Diastole Diseased
DD - 2016

HIGHLIGHTS

Fondazione
Internazionale
Menarini

Pisa (Italy)
March 03th - 05th, 2016

HIGHLIGHTS

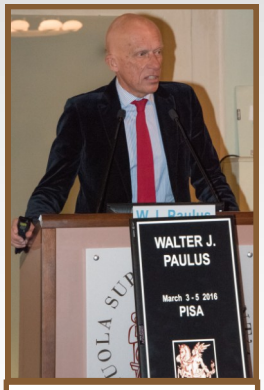
Welcome to Pisa!

Emdin Michele - Taddei Stefano
(Pisa, Italy)

Prof. Emdin and Prof. Taddei, chairmen of the convention, opened the congress works by welcoming all researchers taking part in the event who had come from all over the world and are considered among the leading global experts in this sector. The city of Pisa, despite being small, is nevertheless characterised by an important cultural presence. In fact, it has a concentration of three research and culture centres: the University, founded in 1343, the Scuola Normale di Pisa and the Scuola Superiore S. Anna. Inserted in this context is this conventions that aims to address the main research and clinical aspects of HF and more specifically, diastolic dysfunction, by presenting the highest level currently possible thanks to medical science.

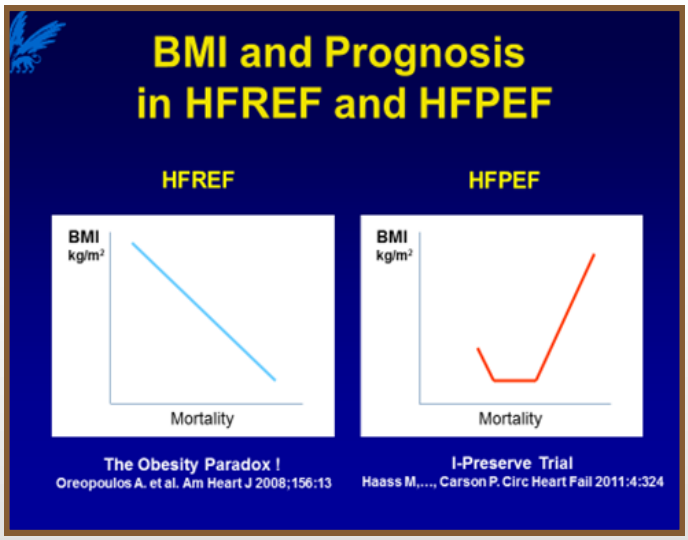
HIGHLIGHTS

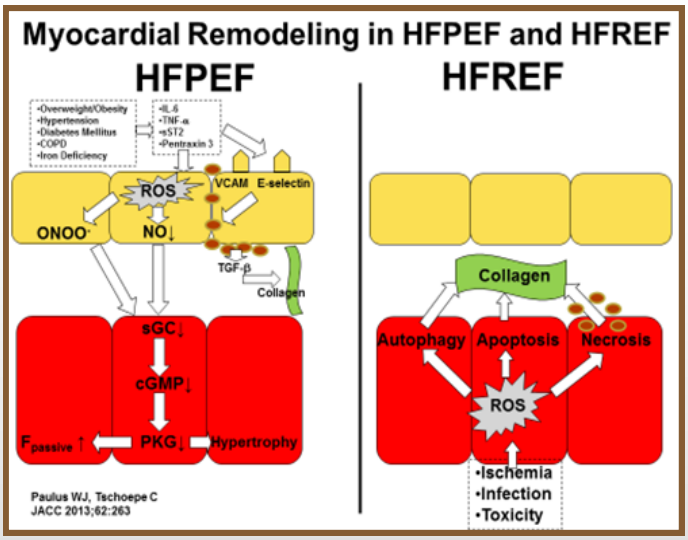
Diastolic disease: the culmination of the different pathological pathways



Walter J. Paulus
(Amsterdam, NL)

In his talk, Prof. Paulus from Amsterdam described the physiopathogenetic aspects of the principal forms of HF (HF): HF with reduced ejection fraction and HF with preserved ejection fraction. In particular he focussed on this second form, describing the physiopathological conditions and the concomitant diseases determining the same. Obesity, type 2 diabetes, and BPCO are the main diseases that give rise to its onset while, among the main triggering causes, the speaker mentioned a sedentary life, cigarette smoking and excessive salt in food. In this way the physiopathology of HF at a cardiomyocyte level occurs in two radically different situations. The remodelling of the myocardium that characterises the physiopathology of HF is triggered in two completely different ways. In patients suffering from HF with reduced ejection fraction the trigger factors that determine the remodelling phenomena are mainly characterised by ischaemia and inflammatory and toxic phenomena which at a myocardial level give rise to autophagia, apoptosis and necrosis. During HF with preserved ejection fraction instead, the trigger factors act at an endothelial level where interleukin 6, TNF – α, sST2 and Pentraxin 3 are the main representatives. This gives rise to endothelial dysfunction which in turn on one hand stimulates the pro-fibrotic phenomena, and on the other, determines at the myocardiocytes' mitochondrial level, significant deficiencies of the metabolic chain of the cyclic GMP with a loss of contractile force and hypertrophy.





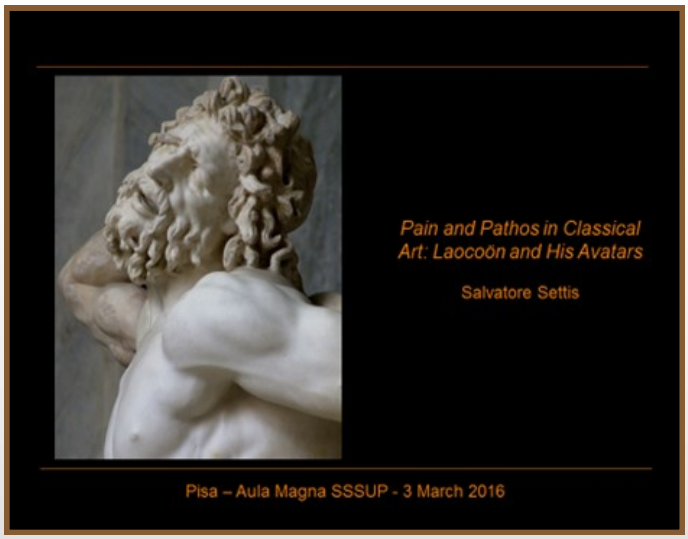
What are the main physiopathological mechanisms that give rise to diastolic dysfunction? What effect does obesity have on the death rate in patients with HF with reduced ejection fraction? What is the effect of cigarette smoking on the cytokines and on endothelial dysfunction?

HIGHLIGHTS

Pain in classical art: the myth of Laocoon

Salvatore Settis
(Pisa, Italy)

Prof. Settis from Pisa, one of the leading experts of classical art in Italy, presented the figure of Laocoon, just like it was found in Rome in 1506, as the symbol of the classical culture still capable of being deeply inserted within the context of the contemporary culture as the universal model of pain and suffering. Laocoon, a character in Greek mythology, was the priest of Troy killed together with his sons by the serpent that came out of the sea, sent by the Athena for having warned his fellow citizens not to accept the wooden horse left by the Greek warriors on the beach in front of the city walls. Laocoon was blamed for having rebelled against the will of the gods and having warned about the danger of that gift in an extreme attempt to save Troy from the total destruction that occurred soon after. Prof. Settis emphasised the relevance of this figure as a symbol of all pain and suffering in our era. Laocoon is a very powerful figure that starts from Titan who transforms man into a monkey, up to current times. For example, the speaker saw Laocoon in a wall painting at Orgosolo, ad where the serpents bear the wording "financial speculation". Here it has been used to represent the pain of the poorer classes. There is no other statue from antiquity as present as this one at the various levels of popular culture.



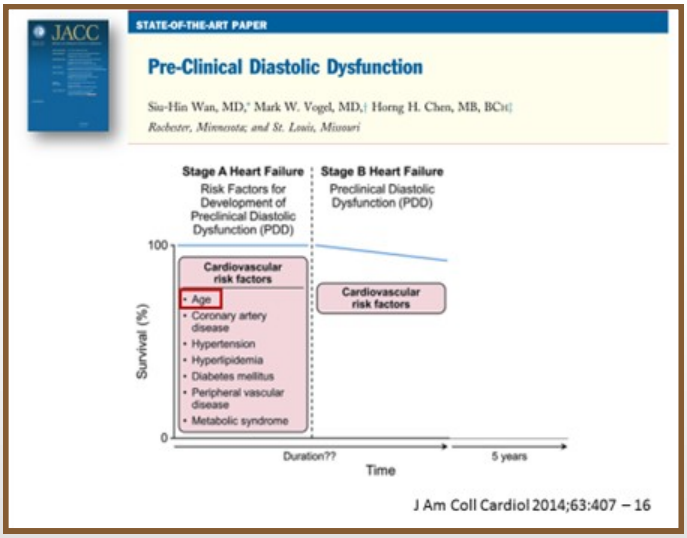
Which have been the main representations of Laocoon produced over the centuries? Which experiments did Dr. Duchenne conduct using the statue of Laocoon as a model? Is there any relationship between Laocoon's expression of pain and the "Scream" by Munch?

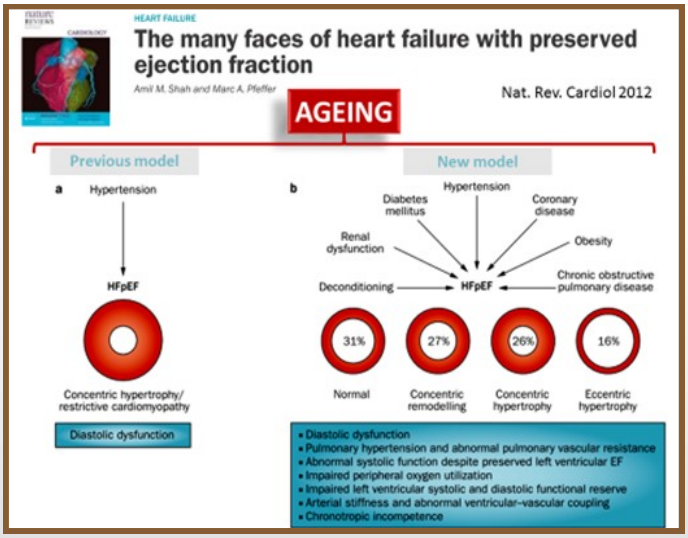
HIGHLIGHTS

Ageing and diastolic dysfunction

Niccolò Marchionni
(Florence, Italy)

Prof. Marchionni from Florence addressed the principal aspects linked to ageing and the diseases related to the same. The ageing phenomena per se, cause permanent inflammatory states that in turn give rise to endothelial dysfunction, the first *movens* that contributes to the determining of the diastolic dysfunction. The speaker than described the relationship between ageing and asymptomatic diastolic dysfunction via the presentation of data collected from 4 population studies. The patients affected by diastolic dysfunction represent a significant percentage of the general population, but only a fraction of these become symptomatic. The switchover from preclinical diastolic dysfunction to the symptomatic form is characterised by a *continuum* of predisposing factors linked specifically to the inflammatory phenomena that involve the endothelium until they give rise to endothelial dysfunction which at the myocardial level, produces a mitochondrial deficiency, an energy deficiency and a contractile deficiency. Among the concomitant diseases that contribute towards generating diastolic dysfunction, the speaker mentioned obesity, type 2 diabetes, high blood pressure, BPCO, and renal failure. These data indicate that the therapeutic approach must also change significantly in these patients. First and foremost, it is necessary to treat the concomitant diseases, secondly, it is essential to identify the physiopathological mechanisms that affect the cardiomyocytes and concentrate specific therapeutic strategies.





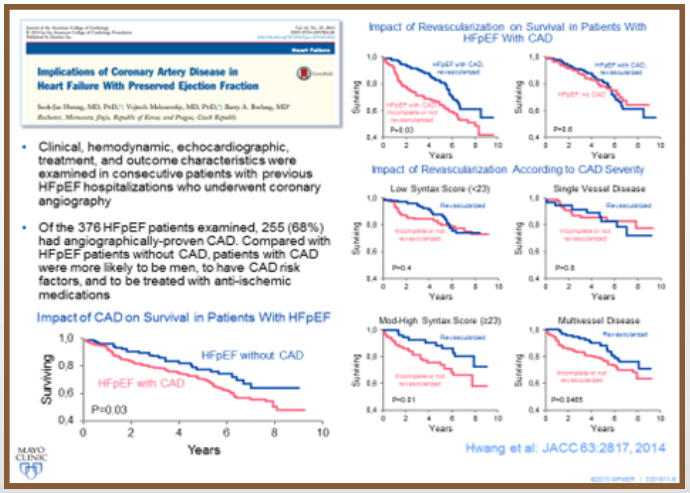
How frequent is asymptomatic diastolic dysfunction? How many patients suffering from diastolic dysfunction become symptomatic? Why does the prevalence of diastolic dysfunction increase with an increase in age of the population? What are the mechanisms that give rise to the switchover from the preclinical to the clinical stage?

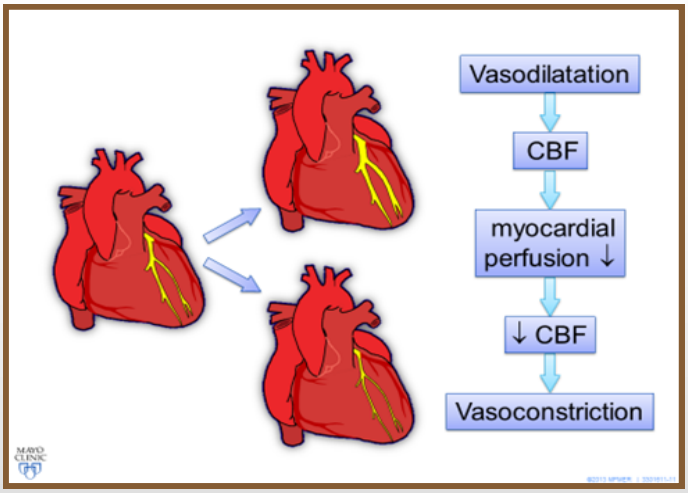
HIGHLIGHTS

Diastole and myocardial ischaemia

Amir Lerman
(Rochester, USA)

Prof. Lerman from Rochester addressed the problem of myocardial ischaemia in the absence of coronary occlusion. Why do patients with an apparently intact coronary tree show ischaemic phenomena at the myocardial level? The speaker presented data collected from case studies of his research group where patients without vascular lesions had a constrictive coronary reaction with the acetylcholine test. At the basis of this phenomenon is a situation of endothelial dysfunction. In normal subjects the coronary response to increased myocardial effort is characterised by vasodilation which in turn gives rise to an increased blood flow. This phenomenon is for the main part endothelial dependent and mediated by the NO. In the presence of endothelial dysfunction and NO synthesis deficiency, the coronary tree responds with vasoconstriction with the increased cardiac effort. This is the mechanism responsible for the onset of ischaemia in these patients. The physiopathological problem is linked to the structural state of the microcirculation, in turn strictly dependent on the endothelial function. In the presence of an altered endothelial function we can therefore talk about dysfunction of the microcirculation. The endothelial dysfunction also manifests at the systemic level, affecting the vascular trees of all the organs. It is the main triggering cause of the physiopathological phenomena responsible for the principal organ deficiencies such as renal failure, stroke and dementia, erectile dysfunction, metabolic syndrome, osteoporosis, and *claudicazio intermittens*, to name just a few of the most important forms. The endothelial dysfunction is also the first *movens* of diastolic dysfunction typical of patients suffering from HF with preserved ejection fraction. Lastly, the speaker presented data on the possible pharmacological treatments.





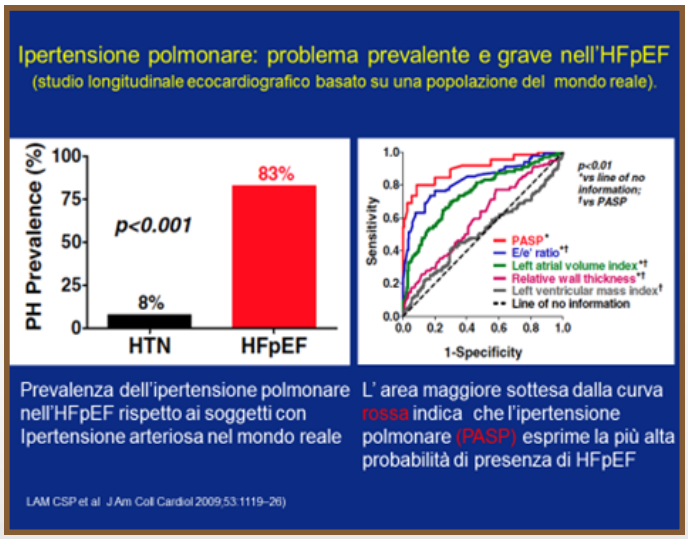
How can we select the prognostic model most suited to patients for correctly evaluating their HF status? What is the prevalence of coronary disease in patients suffering from HF with preserved ejection fraction? Which are the main systemic symptoms of the endothelial dysfunction?

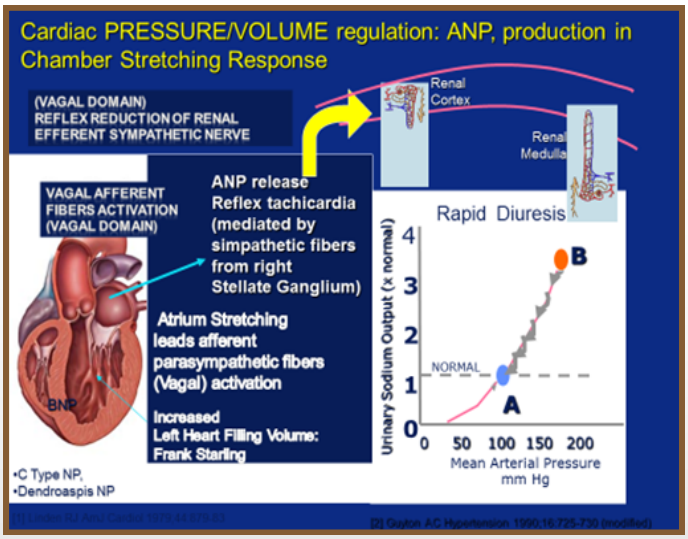
HIGHLIGHTS

Diastole and the kidneys

Prof. Gronda from Milan presented data that link diastolic dysfunction to renal failure. The left ventricular mass and renal functions are closely related, just as the renal function is related to the size of the left atrium, especially in obese patients. What is the significance of these correlations? It is possible to find an underlying common denominator? An initial answer is found in the link between kidney function, age, atrial fibrillation and HF with preserved ejection fraction. Patients suffering from this form of HF also show specific lesions at the level of the kidneys, in particular in the cortical nephrons which are more sensitive to the increase in peripheral vascular resistance. This is the reason why patients with diastolic dysfunction also suffer from renal failure. A datum related to the epidemiology of HF with preserved ejection fraction confirming these correlations is the increased death rate for non-cardiac causes, typical of these patients.

Edoardo Gronda
(Milan, Italy)





What is the prevalence of pulmonary hypertension in patients suffering from HF with preserved ejection fraction?
What are the principal correlations between chronic renal failure and heart disease?
What are the principal causes of death in patients suffering from HF with preserved ejection fraction?

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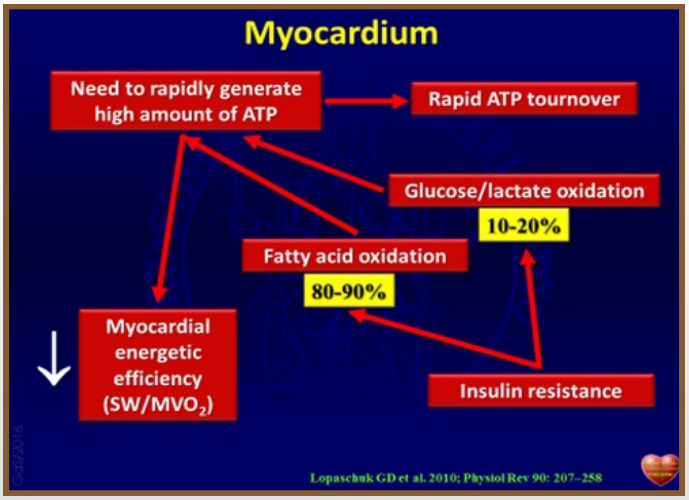
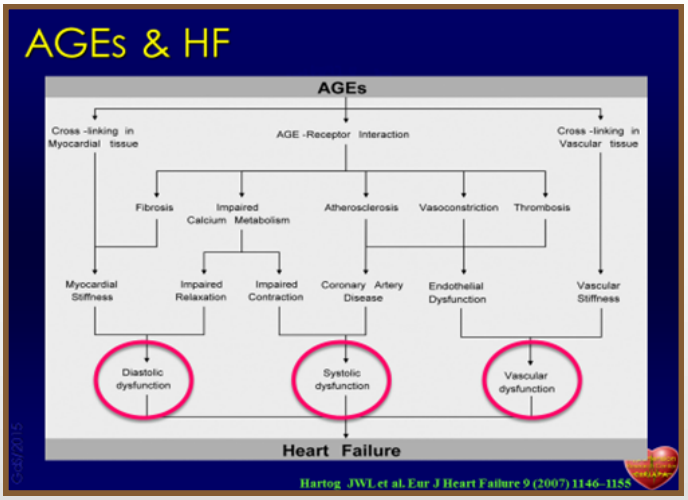
Diabetes mellitus and HF with a preserved ejection fraction

Giovanni De Simone
(Naples, Italy)

Prof. De Simone from Naples presented data on the correlation between diabetes and HF with preserved ejection fraction. At the cardiac level, the majority of the energy is conveyed through the fatty acid pathway and only in a small percentage through the glucose. In the presence of hyperinsulinaemia, this relationship between fatty acids and glucose in the myocardium alters and gives rise to a drop in energy efficiency. In the presence of diabetes mellitus, the energy deficiency caused in the myocardium may lead to diastolic dysfunction. Nevertheless, the speaker stressed how the correlation between HF and diabetes cannot be explained by the presence of diastolic dysfunction alone. There are also other factors, the combined action of which may justify this correlation: the infiltration of fats into the myocardiocytes, the molecular glycation process and malfunctioning of the microcirculation. The infiltration of fats is closely linked to the loss of elasticity by the myocardiocytes. This phenomenon, in turn can be explained by the underlying inflammatory state, responsible for the myocardial remodelling. The glycation processes are supported by the protein turnover, the hyperglycaemia and the presence of oxidative stress. These factors alter the formation of the extracellular matrix and contribute to determining the cardiomyocytary elasticity deficiency. Finally, the deficiencies present at the level of the microcirculation are the result of all these pro-inflammatory phenomena which in first place give rise to endothelial dysfunction and secondly, to microvascular dysfunction. The speaker concluded his talk by highlighting the importance of preventive treatment in diabetic patients also suffering from HF with preserved ejection fraction the cornerstones of which are represented by aggressive treatment of the concomitant diseases as well as the diabetes.

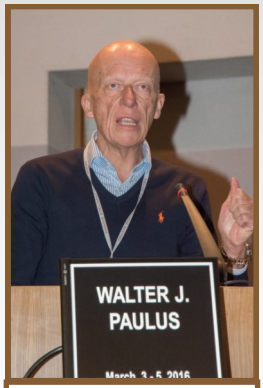




What are the principal energy substrates used by the cardiomyocytes? How do the relationships among the different energy substrates alter in the presence of hyperinsulinaemia? What is the prevalence of diastolic dysfunction in the over 65 year-olds? What is the impact of obesity on the left ventricle?

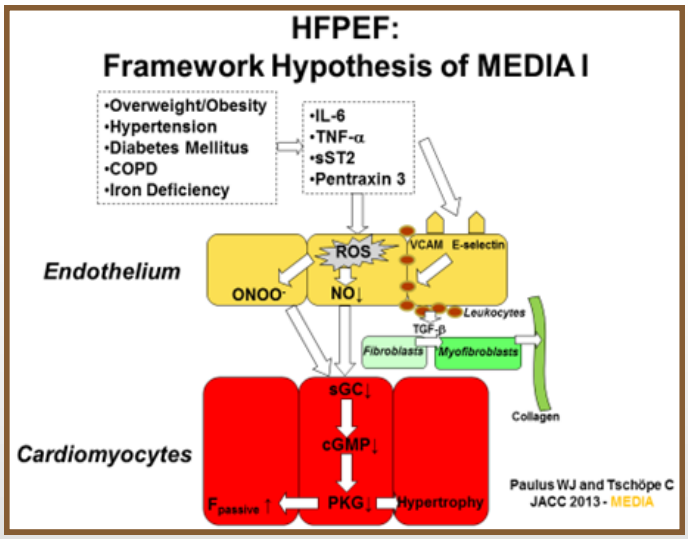
HIGHLIGHTS

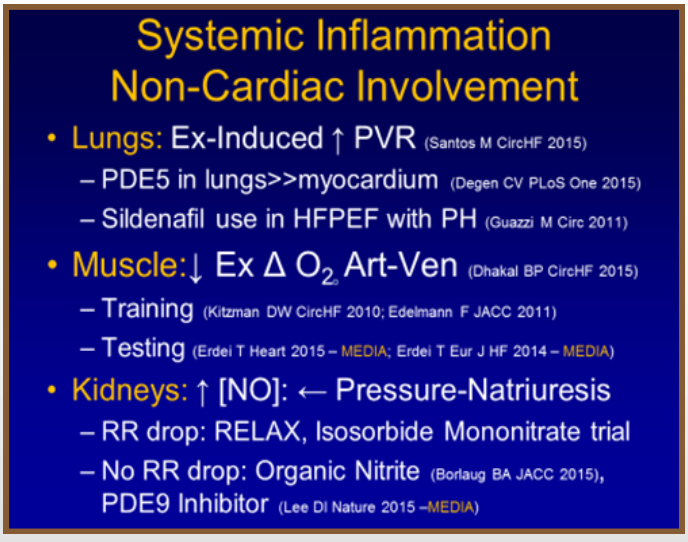
Definition of HF with a preserved ejection fraction



Walter J. Paulus
(Amsterdam, NL)

Prof. Paulus from Amsterdam addressed the physiopathological mechanisms at the basis of this disease. HF with preserved ejection fraction is supported by a deep endothelial dysfunction secondary to systemic inflammation due to oxidative stress which determines the following: at the endothelial level, a deficiency of NO and an increased synthesis of cGMP, a reduction in the myocardial contractility, and cardiac hypertrophy. The systemic inflammation is also responsible for the activation of the vascular adhesion molecules such as VCAM and e-selectin which pass through the endothelium and stimulate the collagen synthesis at the interstitial level. In order to determine these phenomena the presence of concomitant diseases is essential, such as type 2 diabetes, obesity, the metabolic syndrome, arterial hypertension, and renal failure. These are the pathological conditions that contribute to the onset of the chronic inflammatory state that affects the main organs such as lungs, heart, muscles, and kidneys. In other words, HF with preserved ejection fraction is anything but an isolated disease as it fits precisely into a polysyndromic context with an underlying condition of chronic systemic inflammation.





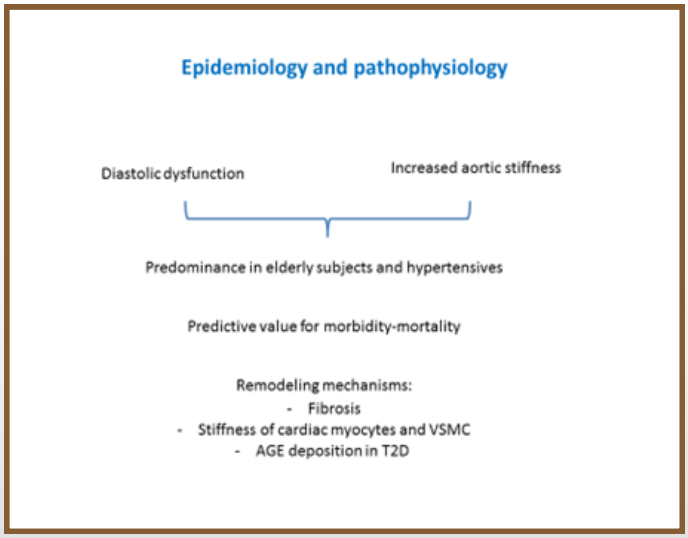
What are the main concomitant diseases of HF with preserved ejection fraction? What are the factors influencing the systemic inflammation condition typical of these patients? What is the role of the vascular adhesion molecules in determining diastolic dysfunction?

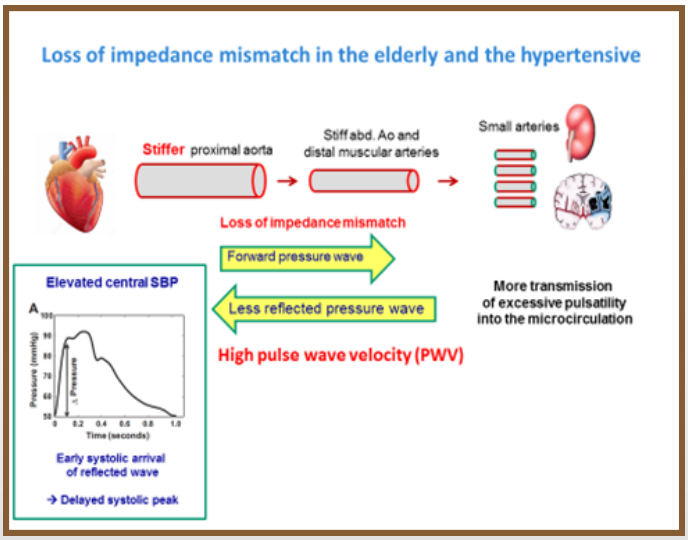
HIGHLIGHTS

Diastolic dysfunction and aortic stiffness

Stephan Laurent
(Paris, France)

Prof. Laurent from Paris addressed the correlation between aortic stiffness and diastolic dysfunction. In patients suffering from HF, vascular stiffness and diastolic dysfunction have various aspects in common. In particular, in the presence of arterial hypertension and an increase in age, the prevalence of diastolic dysfunction and aortic stiffness also increases. Increased vascular stiffness gives rise to a reduction in vascular efficiency and left ventricle function. In particular, the increase in aortic stiffness determines an increase in the post-load and reflected wave which in turn gives rise to an alteration in the diastolic relaxation phase. What do these phenomena mean in clinical terms? In a significant increase in the prevalence of HF and cardiovascular events. Consequently, In the presence of altered diastolic relaxation it is essential to implement therapeutic strategies aimed at reducing the post-load, vascular stiffness and reflected waves. But which therapeutic strategies are the most efficient? Until now the drugs used in treating HF with preserved ejection fraction have not given any reliable results in terms of a reduction in the mortality and morbility rate. The speaker then presented data taken from recent studies conducted with new drugs of recent synthesis.





What are the correlations between aortic stiffness and reflected wave?
How is arterial hypertension correlated to early vascular ageing?
Which consequences give rise to aortic stiffness on the load?

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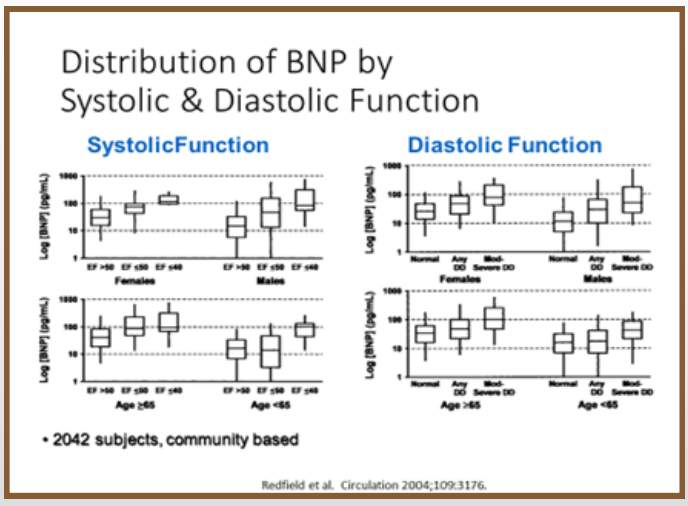
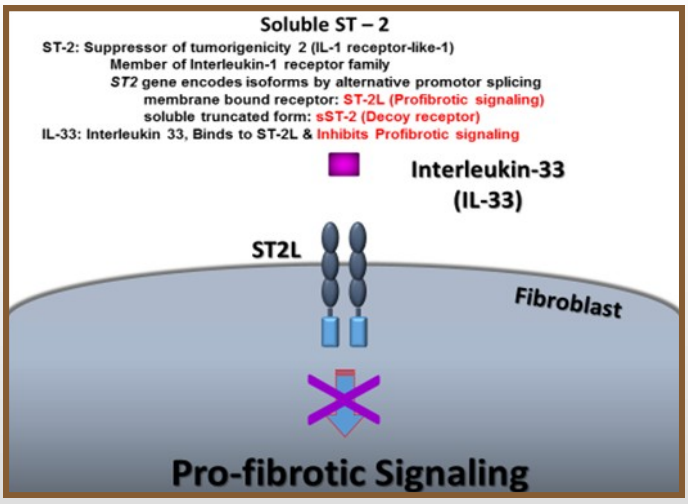
The biomarkers in the diagnosis and prognosis of patients with HF with preserved ejection fraction

Alan Maisel
(San Diego, USA)

Prof. Maisel from San Diego spoke about the biomarkers used in the diagnosis, as well as in the prognostic evaluation of patients suffering from HF. More specifically, he presented data on natriuretic peptides, Troponin, Gal-3 and ST-2. In patients suffering from HF with preserved ejection fraction the BNP has a less strict correlation compared to that observed in patients with reduced ejection fraction. On the other hand, Galectina-3, is particularly sensitive and indicated in patients with preserved ejection fraction. Among these biomarkers, the most innovative is soluble ST-2, well represented in the cardiomyocytes, in which it plays an important role in controlling the hypertrophic phenomena. In addition, this protein has a low degree of variability and is characterised by a more effective predictive capacity during pharmacological treatment. As far as Troponin is concerned, the speaker pointed out how the cardiac subunit cTnT correlates in a significant manner with the presence of left ventricular hypertrophy. Patients with the highest levels of cTnT, irrespective of their age, are the ones with the highest risk of cardiovascular death. Finally, the speaker presented data on the latest molecules identified as the new biomarkers which, when used in multivariate models, identify with a high level of accuracy patients suffering from HF with preserved ejection fraction. The future of the biomarkers is represented by the metabolomes, that is, the specific genetic biomarkers for each individual patient. This opens up the pathway to personalised medicine. Despite these extremely interesting results, the biomarkers can in no way whatsoever replace the physician's opinion based on a clinical assessment. The predictive power of these molecules acquires prognostic value especially when they are used as a diagnostic/prognostic support of the clinical evaluation.





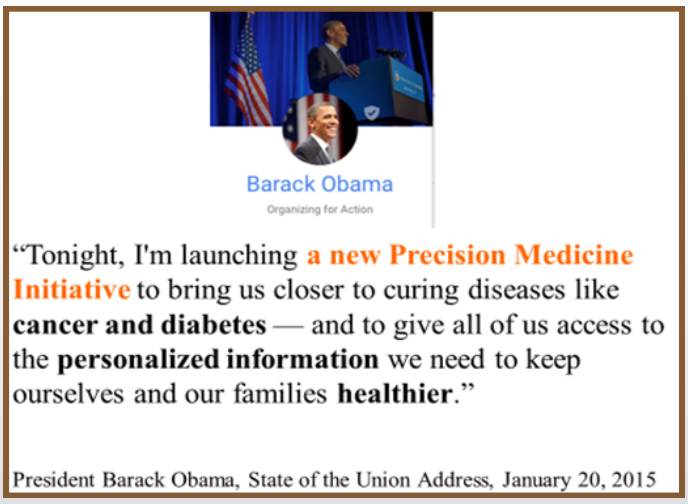
What are the characteristics of the ideal biomarkers? What effect does the administration of Galectina-3 have? Which is the phenotype entailing the highest risk of sudden death? Which are the latest biomarkers identified?

HIGHLIGHTS

The "renaissance" of evidence-based medicine

Gianfranco Gensini
(Florence, Italy)

Prof. Gensini from Florence spoke about *Evidence Based Medicine*, the constitutive characteristics of which include the evidence of the best research linked to clinical practice and the patients' values. The application of EBM in conducting clinical trials has given rise to the production of data strictly linked to the evidence of the disease. In this way it has been possible to draw up the main guidelines in the different fields of medicine with significant benefits in terms of public health. Medicine in the 21st century however contemplates increasingly more complex patients who are elderly and often suffering from multiple diseases. How can we apply a model designed to simplify medicine in complex patients? Do we find ourselves faced by the crisis of this model? Clinical research nowadays used a methodological approach that starts from a search for the interactions among the various emerging biological phenomena. This approach differs greatly from that used last century where, instead of the interaction among the different phenomena, each single phenomenon was considered as an end in itself. Medicine based on evidence therefore needs to modify its own parameters, transforming them into medicine based knowledge, that is, into personalised medicine. Another aspect of this new paradigm is characterised by precision medicine that allows for analysing an impressive series of data in reduced times thanks to new instruments made available by technology. The time seems to have arrived for EBM 2.0 in which the methodological rigour typical of the traditional EBM is applied to the new model of medicine with the dual purpose of analysing medical knowledge in depth while at the same time making it increasingly more tailor-made every individual patient.



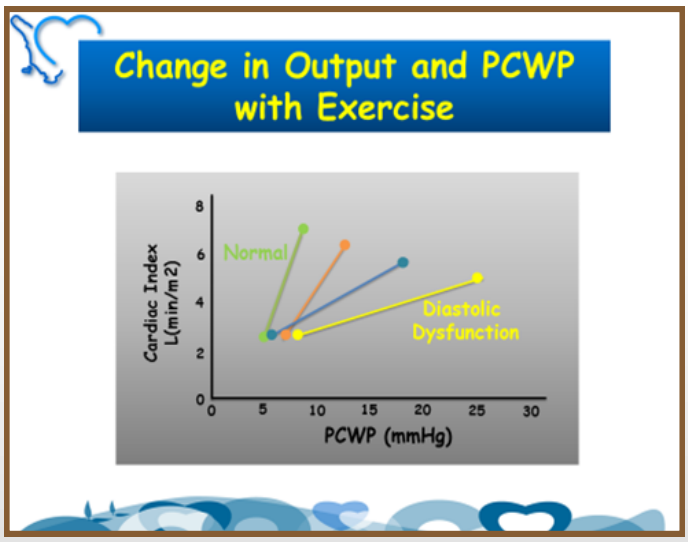
What the principles underlying EBM? Why does EBM now seem to be obsolete? What are the principal aspects of precision medicine? How can we integrate two different models of medicine: evidence based medicine and precision medicine?

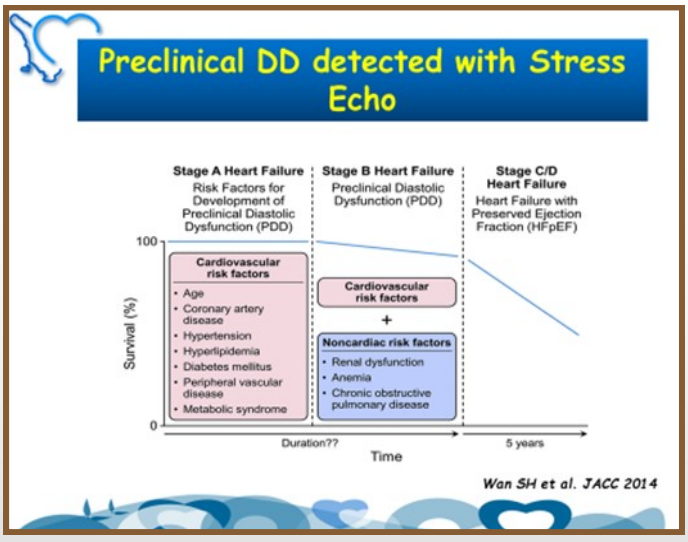
HIGHLIGHTS

Eco stress test and diastole

Christina Petersen
(Pisa, Italy)

Prof. Petersen from Pisa presented interesting data on the application of the echo stress test in patients with diastolic dysfunction starting from the consideration that the E/e' ratio does not reflect the haemodynamic variations during exercise that are present in patients suffering from HF with preserved ejection fraction. The evaluation of the diastolic function includes the measuring of multiple parameters. Among these, the most emblematic are the propagation speed of the flow and the "e' during exercise/e' at rest" ratio. In order to determine the diastolic function, the most indicative test is represented by the echo stress test conducted in a semi-supine position. Thanks to this method it is possible to identify patients suffering from diastolic dysfunction in the early stages when this is not yet symptomatic. Also with this method it is possible to implement a prognostic stratification of these patients. The assessment of the diastolic function should be conducted together with the assessment of the systolic function. The real limit of this method is represented by the lack of a shared standard protocol and the need to define the parameters to be assessed with their relative cut-off values.





What are the clinical indications of the echo stress test? How do the cardiac index and the pulmonary capillary pressure alter in patients suffering from HF with preserved ejection fraction during exercise? What is the prognostic impact of an altered E/e' ratio during exercise?

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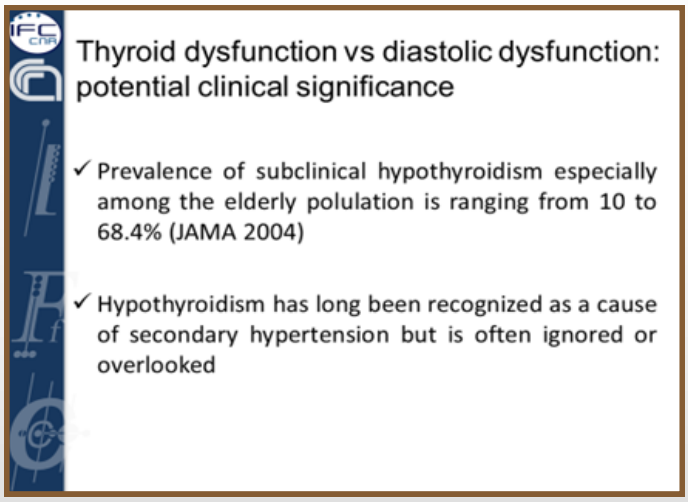
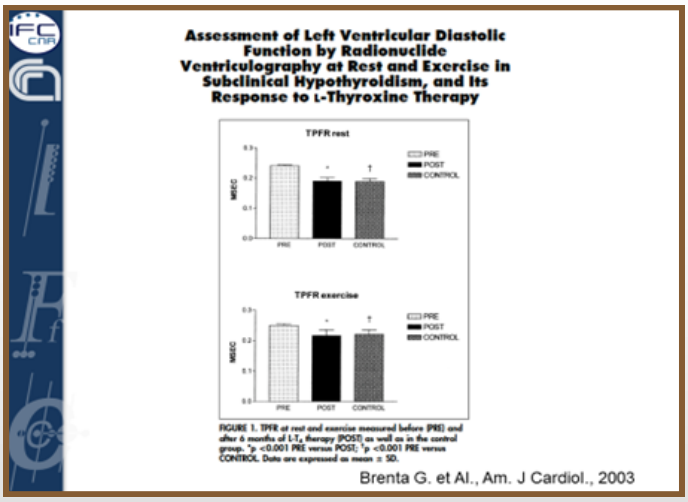
Thyroid hormones and diastole

Giorgio Iervasi
(Pisa, Italy)

Prof. Iervasi from Pisa addressed this topic starting from two considerations: hypothyroidism is found in a subclinical form in the elderly population with a variable prevalence that also reaches 68% of cases. Even though hypothyroidism is a well-known cause of secondary hypertension, it is not always taking into consideration and at times even ignored. As regards the action of the thyroid hormones on the cardiovascular system the mechanisms defined as genomic are well known, meaning those that act at a nuclear level. Conversely, the non-genomic mechanisms, namely, the so-called extranuclear mechanisms have not yet been sufficiently studied. At a cardiac level, the condition of hypothyroidism is able to alter the contractility, reduce the output, lower the frequency, favour the prolonging of the action potential, and giving rise to an increase in the peripheral resistance, in other words, creating the predisposing conditions for developing the diastolic dysfunction. In clinical practice, the diastolic dysfunction is defined on the basis of a whole series of surrogated measurements, mainly of the echocardiographic type. From the studies conducted on patients suffering from hypothyroidism and diastolic dysfunction, thyroid-hormone based treatment not only improves the hypothyroid condition, but also the surrogated parameters of the diastolic dysfunction. Preliminary data suggest that replacement therapy based on the T3 hormone improves the diastolic function in patients suffering from HF and from the syndrome with low levels of T3. Despite these indications, the speaker concluded his talk by stressing the need to implement further studies in order to analyse the relationship as well as the effects of hormone replacement therapy based on thyroid hormones on the physiopathology and on the treatment of the diastolic dysfunction and the progression of HF with preserved ejection fraction.





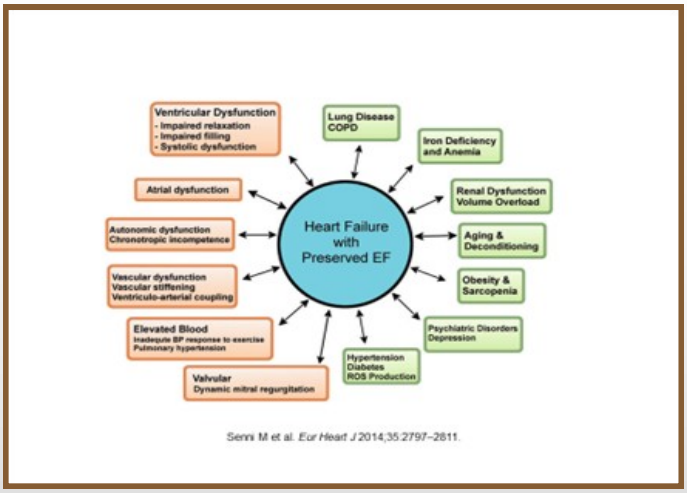
What are the principal actions of the thyroid hormones on the cardiovascular system? What is the action of the thyroid hormones on the calcium uptake? What is the impact of thyroid hormone replacement therapy on the diastolic function of the left ventricle?

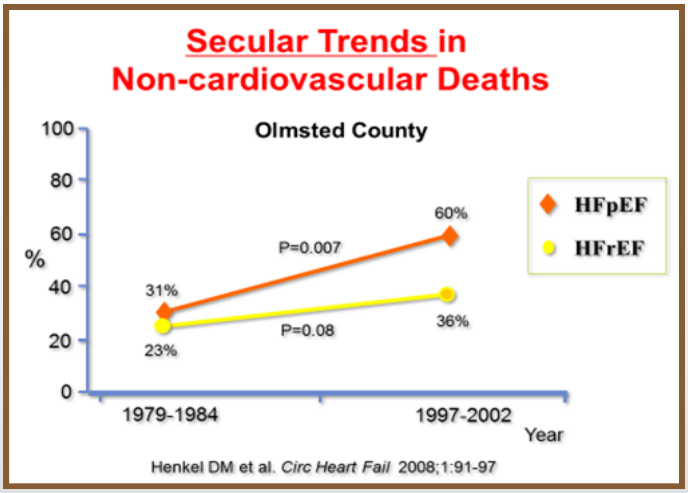
HIGHLIGHTS

Diastolic dysfunction and prognosis: main aspects

Antonello Gavazzi
(Bergamo, Italy)

Prof. Gavazzi from Bergamo addressed this issue starting from the consideration that HF with preserved ejection fraction is a multi-syndrome disease at the basis of which there are concomitant diseases, such as arterial hypertension, diabetes, metabolic syndrome, and renal failure. From the clinical studies conducted on patients suffering from HF it is evident that the death rate per annum is similar in both populations, namely, that with reduced ejection fraction and that with preserved ejection fraction. From the meta-analyses conducted on more than 300,000 patients, survival increases in patients with preserved ejection fraction. In these patients concomitant diseases are present in a decidedly higher percentage than those observed in patients with reduced ejection fraction. The prognosis of these due populations of patients differs essentially not so much with regard to the death rate but instead to the death rate per single cause. Patients with preserved ejection fraction have a higher prevalence of death from non-cardiac causes than patients with reduced ejection fraction. In patients with preserved ejection fraction the prevalence of sudden death is decidedly higher compared to patients with reduced ejection fraction. Another difference observed in these two populations is the secular trends in non-cardiovascular deaths which is significantly higher in patients with preserved ejection fraction compared to patients with reduced ejection fraction. These differences are also due to the various risk factors to which these two populations are exposed. Patients with preserved ejection fraction are more elderly, prevalently females, suffering from a higher number of concomitant diseases, from myocardial fibrosis and with higher levels of Galectin-3. The speaker finished by presenting a predictive model defined as the 3C Score, the main factors of which that are taken into consideration are the age of the patients, the cardiac variables and the concomitant diseases. This model has been implemented for the purpose of giving grater predictive power to the risk factors.

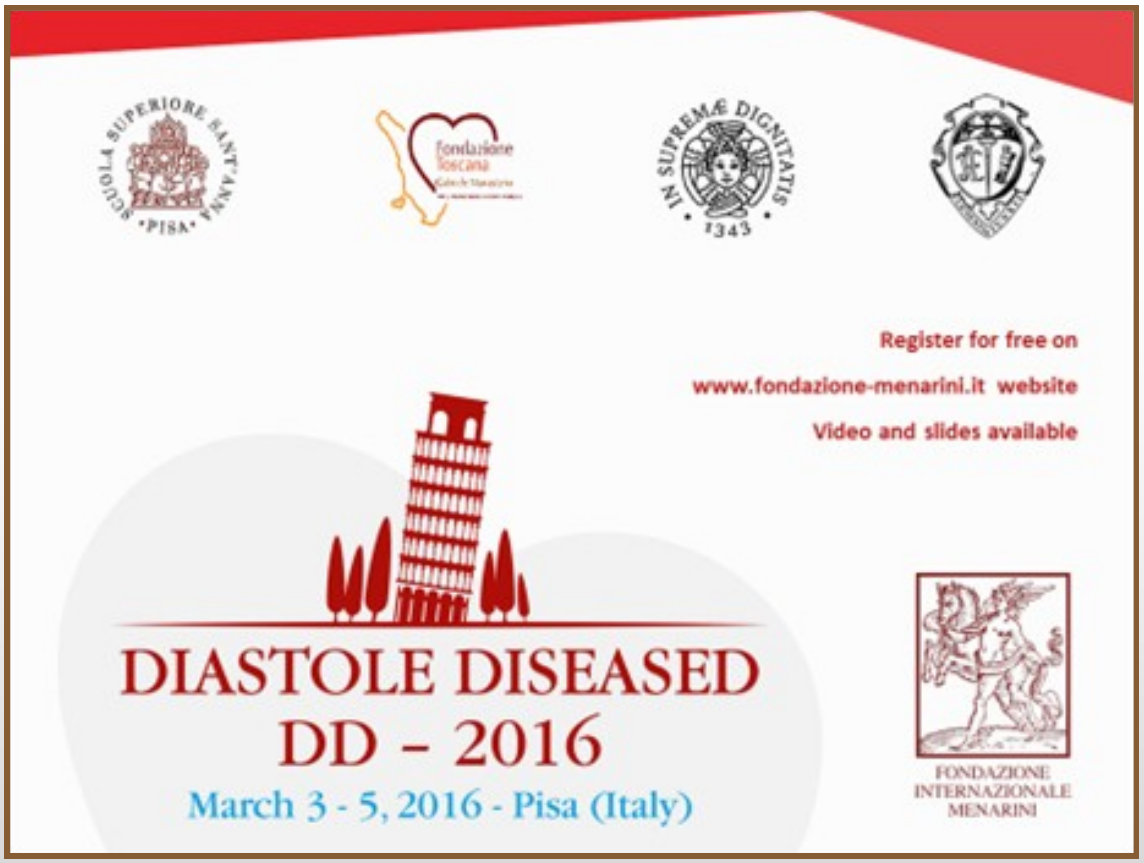




What are the principle characteristics of HF with preserved ejection fraction that make this disease multi-syndromic? What are the outcomes of diseases at one year in patients with preserved ejection fraction? What is the prevalence of sudden death in patients with preserved ejection fraction?

HIGHLIGHTS

These are some of the topics addressed during the congress works.
For a more in-depth analysis please visit the website of the Fondazione **Internazionale Menarini** which also contains the full version of the congress talks.
To follow the presentations in this convention just click on this link: www.fondazione-menarini.it/... and after logging in, access the Multimedia Contents.



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