DIASTOLE DISEASED
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ABSTRACT BOOK

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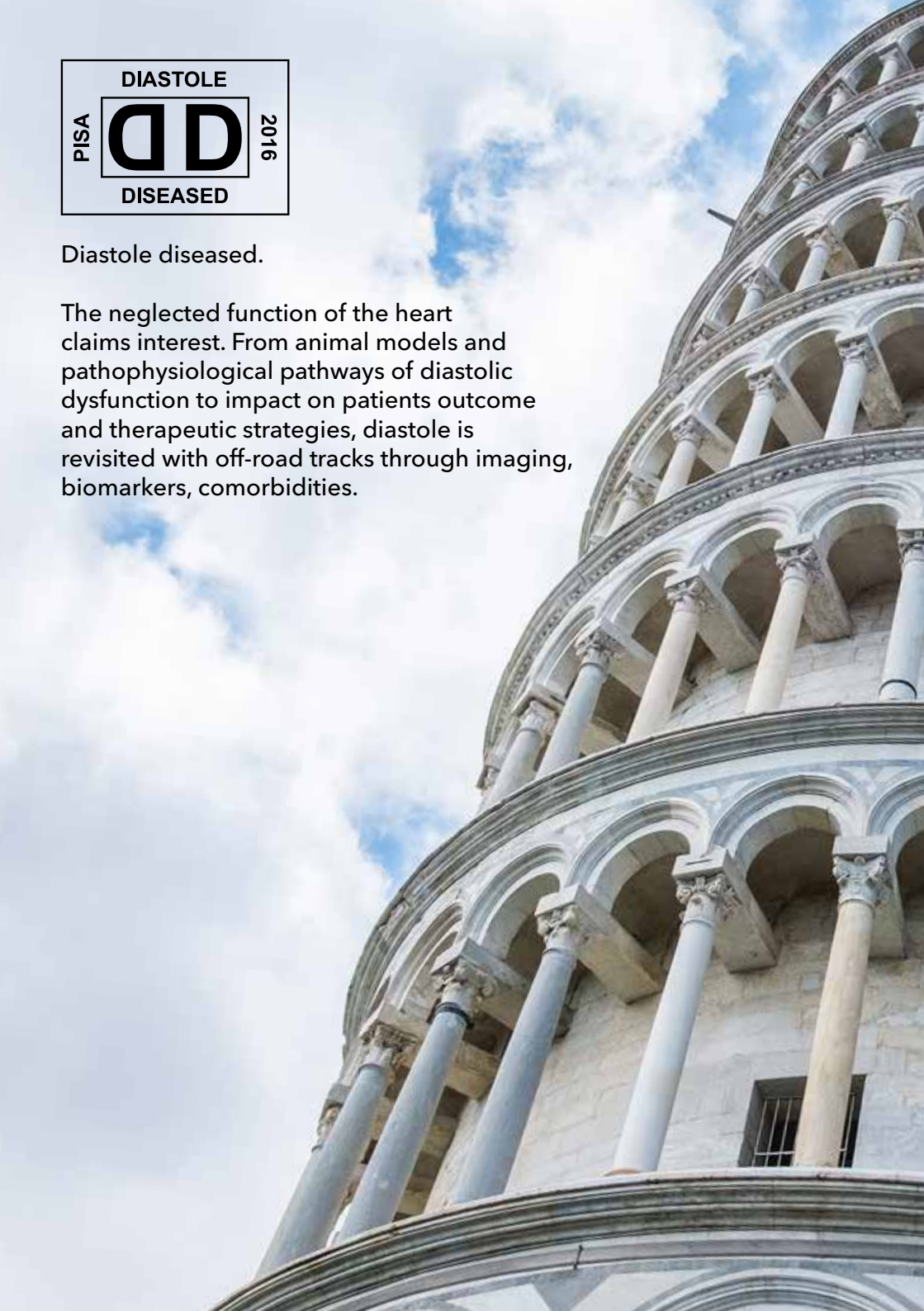

Diastole diseased.

The neglected function of the heart claims interest. From animal models and pathophysiological pathways of diastolic dysfunction to impact on patients outcome and therapeutic strategies, diastole is revisited with off-road tracks through imaging, biomarkers, comorbidities.

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BEST ABSTRACTS ON DD PRESENTED BY YOUNG CARDIOLOGISTS/INTERNISTS

Diastole Diseased

Diastole, the dark side of the heart cycle, has been recognized as a main topic of pathophysiological and clinical interest. Isolated diastolic heart failure is present in nearly half of symptomatic patients, often accompanies systolic heart dysfunction, and is a prominent cause of hospitalization and mortality. Either a unique nosological entity or the final result of cardiac and extracardiac alterations, diastolic heart failure has long represented a problem of definition, nomenclature, diagnosis, a no-man's land to be explored.

The diagnostic approach to healthy and diseased diastole, by combination of ultrasounds, cardiac biomarkers and advanced imaging, including cardiac magnetic resonance has improved dramatically, but diastole as a therapeutic target is still a central unattended problem. The neuroendocrine interpretative model in systolic heart failure led, by the use of pharmacological and nonpharmacological strategies of neurohormonal antagonism to the improvement of patients' prognosis, helped by tailored treatment of underlying etiologies, as well as by the use of device implantation. Conversely, attempts for the treatment of "diseased diastole", either by using the same drug armamentarium applied to systolic failure, or by testing novel rational approaches has up-to-date been unsuccessful.

Opinion makers propose that we should think to diastolic heart failure not as a unique phenotype, but rather as a spectrum of diseases, given the diverse etiology, the different degree of impairment, and the eventual presence of comorbidities, claiming for a "precision" approach, which would warrant the best care of the individual patient even with currently available therapies.

To discuss all these topics, interventions by experts, as well as by young researchers who will join a dedicated program, will cover all pathophysiologic, diagnostic and therapeutic open questions, in order to prepare "the step forward" needed, to claim for an enhanced effort by the clinical community, with more science, more imagination, and a bit "more heart", as the basis for future research in the field of diastole disease.

Thanks to the Fondazione Menarini, we have the unique chance to meet together in one of the most beautiful cities in Tuscany, in a workshop endorsed by all the University and Research organizations, strongly collaborating to translational research projects in the field. We are sure of the final success of such an initiative, which we do want to be the first of several ones.

Michele Emdin and Stefano Taddei
Course Meeting Directors

Diastolic Disease and Ischemia

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Diastolic disease accounts for close to 50% of patients presenting with symptoms of heart failure. In spite of the progression in treatment of patients with systolic dysfunction, the mechanism and treatment of patients with diastolic dysfunction, or what is now termed heart failure with preserved ejection fraction, remain under intense study and investigation for the last decade. Moreover, the mortality of these patients presenting with heart failure with preserved ejection fraction is similar and sometimes higher than patients with heart failure with reduced ejection fraction. Thus, there is an unmet need to investigate the mechanism and potential treatment of this disease.

Ischemic heart disease or general ischemia may be one of the major mechanisms contributing to diastolic dysfunction. Patients presenting with the symptoms of diastolic dysfunction and merely dyspnea even without chest pain may have an underlying significant coronary artery disease. Recent studies demonstrated in a registry that up to 60% of the patients presenting with symptoms and evidence of diastolic dysfunction have underlying coronary disease. These patients have a higher mortality and event rate than patients without underlying coronary disease and benefit from revascularization. The other group of patients that present with diastolic dysfunction and potential mechanisms for ischemia are patients that have no underlying significant coronary artery disease. These patients have multiple hospitalization and event rates, and coronary angiography does not reveal any significant underlying obstructive coronary disease. However, these patients, in the majority of the cases, have underlying ischemia that contributes to diastolic dysfunction. More comprehensive physiological assessment of the microvascular function reveals this phenomenon's prevalence and also is associated with underlying ischemia.

The mechanism of this myocardial ischemia without any obstructive disease is in most cases endothelial dysfunction. Microvascular endothelial dysfunction contributes to generalized ischemia, particularly in the subendocardium region. The underlying mechanism for endothelial dysfunction remains an intense area of investigation. Previous studies demonstrate that there is an increase in oxidative stress and inflammation contributing to microvascular dysfunction. Moreover, the role of the microcirculation not only as function but refraction of the microcirculation is recently a marriage as a potential mechanism for the underlying ischemia. Thus, in patients presenting with dyspnea and evidence of diastolic dysfunction, ruling out underlying mechanisms of ischemia as secondary to obstructive coronary disease in other microvascular dysfunction is essential for the definitive diagnosis and treatment of these patients.

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Diastole diseased in uremic patients

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Diastole diseased (DD) is a condition that is frequently observed among patients in end stage renal disease (ESRD). It is caused by the structural changes of the myocardium that can occur in uremic patients and that are mainly characterised by left ventricular hypertrophy (LVMI) and fibrosis [1-3]. The presence of these abnormalities has been also defined uremic cardiomyopathy. However, with this term it could be in general indicated the influence of chronic kidney disease on the myocardium thus including not only the more frequent LVMI and DD but also the dilatation of the left ventricular (LV) and the impairment of systolic function [3].
There are several pathophysiological mechanisms responsible for myocardial structural changes leading to DD in ESRD patients [1-3]. Both changes in preload and afterload can lead to LVMI in these patients. An increased preload, which is caused by the expansion of intravascular volume (due to fluid retention and to the high flow related to arterio-venous fistulas), can promote the eccentric remodelling of LV. On the other hand an increased afterload, caused by an high arterial systemic resistance (systolic and diastolic hypertension) and a reduced arterial compliance (vascular calcification), can promote a LV concentric remodelling. Both these hemodynamic conditions can be associated not only to LVMI but also to an increased myocardial fibrosis which further impairs diastolic function. It is worth noting that myocardial fibrosis is related not only to hemodynamic changes but also to the effects of several pathophysiologic factors present in chronic kidney disease (CKD) such as uremic toxins, oxidative stress, inflammatory status, hyperparathyroidism, hypovitaminosis D, hyperphosphatemia and activation of rennin angiotensin aldosterone system. Moreover, in ERSD, also myocardial ischemia can cause DD.

Myocardial ischemia can be due to different conditions such as the increased oxygen demand due to LVMI, the microvascular rarefaction, the contemporary presence of coronary disease and anemia.

Finally, the myocardial changes responsible for DD can also hesitate in further maladaptative changes leading to LV dilatation and systolic dysfunction.

Clinical presentation of DD in ESRD patients is strictly related to the interaction between the altered ventricular stiffness and the changes in volume status, particularly in patients treated with dialysis [2]. An increased risk of pulmonary congestion could occur in the case of a fluid overload. On the other hand, hypotension can be observed in the case of an excess in volume depletion after dialysis. Both these conditions negatively affect patients' prognosis. As a consequence, an early detection of DD among ESRD patients is recommended [4]. Echocardiographic study is the most used diagnostic approach in order detect LVMI and the presence of diastolic dysfunction [4-5]. Moreover, the evaluation of diastolic abnormalities is relevant also for stratifying prognosis of patients because they are predictive of mortality [4].

The therapeutic approach of DD in ESRD, like in other conditions causing diastolic dysfunction, is based on the control of systolic and diastolic hypertension, on the reduction of atrial fibrillation ventricular rate and on the treatment of ischemia. Furthermore, there is the need to minimise volume shifts between dialyses in order to avoid symptoms and improve patients' prognosis. The identification of the correct dry weight, the increase in the number of hemodialysis (like short daily hemodialysis or nocturnal home hemodialysis) or the use of peritoneal dialysis represent the more effective strategy to reach this goal [2]. These therapeutical approaches have been proven to reduce the prevalence of LVMI as well as the use of drugs blocking renin angiotensin aldosterone system.

Finally, a significant regression of the diastolic and systolic dysfunction in ESRD can be obtained by kidney transplantation [2-3].

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Heart Failure with Preserved Ejection Fraction

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Heart failure with preserved ejection fraction (HFPEF) accounts for more than 50% of all heart failure cases[1]. Both arterial hypertension and metabolic comorbidities such as overweight/obesity and type 2 diabetes, are very prevalent in HFPEF. Over the last decennium, myocardial structure, cardiomyocyte function and intramyocardial signaling were shown to be specifically altered in HFPEF. A new paradigm for HFPEF development is therefore proposed, which identifies a systemic proinflammatory state induced by metabolic comorbidities as the cause of myocardial structural and functional alterations[2].

The new paradigm presumes the following sequence of events in HFPEF: 1) A high prevalence of comorbidities such as overweight/obesity, diabetes mellitus, chronic obstructive pulmonary disease and salt sensitive hypertension induce a systemic proinflammatory state; 2) A systemic proinflammatory state causes coronary microvascular endothelial inflammation; 3) Coronary microvascular endothelial inflammation reduces nitric oxide (NO) bioavailability, cyclic guanosine monophosphate (cGMP) content and protein kinase G (PKG) activity in adjacent cardiomyocytes; 4) Low PKG activity favours hypertrophy development and raises resting tension because of hypophosphorylation of titin; 5) Both stiff cardiomyocytes and interstitial fibrosis contribute to high diastolic left ventricular (LV) stiffness and HF development.

The new HFPEF paradigm shifts emphasis from left ventricular (LV) afterload excess to coronary microvascular inflammation. This shift is supported by a favourable Laplace relationship in concentric LV hypertrophy and by all cardiac chambers showing similar remodeling and dysfunction. Myocardial remodeling in HFPEF differs from heart failure with reduced ejection fraction (HFREF), where remodeling is driven by loss of cardiomyocytes.

Hitherto, experimental studies mainly tried to reproduce HFPEF in arterial hypertension models and largely overlooked the prominent involvement of metabolic comorbidities. A recent experimental study however investigated ZSF1 rats, which are first generation hybrids between the ZDF (Zucker Diabetic Fatty) and SHHF (Spontaneously Hypertensive Heart Failure) rats[3,4]. Lean and obese ZSF1 rats are hypertensive as they inherited the hypertension gene from male SHHF rats. Obese ZSF1 rats also inherited two different leptin receptor mutations from female ZDF and male SHHF rats. At 20 weeks of age, only obese ZSF1 rats had developed HFPEF. High myocardial stiffness was obvious in isolated cardiac muscle strips of the obese ZSF1 rats and could mainly be attributed to stiffer titin.

In summary, HFPEF and HFREF are distinct heart failure phenotypes. In HFPEF, myocardial dysfunction and remodeling are driven by coronary microvascular inflammation because of metabolic comorbidities whereas in HFREF they are driven by cardiomyocyte death[5].

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Epidemiology

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Heart failure (HF) is a worldwide endemic syndrome.[1-5] Approximately 2% of the adult population is affected by HF with an age dependent prevalence ranging from less than 2% in subjects aged <60 years to >10% in those aged >80 years.[1, 3, 6] Because of aging of the general population and better treatment of the acute cardiovascular events, HF prevalence is projected to increase by 25% in the next 20 years.[7] The burden is further shown by the costs of this syndrome encompassing 2-3% of the total expenditure of the healthcare system and this is projected to increase by ≈200% over the next 20 years .[7, 8] Hospitalizations are the cause of 70-80% of these high costs.[9]

The prevalence of patients with asymptomatic cardiac dysfunction is much higher and has been studied mainly by echocardiography. In a recent systematic review, The median prevalence of systolic and 'isolated' diastolic left ventricular dysfunction was of 5.5% (range 3.3–9.2%) and 36.0% (range 15.8-52.8%), respectively.[5]

Patients with HF have a poor prognosis with high mortality and hospitalization rates due to episodes of acute decompensation. Implementation of evidence based treatment, mostly represented by neurohormonal antagonists and devices, implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT), have led to a reduction in the hospitalizations rate and, to a lesser extent, lower mortality.[10-12] The mortality of HF remains, however, high with an annual rate of 7-8% in outpatients with chronic stable HF and much higher values of 20-25% in patients who have been hospitalized for acute HF.[13]

The most recent data from Olmsted County, Minnesota, based on physicians' clinical codes during outpatients visits or at hospital discharges in the years 2000 to 2010, have shown a significant 37.5% decline in the age- and sex-adjusted incidence of HF over the last decade with, however, no change in the mortality rates which have

remained of 20% at 1 year and of 53% at 5 years after diagnosis. Non-cardiovascular causes were the most common cause of death (54.3%). Hospitalizations were also common (mean, 1.34 per person-year) and were mostly due to non-cardiovascular causes with no change over time of those due to cardiovascular causes and an increase of those for non-cardiovascular causes.[14]

HFpEF

HF is a heterogeneous syndrome. For practical purposes, the most important distinctions remain that between patients with acute and chronic HF as well as that between patients with HF and reduced left ventricular ejection fraction (HFrEF), with a left ventricular ejection fraction (LVEF) $\leq$40%, and patients with a preserved EF (HFpEF) with a LVEF $\geq$50%. The reason why these two classifications are of value is that they define the patients who have been studied in randomized controlled trials. To date, all trials with favourable results have enrolled patients with chronic HFrEF whereas we have no outcome trials showing the efficacy of any drug in patients with either acute HF or with HFpEF. Thus, evidence based guidelines for treatment can be applied only to patients with chronic HFrEF. Epidemiological data show, however, the relative increase in the prevalence of HFpEF, versus HFrEF, in the recent years and it is therefore mandatory to identify effective therapies also for these patients.[14, 15]

Other categories can be added to those of HFrEF and HFpEF. Patients with intermediate values of LVEF, between those of the patients with HFrEF and HFpEf, e.g. a LVEF of 41% to 49% have been defined as HFpEF borderline[3] or with middle-range ejection fraction (HFmEF).[16] Patients with HFmEF encompass 10-20% of the overall patients with HF. Their clinical characteristics and outcomes are intermediate between those of the patients with HFrEF and HFpEF.[16] No data regarding the effects of therapy are available regarding these patients. Many of them may have actually recovered from a condition of HFrEF.

The categories defined as "HFpEF improved",[3] "recovered LVEF"[17, 18] or "better LVEF",[19] regard patients with previous HFrEF who have an improvement in LVEF up to values >40%.[3] Up to 40%,

of the patients with new onset HF may have such an improvement in their LVEF after treatment. These patients have a favourable response to treatment, are more likely to have normal coronary arteries and tend to have higher blood pressure at baseline, consistently with better contractile function.[17, 20, 21] Though better, compared with the patents with HFrEF, their clinical course is characterised by a meaningful rate of events with a slightly lower mortality and a similar rehospitalizations rate, compared with the patients with HFpEF.[18] Importantly, though they may have a normal LVEF, they cannot be confounded with the patients with HFpEF. Their improved LVEF is the expression of a better response to treatment and maintenance of treatment with neurohormonal antagonists may be considered as mandatory, in these patents, differently from those with persistent HFpEF.

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Pericardium and diastolic dysfunction

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The four chambers of the heart are haemodynamically connected by blood flow, physically connected by the structures they share, but interdependent due to the common encasing of the pericardium. The pericardium comprises an inner serous membrane (visceral pericardium) and fibrous, outer layer (parietal pericardium) consisting primarily of collagen. The visceral layer is responsible for lubricating the heart within the thoracic cavity, allowing it to beat in an almost frictionless bath. The parietal pericardium serves to protect the heart from the spread of infection, positions the heart within the thoracic cavity, and prevents extreme distension of the myocardium.

Although it is important for the pericardium to prevent myocardial distension, this characteristic may also constrain diastolic filling. The role of the pericardium as a limiting factor to cardiac filling has been investigated since the late 19th century, when Barnard discovered that an intact cat heart could hold approximately 12 mL of blood.
However, upon removal of the pericardium, the myocardium held an additional 11 mL, nearly doubling the initial total. He also demonstrated that an intact pericardium allowed the heart to sustain an additional 200 mmHg before rupturing. Initially, it was proposed that by limiting diastolic filling, the pericardium reduced stress on the myocardium, thereby preventing cardiac hypertrophy, dysfunction, or rupture.

The normal pericardial sac can hold a 250-350 g heart and approximately 15–50 mL of pericardial fluid. Collagen bundles are the principle structural components of the parietal pericardium and their arrangement is such that the stress-strain relationship of the pericardium is J-shaped. As a result, the pericardium is relatively compliant at low levels of stretch, but shows a sharp decrease in compliance at high levels of stretch. Therefore, small initial increases in total cardiac volume are met with small increases in pressure, but

further increases in cardiac volume are met with large increases in pressure. In fact, the pericardium may set the diastolic limits of the heart. Research has shown that the internal pressure-volume relationship of the four-chambered heart mirrors the J-shaped pressure-volume relationship of the pericardium. When the pericardium is removed from the heart, this relationship shifts to the right, allowing for enhanced myocardial filling at lower pressures.

The pericardium plays an essential role in the modulation of both diastolic and systolic ventricular interdependence.
The influence of the pericardium on systolic ventricular interdependence is small in comparison with its influence on diastolic ventricular interaction. The pericardium limits the total volume within the heart; however, the volume within each of the four chambers may vary while total cardiac volume remains unaltered. With acute changes in myocardial volume and size, the pericardium is stretched and its elastic properties restrict further cardiac dilatation, limiting the ability of the ventricles to further increase end-diastolic volume (EDV) and SV. The pericardium also enhances the effects of changes in right ventricular (RV) volume on left ventricular (LV) diastolic distensibility. When the RV is distended the pericardium bordering the free wall of the RV is stretched outwards, whereas the pericardium adjacent to the LV free wall is pulled inward, serving to reduce LV size and compliance. This diastolic ventricular interdependence is most evident when the increase in RV volume is large enough to shift the pericardium into the stiff portion of its stress–strain, relationship resulting in a sharp increase in pericardial pressure. Pericardial-mediated ventricular interactions and LV compliance are most often evaluated at EDV. However, reductions in RV haemodynamics have been shown to reduce minimal LV pressure, and the pericardium markedly enhances the influence of the RV on LV compliance. Therefore, the pericardium may influence diastolic filling during all phases of diastole. It is clear that diastolic ventricular interaction is of vital importance when examining cardiac function. When cardiac volumes become increased (e.g., during exercise), pericardial pressures rise and the diastolic filling capacities of the ventricles may be limited.

Attempts at further increasing preload may result in several disadvantageous outcomes including increased right atrial pressure (an established surrogate of pericardial pressure), a leftward shift in the interventricular septum, and a decreased LV EDV. Collectively, these characteristics are known as pericardial constraint and are characterized by a taut, unyielding pericardium encompassing the myocardium. Reductions in LV EDV as a result of pericardial constraint can directly limit SV, cardiac output (Q), oxygen consumption ($VO2$), and ultimately functional and (or) exercise capacity. Therefore, endurance-trained individuals exhibit enddiastolic pressure-volume curves similar to those observed in animal hearts following pericardiectomy, whereas the LV pressure-volume curve of the untrained individual mirrors the intact animal heart and pericardium curve. Further evidence that endurance-trained athletes have an altered pericardium comes from the observation of their enhanced filling capacity and ability to increase SV to a greater degree during exercise than untrained individuals can. The response of the athletes to exercise parallels the increases in LV EDV, SV, and exercise capacity seen in animal models following pericardiectomy. It is possible that chronically trained endurance athletes may provide a case in which pericardial compliance can be altered. Animal research has shown that chronic increases in ventricular filling can stimulate pericardial growth. The necessary stimulus may be present in endurance athletes to provoke pericardial remodelling in the form of exercise-induced hypervolemia and years of exercising at high LV EDV. Overall, the enhanced LV compliance found in endurance athletes may be beneficial during exercise conditions, yet detrimental during orthostatic stress.

Patients with congestive heart failure and elevated left ventricular filling pressures demonstrate an abnormal pattern of diastolic filling that is characterized by a redistribution of diastolic filling to early diastole with reduced reliance on late diastolic filling. The diastolic filling pattern superficially resembles that which is seen with constrictive pericarditis. The pericardium, because of the nature of its pressure-volume relation, can influence left ventricular diastolic and systolic pump function. During an acute increase in heart size that results in the stretching of the pericardium, the elastic properties of the

pericardium restrict further cardiac dilatation and curtail the ability of the ventricles to increase stroke volume. In addition, the pericardium enhances the degree to which increments in right ventricular volume would alter left ventricular diastolic distensibility. Ventricular interdependence is enhanced as a direct consequence of pericardial elastic properties. During the heightened venous return associated with marked muscular work, there is an evidence of pericardial constraint in most of the patients with heart failure of varying severity and diverse etiology. The occurrence of pericardial constraint, which is characterized by stroke volume becoming invariant and an equivalent rise in right atrial and pulmonary capillary wedge pressures as work load s raised during incremental upright exercise, and independent of the degree to which maximum oxygen consumption was reduced or, equivalently, the severity of heart failure. In contrast, when pericardial constraint is not apparent during our exercise protocol, stroke volume does not become invariant, and the increments in pulmonary capillary wedge pressure were two- to threefold that of right atrial pressure. Therefore, the pericardium can have a substantial role in determining the limits to left ventricular diastolic and systolic function. In one experimental model it was demonstrated that at physiologic pressures, the pericardium has a significant constraining effect on diastolic filling of the left ventricle, and after opening of the pericardium, an increase in cardiac index and stroke work index was observed. These increases may be attributed to the Frank-Starling response to increased left ventricular preload. The demonstrated improvement in left ventricular systolic performance should be considered when contemplating closure of the pericardium after cardiac operations, especially in patients with preoperative left ventricular dysfunction.

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Biomarkers in HFpEF

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The diagnostic criteria specified in current HF guidelines for HFpEF includes invasive or non-invasive assessment of LVDP such as an LVEDP > 16 mmHg, PCWP >15 mmHg, increased LA volume index > 40ml/m^2. This requirement is based on epidemiologic studies, randomized clinical trials and mechanistic studies demonstrating significant abnormalities in diastolic function in patients with HFpEF. In addition, studies using implantable hemodynamic monitors (IHM) in patients with HFpEF have demonstrated that LVDP is increased even when HFpEF patients are considered compensated; LVDP further increases significantly when HFpEF patients make the transition to ADHF. Thus, LVDP represents an important diagnostic and prognostic index and may be useful in developing novel management strategies in HFpEF. There is a remarkable parallel between these applications of LVDP to HFpEF and application of natriuretic peptides to HFpEF.

Like LVDP, BNP and NT-proBNP have become critical components of the diagnostic criteria for HFpEF proposed in HF guidelines. In addition, BNP and NT-proBNP have become essential inclusion criteria in RCTs in HFpEF. The standard partition values for diagnostic criteria of BNP = 100 pg/ml and NT-proBNP =800 pg/ml have been suggested to support the diagnosis of HFpEF. In addition, like LVDP, baseline values of NT-proBNP and change in NT-proBNP from baseline have prognostic value in patients with HFpEF.Thus, there are similar predictive patterns using LVDP and natriuretic peptides.

Beyond their diagnostic and prognostic capabilities, tailoring therapy based on BNP values may also be efficacious. Three recent studies Habit, Protect and Battlescarred suggested that BNP or NT-proBNP measured in an outpatient setting (every 1-3 months) or measured daily at home was both feasible and efficacious in guiding

treatment in patients across an EF spectrum. In these studies, increased values of BNP were treated by augmenting diuresis and lowering LVDP. For example, Protect was an investigator initiated, prospective randomized study in HF patients with an EF ≤ 40% (mean 28±9%). Total CV events were lower and time to first CV event was longer in patients in whom NT-proBNP was used to guide treatment compared with patients in the standard of care group in whom NT-proBNP was not used to guide treatment. In Habit I (Heart failure assessment with BNP in the home) patients with an EF median 30% and IQR 20-45%, daily home BNP testing was feasible and changes in BNP corresponded to significant changes in risk of CV events.

There are additional biomarkers such as galectin-3 and ST-2 which may reflect the degree and reversibility of fibrosis. Galectin-3, is a beta-galactoside-binding lectin, secreted by macrophages, that may act to increase fibroblast proliferation, activity and transformation into myofibroblast. In so doing Gal-3 may promote a profibrotic fibroblast phenotype, increase collagen synthesis, and enable aldosterone signaling. A number of studies have demonstrated that Gal-3 is increased in HFpEF and predicts worse outcome in HFpEF. Because Gal-3 is related to aldosterone signaling, a high Gal-3 level may help identify those HFpEF patients that are most responsive to treatment with an aldosterone antagonist. ST2 is a member of the interleukin 1 receptor family, ST2 exists in both membrane bound and soluble forms. The functional ligand of ST2 is interleukin 33 (IL-33), a cardiac fibroblast protein. Binding of IL-33 to membrane ST2 produced by increased myocardial biomechanical elicits an antihypertrophic and antifibrotic response. This cardioprotective effect is negated by soluble ST2 which acts as a decoy, prevents binding of IL-33 to membrane bound ST2. Soluble ST2 is in HFpEF and is associated with diastolic dysfunction, fibrosis and decompensation.

Therefore, based on the information described above, these plasma biomarkers that reflect collagen homeostasis and the degree of fibrosis should be useful in defining the degree of remodeling in HHD, augmenting diagnostic criteria for HFpEF, providing prognostic information in HFpEF and enhancing ability to develop tailored treatment in HFpEF.

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RAAS and adrenergic markers

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HFpEF has long been considered as synonimous of HF caused by diastolic dysfunction. The typical case was that of LV hypertrophy, primary or secondary to increased afterload. In this context, there has often been increased expression of the RAS and especially of aldosterone, which role in fibrosis formation has been clearly shown in experimental studies. The blockade of the RAAS has also proven to be effective in these experimental models. Therefore, there has been a kind of consensus about the major role of the RAAS in HFpEF.
Unfortunately, HFpEF is much broad than pure diastolic dysfunction and the role of the RAAS is more equivocal. There have been very few studies about the role of renin, angiotensin or aldosterone as biomarkers in HFpEF. Moreover, the RAAS antagonists have not been very effective in HFpEF in humans.
Knowledge about the sympathetic nervous system (SNS) in HFpEF has much less been studied. Activation of this system is far lesser than in HFrEF. Norepinephrine is no more routinely dosed. MIBG scintigraphy may be a new interesting imaging method to assess the status of the SNS in HFpEF.

Echostress testing of Diastole

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Stress echocardiography is a well none method for detection of myocardial ischemia, function evaluation of mitral valve disease and pulmonary hypertension. The non-invasive approach to diagnose diastolic function during stress is not very well validated and utilized. Heart failure with preserved ejection fraction is called diastolic heart failure (HFpEF). Recent definition of heart failure with preserved ejection fraction include three criteria: LVEF >50%, and LV end – systolic volume < 97 ml/m2 and E/e' ratio of > 15. Many patients with diastolic dysfunction have symptoms, mainly with exercise ,because of the rise in filling pressure that needed to maintain adequate LV filling and stroke volume. Therefore, this strengthens the need to use exercise stress test to assess LV filling pressure. The measurement that has been used most often during stress studies is the E/e' ratio, an important variable in the diagnosis of HFpEF according to European practice guidelines. The standard diastolic stress test should be "physiological" based on exercise with patients in semi-supine position rather than pharmacological stress. Initial workload of exercise should not be too high and the increments in workload should not be too strenuous. Submaximal exercise is likely to be more feasible. A heart rate < 110-120b.p.m will avoid fusion of myocardial and mitral, early and atrial phase velocity, and slower heart rate is better for the frame rate limitation of speckle tracking. Among the parameters used to assess diastolic function, E/e' ratio has been largely assessed to identify/exclude elevated LVFP and DD during supine or semi-supine bicycle exercise but its application in the clinical setting is still limited and requires further validation. E/e' is less valuable than e' alone during exercise. When posture during exercise echo is changed from supine to upright e' decreases and E/e'ratio increases, due to preload dependence of e'. The difference in duration between anterograde and retrograde flow during atrial contraction is an excellent echocardiographic index of LVEDP but it

is hard to obtain during stress. Recent studies showed a relationship between diastolic function and global longitudinal strain (GLS) and suggested to assess also GLS together with diastolic function in patients with HFpEF. In addition there are other diastolic parameters evaluated during echocardiographic stress tests, including Vp, IVRT. However, currently there are no definite and generally accepted protocols to assess diastolic function during stress test. The main questions regards: 1) the parameters to be assessed; 2) the definition of cut-off values of the adopted parameters; 3) the absence of large multicentre studies to assess the clinical and prognostic weight of these parameters.

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Mitochondria and Diastole: a Novel Therapeutic Target in Heart Failure

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Heart failure is a pressing public health problem with no curative treatment currently available.
The existing therapies provide symptomatic relief, but are unable to reverse molecular changes that occur in cardiomyocytes. While the mechanisms of heart failure are complex and multiple, mitochondrial dysfunction seems a critical factor in the development of this disease. Research is focusing on targeting mitochondrial dysfunction in the failing heart to revive the myocardium and either its contractile function as well as diastole.
Mitochondrial biogenesis, mitochondrial oxidative stress, and mitochondrial iron handling are the most promising areas for the development of heart failure therapies..

Cardiac magnetic resonance imaging: delayed enhancementand beyond: T1 mapping & new tools

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The study of diastolic function represents a crucial element in the evaluation of patients affected by cardiovascular diseases, particularly in patients with heart failure with preserved ejection fraction. Echocardiography is the keystone in the detection of diastolic dysfunction. Cardiac magnetic resonance (CMR) offers unique diagnostic features including myocardial tissue characterization and the elevated definition of the endocardial border in respect to blood pool and the opportunity to obtain cine sequences with good temporal resolution. CMR is considered the gold standard imaging technique for the quantification of ventricular systolic function but its role for diastolic function is still under evaluation.

The evaluation of diastolic function by CMR is made by the analysis of the Volume/Time curve generated in left ventricle and left atrium. CMR permit the combined evaluation of both atrial function and ventricular diastolic function.
Left atrial function consists of three distinct periods: reservoir, conduit and booster. The reservoir is the period of atrial filling during ventricular systole. In this period the atrium receives blood from pulmonary drainage (and from mitral regurgitation when present). At the end of systole, the mitral valve opens and the emptying phase of the atrium starts. Atrial emptying is divided into two phases. In the first one, the conduit phase, the atrium acts as a passive chamber permitting the transit of blood directly from venous drainage to the left ventricle. During this time, atrial volume passively decreases due to the negative suction pressure of the left ventricle. In the second phase, the left atrium contracts actively, completing the emptying. During this latter phase, a variable amount of blood (very small in healthy subjects) regurgitates into the pulmonary veins because of the absence of valves.
Diastolic abnormalities of the left ventricle may involve both the conduit and booster phase of left atrial function.

Initially the first impairment of diastolic function consists in abnormal relaxation that may alter the conduit phase of the left atrium by an increase of ventricular stiffness and a decrease of passive suction. During this stage, the left atrium compensates for the decrease of atrial passive emptying by enhancing the booster function. With the worsening of diastolic function, the atrial contraction becomes less able to compensate for the increased ventricular stiffness to maintain adequate emptying, and the left atrium enlarges. Then, in the late stages, atrial fibrosis may further alter atrial function and become the substrate for atrial fibrillation. During atrial fibrillation, the booster function is usually nulled because of a complete dyssynchronous contraction of the atrial myocytes.

The identification of myocardial fibrosis is one of the strengths of CMR. The extent of myocardial fibrosis may be measured using the late gadolinium enhancement (LGE) technique. Gadolinium-chelates are extracellular agents which exit from capillary vessels and remains in the interstitial space. However, in normal myocardium the wash-out is almost complete after 8-10 minutes following the injection. In the presence of fibrosis, the interstitial space is increased because of the presence of a collagen matrix that bridles the gadolinium and cause a very slow wash-out. Then, 8-10 minutes from the injection, myocardial fibrosis is enhanced and normal myocardium is nulled.

In non ischemic heart disease, the presence of fibrosis is associated to progressive stiffness of left ventricular myocardium. Recent data demonstrated that in hypertrophic cardiomyopathy, the extent of fibrosis is directly related to progressive mechanical impairment. When fibrosis is less than 3% of left ventricular mass, patient is asymptomatic, with normal ejection fraction and normal diastolic function. When fibrosis increases to 4-7%, patients experience effort dyspnea with preserved ejection fraction and with initial diastolic dysfunction, that worsens with extent of fibrosis between 8 and 10% when atrial dilation appears that is often complicated by atrial fibrillation. Then, when the extent of fibrosis exceeds the 15 % of LV mass, the loss of contractile cells is sufficient to produce initial systolic dysfunction.

A similar mechanism is also found in other cardiomyopathies. In cardiac amyloidosis the diastolic impairment is caused by a combination of fibrosis and amyloid deposit.

CMR is particularly effective to identify patients with cardiac amyloidosis because of a peculiar pattern of LGE, with early darkening of cavity, impossibility to finding an appropriate inversion time to null myocardium and a diffuse enhancement of subendocardium. This pattern of LGE was described only in cardiac amylodosis and it is very specific. Interestingly, in this cardiomyopathy, the atrial function is impaired with atrial akinesia, also in presence of sinus rhythm, predisposing to thrombotic phenomenon also in absence of atrial fibrillation.

However, in 20% of patients with early stages of cardiac amyloidosis, the specific LGE pattern is absent. For this reason, new technique for tissue characterization by CMR are under investigation.

T1 mapping is a promising CMR technique, based on the fact that any normal tissue has a constant T1 value at the same magnetic field. Then, in pathological conditions myocardial T1 may be different. T1 mapping consists in the measurement of myocardial T1 and generation of maps of T1.

In cardiac amyloidosis myocardial T1 is increased due to the deposit of amyloid. In Fabry disease the deposit of sphingolipids is intracellular and LGE is present very late in the course of disease. In this cardiomyopathy T1 mapping may be able to detect a decreased T1 in almost all the patients with evident hypertrophy and also in 50% of patients without hypertrophy, allowing to detect cardiac involvement in early stage.

The combination of native T1 mapping (pre-contrast T1 measurement) and post-contrast T1 mapping allows to measure the extracellular volume of myocardium (ECV). The ECV represents the percentage of myocardium constituted by interstitial space (20-25%) and vessel (3-5%). Normal ECV is approximately 28-30% of myocardial mass and in case of interstitial deposit or myocardial fibrosis, ECV increased. The measurement of ECV is a promising technique to evaluate initial pathological conditions. ECV increase is seen in ageing, in aortic stenosis, and its associated to increased ventricular stiffness.

In conclusion, CMR is able to evaluated diastolic function and to identify the pathological conditions associated to diastolic dysfunction.

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Nuclear medicine: just a bystander

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Cardiac imaging with single photon emission computed tomography (SPECT) has become one of the most diffuse techniques for the evaluation of myocardial perfusion, allowing to obtain reproducible, semiquantitative, measures of myocardial blood flow distribution. In addition to perfusion data, ECG-gated cardiac SPECT offers the chance to obtain left ventricular (LV) functional parameters that may help to investigate myocardial systolic and diastolic functions. Specifically, different measures of LV diastolic function, such as the "peak filling rate" (PFR) and the "time to peak filling rate" (TPFR), may be automatically obtained from the analysis of SPECT-derived LV filling curves with commercially available software.

SPECT-derived filling parameters correlate with clinically used measures of LV diastolic function and predict the presence of elevated LV filling pressures. Therefore, a quantitation of LV diastolic function could help to improve the functional evaluation of patients submitted to myocardial perfusion scan. Moreover, the relationship between SPECT-derived diastolic parameters at rest and LV filling pressures is independent on the presence and severity of significant coronary artery disease and may help to obtain a better functional characterization of patients submitted to myocardial perfusion imaging.

The possibility to use an ultrafast SPECT protocol, with the post-stress acquisition very close to the end of stress test, may give the chance to better characterize the presence and quantify the magnitude of stress induced alterations of LV systolic and diastolic functions. The additive diagnostic impact of the assessment of stress-induced impairment of LV diastolic function at transthoracic echocardiography has been already reported.

As a matter of fact, recent data indicated that, as for echocardiography, the relationship between SPECT-derived measures of LV diastolic and contractile function persists even under stress conditions, highlighting the feasibility of an integrated evaluation of

myocardial contractility and relaxation in patients with suspected or known ischemic heart disease. This is a very important issue, because the possibility to simultaneously quantitate myocardial regional myocardial perfusion and LV filling dynamics, could give additional functional information in the evaluation and clinical characterization of patients submitted to myocardial perfusion imaging.

Conclusions
In patients with suspected ischemic heart disease a combined evaluation of regional myocardial perfusion and LV contractile and diastolic function both at rest and after stress is feasible with a reduced acquisition time and contained radiation burden.

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Thyroid hormones and diastole

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From a pathophysiological point of view diastolic dysfunction may be simply defined as a condition caused by an increased resistance to the filling of one or both ventricles. Diastolic dysfunction increases with age; hypertension and cardiac ischemia represent the most common reported causes of disease. In clinical practice two-dimensional echography with Doppler is commonly used to evaluate diastolic function by the peak velocity of blood flow across mitral valve during early diastolic filling (E wave), atrial contraction (E wave), E/A ratio, isovolumetric relaxation time (IRT) and only rarely radionuclide angiography is used in patients in whom echocardiography is difficult. Hypothyroidism is a potentially important but overlooked cause of diastolic dysfunction by taking into account that subclinical (mild) hypothyroidism is a very common disease, especially among elderly population, with a prevalence ranging from 10 to 68.4%. Thyroid hormone exerts important and profound effects on the heart and cardiovascular system in general: among these it is noteworthy the action on diastolic relaxation. Since years eighty (1) overt hypothyroidism has been associated with a decreased rate in ventricular diastolic relaxation while B. Biondi was the first to describe diastolic dysfunction in subclinical hypothyroidism at the end of 20th century (2). Notably, restoration of euthyroidism by substitutive thyroid hormone treatment usually results in a substantial reversal of all parameters of diastolic impairment (2-3).

The presence of diastolic dysfunction when thyroid function is explained by an altered intracardiomyocyte calcium handling secondary to a reduced expression -and action- of sarcoplasmic reticulum calcium-adenosine triphosphatase SERCA 2 and overexpression of its counteracting protein Phospholamban, being both proteins under direct control of thyroid hormone system (4). Significant effects of thyroid hormone on diastolic function have been observed also in heart failure patients with low Triiodothyronine (T3) syndrome which is characterized by a reduction in biologically active T3 concentrations in presence of normal values of Thyroxine (T4) and

thyroid stimulating hormone (TSH) secondary to the impairment of T4 into T3 peripheral conversion. This non-thyroidal illness may produce cardiovascular alterations similar to the changes described for hypothyroidism. Improvement in diastolic function was indeed observed after both short-term (three days) and long-term (six weeks) substitutive T3 treatment (5-6).
More recent findings in subclinical hypothyroid patients (7-8), however, give conflicting results; in particular the effect of T4 replacement in restoring a normal diastolic function still remain uncertain.
Additional studies are then necessary to define the right role of a thyroid hormone defect – and of its reversal by therapy - in the pathophysiology and treatment of diastolic dysfunction and diastolic heart failure progression.

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DD and cardiovascular events (stroke, AMI, heart failure)

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Left ventricular (LV) diastolic dysfunction (DD) is associated with increased morbidity and mortality. First of all DD and especially worsening DD is a marker of increased risk. Several conditions such as hypertension, diabetes mellitus, myocardial ischemia, reduced systolic function, as well as restrictive and hypertrophic forms of cardiomyopathy, all negatively affect DD. Rather than static, DD is a dynamic process. When it makes its appearance in the clinical scenario, DD exacerbates all these conditions, with adverse effects on prognosis, while improvement of diastolic function is associated with better survival (1).

In addition to being a marker of increased risk, DD may also represent a direct contributor to adverse outcome (2). It is quite difficult to elucidate whether it is primarily DD or conditions that determine DD that contributes to adverse outcome, but DD may per se affect prognosis by several mechanisms. DD may have a direct impact on major adverse cardiovascular events, i.e. heart failure (HF), coronary disease (acute myocardial infarction) and cerebrovascular disease (stroke).

The relation between DD and HF has received much interest. Several factors may affect the evolution from DD (pathological condition) to HF (clinical condition), such as systolic function, coronary disease, mitral valve disease and atrial arrhythmias. DD may limit cardiac output reserve, exacerbate mitral regurgitation, facilitate atrial fibrillation and increase neuroendocrine activation. These mechanisms lead to the clinical scenario of HF with preserved/reduced ejection fraction (HF), characterized by symptoms of breathlessness, physical inactivity, deconditioning and frailty.
The clinical outcomes of HFpEF are similar to those with HFrEF, including in-hospital morbidity and hospital readmission rates (3). While in-hospital mortality may be slightly higher in HFrEF, 30-day to 1-year mortality post discharge is similar between groups (3).

Patients with either HF syndrome suffer from comparable functional limitations and poor quality of life. Risk factors for mortality in HFpEF include advanced age, renal impairment, anemia and hemodynamic instability (hypotension, tachycardia). There are differences in the etiology of morbidity and mortality between the groups, with morbidity in HFpEF being often driven more by non-HF cardiovascular conditions (4) and ~40% of deaths being linked to non-cardiac causes (5).

Actually, instead of consider HFrEF and HFpEF as two different clinical conditions, they could represent a pathophysiological continuum. DD may exacerbate the clinical condition of a patient with systolic dysfunction, as well as a patient with originally isolated DD may develop systolic dysfunction, with adverse effects on prognosis.

Coronary artery disease affects both systolic and diastolic dysfunction. Acute myocardial infarction causes a loss of contractile fibers which reduces systolic function. Parallel to the effect on systolic function, a myocardial infarction also worsens diastolic function. Active relaxation is delayed following a myocardial infarction, whereas left ventricular stiffness changes depending on the extent of infarction and remodeling. Interstitial edema and fibrosis cause an increase in wall stiffness which is counteracted by dilation. Some index of DD and increased left ventricular filling pressures such as E/E' and left atrial volume predict morbidity and mortality after myocardial infarction, independently by infarction extent.

Since DD is associated with several risk factors for coronary disease and myocardial infarction such as arterial hypertension, age, male sex, diabetes, many patients that suffer from acute myocardial infarction have pre-existing DD. This pre-existing diastolic dysfunction with increased LV filling pressures is a factor that significantly worsen the prognosis of these patients as an acute loss of even relatively small amounts of myocardium is poorly tolerated (6).

On the other side, what is less clear, is whether diastolic dysfunction may per se increase the risk for ischemic heart disease and myocardial infarction. Pressure overload causes myocyte stretch, with increased wall stress and poorer sub-endocardial perfusion. Energy production and energy consumption efficiency are also impaired in DD patients. The net effect is that DD lowers the ischemic threshold (7).

This could explicate the high rate of myocardial infarction in patients with DD, even in absence of obstructive coronary artery disease (8).

Atrial fibrillation represets the most important link between DD and stroke. Patients with increased left ventricular filling pressure have higher chances to develop atrial fibrillation and stroke is the most common complication of atrial fibrillation due to thrombi that develop in left atrium/left atrial appendage. Moreover, the risk of stroke is enhanced by several conditions that affect DD such as hypertension, diabetes, age. The presence of heart failure (even with preserved ejection fraction) is another risk factor for stroke occurrence. Ten to fifteen percent of cardiovascular deaths in patients with DD are due to stroke (9).

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Atrial Fibrillation and Diseased Diastole

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Atrial fibrillation (AF) is the most common arrhythmia confronted on the clinical ground; its prevalence rises with the age and with the concomitant presence of comorbidity like hypertension, diabetes, ischaemic heart disease [1]. The development of this arrhythmia in the population poses various challenges an threads: AF, in fact, may be highly symptomatic and affect the quality of life of those who are affected; it is however also associated with increased mortality in patients with and without structural heart disease, due to the hemodynamic compromise that can derive from AF manifestation; ultimately, AF poses a significant threat due to the trombogenicity of diseased atrial myocardium, with possible development of embolic stroke in those not adequately anticoagulated. The same factors just mentioned are also associated with the development of diastolic dysfunction, which is a significant contributor to systolic heart failure progression, clinical manifestation and prognosis; furthermore, diastolic dysfunction in the absence of significant left ventricular dysfunction delineates a distinct clinical entity, heart failure with preserved ejection fraction (HFpEF), that both European and North American cardiological societies have recognized and addressed in their respective guidelines [2;3].

Atrial fibrillation is a common occurrence in HFpEF [4] and contributes to the worsening of symptoms and to haemodynamic deterioration [5]. Albeit initially patients with HFpEF might have increased atrial contribution to ventricular filling due to impaired early filling (mainly ventricular-dependent) [6], mechanical overload on atrial myocardium leads to chronic remodeling and deterioration of atrial function, paving the way to substrate alteration that are the basis of AF induction and maintenance [7].

This has been also highlighted in some studies where diastolic dysfunction, evaluated either by echocardiography [8] or by measuring invasively left atrial pressures [9] was also associated with a more treatment failures after catheter ablation of AF.

In conclusion, AF and diastolic dysfunction are common in ageing population and in those with structural heart disease; their concomitant occurrence might play a synergistic role in worsening the quality and the duration of life of those who are affected and influence the therapeutic strategy that clinicians consider to tackle these disorders.

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DD and kidney failure

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Cardiovascular disease is the most common cause of death in patients with chronic kidney disease (CKD) (*Coresh J et al, 2007*). Impairment of kidney function is indeed associated with several mechanisms of cardiovascular damage, including left ventricular hypertrophy, cardiovascular fibrosis, increase in left ventricular filling pressure and neurohormonal activation (*Poletti R et al, 2013*). Moreover, a complex pathophysiological interplay between heart and kidney exists, where a primary injury (of both acute or chronic onset) in either organ contributes to functional impairment of the other, leading to the so-called "cardio-renal syndrome".

Sodium and water retention, due to glomerular loss and to renin-angiotensin-aldosterone system activation, is a key feature of patients with CKD and contributes to the increase in circulating volume. This is associated with increased left ventricular stiffness and abnormal myocardial relaxation, thus producing significant increase in left atrial pressure, and pulmonary oedema, even with small variations in preload conditions and often in the presence of preserved left ventricular systolic function. In this view, CKD represents one of the major determinants of diastolic heart failure and - given its influence on patients' prognosis - deserves (early) diagnostic and therapeutic efforts.

At present, echocardiography represents the gold standard for the evaluation of diastolic function, mainly by means of measurement of transmitral pulsed wave Doppler flow and of mitral annular tissue Doppler imaging (TDI). Both transmitral flow (E wave velocity in particular) and TDI are influenced by changes in kidney function (by loading conditions and ventricular stiffness, respectively). Nonetheless, the E/e' ratio seems to be a good predictor of left ventricular filling pressure and a to correlate well with prognosis in patients with CKD (*Kim MK et al, 2013*).

Moreover, circulating levels of natriuretic peptides are increased in CKD, thus further complicating diagnosis of diastolic heart failure in patients with impairment of renal function (*O'Meara E et al, 2013*).

Left ventricular diastolic dysfunction is highly prevalent in patients with CKD, independently from renal replacement therapy (*Miyazato J et al, 2005*). Although it has been reported that in end-stage renal disease patients diastole deteriorates in parallel with the progression of hypertrophy (*Fathi R et al, 2003*), impairment of left ventricular relaxation may occur earlier, even in the absence of hypertrophy (*Nardi E et al, 2007*), thus suggesting that other pathophysiological mechanisms may play a prominent role in the development of diastolic dysfunction in CKD. Indeed, pro-inflammatory pathways, neurohormonal activation and hyperparathyroidism may represent early, non-haemodynamic factors leading to left ventricular fibrosis and stiffness.

In conclusion, diastolic dysfunction shares risk factor, pathophysiological mechanisms and, possibly, therapeutical targets with CKD. Both conditions do frequently coexist in the same patient and are associated with a poor prognosis. A diagnostic effort is therefore required in order to tailor treatment and to improve patients outcome.

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DD and pericardial disease

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The pericardium is a fibrous sac that surrounds the heart. It consists of 2 layers, the visceral and parietal pericardium, containing a small amount of serous fluid. As a result of its relatively inelastic physical properties, the pericardium limits acute cardiac dilatation and enhances mechanical interactions between cardiac chambers. Pericardial inflammation and effusion are two common diseases, which can be rarely complicated by constriction and tamponade[1]. From a pathophysiological point-of-view, pericardial diseases are often in differential diagnosis with myocardial diastolic diseases, since both conditions impair cardiac diastolic filling.

Acute inflammation of the pericardium with or without an associated pericardial effusion is usually idiopathic or viral (nearly 90% of cases), but among less common causes there are tuberculosis, bacterial infections, uremia, collagen diseases, neoplasms or myocardial infarction (early post-infarction pericarditis or late post-pericardiotomic/post-infarction Dressler's pericarditis). Acute pericarditis is usually diagnosed based on its typical clinical, biohumoral, electrocardiographic and echocardiographic findings, and in most cases it is treated with non-steroidal anti-inflammatory drugs. The COPE trial demonstrated a better outcome if all patients receive a 3-month course of colchicines, while the use of steroids should be avoided because of the high risk of recurrence[2]. If relapsing after a 4-6 week disease-free interval, pericarditis becomes "recurrent". If lasting more than 3 months, pericarditis becomes "chronic"; in both cases, a prolonged anti-inflammatory therapy is needed.

Cardiac tamponade occurs when fluid accumulation in the intrapericardial space is sufficient to raise the pressure surrounding the heart to the point where cardiac filling is altered: compression of the heart by a pressurized pericardial effusion results in markedly elevated venous pressures and impaired cardiac output producing shock. Unless promptly diagnosed by clinical and echocardiographic signs

and relieved by percutaneous or surgical drainage, cardiac tamponade can be rapidly fatal.

Pericardial constriction occurs when a scarred, thickened, and frequently calcified pericardium impairs cardiac filling, limiting the total cardiac volume. It is usually the result of long-standing pericardial inflammation, in particular due to mediastinal radiation, chronic idiopathic pericarditis, cardiac surgery, and tuberculous pericarditis. Patients with pericardial constriction typically present elevated systemic venous pressures and low cardiac output. Similarly to restrictive cardiomyopathy, ventricular diastolic filling stops abruptly with a characteristic dip and plateau, because of the stiffened myocardium or pericardium respectively. On the other hand, differently from restrictive cardiomyopathy, the pathophysiological hallmark of pericardial constriction is equalization of the end-diastolic pressures in all four cardiac chambers, because the filling is determined by the limited pericardial volume, not the compliance of the chambers themselves: similarly to cardiac tamponade, in pericardial constriction the total cardiac volume is limited, increasing diastolic pressures in all four cardiac chambers and accentuating their interdependence; if the volume in any cardiac chamber can only increase when there is an equal decrease another chamber, the normal effects of respiration are accentuated such that venous return and right-sided filling occur during inspiration, while left-sided filling and systemic output are increased during expiration. Echocardiography can often distinguish between myocardial diastolic dysfunction (restriction) and pericardial constriction, particularly with Doppler and tissue-Doppler techniques. Nevertheless, myocardial and pericardial morphology and function can be better evaluated with cardiac computed tomography and magnetic resonance, the latter providing superior soft-tissue characterization[3, 4]. Acute onset pericardial constriction can sometimes resolve with anti-inflammatory agents, colchicine, and/or steroids; in more common chronic forms of pericardial constriction, where fibrous/calcification of the pericardium predominates, definitive treatment needs surgical pericardial decortication.

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Drugs for Diastole in Heart Failure

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Heart failure with preserved left ventricular ejection fraction (HFpEF) accounts for approximately 50% of all HF patients, and its outcome is comparable to that associated with systolic HF. Currently, promising therapeutic approaches include soluble guanylate cyclase inhibitors, ivabradine, and Dual angiotensin receptor blocker-neutral endopeptidase inhibitors. However, to this day HFpEF largely remains an orphan condition, due to the disappointing results from several randomized controlled trials. The heterogeneity of conditions underlying HFpEF likely represents one of the primary reasons behind these failures. In the era of molecular medicine, focusing on "pure" conditions rather than on complex syndrome may thus be more rewarding. This talk will focus on recent advances in our understanding of diastolic dysfunction in a unique, genetic model of diastolic HF such as hypertrophic cardiomyopathy.

Human HCM cardiomyocytes have been shown by our group to exhibit marked electrophysiological remodeling leading to abnormal intracellular calcium handling, enhanced arrhythmogenesis and abnormal diastolic function. These defects are selectively reversed in vitro by the late sodium current inhibitor ranolazine. Thus, targeting this single molecular mechanism has the potential to counter several key components of the HCM pathophysiology, including diastolic dysfunction, microvascular ischemia, arrhythmogenesis and, by virtue of a mild negative inotropic effects, dynamic outflow obstruction. These data provided a rationale for the recently completed multicenter, double blind, placebo-controlled pilot study, testing the efficacy of ranolazine on exercise tolerance in symptomatic HCM patients (RESTYLE-HCM; EUDRA-CT 2011-004507-20). While results of Restyle-HCM are awaited soon, a phase 2/3 trial, the LIBERTY-HCM study, has already started testing the efficacy of a new, more specific and potent late sodium current inhibitor, eleclazine. LIBERTY-HCM will test the hypothesis that, as compared

with placebo, eleclazine improves exercise capacity as measured by peak oxygen consumption (VO2) during cardiopulmonary exercise testing in patients with symptomatic HCM from over 40 centers in Europe and the US.

Finally, a “precision medicine” approach is emerging based on the hypothesis that, in selected genetic subsets, HCM is triggered by a hypercontractile state due to reduced inhibitory effect of the myosin-binding protein C on the cardiac myosin head. By selectively reducing the affinity of myosin for actin, the downstream consequences of sarcomere mutations might be countered in HCM patients, including prevention of phenotype development in the early stages of the disease. Phase I studies have been recently launched to assess the effects of MYK-461 (Myokardia, South San Francisco CA), the first allosteric inhibitor of cardiac myosin tested in man, in patients with HCM. While the efficacy of these approaches is still under investigation, both pathways may prove advantageous for larger patient population belonging to the HFpEF archipelago.

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Physical training for treating DD

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The main clinical features in chronic HF are exertional dyspnoea and reduced aerobic capacity. In heart failure with preserved ejection fraction (HFpEF), the degree of impairment in exercise capacity has shown to be similar to the syndrome of HF with reduced ejection fraction (HFrEF).[1] Even though this exercise impairment is an important determinant of poor prognosis and decreased health-related quality of life (QoL), its pathophysiology is complex and rarely explained by a single mechanism. [2]

Eight prospective RCTs that examined the effects of different modalities of physical therapies in HFpEF patients.[3] Findings from these trials suggest that most of these physical therapy protocols can be safely implemented in patients with HFpEF. In terms of efficacy, exercise training seems to improve functional capacity and QoL. Evidence is not convincing regarding changes in echo parameters, biomarkers and other surrogate endpoints. Unfortunately, the effect of physical therapies on major clinical outcomes such as mortality or hospitalisation is unknown.[4]

These findings contrast with the robust information available on exercise-based rehabilitation for HFrEF (30 trials with more than 4000 HFrEF patients) where physical therapy has commonly shown positive results by improving not only major clinical events, QoL and exercise capacity but also echo parameters, biomarkers and other surrogate endpoints of HF severity.[5] The basis for this discrepancy is not well understood; potentially epidemiological differences including aetiology and the burden of associated co-morbidities may be crucial issues.

Because of the limited information available on HFpEF, these results must be considered preliminary. Thus, a number of flaws and pitfalls must be considered before extracting definitive conclusions.

Few trials, few patients. The available evidence stemmed on the information supplied by only eight trials, where the number of participants ranged from 26–64

Heterogeneous interventions. Each trial has employed a different exercise training modality with a singular intensity and duration protocol

Heterogeneous criteria for defining HFpEF. Appropriate diagnosis of HFpEF remains a matter of debate. Overall, diagnostic criteria for defining HFpEF requires the simultaneous and obligatory presence of four conditions to be satisfied: (a) typical signs and symptoms of HF; (b) typical symptoms of HF; (c) normal LVEF with left ventricle not dilated; and (d) relevant evidence of structural heart disease, such as left ventricular hypertrophy, left atrial enlargement, and/or diastolic dysfunction. Only two studies fulfilled all four criteria.[6,7]

Heterogeneous population. In contrast to the evidence presented in population-based studies, patients included in this systematic review are younger and have a lower prevalence of co-morbidities (when it was reported)

Endpoints. We should point out that data on efficacy was only based on intermediate endpoints such as exercise capacity, QoL, diastolic dysfunction or endothelial dysfunction. Besides, every study has used different diagnostic methods for assessing functional capacity.

We believe that this research avenue should be further developed by including larger RCTs, testing different physical therapy modalities, and including patients with more advanced disease, and thus be more representative of the real-world population. At the same time, more trials with a follow-up planned to evaluate long-term effects, especially regarding major clinical and safety endpoints are needed. Equally important is also the cost-effectiveness evaluation

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Surgery of DD: Mythology

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Diastole disease is a common feature of different pathologies of the heart.
Historically, constrictive pericarditis and hypertrophic obstructive heart disease has been referred to the surgeon for treatment. Chronic constriction of the heart from constrictive pericarditis is a well known pathological entity described since the seventeenth century; ignorance of the difference between adhesive pericarditis and constrictive pericarditis left this disease untreated for almost two centuries. The first operation for constrictive pericarditis was performed at the beginning of the twentieth century; after that, an increasing number of surgical series of pericardial removal with symptoms improvement was reported. The translational basis of this approach was demonstrated by Beck (Beck 1931) that succeeded in reproducing the same pathological and clinical features in large animals experiments and also relieved the heart failure symptoms with pericardial removal. The principal hemodynamic abnormality is loss of pericardial compliance, with reliance on elevated ventricular pressure to maintain cardiac filling and output, which eventually leads to primary diastolic heart failure.
Pericardiectomy is effective in early and late phase to relieve symptoms, since complete removal of diseased pericardium can restore satisfactory diastolic filling; most patients experience substantial improvement in NYHA class (Ghavidel A et al 2012). Furthermore, echocardiography follow-up of these patients demonstrated a normalization of longitudinal and radial strain at 12 months after surgery, while global circumferential strain remained lower than controls (Li L et al 2015). On long-term follow up, about 85% of patients are asymptomatic or mildly symptomatic. Notwithstanding, outcome of the patients is dictate mainly by preoperative status (20% mortality at 10 years) and far more by

etiology, being the radiation and post-surgical constrictive pericarditis burdened by 50% and >90% mortality at 10 years.

Hypertrophic-obstructive heart disease is a structural disease with different and multiform etiologies. Abnormalities of ventricular and atrial function that result in suboptimal left ventricular (LV) filling in diastole are thought to be important causes of symptoms and functional limitation in patients with hypertrophic cardiomyopathy (HCM); many of the pathophysiologic mechanisms believed to account for "diastolic" heart failure are floridly expressed in HCM, and HCM may prove a useful "supermodel" for the study of diastolic heart disease and its treatment. The common feature is the development of left atrial enlargement and restrictive filling pattern over time. Septal myectomy, the surgical treatment of choice in still symptomatic patients after appropriate medical therapy and in asymptomatic patients with important LV outflow tract gradient at rest. Surgical excision of ventricular muscle, relieving of the outflow tract obstruction and mitral valve papillary muscle, is associated with reduction of left atrial volume and improvement of left ventricular diastolic function (Tower-Rader A et al 2014); furthermore the symptoms improvement is also multifactorial: decreased wall thickness and intracavitary pressure should result in a favorable shift in the relation between myocardial oxygen supply and demand and decrease sub-endocardial ischemia; ischemia relief in turn can result in better myocardial relaxation, improved diastolic filling, and potentially less long-term fibrosis (Monteiro PF et al 2007). The beneficial effect of septal myectomy in terms of pathophysiology and symptoms relieve are translated into a favorable mid- and long-term outcome, with good survival and low risk of suddend cardiac death when compared to medical treatment only and alcohol septal ablation (Vriesendorp et al 2014).

Myocardial ischemia slows ventricular relaxation and can impair ventricular distensibility resulting in diastolic dysfunction. Surgical revascularization has been found to at least partially reverse the diastolic dysfunction, particularly when associated with left ventricle reshaping techniques; notwithstanding age and age-gender differences in terms of diastolic dysfunction development and impact on mortality even after successful coronary artery bypass grafting.

Also valvular heart disease can affect the diastole. Diastolic dysfunction is associated with severe degenerative aortic valve disease. After surgery, left ventricle filling usually improves, with an increase in LV end-diastolic volume and regression of hypertrophy. This early improvement appears related to the decrease in ventricular mass and volume ratio (Lamb HJ et al. 2002). Likewise, an increase in coronary flow reserve can ameliorate the subtle myocardial ischemia and thus, in turn, improving the diastolic function. Paradoxically, in the early phase after surgery, has been demonstrated an increase in chamber stiffness followed by its decrease in long term as myocytes diameter and fibrosis lower (Villari B et al. 1995). Interestingly, the entity known as "patient-prosthesis mismatch", which occurs in a quite large proportion of patients without any over feature, can contribute to persistent diastolic dysfunction due to elevated LV systolic pressure and limited regression of LV hypertrophy. It appears that diastolic dysfunction is one of the major mechanisms by which mismatch contributes to clinical events of death and hospitalizations in this setting (Brown J et al 2009).

In aortic regurgitation, diastolic dysfunction occurs because of impaired left-ventricular relaxation and increased myocardial stiffness, as demonstrated by biopsies sowing increased cell diameter and fibrous content. In patients with aortic regurgitation and diastolic dysfunction the filling and pulmonary artery pressures are elevated at the beginning only during exercise and later on at rest. Literature about the relationship between aortic regurgitation, valve replacement and outcome is scarce, with one study that found an association between diastolic dysfunction grade and failure to improve ejection fraction after surgery, i.e. increased in type I while decreased in type III, being deceleration time a predictor of ejection fraction improvement after AVR (Cayli M et al. 2009); diastolic dysfunction appears to have a higher prevalence and worse severity late after surgery after valve replacement for aortic regurgitation as opposed to surgery for aortic stenosis. Despite significant decrease in muscle fiber diameter, interstitial fibrosis likely play a major role in the persistently elevated diastolic stiffness constant (Villari B et al. 2009).

Diastolic heart disease can be relieved by surgical treatment in a significant proportion of patients; although these pathologies share the

common features of a diseased diastole, specific pathophysiological mechanisms can contribute to the reversal or failure to reversal of symptoms, thus affecting the patients' outcome. A clear understanding of the underlying effects of each disease, correct focus on diastolic features as a part of the heart failure development process is the key to provide a timed and effective surgical treatment.

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BEST ABSTRACTS ON DD PRESENTED BY YOUNG CARDIOLOGISTS/INTERNISTS

Reverse remodeling and improvement in diastolic function: a retrospective echocardiographic study

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Background:
Reverse remodeling (RR) is defined as the improvement in left ventricular (LV) geometry and systolic function following optimal heart failure pharmacological and/or device therapy. Currently used criteria for the assessment of RR rely on LV volumes and ejection fraction, while clear data are lacking on changes in diastolic function.

Purpose:
We aimed to test whether RR was associated with an improvement in diastolic function.

Methods:
We retrospectively assessed 594 patients, aged 68 ± 11 years, undergoing 2 transthoracic echocardiograms over 12 ± 2 months. Baseline LV ejection fraction was <55% in all cases; systolic dysfunction was of ischemic etiology in 65% of patients. RR was defined as a >=10% reduction in LV end-systolic volume; LV volumes were calculated through the biplane Simpson method. The following parameters were considered in order to evaluate diastolic function: mean E/e' ratio, septal E', lateral E', deceleration time, grade of diastolic dysfunction.

Results:
180 patients (30.3%) showed RR. The E/e' ratio was more frequently reduced at follow-up echocardiography in patients with RR compared to those without RR (P=0.011). Absolute reductions in LV end-systolic volume were directly correlated with reductions in E/e' values (P=0.021), as well as with increases in septal E' (P=0.029), and in deceleration time (P<0.001).

Furthermore, a strong association was observed between RR and improved grade of diastolic dysfunction (P<0.001).

Conclusions:

In this preliminary, retrospective study, the recovery of systolic function over one year was accompanied by some evidences of improved diastolic function.

Relationship between arterial stiffness parameters and diastolic function in a hypertensive population

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Background:
Arterial stiffness might favour the onset of left ventricular diastolic (LVD) dysfunction in hypertensive patients, possibly by increasing cardiac load. However, the relationship between arterial stiffness and LVD function in hypertensive patients has not been clarified.

Aim:
To investigate the relationship between arterial stiffness parameters and LVD function abnormalities in patients with hypertension.

Methods:
The study included 102 hypertensive patients (age 61±11 years, blood pressure –BP- 141±17/79±11 mmHg, 82.4% treated, 32.4% diabetics). Trans-thoracic echocardiogram was performed to calculate the ratio of early to late transmitral pulse Doppler velocities (E/A), mean early diastolic mitral annular velocity (e'_m) and E/e'_m. Furthermore, aortic stiffness (carotid-femoral pulse wave velocity, PWV) and wave reflection (augmentation index, AIx) were measured.

Results:
In the overall population mean E/A was 0.87±0.23 and E/e'_m 9.0±1.6. In the univariate linear regression analysis, E/A correlated with age, left ventricular mass index (LVMi), PWV (r= -0.38, r= -0.23, r= -0.36, respectively, $p < 0.05$ for all). e'_m was correlated to Aix, PWV, LVMi (r= -0.22, r= -0.38, r= -0.38 respectively, $p < 0.05$ for all). E/e'_m correlated with age, systolic and mean BP, AIx, PWV, LVMi (r =0.32, r =0.27, r=0.24, r=0.21, r=0.21, r=0.24, $p < 0.05$ for all). However, in the multiple regression analysis, neither E/A, e'_m or E/e'_m correlated to

stiffness parameters, but were independently associated only to age and mean BP.

Conclusions:
in a sample of hypertensive patients, with no/mild LVD dysfunction, the correlation between LVD parameters and arterial stiffness appears to be dependent on the impact of age and pressure overload on both districts.

Global pulse wave velocity and diastolic dysfunction in postmenopausal women: is there a linkage?

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Background:
Global aortic pulse wave velocity (PWVg) is a non-invasive and accurate method to determine large artery stiffness. Increased arterial stiffness is the major cause of increased systolic pressure and increased pulse pressure in the older patients which has been shown to correlate with myocardial infarction and stroke.

Purpose:
The purpose of our study was to investigate the relationship between PWVg, left ventricular (LV) mass and diastolic function in postmenopausal women.

Methods:
We enrolled 312 consecutive women with echocardiographic assessment to determine PWVg. LV diastolic dysfunction (LVDD) and LV hypertrophy (LVH) were diagnosed according to ASE (American Society Echocardiography) Guidelines.

Results:
The mean age of the 312 women studied was 58.7 years. 22 percent of the women was menstruate, while 78 percent was post-menopausal. Between the post-menopausal women, 168 patients had

LVDD (66.7%), 127 had mild diastolic dysfunction, 40 had moderate diastolic dysfunction and 1 had severe diastolic dysfunction. In the group of post-menopausal patients with diastolic dysfunction, 88.4% had an increased PWVg while 11.6% had a normal PWVg which was highly statistically significant ($p < 0.001$). The patients with a normal PWVg had mild diastolic dysfunction.
Increased left atrial volume indexed for body surface area was present in only 16 women, 12 of whom had increased PWVg, but statistical analysis was not developed because the scarce sample.

Conclusion:
In our population of postmenopausal women, we observed a high relationship between LVDD and PWVg. Our study proves the usefulness of assessment of aortic stiffness on echocardiography examination as a marker of cardiovascular disease and vascular function.

Dromotropic and Chronotropic Incompetence in Heart Failure with Preserved Ejection Fraction (HFpEF)

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Background:
The hallmark of HFpEF is exercise intolerance. One possible contributor is inability to reduce the PR-interval with increasing heart rate (HR) (dromotropy).

Purpose:
To investigate chronotropic and dromotropic incompetence in HFpEF patients.

Methods:
HFpEF patients and controls (healthy (H), hypertensive (HT) and breathless controls (BC) underwent semi-supine bicycle stress tests. Electrocardiograms were examined for PR-interval and HR at: rest; submaximal exercise (HR 100 min^{-1}); peak exercise; and 2 and 5 minutes post-exercise.

Results:
Of 110 subjects enrolled, 24 were excluded (unable to exercise, arrhythmia/conduction disease, pacemaker). Data on 86 patients were analysed (Table).
Resting HR was similar between groups, but maximal HR was lower in patients (BC ($p=0.046$), HT ($p=0.002$) and H ($p=0.013$)), as was ΔHR (overall $p<0.0001$) (Figure). PR interval decreased significantly across all groups between rest and peak (mean -14 ms ± 19, $p=0.025$) with median change with HR of 2.9 ms/-10bpm. Absolute PR and ΔPR changed less in the patient versus the control groups, but were non-significant. ΔPR/ΔHR did not vary by group at any exercise stage. No effect was seen for gender. Beta blockers did not affect PR-interval, but did reduce HR at all stages.

Conclusions:

- HR response to exercise was significantly impaired in patients compared to controls, suggesting that chronotropic incompetence is common in HFpEF.
- A non-significant reduction in dromotropic response was seen in patients versus controls.
- Sample sizes are small and may under-estimate effects. Peak HR decreases with age and may have been affected by older mean patient age. Further data are required to confirm these results.

	Patients	Healthy	Breathless	Hypertensive	All	p-value
N	27	26	18	15	86	
Age (yrs) ± SD	75.1 ± 7.3	66.2 ± 3.5	68.3 ± 4.3	70.3 ± 7.3	70.2 ± 6.7	<0.001
Males (%)	9 (32.1)	12 (46.2)	7 (36.8)	9 (56.3)	37 (43.0)	0.267
Beta blocker (%)	10 (37.0)	0 (0)	5 (27.8)	0 (0)	15 (17.4)	0.002
Resting PR-interval /ms ± SD	183.5 ± 37.5	175.7 ± 26.8	172.2 ± 28.0	170.3 ± 20.3	174.7 ± 25.6	0.716
Submaximal PR /ms ± SD	174.1 ± 36.1	173.0 ± 23.8	167.2 ± 22.8	166.1 ± 18.9	170.0 ± 22.9	0.790
Peak PR /ms ± SD	173.0 ± 36.8	155.2 ± 20.6	156.9 ± 19.5	166.1 ± 28.8	162.1 ± 23.7	0.118
Resting HR /min^{-1} ± SD	66.1 ± 11.6	65.2 ± 6.8	69.7 ± 12.9	65.5 ± 9.1	66.8 ± 10.3	0.727
Submaximal HR /min^{-1} ± SD	96.3 ± 10.3	103.7 ± 3.7	97.3 ± 13.0	103.8 ± 4.3	100.5 ± 8.2	0.005
Peak HR /min^{-1} ± SD	97.5 ± 11.4	129.6 ± 10.3	109.0 ± 22.7	120.9 ± 15.3	114.4 ± 18.7	<0.001

Table: Baseline characteristics and raw data for patient and control groups

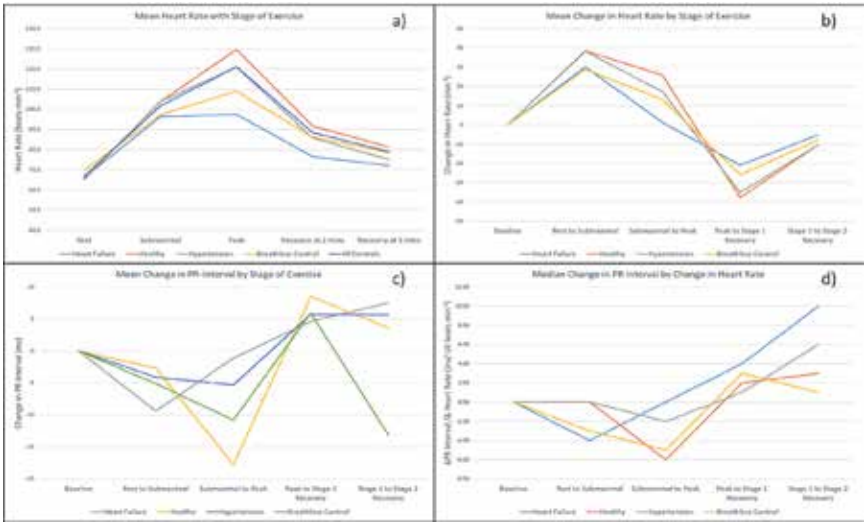

Figure: a) mean heart rate; b) mean change in heart rate; c) mean change in PR-interval; d) median change in PR-interval by change in heart rate by stage of exercise in HFpEF patients and control groups.

Left atrial strain with speckle tracking echocardiography: comparison of two different methods

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Background:
Speckle tracking echocardiography (STE) is a non-Doppler-based method for the angle-indipendent and objective quantification of longitudinal myocardial deformation. It has been recently indicated as a new, effective tool for left atrial (LA) function evaluation. On the basis of ECG reference startpoint, two different methods are currently used for LA function assessment: one with R-wave as reference, obtaining peak atrial longitudinal strain (PALS) for evaluation of conduit and reservoir function, and peak atrial contraction strain (PACS) for evaluation of contractile function; the other with P-wave as reference, obtaining measurement of peak negative epsilon (epsilon neg peak) as index of contractile function, peak positive epsilon (epsilon pos peak), and the sum of those values, i.e. total epsilon (epsilon tot), as indexes of conduit and reservoir function, on the other side. The aim of the study was to evaluate feasibility and reproducibility of the two techniques.

Methods:
We consecutively enrolled 268 patients with good quality 4- and 2-chamber apical views on standard 2-Dimensional (2D) transthoracic echocardiography and no other inclusion/exclusion criteria. STE analysis was performed off-line using a semi-automatic 2D strain software (EchoPAC, GE, USA) by two different independent expert echocardiographers, blind to each other. Each operator calculated LA parameters of longitudinal deformation with both techniques, for each patient. Global PALS was compared to epsilon tot and epsilon pos peak, whereas global PACS was compared to epsilon neg peak. Intra- and inter- operator reproducibility were analyzed with Bland-Altman

analysis in order to assess which of the two STE methods is more reliable and reproducible for evaluation of LA strain.

Results:
Adequate tracking quality was achieved in 96% of segments analyzed. Average post-processing time per patient was 2.1 ± 1.0 min for R-wave method and 6.6 ± 2.6 min for P-wave method. Regarding R-wave method, interobserver variability coefficients of global PALS and PACS were 3.5%, and 4.4%, respectively. For intra-observer variability, the corresponding variability coefficients were 2.7% and 3.6%. Regarding P-wave method, interobserver variability coefficients epsilon neg peak and epsilon pos peak were 9.9%, and 6.4%, respectively. For intra-observer variability, the corresponding variability coefficients were
4.9% and 8.5%.

Conclusion:
In a cohort of patients unselected for cardiovascular conditions, PALS and PACS measurements by R-wave method showed to be more rapid and more reliable and intra- and inter-operator reproducible methods for LA function evaluation according to STE.

Atrial strain correlates with symptoms and quality of life of heart failure patients

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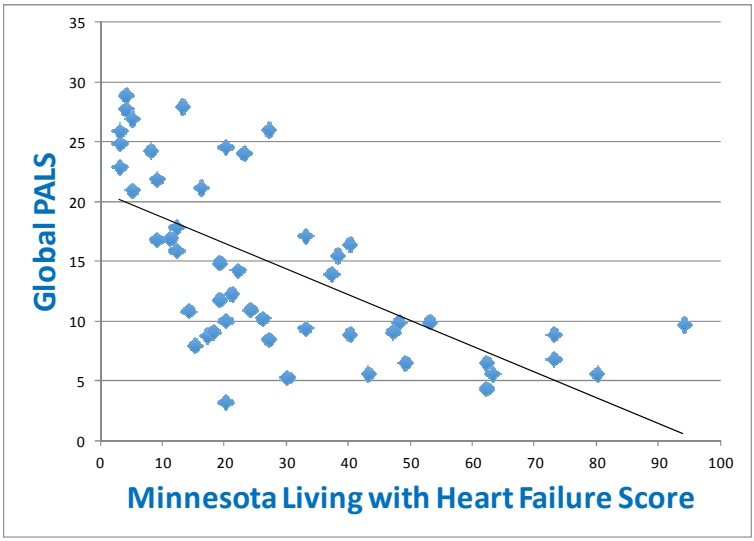
Background:
One of the most important keypoint in the analysis of the patients with heart failure is the relationship between strumental data and quality of life. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is a disease-specific measure of health-related quality of life. The aim of this study was to evaluate the relationship between noninvasive LV and LA analysis and MLHFQ score in patients with HF and reduced ejection fraction.

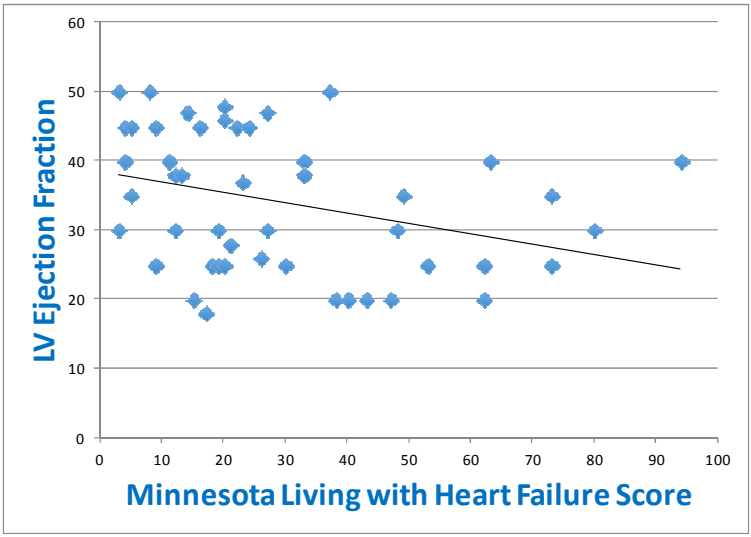
Methods:
115 consecutive ambulatory heart failure patients with reduced LV ejection fraction (<50%) were studied. Patients underwent clinical and echocardiographic examination, both standard transthoracic echocardiography (TTE) and speckle tracking echocardiography (STE) and were asked to perform the MLHFQ.

Results:
Patients were in NYHA Class I (24%), NYHA class II (45%) and NYHA class III (31%). The mean LV ejection fraction was (38.5±9.8%). Strong correlations were obtained between global LA strain and MLHF Score (r=-0.72 p<0.0001) and NYHA Class (r=-0.70 p<0.0001). Poorer correlations were found between MLHF Score and LV ejection fraction (r= -0.32; p=0.05), LV global longitudinal strain (r=-0.28; P=ns). Not significant correlation with MLHF score was found for LA indexed volume (r=0.18; P=ns) and E/E' ratio (r=0.08 P= ns). In multivariate analysis, global LA strain emerged as a determinant of MLHF Score, independent on other confounding factors.

Conclusions:

LA function analysis by STE appears to be a mirror of patients symptoms and quality of life in patients with heart failure and reduced LV ejection fraction.




LV Ejection Fraction
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
Minnesota Living with Heart Failure Score

Tricuspidal pulsed tissue Doppler imaging as a parameter of early diastolic dysfunction

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Background:
Pulsed tissue Doppler imaging (TDI) is currently used to detect both systolic and diastolic left ventricular dysfunction. Recently, right ventricular indices have been shown to be useful in the detection of subclinical and clinical disease such as hypertension, morbid obesity, chronic pulmonary, and systemic disease.

Purpose:
To assess whether in populations of hypertensive, diabetic, dislipidemic or smoker patients without standard echocardiographic signs of cardiopathy, tricuspidal annular TDI diastolic patterns and velocities results abnormal compared to a population without cardiovascular risk factors.

Methods:
We selected from our database 643 age-matched patients with no standard echocardiographic signs of cardiopathy and normal diastolic transmitral pulsed Doppler and mitral lateral TDI pattern. We divided them in 5 groups based on cardiovascular risk factors: hypertension, diabetes mellitus, hypercholesterolemia, cigarettes smoke and no risk factors. Then TDI patterns and velocities on tricuspidal annulus and mitral lateral and septal annulus were analyzed.

Results:
Tricuspidal TDI diastolic impaired relaxation pattern was found in 47,1% of patients with no risk factors, in 51,2% of smokers group, in 68,8% of hypercolesterolemics, in 83,1% and 83,3% of hypertension and diabete groups respectively.

Compared with the group without risk factors, tricuspidal velocities were significantly reduced in hypertension and diabete group (P< 0,05) and mitral septal velocities were reduced in hypertension group (P< 0,05).

Conclusion:

Tricuspidal TDI diastolic pattern and velocities are early impaired in hypertensive and diabetic patients before left ventricular diastolic parameters change.

First evidence of cardiac stem cells from the left ventricular apical tip in patients undergone LVAD implant

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Background:
Recent studies have challenged the dogma that the adult heart is a postmitotic organ and raise the possibility of the existence of resident cardiac stem cells (CSCs). Our study aimed at exploring if the isolation of colonies of CSCs from "ventricular tip" obtained from patients with end-stage heart failure (HF) undergoing left ventricular assist device (LVAD) implantation was possible and how it correlated with LV dysfunctional area extent.

Methods:
Four consecutive patients with ischemic cardiomiophathy and end-stage HF submitted to LVAD implantation were studied. The explanted "ventricular tip" was used as a sample of apical myocardial tissue for the pathological exam. Patients underwent clinical and echocardiographic examination, both standard transthoracic echocardiography (TTE) and speckle tracking echocardiography (STE) before LVAD implantation.

Results:
All patients presented severe apical dysfunction, with apical akinesis/diskinesis and very low levels of apical longitudinal strain (-3.5±2.9%). Despite this, it was demonstrated the presence of CSCs in pathological myocardial samples of "ventricular tip" in all the 4 patients. It was found 6 c-kit cells in 10 fields magnification 40x.

Conclusions:
Multipotent cells can be isolated in the LV apical segment of patients undergone LVAD implantation despite LV apical fibrosis.

Strain Longitudinale
Picco Strain
Picco Strain Sistolico
ANT
SEPT
LAT
INF

Left atrial strain and wedge pressure in patients candidate to heart transplantation

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Background:
Left atrial (LA) deformation analysis by speckle tracking echocardiography (STE) was recently proposed as an alternative approach to estimate LV filling pressures. This study aimed at exploring the correlation of LA longitudinal function by STE and Doppler measurements with direct measurements of LV filling pressures in patients candidate for heart transplantation at baseline and after nitroprusside challenge test.

Methods:
67 hemodynamically stable, end stage heart failure patients who were undergoing right heart catheterization (RHC) were included. Doppler echocardiography and RHC catheterization were simultaneously performed. Echocardiographic measures and STE were obtained as LA peak atrial longitudinal strain (PALS).

Results:
LA PALS was inversely correlated with invasively assessed pulmonary capillary wedge pressure ($r = –0.82$; $P < 0.0001$). LA PALS retained this correlation even after nitroprusside challenge test ($r = -0.88$; $P < 0.0001$), indication patients responder to preload decrease. E/E' showed poor correlation with wedge pressure at baseline and after nitroprusside infusion ($r=0.26$, p=ns; and $r=0.23$, P=ns). Area under the curve optimal cut offs for predicting the wedge pressure > 18 mmHg were for LA PALS 15.0% (AUC:0.91, sensitivity: 97%, specificity: 83%).

Conclusion:
LA strain significantly correlate with pulmonary capillary wedge pressure and its changes after nitroprusside challenge test in patients candidate for heart transplantation. It could be considered a good tool for dynamic estimation of LV filling pressures.

Echocardiographic variations in pulmonary pressure, vascular resistances and biventricular hemodynamics during different phases of Cheyne-Stokes respiration in heart failure patients

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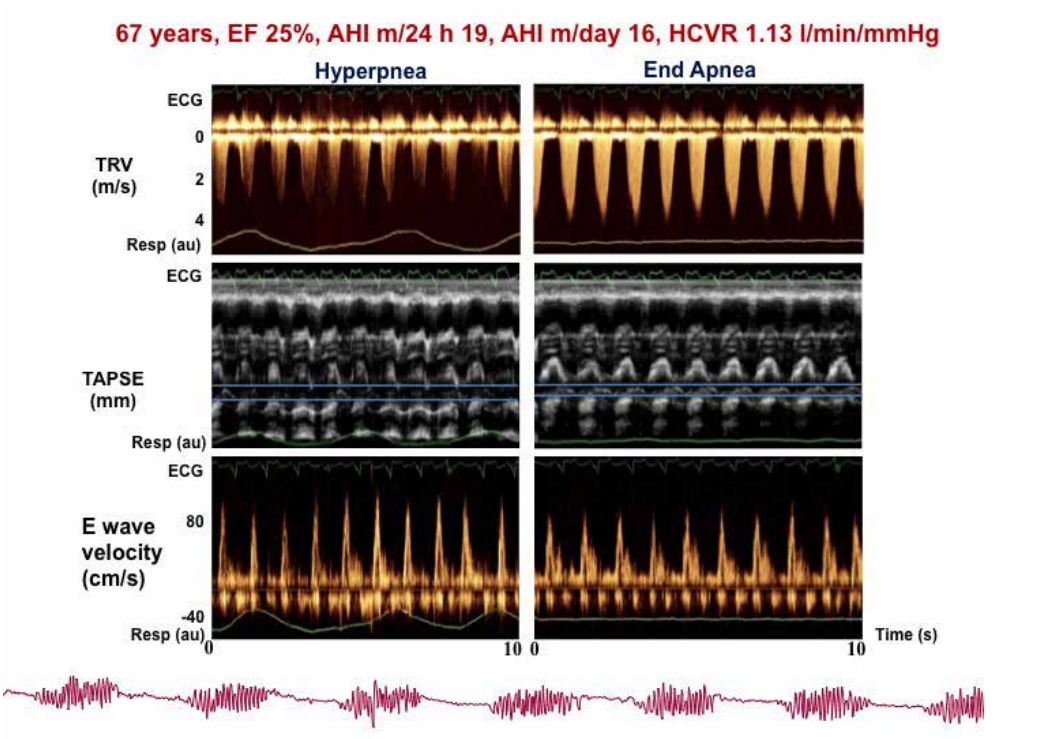
Background and aim:
Cheyne-Stokes respiration (CSR) frequently occurs in patients with heart failure (HF), where not only has it proarrhythmic consequences, but it also fosters negative hemodynamic consequences. We aim to study the echocardiographic changes associated with ventilatory instability in a group of HF patients with 24-hour CSR.

Methods:
7 HF patients (age 69±11 years, LVEF 23.5±6.5%) underwent 24-hour cardiorespiratory screening for CSR and simultaneous echocardiographic and respiratory monitoring, via inductance plethysmography.

Results:
All patients had 24-hour CSR (diurnal apnea-ipopnea index AHI 28±16, nocturnal AHI 33±10 events/hour). During CSR we found an increase in both systolic pulmonary artery pressure (sPAP) from hyperventilation to apnea (H 39.3±11.1 versus A 45.7±14.9 mmHg, p=0.018). The same was found for pulmonary vascular resistances (PVR: H 3.7±1.8 versus A 4.5±2.2 wood units, p=0.046). The increased in sPAP and PVR, was even higher comparing mid-hyperventilation with end-apnea (sPAP 38.7±11.8 versus 47.5±15.3 mmHg, p=0.017; RVP 3.6±1.7 versus 4.7±2.3 wood units, p=0.028), as predictable from O2/CO2 and chemoreflex kinetics. This was paralleled by a slight reduction in tricuspidal annular plane systolic excursion from early-hyperpnea to late-apnea, (14.6±3.4 versus

13.1±2.8 mm, p=0.028), likely due to RV afterload increase, and by E velocity reduction from late-hyperpnea to late-apnea (105.8±27.9 versus 97.6±24.5 cm/s, p=0.046), without significant changes deceleration time or in tissue Doppler indexes, likely due to LV preload decrease.

Conclusions:
In HF patients CSR, likely via recurrent hypoxia and hypercapnia cycles and chemoreflex mediated adrenergic discharge, may cause pulmonary vasoconstriction and an increase in pulmonary arterial pressure, with undesirable consequent changes in right and left ventricular preload-afterload (figure 1).


67 years, EF 25%, AHI m/24 h 19, AHI m/day 16, HCVR 1.13 l/min/mmHg
Hyperpnea
End Apnea
ECG
0
TRV
(m/s)
2
4
Resp (au)
ECG
TAPSE
(mm)
Resp (au)
ECG
E wave
velocity
(cm/s)
80
-40
Resp (au)
0
10
0
10
Time (s)

The Renaissance of Evidence Based Medicine

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Evidence Based Medicine (EBM) is a movement born in Oxford in 1992, first appeared in a paper published in JAMA (Journal of the American Medical Association) in the same year[1].
This approach to teaching clinical medicine centred on good quality evidence produced by randomized clinical trials on the use of drugs, procedures, surgical operations, organizational processes, is mainly based on three elements:

- the analysis of the results of good quality clinical trials;
- the competence ad experience of the clinician;
- patient values

Facing a health problem the clinician on the basis of his/her clinical knowledge and competencies decides the problems to address and the questions to be answered and, according to this process, the evidence produced by good quality clinical trials in the field(s) of interest. The clinician will consider pneumonia when examining a patient with dyspnoea and hyperthermia. In turn, to treat this patient he/she will search for the relevant evidences most suitable for this patient. This process is now easily feasible thanks to Information Communication Technology (ICT) and evidence-based guidelines (the so-called tertiary literature).
Three main possibilities exist:

1. The patient is under 60, in good health
2. The patient is over 80 has one or more clinical problems (diabetes, hypertension, chronic obstructive pulmonary disease, previous myocardial infarction and/or stroke, heart failure
3. The patient is in a condition intermediate between 1 and

Since its beginning EBM almost always relied on evidence obtained in patients under 60, free of comorbidities. In effect, clinical trials designed to assess the effects of treatments carefully avoided "confounding" elements like comorbidities, old age or polypharmacy.

Therefore almost all the evidence available at the beginning of EBM were simple, disease related evidences and allowed do draw definite clinical pathways.
Now, twenty-four years after, patients are older, comorbidities and polymorbidities are almost always present, and no clinical pathways were drawn for these conditions.
In June 2014 the British Medical Journal published a paper[2], by Trisha Greenhalgh and co-workers, entitled "Evidence Based Medicine. A movement in crisis?". Trisha Greenhalgh is a General Practitioner, now Full Professor of General Medicine in Oxford. This paper addressed the above mentioned problems and considered the need for an "EBM Renaissance", aimed to "reset" EBM by some interventions able to enable clinicians to practice "real" EBM by:

- Prioritizing ethical care of patients
- Demanding individualized evidence
- Stressing expert judgement
- Sharing decisions with patients
- Creating a strong patient-clinician relationship

The increased interest in the last years to narrative medicine, which involves careful attention to patient values, to knowledge based medicine, which considers the different evidence not deriving from randomized clinical trial but from pathophysiological and mechanistic studies, and the precision medicine, which is trying to include all the "medomic" measures converging in the individual patients makes very interesting the present approaches to clinical medicine, which could represent somewhat similar to the "Renaissance" in terms of person-centred vision and of multidisciplinary cooperation.

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2) Evidence based medicine: a movement in crisis? Thrish Greenhalgh et al. BMJ 348; g3725, 2014.

Mind amyloidosis!

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Cardiac amyloidosis represents an archetypal form of restrictive heart disease, characterized by profound diastolic dysfunction, associated with a "normal" ejection fraction (EF) that is preserved until the late stage of the disease in the vast majority of patients, independent of the aetiology.[1-3] Therefore cardiac amyloidosis patients typically fulfill the definition of heart failure with preserved ejection fraction (HFpEF).[4]

Obviously, massive cardiac deposition of amyloid fibrils is expected to have a profound impact on diastolic passive properties, due to the massive accumulation in the extracellular space. However, several lines of evidence suggest a clear-cut toxic effect, especially in case of light-chain (AL) amyloidosis. In several experimental models, exposure of the isolated heart,[5] or of cultured cardiomyocytes[6, 7] is associated with rapid and profound diastolic dysfunction. Among many other potential mechanisms, a role of oxidative stress, of lysosomial activity, and of interaction with several key mitochondrial enzymes has been shown.[5-11]

Since diastolic dysfunction has a profound impact on cardiac function and on the clinical presentation of cardiac amyloidosis, the presence of a restrictive pattern of transmitral left ventricular (LV) filling may be viewed as a typical hallmark of the disease, often considered as a “red flag” in diagnosis. However, when we consider a large database of cardiac AL patients, the clinical scenario is somewhat different. In 221 consecutive never-treated subjects, in whom a first diagnosis of cardiac AL amyloidosis was concluded between 2007 and 2010, with EF>50%, and without significant valve disease, previous myocardial infarction, atrial fibrillation, or chronic obstructive lung disease, the extent of diastolic dysfunction was graded according to the ESC guidelines. To this aim, transmitral Doppler early (E) and atrial (A) velocities, E deceleration time, pulmonary venous flow velocity, early diastolic tissue Doppler peak velocity (E’) and E/E’ ratio were recorded at diagnosis. Survival was assessed over a median follow-up of 35.8 months (range, 19-60 months). Quite surprisingly, grade III diastolic dysfunction was only present in 37.1% of the whole cardiac AL population (82/221), grade II and grade I diastolic dysfunction being evident in 84 (38.0%) and 55 (24.9%) patients, respectively. The extent of amyloid deposit, as assessed by interventricular septal thickness, was slightly lower in grade I than in grade III diastolic dysfunction groups (14.2±2.0 vs. 14.7±2.1 mm; $p<0.05$). Both left atrial dimensions and estimated systolic pulmonary pressure progressively increased from grade I to grade III diastolic dysfunction ($p<0.01$ for both). At variance with EF, the grade of diastolic dysfunction was a significant predictor of survival after a 3-year median follow-up ($p<0.001$). Moreover, the extent of diastolic dysfunction is higher in cardiac AL when compared with m-ATTR amyloidosis, as can be derived from a group of 102 patients in a non-endemic area characterized by a large number of different mutations. However, when comparing different transthyretin mutations, many differences are evident. In detail, at variance with Val30Met and Glu89Gln (n=28 and n=20), Ile68Leu and Val122Ile (n=13 and n=6, respectively) mutations are associated with much more severe diastolic dysfunction and NT-proBNP release. The latter mutations present striking structural, functional and prognostic similarities with cardiac AL amyloidosis.

In conclusion, a clear-cut restrictive LV filling is only present in one third of patients with overt cardiac AL amyloidosis, grade I diastolic dysfunction being present in almost one fourth of patients. In cardiac m-ATTR mutations, care should be taken in considering the specific transthyretin mutations and their impact on diastolic dysfunction. In general, despite being an important prognostic factor, the presence of a restrictive pattern of transmitral LV filling cannot be viewed as a "red flag" diagnostic marker in cardiac amyloidosis.

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Left atrium is the glycated hemoglobin of DD

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Heart failure (HF) with preserved left ventricular ejection fraction (HFPEF) is the most prevalent type of HF in the ambulatory setting. Despite its high prevalence, it remains underdiagnosed. In recent years, several mechanisms that could be related to the development of HFPEF have been proposed. Initial studies reported left ventricular (LV) diastolic dysfunction and LV systolic longitudinal dysfunction, as shown by reduced longitudinal myocardial velocities and deformation, suggesting that HFPEF could be an HF stage preceding HFREF. However, the heterogeneity of the patient groups studied (ambulatory, in-hospital, recurrent HF, etc.) has produced somewhat contradictory results. Left atrial (LA) dysfunction has also been associated with the development of HFPEF; initially, LA indexed volume was related to diastolic dysfunction, exercise capacity, and HFPEF syndrome. In HFPEF patients, atrial fibrillation and loss of atrial function have been related to worse clinical outcomes, and atrial strain analysis has been used to study LA function. Two studies have suggested that abnormal LA strain could be related to clinically overt HF and predictive symptoms. In a study of patient groups that did not differ by LA volume, LA strain was significantly decreased in HF patients (HFPEF and particularly HFREF) when compared with patients with diastolic dysfunction but without HF. More recently, impaired LV and LA strain have been described in HFPEF patients, compared with non-HF patients with diastolic dysfunction. In addition, atrial dysfunction as evaluated by LA strain has been related to exercise capacity and cardiovascular outcome. LA volume helps to identify HFPEF with a sensitivity and specificity close to 80%. In HFPEF patients, LA volume and function have been related with exercise capacity. LA function is related to HF diagnosis early after symptoms onset. The association of LA dysfunction or atrial fibrillation with worse clinical outcomes has been reported in previous studies; however, new data also show that these abnormalities are already present in the early stages of the disease.

If LA function could be preserved or even improved, symptoms might improve in patients with HFPEF. More studies are needed to determine whether structural LA changes are reversible, but pharmacological (antiarrhythmic drugs) or non-pharmacological (catheter or surgical ablation) therapies aimed at maintaining sinus rhythm could potentially help to preserve LA function. Subclinical LA dysfunction can currently be identified with non-invasive imaging such as echocardiography; therefore, LA assessment should be mandatory in this type of patients with new-onset HF symptoms.

Given difficulties in the differential diagnosis of HFPEF, the analysis of LA could be useful in daily clinical practice. The presence of an enlarged LA with normal LVEF should make clinicians to consider the possibility of a HFPEF diagnosis. LA indexed volume could be a rapid and simple method to diagnose HF in ambulatory patients with new-onset HF symptoms. Additionally, LA strain analysis could add more evidence of atrial dysfunction and potentially identify those patients at a higher risk of presenting overt HF symptoms.


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