



Chronic Heart Failure in 2016

HIGHLIGHTS



Fondazione
Internazionale
Menarini



*Milan (Italy),
February 25th - 27th, 2016*

HIGHLIGHTS

Welcome to Milan!

Prof. Agostoni, chairman of the convention, opened the congress works by welcoming researchers from all over the world, some of whom are considered the leading global experts in heart failure. The high scientific level of the Convention was a perfect match for the high cultural, artistic and historical level of the city of Milan and Palazzo Clerici which hosted the congress works and which houses the gallery frescoed by Tiepolo. Prof. Agostoni then gave a brief explanation of the main monuments and works in the city of Milan as a sign of welcome and good wishes for the success of the congress works.



Piergiuseppe Agostoni
(Milan, Italy)

A promotional poster for the "International Symposium on: CHRONIC HEART FAILURE IN 2016: PROGNOSIS". The poster features logos for "Centro Cardiologico Monzino" (a red heart with dots), "UNIVERSITÀ DEGLI STUDI DI MILANO" (the university's seal), and "FONDAZIONE INTERNAZIONALE MENARINI" (a winged figure with a horse). The text on the poster includes the event title, dates "Milan (Italy), February 25 - 27, 2016", and registration information: "Register for free on www.fondazione-menarini.it website" and "Video and slides available".



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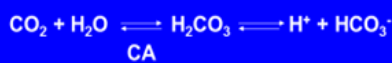
Carbonic anhydrase and the heart: functions and physiopathology

Prof. Swenson from Seattle presented extremely interesting data in his talk about the functions of carbonic anhydrase which is present in 15 isoforms, of which 7 are active at an intracellular level, 2 at a mitochondrial level, 3 linked to the cell membranes and directed towards the external environment and, finally, 1 is secreted in the saliva and the intestinal tract. Carbonic anhydrase is found in various organs such as the liver, stomach, pancreas, central and peripheral nervous tissue and eyes. Although only present in minimum amounts in the heart, it is extremely important in functional terms as it intervenes in regulating the acid base system, stimulating the cardiomyocytic contractility and relaxation, facilitating the lactate uptake and the secretion of H⁺ from the cardiac valve cells which in turn gives rise to the dissolving of Ca⁺⁺, and facilitating the clearance and excretion of CO². In pharmacological terms, the initial inhibitors of carbonic anhydrase synthesised between the 1930s and 50s were sulphanilamide and acetazolamide. In the 1960s, other carbonic anhydrase inhibitors were synthesised, amongst which the most powerful is undoubtedly furosemide. Carbonic anhydrase inhibition in patients suffering from cardiovascular disease has a positive effect on the correction of metabolic alkalosis and hyponatremia. It reduces central sleep apnoea, it has a protective action against contrast-induced nephropathy, it produces systemic vasodilatation, inhibits pulmonary vasoconstriction from hypoxia and finally, it offers beneficial effects on post-infarction remodelling as well as during the acute phase of myocardial infarction, sleep apnoea and other forms. When administered at doses of 250-500 mg/kg, acetazolamide is effective in protecting the myocardium in the post-ischemic phase from the so-called paradox effect that often follows the re-perfusion stage. This action is mediated by the reduction of the cell pH, contrasting the onset of infarction in the tissue after re-perfusion. Acetazolamide also has a protective action on the remodelling phenomena, inhibiting the intracellular alkalinisation via adrenergic stimulation. In this way it limits the onset of hypertrophic phenomena which in turn can give rise to heart failure.



Swenson Erik
(Seattle, USA)

Carbonic Anhydrase: Chemistry and Kinetics



turnover of fast CA isozymes
= 10⁶ sec⁻¹ t_{1/2} = 0.5 msec
uncatalyzed rate t_{1/2} = 30 sec

useful in many functions

- requiring rapid equilibration of H⁺, HCO₃⁻ and CO₂
- can run on the uncatalyzed reaction and residual enzyme activity



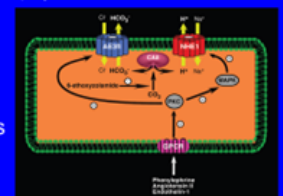
CA Inhibitors in Hypertrophic Remodeling

Remodeling may contribute to heart failure

- via neurohumoral activation by catechols, angiotensin, ET of membrane ion exchangers leading to higher pH
- intracellular alkalinization increases Na⁺ → Ca⁺⁺
- increased Ca⁺⁺ leads to hypertrophy and fibrosis

Membrane and cytosolic CAs rapidly supply H⁺ and HCO₃⁻ for

- Na⁺/H⁺ and Cl⁻/HCO₃⁻ exchangers
- Na-HCO₃ cotransport



What impact does treatment with acetazolamide have on patients suffering from heart failure? What is the effect of acetazolamide on the cell pH?
How does acetazolamide manage to contrast the phenomenon of post-revascularisation cell necrosis?



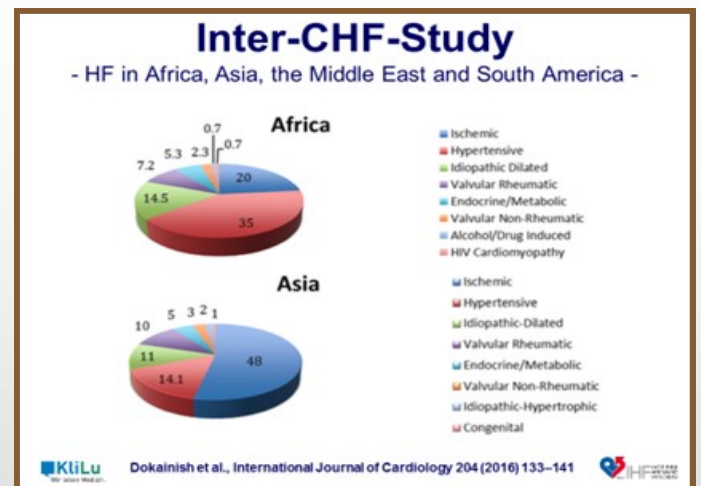
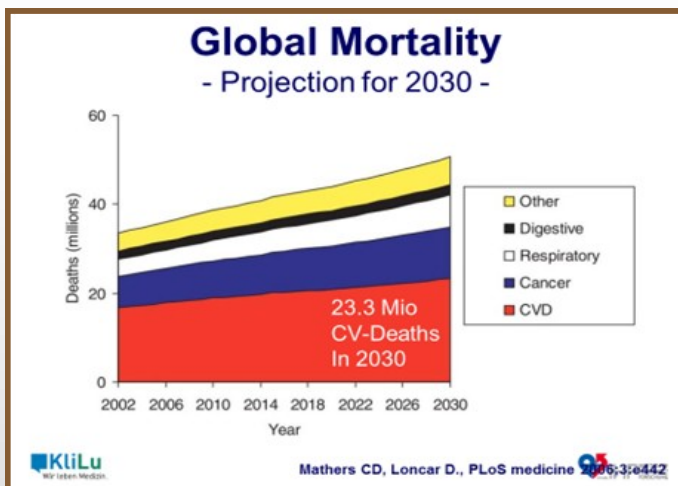
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Prognosis and epidemiology of heart failure

Prof. Gitt from Ludwigshafen analysed the main aspects of the epidemiology of heart failure and its related diseases. In the world today, the prevalence of cardiovascular mortality is rapidly rising, especially in the eastern countries and Africa, in both men and women. The statistics envisage more than 23 million cardiovascular deaths worldwide in 2030, approximately 5 million more than the early years of this century. The majority of these events can be blamed on heart failure as the result of a whole series of underlying diseases such as hypertension, diabetes, idiopathic cardiomyopathy and ischaemic heart disease. More specifically, the prevalence of diabetes seems destined to register a 55% increase by 2035. The prevalence of cardiovascular mortality in the United States has dropped since the beginning of this century, in particular with regard to the acute forms such as myocardial infarction, but not with regard to the chronic forms such as heart failure. In other words, patients saved from acute events finish up by developing chronic heart failure. The costs of heart failure are astronomical, in both economic and welfare terms. The speaker presented data from the United States where the prevalence of heart failure increases drastically with age, in both men and women, and this gives rise to a significant increase in hospitalisation. An additional contribution to the costs derives from the therapeutic protocols that must be applied for a long period since heart failure is a chronic disease that develops over the years. By examining the prevalence of new events in the United States in patients suffering from cardiovascular disease under excellent pharmacological therapy, this disease is registered at around 18% during the first year after the first acute event, and just on 6% for every subsequent year. All these events give rise to an additional reduction in the myocardial function, in the end leading to heart failure. The increased life expectancy, together with improvements in the therapeutic protocols, will produce a significant increase in the prevalence of heart failure at a global level in the future.



Anselm Gitt
(Ludwigshafen, DE)



What is the prevalence of cardiovascular death in men and women on a global level? What is the prevalence of heart failure in the United States? Why are the costs of heart failure increasing? What are the differences in terms of prevalence of heart failure between the United States and Europe?



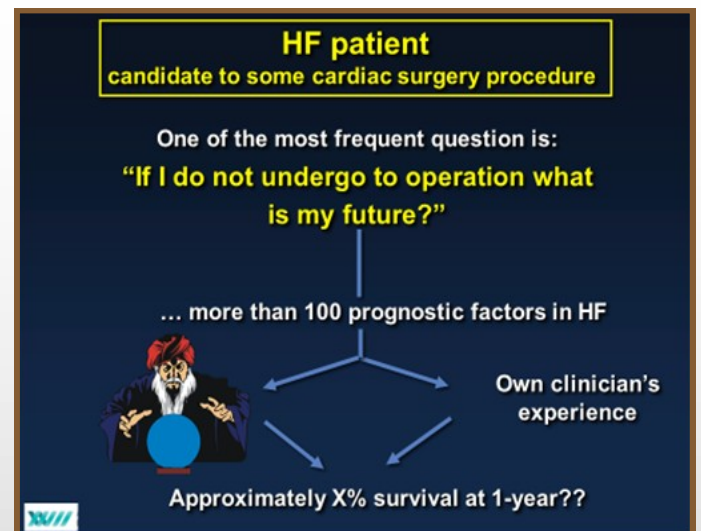
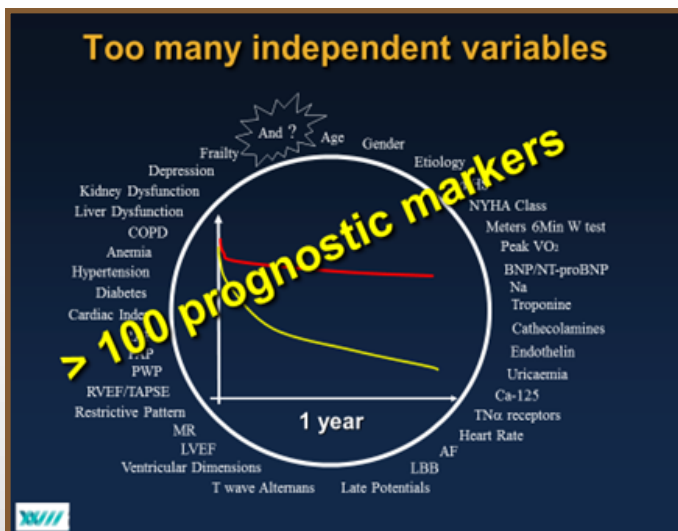
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Prognosis of heart failure in clinical terms

Prof. Senni from Bergamo addressed the problem of the prognosis in patients suffering from heart failure in terms of their clinical management. A crucial aspect of extreme importance is the stratification of their risk since it calls for the choice of well-defined clinical protocols and specific therapeutic selections in personalising the counselling activities with patients and the family nucleus. The process that leads to a correct prognostic assessment of patients suffering from heart failure is very complex. The parameters to be evaluated are innumerable and the outcomes are also extremely variable. This all gives rise to the presence of different prognostic models. The prognostic scores must include several essential characteristics and namely, they must be based on a sufficiently large number of patients, be applicable to the real population, be feasible from a clinical point of view, include the entire spectrum of cardiovascular diseases as well as the concomitant diseases, include the main therapeutic protocols, be based on a robust statistical approach, and ensure excellent performance in terms of AUC, understood as the proportion of correctly classified patients. At this point, the speaker presented the main models available.



Michele Senni
(Bergamo, Italy)



How can we choose the most suitable prognostic model for the patients to ensure a correct evaluation of their heart failure condition? What is the desired level of AUC for a reliable prognostic model? What prognostic model did the speaker indicate as the most "feasible" in clinical terms?



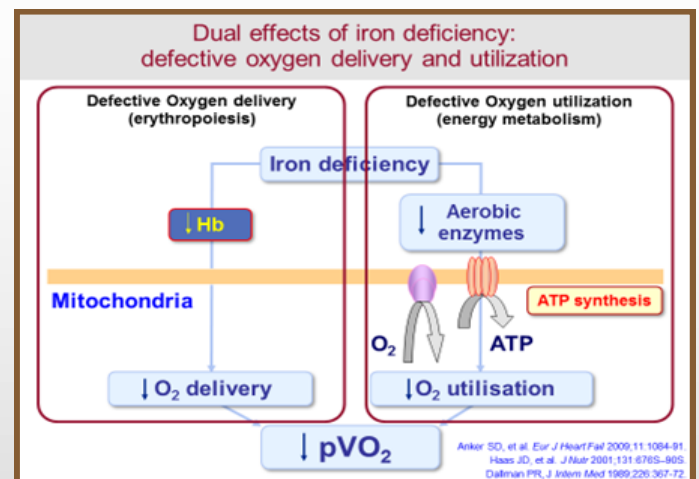
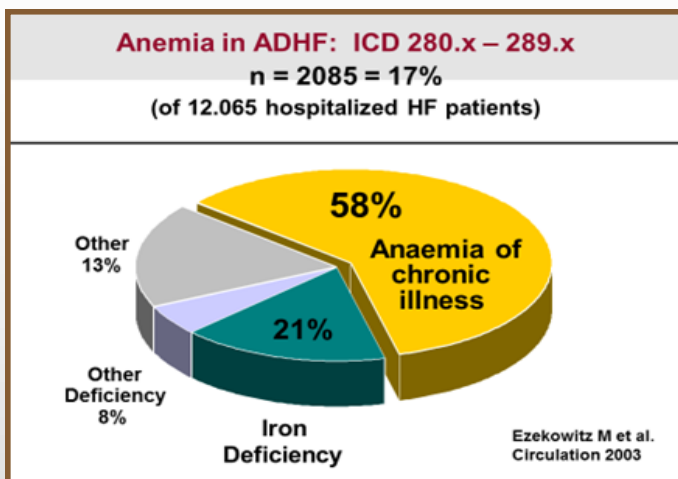
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The role of anaemia and sideropenia in the prognosis of heart failure

Prof. Cohen-Solal from Paris presented data collected from the main clinical trials on the correlation between anaemia and heart failure on one hand, and sideropenia and heart failure on the other. As far as the prevalence of anaemia in patients suffering from heart failure is concerned, this varies between 10% and 69.7% depending on the trials analysed. There is a decidedly frequent correlation supported by numerous causes such as malnutrition, chronic bleeding from the administration of anticoagulants, haemodilution conditions, renal failure and erythropoiesis deficiency. The majority of these patients suffer from anaemia due to chronic diseases such as cachexia and renal failure. While it is true that the presence of anaemia is in a small way correlated to the main principles of gravity of heart failure such as global mortality, cardiovascular death and hospitalisation, it is also true that its correction is not correlated to significant improvements in the outcome of the disease, to the point that in patients suffering from heart failure the administration of EPO is not recommended, also due to the risk of serious adverse events such as thromboembolias and cerebrovascular ischaemias. Iron deficiency in association with heart failure is another story: first and foremost, its prevalence varies from 40% to 70% depending on the presence of acute or chronic heart failure. Its presence gives rise to an oxygen delivery deficiency at a mitochondrial level which in turn leads to defective utilisation at a metabolic level. It is the iron deficiency, not the anaemia that is significantly correlated with the reduced exercise capacity in patients with heart failure. It also determines a worsening of the quality of life and is significantly correlated to a worsening of the outcome in patients suffering from heart failure. These data have determined the introduction of iron deficiency in the guidelines on heart failure of the European Cardiology Society as a concomitant disease that exacerbates the outcome and which must therefore be treated with iron supplementation.



Alain Cohen-Solal
(Paris, France)



What are the consequences of iron deficiency in patients suffering from heart failure? What are the main adverse events from the administration of EPO in anaemic patients with heart failure? What are the principal effects of iron therapy in sideropenic patients with heart failure?



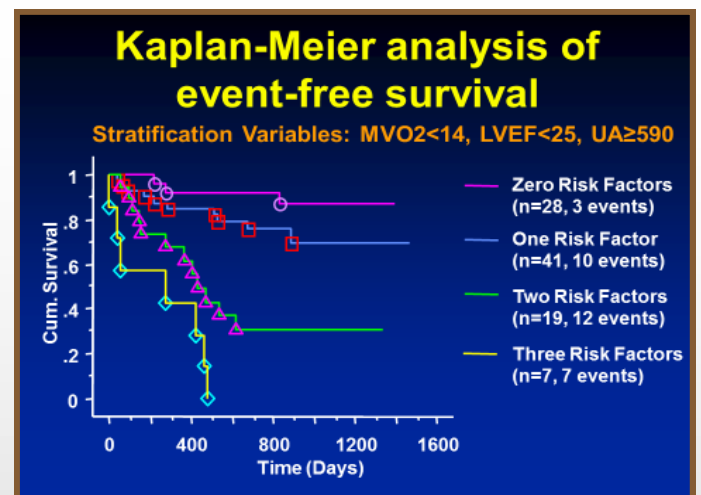
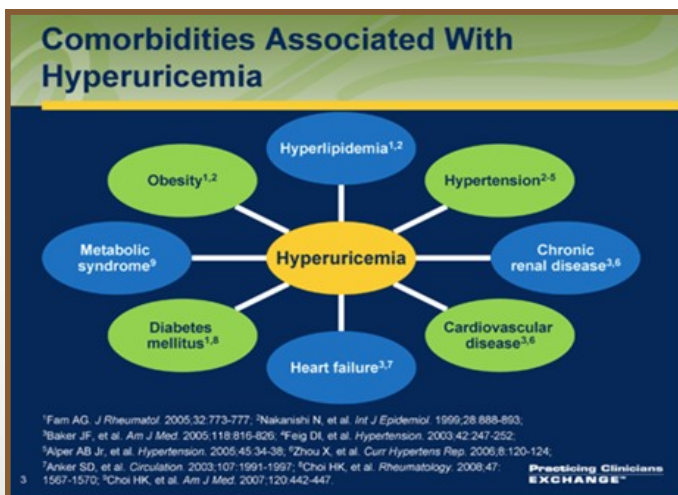
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Uric acid and the prognosis of heart failure

Prof. Coats from Melbourne spoke about the correlation between uric acid and heart failure. Uric acid is the principal agent responsible for gout due to the precipitation of its crystallised compounds in the joints. Heart disease, diabetes, and dyslipidaemia are all underlying diseases which give rise to specific alterations of the metabolism of uric acid. For this reason, uric acid and the alterations of its metabolism can be considered important markers of cardiovascular disease. The increased plasmatic levels of uric acid are associated with altered oxidative metabolism in patients suffering from heart failure, a reduction in the peripheral blood flow, and body wasting. Uric acid is also associated with alterations in the immune system. In patients suffering from heart failure, the presence of several risk factors dramatically worsens the prognosis and one of the risk factors that it is especially important to take into consideration is uric acid. A reduction in the plasmatic levels of uric acid is associated with an improved outcome in chronic heart failure patients, in the endothelial function, and the peripheral blood flow. Conversely, an increase in the plasmatic levels of uric acid is associated with an increase in the cardiovascular risks, giving rise to organ damage and a continuation of various chronic diseases including that of heart failure, the prognosis of which worsens significantly when linked to alterations of the metabolism of uric acid.



Andrew Coats
(Melbourne, AUS)



What are the principal diseases that develop in concomitance with increased plasmatic levels of uric acid? What are the main physiopathological phenomena linked to alterations of the metabolism of uric acid? What is the correlation between survival in patients suffering from heart failure and the plasmatic levels of uric acid? What are the principle dysfunctions of the immune system linked to alterations of the metabolism of uric acid in patients suffering from heart failure?



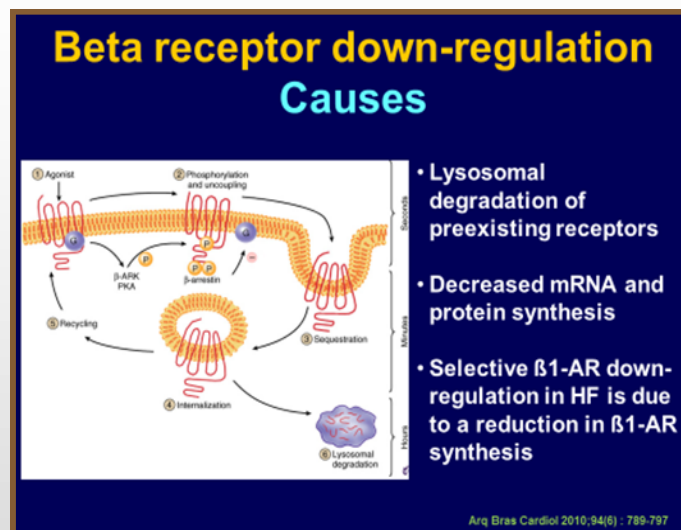
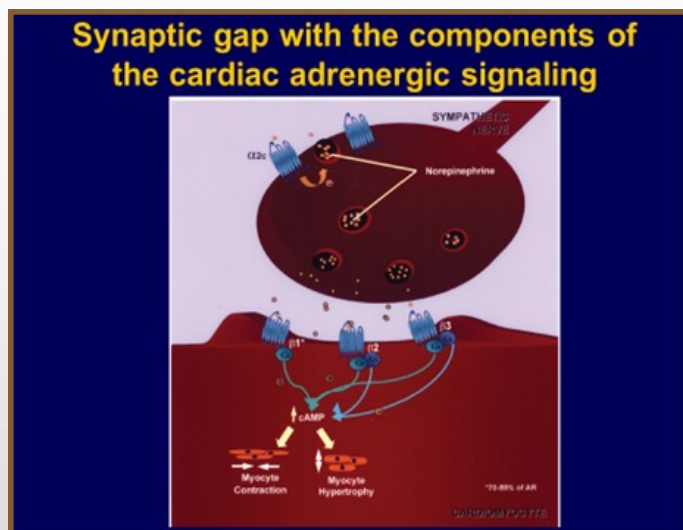
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Beta-blockers, genetics and the prognosis of heart failure

Prof. Seferovic from Belgrade presented very interesting data on this topic: beta-blockers are second-level drugs for treating heart failure that are used in association with the ACE-inhibitors. The β receptors are typically divided into β_1 , β_2 and β_3 receptors. These receptors, as adenylate cyclase activators which in turn give rise to an increase in the cyclic AMP, are distributed throughout various organs and are sensitive to the action of the selective agonists and antagonists. As of 2012, the beta-blockers have been included on the list of drugs recommended for treating heart failure due to the fact that not only they improve the function of the left ventricle, but they also increase the survival rate of patients suffering from heart failure, in particular those in Class 1. In these patients the down regulation phenomenon of the B receptors is present, linked to the lysosomal degradation of the previous receptors. Also present is the phenomenon of desensitisation of the β receptors linked to two mechanisms: an increased phosphorylation of the β -AR receptors and the over-expression of the G_i protein, the polymorphism of the β receptors. An extremely relevant aspect of the pharmacological action of these compounds is linked to their interaction with nitric oxide and the vasodilatory effect that derives from the same. The speaker then addressed the problem of receptor polymorphism in genetic terms; a fundamental aspect as it influences not only the effectiveness of the beta-blockers but more generally, the receptor response to physiological or also physiopathological stimuli. At a pharmacological level, the bond that the single molecules are able to create with the receptors based on the specific polymorphisms is essential for the characterisation of their therapeutic effect, also in terms of outcome.



Petar Seferovic
(Belgrade, Serbia)



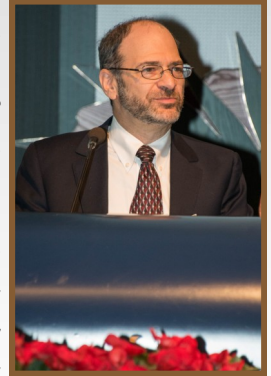
What are the pharmacological bases of the β -blockers mechanism of action? What are the main characteristics of the phenomenon of the down regulation of the β receptors? What are the principal polymorphisms of the β receptors?



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Haematic Biomarkers and prognosis of heart failure

Prof. Emdin from Pisa addressed the topic of biomarkers applied to the stratification of patients suffering from heart failure. Among the classic factors used as biomarkers, the natriuretic peptides play a primary role. Their increase is present right from the pre-clinical stage of heart failure. Not only can the natriuretic peptides be used as a diagnostic tool, but they are also useful to monitor the effect of the pharmacological treatment on patients suffering from heart failure. As prognostic indicators, both in the acute and chronic stages of the condition of heart failure, natriuretic peptides are considered an extremely significant and effective tool. Among these, the most relevant are BNP and pro-BNP. Nevertheless, these biomarkers can be influenced by other factors that end up by altering their plasmatic levels. For this reason, in recent years new biomarkers have been identified, including troponin, which is very sensitive even to the slightest cardiomyocyte damage. The plasmatic levels of troponin are also correlated with the main clinical outcomes of the cardiac remodelling. Another very interesting biomarker is galectin 3, involved in the phenomena of inflammation and pro-fibrotic processes. This biomarker has also demonstrated its effectiveness in predicting the future development of acute heart failure in the younger population. This biomarker can be considered a disease target as well as a useful diagnostic tool. Additional new biomarkers currently being studied are ST2, a member of the IL-1 receptor family secreted by the myocytes and a possible mediator of hypertrophy and myocardial fibrosis. Other new biomarkers are under investigation such as copeptin, adrenomedullin, endothelin 1, NGAL and cystatin C.



Michele Emdin
(Pisa, Italy)

Clinical value of biomarkers

- *Pathophysiological pathway marker*
- *Screening tool*
- *Diagnostic tool*
- *Staging biomarker*
- *Prognostic indicator*
- *Markers of therapeutical response*
- *Surrogate endpoint*

Vassan S. Biomarkers of cardiovascular disease: molecular basis and practical consideration. Circulation 2006; 113: 2335-42

Conclusions: biomarkers and precision medicine in HF

- A multi-marker strategy that utilizes the various mechanisms for biomarker release **may become the** approach used in the future.
- Personalization of heart failure care **may be the future** for biomarkers in HF; **however more data comparing this strategy and other meticulously designed head to head trials of individual and panels of markers are needed.**

What is the main natriuretic peptides mechanism of action? What are the main natriuretic peptides limits in the prognosis of patients suffering from heart failure? What are the main biomarkers, differing from the natriuretic peptides, that have been studied over recent years? What is the correlation between the new biomarkers and the main outcomes of disease?



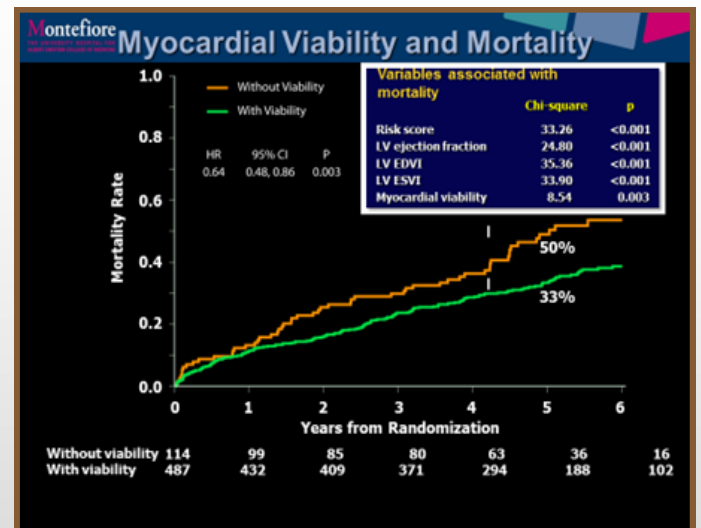
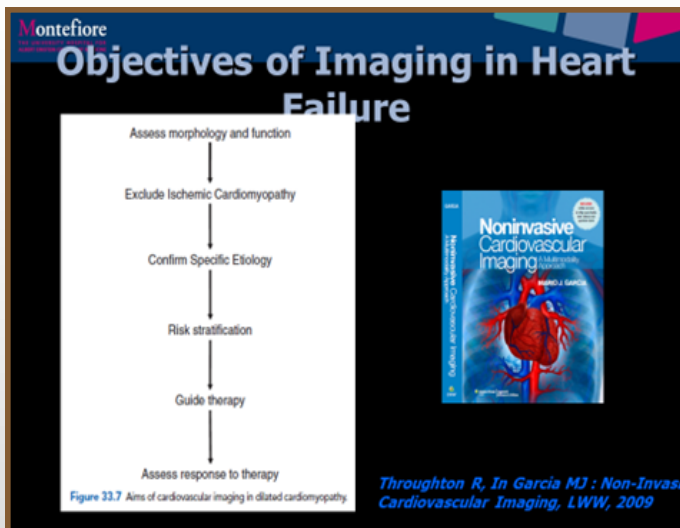
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Imaging and prognosis of heart failure

Prof. Piña from New York addressed this topic by stating that, thanks to the imaging techniques, it is possible to carry out new diagnoses linked to the main parameters, both structural and related to the cardiac function, such as the structure of the left ventricle, the ejection fraction, the ventricular relaxation condition, and other parameters of an anatomical nature. In functional terms, with the imaging techniques it is possible to collect useful indications regarding the presence of global systolic and diastolic dysfunction as well as the presence of regional myocardial dysfunctions. The imaging techniques are also effective in identifying any morphological alterations such as dilation, hypertrophy and restrictions. With these techniques, it is also possible to diagnose diseases, such in case of amyloidosis, which is characterised by specific cardiac imaging pictures, or in case of dilated cardiomyopathy with both the ischaemic and non-ischaemic forms. Another characteristic of the myocardium that can be studied in an accurate manner with imaging techniques is its level of “vitality” following ischaemic damage or tissue necrosis due to myocardial infarction. There are numerous pathological pictures that can be studied with imaging techniques at the cardiac level in both diagnostic and prognostic terms. The “deceleration time” is an extremely important parameter in terms of prognostic evaluation of the various cardiac pathologies. As regards the predicting of the outcomes, an innovative imaging technique is represented by the quantification of the noradrenalin uptake, which is reduced in a significant manner in patients suffering from heart failure by means of the use of an analogue radiomarked with iodine -123 in the NE. The speaker then analysed the data of the ADMIRE study in patients suffering from heart failure.



Ileana Piña
(New York, USA)



What are the main imaging techniques used in the diagnosis of heart diseases? What are the main fields of use for the imaging techniques? What are the main characteristics of the ADMIRE HF study?



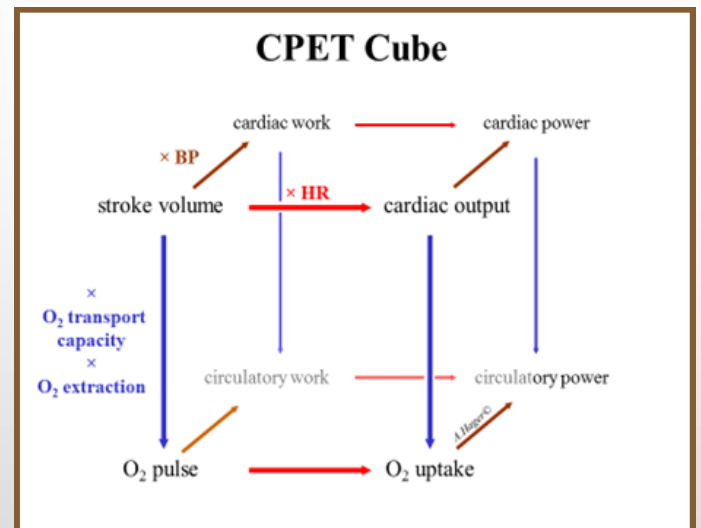
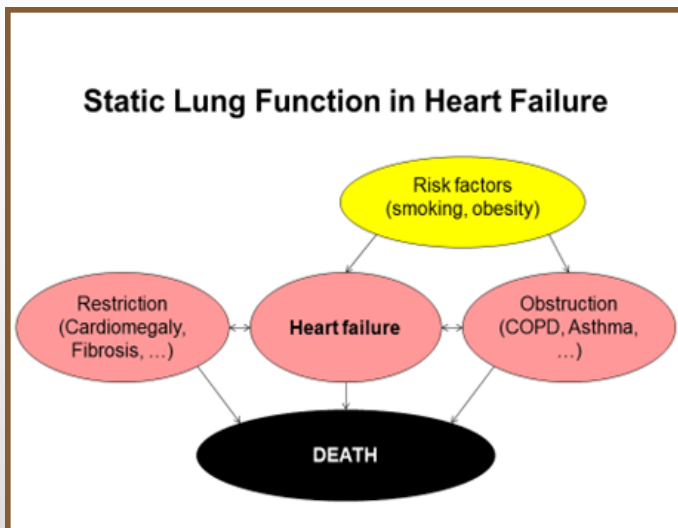
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The prognosis of heart failure: focus on ventilation

Prof. Hager from Monaco addressed the topic of pulmonary function in the presence of heart failure. Only in 50% of the cases of congenital heart defects does the Forced Vital Capacity (FVC) tend to be normal (>80% predicted). The reduction of this index to levels < 70% is associated with a worsening of the prognosis in terms of survival. The periodic respiration monitored during the day, at night and in conditions of exercise, has a prognostic value in patients suffering from heart failure. Of extreme importance is the cardiopulmonary exercise testing (CPET) characterised by specific measurements such as the peak oxygen volume (Peak $\dot{V}O_2$), the relationship between the expiratory volume and the volume of CO_2 , and the so-called “oscillatory ventilation” that represents the ventilatory variability of the respiration during exercise. The speaker then described the physiological cardiopulmonary model at the basis of the test, where, in final analysis, the valid parameters for all patients are the “ O_2 pulse” and the “ O_2 uptake” that represent the volume of oxygen consumed by the body with each heart beat and the volume of oxygen consumed by the body in one minute respectively. Among all the parameters applicable for prognostic purposes in patients suffering from pulmonary hypertension secondary to left cardiac disease, the most significant seems to be the relationship between the expiratory volume and the volume of CO_2 . Finally, the presence of “oscillatory ventilation” appears to have a decidedly negative prognostic significance. The parameters that describe the pulmonary function in static conditions, such as the residual volume and the total pulmonary capacity, can be associated with the heart failure condition. Nevertheless, in order to give indications in a prognostic sense, they must be associated with common risk factors.



Halfred Hager
(Monaco, Germany)



What are the main indicators of the static pulmonary function? Just how indicative is the periodic breathing in patients suffering from heart failure? What is the prognostic value of the CPET? What measures the V_E/VCO_2 – slope?



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Pulmonary hypertension and heart failure

Prof. Dumitrescu from Cologne addressed this topic starting from considerations of an etiopathogenetic and epidemiological nature. The prevalence of pulmonary hypertension in patients suffering from heart failure can vary between 30% and 50%. This variability is in part linked to the definition of pulmonary hypertension that has been selected in the various studies. The correlation between pulmonary hypertension, systolic blood pressure and age is of primary importance: with an increase in this parameter, there is a rise in the systolic pressure values and in the pulmonary blood pressure values. This increase in turn shows a negative correlation with the survival curve. In physiopathological terms, in patients suffering from heart failure there is an increase in the average pulmonary pressure and in the pressure of the left atrium. However, in case of imbalance of the fluids at the pulmonary level, we can observe a greater increase in the pulmonary arterial pressure compared to the left atrial pressure, with a relative increase in the transpulmonary pressure curve. This condition gives rise to a worsening of the clinical picture of heart failure. Nevertheless, it is not just a problem of pressure, in fact it is equally important to assess the heart function both at rest and during exercise, as well as the impact that the different concomitant heart diseases can have on these parameters. The speaker then analysed the pulmonary hypertension situation in patients suffering from heart failure with reduced and preserved ejection fraction, where the prognosis of patients suffering from heart failure with preserved ejection fraction in presence of pulmonary hypertension is worse than that of patients suffering from heart failure with reduced ejection fraction. The application of the cardiopulmonary respiration test is a great help in the stratification of the risk in these patients for prognostic purposes, just as it is equally important to carry out a complete haemodynamic profile. The speaker's final message was that of not forgetting to study the right ventricle in order to have a correct prognostic evaluation of patients suffering from left heart failure.

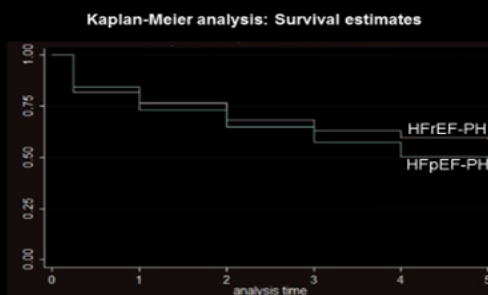


Daniel Dumitrescu
(Cologne, Germany)

Evaluation of chronic heart failure – The right ventricle:



Comparing outcomes in HFrEF-PH vs HFpEF-PH



Salamon JN et al., *J Card Fail* 2014; 20(7): 467-475

What is the prevalence of pulmonary hypertension in patients suffering from heart failure? How important is the right ventricular function in these patients? How much does the prognosis worsen in patients suffering from pulmonary hypertension in presence of other concomitant heart diseases?



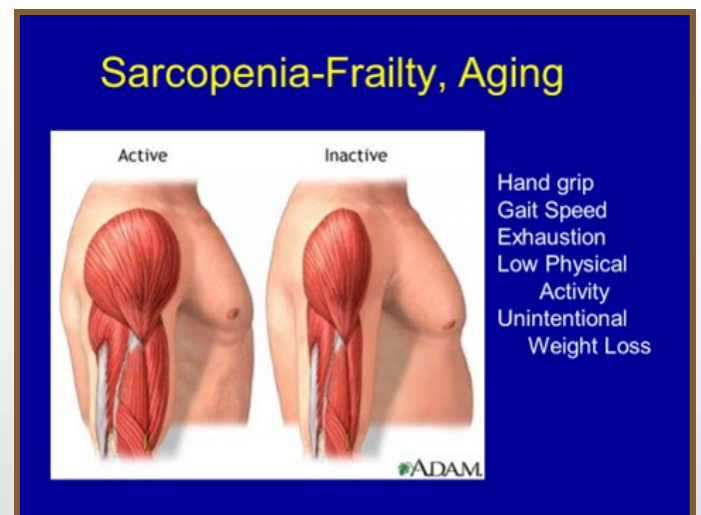
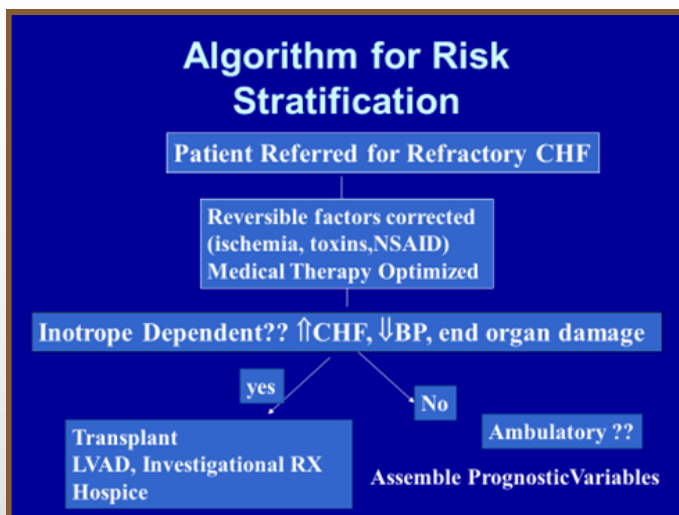
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Prognosis of heart failure and physical exercise: the role of oxygen

Prof. Mancini from New York presented very interesting data on the evaluation of the VO_2 levels in the prognosis of patients suffering from heart failure. In the United States, the stratification of the risk of patients suffering from heart failure is essential in order to determine the therapeutic approach, and more specifically, for selecting candidate patients for heart transplants. How does the evaluation of VO_2 have an impact on these strategies? Could the frailty parameter be the most indicative in terms of predicting survival? And even more importantly, can the evaluation of VO_2 give specific indications as to the effectiveness of the therapeutic approach? The speaker attempted to answer these questions by presenting data produced by her work group over the years. The predictive value of VO_2 in candidate patients for heart transplants has been assessed in a study on 114 patients. The cut-off of 14 was chosen; the patients with a VO_2 level >14 who had undergone transplants showed a better survival rate than transplanted patients with VO_2 levels <14 . The speaker then presented a series of additional data in which the VO_2 demonstrated higher predictive values than the other factors contemplated in the Seattle Heart Failure Model. VO_2 is also able to provide valid indications in the assessment of the outcome during pharmacological treatment. The levels of VO_2 maintain their predictive value in elderly patients as well. These results have given rise to the inclusion of the VO_2 evaluation in the guidelines for selecting candidate patients for heart transplants. The use of this parameter acquires additional efficacy when it is accompanied by other parameters, including the VE/VCO_2 ratio - slope.



Donna Mancini
(New York, USA)



What is the role of VO_2 in the prognostic assessment of patients suffering from heart failure?

What is the algorithm for the stratification of the risk applied in the United States?

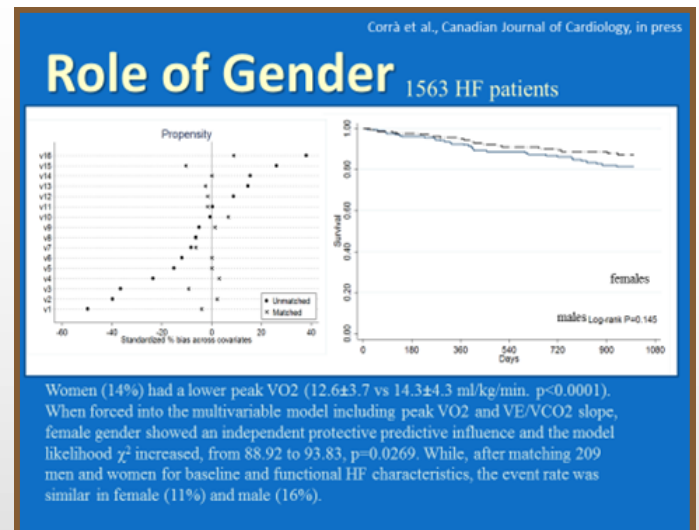
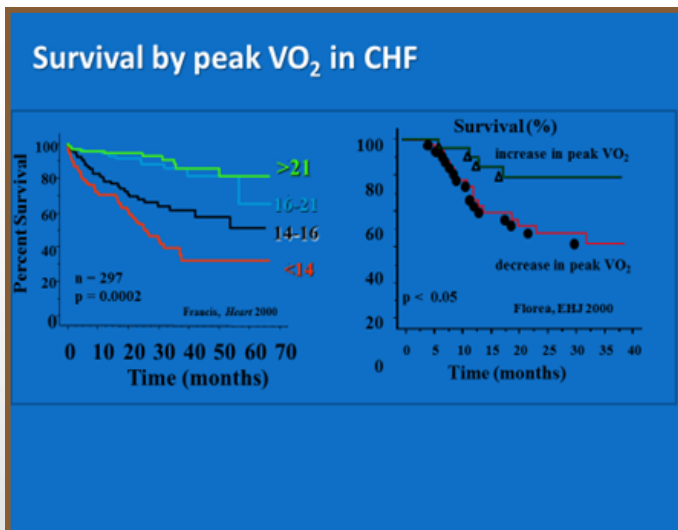
What are the principal parameters monitored during the cardiopulmonary test?



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The multiparametric approach to the prognosis of heart failure

Prof. Agostoni from Milan addressed this topic starting from the evolution of the use of VO_2 in the prognostic evaluation of patients suffering from heart failure. From a cut-off value of 14, the patients were then stratified according to 4 peak values: <14, between 14 and 16, between 16 and 21, and >21. During recent years patients suffering from heart failure have also changed, above all due to the improvement in the therapeutic strategies applied. The speaker then described a series of data relating to the main parameters taken into consideration during the conducting of the cardiopulmonary function test, such as age, gender, obesity conditions, low respiratory exchange, anaemia, cardiomyopathy, renal failure and atrial fibrillation. In all these cases the VO_2 maintained a strong predictive value. What happens when patients suffering from severe heart failure are considered? The VO_2 still maintains its predictive value. The speaker finally presented data on the new prognostic model known as the MECKI score, where the VO_2 is accompanied by other parameters closely linked to the conditions of the disease. This new model has demonstrated a high predictive effectiveness with regard to the outcome of the disease in the various patient categories. The use of these methods is extremely valid for understanding the cardiac physiology and for stratifying heart failure for prognostic purposes and, more generally, for staging purposes. It is however necessary to integrate these data with those collected from the clinical field in order to have a complete and “reliable” picture of our patients suffering from heart failure.



What has been the evolution situation of VO_2 over the last decade for the prognostic evaluation of patients suffering from heart failure? What changes have there been in the population of patients suffering from heart failure? Does the identification of the aerobic threshold have a real prognostic value?



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These are but a few of the topics addressed during the congress works. For a more in-depth analysis please visit the website of **Fondazione Internazionale Menarini** which also contains the full versions of the congress talks.

To follow the presentations in this convention just click on this link: www.en.fondazione-menarini.it/... and after logging in, access the multimedia material.



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International Symposium on:
CHRONIC HEART FAILURE IN 2016:
PROGNOSIS

Milan (Italy), February 25 - 27, 2016

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