracic echocardiography is an essential imaging method in the evaluation of HF patients because of its availability and cost-efficiency.

The evaluation of the LVEF is of major importance for the HF patient and the current guidelines indicate the use of 2DE [7], namely the Simpson biplane method. As a alternative, the guidelines also suggest the use of 3DE for the calculation of LVEF, but only in experienced laboratories. The measurements performed with 3DE have been shown to be more accurate than 2DE, making them closer to the “gold standard”, which is CMR.

The measurement of LVV is an integral part of LVEF measurement, as well as cardiac regional wall motion abnormalities, both contributing to the overall etiologic assessment.

The evaluation of the diastolic function is routinely performed in all HF patients but is particularly useful in the diagnosis of HFpEF. The assessment of the diastolic function involves various echocardiographic parameters, classified as functional and structural. From a functional perspective, the diastolic profile is central, and it is determined through the measurement of the E and A waves (E/A), as well as E’ on tissue Doppler (E/E’). The functional evaluation is completed with the structural evaluation, which includes the measurement of le left atrial volume (LAV), using the indexed values, as well as the LV mass.

The integration of the previously described parameters can clarify the diagnosis of HFpEF and can complete the evaluation of those with HFrEF and HFmrEF.

The evaluation of the right ventricle (RV) is mandatory in all HF patients. The evaluation is firstly structural – the RV diameter, RV area, as well as functional- the tricuspid annulus systolic excursion (TAPSE), fractional area chage (FAC), and in experience centers, E3D can be used to calculate the RV ejection fraction (RVEF) and RV volumes. The right heart assessment can be completed by the quatification of the right atrial (RA) dimensions, as well as pulmonary pressure estimation, as pulmonary hypertension (PHT) can have important prognostic implications.

Any echocardiographic assessment of HF patients includes valvular disease diagnosis.

Bidimensional ecocardiogprahy is useful for the practicing clinician as it offers a complex assessment of the HF patiens, as previously shown, and is widely available, cost-efficiency and short length of examination, compared to CMR, which is generally unavailable in low-income countries, has high costs and a long examination time which can cause significant discomfort for the patient. Both imaging techniques have the advantage of not exposing the patient to ionizing radiation.

There are limitations to both 2DE and CMR. 2DE has limited feasibility in patients with obesity and pulmonary emphysema. On the other hand, CMR cannot be used in older generation cardiac device recipients, those with abandoned cardiac leads. In conclusion, none of these imaging methods can evaluate all patients with HF.

The accuracy of CMR is higher than that of 2DE for any volumetric assessment, as well as the LV mass [8]. The superiority of CMR in the measurement of cardiac volumes derives from its three-dimensional nature, with high spatial and contrast resolution [9]. 2DE underestimates cardiac volumes because it uses geometric assumptions. Furthermore, some of the errors in the 2DE measurements also derive from inadequate acquisitions, generally as a consequence of the phenomenon known as “foreshortening”. Regardless, the only standardisation of cardiac volumes available is derived from 2DE [7]. This is not true of RV volumes, as there are no formulas capable of appreciating the volume of such a complex shape. 3DE can be used to measure RV volumes and RVEF, but the current “gold standard” remains CMR.

The LVEF calculated using 2DE has been found to be overestimated when compared to CMR [10, 11]. An improvement of the 2DE measurements can be obtained after the use of contrast, for a better delineation of the endocardium [11].

The superiority of 2DE in the evaluation of HF patients is in the diastolic function evaluation, which is not a feature of CMR. Valvular disease severity is also better achieved with 2DE.

Regarding the reproducibility of 2DE measurements, evidence by Otterstad et al [12] show good intra-observer and inter-observer reproducibility for LVV and LVEF, using the same images. However, the reproducibility is reduced for test-retest measurements, when several factors contribute to errors, such as physiologic factors, the angulation of the probe during image acquisition and, last but not least, the experience level of the user. On the other had, CMR has a superior reproducibility that 2DE for the intra-observer and inter-observer measurements, as well as the test-retest measurements for LVV and LVEF [9].

For both methods, there is a degree of variability in the measurements according to the experience of the user, however, the variability is lower for the CMR measurements [13]. One proposed explanation for the lower reproducibility of 2DE is the higher degree of error sources, especially in a less experienced user, errors than can be derived from both the image acquisition, as well as the image analysis.

In conclusion, both 2DE and CMR are imaging methods with good feasibility, accuracy and reproducibility in the diagnosis and follow-up of patients with HF, however none are able to provide a complete assessment, the combination of the methods in one individual patient is considered ideal.

2.2 Evaluation using there-dimensional echocardiography- general data, advantages and disadvantages compared to cardiac magnetic imaging

Three-dimensional echocardiography is an imaging method which continues to evolve since its introduction in the field of cardiology. The main advantage of 3DE is its ability to evaluate the cardiac chambers in all their dimensions, without the use of geometric assumptions. 3DE has been studied in the evaluation of HF patients and has shown significant value in the measurement of cardiac volumes, particularly LVV and RV volumes (RVV). Furthermore, 3DE has an incremental role in the evaluation of valvular disease and is currently incorporated in standard transoesophageal evaluation for valvular disease.

The accuracy of LVV by 3DE has been shown to be superior to 2DE in several studies. The same has been shown for the reproducibility of the measurements [14]. Given its superior accuracy and reproducibility, the current guidelines recommend the use of 3DE for the measurement of LVEF and LVV, in experienced centres.

Regardless of its superior accuracy and reproducibility when compared to 2DE, the 3DE underestimates LVV in comparison to CMR [15]. The main explanation for this difference is believed to be derived from the lower spatial resolution of 3DE, which make the differentiation of the endocardium from the LV trabeculae a challenge. The addition of contrast material to the 3DE evaluation has been attempted, but with limited results [11]. Furthermore, 3DE derived LVEF has been shown to be lower than 2DE LVEF, but still overestimated when compared to CMR [15].

Regarding the atrial volumes, most studies have been focused on the LA. Similar to LVV, the LAVs measured by 3DE are more accurate than 2DE, when compared to CMR and have good reproducibility [16]. Given the improved accuracy of LAV by 3DE, there is a need to define the normality intervals for this technique, as they are not superposable to 2DE. The ultimate result could then be a reclassification of diastolic dysfunction.

3. Prognostic factors in heart failure with reduced ejection fraction

Heart failure is associated with high incidence and prevalence in the general population, with major socio-economic impact. Regardless of the information gained about the pathophysiology of HF and novel therapeutic solutions, the mortality in HF remains high.

The best-known prognostic factor for mortality in HF is LVEF. Its prognostic value has been validated in numerous major clinical trials, such as the CHARM study [17], which had as a primary objective the impact of valsartan on mortality in a wide variety of patients with HF. On follow-up it has been concluded that LVEF correlates strongly with cardiovascular mortality and HF hospitalisation, with a rise in the number of events with every 10% of LVEF decline. There was no correlation reported between LVEF and stroke or non-cardiovascular deaths. The value of LVEF in the prognosis of patients with HFrEF has been confirm in another major trial, the Val-HeFT study [18].

Another prognostic tool in HFrEF, which can be added to LVEF, is the diastolic profile. Evidence shows that a restrictive diastolic profile is associated with a worse prognosis [19]. The reversibility of the restrictive profile using pharmacologic challenge with nitro prussiate has also been linked to a worse prognosis when a reversibility cannot be attained [20].

Another imaging tool used in the prognostic assessment of HFrEF is the RV function. The initial studies that confirmed that a depressed RV function is associated with a worse prognosis used ionizing techniques such as radio isotopic ventriculography [21] and cardiac catheterisation [22]. Currently, RV evaluation is performed with 2DE. The most frequently used parameter is TAPSE, because of its ease of use and good prognostic value which has been shown in numerous studies [23,24]. The prognostic value of TAPSE is further increased by adding PAP, as some studies have shown [23]. Another prognostic factor derived from the 2DE evaluation of the RV is FAC, showing an inversely proportional relation to prognosis. Furthermore, recent studies have shown a added value of RV free wall S', compared to TAPSE and FAC [25].

In recent years, LAV has also been shown to be a prognostic marker in HFrEF. Some studies have shown that LAV derived from 2DE has independent predictive value in patients with HFrEF and a superior value in the prognostic evaluation, when compared to the diastolic profile [26]. Furthermore, LAV derived fron 2DE has been shown to have prognostic value in other pathologies and even in populations of normal individuals [27], which warrants further studies centred on this parameter.

Three-dimensional echocardiography has recently been introduced as an alternative to 2DE in the evaluation of cardiac volumes and is gathering evidence regarding its prognostic value in HFrEF, predominantly showing a superior value to its 2DE counterparts.

4. Prognostic parameters in heart failure with moderately-reduced ejection fraction

Heart failure with moderately-reduced ejection fraction is a recent addition to the current HF guidelines. As such, there is limited knowledge on the progression of this subgroup of patients or whether they have a different pathophysiology.

As previously mentioned, patients with HFmrEF have some common elements with HFpEF, such as age, the predominance of female gender, HT and DM [5.6]. However, these patients are known to have a higher prevalence of ischemic heart disease, similar to patients with HFrEF. As such, it is clear that the prognostic factors for HFpEF and HFrEF are not superposable for HFmrEF. However, according to the CHARM study [17], patients with LVEF<45% have a higher mortality compared to those with LVEF>45%.

Furthermore, a large study developed in Sweden has shown renal failure to be a marker for poor prognosis in patients with HFmrEF and HFrEFm compared to the predictive value it has in those with HFpEF [27]. In another similar in structure study, it has been shown patients with HFmrEF who are older than 85 years and have associated pulmonary obstructive disease have a worse prognosis [28].

The clarification of the etiology and pathophysiology of HFmrEF is needed in order to better understand whether it is a separate entity or it is a transitional phase between HFpEF and HFrEF.

II. PERSONAL CONTRIBUTIONS

5. Work hypothesis and general objectives

Three-dimensional echocardiography is a relatively new imaging technique, that promises to be superior to 2DE in accuracy, as well as reproducibility for the measurement of cardiac volumes[14,15], however the evidence is still scarce and further studies are needed in order to introduce it into common clinical practice. The current guidelines [7] recommend using 3DE for the measurement of cardiac volumes and LVEF only in centres with experience in the method. Furthermore, the same guidelines encourage research using this method.

In order to further the research using 3DE, we have evaluated this technique, in comparison to 2DE, in a population of patients with HF, one of the most prevalent cardiovascular pathologies encountered in the population. The potential implications of a novel imaging technique that evaluates LVEF is the reclassification of patients with an indication for device therapy. Furthermore, we propose the 3DE evaluation of all cardiac chambers with the aim of establishing their prognostic value, in a population of patients with HFrEF and HFmrEF.

The main objectives of this study are as follows:

- To establish the feasibility and reproducibility of 3DE in comparison to 2DE, in a population of patients with HFrEF and HFmrEF;
- To establish the prognostic value of 3DE compared to 2DE, in a population of patients with HFrEF and HFmrEF.

6. Research method

We aimed to achieve our previously stated objectives by means of a prospective study, of observational nature, that included patients with HFrEF and HFmrEF, admitted to the Cardiology department of the University and Emergency Hospital Bucharest, for HF decompensation, starting 2015. The study has been approved by the Committee of Ethics of the Hospital, and all the patients included in the study have signed an informed consent.

The exclusion criteria are as follows: acute myocardial infarction, severe valvular disease, permanent atrial fibrillation, inadequate acoustic window, and inability to maintain breath-hold instructions during echocardiographic acquisitions.

All patients have been evaluated with 2DE and 3DE during hospitalisation, after compensation of HF symptoms, without medical interventions between the acquisitions. The same rules have been applied to the test-retest evaluation, which has been performed by two users with different levels of training in echocardiography.

At baseline visit, demographic data were documented, as well as NYHA class, previous medication, underlying etiology, NTproBNP value at admission.

The patients were followed-up remotely and, at 5 years, the study endpoints were documented: cardiovascular mortality, heart failure decompensation and a composite endpoint (CE) of mortality, Hf hospitalisation and myocardial infarction. The data were obtained via phone contact with the patient and patient family.

7. The reproducibility of left ventricular volumes and left ventricular ejection fraction measured by 2DE versus 3DE, in patients with heart failure with reduced ejection fraction and moderately-reduced ejection fraction, according to level of expertise

7.1 Introduction

The accuracy of LVV and LVEF is essential in patients with HFrEF in order to establish the indication for disease-modifying pharmacologic treatment, as well as interventional treatment, particularly for patients with LVEF<35%. Furthermore, serial measurements of LVV and LVEF are essential in patient follow-up [29] and prognosis [30-32]. The main tool used for these measurements is 2DE because of its availability, good reproducibility and low costs [33]. However, 2DE uses geometric assumptions for LVV measurement, which can lead to errors in the measurement of enlarged and asymmetrical LVs [34]. Two-dimensional measurements are also affected by foreshortening, with a consequent reduction in reproducibility and accuracy [35].

Conversely, 3DE can overcome the previously mentioned limitations of 2DE and provide better reproducibility and improved accuracy when compared to the "gold standard" of CMR [36].

Our study aims to evaluate the feasibility and reproducibility od 3DE LVV and LVEF measurements, when performed by users with different levels of expertise in 2DE and 3DE.

7.2 Method

60 consecutive patients were included, with the diagnosis of HFrEF and HFmrEF, hospitalised for HF decompensation. The inclusion and exclusion criteria have been described in detail in *Chapter 6*.

All 2D and 3DE acquisitions were obtained by one expert user, with more than 5 years of experience in both 2D and 3D echocardiography, during the same echocardiographic study, using a commercially available echo machine (Vivid E9, GE Vingmed, Horten, Norway).

Echopac BT 12, GE Vingmed).

Three cardiologists from our echocardiography laboratory, with different levels of training in 2DE, were named beginner (6 months of experience in 2DE, with 300 echocardiograms performed), medium (1 year of experience in 2DE, with 600 echocardiograms performed) and advanced (>2 years experience in 2DE, with more than 1000 echocardiograms performed) . The expert user performed a 1-month training in 3DE for the beginner, medium and advanced users, by focusing on how to measure the LVVs and LVEF from the 3DE data sets. Theoretical and practical notions were delivered to the trainees, to align their workflow with the general recommendations.

The expert user and all the other users measured the same LVV and LVEF from the 2DE and 3DE acquisitions, blinded to the identification information. The measurements were performed offline with the Echopac software.

Statistics. Continuous data are expressed as the mean ± standard deviation, whereas categorical data are expressed as the frequency or percentage (%). Measurements of LVVs and LVEF performed with different echocardiographic methods were compared using Student's t-test analysis. Pearson correlations were used to compare the measurements performed by the expert, beginner, medium and advanced users. The intra-observer reproducibility of the measurements was assessed using intra-class coefficients (ICCs), while agreements between methods and trainees were expressed using Bland Altman plots. A p value <0.5 was considered to indicate significance. Data analysis was performed using statistical software analysis (SPSS 20, IBM) and MedCalc (MedCalc Software).

7.3 Results

Comparison between 2-DE and 3-DE measurements of LVVs and LVEF provided by trainees in 3D echocardiography

The beginner, medium and advanced users provided 2-DE measurements of LVVs and LVEF that correlated with the measurements provided by the expert user (Figure 7.1). Moreover, the beginner, medium and advanced users provided 3DE measurements of LVVs and LVEF that highly correlated with the measurements provided by the expert user (Figure 7.2). Compared with the 2DE measurements performed by the expert user, the trainees in echocardiography exhibited good reproducibility of LVVs, but lower reproducibility of LVEF. However, after only a 1-month training in 3DE, the trainees provided more reproducible results for LVVs and LVEF measured by 3DE, as compared with the measurements performed by the expert user in echocardiography.

Agreement analysis using Bland Altman plots revealed no systematic biases for the measurements of LVEDVs performed with 2DE. However, the trainees exhibited a tendency to underestimate LVESVs when using 2DE. Therefore, trainees tended to "overestimate" LVEF calculated with 2DE, by comparison with the LVEFs calculated with 3DE. Conversely, there were no systematic biases between the measurements of LVVs and LVEF provided by the expert user and the trainees when using 3DE.

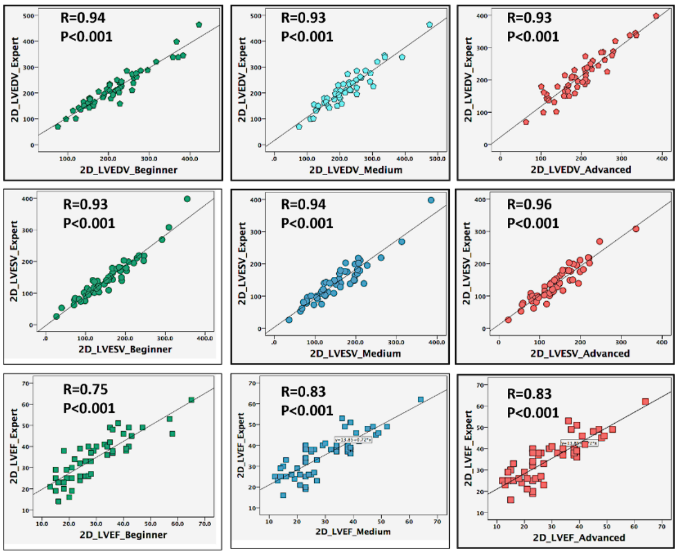

Figure 7.1 Correlation between LVV and LVEF by 2DE measured by the expert user and the users with various levels of training in 2DE

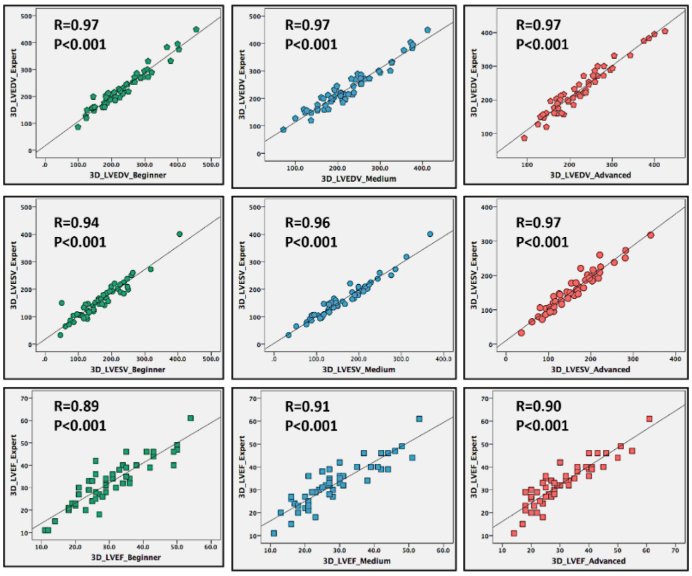

Figure 7.2 Correlation between LVV and LVEF by 3DE measured by the expert user and the users with various levels of training in 2DE

7.4 Discussions

Measurements of LVVs and LVEF are important determinants of clinical decisions in patients with HFrEF and frequently used as an endpoint in clinical trials [32, 37, 38].

The most frequently used technique for assessing LV size and function is 2DE because it is a rapid, non-invasive and cost-effective technique [34]. However, measurements of LVVs and LVEF by 2DE are limited by the geometric assumptions of left ventricular shape and by the foreshortening of the left ventricle, which reduce both the accuracy and reproducibility of the method [40].

Our study indicates that 3DE can be used by cardiologists with different levels of training in 2DE, after a short period of training in 3DE, with similar feasibility, but better reproducibility than 2DE. The main results of our study indicated that, in patients with HFrEF and HFmrEF, with a wide range of left ventricle shapes, LVVs and LVEF, 3DE provides feasible and more reproducible measurements of the LVVs and LVEF than 2DE, when used by novel trainees in 3DE, regardless of their basic level of training in 2DE; there is substantial agreement between 3DE and 2DE in measurement of LVEF, when used by trainees with different basic levels of training in 2DE and after just 1 month of training in 3DE.

Jenkins et al. [41] showed that 2DE has superior feasibility in the measurement of LVV and LVEF compared to 3DE. As expected, our trainees obtained feasibilities for 2DE measurements in line with their level of expertise in 2DE. However, after only 1 month of training in 3DE post-processing, trainees obtained similar feasibility for 3DE measurements of LVVs and LVEF, irrespective of their basic level of training in 2DE.

It was reported that reproducibility is lower when measuring LVVs and LVEF with 2DE than with 3DE, and this limitation might be overcome by the use of contrast agents in the 2DE techniques [42]. In our study, when the 2DE measurements provided by trainees were compared with those of the expert user, their reproducibility was in line with their basic level of training in 2DE. However, when compared again with the expert user, the trainees had increased reproducibility in 3DE measurements regardless of their basic training in 2DE.

Our study indicates that 3-DE might be a more accurate and reproducible method for following up patients with various LV shapes and volumes after a short period of training in 3-DE.

To the best of our knowledge, there is only one study that mentions the benefits of 3DE when comparing its use by experienced and non-experienced observers, which has been conducted by Hien et al [43]. The study was performed with transesophageal echocardiography and aimed to compare how experts and beginners localize the prolapsing segments of the mitral valve in patients with organic mitral regurgitation. Our study found

that trainees in echocardiography might have increased accuracy and reproducibility for 3DE measurements of LVVs and LVEF performed in patients with dilated left ventricles and a
wide range of LVEFs, by comparison with 2DE. As such, we consider 3DE to be a good if not even superior method for the serial measurements of LVV and LVEF in patients with HFrEF and HFmrEF, even when the examination is performed by beginners in the technique.

A recent meta-analysis reported that 3DE is the method with the highest accuracy in measuring LVEF, by comparison with CMR [44]. In our study, the LVEFs measured with 3DE by each of the echocardiographers included in the study were lower than the LVEFs measured with 2DE. Our results agree with another study [45], which indicated that 3DE usually
provides lower LVEF values than 2DE.

7.5 Conclusions

Trainees with different basic levels of expertise in 2DE, after only 1 month of training in 3DE, provided more reproducible measurements of LVVs and LVEF than obtained with 2DE. The increased reproducibility of the 3D measurements was not related to the basic level of training in 2D echocardiography, Therefore, 3DE might be a feasible and more reliable method for the follow-up of patients with HFrEF and HFmrEF, with dilated and distorted left ventricles.

8. The reproducibility of 2DE versus 3DE for the measurement of left atrial volumes, in patients with heart failure with reduced ejection fraction and moderately-reduced ejection fraction, according to level of expertise

8.1 Introduction

The assessment of the left atrium (LA) has gained significant interest in recent years because of its diagnostic and prognostic role in cardiovascular diseases.

The LA size is a key variable in the diagnosis of diastolic left ventricular dysfunction [46]. Consequently, LA size and function play a role in the diagnosis of heart HFpEF, whose main underlying mechanism is diastolic LV dysfunction [47]. Left atrial size has been shown to be a predictor of survival in cardiovascular pathologies, such as ischemic cardiomyopathy [48] and HFrEF [49].

The main method used in the assessment of LA size is transthoracic echocardiography, due to its availability and cost-efficiency. For the estimation of LA size using 2DE, the current guidelines recommend the calculation of maximum LA volume (LAV_max) using either the disk summation (BD) or the area-length (AL) biplane algorithms [7]. However, these measurements rely on geometric assumptions and are potentially biased by foreshortening. Three-dimensional echocardiography eliminates these biases and has been more accurate than 2DE in measuring LAVs when compared to CMR [50]. Furthermore, 3DE has been shown to be a feasible method, with reproducibility superior to 2DE for LAVs [50, 51].

We aime to assess the feasibility and reproducibility of 3DE measurements of LAVs, when used by operators with different levels of expertise in 3DE, in comparison to 2DE.

8.2 Method

30 patients were enrolled prospectively **(**59±14 years, 20 male), in sinus rhythm. The inclusion and exclusion criteria are described in *Chapter 6.*

The study design included two users, with similar levels of expertise in 2DE (over 2 years experience with 2DE, over 1000 echocardiographic examinations performed), but different levels of expertise in 3DE. The users were defined according to their level of expertise in 3DE, as Beginner (6 months in practical and theoretical training in 3DE) and

Advanced (over 4 years experience with 3DE). The two users performed complete 2DE and 3DE acquisitions of the patients, during the same clinic visit.

Intra-observer variability and intra-observer measurements were performed according to the known method. Test-retest variability was determined by measuring different datasets, acquired by the Advanced user and the Beginner user. The measurements were performed by the Beginner user.

Statistics. The methods used were described in *Chapter 7*.

8.3 Results

The Advanced user measured both 2DE and 3DE datasets in all patients. Mean LAV_max was 80±24 ml when calculated with 2DE using the AL method, 78±16 ml using the BD method, and 84±34 ml when measured with 3DE. Mean LAV_min was 45±23 ml when calculated with 2DE using the AL method, 40±23 ml using the disk summation method, and 40±16 ml when measured with 3DE.

Intra-observer variability

As expected, there was good intra-observer reproducibility for the 2DE measurements, particularly for the LAV_max. However, a similarly good reproducibility was documented for the 3D measurements of the LAV_max and superior reproducibility was documented for the LAV_min, when performed by a user with beginner level in 3DE (Table 8.1).

Agreement analysis using Bland-Altman plots revealed no systematic bias for the LAV_max or LAV_min measured by 2DE or 3DE. The limits of agreement between the 2DE and the 3DE measurements of LAV_max were similar, however 3DE measurements of LAV_min were considerably tighter (Table 8.1).

	2D LAV_max Area Length	2D LAV_max Biplane	2D LAV_min Area Length	2D LAV_min Biplane	3D LAV_max	3D LAV_min
ICC	0.98	0.99	0.95	0.95	0.97	0.99
CI	0.97-0.99	0.98-0.99	0.91-0.98	0.90-0.98	0.95-0.99	0.995-0.999
Bias	0.42	0.16	1.17	1.28	-0.25	0.28
LOA	-10; 11	-8; 9	-15; 18	-15; 17	-10; 9	-3; 3

Table 8.1 Intra-observer variability (adapted from Velcea A. et al. Three-dimensional echocardiography is a feasible and reproducible method for the measurement of left atrial volumes, regardless of expertise level, MAEDICA 2022;17(1):4-13)

Inter-observer variability

There was good inter-observer reproducibility for the 2DE LAVs when measured by observers with similar levels of expertise in 2DE. However, similarly reproducible results were obtained for the 3DE LAVs, when measured by users with significantly different levels of training in 3DE (Table 8.2).

Agreement analysis using Bland-Altman plots revealed no systematic bias for the LAV_max or LAV_min measured by 2DE or 3DE, between the two users. The 3DE measurements showed lower bias compared to the 2DE measurements for LAV_max and LAV_min (Table 8.2).

	2D LAV_max Area Length	**2D LAV_max Biplane**	**2D LAV_min Area Length**	**2D LAV_min Biplane**	**3D LAV_max**	**3D LAV_min**
ICC	0.98	0.98	0.97	0.96	0.98	0.98
CI	0.96-0.99	0.97-0.99	0.94-0.98	0.91-0.98	0.96-0.99	0.97-0.99
Bias	-2.17	-1.58	2.17	3.17	-0.51	-0.45
LOA	-13;9	-11;8	-10;15	-13;19	-9;8	-8;7

Table 8.2 Inter-observer variability (adapted from Velcea A. et al. Three-dimensional echocardiography is a feasible and reproducible method for the measurement of left atrial volumes, regardless of expertise level, MAEDICA 2022;17(1):4-13)

Test-retest variability

There was lower, yet acceptable (r>0.8) reproducibility for the 2DE LAVs when measured on separately acquired datasets, by the same user with advanced level of training in 2DE. However, reproducibility was superior for 3DE LAVs, when measured by the same user, with beginner level of training in 3DE (Table 8.3).

Agreement analysis using Bland-Altman plots revealed no systematic bias for the LAV_max or LAV_min, regardless of the method used. The limits of agreement were significantly tighter for the 3DE measurements (Table 8.3).

	2D LAV_max Area Length	2D LAV_max Biplane	2D LAV_min Area Length	2D LAV_min Biplane	3D LAV_max	3D LAV_min
ICC	0.84	0.92	0.85	0.86	0.97	0.95
CI	0.66-0.92	0.91-0.98	0.69-0.93	0.71-0.93	0.94-0.98	0.91-0.98
Bias	4.39	1.82	2.35	2.32	-0.73	1.93
LOA	-22;31	-13;17	-22;27	-20;25	-11;10	-10;14

Tabel 8.3 Test-retest variability (adapted from Velcea A. et al. Three-dimensional echocardiography is a feasible and reproducible method for the measurement of left atrial volumes, regardless of expertise level, MAEDICA 2022;17(1):4-13)

8.4. Discussions

The reproducibility of the 2DE measurements in our study was similar to that previously reported ă51î. Regarding the agreement between the 2DE measurements, there was no systematic bias, however the limits of agreement, while acceptable for the intra-observer measurements, were arguably significant for the inter-observer and test-retest measurements. The percentage bias was under 10% for all measurements. Similar values were reported in previous studies [50], some reporting even higher bias for 2DE, particularly for the test-retest measurements [51]. This bias is believed to emerge from the variation in the acquisition of the LA with 2DE, even when significant efforts are made to obtain the maximum longitudinal axis, as was the case in our study.

We reported non-inferior reproducibility of the 3DE measurements compared to the 2DE measurements, which is an important finding, given the limited training in 3DE the Beginner user had received. The agreement between the 3DE measurements was superior to the 2DE measurements when measurements were performed by users with different levels of training in 3DE. In previous studies, reproducibility for LAV measurements by 3DE has been shown to be superior to 2DE, when measured by experienced operators [50]. Badano et al. [50] also reported on the reproducibility of 3DE between advanced operators and trainees, showing a decrease in reproducibility with less experience, however still superior to the reproducibility of 2DE. In the same study, it has been shown that the reproducibility of LAV_min and LA ejection fraction was more significantly impacted by the level in training in 3DE than LAV_max. In our study, the 3DE LAV_min has better limits of agreement than LAV_max, regardless of the level of training in 3DE.

The reproducibility of the 3DE measurements remained comparably high even for the test-retest measurements, when one of the acquisitions was obtained by a user with limited training in 3DE and the images were both assessed by the same user, with beginner level in 3DE. To our knowledge, this variant of the test-retest method has not been evaluated for the reproducibility of 3DE LAV to date.

8.5 Conclusions

Three-dimensional echocardiography is a technique that promises to improve the overall assessment of patients with HF, showing good feasibility and reproducibility, superior to 2DE, regardless of the level of training in the method.

9. The prognostic value of left heart parameters, measured by 2DE versus 3DE, in a population of patients with heart failure with reduced ejection fraction and moderately-reduced ejection fraction

9.1 Introduction

Heart failure is a disease with important socio-economic impact at a global scale. To date, there are no predictive models for cardiovascular events in this patients population, the majority of therapeutic decisions are relying on LVEF. The method used in common clinical practice for the measurement of LVEF is 2DE. However, as mentioned in previous chapters of this work, this technique has limited accuracy and reproducibility because of its bidimensional nature.

In the last decades, various predictive models for the prediction have been tested in patients with HFrEF. Regarding the imaging parameters used in prognostic models, other that LVEF and LVV, LAV have also been proposed [52-57]. As for LVEF, 2DE is the main method used to evaluate LAVs.

A method that promises to be superior to 2DE is 3DE, as it does not rely on geometric assumptions, but is widely available and cost-efficient. As such, we aimed to evaluate the prognostic value of LV and LA parameters, using 2DE and 3DE, in a population of patients with HFrEF and HFmrEF.

9.2 Method

120 consecutive patients were included (92 male), with the diagnosis of HFrEF or HFmrEF, with various underlying aetiologies, admitted for HF decompensation. The inclusion and exclusion criteria are detailed in *Chapter 6*.

Echocardiography. The 2DE and 3DE acquisitions were performed during the same examination, using a Vivid E9, GE Vingmed, Horten, NO machine. The acquisitions were performed according to the most recent recommendations of the European Association of Cardiovascular Imaging [7].

Statistical analysis. Continuous variables were reported as mean ± standard deviation, categorical variable were reported as frequency or percentage (%). The continuous variable with normal distribution were compared using Student T-test, white those not normally distributed were compared using the Kruskall-Wallis test. Comparisons between categorical variables were performed using the Chi-Square test.

Pearson correlation coefficient was used for the correlation between echocardiographic parameters and outcomes.

The independent predictors for outcome were deduced using Cox analysis. The statistics were performed in a manner which avoided multicollinearity. Two main models for the multivariate analysis were constructed, one for 2DE and one for 3DE parameters.

Recever Operator Characteristics (ROC) curves were used to evaluate the predictive value of the left heart echocardiographic parameters. The values with the best specificity and sensibility were used to construct Kaplan-Meier curves. The log-rank test was used to compare the survival plots.

A p value <0.5 was considered to indicate significance. Data analysis was performed using statistical software analysis (SPSS 20, IBM) and MedCalc (MedCalc Software).

9.3 Results

120 patients were included (92 male, 60±17 years). During follow-up (5±3 years), 42 suffered cardiovascular deaths, 61 had CE and 55 had admissions for HF decompensation.

The general characteristics of the patients, according to mortality at the last follow-up are described in Table 9.1.

	Total (n=120)	Dead (n=42)	Alive (n=78)	P value
Demographic data				
Age (mean±SD)	60±17	67±11	59±13	**0.04***
Male	92 (76)	35 (76)	57 (73)	0.2
Cardiovascular parameters				
Diabetes	38 (31)	14 (36)	24 (64)	0.7
HT	81 (68)	29 (70)	52 (66)	0.6
Dyslipidemia	83 (69)	30 (71)	53 (68)	0.7
CABG	6 (5)	3 (7)	3 (4)	0.4
MI	54 (45)	22 (52)	32 (41)	0.2
HF class				
NYHA II	77 (64)	18 (42)	59 (75)	**0.001***
NYHA III-IV	43 (36)	24 (57)	19 (24)	**0.001***
Wide QRS	43 (35)	13 (31)	30 (38)	0.4
Medication				
ACEI/sartan	86 (71)	30 (71)	56 (71)	0.9
Betablocker	105 (87)	31 (73)	74 (94)	**0.001***
MRA	101 (84)	32 (76)	69 (88)	0.07

Tabel 9.1 General characteristic according to survival at follow-up

9.3.1 The prognostic value of left ventricular parameters

The patients who died at follow-up were older, had more advanced NYHA class and were less likely to receive a betablocker. Regardless of method, the patients who died had larger LVV, but significant difference was reported only for end systolic LVV (ESLVV) by 3DE (Table 9.2). Regarding LVEF, it was noted to be more depressed in those who died, but statistical difference was found only for 3DE LVEF. Furthermore, for those with CE, they had a higher proportion of dyslipidaemia and were older than those who did not suffer CE at follow-up. Regarding the echo parameters, the only statistically significant difference was noted for 3DE LVEF. There were no significant differences in clinical or imaging parameters between those who experienced HF hospitalisation and those who did not.

	Total (n=120)	Dead (n=42)	Alive (n=78)	P value
2D				
EDLVV (ml)	196±69	208±79	193±66	0.21
ESLVV (ml)	138±65	149±74	135±62	0.32
LVEF (%)	32±90	29±80	32±10	0.12
LV_SI	0.7±0.6	0.8±10	0.6±0.5	0.11
3D				
EDLVV (ml)	218±72	237±79	214±71	0.13
ESLVV (ml)	152±67	174±75	146±65	**0.04***
LVEF (%)	30±90	26±70	33±90	**0.05***
LV_SI	0.5±0.4	0.7±0.8	0.4±0.09	**0.05***

Table 9.2 Left ventricular dimensions, function and shape according to the mortality at follow-up

The measurements of the same parameters with 2DE and 3DE showed significant differences with higher values for 3DE in the following- ESLVV, EDLVV and SI_VS. While the LVEF was lower by 3DE compared to 2DE, the difference was no statistically significant (p=0.1).

In the present study, 3D LVEF had a superior AUC than 2D LVEF (Table 9.3).

	Cut-off value	AUC	Specificity	Sensibility
LVEF_2D	<35	0.583	40	87
LVEF_3D	<35	0.675	50	95

Table 9.3 ROC analysis for the 35% cut-off value for LVEF

Cox regression was used to identify independent predictors for the three main endpoints of the study. Age was the only predictor for mortality in the univariate analysis. The only imaging parameter that was found to be an independent predictor for mortality in the univariate and multivariate analysis was 3D LVEF (Table 9.4). However, 3D LVEF was not able to predict the other events. The multivariate model included age, sex, ischemic substrate and NYHA class.

	Univariate regression HR (IC)	P value	Multivariate regression HR (IC)	P value
Age	1.478 (1.004-3.415)	**0.02**	1.038 (0.989-1.090)	0.13
Gender	1.020 (0.977-1.065)	0.36	1.323 (0.535-3.275)	0.54
MI	1.089 (0.471-2.519)	0.84	0.590 (0.217-1.606)	0.30
NYHA class	0.665 (0.160-3.662)	0.73	0.952 (0.192-4.709)	0.95
LVEF_2D	0.970 (0.933-1.008)	0.11	0.957 (0.916-1.000)	0.51
LVEF_3D	0.958 (0.918-0.998)	**0.04***	0.936 (0.886-0.990)	**0.02***

Table 9.4 Independent predictors for mortality by univariate and multivariate analysis

9.3.2 The prognostic value of left atrial echocardiographic parameters

The results showed that those who died had significantly larger LAV_max, by both 2DE and 3DE, also larger LAV_min by 3DE (Table 9.5). For the CE, significant differences were noted for LAV_max and LAV_min (both indexed and non-indexed) by both methods as well as LA_SI by 2DE. Those who experienced HF hospitalisation has significantly larger LAV_max by 3D (indexed and non-indexed), LAV_max by 2D (non-indexed) and LAV_min by both methods.

	Total (n=120)	Dead (n=42)	Alive (n=78)	P value
E3D				
LAV_max (ml)	94±31	102±35	89±28	**0.05***
LAV_max_indexed (ml/m²)	50±17	53±15	48±18	0.19
LAV_min (ml)	60±12	62±10	51±12	**0.01***
LAV_min_indexed (ml/m²)	32±8	36±6	25±8	**0.02***
LA_SI	0.7±0.1	0.82±0.12	0.75±0.2	0.06
E2D				
LAV_max (ml)	83±32	92±34	77±30	**0.02***
LAV_max_indexed (ml/m²)	43±18	47±13	41±20	0.16
LAV_min (ml)	55±27	65±26	49±27	**0.005***
LAV_min_indexed (ml/m²)	28±13	37±12	26±11	**0.008***
LA_SI	0.6±0.08	0.60±0.05	0.62±0.09	0.35

Table 9.5 Left atrial size and shape parameters according to mortality at follow-up

All 2DE parameters correlated with the mortality, however LAV_max indexed and LA_SI by 3DE did not. All of the parameters, 2DE and 3DE, correlated with the other endpoints, but the correlations were weak.

By ROC analysis, LAV_max indexed by 3DE with a cut-off of 34 ml/m2 has superior sensitivity and specificity to the 40 ml/m2 cut-off of 2DE.

The Kaplan Meier curves show significant differentiation for the LAV_max indexed of 34 ml/m2, for all endpoints.

Univariate Cox analysis has found age, LVEF_3D and LAV_max_indexed_3D to be the only independent predictors for mortality in this group of patients.

Using linear hierarchical regression analysis, the prognostic value of LAV by 2DE and 3DE was evaluated. Four models were constructed, two for each imaging method. All four models had clinical parameters at step 1 (age, ischemic disease, HT, DM and NYHA class), step 2- addition of LVEF by one of the methods, step 3- LAV_max_indexed by one of the methods and in the last step LAV_min_indexed was added.

For the 2DE model that included steps 1 to 3, significant predictive value was obtained for HF hospitalisation only. For the 3DE model that included steps 1 to 3, significant predictive value was obtained for HF hospitalisation and CE. No added value derived from the addition of LAV_min for either method.

9.4. Discussions

We included patients with HFrEF and HFmrEF, evaluated with 2DE and 3DE, in order to determine if 3DE derived parameters could bring additional value to the current prognostic tools.

In our study, the LVV were significantly different between the two methods, however LVEF was not significantly different. These results are superposable to those derived from studies with large number of patients, some with a subgroup of HFrEF [59]. One explanation for these results is that the error of measurement is relatively similar for the end systolic volumes and end diastolic volumes.

The present study found LVV by 3DE to be larger than those measured by 2DE and showed that those with larger volumes have higher mortality, results which parallel other studies in the literature [60]. Furthermore, in our study, we found the same to be true of those with EC.

Regarding the independent predictors for cardiovascular events, the only parameter that maintained its value in the adjusted analysis was LVEF by 3DE. In other studies [58, 59], age, LVEF by 2DE and LVEF by 3DE, as well as deformation parameters such as

GLS were found to be independent predictors for mortality. In our study, we found age to be an independent predictor only in the univariate analysis. Regarding LVEF by 2DE, it did not predict mortality in this group of patients, probably as a result of the high proportion of patients with ischemic substrate for which 2DE is expected to derive the most errors, but also as a result of the relatively low number of patients included in the study.

Like other recent studies [59], AUC for LVEF by 3DE was larger than AUC for LVEF by 2DE. Medvedovsky et al. [59] have shown that the best AUC in their study was derived from GLS by 3DE, which was also reflected in the survival analysis by Cox regression adjusted for clinical factors, as well al Kaplan Meier analysis, divided by tertiles. Conversely, we used the guideline-derived cut-offs for LVEF of 35%. For this value, LVEF by 3DE achieved a good prediction of mortality.

As other studies have shown, we found the LAVs measured by 2DE to be significantly different than those measured by 3DE. The large studies comparing the two methods for the measurement of LAVs, particularly the one published by Badano et al. [50], have been developed using large populations of normal individuals. Our patient population was significantly smaller and included a majority of dilated atria, with various shapes.

Both 2DE and 3DE LAV_max, with different cut-offs, managed to predict survival in this group of patients. The same can be applies to the other endpoints of the study. A study that contradicts our findings, published by Wu et al. [61], did not show LAV_3D to be a good predictor of outcome, however the population examined was different from our study.

In our study, through the use of hierarchical linear regression, with four models, significant predictive value using the 2DE parameters was found only for HF hospitalisation. For the 3DE model, there was prognostic value for CE and HF hospitalisation. No model could predict mortality.

In conclusion, the prediction of mortality in patients with HFrEF and HFmrEF is a complex task, given its multifaceted nature, various phenotypes, and evolution, in patients with comorbidities, from which the difficulty in determining an efficient prognostic model derives.

9.5 Conclusions

In our study, we found LVEF by 3D to be a good predictor for cardiac events, superior to 2D LVEF. The added value of LAV, by either method, was not significant in the prediction of cardiovascular mortality in this group of patients but was able to improve the prediction of the other cardiovascular events.

10. The prognostic value of right heart parameters by 2DE and 3DE, in patients with heart failure and reduced ejection fraction and patients with moderately-reduced ejection fraction

10.1 Introduction

Right ventricular dysfunction is known as a negative prognostic factor in patients with HFrEF. The evaluation of the RV is complicated because of the cavity's complex shape, with a volume that cannot be calculated with mathematic formulas. In clinical practice, the most frequently used technique for the evaluation of the RV is 2DE. Of the 2DE parameters, TAPSE is the most evaluated. Regardless of its limitations in evaluating such a complex three-dimensional structure, it has the advantage of good reproducibility and has been shown to be a valuable prognostic marker [62-65]. The "gold standard" for the measurement of RVEF and RV volumes (RVV) is CMR. However, CMR has low availability, high costs and several contraindications. As such, a method which promises to be close to CMR is 3DE. Studies have already been developed for the validation of RVV and RVEF by 3DE in normal individuals [66], however the prognostic value of these parameters is still unknown.

We aimed to establish the prognostic value of 3DE derived right heart parameters, compared to the standard of 2DE, in a population of patients with HFrEF and HFmrEF.

10.2 Method

The method has been described in *Chapter 6*.

The echocardiographic evaluation has been performed as mentioned in *Chapter 9*.

Statistics. Similar to the method described in *Chapter 9*.

10.3 Results

For the 2DE derived parameters of RV size (RV area, diameter), there were no notable differences between those who died and the survivors. We did not find a significantly lower TAPSE by 2DE in those who died, however the RA volumes (RAV) were larger in these patients.

For the 3DE derived parameters, we found that RVV were larger in those who died, but statistical significance was reached only for the end systolic volumes. Furthermore, we found that those who died had lower RVEF, as well as lower FAC by 3DE and TAPSE by 3DE. Lastly, the RAVs were significantly larger in those who died at follow-up.

Correlation analysis with the endpoints was performed and we found weak correlations with the 2DE parameters and stronger (r>0.4) for the 3DE parameters.

As previously mentioned, age was found to be an independent predictor for death in these patients, but not for the other endpoints. Furthermore, NTproBNP also had predictive value in this group of patients. Of the standard echocardiographic parameters, E/E' and PAP were independent predictors for all the endpoints. Of the 2DE parameters, FAC_2D showed predictive value for all study endpoints (Table 10.1). Of the 3DE parameters, the end systolic RVV, RVEF and FAC_3D are independent predictors in the univariate analysis for all endpoints (Table 10.2).

2DE	Alive	Dead	P value
Age (years)	59±12	66±11	**0.002***
E/E'	9.58±7.97	16±8.25	**0.001**
PAP (mm Hg)	30±16	42±25	**0.045***
2D EDRV diameter (mm)	35±6	35±7	0.94
2D EDRV area (cm²)	21±10	20±6	0.49
2D ESRV area (cm²)	12±5	13±6	0.20
2D FAC (%)	33±13	38±12	**0.04***
2D TAPSE (mm)	19±4	18±4	0.62
S' RV free wall (cm/sec)	11±3	11±3	0.51
RV global strain (%)	14±6	13±5	0.35
RV free wall strain (%)	20±8	18±7	0.32
2D RA diameter (mm)	40±6	41±7	0.33
2D RA area (mm²)	17±3	18±5	**0.09***
2D RAV_max (ml)	52±18	64±29	**0.004***
2D RAV_max_indexed (ml/m²)	26±9	32±13	**0.02***

Table 10.1 Binary logistic regression for clinical and 2DE parameters, according to endpoint

3DE	Alive	Dead	P value
3D diametru TDVD (mm)	43±7	47±8	**0.006***
3D EDRVV (ml)	153±53	172±57	0.126
3D EDRVV_indexed (ml/m²)	80±23	87±26	0.200
3D ESRVV (ml)	90±42	119±46	**0.004***
3D ESRVV_indexed (ml/m²)	46±20	61±26	**0.003***
3D RVEF (%)	42±9	32±7	**<0.001**
3D RV_SV	63±15	53±17	**0.006**
3D FAC (%)	39±10	28±11	**<0.001***
3D RAV_max (ml)	52±17	68±30	**0.001***
3D RAV_max_indexed (ml/m²)	27±9	34±15	**0.006***
3D RAV_min (ml)	29±12	42±23	**<0.001***
3D RAV_min_indexed (ml/m²)	27.4±9	34±14	**0.011***

Table 10.2 Binary logistic regression for 3DE parameters, according to endpoint

ROC analysis was performed and showed that RVEF<40% can predict mortality with a sensitivity of 89% and specificity of 69% (AUC 0.81), while a RVEF<35% has a sensitivity of 90% and specificity of 71% (AUC 0.82). The same analysis has been performed for FAC_3D, with good results (sensitivity 82%, specificity 65%, AUC 0.79).

ROC analysis was performed for FAC_2D also, and for the guideline-indicated cut-off of 35% we found a sensitivity of 61% and specificity of 62% (AUC=0.56).

Kaplan Meier survival analysis using the 35% cut-off for RVEF showed a good separation of the survival curves (χ^2 7.64 (p=0.006)) (Figure 10.1). The same analysis for FAC_3D < 35% resulted in χ^2 4.08 (p=0.02). Conversely, FAC_2D <35% did not allow for a good separation of the survival curves.

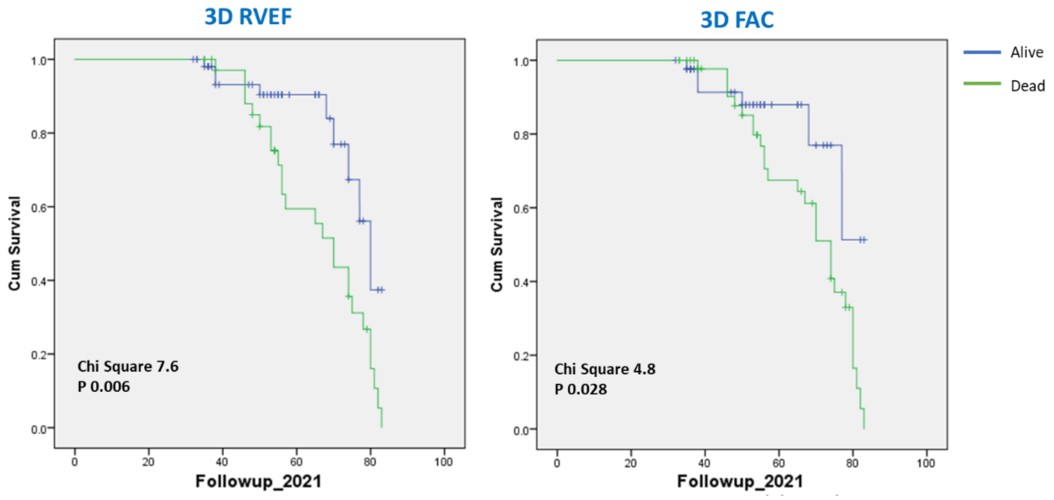

Figure 10.1 Kaplan Meier analysis for survival, for RVEF with a cut-off of 35% and FAC_3D of 35%

Multivariate analysis was performed for mortality, by adding age, LVEF by 3D and RVEF, which was a model with statistical significance. The addition of other parameters validated in the univariate analysis did not improve the model. The 2DE equivalent was also analysed. We included age, LVEF_2D and FAC_2D, however the statistical value of the model is cancelled when adding FAC_2D.

10.4 Discussions

The main results of this study can be summarised as follows: RVEF and FAC_3D have independent predictive value for mortality, HF hospitalisation and CE.

There are studies in the literature that have evaluated risk scores for HFrEF, that included clinical factors, the most well-known being a study based on the evaluation of eplerenone in HF, namely Eplerenone in Heart Failure in Mild Patients Hospitalisation and Survival Study in Heart Failure (EMPHASIS-HF risk score) [67]. This score includes age, blood pressure, glomerular filtration rate, HF hospitalisation, haemoglobin, history of MI, body mass index and heart rate. In the present study, of the clinical factors, only age and NTproBNP were independent predictors for mortality.

Pulmonary hypertension is a known negative prognostic factor in HFrEF, as well as its correlation with RV dysfunction evaluate by TAPSE_2D. However, Ghio et al. [63] have shown that this combination of pulmonary hypertension and RV disfunction is not always present in HFrEF, many of these patients have isolated RV dysfunction. In the present patient population, PAP was an independent predictor for events in the univariate analysis, but not in the multivariate analysis. However, TAPSE_2D was not found to be a predictor of events, possibly because of the low variability of this parameter in this group of patients.

Another 2DE-derived parameter used in the evaluation of the RV is FAC. FAC is a more complex parameter, which can give a superior evaluation of the RV function, when compared to parameters such as TAPSE, as it can give information on both longitudinal and radial RV function. One study found FAC_2D to be a good predictor for mortality and other cardiovascular events (like need for assist-devices) in patients with HFrEF [68]. In our study, we found that FAC_2D was an independent predictor for cardiovascular events, even in the multivariate analysis.

The predictive value of the 3DE-derived parameters is understudied at present. The data from unicentric and retrospective trial suggests that RVEF is a good predictor for mortality and cardiovascular events in patients with HFrEF and is superior to the predictive capabilities of 2DE parameters. Similar to the data published by Nagata et al. [69], we found RVEF to be a good predictor for cardiovascular mortality, even in adjusted analysis.

10.5 Conclusions

Three-dimensional echocardiography promises to improve the quality of RV assessment and present evidence shows that 3DE-derved RV parameters are superior predictors of cardiovascular events than 2DE parameters.

III. Conclusions

In the present work, we aimed to evaluate the feasibility and capacity of added prognostic value of 3DE-derived parameters, when compared to 2DE, in a population with HFrEF and HFmrEF. We consider the main study objectives to be reached, as we have shown superior reproducibility for 3DE LVV and LAV, even in unexperienced users. Regarding the prognostic value of the 3DE parameters, when compared to 2DE parameters, superiority has been shown for 3DE in the majority of cases.

The contributions the present work brings to the vast domain of cardiovascular research are summarised below.

Regarding the reproducibility of the 3DE techniques, we performed reproducibility analysis for LVV and LAV. For the LV, we concluded that users with different levels of training in 2DE, after a month of training in 3DE, obtained measurements for the LVV and LVEF that were superior to the 2DE equivalents [70]. We concluded that 3DE is a more reproducible and feasible method for the follow-up of patients with HFrEF and HFmrEF, with important LV remodelling. The element of novelty derived from this analysis is the evaluation made by echocardiographers with different levels of training in 2DE and 3DE, whose measurements were compared, concluding that even after a short period of training in 3DE, the reproducibility of the 3DE measurements was superior to 2DE. This is an important point, as one of the reasons for which 3DE has not been introduced to common clinical practice is the lack of evidence on its performance in less experienced hands. The measurement of LVV and LVEF are central to the evaluation of any HF patient, for both classification and management. For the patient management, the LVEF influences both pharmacologic interventions, as well as the decision-making process for invasive therapies such as ICD and CRT [71].

Regarding the LA parameters, we concluded that 3DE has a good reproducibility and feasibility, superior to 2DE, regardless of the level in training in 3DE, like the LV results. We used a particular method for the evaluation of reproducibility, as in addition to the standard procedure, we included acquisitions and measurements performed by users with different levels of training in 3DE. Even though the LAV is not as important as LVEF in the evaluation of patients with HF, the need for good reproducibility in LAV measurements cannot be ignored.

For the evaluation of the prognostic value of 3DE parameters versus 2DE parameters, we analysed the left heart parameters and right heart parameters separately.

The prognostic value of LVV and LVEF by 2DE have been intensely investigated since the beginning of the primary prevention era. In the study patient group, the majority of patients had an ischemic substrate and LVEF by 3DE was shown to have a superior prognostic value to 2DE and was an independent predictor for cardiovascular events in the univariate and multivariate analysis.

The prognostic value of LAV has recently been in the hotspot of cardiovascular research, as it has been shown to a be a prognostic marker in various pathologies such as mitral regurgitation, aortic stenosis, and AF. LAV by 3DE has been shown to be an independent predictor for cardiovascular events in this patient population, but only in the univariate analysis.

Regarding the right heart parameters, we have shown that FEVD has superior prognostic value for all cardiovascular events, when compared to the 2DE parameters. Furthermore, we have established a potential cut-off for the RV dysfunction and have shown that the guideline-indicated cut-off of 35% for FAC_2D was not as efficient in separating the survival curves as RVEF in this group of patients. In combination with clinical and classic echocardiographic parameters, FEVD was able to predict mortality with high accuracy in a multivariate model.

Finally, we conclude that the initial hypothesis of the study was correct, as sufficient evidence has been provided to bring 3DE closer to clinical practice, as it has been found to be reproducible, regardless of level of training and with good prognostic value compared to its 2DE counterparts.

BIBLIOGRAPHY

1. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891-975.
2. Yancy C, Jessup M, Bozkurt B et al.2013 ACCF/AHA Guideline for the Management of Heart Failure, J Am Coll Cardiol. 2013 Oct, 62 (16) e147-e239.
3. Bloom, M., Greenberg, B., Jaarsma, T. et al. Heart failure with reduced ejection fraction. Nat Rev Dis Primers 3, 17058 (2017). https://doi.org/10.1038/nrdp.2017.58
4. Marc A. Pfeffer, Amil M. Shah, Barry A. Borlaug, Heart Failure With Preserved Ejection fraction-in Perspective, Circ Res. 2019;124:1598-1617.
5. Fonarow GC, Stough WG, Abraham WT et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50:768–77
6. Cheng RK, Cox M, Neely ML, et al. Outcomes in patients with heart failure with preserved, borderline, and reduced ejection fraction in the Medicarepopulation. Am Heart J 2014;168:721–30.
7. Lang RM, Badano LP, Mor-Avi V et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70.
8. Hudsmith LE, Petersen SE, Francis JM, Robson MD, Neubauer S. Normal human left and right ventricular and left atrial dimensions using steady state free precession magnetic resonance imaging. J Cardiovasc Magn Reson. 2005;7:775–782.
9. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2000;2:271–278.
10. Nowosielski M, Schocke M, Mayr A et al. Comparison of wall thickening and ejection fraction by cardiovascular magnetic resonance and echocardiography in acute myocardial infarction. J Cardiovasc Magn Reson. 2009;11:22.
11. Hoffmann R, Barletta G, von Bardeleben S et al. Analysis of left ventricular volumes and function: a multicenter comparison of cardiac magnetic resonance imaging, cine ventriculography, and unenhanced and contrast-enhanced two-dimensional and three-dimensional echocardiography. J Am Soc Echocardiogr 2014; 27(3):292–301.

12. Otterstad JE, Froeland G, St John Sutton M, Holme I. Accuracy and reproducibility of biplane two-dimensional echocardiographic measurements of left ventricular dimensions and function. Eur Heart J. 1997;18:507–513.
13. Steen H, Nasir K, Flynn E et al. Is magnetic resonance imaging the 'reference standard' for cardiac functional assessment? Factors influencing measurement of left ventricular mass and volumes. Clin Res Cardiol. 2007;96:743–751.
14. Jacobs LD, Salgo IS, Goonewardena S, et al Rapid online quantification of left ventricular volume from real-time three-dimensional echocardiographic data. Eur Heart J 2006;27:460–8.
15. Mor-Avi V, Jenkins C, Kuhl HP, et al. Real-time 3-dimensional echocardiographic quantification of left ventricular volumes: multicenter study for validation with magnetic resonance imaging and investigation of sources of error. J Am Coll Cardiol Img 2008;1:413–23.
16. Mor-Avi V, Yodwut C, Jenkins C, et al. Realtime 3D echocardiographic quantification of left atrial volume: multicenter study for validation with CMR. J Am Coll Cardiol Img 2012;5:769–77.
17. Solomon SD, Anavekar N, Skali H et al. Candesartan in Heart Failure Reduction in Mortality (CHARM) Investigators. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation. 2005;112(24):3738. Epub 2005 Dec 5.
18. Wong M, Staszewsky L, Latini R et al. Severity of left ventricular remodeling defines outcomes and response to therapy in heart failure: Valsartan heart failure trial (Val-HeFT) echocardiographic data. J Am Coll Cardiol. 2004;43(11):2022.
19. Xie GY, Berk MR, Smith MD, Gurley JC, DeMaria AN Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure. J Am Coll Cardiol. 1994;24(1):132.
20. de Groote P, Millaire A, Foucher-Hossein C et al. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. J Am Coll Cardiol. 1998;32(4):948.
21. Ghio S, Gavazzi A, Campana C et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol. 2001;37(1):183.
22. S, Recusani F, Klersy C, Sebastiani R et al. Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congestive heart failure secondar to idiopathic or ischemic dilated cardiomyopathy. Am J Cardiol. 2000;85:837–842.
23. Guazzi M, Bandera F, Pelissero G et al. Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: an index of right ventricular contractile function and prognosis. Am J Physiol Heart Circ Physiol. 2013;305:H1373–H1381.

24. Damy T, Viallet C, Lairez O et al. Comparison of four right ventricular systolic echocardiographic parameters to predict adverse outcomes in chronic heart failure. Eur J Heart Fail 2009; 11: 818 – 824.
25. Pozzoli M, Traversi E, Cioffi G, Stenner R, Sanarico M, Tavazzi L Loading manipulations improve the prognostic value of Doppler evaluation of mitral flow in patients with chronic heart failure. Circulation. 1997;95(5):1222.
26. Rossi A, Cicoira M, Zanolla L, et al. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. J Am Coll Cardiol. 2002;40(8):1425.
27. Löfman I, Szummer K, Dahlström U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. Eur J Heart Fail 2017 Mar 29.
28. Coles AH, Tisminetzky M, Yarzebski J, et al. Magnitude of and prognostic factors associated with 1-year mortality after hospital discharge for acute decompensated heart failure based on ejection fraction findings. J Am Heart Assoc 2015;4: e002303.
29. McDonagh TA, Metra M, Adamo M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC, European Heart Journal, Volume 42, Issue 36, 21 September 2021, Pages 3599–3726.
30. Dickstein K, Kjekshus J, Group OSCotOS. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet. 2002;360(9335):752-60.
31. Packer M, Fowler MB, Roecker EB et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation. 2002;106(17):2194-9.
32. Pfeffer MA, Swedberg K, Granger CB et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003;362(9386):759-66.
33. St John Sutton M, Pfeffer MA, Plappert T et al. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. Circulation. 1994;89(1):68-75.
34. Badano LP, Boccalini F, Muraru D et al. Current clinical applications of transthoracic three-dimensional echocardiography. J Cardiovasc Ultrasound. 2012;20(1):1-22.
35. Chukwu EO, Barasch E, Mihalatos DG et al. Relative importance of errors in left ventricular quantitation by two-dimensional echocardiography: insights from three-dimensional

echocardiography and cardiac magnetic resonance imaging. J Am Soc Echocardiogr. 2008;21(9):990-7.

36. Dorosz JL, Lezotte DC, Weitzenkamp DA, Allen LA, Salcedo EE. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. J Am Coll Cardiol. 2012;59(20):1799-808.
37. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429-35.
38. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325(5):293-302.
39. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70.
40. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70.
41. Jenkins C, Chan J, Hanekom L, Marwick TH. Accuracy and feasibility of online 3-dimensional echocardiography for measurement of left ventricular parameters. J Am Soc Echocardiogr. 2006;19(9):1119-28.
42. Wood PW, Choy JB, Nanda NC, Becher H. Left ventricular ejection fraction and volumes: it depends on the imaging method. Echocardiography. 2014;31(1):87-100.
43. Hien MD, Grossgasteiger M, Rauch H et al. Experts and beginners benefit from three-dimensional echocardiography: a multicenter study on the assessment of mitral valve prolapse. J Am Soc Echocardiogr. 2013;26(8):828-34.
44. Rigolli M, Anandabaskaran S, Christiansen JP, Whalley GA. Bias associated with left ventricular quantification by multimodality imaging: a systematic review and meta-analysis. Open Heart. 2016;3(1):e000388.
45. Rodríguez-Zanella H, Muraru D, Secco E, et al. Added Value of 3- Versus 2-Dimensional Echocardiography Left Ventricular Ejection Fraction to Predict Arrhythmic Risk in Patients With Left Ventricular Dysfunction. JACC Cardiovasc Imaging. 2019;12(10):1917-1926.
46. Nagueh SF, Smiseth OA, Appleton CP et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17(12):1321-60. Epub 20160715.

47. Smiseth OA, Morris DA, Cardim N et al. Multimodality imaging in patients with heart failure and preserved ejection fraction: an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2021. Epub 20211103.
48. Sabharwal N, Cemin R, Rajan K et al. Usefulness of left atrial volume as a predictor of mortality in patients with ischemic cardiomyopathy. Am J Cardiol. 2004;94(6):760-3.
49. Lim TK, Dwivedi G, Hayat S et al. Independent value of left atrial volume index for the prediction of mortality in patients with suspected heart failure referred from the community. Heart. 2009;95(14):1172-8. Epub 20090408.
50. Badano LP, Miglioranza MH, Mihaila S et al. Left Atrial Volumes and Function by Three-Dimensional Echocardiography: Reference Values, Accuracy, Reproducibility, and Comparison With Two-Dimensional Echocardiographic Measurements. Circ Cardiovasc Imaging. 2016;9(7).
51. Jenkins C, Bricknell K, Marwick TH. Use of real-time three-dimensional echocardiography to measure left atrial volume: comparison with other echocardiographic techniques. J Am Soc Echocardiogr. 2005;18(9):991-7.
52. Di Tullio MR, Sacco RL, Sciacca RR, et al. Left atrial size and the risk of ischemic stroke in an ethnically mixed population. Stroke 1999;30:2019-24.
53. Benjamin EJ, D'Agostino RB, Belanger AJ, et al. Left atrial size and the risk of stroke and death: the Framingham Heart Study. Circulation 1995;92:835-41.
54. Tsang TSM, Barnes ME, Gersh BJ, et al. Prediction of risk for first agerelated cardiovascular events in an elderly population: the incremental value of echocardiography. J Am Coll Cardiol 2003;42:1199-205
55. Osranek M, Bursi F, Bailey KR, et al. Left atrial volume predicts cardiovascular events in patients originally diagnosed with lone atrial fibrillation: three-decade follow-up. Eur Heart J 2005;26: 2556-61
56. Rossi A, Cicoira M, Zanolla L, et al. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. J Am Coll Cardiol 2002;40:1425-30.
57. Beinart R, Boyko V, Schwammenthal E, et al. Long-term prognostic significance of left atrial volume in acute myocardial infarction. J Am Coll Cardiol 2004;44:327-34.
58. Hugo Rodríguez-Zanella, Denisa Muraru, Eleonora Secco, Francesca Boccalini, Danila Azzolina, Patrizia Aruta, Elena Surkova, Davide Genovese, Giacomo Cavalli, Giuseppe Sammarco, Niccolò Ruozi, Rosaria M. Tenaglia, Oscar Calvillo-Argüelles, Chiara Palermo, Sabino Iliceto, Luigi P. Badano, Added Value of 3- Versus 2-Dimensional Echocardiography Left Ventricular Ejection Fraction to Predict Arrhythmic Risk in Patients With Left Ventricular Dysfunction, JACC: Cardiovascular Imaging, Volume 12, Issue 10, 2019, Pages 1917-1926.
59. Medvedofsky D, Maffessanti F, Weinert L, et al. 2D and 3D echocardiography-derived indices of left ventricular function and shape: relationship with mortality. J Am Coll Cardiol Img 2017.

60. Solomon SD, Anavekar N, Skali H, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA; Candesartan in Heart Failure Reduction in Mortality (CHARM) Investigators. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation. 2005 Dec 13;112(24):3738-44.
61. Wu VC, Takeuchi M, Kuwaki H et al. Prognostic value of LA volumes assessed by transthoracic 3D echocardiography: comparison with 2D echocardiography. JACC Cardiovasc Imaging. 2013 Oct;6(10):1025-1035.
62. Gavazzi A, Tavazzi L. Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congestive heart failure secondaryto idiopathic or ischemic dilated cardiomyopathy. Am J Cardiol. 2000;85:837–842.
63. Ghio S, Guazzi M, Scardovi AB et al. All Investigators. Different correlates but similar prognostic implications for right ventricular dysfunction in heart failure patients with reduced or preserved ejection fraction. Eur J Heart Fail. 2017;19:873–879.
64. Dini FL, Carluccio E, Simioniuc A et al. Network Labs Ultrasound (NEBULA) in Heart Failure Study Group. Right ventricular recovery during follow-up is associated with improved survival in patients with chronic heart failure with reduced ejection fraction. Eur J Heart Fail. 2016;18:1462–1471.
65. Damy T, Kallvikbacka-Bennett A, Goode K et al. Prevalence of, associations with, and prognostic value of tricuspid annular plane systolic excursion (TAPSE) among out-patients referred for the evaluation of heart failure. J Card Fail. 2012;18:216–225.
66. Muraru D, Onciul S, Peluso D et al. Sex- and method-specific reference values for right ventricular strain by 2-dimensional speckle-tracking echocardiography. Circ Cardiovasc Imaging. 2016;9:e003866.
67. Collier TJ, Pocock SJ, McMurray JJ et al. The impact of eplerenone at different levels of risk in patients with systolic heart failure and mild symptoms: insight from a novel risk score for prognosis derived from the EMPHASISHF trial. Eur Heart J. 2013;34:2823–2829.
68. Zornoff, L.A.M.; Skali, H.; Pfeffer, M.A.et al. Right Ventricular Dysfunction and Risk of Heart Failure and Mortality After Myocardial Infarction. J. Am. Coll. Cardiol. 2002, 39, 1450–1455.
69. Nagata Y, Wu VC, Kado Y et al. Prognostic Value of Right Ventricular Ejection Fraction Assessed by Transthoracic 3D Echocardiography. Circ Cardiovasc Imaging. 2017 Feb;10(2):e005384.
70. Mihăilă-Bâldea S, **Velcea AE**, Rimbaș RC et al. 3-D Echocardiography Is Feasible and More Reproducible than 2-D Echocardiography for In-Training Echocardiographers in Follow-up of Patients with Heart Failure with Reduced Ejection Fraction, Ultrasound in Medicine and Biology, Volume 47, Issue 3, 499 – 510.

71. **Velcea AE**, Mihăilă-Bâldea S, Nicula AI, Vinereanu D. The role of multimodality imaging in the selection of implantable cardioverter-defibrillators: a narrative review. J Clin Ultrasound, 2022, 50, 1066-1072.
72. **Velcea AE**, Mihăilă-Bâldea S., Vinereanu D. Three-dimensional echocardiography is a feasible and reproducible method for the measurement of left atrial volumes, regardless of expertise level, MAEDICA 2022;17(1):4-13.

Annex

List of published articles

Articole

- **Velcea AE**, Mihăilă-Bâldea S, Nicula AI, Vinereanu D. The role of multimodality imaging in the selection of implantable cardioverter-defibrillators: a narrative review. J Clin Ultrasound, 2022, 50, 1066-1072.
  https://onlinelibrary.wiley.com/doi/abs/10.1002/jcu.23281?mi=3ft2at&af=R&SeriesKey=10970096&content=articlesChapters&target=default
- **Velcea AE**, Mihăilă-Bâldea S., Vinereanu D. Three-dimensional Echocardiography is a Feasible and Reproducible Method for the Measurement of Left Atrial Volumes, Regardless of Expertise Level, Maedica. 2022;17(1):4-13.
  https://www.maedica.ro/articles/2022/1/2022_17(20)_No1_pg4-13.pdf
- Mihăilă-Bâldea S*, **Velcea AE***, Rimbaș RC et al. 3-D Echocardiography Is Feasible and More Reproducible than 2-D Echocardiography for In-Training Echocardiographers in Follow-up of Patients with Heart Failure with Reduced Ejection Fraction, Ultrasound in Medicine and Biology, Volume 47, Issue 3, 499 – 510.
  https://www.umbjournal.org/article/S0301-5629(20)30485-3/fulltext
  *Equal rights
- **Velcea AE**, Suran M, Vinereanu D. The Challenges of Tachycardia Induced Cardiomyopathy - a Case Report. Romanian Journal of Cardiology. 2021;31(2): 391-394.
  https://doi.org/10.47803/rjc.2021.31.2.391