International PhD program in Cardiovascular Pathophysiology and Therapeutics

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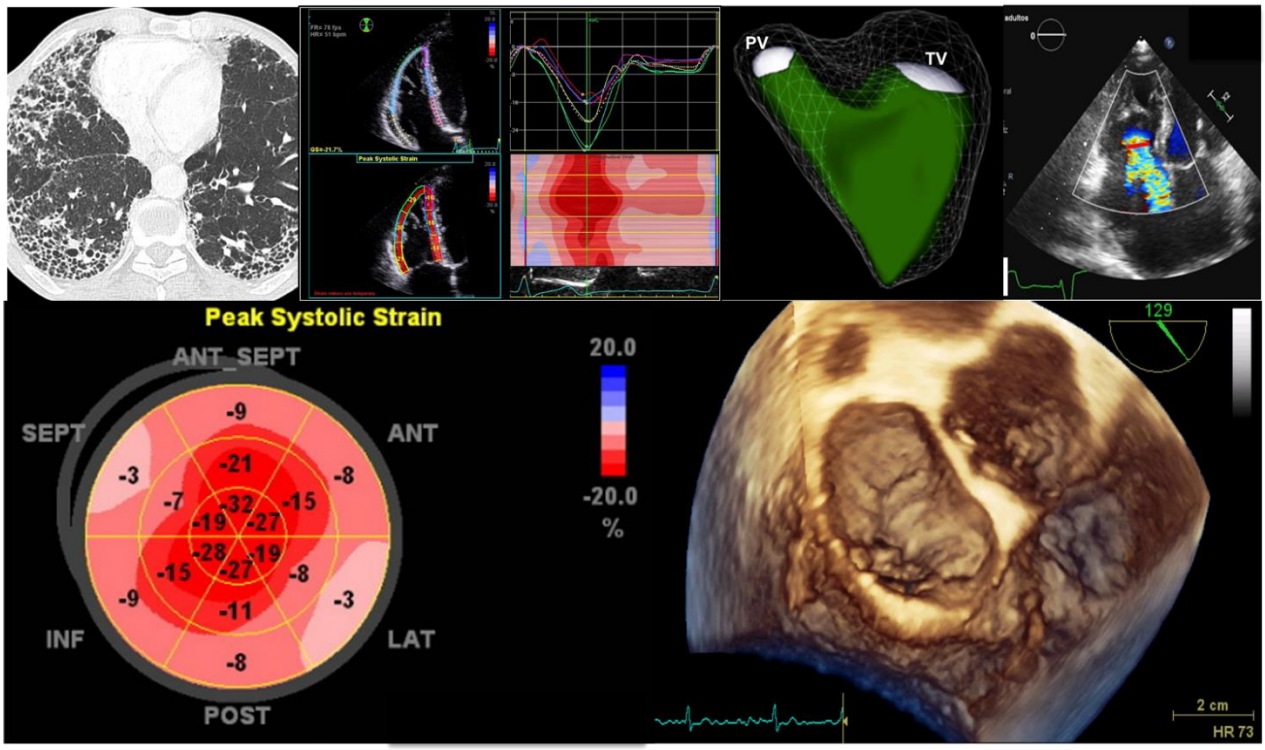

New perspectives in cardiac imaging based on novel echocardiographic techniques

PhD thesis

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New perspectives in cardiac imaging based on novel Echocardiographic techniques

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"A good researcher is also a good clinician"

Maurizio Galderisi

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Chapter 1. General introduction and outline of the thesis

The use of cardiac ultrasound has currently become a pivotal tool in the hand of the clinician that integrate sign and symptoms of the clinical examination and giving relevant information to diagnose and treat cardiovascular disease. It's high availability and the absence of radiation exposure made this diagnostic technique the preferred one in the setting of first diagnosis (i.e. screening) and follow up. The advancement in software and hardware empowered the accuracy and the resolution of the imaging overcoming almost entirely the main limitation of this tool; the inadequate acoustic windows.

Another limitation that affect cardiac ultrasound is the suboptimal interobserver reproducibility due to subjective evaluation for most of the measurement computed during echocardiographic examination, particularly when assessing the global and regional systolic function of the left ventricle. Indeed, left ventricular ejection fraction (LVEF) is considered the most representative parameter of systolic function among cardiologist and non-cardiologist. However, its suboptimal reproducibility makes arduous to determine subtle changes in systolic function during the follow up. Additionally, LVEF is affected by changes in pre- and after-load, furtherly jeopardize the assessment of LV function in those conditions where dynamic changes in volume load are on the agenda, namely in valvular heart disease and in patients undergoing chemotherapy for cancer.

Speckle tracking echocardiography (STE) meant to overcome mostly this limitation by using a semiautomated software that allows to determine the deformation (strain) of the myocardial fibers through the cardiac cycle (1). Among direction strain (i.e. longitudinal, circumferential, radial

strain), the assessment of the global longitudinal strain (GLS) showed to be a pivotal diagnostic tool with prognostic impact in different conditions such as hypertension, cardiomyopathies, valvular heart disease and in the LV surveillance during anti- cancer treatment. (1-5)

Part I. Cardio-oncology - From diagnosis to treatment

Nowadays, cancer therapy (CT) progressively prolongs survival in oncologic diseases. Nevertheless, it may expose patients to lifethreatening complications involving cardiovascular system. Thus, cardiotoxicity may become one of the main determinants of quality of life impairment and mortality in this specific population.(5,6)

Anti-cancer drugs can lead to several adverse cardiovascular effects, such as arterial hypertension, myocardial ischaemia, thromboembolic complications, arrhythmias, and conduction disturbances.(7) However, the most frequent and clinically relevant form of cardiotoxicity corresponds to a dilated and hypokinetic cardiomyopathy leading to overt heart failure (HF).(7) 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), while other agents, such as trastuzumab (TRZ), lead to a non-dose-related but reversible cardiac impairment (Type II cardiotoxicity).(9-11) The sequential or concurrent use of these two different types of agents may increase myocardial injury and CTRCD is often the result of the combined detrimental effect of the two therapies.(11) A timely initiation of cardioprotective treatment for CTRCD is pivotal to continue the ongoing CT till completion and reduce the risk of overt HF. Cardiac treatment of CTRCD is currently guided by 2D echocardiographic evaluation of left ventricular (LV) ejection fraction (EF).(12)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.(13) As an alternative, global longitudinal strain (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.(14)

Part II. Valvular Heart Disease - Novel diagnostic assessment

In the evaluation of patients with valvular heart disease (VHD) clinical history, physical examination and previous diagnostic studies are pivotal to frame the severity of this disease. Nevertheless, diagnostic imaging represents a necessary approach to a careful evaluation of concomitant valve lesions and to screen other lesions that might be misdiagnosed as VHD such as subaortic membrane, ventricular septal defect or dynamic obstruction. Echocardiography is considered the preferred diagnostic modality to evaluate valve disease, providing information on both structure and function of the valves. The management of mitral regurgitation (MR), the most common valvular heart disease in the developed world [15], is mainly based on symptoms and signs of left ventricular (LV) dysfunction [16,17]. Nevetherless, physicians face difficulties in detecting subtle progression of symptoms related to MR deterioration. Patients might unwittingly limit their physical activity because of worsening exercise capacity and overt symptoms. In this clinical setting, physicians are requested to perform a strict follow-up mainly using echocardiographic parameters to detect early signs of LV failure. Nowadays, standard echocardiographic parameters, mainly two-dimensional derived LV ejection fraction (LVEF), are the most used for evaluating LV function and prognosis in patients with MR [18]. However, despite a preserved LVEF, patients with chronic MR often hide an underlying myocardial contractility impairment [19]. LVEF does not take into account the amount of blood flow pushed back in the low-pressure left atrial (LA) cavity, which does not contribute to the effective stroke volume.

Accordingly, patients with chronic MR and impaired LVEF may already have developed an irreversible, undiagnosed myocardial damage. The efforts of cardiologists should be addressed to search for alternative parameters that could unmask subtle, insidious changes in LV contraction. LV deformation as assessed by speckle tracking echocardiography (STE) has proven to detect subclinical cardiac involvement and have prognostic value in different pathologic conditions [20,21]. Analysis of myocardial LV deformation by STE also identified early LV dysfunction in patients with asymptomatic severe MR. GLS have demonstrated to predict 5-years all-cause mortality risk in patients with acute heart failure independently from LVEF values [22]. LV global longitudinal strain (GLS) at rest is also a strong predictor of long-term prognosis in a large population of symptomatic patients with severe primary MR and preserved LVEF [23].

Part III. Cardiomyopathies - the role of cardiac imaging for early diagnosis and follow up

Two-dimensional and Doppler echocardiography remains the first line imaging tool for most forms of heart muscle disease. Some features are important diagnostic red flags. As with the electrocardiogram, these are only useful when interpreted in the context of other phenotypic findings.

In Anderson-Fabry disease (AFD), a rare X-linked metabolic disorder due to deficiency in lysosomal enzyme activity of a-galactosidase A (a-GAL), pathological accumulation of glycosphingolipids occurs in several tissues and a multi-organ progressive dysfunction.(24,25) Renal failure, cardiomyopathy, as well as peripheral and central nervous system alterations are the main causes of morbidity and mortality.(24)AFD cardiomyopathy has been described in both genders, in a specific late-onset cardiac variant, and is largely associated with left ventricular (LV) hypertrophy (LVH), impaired diastolic function, and late systolic dysfunction. (26-28) LVH is due to

glycosphingolipids myocyte accumulation in early phases and to myocardial replacement fibrosis in the late disease stages.6–9 AFD can mimic clinical and structural features of hypertrophic cardiomyopathy (27,28) and be observed in up to 6% of men and 12% of women with late-onset hypertrophic cardiomyopathy.(28,29). Speckle-tracking echocardiography is an advanced ultrasound technique, which provides comprehensive information on myocardial mechanics.(30,31) Among the different myocardial deformation components, global longitudinal strain (GLS) has shown the best ability in detecting subclinical cardiac involvement.(30) The regional distribution of longitudinal strain (LS) has also shown typical patterns in different types of LVH, (32) mainly in cardiac amyloidosis, which is characterized by a typical LS reduction in basal LV segments, with a relative apical sparing.(33,34) A reduction of GLS has also been associated with myocardial fibrosis as identified by native T1 mapping in early AFD,(35) but little is known about the regional LS distribution in the subclinical stages of AFD cardiomyopathy.

GLS was also demonstrated to be associated with the extent of myocardial fibrosis and degree of LV filling pressures in the hypertensive setting (36,37).

LV global mechanics involves a complex system of differently oriented but intimately connected myocardial fibers constituting LV architecture, which, with a not homogenous deformation of basal, mid, and apical ventricular segments, provides coordinated LV contraction.

Part IV. Cardiovascular and systemic disease – a dangerous liaison

Numerous systemic diseases such as arterial systemic hypertension, diabetes mellitus, obesity, haemochromatosis, sarcoidosis, systemic sclerosis, storage disorders (e.g. Fabry, Pompe) endomyocardial fibrosis, and others can affect the heart. Since signs of cardiac involvement by systemic disorders can be subtle, a comprehensive echocardiographic examination is required.

The occurrence of Pulmonary arterial hypertension (PAH) is frequently found in the early stages of pulmonary disease such as idiopathic pulmonary fibrosis (IPF) and the outcome is directly related to the capacity of right ventricular (RV) function to adapt to the elevated afterload [38,39]. The combination of severe vascular and fibrotic abnormalities induces changes in right ventricular (RV) structure and function until heart failure onset [40]. 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 [41]. Also, an impairment of left ventricular (LV) diastolic filling has been observed, whereas LV systolic function appears to be preserved [42]. STE has shown to be suitable for diagnosing early cardiac dysfunction in different systemic diseases [43,44]. Conversely, LV and RV function have been poorly explored by advanced echo technologies in fibrotic interstitial lung diseases (ILDs) and no comparison of strain and 3D echocardiographic imaging exists between patient affected by IPF and non idiopathic pulmonary fibrosis (no-IPF).

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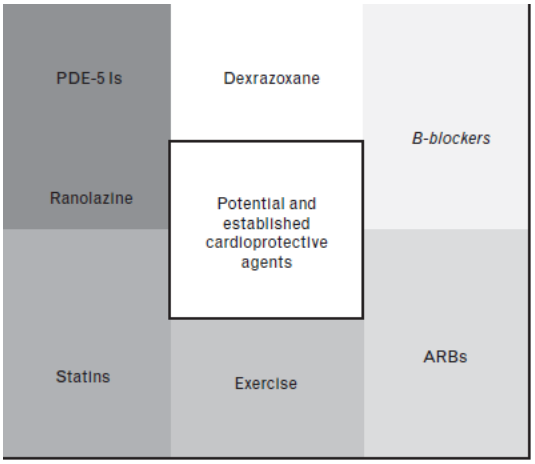
Chapter 1. Chemotherapy-induced cardiotoxicity: new insights into mechanisms, monitoring, and prevention

Chemotherapy-induced cardiotoxicity (CTX) remains a determining factor for the quality of life and mortality of patients treated with potentially cardiotoxic drugs. Considerable advances have been made in this field with increase in awareness regarding chemotherapy-induced CTX, which has changed the treatment approach to include cardiovascular risk among the first factors to be evaluated before therapy. Moreover, a better understanding of the pathophysiology of chemotherapy-induced CTX has also facilitated early identification of patients at risk with the help of new imaging technologies. The newly developed imaging tools in cardio-oncology have led to the introduction of novel parameters for evaluation of myocardial function. This, together with a renewed standardization of measurements, has increased the adherence to monitoring protocols. With respect to treatment and prevention, researchers have started focusing attention on the development of new strategies as well as new cardioprotective agents that will play a crucial role in the prevention of CTX in the near future.



Gradient of evidence in cardioprotective strategies from white to darker colors.

Chapter 3. Redox Imbalances in Ageing and Metabolic Alterations: Implications in Cancer and Cardiac Diseases.

Metabolic syndrome (MetS) is a well established risk factor for cardiovascular (CV) diseases. In addition, several studies indicate that MetS correlates with the increased risk of cancer in adults. The mechanisms linking MetS and cancer are not fully understood. Several risk factors involved in MetS are also cancer risk factors, such as the consumption of high calorie-food or high fat intake, low fibre intake, and sedentary lifestyle. Other common aspects of both cancer and MetS are oxidative stress and inflammation.

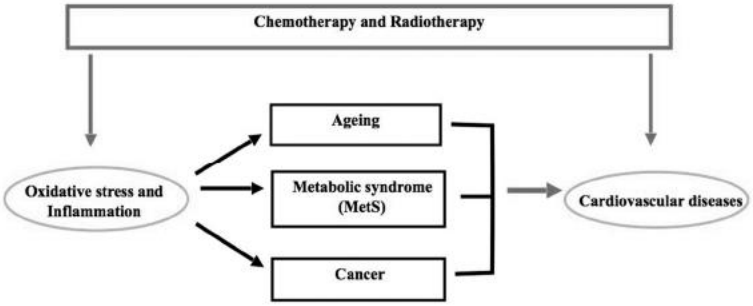
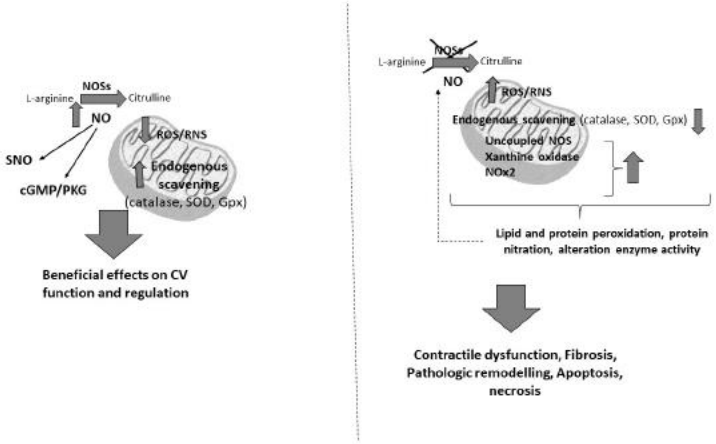


Figure 1. Metabolic syndrome and cardiotoxicity.



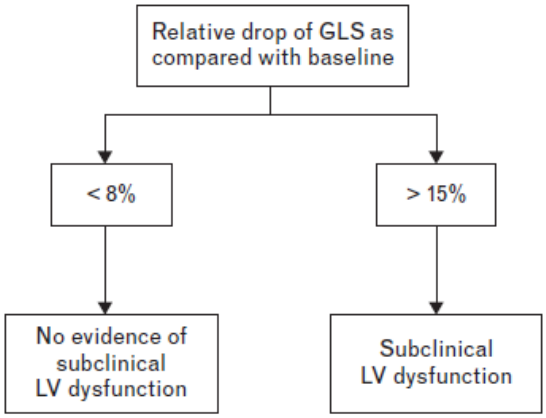
Mechanism action of reactive oxygen species (ROS). (RNS, Radical Nitrogen Species; CV, cardiovascular).

In addition, some anticancer treatments can induce cardiotoxicity, including, for instance, left ventricular (LV) dysfunction and heart failure (HF), endothelial dysfunction and hypertension. In this review, we analyse several aspects of MetS, cancer and cardiotoxicity from anticancer drugs.

We focus on oxidative stress in ageing, cancer and CV diseases, and we analyse the connections among CV risk factors, cancer and cardiotoxicity from anticancer drugs.

Chapter 4. SUCCOUR investigators. Rationale and Design of the Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes: The SUCCOUR Trial.

OBJECTIVES This study sought to evaluate the hypothesis that global longitudinal strain (GLS) guidance of cardioprotective therapy would improve cardiac function of at-risk patients undergoing potentially cardiotoxic chemotherapy, compared with usual care.

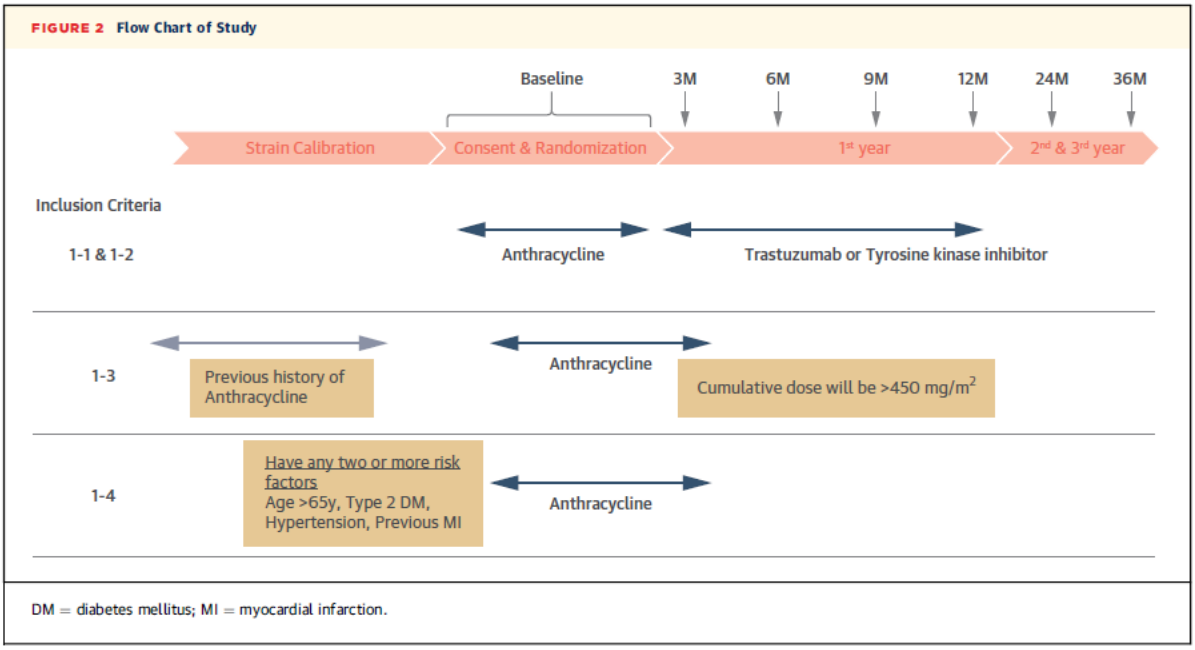


Early detection of subclinical cardiotoxicity using global longitudinal strain in oncologic patients undergoing anticancer therapy.

BACKGROUND The conventional criteria for diagnosis of chemotherapy-related cardiac dysfunction (CTRCD) are dependent on the recognition of heart failure symptoms and/or changes in left ventricular ejection fraction. However, the measurement variability of left ventricular ejection fraction necessitates broad diagnostic ranges, with the consequence of low sensitivity for CTRCD. Observational data have shown GLS to be a robust and sensitive marker to predict CTRCD and thereby guide the initiation of cardioprotective therapy, but these data are insufficient to justify changing the diagnostic criteria for CTRCD.

METHODS The SUCCOUR trial is an international multicenter prospective randomized controlled trial. Patients who are taking cardiotoxic chemotherapy (n ¼ 320) with at least 1 risk factor will be randomly allocated into GLS- and ejection fraction–guided strategies. All participants will be followed over 3 years for the primary endpoint (change in 3- dimensional ejection fraction) and other secondary endpoints.

RESULTS Among the first 185 patients (age 54 ± 13 years; 93% women) from 23 international sites, 88% had breast cancer, 9% had lymphoma, and 3% had other cancers. Heart failure risk factors were prevalent: 34% had hypertension and 10% had diabetes mellitus. The most common chemotherapy regimen during this study was the combination of anthracycline and trastuzumab. The baseline 3-dimensional left ventricular ejection fraction was 61 4%, and GLS was 20.3 ± 2.5%. Of 93 patients followed up in the first year of the study, 10 had to withdraw for noncardiac reasons. Of 40 patients randomized to the GLS-guided arm, 15 have been started on cardioprotective therapy, whereas 4 of 46 patients in the ejection fraction–guided arm have been started on therapy.



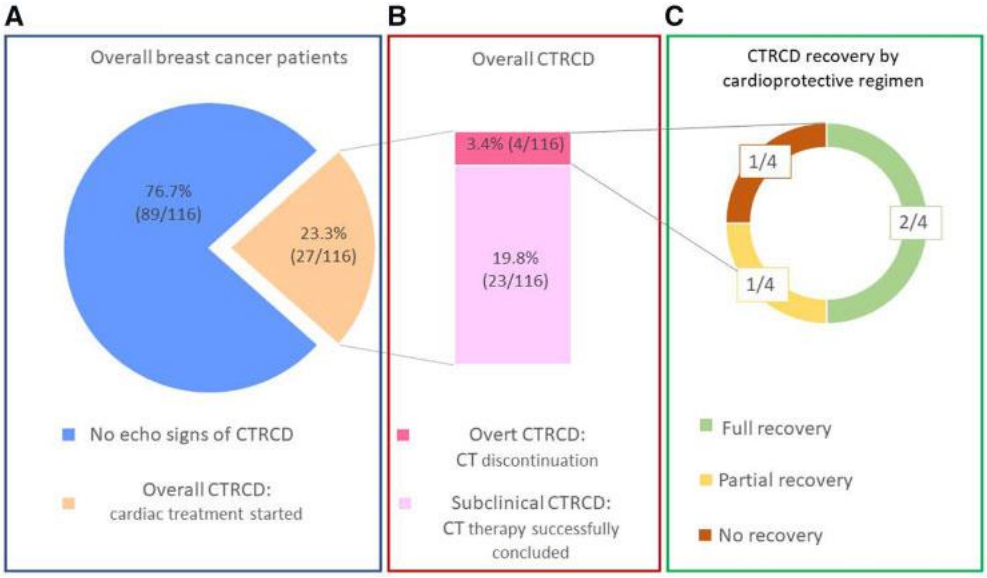
CONCLUSIONS The SUCCOUR trial will be the first randomized controlled trial of GLS and will provide evidence to inform guidelines regarding the place of GLS for surveillance for CTRCD. (Strain sUrveillance of Chemotherapy for improving Cardiovascular Outcomes [SUCCOUR]; ANZ Clinical Trials ACTRN12614000341628)

Chapter 5. Strain-oriented strategy for guiding cardioprotection initiation of breast cancer patients experiencing cardiac dysfunction

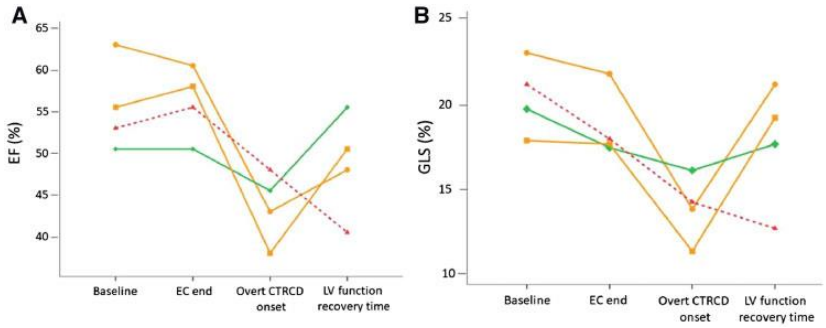
Aims This study assessed the impact of the strain-guided therapeutic approach on cancer therapy-related cardiac dysfunction (CTRCD) and rate of cancer therapy (CT) interruption in breast cancer.

Methods and results. 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, heart failure, primary cardiomyopathies, permanent or persistent atrial fibrillation, and inadequate echo-imaging were exclusion criteria. Patients underwent an echo-Doppler exam with

determination of ejection fraction (EF) and global longitudinal strain (GLS) at baseline and every 3 months during CT.



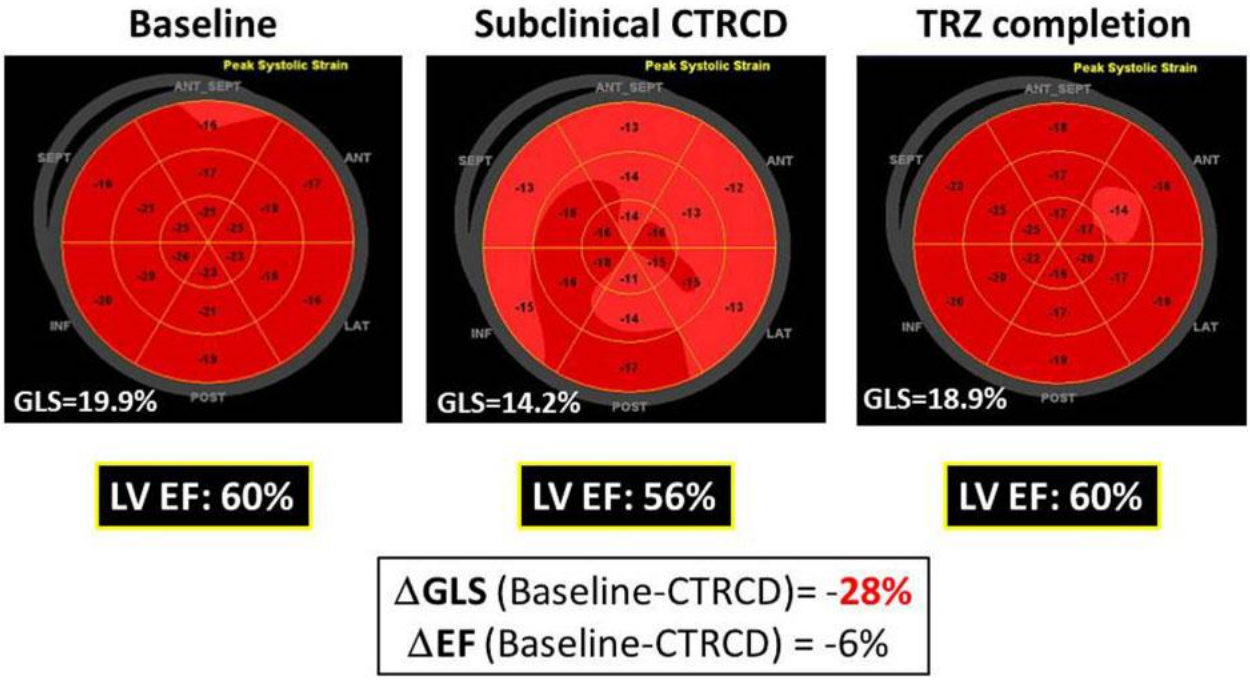
All patients developing subclinical (GLS drop >15%) or overt CTRCD (EF reduction <50%) initiated cardiac treatment (ramipril carvedilol). In the 99.1% (115/116) of patients successfully completing CT, GLS and EF were significantly reduced and E/e0 ratio increased at therapy completion. Combined subclinical 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.

Conclusion. These findings highlight the usefulness of 'strain oriented' approach in reducing the rate of overt CTRCD and CT interruption by a timely cardioprotective treatment initiation.

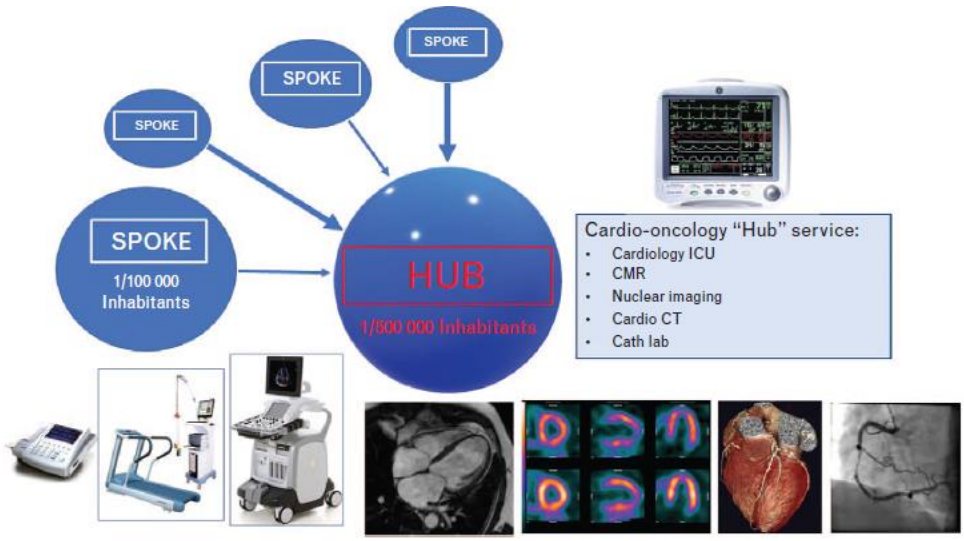


Clinical case of a patients developing subclinical CTRCD at the XI TRZ cycle but completing successfully TRZ thanks the timely cardioprotective treatment. Bull's eyes of GLS at baseline (left), at the time of subclinical CTRCD (mid), and at cancer therapy completion (right). CTRCD, cancer therapy-related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

Chapter 6. Rationale and proposal for Cardio-oncology Services in Italy

In the last 20 years, a substantial improvement in the efficacy of cancer treatment has induced a progressive increase of cancer survival, with an obvious parallel increase of morbidity and mortality related to the adverse effects of anticancer therapy, in particular, cardiovascular

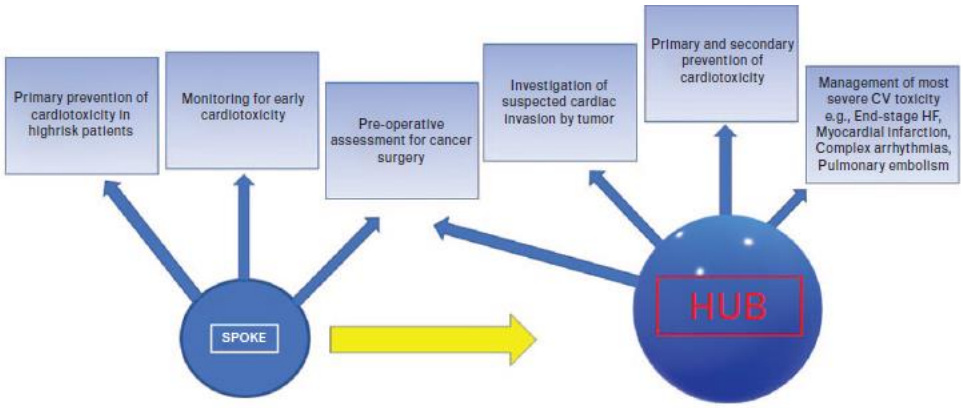
complications. In relation with the peculiar aspects related to the cardiac and vascular toxicity, clinical management of patients should be ideally reserved to experts in the field of this novel medical discipline, which has been defined as cardio-oncology. The rationale for this choice corresponds to the aim of identifying patients more prone to develop cardiovascular damage, prevent overt cardiotoxicity and make active surveillance of treated patients for early identification of cardiac and vascular involvement during short and long-term follow-up. Due to the burden of treated cancer patients, the development of dedicated cardiooncology services become one of the main goals of the contemporary medicine, needed to accomplish the peculiar mission of guiding the patients through the narrow path of cancer survival without the expense of cardiovascular damaging.



The main purpose of cardio-oncology services is to provide dedicated cardiologic care to cancer patients affected by concomitant (subclinical or overt) cardiovascular diseases, either preexisting the cancer onset or acquired during and after the time course of anticancer therapy. In this article, we describe a possible spoke-hub model of Cardio-Oncology Services, which could be appropriately applied in Italy. Rationale, organization, definition of referral criteria, strategies,

interventional programs, long-term surveillance and home assistance of this model are described and discussed.

Implications. The modern medicine takes now in great account the interaction of different specialized disciplines in order to improve the quality of care, the patient's management and the outcome. In this context, the standardization of Cardio-Oncology procedures might be auspicable to face effectively cancer-related adverse effects. Cardio-oncology Services should be efficiently created to provide a suitable prevention and management of the main cardiovascular complications occurring during or after completion of the various anticancer therapies. A spoke-hub system is proposable as a possible winning strategy in Italy, making possible a dedicated cardiac care of oncologic patients in all the national territories.



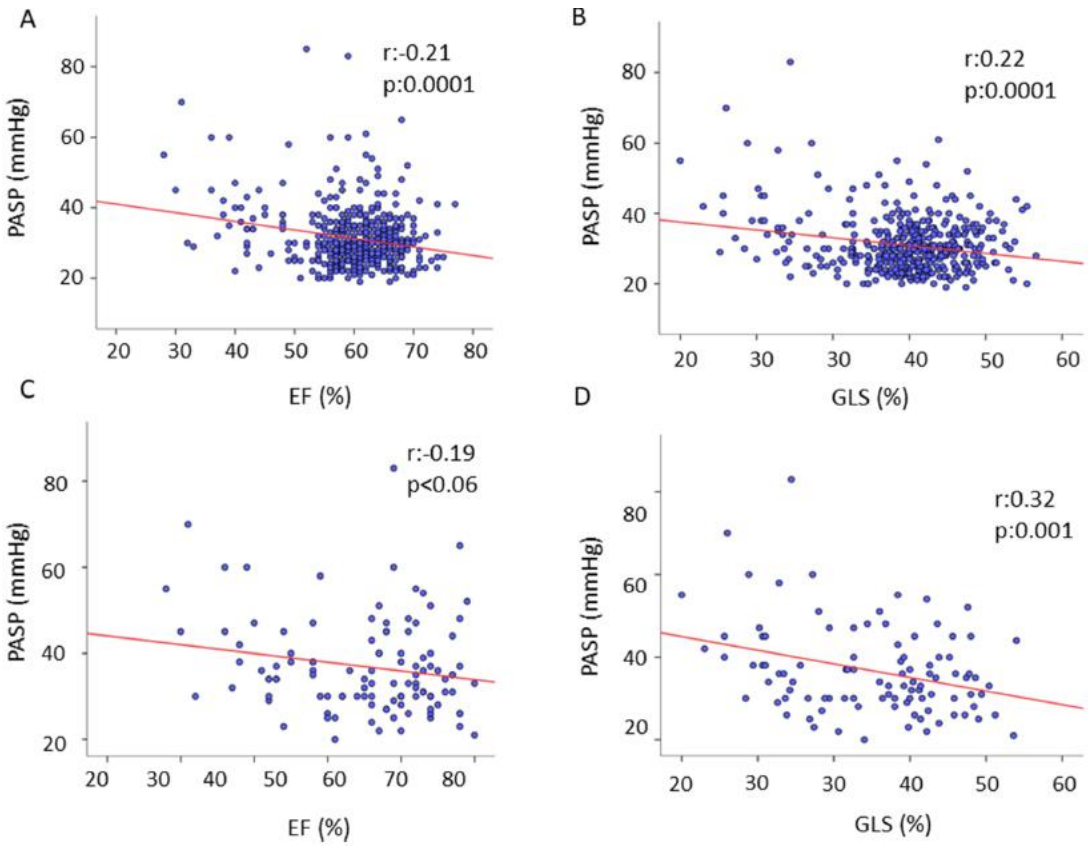
A greater interaction among oncologists/hematologists is needed to achieve this goal, sharing the respective knowledge and competence with other medical disciplines involved in the assistance of this very delicate clinical setting.

Part II. Valvular Heart Disease - Novel diagnostic assessment

Chapter 7. Global longitudinal strain is a hallmark of cardiac damage in mitral regurgitation: the Italian arm of the European Registry of mitral regurgitation (EuMiClip).

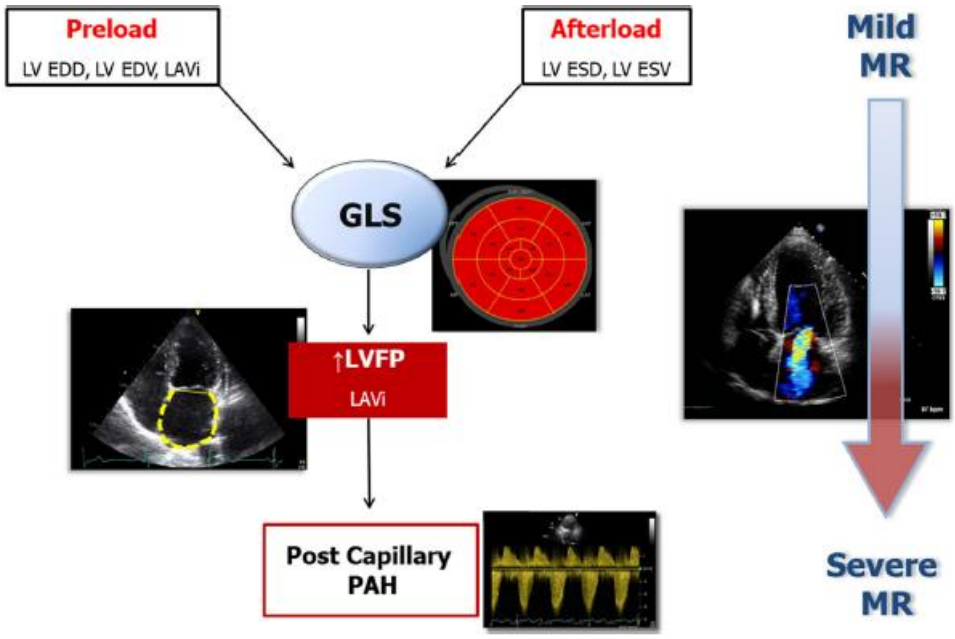
Background: The search for reliable cardiac functional parameters is crucial in patients with mitral regurgitation (MR). In the Italian arm of the European Registry of MR, we compared the ability of global longitudinal strain (GLS) and left ventricular (LV) ejection fraction (LVEF) to detect cardiac damage in MR.

Methods: Five hundred four consecutive patients with MR underwent a complete echo-Doppler exam. A total of 431, 53 and 20 patients had degenerative, secondary and mixed MR, respectively. The main echocardiographic parameters, including LV and left atrial (LA) size measurements, pulmonary artery systolic pressure (PASP) and GLS were compared between patients with mild MR (n = 392) vs. moderate to severe MR (n = 112).



Results: LVEF and GLS were related one another in the pooled population, and separately in patients with mild and moderate/severe MR (all $p < 0.0001$). However, a certain number of patients were above the upper or below the lower limits of the 95% confidence interval (CI) of the normal relation in the pooled population and in patients with mild MR. Only 2 patients were below the 95% CI in moderate to severe MR. After adjusting for confounders by separate multivariate models, LVEF and GLS were independently associated with LV and left atrial size in

the pooled population and in mild and moderate/severe MR. GLS, but not LVEF, was also independently associated with PASP in patients with mild and moderate to severe MR.



Conclusions: Both LVEF and GLS are independently associated with LV and LA size, but only GLS is related to pulmonary arterial pressure. GLS is a powerful hallmark of cardiac damage in MR.

Chapter 8. Mid-term outcome of severe tricuspid regurgitation: are there any differences according to mechanism and severity?

Aims Patients with significant tricuspid regurgitation (TR) addressed according the new classification in torrential TR may have different prognosis compared with just severe TR patients. We sought to determine distribution and mechanism of consecutive severe TR patients, in accordance with aetiology and severity by applying the new proposed classification scheme and their long-term outcomes.

Methods and results Between January and December 2013, 249 patients with significant TR referred to the cardiac imaging unit (mean age 79.9 ± 10.2 years; 29.8% female) were included.

Patients were divided according to aetiology in six groups, and TR severity was reclassified into severe, massive, and torrential TR. The follow-up period was of 313 ± 103 days.

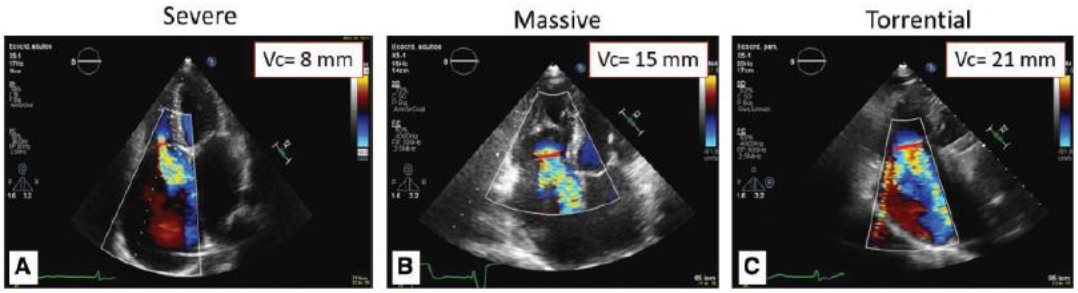
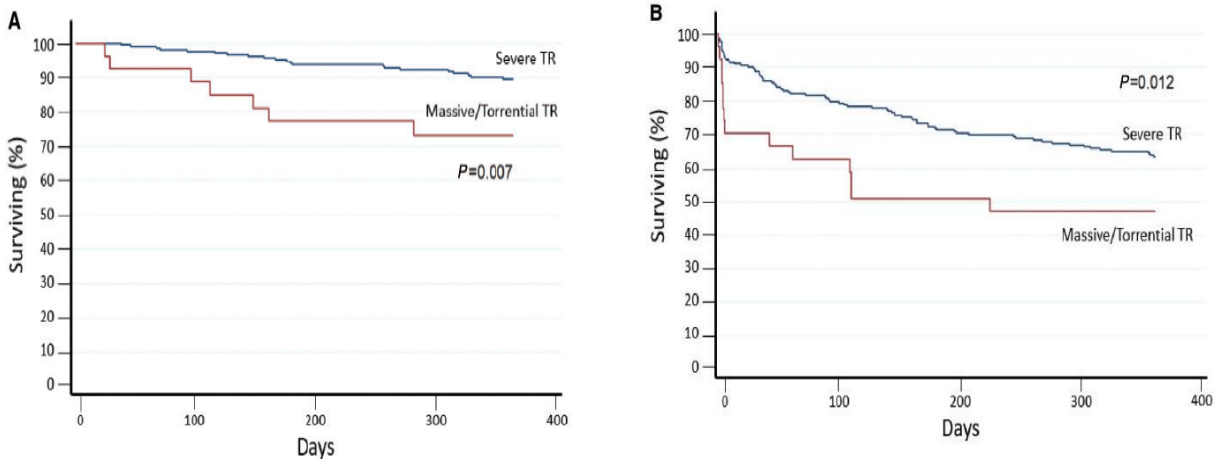


Table on the proposed expansion of the «severe» grade

Variable	Mild	Moderate	Severe	Massive	Torrential
VC (biplane)	<3 mm	3-6.9 mm	7-13 mm	14-20 mm	≥21 mm
EROA (PISA)	<20 mm^2	20-39 mm^2	40-59 mm^2	60-79 mm^2	≥80 mm^2
3D VCA or quantitative EROA			75 – 94 mm^2	95-114 mm^2	≥115 mm^2

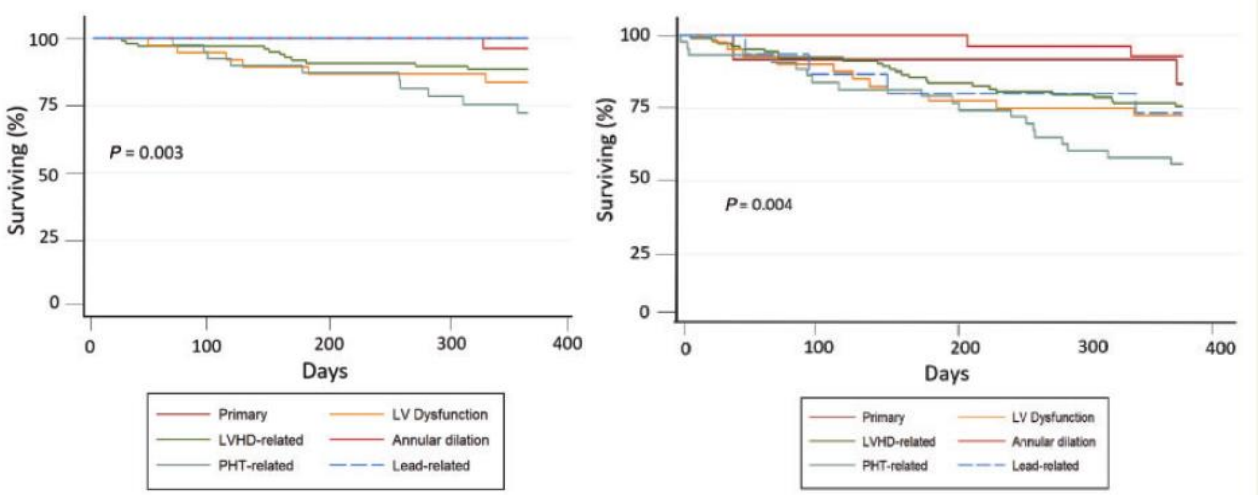
When considering cardiovascular mortality, patients in the massive/torrential group showed the highest number of events (P < 0.007). Patients with TR due to pulmonary diseases had the worst prognosis according to different aetiology.



Noteworthy, the best predictors for the combined endpoint [cardiovascular mortality and readmission admission for heart failure (HF)] were TR severity according to the new classification [hazard ratio (HR) 2.48, 95% confidence interval (CI) 1.25–4.93] and clinical scores such as New York Heart Association classification and congestive status (HR 1.78, 95% CI 1.28–2.49; HR 2.08,

95% CI 1.06–4.06, respectively).

Conclusion Patients with massive/torrential TR and patients with comorbidities, especially



pulmonary disease, were identified as populations at higher risk of death and readmission for HF. New classification scheme and clinical assessment may establish who may benefit the most of intensive therapeutic treatments and intervention on the tricuspid valve.

Chapter 9. Right ventricle assessment in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation.

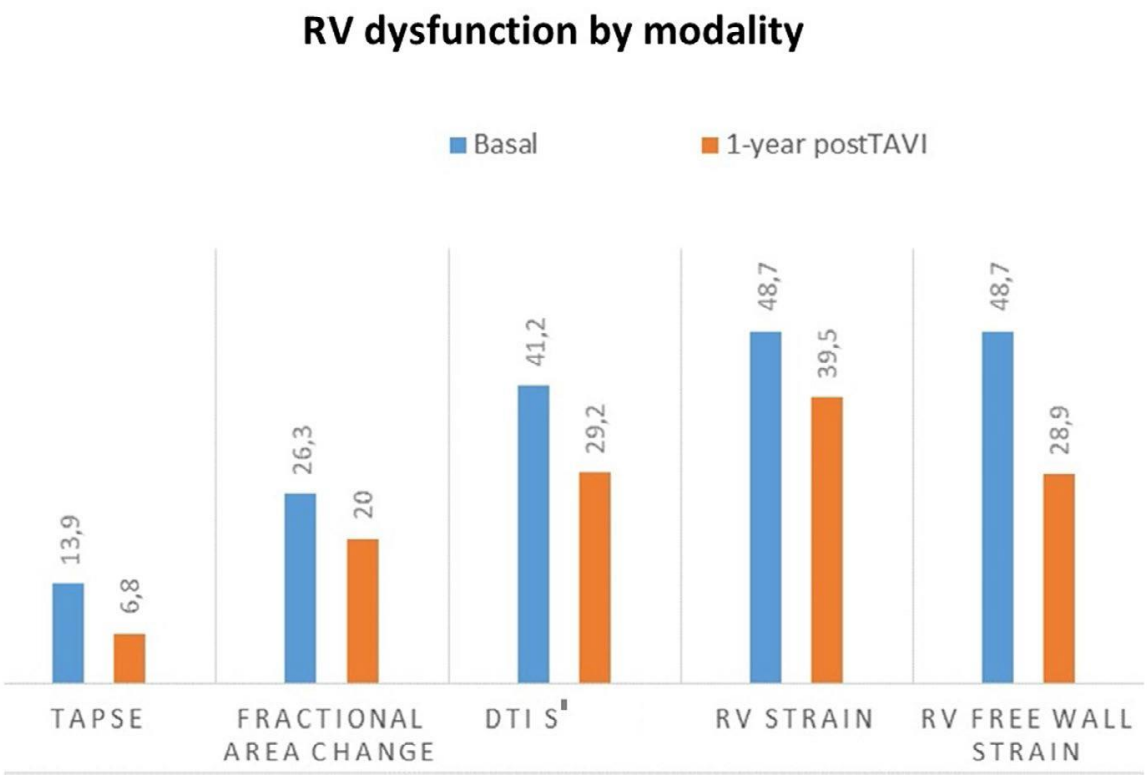
Introduction: Limited data are available regarding the evaluation of right ventricular (RV) performance in patients with aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI).

Objective: To evaluate the prevalence of RV dysfunction in patients with severe AS undergoing TAVI and long-term changes.

Methods: Consecutive patients with severe AS undergoing TAVI from January 2016 to July 2017 were included. RV anatomical and functional parameters were analyzed:

RV diameters, fractional area change, tricuspid annular plane systolic excursion (TAPSE), S-wave tissue Doppler of the tricuspid annulus (RV-S'TDI), global longitudinal strain (RV-GLS), and free wall strain (RV-FWS). Preprocedure and 1-year echo were analyzed.

Results: Final population included 114 patients, mean age 83.63 ± 6.31 years, and 38.2% women. The prevalence of abnormal RV function was high, variable depending on the parameter that we analyzed, and it showed a significant reduction 1 year after TAVI implantation: 13.9% vs 6.8% (TAPSE < 17mm), P = .04; 26.3% vs 20% (fractional area change < 35%), P = .048; 41.2% vs 29.2% (RV-S'TDI < 9.5cm/s), P = .04; 48.7% vs 39.5% (RV-GLS > [20]), P = .049; and 48.7% vs 28.9% (RV-FWS > [20]), P = .03.



Significant differences were noted between patients with low-flow (LF) vs normal-flow (NF) AS in RV dysfunction prevalence as well as in RV function recovery which is less evident in LF compared with NF patients.

Conclusions: RV dysfunction is high among symptomatic AS patients undergoing TAVI, with variable prevalence depending on the echocardiographic parameter used.

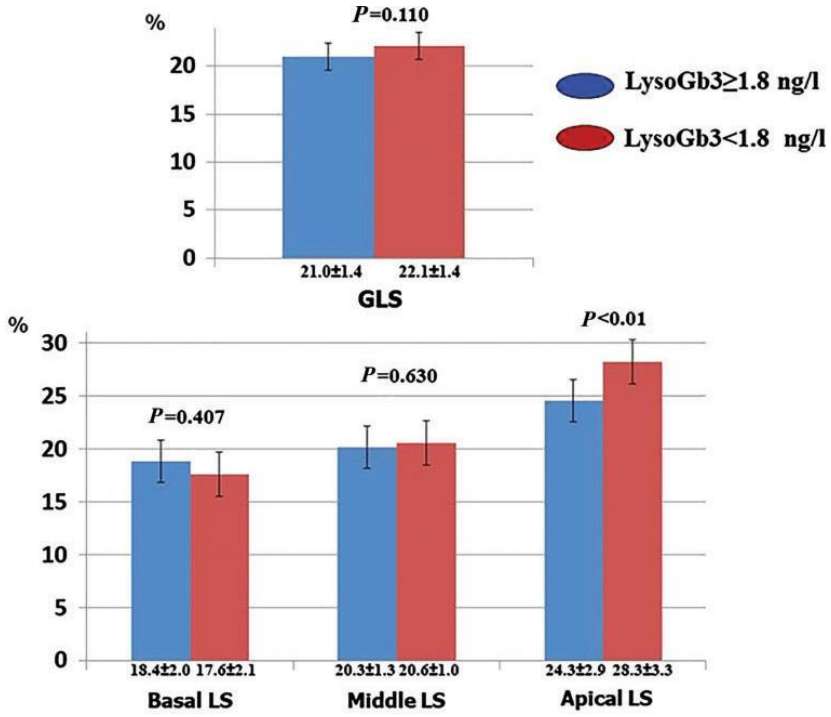
Part III. Cardiomyopathies - the role of cardiac imaging for early diagnosis and follow up

Chapter 10. Prominent longitudinal strain reduction of left ventricular basal segments in treatment-naıve Anderson-Fabry disease patients

Aims. Little is known about regional longitudinal strain (LS) distribution in early stages of Anderson-Fabry disease (AFD) cardiomyopathy. We investigated regional left ventricular (LV) patterns of LS strain and base-to-apex behaviour of LS in treatment-naı¨ve 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 echo Doppler 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).

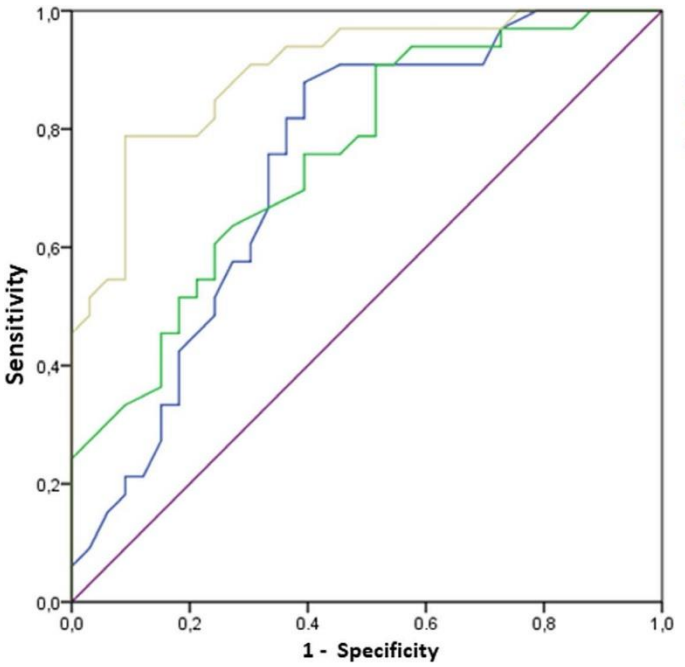


Conclusion. In naive AFD patients, we observed an early reduction of LV LS, involving mainly LV basal myocardial segments. Nevertheless, the association found between the higher lysoGB3 levels and the lower apical cap LS demonstrates that apical segments LS, despite still normal, is not spared at diagnosis.

Chapter 11. Layer-specific longitudinal strain in Anderson–Fabry disease at diagnosis: A speckle tracking echocardiography analysis

Background: Speckle tracking advancements make now available the analysis of layer-specific myocardial deformation. This study investigated multilayer longitudinal strain in Anderson–Fabry disease (AFD) patients at diagnosis.

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 left ventricular (LV) transmural global longitudinal strain (GLS), subendocardial longitudinal strain (LSsubendo), subepicardial longitudinal strain (LSsubepi), and strain gradient (LSsubendo–LSsubpepi).



	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

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

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. 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

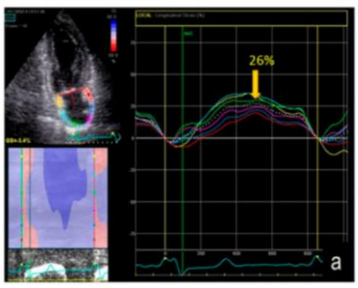
in the AFD group. At receiver operating curve curves, LSsubepi best discriminated AFD and normals.

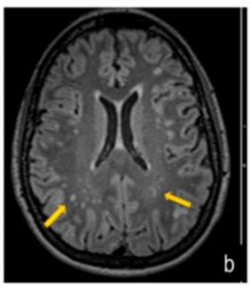
Conclusions: In newly diagnosed, untreated AFD patients, layer-specific strain imaging highlights an impairment of LV longitudinal deformation, mainly involving subepicardial strain and causing increase in longitudinal strain myocardial gradient. These findings could be useful for identifying the mechanisms underlying early LV dysfunction in AFD patients.

Chapter 12. Association between Left Atrial Deformation and Brain Involvement in Patients with Anderson-Fabry Disease at Diagnosis

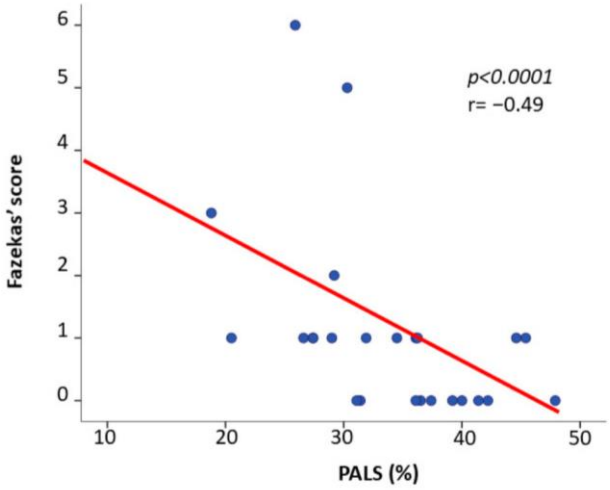
Background: Anderson-Fabry disease (AFD) can induce both central nervous system white matter lesions (WMLs) and cardiac abnormalities including left atrial (LA) dysfunction. We sought to evaluate the possible interrelations of LA structure and function impairment with the presence of WMLs in AFD patients.

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 magnetic resonance imaging with a visual quantification of WMLs by Fazekas' score (FS) on 3D FLAIR images.





Results AFD patients had significantly higher left ventricular (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 di difference in LA volume index and LVMi.



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). Conclusions In the absence of significant alterations in LA size, AFD patients had lower PALS compared to controls. The inverse association between PALS and presence of WMLs indicates a possible parallel early involvement of heart and brain.

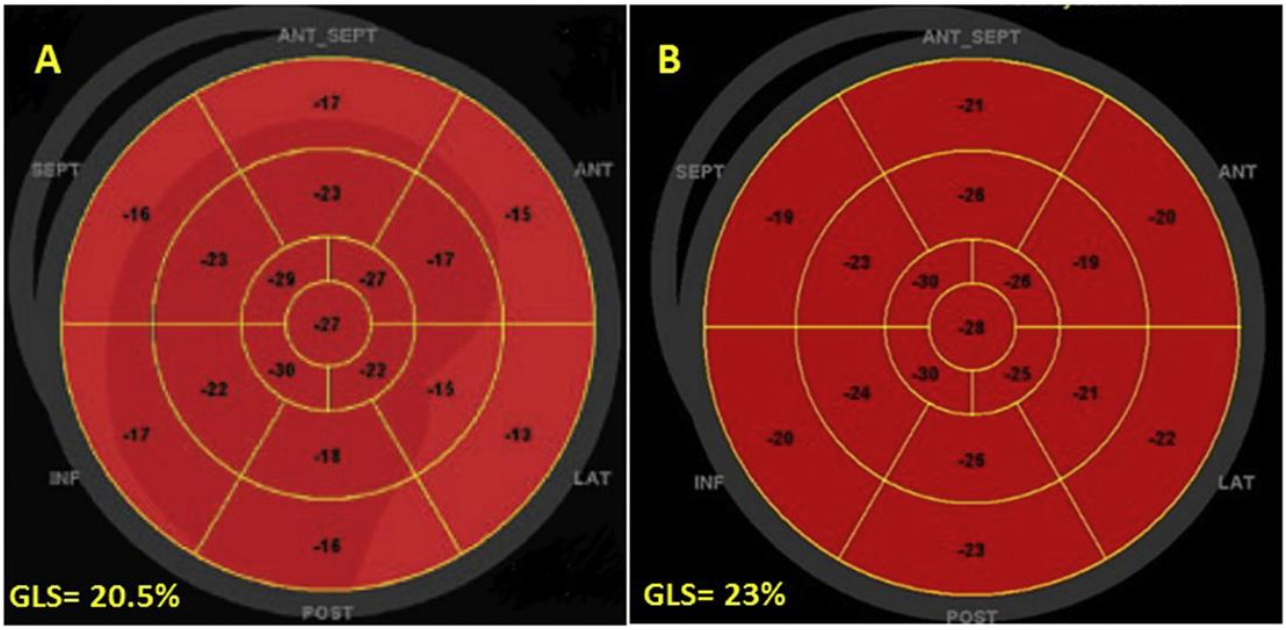
Chapter 13. Prominent basal and middle strain longitudinal involvement in newly diagnosed and never treated hypertensive patients without clear-cut hypertrophy.

Background: Left ventricular (LV) global longitudinal strain (GLS) can detect an early dysfunction in arterial hypertension. We investigated regional LV patterns of longitudinal strain (LS) and base-to-apex behaviour in newly diagnosed, never-treated hypertensive patients (HTN) without LV hypertrophy.

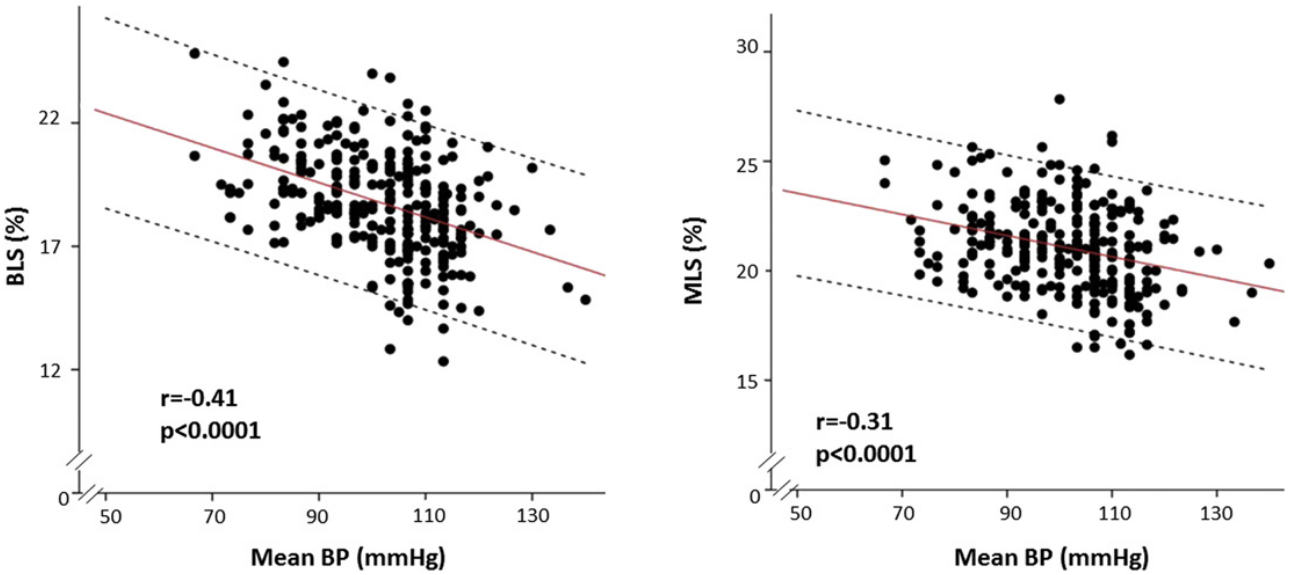
Methods: 180 HTN and 115 healthy controls underwent standard echocardiography, including regional LS and GLS assessment (in absolute values). The average LS of six basal (BLS), six middle

(MLS), and six apical (ALS) segments and relative regional strain ratio= [ALS/(BLS + MLS)] were also computed.

Results: The two groups were comparable for sex, age and heart rate. Body mass index (BMI), systolic, diastolic and mean blood pressure (BP) (all p b 0.0001) were higher in HTN. Despite LV ejection fraction (EF) was comparable, GLS, BLS and MLS resulted lower in HTN (all p b 0.0001), without difference in ALS. Relative regional strain ratio resulted higher in HTN (p b 0.001).



Dividing HTN group according to lower normal values derived from the controls, BLS was able to identify a higher rate of LV dysfunction than GLS. By a multiple linear regression analysis performed in the pooled population after adjusting for age, sex, BMI, end-systolic stress, relative wall thickness and LV mass index, the association between BLS and mean BP remained significant (β coefficient = −0.42, p b 0.0001), despite the significant impact of male sex. In a similar model, MLS and mean BP resulted also independently associated (β = −0.21, p b 0.002).



Conclusions: Despite normal LV EF, LS dysfunction is detectable in HTN, mainly involving basal and middle segments, resulting in higher relative regional strain ratio.

Chapter 14. Interrelation between midwall mechanics and longitudinal strain in newly diagnosed and never-treated hypertensive patients without clinically defined hypertrophy.

Background: In hypertensive patients, an impairment of midwall myocardial mechanics was described in presence of left ventricular (LV) concentric geometry. Under these circumstances, also LV longitudinal dysfunction was found.

Purpose: Our aim was to evaluate longitudinal and circumferential systolic function and correlations between these two functional components in newly diagnosed

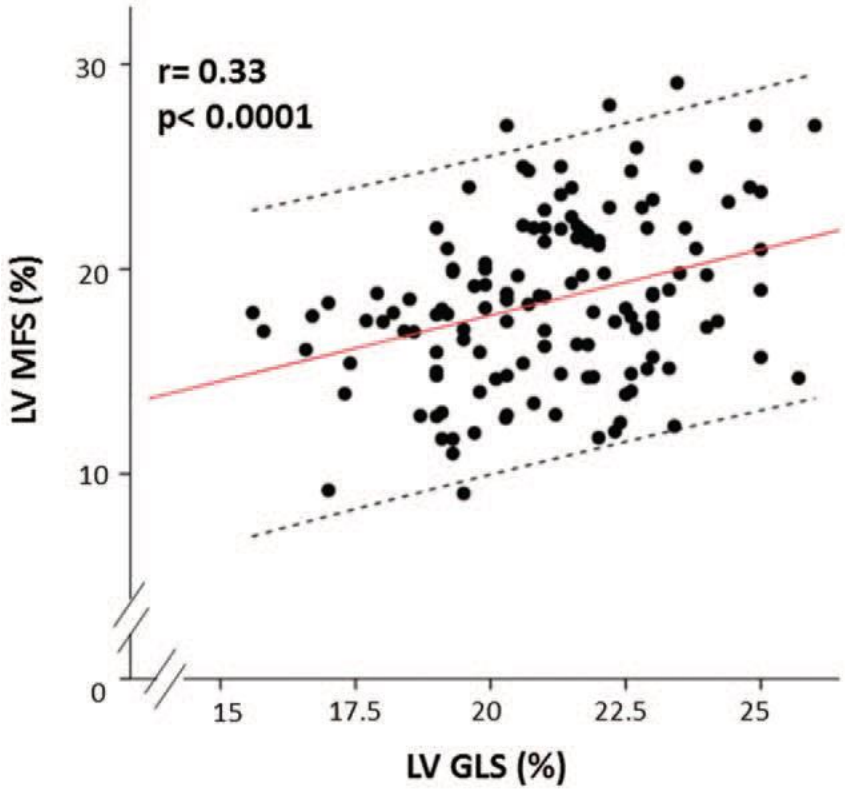
hypertensive patients without clinically defined LV hypertrophy (LVH). One hundred and thirty-eight newly diagnosed, never-treated hypertensive patients without

LVH and a control group of 105 healthy normotensive individuals underwent two-dimensional and speckle tracking echocardiography. Global longitudinal strain (GLS)

was derived (in absolute value) and midwall fractional shortening (MFS) computed. In addition, the hypertensive population was divided into two groups according to GLS: normal GLS (<20%, n=94) and reduced GLS (<20%, n=44).

Results: Hypertensive patients had lower MFS (P<0.001) and GLS (P<0.0001) than healthy controls. By dividing hypertensive patients according to GLS thresholds of

normalcy, MFS was lower in patients with GLS less than 20% (P<0.0001) while no significant difference was found in LV geometry, ejection fraction and diastolic parameters in comparison with patients with GLS at least 20%. In the pooled hypertensive population, GLS resulted positively related to MFS (r=0.33, P<0.0001).



By a multiple linear regression analysis, after adjusting for female sex, age, BMI, circumferential end-systolic stress, average e0, ejection fraction and relative wall thickness, MFS remained independently associated with GLS (b=0.222, P<0.005).

Dependent variable	Correlate	Standardized β coefficient	*P* value
GLS (%)	Female sex	0.178	0.042
	Age (years)	−0.212	0.079
	BMI (kg/m^2)	−0.038	0.654
	cESS (kdynes/cm^2)	−0.078	0.437
	Average e′ (cm/s)	0.261	0.03
	MFS (%)	0.310	<0.005
	RWT	−0.071	0.486
	LV EF (%)	0.026	0.751

Cumulative $R^2 = 0.21$, SEE = 1.9%, $P < 0.0001$. cESS, circumferential end-sytolic stress; EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricular; MFS, midwall fractional shortening; RWT, relative wall thickness; SEE, standard error of estimate.

Conclusion: In newly diagnosed and never-treated hypertensive patients without LVH, an early LV systolic dysfunction is testified by the reduction of both MFS and GLS. These two parameters resulted independently associated after adjusting for several confounders.

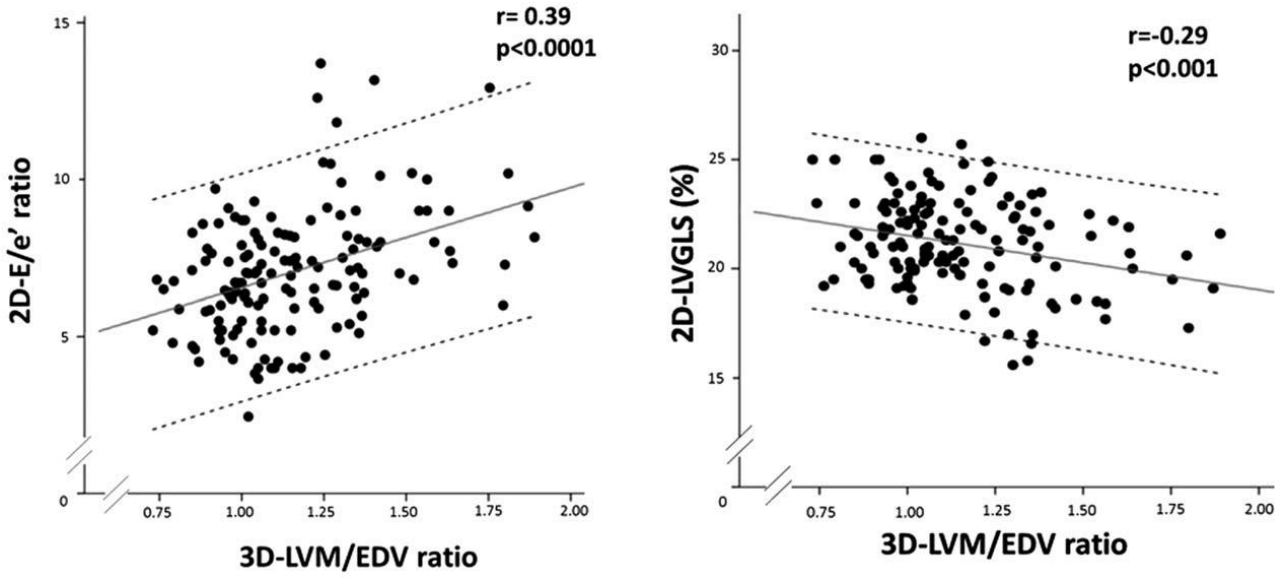
Chapter 15. Impact of left ventricular mass/end-diastolic volume ratio by three-dimensional echocardiography on two-dimensional global longitudinal strain and diastolic function in native hypertensive patients.

Background: In hypertensive patients, high left ventricular (LV) mass/end-diastolic volume ratio (LVM/EDV) is related to LV dysfunction and myocardial fibrosis.

Purpose: We examined the ability of 3D-echo-derived LVM/EDV ratio in identifying early systolic and diastolic dysfunction in relation with LV concentric geometry in native hypertensive patients.

Methods: One-hundred and forty-four newly diagnosed, never treated hypertensive patients underwent 2D-echo, including computation of 2D-derived global longitudinal strain (GLS), and 3D-echo. The study population was divided into two groups: elevated 3D-LVM/EDV (≥1.23 in women and >1.22 in men), corresponding to LV concentric geometry (n=50), and normal ratio (<1.23 in women and <1.22 in men) corresponding to LV normal or eccentric geometry (n=94).

Results: The two groups were comparable for sex, heart rate, BMI, and blood pressure (BP). Patients with elevated 3D-LVM/EDV ratio were older and had lower GLS (P<0.001) than patients with normal LVM/EDV ratio. Transmitral E/A ratio (P<0.0001) and e' velocity (P<0.0001) were lower, and E/e0 ratio (P<0.0001) higher in patients with elevated LVM/EDV ratio. In the pooled population, LVM/EDV ratio was positively correlated to E/e' (r=0.39, P<0.0001) and negatively to GLS (r=-0.29, P<0.001).



By separate multilinear regression analyses, after adjusting for sex, age, heart rate, mean BP and BMI, LVM/EDV ratio – but not 2D-relative wall thickness – was independently associated with E/e0 (b=0.304, P¼0.003) and GLS (b=-0.501, P<0.0001).

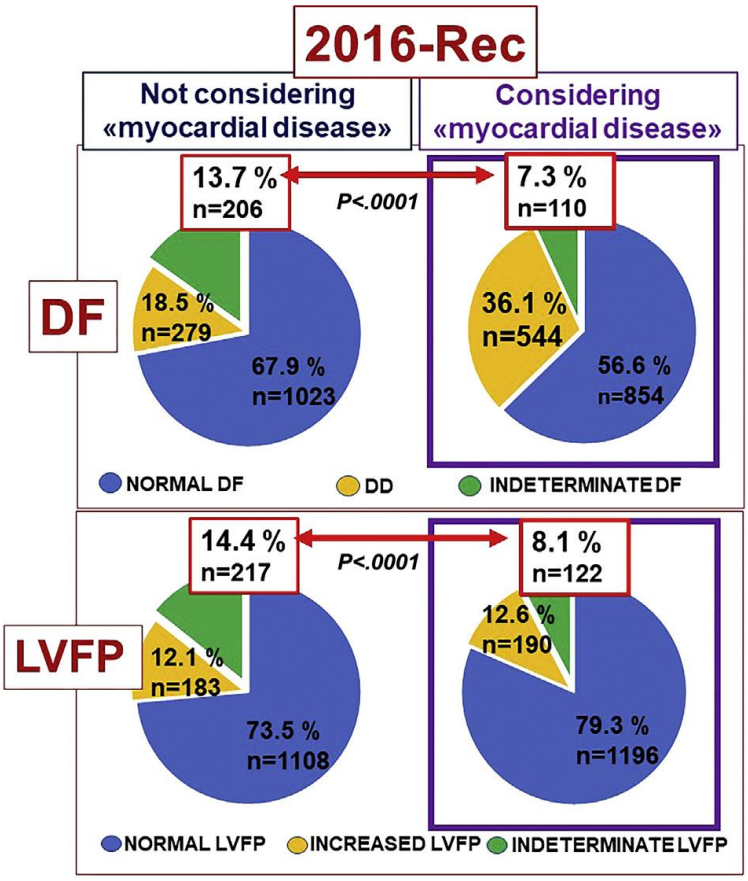
Conclusion: Three-dimensional echocardiographic assessment of LV concentric geometry allows identifying an early diastolic and longitudinal systolic dysfunction in native hypertensive patients. In particular, 3D-LVM/EDV ratio is independently associated with both E/e' ratio and GLS.

Chapter 16. Practical Impact of New Diastolic Recommendations on Non-invasive Estimation of Left Ventricular Diastolic Function and Filling Pressures.

Background: In 2016, an update of the 2009 recommendations for the evaluation of left ventricular (LV) diastolic function (DF) was released by the American Society of Echocardiography and the European Association of Cardiovascular Imaging. The aims of this study were to assess the concordance between the 2016 and 2009 recommendations and to test the impact of the consideration of ‘‘myocardial disease’’ recommended in the 2016 update on the evaluation of diastolic dysfunction (DD) and LV filling pressures in patients with normal and reduced LV ejection fractions referred to a general echocardiography laboratory.

Methods: A total of 1,508 outpatients referred to an echocardiography laboratory during a predefined 5-month period were prospectively enrolled. All patients underwent targeted clinical history and Doppler echocardiographic examination. DD and LV filling pressures were assessed according to 2009 and 2016 recommendations. Concordance was calculated using the k coefficient and overall proportion of agreement.

Results: Overall proportion of agreement between the two recommendations was 64.7% (k = 0.43). Comparing the 2009 and 2016 recommendations, 47.5% and 36.1% patients, respectively, had DD ($P < .0001$), and 22.7% and 12.6% had elevated LV filling pressures ($P < .0001$).



This difference remained significant in the setting of patients with normal LV ejection fractions (21.6% vs 10.7%, P < .0001). In the application of the 2016 recommendations, whether or not the presence of ‘‘myocardial disease’’ was considered, the prevalence of indeterminate diastolic function was, respectively, 7.3% versus 13.7%, while patients in whom the DD grade could not be determined were 8.1% versus 14.4% (P < .0001 for all).

Conclusions: Considering the presence of myocardial disease when applying the 2016 recommendations resulted in a lower prevalence of inconclusive diagnosis.

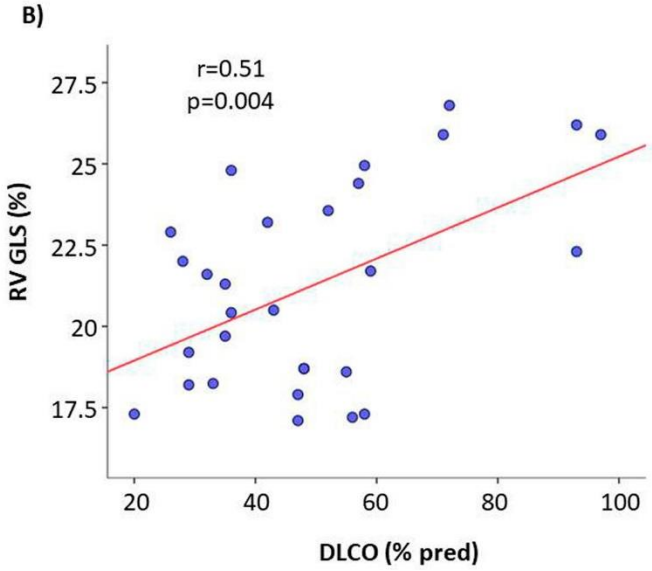
Part IV. Cardiovascular and systemic disease – a dangerous liaison

Chapter 17. Impaired Right and Left Ventricular Longitudinal Function in Patients with Fibrotic Interstitial Lung Diseases.

Background: Left ventricular (LV) and right ventricular (RV) dysfunction is recognized in idiopathic pulmonary fibrosis (IPF). Little is known about cardiac involvement in non-idiopathic pulmonary fibrosis (no-IPF). This issue can be explored by advanced echocardiography.

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, heart failure, primary cardiomyopathies, chronic obstructive lung diseases, pulmonary embolism, primary pulmonary hypertension. Lung damage was evaluated by diffusion capacity for carbon monoxide (DLCOsb). All participants underwent an echo-Doppler exam including 2D global longitudinal strain (GLS) of both ventricles and 3D echocardiographic RV ejection fraction (RVEF).

Results: We observed LV diastolic dysfunction in IPF and no-IPF, and LV GLS but not LV EF reduction only in IPF. RV diastolic and RV GLS abnormalities were observed in IPF versus both controls and no-IPF.



RV EF did not differ significantly between IPF and no-IPF. DLCOsb and RV GLS were associated in the pooled pulmonary fibrosis population and in the IPF subgroup (= 0.708, p < 0.001), independently of confounders including pulmonary arterial systolic pressure.

Table 4. Independent determinants of RV GLS by multiple regression analyses.

		In the Pooled ILDs Population [a]		In IPF Subgroup [b]		In No-IPF Subgroup [c]	
Dependent Variable	Covariate	B Coefficient	*p*	B Coefficient	*p*	B Coefficient	*p*
RV GLS	BMI	−0.186	0.214	−0.267	0.139	−0.227	0.339
	HR	−0.027	0.851	−0.045	0.794	−0.190	0.536
	PASP	−0.053	0.712	−0.203	0.239	−0.304	0.277
	$DLCO_{sb}$	0.583	<0.0001	0.708	<0.001	0.219	0.464

(a) Cumulative $R^2 = 0.575$, SEE = 2.22%, $p < 0.007$; (b) Cumulative $R^2 = 0.729$, SEE = 1.91 %, $p = 0.009$; (c) Cumulative $R^2 = 0.729$, SEE = 1.91 %, $p = 0.009$; ILDs = interstitial lung diseases; IPF = idiopathic pulmonary fibrosis; DLCOsb= single-breath lung diffusion capacity of carbon monoxide; PASP = pulmonary arterial systolic pressure; RV = right ventricular; GLS = Global longitudinal strain; SEE = standard error estimated.

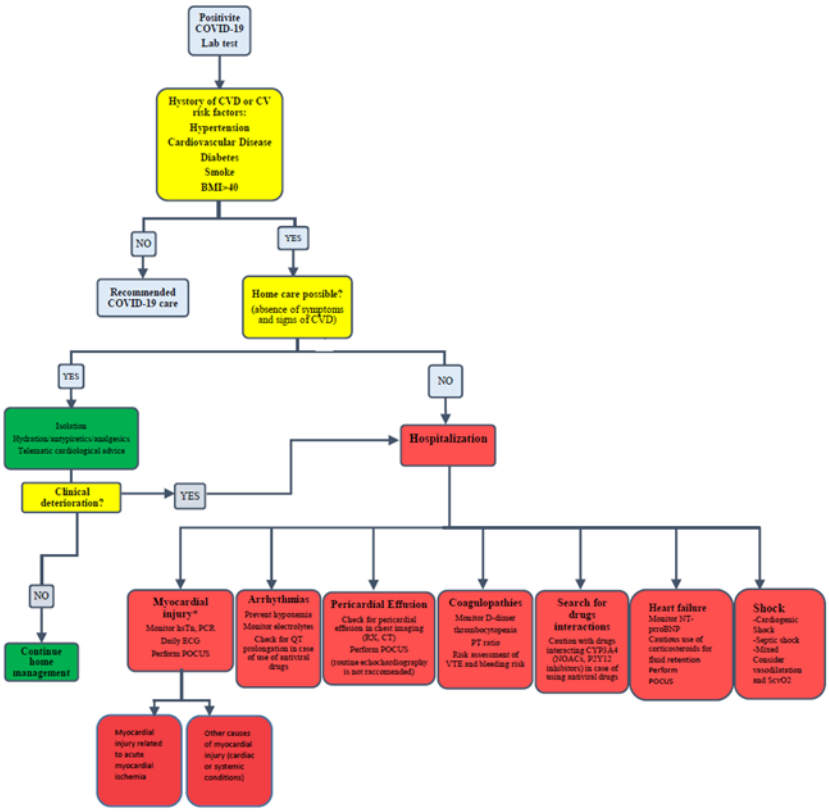
Conclusion: Our data highlight the unique diagnostic capabilities of GLS in distinguishing early cardiac damage of IPF from no-IPF patients.

Chapter 18. Epidemiology, prognosis, and clinical manifestation of cardiovascular disease in COVID-19.

Introduction: At the end of 2019, a novel coronavirus was identified as the cause of a pneumonia cluster in Wuhan, China. Since then, the contagion has rapidly spread all over the world resulting in a global pandemic. Since frequent cardiovascular (CV) system involvement has soon been detected in patients occurring coronavirus disease 2019 (COVID-19), we would provide a simple review available to cardiologists who are going to be involved in the management of COVID-19 patients from several levels: from diagnosis to prevention and management of CV complications.

Areas covered: We investigate the role of CV diseases in COVID-19: from incidence of CV comorbidities to their negative impact on prognosis. We also search Literature in order to identify the main CV manifestations in patients occurring virus infection and their management by cardiologists.

Expert opinion: Specific treatments for CV involvement associated with COVID-19 are still debated. Results from ongoing trials are needed to further clarify issues about the therapeutic approach, which is constantly changing according the continuous flow of published evidences. Finally, it seems necessary to sensitize all population to raise awareness on CV diseases in COVID era, to hinder underestimation of both new-onset acute CV diseases and consequences of chronic mistreated CV diseases.



Article highlights:

• CV diseases and risk factors have worse prognosis and higher mortality in COVID-19

• Direct toxicity, inflammation and thrombosis are responsible for CV events

• Referral to cardiology should include assessment for thrombotic and bleeding risk

• Risk of cardiac adverse events must be closely monitored during COVID-19 treatment.

Chapter 19. Cardiopulmonary exercise testing and echocardiographic exam: an useful interaction.

Cardiopulmonary exercise test (CPET) is a functional assessment that helps to detect disorders affecting the system involved in oxygen transport and utilization through the analysis of the gas

exchange during exercise. The clinical application of CPET is various, it including training prescription, evaluation of treatment efficacy and outcome prediction in a broad spectrum of conditions. Furthermore, in patients with shortness of breath it provides pivotal information to bring out an accurate differential diagnosis between physical deconditioning, cardiopulmonary disease and muscular diseases. Modern software allows the breath-by-breath analysis of the volume of oxygen intake (VO2), volume of carbon dioxide output (VCO2) and expired air (VE). Through this analysis, CPET provides a series of additional parameters (peak VO2, ventilatory threshold, VE/VCO2 slope, end-tidal carbon dioxide exhaled) that characterize different patterns, helping in diagnosis process. Limitations to the routine use of CPET are mainly represented from the lack of measurement standardization and limited data from randomized multicentric studies.

The integration of CPET with exercise stress echocardiography has been recently introduced in the clinical practice by integrating the diagnostic power offered by both the tools. This combined approach has been demonstrated to be valuable for diagnosing several cardiac diseases, including heart failure with preserved or reduced ejection fraction, cardiomyopathies, pulmonary arterial hypertension, valvular heart disease and coronary artery disease.

Future investigations are needed to further promote this intriguing combination in the clinical and research setting.

EUROPEAN CURRICULUM VITAE FORMAT

PERSONAL INFORMATION

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EDUCATION AND TRAINING

• Dates (from – to)	**FROM 01/10/2006 TO 26/07/2012**
• Name and kind of istitution	Medical school Federico II, University Hospital, via Pansini,5 Napoli
• Degree obtained	Student
• Dates (from – to)	**FROM 08/08/2013 TO 08/08/18**
• Name and kind of istitution	A.O.U. Federico II via Pansini,5 Napoli
• Degree obtained	Residency in Emergency Medicine
• Dates (from – to)	**FROM 08/11/2017 TO PRESENT**
• Name and kind of istitution	A.O.U. Federico II via Pansini,5 Napoli
• Degree obtained	PhD Student in Cardiovascular Physiopathology and Therapeutics (CardioPath) programme
• Dates (from – to)	**FROM 15/06/2020 TO PRESENT**
• Name and kind of istitution	A.O.U. Federico II via Pansini,5 Napoli
• Degree obtained	Research fellow in Internal Medicine (MED/09)

Employment:

Echocardiographer at Standard and Advanced Echo-Lab Federico II University Hospital, Naples (Director: Prof Maurizio Galderisi) 2011-today

Clinical fellow at the Department of Internal Medicine of Federico II University Hospital, Naples (Director: Prof Paolo Rubba) 2013-2015

Visiting fellow at Emergency Medicine AORN “San Paolo”, Naples (Director: Dott. Fernando Schirarldi) Agoust 2014-October 2014

Training at Laboratory of Vascular echography in Sant’Orsola Malpighi Hospital, Bologne (dir. Dott. Alfio Amato) in November 2014.

Training at Laboratory of Echocardiography at San Raffaele Hospital, Milan (dir. Dott. Eustachio Agricola) in September 2016 and September 2017.

Clinical fellow at the Coronary Care Unit of Federico II University Hospital, Naples (Director: Prof Bruno Trimarco) 2015-2017

Research fellow at Department of Advanced Biomedical Science, Federico II University Hospital from June 2020 to now

International awards:

Winner of the Young Investigator Award Clinical Science with the abstract “Advantage of using ASE/EACVI criteria for detection of subclinical cardiotoxicity in breast cancer patients undergoing anthracycline and trastuzumab therapy” at the Euro Echo Congress ,Seville 2015.

Winner of PhD student and young researchers with the abstract “Base-to-apex myocardial longitudinal gradient: an early sign of left ventricular dysfunction in treatment naïve Anderson Fabry disease patients” in the 5th Fabry expert lounge meeting, Madrid 2018.

Teaching

Speaker, chair and tutor in several echocardiography courses

Personal capabilities and competences

Clinical experience in the management of cardiovascular involvement in arterial hypertension, valvular heart diseases, metabolic diseases and onco-hematologic complication.

Skills in transthoracic and transesophageal echocardiography, stress echo, 3D echocardiography, peripheral and transcranial Doppler ultrasound

Foreign clinical and scientific experiences:

Fellow at Laboratory of cardiac imaging and Intensive Coronary Care Unit at Ramon y Cajal Hospital, Madrid, Spain (dir. Prof. Jose Luis Zamorano) from September 2017 until October 2018.

Scientific affiliation in International Society

Member of the European Society of Cardiology (ESC), European Association of Cardiovascular Imaging (EACVI), Italian Society of Emergency Medicine (SIMEU), Italian society of Internal Medicine (SIMI) and Italian society of Cardiology (SIC)

Realization of project activity:

Member of the Steering Committee of the EACVI/HFA Cardio Oncology Toxicity (COT) joint registry

Member of the Steering Committee and data manager for the Multicentric Study on Atrial Strain COmparison between Two different modalities (MASCOT study) of the European Association of Cardiovascular Imaging HIT (Heart Imagers of Tomorrow), European Society of Cardiology

Research interest:

Toxicity of Onco-hematologic drugs.

Cardiac involvement in metabolic diseases.

Storage and infiltrative diseases.

Heart valve diseases

Cardiac imaging and in particular Echocardiography (standard and new technology).

Scientific Society assignment

Member of the Educational Committee dell' European Association of Cardiovascular Imaging, period 2015-2016.

Member of the HIT committee (data manager) dell 'European Association of Cardiovascular Imaging, period 2016- until today.

Reviewer on the ESC-el platform of the European Association of Cardiovascular Imaging from 2015 until today

Member of nucleus of Italian working group on Cardiotoxicity and cardioprotection of the Italian society of Cardiology 2018-to now

Communication coordinator of the Council of CardiOncolgy of the European Association of Cardiology from 2020 to now

Member of working group of Cardiac Imaging of Italian society of Cardiology 2016 to now

Member of the following International Journal Editorial

Frontiers in Cardiovascular Medicine

European heart Journal – Case Report

Board Bibliometric indices:

H index = 14 Total citation 713 by 627 documents

Author of 68 publications on PubMed

Publications

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2. Galderisi M, Rigo F, Gherardi S, Cortigiani L, **Santoro C**, Sicari R, Picano E.
   The impact of aging and atherosclerotic risk factors on transthoracic coronary flow reserve in subjects with normal coronary angiography.

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Invited speaker at national and international congresses:

1. Speaker at EACVI webinar: “Intracardiac tumors and masses (DICE)”. Oct 31 2014

2. Speaker at American Heart Congress New Orleans 11-16 November 2016: Echocardiography in the Context of Multimodality Imaging: Radiation Heart Disease

3. Speaker at Korean Society of Echocardiography Seul,South Korea 25-26 Nov2017
   “The Role of Echo in Prevention of Chemotherapy Cardiotoxicity “

4. Speaker at Euro Echo congress Lisboa, Portugal, 6-9 Dec 2017,
   “Toxicity: multimodality analysis of chemotheraphy induced cardiac damage”

5. Speaker at Euro Echo congress Milan, Italy 5-8 Dec 2018
   "The assessment of regional wall motion: the importance of the learning curve"

6. Speaker at Italian national congress of Cardiology, Rome, Italy 13-16 Dec 2018
   "Cardiomiopatia ipertrofica: il ruolo dell'ecocardiografia nel calcolatore della morte improvvisa"

7. Speaker at Euro CMR congress Venice, Italy 2-4 May 2019
   "Imaging techniques to improve management in severe tricuspid regurgitation"

8. Speaker at ESC congress, Paris, France 31 Aug-04 Sept 2019
   "Left atrial dysfunction assessed by strain correlates with symptoms and severity of aortic stenosis"

9. Speaker at ARCA imaging national congress, Matera, Italy 13-14 Sept 2019
   ""Un fenotipo, mille genotipi: le nuove tecnologie ecocardiografiche e la diagnosi

   differenziale tra forme di cardiomiopatia ipertrofica"

10. Speaker at ESCR Congress, Antwerp, Belgium 24-26 Oct 2019 "Global clinical perspective on oncology-related & drug induced cardiomyopathies"

11. Speaker at PLACE congress, Rome, Italy 22-23 Nov 2019: Specialised use of strain-indicazioni correnti e future direzioni in strain echocardiography"

Author of 7 book chapters on Cardiology and Cardiac Imaging:

1. Galderisi M, Ilardi F, **Santoro C**. Pericardial Disease in Oncologic Patients. In: Anticancer Treatments and Cardiotoxicity. Mechanisms, Diagnostic and Therapeutic Interventions. 2017, p151-159

2. Galderisi M, **Santoro C**. M-mode echocardiography in Ekokardiografia klinike, 2018 Botime Pegi Editor. ISBN-10(13): 978-9928-175-90-8

3. **Santoro C**, Galderisi M. Doppler echocardiography in Ekokardiografia klinike, 2018 Botime Pegi Editor. Tirana (Albany) ISBN-10(13): 978-9928-175-90-8

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5. **Santoro C.**, Esposito R., Fernández-Golfín C., Galderisi M., Zamorano Gomez J.L. (2019) Diagnosis of Cardiac Damage: Role of Stress Echo. In: Russo A., Novo G., Lancellotti P., Giordano A., Pinto F. (eds) Cardiovascular Complications in Cancer Therapy. Current Clinical Pathology. Humana Press. Online ISBN 978-3-319-93402-0

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7. Zamorano Gomez J.L, **Santoro C**. Del Castillo A.M. (2019) Evaluation of patients with heart valve disease. In: Zamorano, J., Lancellotti, P., Pierard, L., Pibarot, P.- Heart Valve Disease: State of the Art. Springer International Publishing ISBN 3030231046, 9783030231040

Speaker of the following oral communication / poster at National and International Congresses:

1. C. Santoro, F De Stefano,A Buonauro, Muscariello R, Ippolito R, De Palma D,Schiano Lomoriello V, Galderisi M Subclinical myocardial dysfunction by three-dimensional speckle tracking echocardiography in

asymptomatic patients with myotonic dystrophy J. Cardiovasc Med 2013 Società Italiana di Cardiologia (S.I.C.) Roma 14-16 Dic 2013

2. C. Santoro, Arpino G, De Stefano F, Esposito R, Muscariello R, Lauria R, De Placido S, de Simone G, Galderisi M Head-to-head comparison of standard echo Doppler and three-dimensional Speckle Tracking Echocardiography in detection of subclinical anthracycline cardiotoxicity in breast cancer JACC 2014, March 29 - 31, 2014 Washington DC

3. C. Santoro, R. Raia, P. Ieranò, F. De Stefano, D. De Palma, G. Arpino, S. de Placido, G. de Simone, M. Galderisi Additional value of two-dimensional and three-dimensional speckle tracking echocardiography in detecting early cardiotoxicity of anthracycline and trastuzumab in breast cancer patients Eur Heart J Cardiovasc Imaging ESC Congress, Barcelona 30 Aug- 03 Sept 2014

4. C. Santoro, M. Sanduzzi Zamparelli, V. Schiano Lomoriello, A. Rocco, S. Cocozza, A. Buonauro, G. Nardone, M. Galderisi Detection of myocardial injury by three-dimensional speckle tracking echocardiography in chronic hepatitis C infection Eur Heart J Cardiovasc Imaging EACVI Congress, Vienna 03 - 06 Dec 2014

5. C. Santoro, R. Esposito, V. Schiano Lomoriello, R. Raia, D. De Palma, R. Ippolito, P. Ierano, G. Arpino, G. De Simone, M. Galderisi Additional value of two-dimensional and three-dimensional speckle tracking echocardiography in detecting 1 year cardiotoxicity of anthracycline and trastuzumab in breast cancer patients Eur Heart J Cardiovasc Imaging EACVI Congress, Vienna 03 - 06 Dec 2014

6. C Santoro, M Galderisi, T Niglio, M Santoro, E Stabile, A Rapacciuolo, L Spinelli, G de Simone, G Esposito, B Trimarco Regional longitudinal strain correlates with TIMI frame count and extension of myocardial damage after acute anterior STEMI Eur Heart J Cardiovasc Imaging EACVI Congress, Vienna 03 - 06 Dec 2014

7. C. Santoro, M. Galderisi, MF. Costantino, G. Tarsia, P. Innelli, E. Dores, G. Esposito, A. Matera, G. De Simone, B. Trimarco Impact of patient prosthesis mismatch on left ventricular filling pressure increase after transcatheter aortic valve implantation Eur Heart J Cardiovasc Imaging EACVI Congress, Vienna 03 - 06 Dec 2014

8. C. Santoro, R. Esposito, R Sorrentino, G Alcidi, A Pellegrino, L Spinelli, A Pisani, B. Trimarco, M. Galderisi Right ventricular myocardial involvement in Anderson-Fabry disease at diagnosis: a three-dimensional strain imaging study Eur Heart J Cardiovasc Imaging EACVI Congress, Portugal 06 - 09 Dec 2017

9. A. Pardo Sanz, C. Santoro, R. Hinojar, A. Garcia, L. Salido Tahoces, M. Abellas, A. Marco, A. Gonzalez, JJ. Jimenez Nacher, D. Del Val, S. Del Prado, M. Valverde, R. Hernandez-Antolin, JL. Zamorano, C. Fernandez-Golfin. Differences in right ventricular function in patients with severe aortic stenosis with normal flow/low flow undergoing TAVI. Eur Heart J ESC Congress, Munich 25-29 Aug 2018.

10. C. Santoro, A. Pardo Sanz, R. Hinojar-Baydes, A. García, E. Ortega, M. Abellás Sequeiros, A. González Gómez, J.J. Jiménez Nácher, L. Salido Tahoces, R. Hernández Antolín, J.L. Zamorano Gómez y C. Fernández Golfín. Cambios precoces en los parámetros deformación auricular y ventricular izquierda por ecocardiografía Speckle tracking tras el implante de TAVI. Congreso Nacional de Cardiologia Sevilla 25-27 Octubre.

11. C. Santoro, A. Pardo Sanz, R. Hinojar-Baydes, A. García, M. Abellás Sequeiros, L. Salido Tahoces, Á. Marco del Castillo, A. González Gómez, J.J. Jiménez Nácher, R. Hernández Antolín, J.L. Zamorano Gómez y C. Fernández Golfín ¿Existen diferencias en la función auricular izquierda por técnicas de deformación miocárdica en pacientes con estenosis aórtica severa en función del flujo? Congreso Nacional de Cardiologia Sevilla 25-27 Octubre.

12. C. Santoro, Á. Marco del Castillo, A. González Gómez, J.M. Monteagudo Ruiz, M. Abellas Sequeiros, A. García, R. Hinojar-Baydes, J.J. Jiménez Nácher, J.L. Moya Mur, J.L. Zamorano Gómez y C. Fernández Golfín. Predictores de mortalidad y rehospitalización en pacientes con insuficiencia tricuspídea severa. Congreso Nacional de Cardiologia Sevilla 25-27 Octubre

13. C. Santoro, R. Soloperto, O. Casciano, R. Esposito, F. Luciano, M. Canonico, M. Lembo, G. Arpino, S. De Placido, M. Galderisi - University Hospital Federico II, Naples, Italy Right ventricular dysfunction parallels left ventricular functional involvement in women with breast cancer experiencing subclinical cardiotoxicity. ESC Congress 2020 – The Digital Experience

Direction or participation in the research group characterized by national or international collaborations

Active participation to “Euro Filling Study” of the European Association of Cardiovascular Imaging coordinated by Prof. Patrizio Lancellotti University of Liège, Liège, Belgium.

Active participation to “Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes: The SUCCOUR Trial” coordinated by Prof T.H. Marwick University of Tasmania, Australia.

Active participation to research group on Anderson-Fabry disease “The AFFINITY group”.

Active participation to the Study Group of Echocardiography of the Italian Society of Cardiology for the two-year period; 2018-today.

Active participation to the Study Group of Cardiotoxicity and cardioprotection of the Italian Society of Cardiology for the two-year period; 2018-today.

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

CORSE	Basic Life Support-Defibrillator (BLS-D), (Advanced Life Support) ALS
MOTHER TONGUE	**ITALIAN**
OTHER LANGUAGES	
	ENGLISH
• Reading skills	Excellent
• Writing skills	Excellent
• *Verbal skills*	Excellent
	SPANISH
• *Reading Skills*	Excellent
• Writing Skills	Excellent
• *Verbal skills*	Excellent

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