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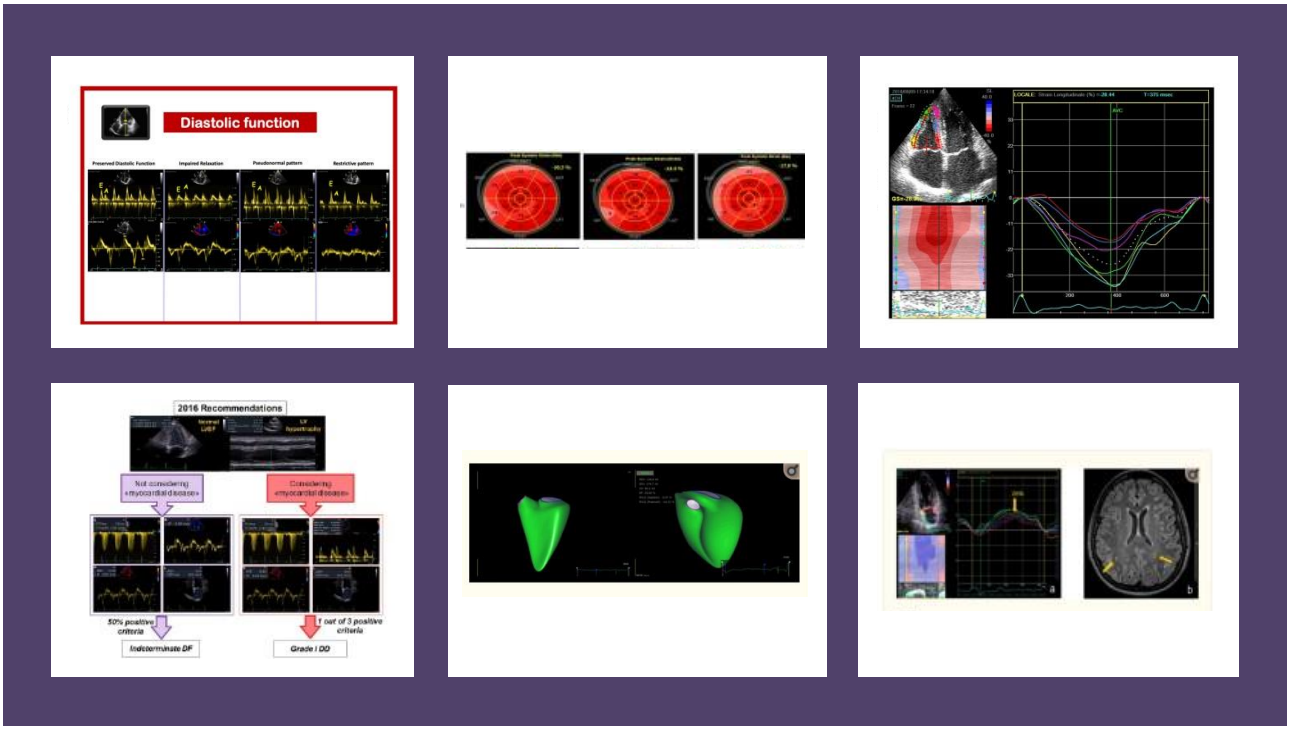

The incremental value of advanced echocardiography in the clinical setting

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“Life is an experimental journey undertaken involuntarily”

Fernando Pessoa

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CHAPTER 1

Introduction and outline of the thesis

Echocardiography is a non-invasive diagnostic technique which provides information regarding cardiac function and hemodynamics. Non-invasive imaging of the heart continues to evolve and improve. Cardiovascular ultrasound plays an important role in the diagnosis and assessment of responses to therapy of many cardiac conditions. Even as the clinical applications of newer techniques such as cardiac computed tomography and cardiac magnetic resonance (CMR) imaging increase, the role of echocardiography remains strong since it has unique capabilities. Features of ultrasound machines such as three dimensional (3D), two-dimensional (2D) and trans-esophageal echo, spectral and color Doppler imaging, strain imaging and even intra-cardiac imaging can be performed on devices that are increasingly portable. By virtue of its ability to simultaneously assess biventricular and valvular function and provide important hemodynamic information from Doppler flow measurements, and of its ease of use, safety, lack of radiation, low cost and portability, echocardiography has come to play a key role in diagnosis, management, therapy and follow up of cardiovascular diseases.

In the last decade, new, increasingly automated techniques for sophisticated analysis of cardiac mechanics have emerged to address the issue of reader's experience and inter-measurement variability in interpretation. Two of such techniques have dominated the research arena of echocardiography: (1) speckle tracking echocardiography (STE) (2) 3D echocardiography. Both types of measurements lend themselves to the derivation of multiple parameters of myocardial function.

STE-derived myocardial strain is a useful diagnostic measurement providing comprehensive information on myocardial mechanics and ventricular function. 2D strain is a measure of regional and global contractility that uses frame-by-frame tracking of unique speckles in the myocardium with an algorithm that allows tracking of the speckle location on sequential images using correlation criteria and sum of absolute differences. In addition to generating strain curves in individual segments, algorithms exist to average strain over the entire chamber, in order to derive global longitudinal strain (GLS). A significant advantage of 2D strain tracking methods is that they are not angle dependent within the acquired imaging plane, but proper alignment of image planes is still important. 2D strain has been applied and validated in the left ventricle (LV) and has recently been studied to also assess right ventricular (RV) function [1, 2]. In particular, GLS has shown the best ability in detecting subclinical cardiac involvement. LV GLS was found to have incremental prognostic value over routinely assessed parameters, such as ejection fraction (EF), in the context of the detection of inducible ischemia [3] and of heart failure (HF) with preserved EF [4] and chemotherapy-induced cardiotoxicity [5], among other indications. Recent studies demonstrated the value of RV strain in diseases such as HF [6, 7], pulmonary artery hypertension (PAH) [8], and amyloidosis [9] and to predict RV failure after LV assist device implantation [10]. RV strain was found to have independent additional prognostic value when compared to LV strain alone [11].

Non-invasive myocardial work (MW) quantification has emerged in the last years as an alternative tool for myocardial function assessment. One of its' major strengths is the ability to overcome GLS and LV EF limitations such as load-dependency and provide a loading-independent evaluation of myocardial performance[12]. This method is based on systolic blood pressure and GLS during systole and isovolumic relaxation, integrates information on LV active systolic and diastolic work and represents a non-invasive method for assessing regional myocardial work by LV pressure–strain

loop analysis[13]. Age-adjusted reference values for myocardial work indices, applicable for either sex have been derived from a large sample of apparently healthy individuals from a population based-cohort[14]. MW allows an in-depth evaluation of myocardial systolic performance across a broad range of physiologic and pathologic conditions beyond traditional echocardiographic techniques. Validation studies have demonstrated that the non-invasive estimation of MW indices obtained from LV pressure-strain loop strongly correlates with invasive measurement of stroke work and with cardiac metabolism. This has allowed a broad application of MW measurement in several clinical settings.

One of the most significant developments of the last decade in ultrasound imaging of the heart was the evolution of 3D imaging from slow and labor-intense offline reconstruction to real-time volumetric imaging. This imaging modality provides valuable clinical information that empowers echocardiographers with new levels of confidence in the diagnosis of heart disease. The introduction of new matrix transducers, as well as advances in image acquisition and analysis have increased the use of real-time 3D (RT3D) echocardiography in the clinical setting. RT3D echocardiography has clearly demonstrated the ability in improving the accuracy of evaluation of cardiac chamber volumes by eliminating the need for geometric modeling and the errors caused by foreshortened apical views [15, 16]. As a result, more and improved imaging modalities are available for evaluating cardiac anatomy, ventricular function, blood flow velocity, and valvular diseases.

The goal of this thesis is to focus on the currently available techniques that allow quantitative and qualitative assessment of myocardial function via image-based analysis of local myocardial dynamics, including STE and 3D echocardiography. This document describes the current and potential clinical applications of these techniques and their strengths and weaknesses, while

highlighting normal and abnormal findings in the context of different cardiovascular pathologies (Table 1).

Outline of the thesis: The thesis is divided in five parts:

PART I: The evaluation of left ventricular function: from diastolic dysfunction to heart failure

Dyspnoea is a presenting symptom for patients with "systolic" and "diastolic" HF. It is often due to elevated LV filling pressure (LVFP), but can be due to pulmonary disease or other non-cardiac reasons. While physical examination is useful, it has its limitations. Accordingly, non-invasive imaging has an important role in the diagnostic evaluation of patients with known or suspected HF. Echocardiography is usually the first test obtained and is used to determine LV volumes, LVEF, and mass as well as right ventricular size and function, left and right atrial volumes, valvular lesions, and pulmonary artery pressures. Additionally, LV diastolic function (DF) can be estimated. LV diastolic dysfunction (DD) and, by extension, impaired LVFP are among the main determinants of decompensation, symptoms and prognosis in patients with HF [17]. Accordingly, echo-Doppler evaluation of LV DF is of pivotal importance for a comprehensive clinical assessment and therapeutic management of patients and has widely shown its prognostic value in the clinical setting [18, 19, 20, 21, 22]. Moreover, integrated echo-Doppler estimates of LVFP have been tested and validated against simultaneous invasive measurements of LVFP (i.e. heart catheterization). In this section on the thesis, we focus on the currently available tools for the echocardiographic evaluation of DD (Chapter 2) and advanced HF (Chapter 3).

PART II: Echocardiography in Anderson-Fabry Disease: the incremental value of Speckle Tracking Imaging

This section of the thesis focuses on Anderson-Fabry disease (AFD). AFD is a rare X-linked metabolic disorder due to deficiency in lysosomal enzyme activity of a-galactosidase A (a-GAL),

resulting in pathological accumulation of glycosphingolipids in several tissues and a multi-organ progressive dysfunction [23]. AFD cardiomyopathy has been described in both genders, in a specific late-onset cardiac variant, and is largely associated with left ventricular hypertrophy (LVH), impaired diastolic function, and late systolic dysfunction [24]. LVH is due to glycosphingolipids myocyte accumulation in early phases and to myocardial replacement fibrosis in the late disease stages. Enzyme replacement therapy demonstrated to be effective in reducing the accumulation of glycosphingolipids in the different tissues, with clear benefit on cardiac function when started promptly [25]. Therefore, early diagnosis and treatment of cardiac involvement in patients and in affected family members is a crucial aspect of AFD management. Speckle-tracking echocardiography is an advanced ultrasound technique, which provides comprehensive information on myocardial mechanics, in particular GLS has shown the best ability in detecting subclinical cardiac involvement. Different studies using 2D speckle tracking echocardiography demonstrated an alteration of myocardial deformation components such as longitudinal and circumferential strain in AFD patients [26, 27, 28]. An early reduction of GLS has been clearly demonstrated in this clinical setting. GLS has also been used to differentiate AFD from other types of LVH [29].

In this part of the thesis, we evaluate the incremental value of STE in treatment-naive AFD patients. We investigate specific regional patterns of LS, base-to-apex behavior of longitudinal deformation (Chapter 4) and layer specific longitudinal deformation (Chapter 5). Moreover, we evaluate the association between left atrial (LA) deformation (i.e. LA strain) and brain involvement in patients with Anderson-Fabry disease at diagnosis (Chapter 6). Finally, we provide an overview of the value and perspectives of standard and advanced cardiovascular imaging in AFD (Chapter 8).

PART III: The Right Ventricle: insights from the "forgotten chamber"

The RV has previously been viewed as less important than the left. This misconception has been perpetuated, in part, because common cardiac diseases affect the LV more often than the right and in part because of the difficulties associated with imaging the RV in a noninvasive fashion, particularly with echocardiography. There is a growing body of evidence, however, which emphasizes the importance of a properly functioning right heart in the maintenance of normal overall hemodynamics. The significant impact of RV performance on patients' clinical status and outcome has been progressively realized over the past decades, however, leading to increased efforts in developing techniques that can reliably evaluate this chamber.

Difficulties for the echocardiographic imaging of the right ventricle include: complex shape, which limits the application of geometric models for volume-function quantification, retrosternal position, which creates an acoustic barrier for ultrasound waves, distinct embryologic origin and hemodynamic environment (high-volume, low-pressure system) that significantly differs from the LV and is associated with thinner walls and prominent trabeculations, which are more difficult to characterize [30].

Echocardiography remains the mainstay of RV imaging in clinical practice with methods such as fractional area shortening, tricuspid annular plane systolic motion and Doppler tissue imaging of the tricuspid annulus. Emerging echocardiographic techniques include speckle tracking of the RV and 3D ultrasound, which offers potential advantages for absolute quantification of RV volumes. RV Strain is a useful parameter for estimating RV global and regional systolic function. RV GLS is calculated as the percentage of systolic shortening of the RV free wall from base to apex. The term RV GLS usually refers to either the average of the RV free wall and the septal segments or the RV free wall segments alone. Peak global longitudinal RV strain excluding the interventricular

septum has been recently reported to have prognostic value in various disease states, such as HF [31, 32], PAH [33], and amyloidosis [34] and to predict RV failure after LV assist device implantation [35].

RV RT3DE overcomes the complex geometry problems, thus enabling a complete and comprehensive assessment of RV chambers internal volume and the determination of RV EF. Direct visualization of the entire RV with 3D echocardiography is possible using the full-volume mode acquisition. This capability is particularly attractive for the RV, as it has the potential advantage to measure cardiac chambers without geometric assumptions. In addition, multiplane reconstruction analysis allows accurate evaluation of segmental RV geometry and function. RT3DE techniques [36, 37] have been validated for RV volume quantification, and may provide important mechanistic and prognostic value in various clinical scenarios, such as congenital heart disease [38, 39] or functional tricuspid regurgitation [40]. Moreover, several studies have shown that it is a feasible and accurate method to assess global and regional RV function in healthy volunteers and patients with PAH [41, 42].

The quantification of RV geometry and function by 3DE is reproducible and accurate even when compared with CMR [43, 44], which still represents the gold standard for RV evaluation [45]. Further advancement of 3D STE now allows also the assessment of RV regional and global longitudinal deformation, which has a predominant role in RV contraction processes because of the longitudinal arrangement of RV myocardial fibers.

In this part of the thesis, we report the cluster of research projects that focus on the importance of the advanced imaging techniques applied to the right ventricle in different clinical scenarios such as Fibrotic Interstitial Lung Diseases (Chapter 8), patients with Systemic Lupus Erythematosus

(Chapter 9), patients undergoing pericardiectomy during cardiac surgery (Chapter 10), and patients with Cor Pulmonale (Chapter 11).

PART IV: Cardiotoxicity: the incremental value of Speckle Tracking Imaging

Advances in treatment have led to improved survival of patients with cancer, but have also increased morbidity and mortality due to treatment side effects [46, 47]. Cardiovascular diseases (CVDs) are one of the most frequent of these side effects [48]. Myocardial dysfunction and HF, frequently described as cardiotoxicity, are the most concerning cardiovascular complications of cancer therapies and cause an increase in morbidity and mortality among cancer survivors. A collaborative effort among specialists involved in the treatment of patients with cancer is critical to prevent and manage cardiotoxicity while not compromising cancer care, to maximize the patient's overall outcome. A correct and timely recognition of cardiotoxicity is pivotal to avoid both the failure to prevent adverse events and the inappropriate interruption of a potentially lifesaving cancer treatment. However, the prediction of long-term cardiovascular prognosis is frequently challenging because patients with cancer typically receive multiple cancer drugs and sometimes radiation, with the potential for cardiotoxic effects from interactions among the different therapeutic modalities [49].

Cancer therapy-related cardiac dysfunction (CTRCD) can be due to different kinds of treatment. Anthracyclines provoke a dose-cumulative myocardial damage with irreversible cellular necrosis (Type I cardiotoxicity). Doxorubicin is associated with a 5% incidence of congestive HF when a cumulative lifetime dose of 400 mg/m2 is reached, and higher doses lead to an exponential increase in risk, up to 48% at 700 mg/m2 [50]. The cardiotoxicity of anthracyclines may be acute, early or late. Early effects occur within the first year of treatment, while late effects manifest themselves after several years (median of 7 years after treatment). Anthracycline-induced cardiotoxicity is most likely a phenomenon characterized by continuous progressive decline in

LVEF. Many affected patients may initially be asymptomatic, with clinical manifestations appearing years later, often in the context of other triggering factors, which may indicate that anthracyclines negatively affect compensatory mechanisms [51]. Other conventional chemotherapies that can induce myocardial dysfunction and HF are cyclophosphamide, cisplatin, ifosfamide and taxanes (paclitaxel and docetaxel). More recently, immunotherapies and targeted therapies have led to substantial improvement in the efficacy of cancer drugs. Inhibition of human epidermal growth factor receptor 2 (HER2) signalling with either antibodies [trastuzumab, pertuzumab, trastuzumab-emtansine (T-DM1)] or TKIs (lapatinib) have improved outcomes of patients with HER2-positive breast cancer when used in conjunction with chemotherapies [52]. Concomitant or previous use of anthracyclines substantially increases the cardiotoxicity of trastuzumab. In a retrospective observational study based on the International Classification of Diseases codes (without access to LVEF data), the cumulative incidence of the composite of cardiac dysfunction or HF in patients treated with anthracyclines and trastuzumab was 6.2% and 20.1% after 1 and 5 years, respectively [53]. Conversely to anthracyclines-induced cardiotoxicity, trastuzumab-induced LV dysfunction and HF are usually reversible with trastuzumab interruption and/or treatment with HF therapies [54]

In this clinical setting, screening, risk stratification and early detection strategies are necessary. The first step to identify patients at increased risk for cardiotoxicity consists of a careful baseline assessment of cardiovascular risk factors. It is critical to detect subclinical cardiac abnormalities, which may influence clinical decisions regarding the choice of chemotherapy, indication for cardioprotection or increased surveillance frequency (e.g. asymptomatic LV dysfunction). Strategies for screening, detection and follow-up of cardiotoxicity include cardiac imaging (echocardiography, nuclear imaging, CMR) and biomarkers (troponin, natriuretic peptides)[55].

Echocardiography is the method of choice for the detection of myocardial dysfunction before, during and after cancer therapy [56, 57]. Unless 3D echocardiography is used, which is the best echocardiographic method for measuring LVEF when endocardial definition is clear, the 2D biplane Simpson method is recommended for estimation of LV volumes and ejection fraction in these patients. CTRCD is defined as a decrease in the LVEF of >10 percentage points, to a value below the lower limit of normal [58]. Several recent studies have shown the value of deformation imaging for early detection of LV dysfunction secondary to cancer therapy [59]. GLS has been reported to accurately predict a subsequent decrease in LVEF [60,61]. A relative percentage reduction of GLS of >15% from baseline is considered abnormal and a marker of early LV subclinical dysfunction. In case of CTRCD, timely initiation of cardioprotective treatment for CTRCD is pivotal to continue the ongoing CT till completion and reduce the risk of overt HF. Several studies have demonstrated an improvement in early detection of LVEF decrease when troponins and speckle tracking echocardiography are used every 3 months during adjuvant trastuzumab treatment.

Cancer medications may produce nonvalvular AF through various mechanisms. The most common factors include release of proinflammatory substances (cytokines), calcium homeostasis alterations, and direct damage on the myocardium [62]. Anthracyclines reduce the antioxidant effect on cardiomyocytes [63, 64] and increase vagal and adrenergic tones, because of hypotension, myocardial ischemia, and electrolyte abnormalities. These mechanisms are also induced by alkylating agents, gemcitabine, 5-fluorouracil, antimetabolites, docetaxel, rituximab, paclitaxel, and alemtuzumab. Nonvalvular AF in cancer patients needs a multidisciplinary approach. First, it is mandatory to identify patients more prone to AF development, such as those affected by arterial hypertension, diabetes, or coronary artery disease. Patients at elevated risk for AF should be treated by cancer drugs which are known to be less aggressive and poorly associated with AF.

When AF occurs during cancer therapy, the decision whether to continue, adjust the dosage, or withdraw cancer medications is fundamental. Particular attention will be taken to achieve an optimal control of heart rate and to restore normal sinus rhythm with antiarrhythmic drugs, mainly amiodarone. This evaluation is particularly important to graduate anticoagulation and to prevent and manage symptoms/signs of HF. Patients with larger left atrium and more impaired LA function should be addressed toward a less aggressive cancer treatment, with drugs which are not associated or are poorly related with the risk of AF development. A correct and comprehensive echocardiographic assessment could even induce the oncologist to change the cancer management balancing the oncologic and the cardiac risk, taking well into account that the thrombotic and the bleeding complications exert an equal burden in this delicate clinical setting.

This section of the thesis is a collection of our research projects aimed at investigate the role of standard and advanced Echocardiography (Speckle tracking Imaging) in Cancer therapeutics–related cardiac dysfunction (CTRCD). In particular, we will focus on LV systolic dysfunction (Chapter 12) and atrial fibrillation (AF) (Chapter 13).

Part V: Conclusions

PART I: The evaluation of left ventricular function: from diastolic dysfunction to heart failure

CHAPTER 2

Practical Impact of New Diastolic Recommendations on Noninvasive Estimation of Left Ventricular Diastolic Function and Filling Pressures.

In 2016, the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) released an updated version [65] of the recommendations for the evaluation of LV DF and the estimation of LVFP by Doppler echocardiography, previously published in 2009 [66]. The updated recommendations promote a practical approach for DD diagnosis and LVFP estimation, pointing out the most useful, reproducible, and feasible 2D echocardiographic and Doppler measurements with the goal of increasing their utility in daily clinical practice. New recommendations suggest a two-step process. The first work flow, to be applied in patients with normal LV ejection fractions (LVEF>53%), allows echocardiographic diagnosis of DD. The second work flow is indicated for the estimation of LVFP and DD grading in patients with DD, in those with reduced LVEFs (<53%), and in those with normal LVEFs and significant ‘‘myocardial disease’’ (e.g., presence of LV hypertrophy [LVH], ischemic or significant valvular heart disease). Almeida et al. [67] retrospectively evaluated the impact of the 2016 recommendations in comparison with the 2009 version in a large population of patients with normal LVEFs, showing poor concordance and a significantly lower rate of DD when applying the 2016 recommendations. However, the 2016 recommendations were applied incorrectly, as they did not assimilate patients with myocardial disease to those with DD.

Aim: In this study we prospectively evaluated the concordance of the ASE/EACVI 2009 and 2016 recommendations in the diagnosis of DD and in the estimation of LVFP in consecutive patients, with normal and reduced LVEF, referred to our echocardiographic laboratory.

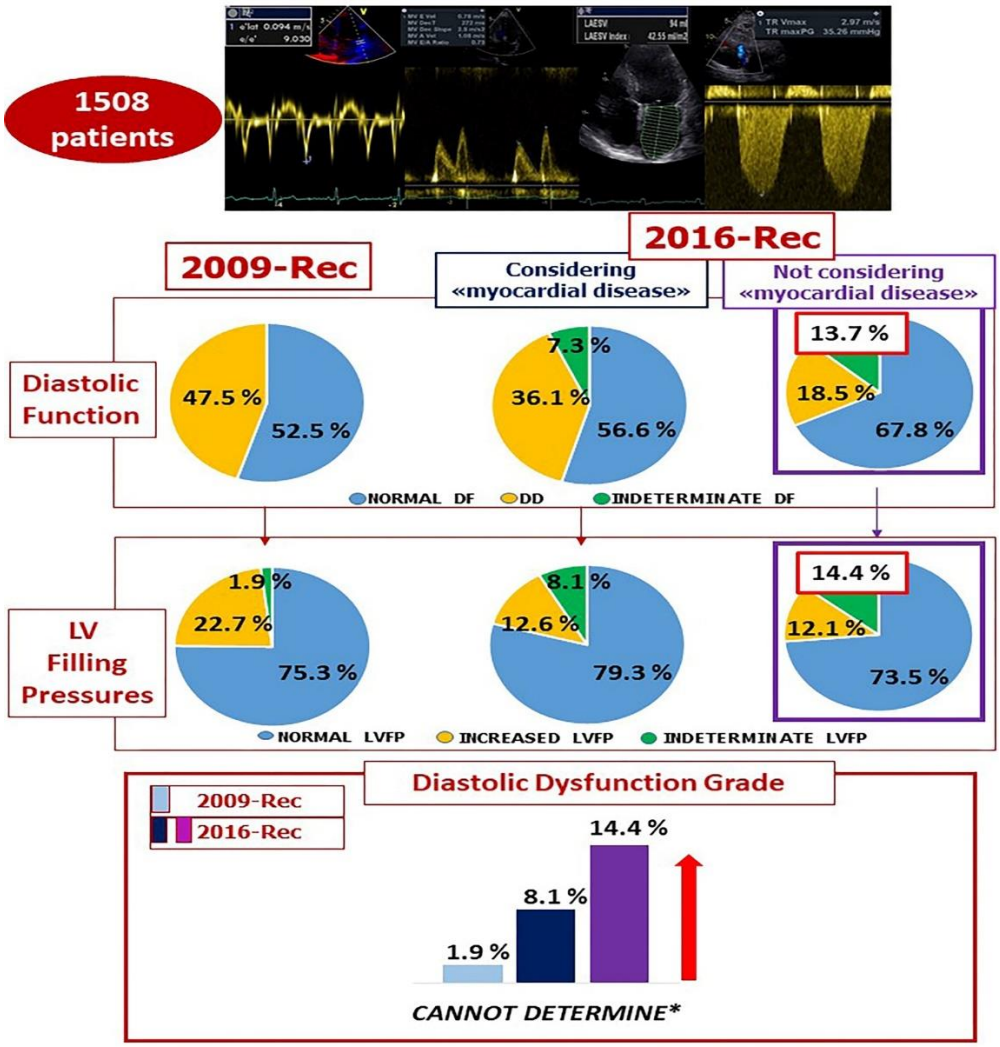


Figure 1. Application of the first step workflow of 2016 recommendations to all patients with normal LVEF, considering or not considering the presence of "myocardial disease".
Comparison of the estimates of DD and LVFP between the correct application of 2016 recommendations, i.e., considering myocardial disease (left) versus 2016 recommendations applying the first step workflow to all patients with normal LVEF (right, purple boxes). Not considering "myocardial disease" in the decision tree results in a significantly higher prevalence of patients with inconclusive diagnosis.
Red arrows = statistically significant difference of inconclusive diagnosis. DD = Diastolic dysfunction, DF = Diastolic function, LVFP = LV filling pressure.

Methods: We prospectively enrolled 1508 outpatients referred to our echo lab in a pre-defined 5 months period. All patients underwent targeted clinical history and echo-Doppler exam. We assessed DD and LVFP according to 2009 and 2016 recommendations (Figure 1). Concordance was calculated by kappa coefficient (K) and overall proportion of agreement. Moreover, we tested the impact of “myocardial disease” on the prevalence and grading of DD according to the 2016 recommendations.

Results: Overall proportion of agreement between the two recommendations was 64.7 %, K=0.43. Comparing 2009 and 2016recommendations, 47.5% versus 36.1% patients respectively had DD ($p<0.0001$) and 22.7% vs. 12.6% had elevated LVFP ($p<0.0001$). This difference remained significant in the setting of patients with normal LV ejection fraction (LVEF) (21.6 vs 10.7%, $p<0.0001$). In the application of 2016 recommendations, considering or not the presence of “myocardial disease”, prevalence of indeterminant DF was respectively 7.3% versus 13.7%, while patients with "cannot determine" DD grade were 8.1% versus 14.4% (all $p<0.0001$).

Discussion: The application of the novel recommendations highlighted: (I) a lower prevalence of DD and increased LVFP in the overall population, at the expense of a higher prevalence of inconclusive diagnosis of DF and of DD grade, compared with the 2009 recommendations, (II) a moderate overall concordance between the two recommendations for DD estimation, and most importantly (III) the impact of considering the presence of “myocardial disease” in the setting of patients with normal LVEF, when applying the 2016 recommendations. A key point of the novel recommendations is related to the application of the concept of “myocardial disease”. We assigned “myocardial disease” when structural heart disease (i.e., LVH, and significant valvular heart disease) and/or CAD (i.e. in presence of regional wall motion abnormalities) were present. To the best of our knowledge, the present study is the first head-to-head comparison of the two recommendations assimilating patients with normal LVEF and evidence of “myocardial disease” to patients with reduced LVEF, as

recommended by the 2016 version. The assumption of the presence of "myocardial disease" resulted in a lower rate of inconclusive diagnoses ("indeterminate" DF as well as “cannot determine” DD grade). (Figure 2).

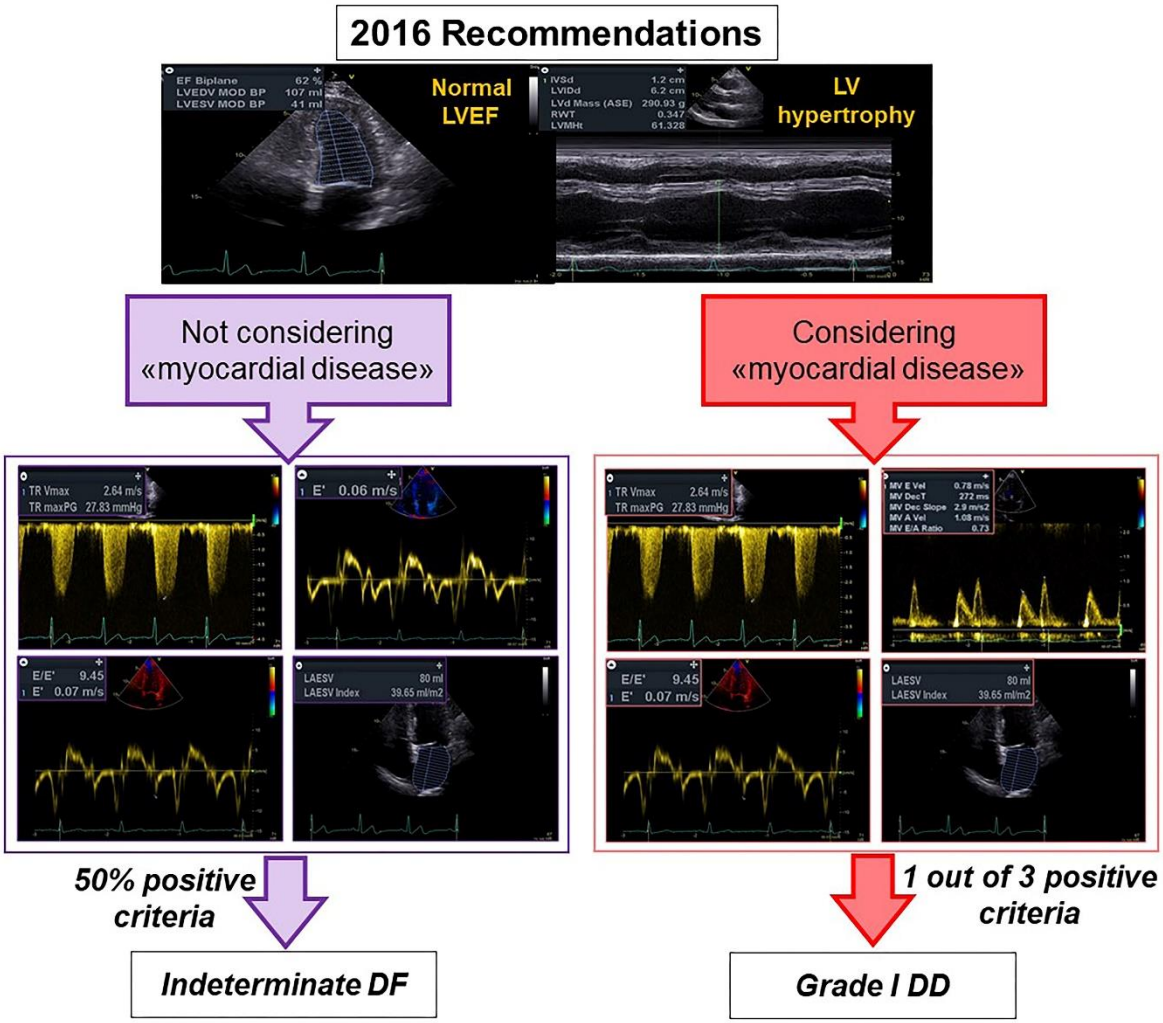


Figure 2. **Sample of the impact of «myocardial disease» evaluation in the estimate of DF according to 2016 recommendations in a patient with normal LVEF.** DF estimate without (purple box, right panel) and with (red box, left panel) the consideration of “myocardial disease” (LVH) in a patient with normal LVEF. The consideration of LV hypertrophy, as a marker of «myocardial disease», changes the diagnosis of DF from assignment of "indeterminate" DF to Grade I DD.
DD= diastolic dysfunction, DF diastolic function, LVEF = left ventricular filling pressures, LVH= left ventricular hypertrophy.

The current study confirms the previously observed lower prevalence of DD and increased LVFP and higher rate of inconclusive diagnoses assessed with the 2016 recommendations, compared to the 2009 version. Moreover, it represents the first comparison of the two recommendations

assimilating patients with normal LVEF and evidence of "myocardial disease" to patients with reduced LVEF, as recommended by the 2016 update. When applying the 2016 recommendations, the incorporation of "myocardial disease" provided higher prevalence of DD and lower prevalence of inconclusive diagnosis.

This work highlights the critical role of the physician in the application of the DF recommendations, as they should be based on a general and comprehensive echocardiographic assessment combining the available echocardiographic data with patients' clinical information. Nevertheless, the higher prevalence of patients in whom DD diagnosis is not achievable does not necessarily represent a limitation but, in the presence of overt symptoms and reasonable clinical suspicion, should be a starting point for further diagnostic testing, such as stress echocardiography advanced echocardiographic technologies (left atrial strain), or even cardiac catheterization.

Highlights:

- Concordance between 2009 and 2016 diastolic function recommendations was assessed in outpatients referred for echocardiograms
- The use of the 2016 recommendations results in a lower rate of diastolic dysfunction diagnosis
- Less patients are diagnosed with increased left ventricular filling pressures
- The introduction of tricuspid regurgitation velocity seems to a be decisive parameter
- Considering patients' myocardial disease reduces the rate of indeterminant conclusions

CHAPTER 3

Basic and advanced echocardiography in advanced heart failure: an overview

The present review presents an overview of the currently available tools for the echocardiographic examination of patients with ACHF, with its advantages and limitations, based on the latest

supporting evidences. Advanced chronic HF (ACHF) represents the final stage in the progression of HF [68]. It is characterized by the onset of symptoms at rest and is refractory to conventional medical therapy, corresponding to a New York Heart Association (NYHA) class IV—American Heart Association (AHA) stage D.

Table 1. Clinical, hemodynamic, biochemical, and functional criteria used to recognize ACHF, according to the new position statement of the Heart Failure Association of the European Society of Cardiology (ESC).

Table 1 Updated HFA-ESC criteria for defining advanced heart failure. All these criteria must be present despite optimal guideline-directed treatment [3]

1. Severe and persistent symptoms of heart failure (NYHA class III (advanced) or IV).
2. Severe cardiac dysfunction defined by: a reduced LVEF ≤ 30%, isolated RV failure (e.g., ARVC) or non-operable severe valvular or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF.
3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing > 1 unplanned visit or hospitalization in the last 12 months.
4. Severe impairment of exercise capacity showed by inability to exercise or low 6MWTD (< 300 m) or pVO2 (< 12–14 mL/kg/min), estimated to be of cardiac origin.

ARVC arrhythmogenic right ventricular cardiomyopathy, *BNP* B-type natriuretic peptide, *ESC* European Society of Cardiology, *HFA* Heart Failure Association, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *NT-proBNP* N-terminal pro-BNP, *NYHA* New York Heart Association, *pVO2* peak exercise oxygen consumption, *RV* right ventricular, *6MWTD* 6-min walk test distance

Echocardiography is a first-line diagnostic and prognostic technique in every stage of HF; moreover, the recent technological advances provide new structural and functional indices of the four cardiac chambers that showed to be comparable to advanced imaging or invasive hemodynamic parameters (Figure 1). This allows us to operate an accurate study of ACHF with first- and second-level echocardiographic techniques, which are now being integrated in daily clinical practice. Moreover, echocardiography gains particular importance in the clinical and therapeutical approach to subjects with ACHF due to the importance of sensitive indexes to predict prognosis for the treatment of these fragile patients. The development of even more accurate tools in the assessment of cardiac structure and function has helped to reach a complete approach for these patients to

obtain a feasible and complete hemodynamic and functional classification of the disease. The present review presents an overview of the currently available tools for the echocardiographic examination of patients with ACHF both in the acute and chronic care setting, with its advantages and limitations, based on the latest supporting evidence. We discuss several basic and advanced echocardiographic indices, clarifying the advantages and disadvantages of their use in ACHF, which would lead a more optimized and judicious use of this important imaging modality.

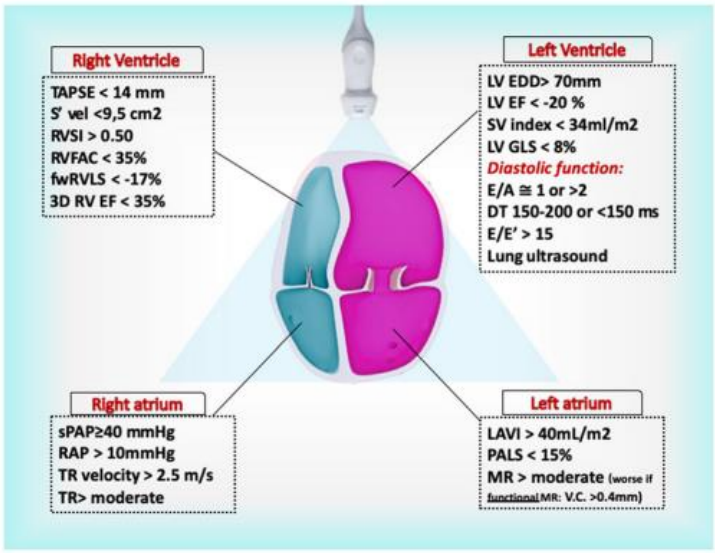


Figure 1. Echocardiographic markers for a comprehensive analysis of the 4 cardiac chambers in advanced chronic heart failure (ACHF) patients. 3D RV EF, three-dimensional right ventricular ejection fraction; DT, deceleration time; E/A, peak early diastolic E^ wave/peak late diastolic A^ wave; E/E', peak early diastolic E^ wave/medium velocity of early mitral annular in the three points of mitral annulus descent; fwRVLS, free wall right ventricular longitudinal strain; LAVI, left atrial volume index; LV EDD, left ventricular end diastolic diameter; LV EF, left ventricular ejection fraction; LV GLS; left ventricular global longitudinal strain; MR; mitral regurgitation; PALS, peak atrial longitudinal strain; RAP, right atrial pressure; RVFAC, right ventricular fractional area change; RVSI, right ventricular sphericity index; s' vel, peak systolic tricuspid annular velocity; sPAP, systolic pulmonary artery pressure; SV index, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Among the advanced echocardiographic techniques, GLS was recently defined as the most robust deformation marker of alteration in myocardial mechanics with or without LV dilation [69].

GLS reduction reflects the gradual development of LV dysfunction since the first stages; therefore, it is useful as an early diagnostic and prognostic marker in HF [70]. In patients with HF with reduced EF, GLS was an index of myocardial fibrosis [71] and an independent predictor of all-cause mortality, superior to other echocardiographic parameters, particularly in male subjects and in sinus rhythm [72], and of major adverse cardiac events both in HF with preserved EF and HF with reduced EF patients [73], which provides an additive prognostic value to EF [74].

PART II: Echocardiography in Anderson-Fabry Disease: the incremental value of Speckle Tracking Imaging

CHAPTER 4

Prominent longitudinal strain reduction of left ventricular basal segments in treatment-naive Anderson-Fabry disease patients

The regional distribution of longitudinal strain (LS) has shown typical patterns in different types of LVH [75], mainly in cardiac amyloidosis, which is characterized by a typical LS reduction in basal LV segments, with a relative apical sparing [76,77]. A reduction of GLS has also been associated with myocardial fibrosis as identified by native T1 mapping in early AFD [78], but little is known about the regional LS distribution in the subclinical stages of AFD cardiomyopathy.

Aim: The present study was designed to investigate specific regional patterns of LS and base-to-apex behavior of longitudinal deformation in treatment-naive AFD patients.

Methods and results: Twenty-three consecutive AFD patients at diagnosis and 23 healthy controls without cardiovascular risk factors and matched for age and sex to the patients, underwent a comprehensive evaluation of target organs. An echoDoppler exam, including determination of regional and global LS strain (GLS) was obtained. The average LS of 6 basal (BLS), 6 middle (MLS), and 5 apical (ALS) segments and relative regional strain ratio [ALS/(BLS þ MLS)] were also calculated. Ejection fraction and diastolic indices did not differ between the two groups. LV mass index was greater in AFD ($P < 0.01$). GLS ($P = 0.006$), BLS ($P < 0.0001$), and MLS ($P = 0.003$), but not ALS, were lower in AFD patients and relative regional strain ratio was higher in AFD ($P < 0.01$) than in controls. These analyses were confirmed separately in the two genders and even after excluding

patients with wall hypertrophy. By subdividing AFD patients according to lysoGB3 levels, 9 patients with lysoGB3 >_ 1.8 ng/L had lower ALS compared to 11 patients with lysoGB3 < 1.8 ng/L (P < 0.01).

Discussion: The present study demonstrates that (i) naive AFD patients at diagnosis present a mild but significant reduction of GLS in comparison with healthy controls; (ii) polar maps of regional LS allow to differentiate one normal/near normal regional pattern and three distinct pathological patterns, in which LV basal segments are always more compromised than middle and apical segments (Figure 1); (iii) the relative regional strain ratio is higher in AFD than in healthy controls; and (iv) higher lysoGB3 levels are associated with lower, despite normal, ALS values in AFD patients. In naive AFD patients, we observed an early reduction of LV LS, involving mainly LV basal myocardial segments.

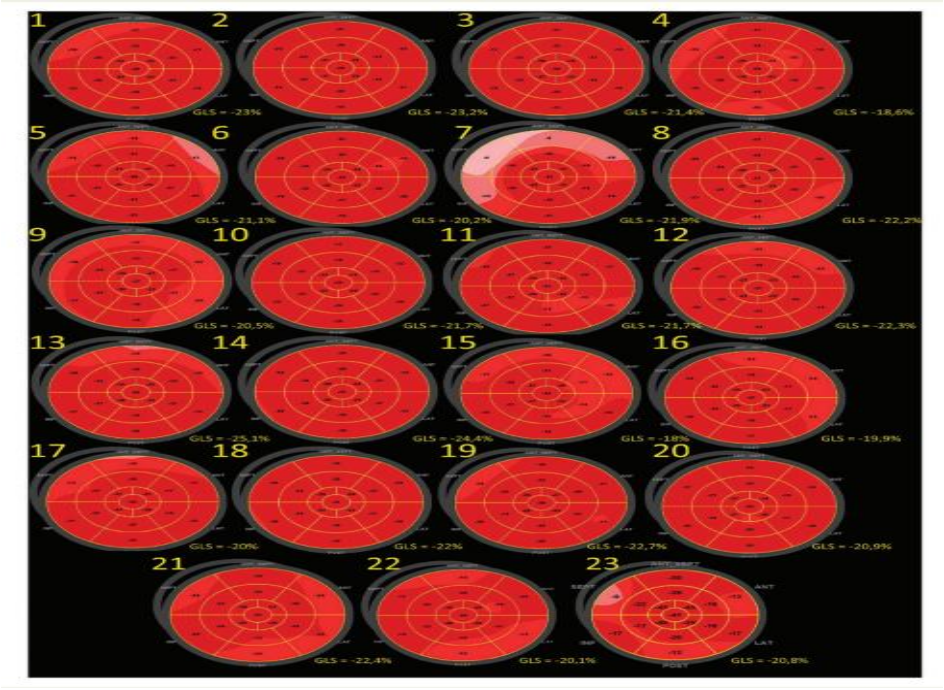


Figure 1. Polar maps (bull's eyes) of regional longitudinal strain (LS) in individual AFD patients. Four distinct patterns are recognizable: (1) normal or near normal regional LS (Patients n 2, 3, 6, 10, 14, 18, and 20); (2) LS reduction in septal and anterior regions (Patients n 1, 5, 7, 12, 13, 17 and 19); (3) LS reduction in both septal/anterior and infero-lateral regions (Patients n 4, 9, 15, 16, 21, 22 and 23); (4) LS reduction in infero-lateral region (Patients n 8 and 11). Independent of the

involved region, LS of basal segments appears to be more impaired in the majority of patients with abnormal LS patterns.

Our study highlights, in naıve AFD patients enrolled in a single centre, an early myocardial involvement assessed by using speckle-tracking echocardiography. The prominent dysfunction of LS at LV base, evident at diagnosis and even in patients without clear-cut wall hypertrophy, deserves physiopathologic hypotheses about its effects on LV performance, possibly identifying AFD patients who are more prone to heart failure development. LV base longitudinal motion is the main determinant of LV systolic function, accounting for about 60% of the stroke volume in normal as in supranormal and diseased hearts. Nevetherless, the association found between the higher levels of lysoGB3 and LS of the apical cap demonstrates that apical segments are not completely spared, even at initial disease stages. Follow-up studies of AFD population will be useful to understand if the progression of regional LS pattern, from the prominent LV base involvement to the compromise of other LV segments, could have prognostic implications and if ERT could blunt or even revert the progression of myocardial involvement in this clinical setting.

CHAPTER 5

Prominent longitudinal strain reduction of left ventricular basal segments in treatment-naive Anderson-Fabry disease patients

Recent advancements in speckle tracking technology make now available the analysis of layer-specific myocardial deformation, allowing focused longitudinal strain measurements at subendocardial and subepicardial level (LSsubendo and LSsubepi, respectively). The usefulness of multilayer strain has been proven in different diseases, including HF, arterial hypertension, chronic

ischemic disease, and acute coronary syndrome [79,80]. Normal reference values of multilayer strain have been generated in our echo laboratory [81]. The use of multilayer strain might provide interesting information also in AFD. Although longitudinal strain has been found to be a functional expression of myocardial fibrosis in this pathology [82], no information is available about the transmural distribution of longitudinal strain reduction, while fibrosis seems to involve midwall myocardial layer, sparing the subendocardium [83, 84, 85]. It could be noteworthy to analyze the layer-specific strain distribution in the early disease stages, when other factors than myocardial fibrosis, such as Gb3 accumulation itself and related inflammation, could interact disproportionately on different myocardial layers.

Aim: This study was designed to assess layer-specific longitudinal strain in naïve, untreated AFD patients.

Methods: In a case–control study, 33 newly diagnosed, untreated AFD patients and 33 healthy age- and sex-matched healthy controls underwent a complete echocardiogram, including assessment of LV transmural GLS, subendocardial longitudinal strain (LSsubendo), subepicardial longitudinal strain (LSsubepi), and strain gradient (LSsubendo–LSsubpepi).

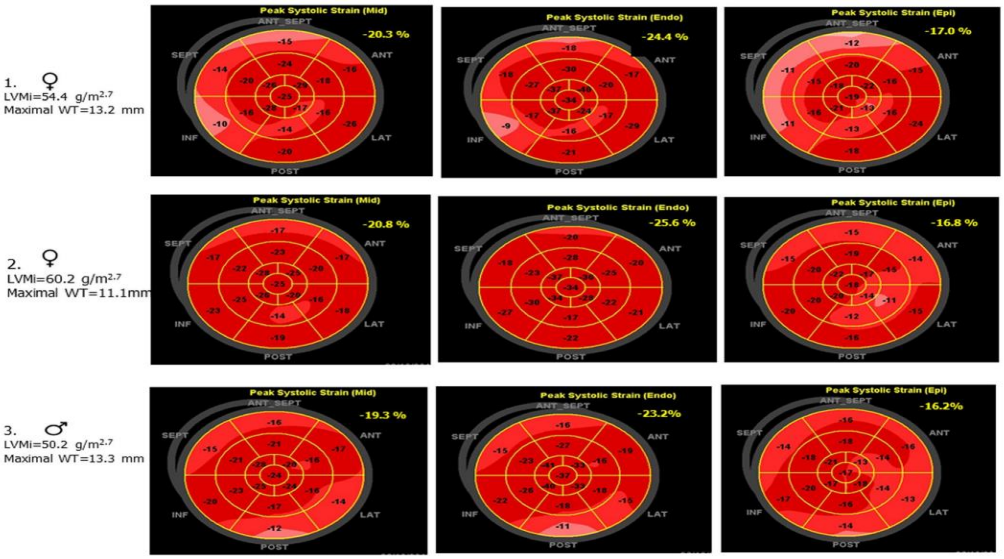
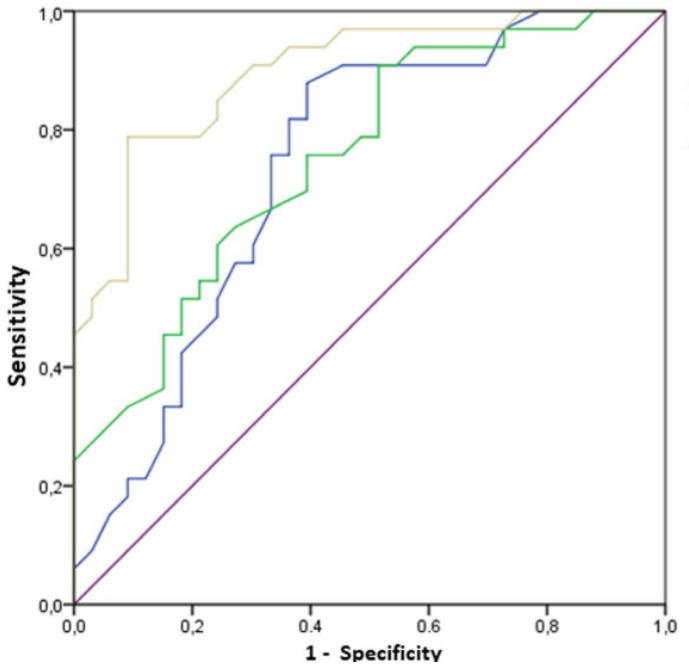


Figure 1. Samples of three Anderson–Fabry disease patients with an abnormal reduction of LSsubepi, but not of transmural global longitudinal strain (GLS) and LSsubendo. The first two patients are women and the third a man. All the three patients have clear-cut left ventricular hypertrophy and increased maximal wall thickness. Peak systolic strain (Endo) = LSsubendo; Peak systolic strain (Epi) = LSsubepi; Peak systolic strain (MID) = Transmural GLS

Results: Anderson–Fabry disease patients had similar blood pressure, heart rate, and ejection fraction but higher body mass index in comparison with controls. LV mass index, maximal, and relative wall thickness were significantly greater in AFD patients. LSsubendo was significantly higher than LSsubepi in both groups, but GLS ($P < 0.0001$), LSsubendo ($P = 0.003$), and particularly LSsubepi (21.4 ± 1.7 vs 18.8 ± 1.4%, $P < 0.0001$) were lower in AFD patients than in controls (Figure 1). Accordingly, LS gradient was higher in AFD patients ($P = 0.003$). Three patients symptomatic for dyspnoea presented a combination of LV hypertrophy and reduced LSsubepi.

After adjusting for confounders by multivariate analyses, LV mass index or maximal wall thickness were independently and inversely associated with transmural GLS and LSsubepi, but not with LSsubendo in the AFD group. At receiver operating curve curves, LSsubepi best discriminated AFD and normal (Figure 2).



	AUC	95% CI	p
Strain Gradient	0.738	0.616 to 0.861	< 0.001
GLS	0.753	0.824 to 0.972	<0.0001
LSsubepi	0.898	0.637 to 0.868	<0.0001

	Diff AUC	SE	p
GLS vs LSsubepi	-0.145	0.07	0.03
Strain Gradient vs LSsubepi	-0.160	0.07	0.03
Strain Gradient vs GLS	-0.015	0.08	0.8

Figure 2. Receiver operator characteristics (ROC) curves discriminating Anderson–Fabry disease and normal controls. GLS = transmural global longitudinal strain; LSsubepi = subepicardial longitudinal strain

Discussion: The present study demonstrates that in newly diagnosed, untreated AFD patients: (a) longitudinal strain decrease involved all myocardial layers, (b) LSsubepi decrease is greater than that of LSsubendo, inducing a significant increase of transmural (endo-epi) myocardial gradient (Figure 1), (c) LV mass or maximal wall thickness increases, both AFD features, are inversely and independently associated with transmural GLS and LSsubepi, whereas their association with LSsubendo does not achieve the statistical significance (Figure 3).

TABLE 3 Independent correlates of longitudinal strain components in Anderson–Fabry disease (AFD) population

Dependent variable	Covariate	Standardized β coefficient	*P* value
Transmural GLS	Age	−0.588	<0.001
	BMI	−0.019	0.924
	Female gender	0.237	0.140
	LV mass index	−0.547	<0.01
LSsubendo	Age	−0.639	<0.001
	BMI	0.037	0.858
	Female gender	0.235	0.158
	LV mass index	−0.392	0.065
Lsubepi	Age	0.450	<0.01
	BMI	−0.038	0.858
	Female gender	0.222	0.194
	LV mass index	−0.573	<0.01

Note: Cumulative $R^2 = 0.45$, SEE = 1.24, $P < 0.002$.
Cumulative $R^2 = 0.41$, SEE = 1.59, $P = 0.004$.
Cumulative $R^2 = 0.37$, SEE = 1.24, $P = 0.009$.

Figure 3. Independent correlates of longitudinal strain components in Anderson–Fabry disease (AFD) population

In newly diagnosed, untreated AFD patients, layer-specific strain imaging highlights an impairment of LV longitudinal deformation, mainly involving subepicardial strain and causing increase in longitudinal strain myocardial gradient. Notably, the prominent reduction of LSsubepi remained evident even analyzing only patients without clear-cut LVH, largely corresponding to the very initial disease stages. It is conceivable that a reduced subepicardial strain—in particular when associated with clear-cut LVH—could render the patients more prone to the development of HF

symptoms. Taken all together, our data could open new insights for identifying the mechanisms underlying early LV dysfunction in AFD patients.

CHAPTER 6

Association between Left Atrial Deformation and Brain Involvement in Patients with Anderson-Fabry Disease at Diagnosis.

In AFD patients, cardiac involvement frequently occurs as rhythm and conduction disturbances, and AF [86]. In this clinical setting, the assessment of LA structure and function should be part of the echocardiographic work-up.

On the other hand, although transient brain ischemia and major stroke are the most paradigmatic sequelae of central nervous system involvement in AFD, non-specific periventricular and deep white matter lesions (WMLs) along with silent lacunar infarctions are far more common, arising also in asymptomatic or poorly symptomatic patients [87]. As in several other conditions, the presence of white matter hyperintensities, ischemic lacunae and/or prominent perivascular spaces are all suggestive of chronic small vessels disease. At present time, the etiopathogenesis of these phenomena is still largely unclear, being only partially explained by Gb-3 accumulation within the endothelium. Among different methods, assessing the extent of WMLs, Fazekas' Score (FS), first proposed in 1987 [88], is one of the most used visual semi-quantitative scale to assess WML load by magnetic resonance imaging (MRI). This scale distinguishes deep and periventricular white matter, assigning to each a grading depending on the size and confluence of the WMLs; in particular, the score is the sum of two 4-point scales (ranging from 0 to 3 each) assessing

periventricular and deep white matter hyperintensities, with the total rate ranging from 0 to 6 (with higher values associated to higher lesion burden).

Little is known about the interaction between LA features and brain involvement in AFD patients. To date, the assessment of LA size and function can be performed by combining standard echo measurements with speckle tracking derived peak atrial longitudinal strain (PALS), an accurate and reproducible indicator of LA deformation [89]. Worthy of note, reduced PALS has been demonstrated to be associated with AF recurrence in the general population, after ablation or cardioversion [90, 91]. PALS has been also evaluated in AFD, which was reduced in comparison with healthy controls [92].

Aim: The present study aimed to evaluate possible association between LA structure and function and presence of WML assessed by FS in patients suffering from AFD.

Methods: 22 AFD patients and 22 controls, matched for age and sex, underwent an echo-Doppler exam including quantification of peak atrial longitudinal strain (PALS). AFD patients underwent also a 3-T brain MRI with a visual quantification of WMLs by Fazekas' score (FS) on 3D FLAIR images. Results AFD patients had significantly higher LV mass index (LVMi) and relative wall thickness, and lower PALS compared to controls. Among AFD patients, 9 showed a FS = 0, and 13 a FS > 1. AFD patients with FS ≥ 1 showed lower PALS (29.4 ± 6.7 vs. 37.2 ± 3.9%, $p = 0.003$) than those with FS = 0, without difference in LA volume index and LVMi (Figure 1). In AFD patients, FS was inversely related to PALS ($r = -0.49$, $p < 0.0001$), even after adjusting for LVMi ($r = -0.43$, $p < 0.05$).

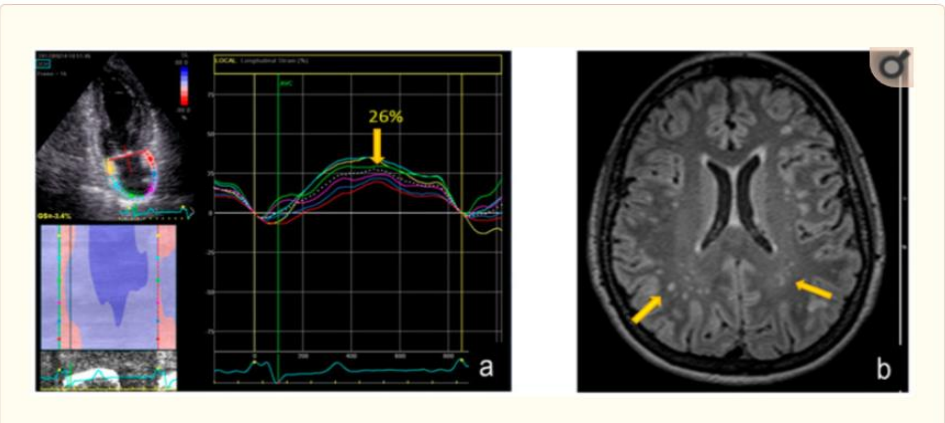


Figure 1. Reduction of PALS: upper left corner: two-dimensional echocardiography apical 2-chamber view, bottom left corner: color rendering of LA strain variation during cardiac cycle, right side: LA strain curves (a) and parallel axial FLAIR MRI image (b) showing multiple white matter hyper intensities lesions (arrows) in AFD patient. Fazekas score is = 1. Legend: PALS = peak atrial longitudinal strain; LA= left atrium; FLAIR = fluid attenuated inversion recovery; MRI = magnetic resonance imaging; AFD = Anderson-Fabry disease.

Discussion: To the best of our knowledge, this is the first study to explore the relationships between LA function deterioration and brain involvement, i.e., presence and extension of WMLs evaluated through the FS, in AFD treatment-naïve patients. The present study demonstrates that (I) treatment-naive AFD patients at diagnosis show a significant reduction of GLS and PALS in comparison with healthy controls (Figure 1), whereas ejection fraction, PACS and LA volume index do not differ between the two groups; (II) patients with greater PALS impairment present a larger involvement of the central nervous system according to FS (≥1); (III) an inverse relation between PALS and FS is detectable in AFD patients.

Our results confirm the concept that PALS may be considered an early predictor of target organ damage in AFD patients [93]. On the grounds of the significant association found in the present study between PALS reduction and FS scoring, it is conceivable that AFD patients with PALS abnormalities could be addressed to the performance of brain MRI in order to detect parallel

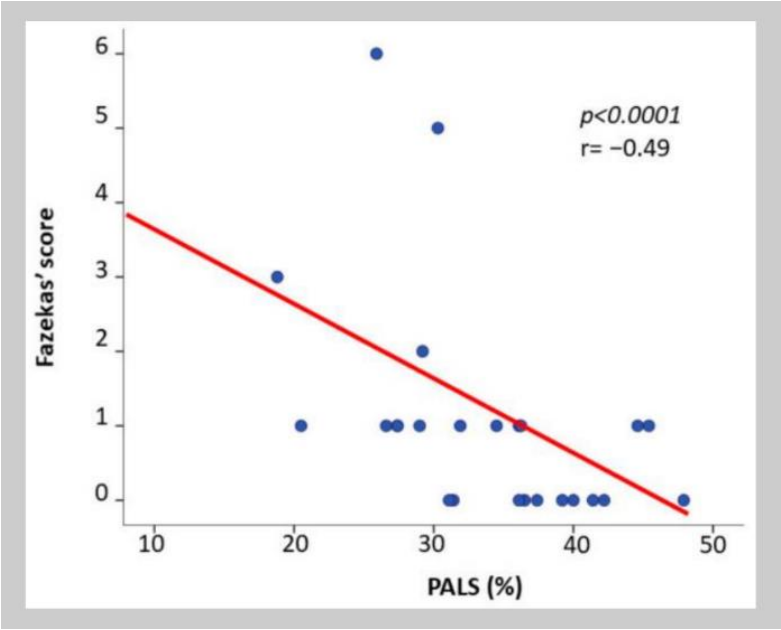


Figure 2. Scatterplot and regression line of the inverse relation between peak atrial longitudinal strain and Fazekas Score in Anderson-Fabry Disease patients.

involvement of white matter and initiate a very early enzyme replacement therapy, in agreement with the European Fabry Working Group recommendations [94]. This kind of therapy has in fact demonstrated to exert a protective effect on central nervous system, by reducing the stroke risk and stabilizing WMLs progression [95] and could be therefore promoted in AFD patients with LA strain dysfunction.

CHAPTER 7

Cardiac Imaging in Anderson-Fabry Disease: Past, Present and Future

"Fabry disease-often seen, rarely diagnosed" is how Hoffmann and Mayatepek titled their AFD review [96]. Current screening practices likely capture only a small portion of AFD. However, AFD is not a very rare disorder, particularly in high-risk populations in which screening is usually omitted. Particular attention should be given to patients presenting with kidney damage, cryptogenic

stroke, unexplained LVH, gastrointestinal symptoms, hearing impairment, lymphedema, diminished perspirations, acroparesthesias, corneal opacities and angiokeratoma, which are considered clinical markers associated with AFD. AFD should be suspected in patients with a family history or in those who present with the clinical features that suggest the diagnosis. The diagnosis is typically confirmed by enzymatic and/or molecular genetic testing. In this review article, we highlight the value and perspectives of standard and advanced cardiovascular imaging in Anderson-Fabry disease. Cardiac imaging is involved in many aspects of the management of Fabry patients: (i) the initial diagnostic suspicion of AFD in case of evidence of unexplained heart damage associated with extracardiac AFD red flags, (ii) the differential diagnosis with other cardiomyopathies, (iii) the early detection of heart damage in patients with already diagnosed AFD and its evolution monitoring, (iiii) to allow decisions regarding the initiation of chaperone or enzyme replacement therapy, and to guide its follow-up.

The echocardiographic examination is the first-line technique to suspect and manage AFD. However, there are no pathognomonic echocardiographic features of AFD. STE has an incremental value in differentiating between primary and secondary LVH and in the differential diagnosis with storage diseases. Moreover, STE enables early detection of intrinsic myocardial dysfunction before LVEF reduction (Figure 1).

Advanced Echocardiography	Description	Features
GLS	-Reduction in LV GLS with a prevalent involvement of the infero-lateral wall of the LV	-Correlates with LGE at CMR
GCS	-Reduction in the normal base-to-apex CS gradient	-Differential diagnosis with HCM where GCS increases with a preserved base-to-apex gradient
RVLS	-Reduction in the RV Longitudinal strain	-Early sign of RV dysfunction

GLS: global longitudinal strain; LGE: late gadolinium enhancement; CMR: cardiovascular magnetic resonance; GCS: global circumferential strain; HCM: hypertrophic cardiomyopathy; RVLS: right ventricle longitudinal strain.

Figure 1. Advanced echocardiography in AFD cardiomyopathy. GLS: global longitudinal strain; LGE: late gadolinium enhancement; CMR: cardiovascular magnetic resonance; GCS: global

circumferential strain; HCM: hypertrophic cardiomyopathy; RVLS: right ventricle longitudinal strain.

CMR has emerged as a powerful imaging tool to identify lesions of AFD in patients in whom echocardiography fails to detect relevant LVH or other cardiac damage. Its strength is in characterizing tissue using LGE or T1 and T2 mapping. LGE imaging is the non-invasive gold standard for the evaluation of replacement fibrosis/scarring. The tissue damage highlighted by LGE, initially located in the basal inferolateral wall, has prognostic implications and predicts a lack of response to enzyme replacement therapy. Low native myocardial T1 values could represent a useful, early biomarker of cardiac involvement in AFD, superior to left ventricular hypertrophy and LGE imaging. T2 mapping is sensitive to inflammation. Studies with T2 mapping, supported by histological studies, deny the model of AFD as simple storage cardiomyopathy and have led to the identification of an important role of chronic inflammation in the early progression of the disease. This recognition may have implications on future management strategies including consideration for immunosuppressive therapy in the hope of improving the course of AFD. These observations justify an increasing role of CMR in the routine clinical evaluation of patients with AFD. As with echocardiography, CMR findings in themselves are not diagnostic of AFD and must be considered within the clinical contest of an individual patient and confirmed with enzymatic and genetic analysis. An integrated multi-modality imaging approach including both echocardiography and CMR might be optimal for the management of AFD patients. In the future, echocardiography, by its large availability and low cost, will remain the initial imaging modality of choice in patients with proven or suspected AFD, but the role of CMR will be likely to increase so much as to also become an essential diagnostic test in the initial evaluation.

PART III: The Right Ventricle: insights from the "forgotten chamber"

CHAPTER 8

Impaired Right and Left Ventricular Longitudinal Function in Patients with Fibrotic Interstitial lung Diseases

Interstitial lung diseases (ILDs) include more than 200 disorders, characterized by a variable degree of inflammation and fibrosis leading to an often irreversible loss of lung function, wide spectrum in the clinical course, treatment, and prognosis. Among idiopathic interstitial pneumonia, idiopathic pulmonary fibrosis (IPF) is the most common form, affecting 30 persons per 100,000 in the general population. Because of its worse prognosis and challenging treatment, pneumological and cardiac aspects of IPF have been deeply investigated. The combination of severe vascular and fibrotic abnormalities induces changes in right ventricular (RV) structure and function until HF onset [97]. PAH is frequently found in the early stages of IPF and the outcome is directly related to the capacity of right ventricular (RV) function to adapt to the elevated afterload [98]. RV enlargement and dysfunction, as evaluated by standard echocardiography, have been well described in IPF and can be used to identify patients with high risk of mortality [99]. LV and RV function have been poorly explored by advanced echo technologies in fibrotic ILDs other than IPF (defined in this study as no-IPF) and no comparison of strain and 3D echocardiographic imaging exists between IPF and no-IPF patients.

Aim: The aim of the present study was to analyze LV and RV structure and function in patients with ILDs, including both IPF and no-IPF, by using 2D strain to both ventricles and 3D to the right ventricle. Relationships between lung function and cardiac parameters were also evaluated.

Methods: Thirty-three clinically stable and therapy-naive fibrotic IPF and 28 no-IPF patients, and 30 healthy controls were enrolled. Exclusion criteria were autoimmune systemic diseases, coronary disease, HF, primary cardiomyopathies, chronic obstructive lung diseases, pulmonary embolism, primary PAH. Lung damage was evaluated by diffusion capacity for carbon monoxide ($DLCO_{sb}$). All participants underwent an echo-Doppler exam including 2D global longitudinal strain (GLS) of both ventricles and 3D echocardiographic RV ejection fraction (RVEF).

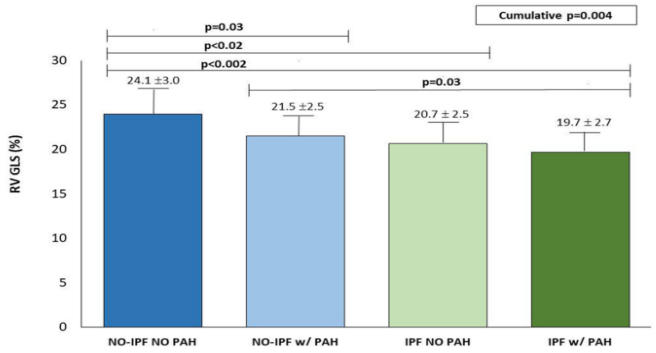


Figure 1. Behavior of RV GLS (mean ± SD) in no-IPF and IPF without and with PAH. RV GLS is significantly lower in IPF with or without PAH in comparison with both no-IPF groups.

Results: We observed LV diastolic dysfunction in IPF and no-IPF, LV EF did not differ significantly between IPF, no-IPF, and controls, whereas LV GLS was lower in IPF than in no-IPF ($p = 0.003$) and controls ($p < 0.0001$). RV diastolic and RV GLS abnormalities were observed in IPF versus both controls and no-IPF. RV GLS was gradually reduced passing from no-IPF without and with PAH to IPF patients but did not differ significantly between IPF without and with PAH (Figure 1). RV EF did not differ significantly between IPF and no-IPF. $DLCO_{sb}$ and RV GLS were associated in the pooled pulmonary fibrosis population and in the IPF subgroup ($\beta = 0.708$, $p < 0.001$), independently of confounders including pulmonary arterial systolic pressure.

Discussion: Our findings demonstrate that IPF presents (I) LV diastolic dysfunction, which is detectable even in no-IPF patients, and a subclinical LV systolic dysfunction, testified by the reduction of LV GLS but not of LV EF, which cannot be observed in no-IPF patients; (II) a clear alteration of RV geometry and of both systolic (RV EF and GLS) and diastolic function, and a substantial PASP increase in comparison with controls, whereas no-IPF patients present only an alteration of RV diastolic dysfunction and a lower degree of PASP increase. Moreover, (III) an independent association between $DLCO_{sb}$ and RV longitudinal dysfunction is found in the pooled ILDs population, it being evident in the IPF group but not the no-IPF group.

A significant difference in RV size (increased RV transverse basal and midcavity diameters) and function (reduced TAPSE) was found only in the IPF when compared to controls. Among the different echocardiographic parameters investigated, only RV GLS differentiated the two ILDs subgroups, it being significantly lower in IPF than in no-IPF. Of note, 3D-echocardiographic-derived RV EF had not the same diagnostic ability since it was significantly reduced in both IPF and no-IPF in comparison with healthy controls. Combined, these findings are completely new and provide evidence of the additional diagnostic capabilities of RV strain imaging in ILDs. It is conceivable that microvascular injury, largely demonstrated as an early stage of IPF lungs [100], could be extended also to the RV subendocardial layer, of which GLS is a reliable marker [101].

CHAPTER 9

Three-dimensional echocardiographic evaluation of the right ventricle in patients with uncomplicated systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder associated with chronic inflammation and immune complex deposition in involved organs [102]. Cardiovascular diseases are

one of the most important causes of morbidity and mortality in patients with SLE [103]. In addition, pleuro-pulmonary diseases, such as pleurisy, interstitial pneumonia and pneumonia, are common in this disorder. PAH is also common in SLE patients, its prevalence ranging from 9.3% up to 14% [104]. Several studies have demonstrated cardiac involvement in SLE patients [105]. In patients without history of cardiac disease and in the early disease stages, LVH and systolic dysfunction, LV diastolic dysfunction with or without elevated filling pressures, valvular abnormalities and left atrial dilation have been reported [106]. By contrast, the involvement of the right ventricle in SLE patients is largely unknown.

Aim: In this study we assessed standard and 3DE RV parameters in patients with uncomplicated SLE compared to healthy controls matched by gender, age and ethnicity. Our aim was to identify possible subclinical RV alterations in this group of patients.

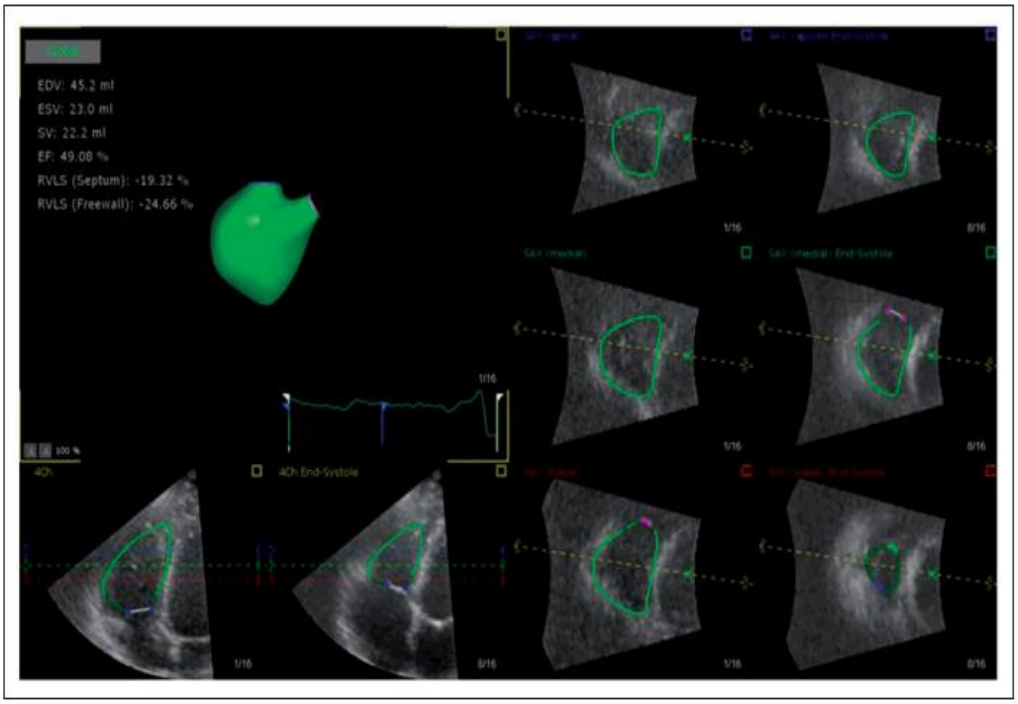


Figure 1. Final 3D reconstruction and report of RV parameters obtainable by 3D echocardiography. EF: ejection fraction; EDV: end-diastolic volume; ESV: end-systolic volume; RVLS: right ventricular strain; SV: stroke volume.

Methods: Fifty SLE patients without concomitant cardiac disease and 50 healthy controls, matched for age and gender, were enrolled. Disease damage was evaluated by inflammatory markers and SLE damage index. All patients underwent an echo-Doppler examination with 3DE assessment of RV function (Figure 1), RV septal and lateral longitudinal strain.

Results: The two groups had comparable body mass index and blood pressure. RV transversal middle diameter and pulmonary arterial pressure were significantly higher in SLE compared to controls. By 3DE, RV endsystolic volume (p ¼ 0.037) was greater, whereas stroke volume (p ¼ 0.023), ejection fraction (p < 0.0001) and septal and lateral longitudinal strain (both p < 0.0001) were lower in SLE. SLE damage index ≥ 1 was negatively associated with tricuspid annular plane systolic excursion (TAPSE) (p < 0.002), tricuspid E/A ratio (p ¼ 0.003), RV ejection fraction (p < 0.05), lateral longitudinal strain (p < 0.0001) and septal longitudinal strain (p ¼ 0.04). By separate multivariate models, after adjusting for age, C reactive protein and proBNP, SLE damage index was independently associated with TAPSE (p ¼ 0.009) and RV lateral longitudinal strain (p ¼ 0.007).

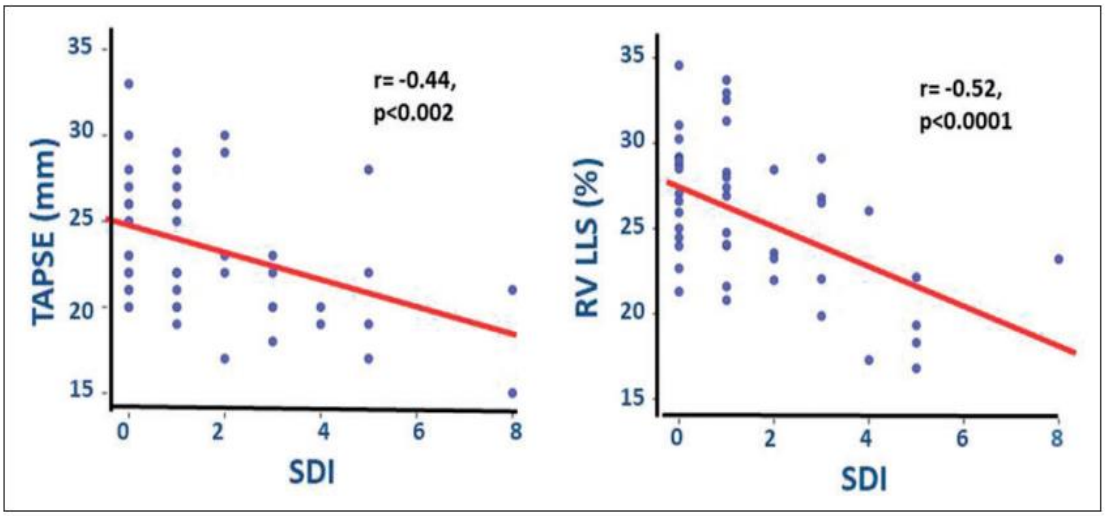


Figure 2. Scatterplot and regression lines of individual values of SDI (x-line) and corresponding values of TAPSE (left panel) and RV LLS (right panel) (y-lines) in the SLE population. RV: right ventricular; LLS: Longitudinal lateral strain; TAPSE: tricuspid annular plane systolic excursion.

Discussion: The results of the present study show the power of 3DE in detecting subclinical abnormalities of RV structure and function in asymptomatic for cardiac symptoms and free of concomitant cardiac disease SLE patients. In particular, in SLE patients with PAH, the standard echocardiographic examination identified only a mild RV enlargement, whereas 3DE volumetric assessment confirmed RV dilation but also highlighted a significant reduction of RV systolic chamber function (EF). 3D STE allowed detecting a reduction of both lateral and septal LS. In addition, the disease damage as evidenced by SDI was independently associated with the degree of RV longitudinal dysfunction, (i.e. with 3D STE-derived lateral LS and, to a minor extent, with TAPSE) (Figure 2). The present study demonstrates that SLE patients present an early, subclinical reduction of RV longitudinal function which is detectable by 3D STE, but not by standard or 3D volumetric assessment. Advanced echocardiographic technologies could be used in this clinical setting to identify patients at higher risk for RV failure development and, possibly, during the follow-up of therapies.

CHAPTER 10

Right ventricular function after cardiac surgery: the diagnostic and prognostic role of echocardiography.

Right ventricle assumes great importance after cardiac surgery mostly because of its relevant prognostic impact. RV post-surgical dysfunction's underlying mechanisms are still not clear (Figure

1). Beyond all the hypothesized etiologies, a complete assessment of RV size, longitudinal and global function should be performed before and after the intervention.

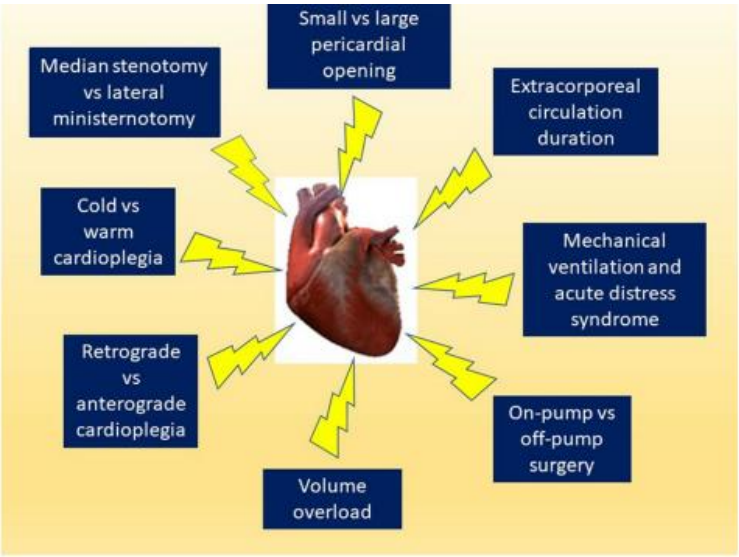


Figure 1. Imaging illustrating the different hypothesis behind the reduction of RV function after cardiac surgery

Echocardiography, with both first and second level parameters, offers the possibility to accurately analyze the right ventricle and optimize these patients' management. 3D and STE, represents non-invasive and reliable tools for this purpose. This paper describes the pathophysiology of the right ventricle, the most used echo indexes of RV function, whether they alter after surgery, the different supposed mechanisms of RV dysfunction and its role in the prognosis of patients undergoing cardiac surgery.

RV longitudinal strain (RVLS, Figure. 2) has shown good feasibility and reproducibility. The average value of longitudinal deformation of the six segments of the RV represents global RVLS [107]; however, free wall RVLS as emerged as an even more accurate parameter in detecting RV dysfunction in some clinical settings, including advanced HF [108]. In the absence of second level

tools, the combined use of TAPSE, s', and RVFAC is not just considerable as a basic surrogate but allows a good assessment of RV function in a short time and with high availability.

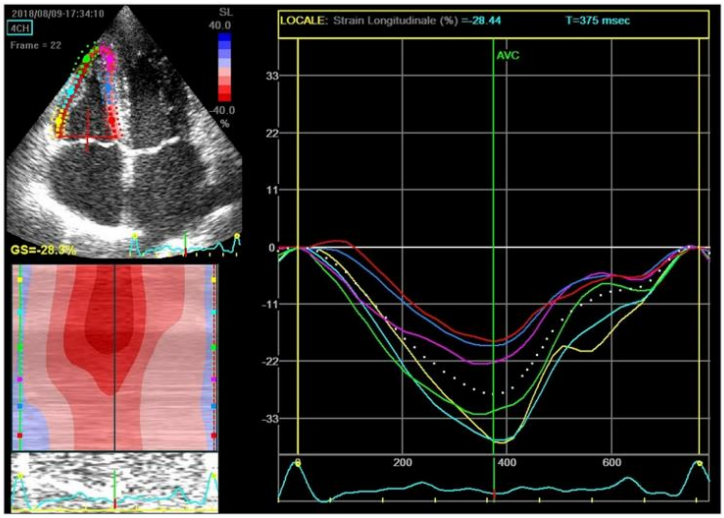


Figure 2. Global right ventricular longitudinal strain (RVLS). To perform the analysis, an apical four chambers with the complete inclusion of RV wall in the image must be acquired. The operator must accurately trace the endocardial border by a pointand-click approach, obtaining a region of interest composed of six segments (three at interventricular septum, three at free wall). The mean value of the longitudinal deformation of these six segments represents the global RVLS

A complete exam systematically including TAPSE, s', and RVFAC assessment should be performed soon after the surgery and repeated after 3 and 6 months to verify the possible complete restitution of RV longitudinal function. In the case of available second level echocardiographic tools, evaluation of 3DEF and RV longitudinal strains should complete the screening.

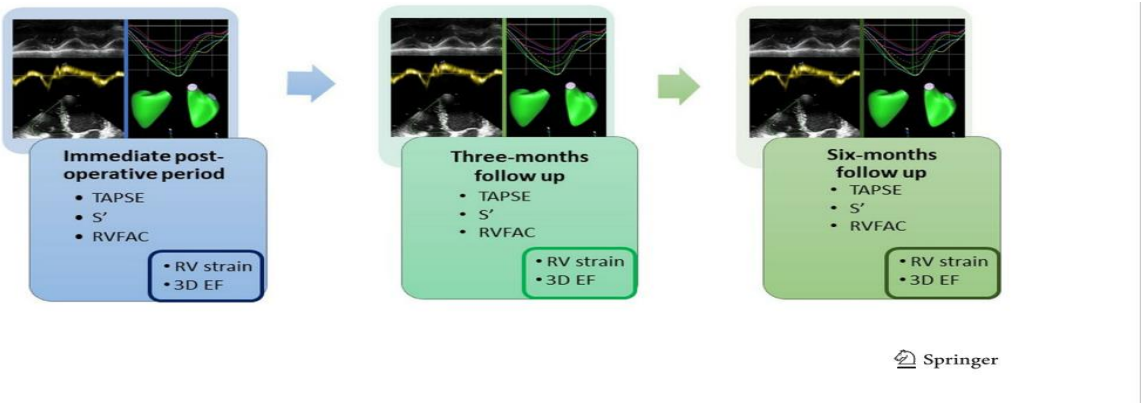


Figure 7 Proposed algorithm for a step-by-step evaluation of postoperative RV function.

In the case of a mild-moderate RV dysfunction without hemodynamic impact, a tailored follow-up of the patient with particular attention on the evolution of biventricular function is indicated. It is not uncommon to find a complete restoration of RV longitudinal deformation with time. In the immediate post-operatory setting, in the case of true RV failure, echocardiography helps the intensivists to validate the diagnosis together with the clinical clues and to guide therapeutic support. Starting from the need for a preload optimization, ultrasounds guide fluids administration in case of low RV filling pressure (i.e., low RA pressure) to optimize cardiac output.

CHAPTER 11

Cor pulmonale: the role of traditional and advanced echocardiography in the acute and chronic settings.

Cor pulmonale is the condition in which the right ventricle undergoes morphological and/or functional changes due to diseases that affect the lungs, the pulmonary circulation, or the breathing process. Depending on the speed of onset of the pathological condition and subsequent effects on the right ventricle, it is possible to distinguish the acute cor pulmonale from the chronic type of disease. The echocardiographic evaluation is a cornerstone in both the diagnosis and the prognostic stratification of these patients. In general, when RV afterload is acutely increased, the results are a dilatation and an impaired function, whereas when the pressure increase is gradual, the RV has time to adapt and is more likely to present complex remodelling features, including RV hypertrophy. Moreover, echocardiography plays a central role in the diagnostic and therapeutic work-up of these patients, because of its non-invasive nature and wide accessibility, providing its greatest usefulness in the acute setting. It also represents a valuable tool for tracking right ventricular function in patients with cor pulmonale, assessing its stability, deterioration, or improvement during follow-up. In fact, not only it provides parameters with prognostic value, but

also it can be used to assess the efficacy of treatment. This review presents the current evidences of the role of echocardiography in both acute and chronic cor pulmonale, including new techniques, such as 3DE (Figure 1) and STE, which have proven valuable tools for distinguishing between the acute and the chronic form.

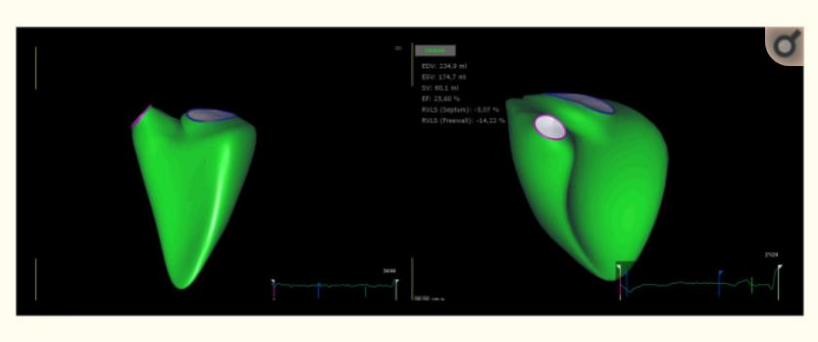


Figure 1. Morphological and functional difference between a healthy right ventricle and an impaired RV by 3D-echocardiography. The image on the left shows a healthy right ventricle (RV) that has a preserved triangular morphology, whereas the image on the right side shows a failing RV, with a markedly altered morphology and an impaired function, as indicated by the echocardiographic parameters listed in the picture. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; RVLS, right ventricular longitudinal strain; SV, stroke volume

This review points out how several functional and morphological echocardiographic RV parameters, especially those derived from new techniques, represent valuable and easily accessible tools for the clinician in order to assess RV function in patients with both acute (Figure 2) and chronic cor pulmonale (Figure 3) and periodically reassess functional stability, deterioration or improvement over time. Regarding future perspectives, further studies are required to investigate how new echocardiographic parameters could improve discrimination between acute and chronic cor pulmonale, which would be particularly useful in defining the optimal therapeutic strategy. Furthermore, it might be intriguing to establish the role of echocardiography in COPD patients, whether it is in aid of identifying patients with a proportionally greater lung destruction or an inflammation of the airways, or investigating the new phenotype “cor pulmonale parvus.”

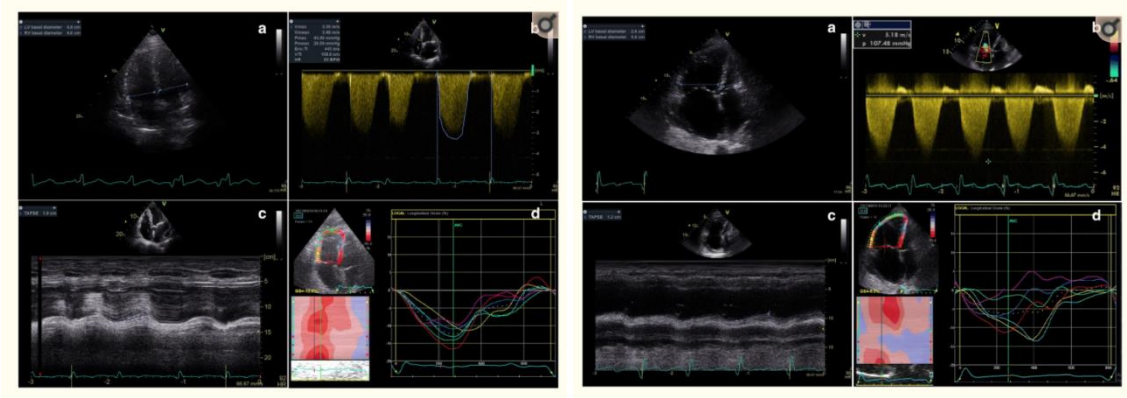


Figure 2. Left Panel: Relevant echocardiographic parameters found in acute pulmonary embolism. This figure shows the most common findings that can be found in the setting of acute pulmonary embolism. (a) Ratio between right ventricular (RV) and left ventricular (LV) basal diameters, often enough > 1, meaning a RV dilatation. (b) Right atrio-ventricular gradient, rarely above 60 mm Hg in the acute setting. (c) Tricuspid annular plane systolic excursion (TAPSE), which in acute setting is not necessarily reduced compared with controls. (d) Reduced RV longitudinal strain
Right Panel: Relevant echocardiographic parameters found in chronic cor pulmonale. This figure shows the most common findings that can be found in the setting of chronic cor pulmonale. (a) Ratio between right ventricular (RV) and left ventricular (LV) basal diameters, often enough > 1, meaning a RV dilatation. (b) High right atrio-ventricular gradient, typical of chronic pulmonary hypertension. (c) Reduced tricuspid annular plane systolic excursion (TAPSE), reflecting a reduced RV longitudinal function. (d) Reduced RV longitudinal strain

PART IV: Cardiotoxicity

CHAPTER 12

Strain-oriented strategy for guiding cardioprotection initiation of breast cancer patients experiencing cardiac dysfunction.

Do date, cardiac treatment of CTRD is guided by LVEF [109]. However, EF is affected by several limitations including its load-dependence, the need of geometric assumption for its calculation and, above-all, its substantial biological (day-to-day) variability that makes subtle changes often doubtful and questionable [110]. As an alternative, GLS, easily obtainable by speckle tracking echocardiography, has shown optimal feasibility and temporal reproducibility and its changes may precede EF reduction in the general population and in oncologic patients as well [111]. The lack of definite results on clinical outcomes produced by a GLS-oriented strategy, i.e. the impact of a strain-guided cardioprotective therapy initiation on the development of overt HF, makes this innovative approach not ready yet for addressing the decision-making in this clinical setting.

Aim: the present study was designed to assess the impact of the strain-oriented therapeutic approach in reducing the development of overt CTRCD and the rate of CT interruption in breast cancer patients.

Methods: We enrolled 116 consecutive female patients with HER2-positive breast cancer undergoing a standard protocol by EC (epirubicine þ cyclophosphamide) followed by paclitaxel þ trastuzumab (TRZ). Coronary artery, valvular and congenital heart disease, HF, primary cardiomyopathies, permanent or persistent AF, and inadequate echo-imaging were exclusion criteria. Patients underwent an echo-Doppler exam with determination of EF and GLS at baseline

and every 3 months during CT. All patients developing subclinical (GLS drop >15%) or overt CTRCD (EF reduction <50%) initiated cardiac treatment (ramipril, carvedilol) (Figure 1).

Results: In the 99.1% (115/116) of patients successfully completing CT, GLS and EF were significantly reduced and E/e' ratio increased at therapy completion. Combined subclinical and overt CTRCD was diagnosed in 27 patients (23.3%), 8 at the end of EC and 19 during TRZ courses. Of these, 4 (3.4%) developed subsequent overt CTRCD and interrupted CT. By cardiac treatment, complete EF recovery was observed in two of these patients and partial recovery in one. These patients with EF recovery re-started and successfully completed CT. The remaining patient, not showing EF increase, permanently stopped CT. The other 23 patients with subclinical CTRCD continued and completed CT.

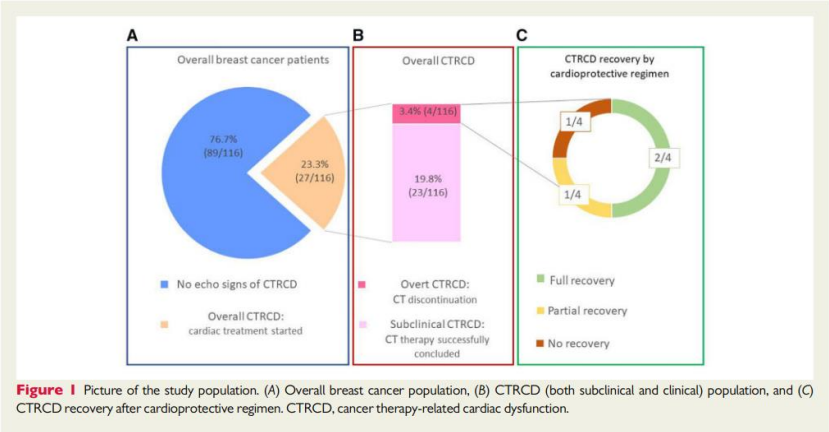


Figure 1 Picture of the study population. (A) Overall breast cancer population, (B) CTRCD (both subclinical and clinical) population, and (C) CTRCD recovery after cardioprotective regimen. CTRCD, cancer therapy-related cardiac dysfunction.

Figure 1 Picture of the study population. (A) Overall breast cancer population, (B) CTRCD (both subclinical and clinical) population, and (C) CTRCD recovery after cardioprotective regimen. CTRCD, cancer therapy-related cardiac dysfunction

Discussion: Our study demonstrates that in a population of HER2-positive breast cancer patients undergoing adjuvant therapy: (i) the use of GLS allows to identify subclinical CTRCD when EF is still normal, with a prevalence of 23.3% (27/116); (ii) all the 23 patients developing subclinical CTRCD without progression towards overt HF were able to complete CT without interruption, thanks to

the help of cardioprotective treatment; (iii) among the four patients developing subsequent overt CTRCD, three could complete CT with an adequate cardioprotective treatment; (iv) in the subgroup of patients without CTRCD (76.7%) a reduction in EF and GLS and an increase in E/e' ratio was detected at the end of CT in comparison with baseline.

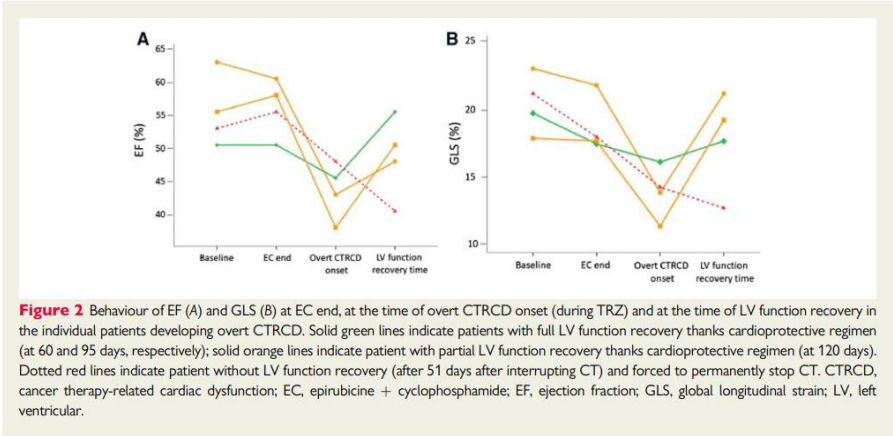


Figure 2 Behaviour of EF (*A*) and GLS (*B*) at EC end, at the time of overt CTRCD onset (during TRZ) and at the time of LV function recovery in the individual patients developing overt CTRCD. Solid green lines indicate patients with full LV function recovery thanks cardioprotective regimen (at 60 and 95 days, respectively); solid orange lines indicate patient with partial LV function recovery thanks cardioprotective regimen (at 120 days). Dotted red lines indicate patient without LV function recovery (after 51 days after interrupting CT) and forced to permanently stop CT. CTRCD, cancer therapy-related cardiac dysfunction; EC, epirubicine + cyclophosphamide; EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricular.

Figure 2. Behaviour of EF (A) and GLS (B) at EC end, at the time of overt CTRCD onset (during TRZ) and at the time of LV function recovery in the individual patients developing overt CTRCD. Solid green lines indicate patients with full LV function recovery thanks cardioprotective regimen (at 60 and 95 days, respectively); solid orange lines indicate patient with partial LV function recovery thanks cardioprotective regimen (at 120 days). Dotted red lines indicate patient without LV function recovery (after 51 days after interrupting CT) and forced to permanently stop CT. CTRCD, cancer therapy-related cardiac dysfunction; EC, epirubicine þ cyclophosphamide; EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricular.

In the present study, we applied the GLS strategy suggested by the ASE/EACVI Expert Consensus to identify subclinical CTRCD5 and timely started cardioprotection. To the best of our knowledge, this is the first study to demonstrate that in a population of HER2-positive breast cancer patients undergoing CT the GLS-based approach and the consequent and timely initiation of cardioprotection with concomitant ACE-inhibitors and beta-blockers, may have a clear impact on the onset of subsequent overt HF and on CT withdrawn.

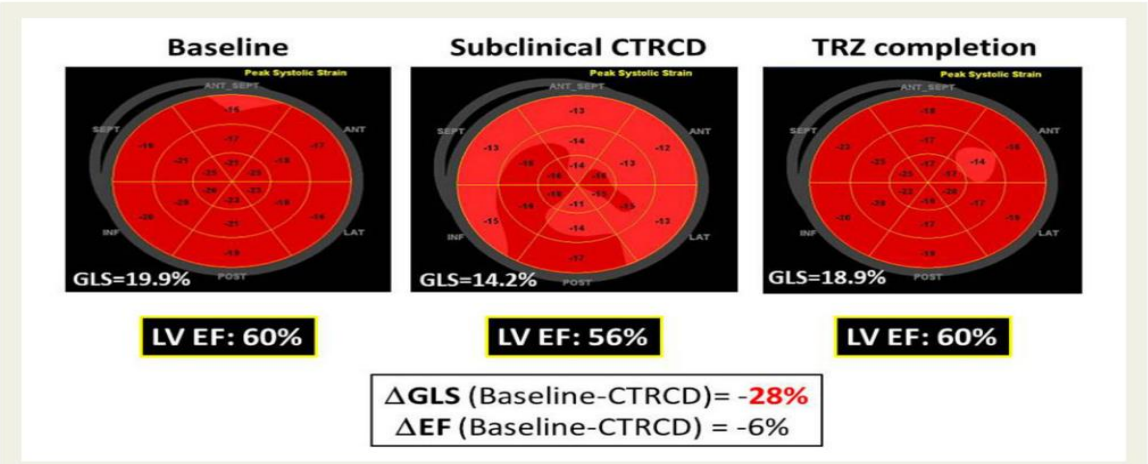


Figure 3. Clinical case of a patients developing subclinical CTRCD at the XI TRZ cycle but completing successfully TRZ thanks the timely cardioprotective treatment. Bull's eyes of GLS at baseline (left), at the time of subclinical CTRCD (mid), and at cancer therapy completion (right). CTRCD, cancer therapy-related cardiotoxicity; EF, ejection fraction; GLS, global longitudinal strain; TRZ, trastuzumab.

It is noteworthy that, by applying this strategy, the incidence of overt CTRCD (3.4%) was substantially lower than that reported in other recent investigations (from 7% to 34%) [112, 113]. Most importantly, all the 23 patients developing subclinical CTRCD without progression towards overt HF were able to complete CT without interruption, also obtaining an almost complete recovery of both GLS and EF thanks to the cardioprotective regimen. Our study puts a spotlight on the 'GLS-oriented' approach in detecting CTRCD and its prompt treatment, a matter that both cardiologists and oncologists will have to be aware of in the future years. This strategy may effectively prevent overt and irreversible HF and avoid the possible subsequent interruption of CT, with clear negative reflections on cancer progression end relapse. Ongoing and future studies could open new horizons and possibly even define the lowest value of GLS to be considered as clinically relevant.

CHAPTER 13

Atrial Fibrillation, Cancer and Echocardiography

Nonvalvular AF is a relatively frequent arrhythmia in cancer patients; it is possibly due to direct effect of cancer or consequence of cancer therapies [114]. AF creates important problems for both therapeutic management and prognosis in cancer patients [115]. The anticoagulation of cancer patients presenting AF is a main issue because of the difficult balance between thromboembolic and bleeding risks, both elevated in this clinical setting [116]. The echocardiographic evaluation has a pivotal importance in cancer patients affected from any kind of nonvalvular AF. This is due to several reasons which should correspond to subsequent, well-established items, also following European Association of Cardiovascular Imaging (EACVI) standardization of the echo report.[117] A comprehensive echo Doppler examination is mandatory. Transesophageal echocardiography (TEE) is fundamental to identify the possible sources of systemic embolism in a clinical setting, which is very prone to the thrombotic risk. The performance of a TEE precardioversion is highly encouraged to detect possible thrombi in LA appendage. In addition, some echo LA parameters such LA size (mainly LAVi) and function (LA emptying fraction or, better, LA strain) (Figure 1) become even more important than in cancer-free AF patients in the prediction of sinus rhythm restoration and/or the possible recurrence of AF paroxysmal episodes in patients who have recovered their normal rhythm and to predict the subsequent development of HF.

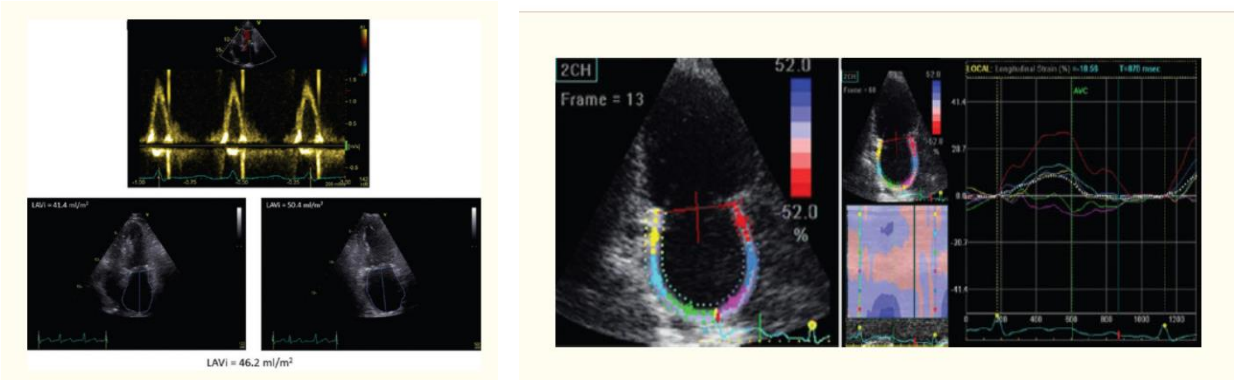


Figure 1. Left Panel: Left atrial dilation in a breast cancer patient with paroxysmal atrial fibrillation. In the top, transmitral pattern showing the absence of A velocity due to atrial fibrillation. In the bottom, left atrial volume in apical four-chamber (left) and two-chamber (right) part. Left atrial volume index is 46.2 ml/m2
Right Panel: Reduction of left atrial strain in apical two-chamber view in a patient with chronic lymphatic leukemia experiencing paroxysmal atrial fibrillation during ibrutinib therapy

This is in fact a key action, not only from the cardiologic point of view but also for the oncologic perspectives in individual situations. When AF occurs during cancer therapy, the decision whether to continue, adjust the dosage, or withdraw cancer medications is fundamental. Particular attention will be taken to achieve an optimal control of heart rate and to restore normal sinus rhythm with antiarrhythmic drugs, mainly amiodarone. This evaluation is particularly important to graduate anticoagulation and to prevent and manage symptoms/signs of HF. Patients with larger left atrium and more impaired LA function should be addressed toward a less aggressive cancer treatment, with drugs which are not associated or are poorly related with the risk of AF development. A correct and comprehensive echocardiographic assessment could even induce the oncologist to change the cancer management balancing the oncologic and the cardiac risk, taking well into account that the thrombotic and the bleeding complications exert an equal burden in this delicate clinical setting.

PART IV: Conclusions.

The articles described in this thesis, albeit ranging in a very broad field of cardiovascular diseases, share the study and application of advanced echocardiographic techniques that have gained more and more importance in the field of cardiovascular imaging in the past decade.

STE and, by minor extent 3D echocardiography, have shown their incremental value in various clinical settings, proving their usefulness in diagnosis, prevention and treatment of cardiovascular diseases.

In this research journey, we demonstrated the additional diagnostic value of STE (in the form of GLS, layer specific strain and PALS) in AFD patients. In this clinical setting, LV STE enables the early detection of intrinsic myocardial dysfunction before LVEF reduction and PALS may be considered an early predictor of target organ damage.

We demonstrate the incremental value of STE and 3D echocardiography applied to the right ventricle in different clinical scenarios such as Fibrotic Interstitial Lung Diseases and in patients with Systemic Lupus Erythematosus. Patients with IPF and patients with SLE present an early, subclinical reduction of RV longitudinal function and impairment of geometry, which is only detectable by advanced echocardiographic tools. Moreover, we describe the incremental value of these echocardiographic tools in patients undergoing pericardiectomy during cardiac surgery, and patients with Cor Pulmonale.

In the setting of CTRD, we demonstrate that in a population of HER2-positive breast cancer patients undergoing CT the GLS-based approach and the consequent and timely initiation of cardioprotection with concomitant ACE-inhibitors and beta-blockers, may have a clear impact on the onset of subsequent overt HF and on CT withdrawn. This strategy may effectively prevent

overt and irreversible HF and avoid the possible subsequent interruption of CT, with clear negative reflections on cancer progression end relapse

Indeed, ongoing and future studies are needed to definitely prove the incremental value of these advanced echocardiographic tools, in order to ampliate their use in the routine clinical practice.

Table 1. Summary table of all the articles.

	Title	Aim of the Study	Methods	Results
Studies focused on left ventricular function: from diastolic dysfunction to heart failure				
Sorrentino R. et al J Am Soc Echocardiogr. 2020; 33:171-181	Practical Impact of New Diastolic Recommendations on Noninvasive Estimation of Left Ventricular Diastolic Function and Filling Pressures	Prospectively evaluate the concordance of the ASE/EACVI 2009 and 2016 recommendations in the diagnosis of DD and in the estimation of LVFP in patients with normal and reduced LVEF	We assessed DD and LVFP according to 2009 and 2016 recommendations in 1508 patients. Tested the impact of "myocardial disease" on the prevalence and grading of DD according to the 2016 rec.	The use of the 2016 recommendations results in a lower rate of DD and increased LVFP, at the expense of a higher prevalence of inconclusive diagnosis of DF and of DD grade, compared with the 2009 recommendations. Considering patients' myocardial disease reduces the rate of indeterminant conclusions. This work highlights the critical role of the physician in the application of the DF recommendations, as they should be based on a general and comprehensive echocardiographic assessment combining the available echocardiographic data with patients' clinical information
Pastore MC. et al Heart Fail Rev. 2020 25:937-948.	Basic and advanced echocardiography in advanced heart failure: an overview.	To present an overview of the currently available tools for the echocardiographic examination of patients with HF, with its advantages and limitations,	N/A	N/A

		based on the latest supporting evidences		
Studies on Anderson-Fabry Disease (AFD): the incremental value of Speckle Tracking Imaging				
Esposito R. et al Eur Heart J Cardiovasc Imaging. 2019;20:438-445	Prominent longitudinal strain reduction of left ventricular basal segments in treatment-naïve AFD patients.	To investigate specific regional patterns of LS and base-to-apex behavior of longitudinal deformation in treatment-naive AFD patients.	23 consecutive AFD patients at diagnosis and 23 healthy controls without cardiovascular risk factors and matched for age and sex underwent a comprehensive evaluation of target organs and cardiac echoDoppler exam, including determination of regional and global LS strain (GLS)	Naive AFD patients at diagnosis present a mild but significant reduction of GLS which mainly involves basal myocardial segments, in comparison with healthy controls
Esposito R. et al Echocardiography. 2019;36:1273-1281. Epub 2019 Jun 27.	Layer-specific longitudinal strain in Anderson-Fabry disease at diagnosis: A speckle tracking echocardiography analysis.	Assess layer-specific longitudinal strain in naïve, untreated AFD patients.	33 newly diagnosed, untreated AFD patients and 33 matched controls underwent a complete echocardiogram, including assessment of LV transmural GLS, subendocardial longitudinal	Longitudinal strain decrease involves all myocardial layers. LSsubepi decrease is greater than that of LSsubendo, inducing a significant increase of transmural (endo-epi) myocardial gradient. LV mass or maximal wall thickness increasesare inversely and independently associated with

			strain (LSsubendo), subepicardial longitudinal strain (LSsubepi), and strain gradient (LSsubendo–LSsubpepi).	transmural GLS and LSsubepi,
Esposito R. et al J Clin Med. 2020;9:2741	Association between Left Atrial Deformation and Brain Involvement in Patients with AFD at Diagnosis.	Evaluate possible association between LA structure and function and presence of white matter lesions (WMLs) assessed by brain magnetic resonance imaging derived Fazekas' Score (FS) in patients suffering from AFD.	22 AFD patients and 22 controls, matched for age and sex, underwent an echo-Doppler exam including quantification of peak atrial longitudinal strain (PALS). AFD patients underwent also a 3-T brain MRI with a visual quantification of WMLs by Fazekas' score FS on 3D FLAIR images	treatment-naive AFD patients at diagnosis show a significant reduction of GLS and PALS in comparison with Treatment-naive AFD patients at diagnosis show a significant reduction of GLS and PALS in comparison with healthy controls whereas ejection fraction, peak atrial contraction strain and LA volume index do not differ between the two groups. Patients with greater PALS impairment present a larger involvement of the central nervous system according to FS (≥1). An inverse relation between PALS and FS is detectable in AFD patients.
Esposito R. et al. J Clin Med. 2020;9:2741	Cardiac Imaging in AFD: Past, Present and Future.	Explore the value and perspectives of standard and advanced echocardiography and CMR in Anderson-Fabry disease initial	N/A	N/A

		diagnosis, differential diagnosis, detection of organ damage and timing of therapy initiation		
Studies exploring the Right Ventricle: insights from the "forgotten chamber"				
Buonauro A et al. J Clin Med. 2020;9:587	Impaired Right and Left Ventricular Longitudinal Function in Patients with Fibrotic Interstitial lung Diseases (ILDs)	To analyze LV and RV structure and function in patients with ILDs, including both idiopathic PF (IPF) and no-IPF, by using 2D strain to both ventricles and 3D to the right ventricle. Relationships between lung function and cardiac parameters were also evaluated	33 and therapy-naive fibrotic IPF and 28 no-IPF patients, and 30 healthy controls underwent an echo-Doppler exam including 2D GLS of both ventricles and 3D echocardiographic RV ejection fraction (RVEF). Lung damage was evaluated by diffusion capacity for carbon monoxide (DLCOsb).	IPF patients present LV diastolic dysfunction, which is detectable even in no-IPF patients, and a subclinical LV systolic dysfunction, testified by the reduction of LV GLS but not of LV EF, which cannot be observed in no-IPF patients. An independent association between DLCOsb and RV longitudinal dysfunction is found in the pooled ILDs population, it being evident in the IPF group but not the no-IPF group
Buonauro A et al. Lupus. 2019 [Epub ahead of print]	Three-dimensional echocardiographic evaluation of the right ventricle in patients with uncomplicated systemic lupus	To assess standard and 3DE RV parameters in patients with uncomplicated SLE compared to healthy controls matched in order to identify	50 SLE patients without concomitant cardiac disease and 50 healthy underwent an echo-Doppler examination with 3DE assessment of	In SLE patients with PAH, the standard echocardiographic examination identified only a mild RV enlargement, whereas 3DE volumetric assessment confirmed RV dilation but also highlighted a significant reduction of RV systolic chamber function.

	erythematosus.	possible subclinical RV alterations in this group of patients	RV function, RV septal and lateral LS. Disease damage was evaluated by inflammatory markers and SLE damage index (SDI).	disease damage as evidenced by SDI was independently associated with the degree of RV longitudinal dysfunction
Mandoli GE et al. Heart Fail Rev. 2019;24:625-635	Right ventricular function after cardiac surgery: the diagnostic and prognostic role of echocardiography.	To describe the pathophysiology of the right ventricle, the most used echo indexes of RV function, whether they alter after surgery, the different supposed mechanisms of RV dysfunction and its role in the prognosis of patients undergoing cardiac surgery.	N/A	N/A
Mandoli GE et al. Heart Fail Rev. 2021;26:263-275	Cor pulmonale: the role of traditional and advanced echocardiography in the acute and chronic settings.	To highlight the value of functional and morphological echocardiographic RV parameters, especially those derived from new techniques, represent valuable and easily accessible tools for the clinician in order to assess RV	N/A	N/A

		function in patients with both acute (Figure 2) and chronic cor pulmonale		
Studies focused on cancer related cardiotoxicity				
Santoro C et al. Eur Heart J Cardiovasc Imaging. 2019;20:1345-1352	Strain-oriented strategy for guiding cardioprotection initiation of breast cancer patients experiencing cardiac dysfunction	To assess the impact of the strain-oriented therapeutic approach in reducing the development of overt CTRCD and the rate of CT interruption in breast cancer patients.	116 consecutive female patients with HER2-positive breast cancer undergoing a standard protocol by EC (epirubicine cyclophosphamide) followed by paclitaxel and trastuzumab underwent an echo-Doppler exam with determination of EF and GLS at baseline and every 3 months during CT. All patients developing subclinical (GLS drop >15%) or overt CTRCD (EF reduction <50%) initiated cardiac treatment (ramipril, carvedilol)	GLS allows to identify subclinical CTRCD when EF is still normal, with a prevalence of 23.3% (27/116). GLS-based approach and the consequent and timely initiation of cardioprotection with concomitant ACE-inhibitors and beta-blockers, may have a clear impact on the onset of subsequent overt HF and on CT withdrawn.
Galderisi M. et al J Cardiovasc Echogr. 2020;30(Suppl 1):S33-S37	Atrial Fibrillation, Cancer and Echocardiography	Outline the value of a correct and comprehensive cardiologic and echocardiographic assessment in the setting of cancer patients experiencing AF	N/A	N/A

		for both therapeutic management and prognosis. Moreover, the anticoagulation of cancer patients presenting AF is a main issue because of the difficult balance between thromboembolic and bleeding risks		

AFD= Anderson Fabry Disease; CMR= cardiac magnetic resonance; CT= chemo-therapy; CTRCD= Cancer therapy-related cardiac dysfunction; DD= diastolic dysfunction; GLS= Global longitudinal stain; HF= Heart failure; ILDs= Fibrotic Interstitial lung Diseases; LA= left atrium; LS= longitudinal strain; LVFP= left ventricular filling pressures; N/A= not applicable; RV= right ventricle; SLE= systemic lupus erythematosus

EUROPEAN CURRICULUM VITAE FORMAT

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• Main activities and responsibilities	Clinical care, echocardiography, clinical research

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• Title of qualification awarded	Medical Doctor
• Level in national classification (if appropriate)	

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SCIENTIFIC PUBLICATIONS:

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PERSONAL PRESENTATIONS AT CONGRESSES:

1. Real-time 3-D strain deformation in pregnant women: comparison between term pregnancy and post-partum. 77° Congresso Nazionale della Società Italiana di Cardiologia. **Regina Sorrentino** (Abstract Presenter)
2. Real-time three-dimensional strain deformation in pregnant women: comparison between term pregnancy and post-partum**.** **Regina Sorrentino**, Roberta Esposito, Ciro Santoro, Enrica Pezzullo, Francesco Lo Iudice, Vincenzo Sellitto, Vincenzo Schiano Lomoriello, Maria Lembo, Carla Riccardi, Costantino Di Carlo, Bruno Trimarco, Maurizio Galderisi. Euroecho Imaging Conrgess 2016 (Abstract Presenter)
3. Impact of hemodialysis on three-dimensional left ventricular myocardial deformation in end-stage renal disease: relationships with preload reduction. **R. Sorrentino**, C. Santoro, R. Esposito, E. Pezzullo, A. Buonauro, V. Schiano-Lomoriello, S. Cocozza, A. Vaccaro, B. Trimarco, M. Galderisi. EuroEcho Imaging Congress 2016 (Abstract Presenter).
4. Peri-procedural jailing of septal perforator branch retrospectively identified using speckle tracking echocardiography. **R. Sorrentino**, F. Lo Iudice, E. Stabile, T. Niglio, I. F. Laurino, B. Trimarco, M. Galderisi. Euroecho Imaging Congess 2016 (Clinical Case Presenter)
5. Impact of reclassification of new diastolic recommendations on non-invasive estimation of left ventricular filling pressures.R**egina Sorrentino**, Sara Cocozza, Andrea Vaccaro, Maria Scalamogna, Maria Lembo, Federica Luciano, Robe rta Esposito, Bruno Trimarco, Maurizio Galderisi. 78° Congresso Nazionale della Società Italiana di Cardiologia. (Oral comunication)

6. Impatto clinico della diagnosi subclinica di cardiotossicità con lo strain imaging. 9° Arca imaging. **Regina Sorrentino** (Clinical Case Presenter).
7. Eco-stress farmacologico: il dipiridamolo e la riserva coronarica. Corsi della Cardiologia Universitaria Federico II - CORSO DI ECOCARDIOGRAFIA: LIVELLO INTERMEDIO - Corso teorico-pratico 2017 **Regina Sorrentino** (Tutor)
8. Cuore e Vasi nel paziente iperteso ed in quello diabetico. Valutazione con ecocardiografia standard. Corsi della Cardiologia Universitaria Federico II - CORSO DI ECOCARDIOGRAFIA: LIVELLO INTERMEDIO - Corso teorico-pratico 2017. **Regina Sorrentino** (Tutor)
9. La ranolazina: dai trial alla pratica clinica. Corso teorico pratico sulla cardiopatia ischemica cronica: dalla diagnostica di imaging alla terapia. Napoli 2018 **Regina Sorrentino.** (Tutor)
10. Echocardiography in non-ischemic cardiomyopathies - Prominent reduction of subepicardial strain and increase of transmural myocardial gradient in native Anderson-Fabry disease: a speckle tracking echocardiography study. **Regina Sorrentino. Winner of the Moderated poster session**, ESC congress 2018 (Abstract presenter).
11. Impact of novel recommendations for the evaluation of left ventricular diastolic function in estimating filling pressures in the clinical practice. **Regina Sorrentino** ESC congress 2018 (Abstract presenter).
12. Impact of new recommendations on non-invasive evaluation of left ventricular diastolic function in oncologic patients **Regina Sorrentino** Euroecho congress 2018 (Abstract presenter)

PERSONAL SKILLS AND COMPETENCES

Acquired in the course of life and career but not necessarily covered by formal certificates and diplomas.

Practical 6-years experience in transthoracic standard and advanced echocardiography and stress echocardiography (physical and pharmacological)

MOTHER TONGUE **[ITALIAN]**

OTHER LANGUAGES

[ENGLISH]

• Reading skills	EXCELLENT
• Writing skills	EXCELLENT
• Verbal skills	GOOD

[FRENCH]

EXCELLENT
GOOD
GOOD

List of publications

Esposito R, Ilardi F, Schiano Lomoriello V, Sorrentino R, Sellitto V, Giugliano G, Esposito G, Trimarco B, Galderisi M. Identification of the main determinants of abdominal aorta size: a screening by Pocket Size Imaging Device. Cardiovasc Ultrasound. 2017 Jan 13;15(1):2

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Esposito R, Santoro C, Sorrentino R, Alcidi G, De Roberto AM, Santoro A, Tufano A, Trimarco B, Galderisi M. The role of cardiovascular ultrasound in diagnosis and management of pulmonary embolism. Future Cardiol. 2017 Aug 23

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Buonauro A, Sorrentino R, Esposito R, Nappi, Lobasso A, Santoro C, Rivellese C, Sellitto V, Rossi FW, Liccardo B,Tufano A, Galderisi M, de Paulis A. Three-dimensional echocardiographic evaluation of the right ventricle in patients with uncomplicated systemic lupus erythematosus. Lupus. 2019 [Epub ahead of print]

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