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Innovation in cardiology: *still a wishful thinking?*

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A B S T R A C T   B O O K

CONTENTS

Epigenetics, Nutrition and the Biological Clock

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The circadian clock controls a remarkable array of physiological and metabolic functions.
As both genetic mutations and non-genetic interferences that disrupt the circadian clock lead to metabolic disorders, it is essential to understand how circadian rhythms and
metabolic processes interact on a cell and tissue-specific level. Accumulating evidence indicates that non-transcriptional control contributes to clock-driven regulation of metabolism. For example, we have shown that many small metabolites oscillate in expression, establishing an intimate link between metabolic homeostasis and circadian rhythms. We have recently discovered that the circadian clock controls a remarkable fraction of acetylation events, which lead to regulation of mitochondrial enzymes activity. As circadian rhythms are intimately linked to aging, and caloric restriction remarkably influences both processes, we have been filling this void in knowledge by revealing the molecular and cellular links between nutrition, metabolism and epigenetic control. We have also been linking the metabolome to the circadian acetylome, which has established that these two cycle in a coordinated manner and their functional regulation leads to control of the circadian epigenome. As accumulating evidence stresses the role of the circadian clock in linking enzymatic control and cellular metabolism, this research has far-reaching implications for human physiology and disease.

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Genetics for Drug Selection

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Not all, in fact usually a minority, of patients respond to a particular CV therapy

In human populations the spectrum of drug response ranges from a high (~80%) percentage of responders in analgesics (COX-2 inhibitors) to 10-20% (many anti-tumor agents).[1] Response to cardiovascular interventions is generally in the 20-40% range, as shown in Figure 1:[2]
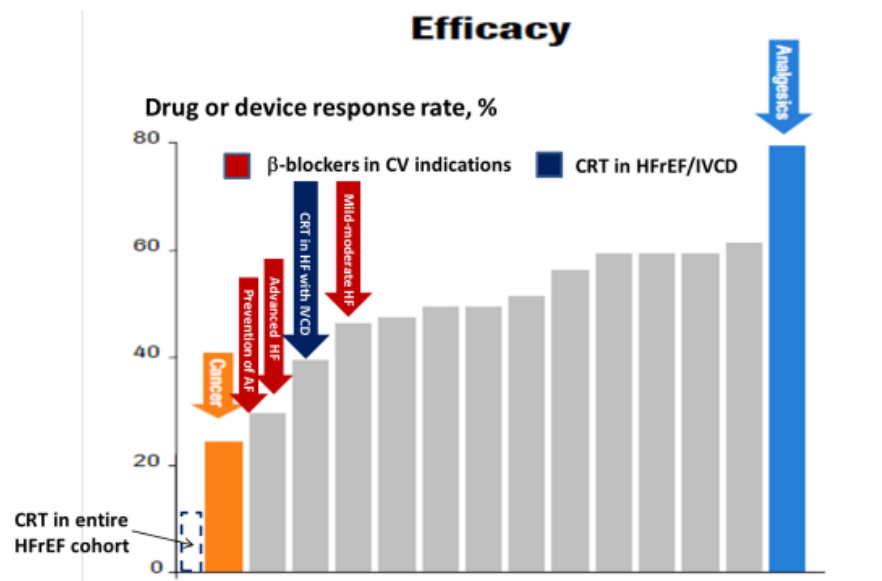

Figure 1. % of population responding to various drug lasses

What is needed in cardiovascular therapy, whether in clinical trial designs or in medical practice, is a way to enrich the eligible treatment cohort by identifying a responsive subpopulation, such as has been illustrated in Figure 1 for cardiac resynchronization therapy (CRT). For CRT 30-40% of HFrEF patients with a substantial IVCD (QRS ≥150 ms) respond to therapy,[3,4] but if all HFrEF patients were treated regardless of intraventricular conduction characteristics the response rate would be <15%, or undetectable in a standard size clinical trials and not cost-effective in clinical practice. This is an overt example of precision medicine, i.e. identifying a treatment-responsive subpopulation through the use of a surrogate marker of cardiac dyssynchrony, QRS lengthening.

For heart failure therapy, can genetics be used to identify responsive subpopulations?

The answer is *yes* in theory, but for heart failure therapy this turns out to be quite challenging. Unlike for cancer, where a somatic cell mutation can be biopsied from a tumor and its unique molecular/biochemical characteristics used to design or select for a drug that favorably interacts with abnormal cell function, genetic variants that affect drug response in HFrEF are typically germline in origin. This genetic variation may be common (polymorphisms, prevalence ≥1%) or rare (mutations, prevalence <1%), but for any impact on HFrEF polymorphic variation, in particular in single nucleotides leading to an amino acid change ("Nonsynonymous SNPs") is where the therapeutic potential lies.

Although genetic variation between individuals is quite small and averages only 0.25%, because of the large size of the human genome (~2.8 B base pairs) there is considerable potential for genetic variation to affect drug response.[5] This is particularly true within the neurohormonal inhibitor (NHI) class, where genetic variation in drug targets or other proteins that affect response is relatively common. Table 1 lists some of the evidence that NHI or even device response in HFrEF may be affected by genetic variation.

Almost all the genetic variants listed in Table 1 exhibit allele frequencies that differ by race, typically for sub-Saharan African ancestry vs. all other races, which gives rise to racial differences in NHI response.[5]

Table 1. Summary of signaling molecule polymorphism effects* by drug or device class[5]

Drug or class	Polymorphism (effects on response in HF)
Standard β-blockers	GRK5 Gln41Leu (↓ by Leu carriers); ADRB2 Gln27Glu (carvedilol ↑ in Glu genotypes) ACE Del/intron16/Ins (↑ in Del homozygotes)
Bucindolol (β-blocker/sympatholytic)	ADRB1 Arg389Gly (↑ in Arg homozygotes, ↓ in {389Gly + ADRA2C 322-325Del} genotypes; EDN1 Lys198Asn (gene dose-related ↓ in Asn genotypes); ECE1 Thr341Ile (↓ in Ile genotypes)
ACE inhibitors	ACE Del/intron16/Ins (↑ in Del homozygotes)
Angiotensin AT-1 receptor blockers	↑ biomarker (NT-proBNP) response in AGTR1 1166C genotypes
Hydralazine/isosorbide dinitrate	NOS3 Glu298Asp (↑ in Glu homozygotes); CYP11B2 T-344C (↑ in -344T homozygotes); GNB3 825T(↑ in TT homozygotes)
Cardiac resynchronization therapy	ADRB2 Gln27Glu (↑ in Glu homozygotes); NR3C2 Ile180Val(↑ in Ile homozygotes)
ICD appropriate discharge for VT/VF	SCN5A Ser1103Tyr (↑ events in Tyr carriers)

*Arrows indicate directionality of therapeutic response modification

Should genetic profiling be used to select patients for NHI administration?

The answer at this time is no, because with just a few exceptions [6-9] most of the evidence used to populate Table 1 derives from unconfirmed small studies. In general larger, Ph 3 trials in this area are lacking, and are needed. The possible design of such trials will be discussed, along with examples of some ongoing trial activity.

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Back to phenotype: a new classification of heart failure

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Heart failure (HF) is a clinical syndrome that arises when structural and/or functional alterations of the heart determine the inability to pump sufficient blood for metabolic systemic requests or when the heart is still able to comply this demand, but with an increase of heart filling pressures. Neubauer proposed a fascinating definition of HF as "*an engine out of fuel*"[1]. Although the pump-deficiency is involved in the development of both acute and chronic heart failure, these two conditions differ in term of duration of the disease and the organ damage produced. The prevalence of HF is higher in people more than 50 years old, while the incidence is directly correlated with age[2], so it is constantly increasing due to the aging of general population, especially in West Countries and it is going to raise over and over in the next decades[4]. Moreover, hospitalization and mandatory domestic treatments implicate a consistent health-expense[3]. The New York Heart Association (NYHA) developed a functional classification for HF patients divided in four categories based on how much they are limited during physical activity (Class I: no symptoms and no limitation in ordinary physical activity; II: slight limitation during ordinary activity; III: marked limitation during less-than-ordinary activity; IV: symptoms even at rest). Current guidelines suggest to drive therapy on the basis of this classification. However, NYHA classification presents important limitations: it is based excessively on the patient and physician's subjectivity, being only a subjective and qualitative evaluation. A more correct and more precise prognostic stratification would allow the physician to identify the best treatment, not only in terms of efficiency but also of cost-benefit. A classification of this kind would be for the physician a fundamental tool for the patient management. In fact, it is essential for HF patients remind comorbidities and their severity in order to choose the more accurate treatment, within a very wide range of possible therapeutic options.

Starting from these considerations, it has been recently presented by our group, a new classification for HF, called HLM, designed from the TNM staging, well-established in Oncology. This first step of HLM represents the parameter "H" (HEART), which can be considered analogous to the parameter "T" (TUMOR) of TNM, identifying four stages (H1-4). The next step is the evaluation of pulmonary involvement, through the specific parameter "L" (LUNG); the lungs, in fact, for their peculiar anatomical and functional connection to the heart, can be considered as the "nodes" of the heart, continuing the analogy with the TNM (L0-L4). Finally, remembering the etymological meaning of the term "metastasis", from the ancient Greek language, "displacement", always in analogy with the concept of cancer metastasis, is considered the systemic organ's malfunction, "M" (MALFUNCTION), due to HF, such as kidney, liver, brain and hematopoietic system, which is the third and last parameter of the classification (M0-M3). The HLM is a simple and effective classification of HF, that takes into account the systemic involvement of other organs and systems, in addition to symptoms and the evaluation of cardiac damage, thus trying to overcome the classifications used so far, to allow a more accurate prognostic stratification of HF patients. With the evaluation of cardiac function, pulmonary and peripheral organs, HLM classification leads to a better anatomical and functional assessment of HF patients compared with NYHA. Improved prognostic stratification could result also in increased economic and ethics appropriateness in the management of HF patients. For patients at initial phases, it will be possible to use a traditional therapeutic strategy as diuretics, beta-blockers and digitalis. New generation therapeutic approaches, certainly more expensive, as inotropes or implantable devices, will be given to second and third line of disease. Moreover, the presence of "metastasis" at the level of other organs should authorize the physician to use treatments definitely cardioprotective, but also nephrotoxic and hepato-protective, thus justifying the high costs in proportion to the obtained benefits, according to a better economic appropriateness. Finally, in the terminal stages of the disease, according to a principle of ethical appropriateness, palliative therapeutic interventions will be used.

Therefore, HLM staging wants to overcome NYHA classification in term of excessive simplicity. In clinical practice, it was created an electronic case report form (CRF) and a multicentric prospective observational study is ongoing in order to confirm the usefulness of HLM classification in terms of prognostic stratification.

Cardiovascular Disease Today: From Pathophysiology to New Prevention Modalities

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Cardiovascular diseases remain the most important cause of morbidity and mortality throughout the world but in particular in European countries. Although the most important risk factors are known since decades and life style changes are recommended on a regular basis to all patients at risk, the implementation of preventive measures remains difficult. Indeed, for life style changes educational programs with specialized nurses have proved effective and should be implemented at a large scale in order to reduce the disease burden in the future.

Medical therapy of cardiovascular risk factors for the prevention of myocardial infarction, stroke and death have proven to be extremely effective particularly in hypertension and lipid disorders. High blood pressure is currently treated mainly with inhibitors of the renin angiotensin system (ACE-inhibitors and angiotensin receptor antagonists), betablockers, diuretics and calcium antagonists. In large randomized trials the combination of an inhibitor of the renin angiotensin system and a calcium antagonist have proven to be superior to the combination of a betablocker and diuretic in reducing mortality in hypertensive patients. Furthermore, hypertensives often have lipid disorders and, therefore, the addition of a statin and aspirin prove to reduce the event rate both as regards heart disease and stroke.

With the introduction of statins, LDL-cholesterol can be reduced significantly and both in secondary and primary intervention these drugs have shown to be highly effective in preventing myocardial infarction, stroke and death. Nevertheless, there is a remaining risk even in patients treated according to the ESC guidelines. Therefore, new drugs have been developed to further reduce LDL-cholesterol according to the principle "*the lower the better*".

For the clearance of LDL-cholesterol, LDL-receptors on liver cells are crucial. Their expression is genetically modulated, but markedly modulated by the release of a protein from hepatocytes, i.e. pro-proteinconvertase subtilisin/kexin type 9 or PCSK9. Indeed, the longevity gene SIRT1 regulates the release of this protein from hepatocytes and in turn the expression of LDL-receptors and LDL-cholesterol plasma levels. Therefore, at an experimental level SIRT1 activators reduce not only LDL-cholesterol but also atherosclerosis in the mouse. In humans, this has not been tested yet. However, monoclonal antibodies against PCSK9 have been developed and shown to reduce LDL-cholesterol as well as lipoprotein$_{(a)}$ and most likely also cardiac events as already indicated in Phase II trials. As humans have the highest LDL-cholesterol levels and are prone to atherosclerosis already in ancient times as suggested by CT-coronary angiography in mummies from Egyptian times, it appears important to further lower LDL-cholesterol with these novel drugs in high risk patients in the future. They will first be used in patients with familial hypercholesteremia and possibly those with acute coronary syndromes.

Diabetes is the cancer of the blood vessels and associated with a high disease burden on the heart, kidney and the peripheral arteries. So far, most drugs that lower glucose levels as well as long-term sugar as assessed by hemoglobin$_{1Ac}$ were unable to markedly influence the occurrence of macrovascular complications such as myocardial infarction, renal failure and stroke. However, a recent breakthrough occured with the introduction of inhibitors of the sodium-glucose transporter in the renal tubules such as empagliflozin. Indeed, in a large randomized trial this drug for the first time was able to reduce cardiovascular mortality in patients with diabetes. Thus, it appears that drugs that excrete glucose rather than facilitating its entry into muscular and fat tissues as most traditional drugs do, is able to provide cardiovascular protection.

Unfortunately, HDL-cholesterol although predictive in epidemiological studies even in patients on statins, so far has not proven to be an important therapeutic target.

Of note, most trials trying to increase HDL-cholesterol with niacin or cholesterol ester transport inhibitors (CETP inhibitors) have failed. Basic research has shown that the HDL-cholesterol particles are a carrier for many proteins, mRNAs and cytokines and, therefore, change their biological properties as the disease develops. Therefore, particularly in high risk patients such as those after an acute myocardial infarction, HDL may be biologically dysfunctional and this may explain the failure of most of the trials aiming at increasing HDL-cholesterol in high risk patients for prevention. Indeed, even the infusion of reconstituted HDL was unable to change the extent of coronary artery disease as assessed by angiography or IVUS except in one small study so far not reproduced.

Finally, it appears that aging and longevity genes are the final common pathway of cardiovascular disease. Of note, we could show that the aging gene p66^{shc} coding for an adaptor protein increasing free radical secretion from mitochondira not only shortens life spam, but also markedly aggravates atherosclerosis and diabetic vascular disease as well as stroke. In contrast, the longevity gene SIRT1 prevents the development of atherosclerosis as indicated above. Finally, transcription factors that regulate important genes such as nitric oxide synthase, i.e. junD, are downregulated with aging and junD knockout mice not only have a markedly reduced life spam but also vascular dysfunction.

Thus, in summary, the knowledge about the mechanisms of occurrence of cardiovascular diseases has markedly increased over the last decades and led to important and effective treatment strategies to prevent myocardial infarction, stroke and death. However, the remaining disease burden asks for the introduction of novel drugs and the understanding of even so far unrecognized molecular mechanisms that may represent novel therapeutic targets in the future.

Arterial Hypertension

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Appropriate management of patients with arterial hypertension represents one of the main goals for cardiovascular disease prevention. Despite the fact that the treatment of arterial hypertension has been one of the major achievements of clinical medicine over the last 50 years, there is no doubt that several aspects of the management of hypertensive patients require attention. As an example, available data indicate that, even in well treated hypertensive patients, residual cardiovascular (CV) risk remains increased. In fact, the risk of cardiovascular events in controlled hypertensives still remains higher as compared to normotensives. Several explanations have been proposed for this finding. One possible mechanism might be the presence of silent cardiovascular abnormalities that might contribute to the increase in CV risk. In some patients (and in everyday clinical practice) full regression of organ damage is difficult to obtain, thus CV risk may remain high. As an example, it has been suggested that after regression of left ventricular hypertrophy (LVH), a "residual risk" could still be present. This could be explained, at least in part, by the presence of higher LV mass although within the normal range in these patients. The same observation might also be valid for preclinical vascular and renal damage. The presence of a significant residual risk might also be explained by inaccuracies in BP measurement: some patients with well controlled BP during the visit have increased "central" (aortic) BP and/or increased "out of office" BP. Another relevant issue is also represented by the optimal "on treatment" BP value. Recent results suggest that CV risk might be further reduced by lowering BP values to less than 120 mmHg. In fact, the results of the recent SPRINT study suggest that, in patients with systolic blood pressure (SBP) $\geq$130 mmHg and high CV risk, intensive treatment (i.e. treatment of patients to a BP goal <120 mmHg) might lead to a 25% lower relative risk of major cardiovascular events and a 27% lower relative risk of death as

compared to a "standard" approach (i.e. treatment of patients to a BP goal <140 mmHg). These results deserve large discussion before being safely applied in clinical practice, but will probably have a major influence on the treatment of hypertensive patients in the near future. Further reduction in CV risk might hopefully be obtained in the future also by the development of several new drugs currently under investigation for the treatment of arterial hypertension. Among them, angiotensin-receptor-neprilysin-inhibitors (ARNI) appear particularly promising. Recently, in patients with heart failure and reduced systolic function, LCZ696 was significantly superior to enalapril in reducing the risk of death and of hospitalization for heart failure. Furthermore, this drug provides additive reduction of blood pressure as compared to valsartan with a good safety profile, as shown in a randomized trial in 1328 patients with mild-to-moderate hypertension, and therefore it seems very promising also for the treatment of hypertensive patients. Other drugs, such as aldosterone-synthase inhibitors, dual vasopeptidase inhibitors, renin-prorenin blockers, aminopeptidase-A inhibitors, nitric oxide donors, AGE-breakers, AT2 receptor agonists, ACE-2 activators and rho kinase inhibitors may represent future options for the treatment of hypertensive patients. In the next years the results of ongoing studies will also provide information on the efficacy and safety of new interventional approaches for the treatment of arterial hypertension.

Cancer and Cancer Therapy

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During last years, the both combination of early cancer diagnosis and the greater use of traditional and novel treatment modalities has reduced cancer-related morbidity and mortality. Effective cancer therapies, however, can result in short- and long-term cardiac toxicity that can negatively impact quality of life and survival. Cancer therapy has been shown to cause a wide variety of cardiac toxicities, including arrhythmias, myocardial ischemia, coronary artery disease, hypertension, and myocardial dysfunction (1-2). Although there are many chemotherapeutic agents that can be associated with left ventricular (LV) dysfunction. Antracycline (ANT), widely used in the management of multiple malignancies, are the best-known agents associated with higher risk of heart failure (HF) development (1). The classic model of ANT-induced cardiotoxicity involves oxidative stress with the generation of reactive oxygen species. An alternative model posits that toxicity is caused by the disabling of the function of topoisomerase II beta (TOP2B) (3). The relationship between ANT cumulative dose and cardiotoxicity risk is well recognized. Other risk factors that may increase the likelihood of HF development after ANT treatment include pre-existing cardiovascular diseases, hypertension, increased length of time since ANT completion, female gender and genetic predisposition. Moreover, previous or concurrent treatment with other agents known to have cardiotoxic effects might influence development and recovery from ANT-induced cardiomyopathy (1). In particular, the use of ANT and Trastuzumab, especially in combination, may pose a specific risk for HF development (1). Unlike the ANT-induced cardiotoxicity, the effects of Trastuzumab do not appear to be dose-related, and have been described as reversible with no accompanied ultrastructural abnormalities (1). Cardiotoxicity related to cancer therapy is currently categorized into 2 types: Type I or irreversible cardiotoxicity, seen classically with ANT, and Type II or reversible cardiotoxicity, seen traditionally with the use of

Trastuzumab. However the distinction between type I and type II may be more complicated. Trastuzumab can trigger irreversible cardiac damage in patients with severe preexisting cardiac disease, or potentiate ANT Type I cardiotoxicity (**Errore. Il segnalibro non è definito.**). Moreover recent studies have shown that early institution of standard HF therapies, such as angiotensin-converting enzyme inhibitors and β-blockers, can attenuate, and sometimes reverse ANT-induced cardiac dysfunction (1). Thus, monitoring and management algorithms for either type of chemotherapy-induced cardiomyopathy are evolving around the central paradigm of early recognition and early treatment, however the optimal screening strategy remains unclear. The ESMO guidelines recommend close monitoring of cardiac function during ANT therapy, however, it does not specify how often these patients need to be followed, and which method should be used (1). Evaluation of LV ejection fraction (LVEF) is the traditionally preferred method for assessing cardiac function during anticancer treatment, although no clear consensus has been reached on the percentage of change, which may represent a clinically relevant decline in myocardial contractile function, requiring intervention (**Errore. Il segnalibro non è definito.**). Moreover, the reduction in LVEF constitutes the late phase of LV dysfunction that occurs once the heart's compensatory mechanisms to preserve contractility have been expended. Novel echocardiographic techniques, including myocardial velocity strain, and strain rate imaging, may be more sensitive in the detection of LV dysfunction than the evaluation of LVEF (1). All studies of early myocardial changes with chemotherapy demonstrate that alterations of myocardial deformation precede significant changes in LVEF: an early reduction, from 10% to 15%, in global longitudinal strain during therapy appears to be the most useful parameter for the prediction of cardiotoxicity. The ability of strain changes to predict subsequent cardiotoxicity however, needs to be examined in larger multicenter studies (1).

In the last decade, a new approach, based on the use of cardiac biomarkers, in particular troponin, has emerged, and has proven to be a more sensitive and more specific tool for early, real-time identification, assessment and monitoring of anticancer drug-induced cardiotoxicity (11).

Several studies have shown that elevations in serum troponin during chemotherapy might identify patients at risk for acute cardiotoxicity, but the use of biomarkers to predict delayed toxicity remains unclear (10). Troponin, used in combination with an imaging technique that can detect subclinical LVD, could potentially be more useful (11-12).

Strategies that limit the development of cardiotoxicity in the first place (primary prevention) seem most desirable (13). Current strategies to prevent cardiac toxicity include limiting the cumulative Anthracycline dose, prolonging infusion times to limit peak serum concentrations of Anthracycline, using liposomal formulations of Anthracycline, administering Anthracycline and Trastuzumab sequentially rather than concurrently. Some studies showed that cardioprotective agents (i.e. dexrazoxane, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers) used pre-chemotherapy, can prevent clinical HF and chemotherapy-related cardiotoxicity (14). Further prospective studies are needed to evaluate the efficacy of specific drugs for preventing chemotherapy-induced cardiotoxicity.

The ideal primary prevention protocol would involve genetic susceptibility testing. Since 2005, the importance of gene variants has been addressed in a dozen case-control studies. In two studies, ANT-induced cardiotoxicity appears at least in part be driven by single nucleotide polymorphisms (SNPs) of 6 genes involved in ANT pharmacokinetics (15-16). In our experience we wanted to analyse the possible role of these SNPs, to predict cardiac biomarkers elevation during treatment with Epirubicin. We identified a significant association only between one of the 6 SNPs analyzed (ABCB4 gene) and early elevation of cardiac troponin. This gene encodes for proteins involved in processes known to affect Epirubicin transport into cells. Our findings, although limited by the low patients number at this time, show that to discriminate individuals at higher and lower risk for cardiac cells injury, induced by Epirubicin treatment, might be possible also through the study of patient's genetic information. Our future aim is to identify other SNPs linkage that could better predict patients at higher risk for cardiotoxicity development.

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Life and death of the myocyte as a cause of remodelling

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Chronic heart failure (CHF) is a common and disabling syndrome with a poor prognosis.

Fatigue and shortness of breath, the two common and disabling symptoms in patients with CHF, are very often associated to further enlargement of the affected ventricle with relative changes in its shape, geometry and function. This phenomenon has been named *"ventricular remodelling"*. It occurs mainly as a consequence of large infarction and it consists of two main phases: a – *early remodelling* – which occurs at the site of myocardial damage resulting in the thinning of the ventricular wall, scar formation and consequent enlargement and re-shaping of the ventricular chamber; b – *late phase remodelling* – which might occur months or even years after the initiating insult in the still viable myocytes (i.e. in region of the ventricle not affected by the infarction). While the first phase of remodelling can be considered a positive, repairing process allowing the formation of a scar, the second phase, involving viable myocytes, is deleterious and responsible for the progression of the syndrome. Remodelling myocytes shows a typical switch forward the embryonic phenotype (i.e. they re-express atrial natriuretic peptides in the ventricles, embryonic myofilaments and Ca^{++} related proteins) and classical features of apoptosis and/or hypertrophy. Interestingly, these two processes, although activated and regulated by similar intracellular cascade, represent opposite signals for the myocytes: a signal of death – *apoptosis* and a signal of life – *hypertrophy*. This is not at all surprising as the so called "*cell life and death cycle*" is an intrinsic component of nature itself. Almost every cell of the organism undergoes "the cell cycle" (i.e. a red blood cell lives for 120 days; a neutrophil for 7 hours!). The adult myocytes, however, is a terminal cell; usually it is not able to reproduce and death is not genetically programmed (apoptosis) but occurs by necrosis as consequence to a non-expected event (i.e. the occlusion of a coronary artery by a

thrombus). The embryonic myocytes, contrary to the adult one, undergoes the full cell cycle: it dies by apoptosis and it is able to reproduce. The re-instatement of apoptosis and development of hypertrophy could be part of the switch forward the embryonic phenotype with re-instatement of the early embryonic genetic programme. Thus, hypertrophy and apoptosis can be considered as "*sons*" of the same "*mother*": the local, tissue neuroendocrine-neurohumoral response to a mechanical stretch of the myocytes. The stretch is consequent to the geometric changes imposed on the viable myocytes by the necrotic ones. Recognized stimuli for the switch are angiotensin II, norepinephrine and aldosterone although many other inducers are likely to play a role. This explains the anti-remodelling effect of ACE-inhibitors, β-blockers and anti-aldosterone substances. As expected, life and death cycle is very closely regulated by several autocrine systems one of which is linked to the interleukine-6 family via a regulatory protein named GP-130. Activation of the GP-130 slows down the death signals, thus favouring hypertrophy and reducing fibrosis. Although hypertrophic myocytes cannot be considered normal, it has been suggested that when they are matching the myocyte loss, CHF is in a steady state. However, when apoptosis takes prevalence over hypertrophy, the disease progresses forward terminal stages. This "molecular-genetic" view of the remodelling processes is interesting not only from the physiopathological point of view, but also from a therapeutic one, suggesting that antiapoptotic and pro-life agents could be considered in a near future as novel treatment for CHF.

Epidemiology of Heart Failure

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Heart failure (HF) has been singled out as an epidemic and is a staggering clinical and public health problem, associated with significant mortality, morbidity, and healthcare expenditures, particularly among those aged ≥65 years. There are several challenges in the epidemiology of HF. First it is he difficulties in case definition. The diagnosis of heart failure, especially when relying solely on symptoms and signs (which ii often the case in primary care), is fraught with difficulties. Many patients deemed to have heart failure will simply be found to be obese, have a poor physical condition, pulmonary disease, or ischaemia on further examination.

There are difficulties in defining cases, differences in different populations, according to ages, gender, economical status. There are temporal changes in survivals, due to changes in therapy, in risk factor management.

The case mix of HF is changing over time with a growing proportion of cases presenting with preserved ejection fraction for which there is no specific treatment. Heart failure traditionally was seen to result from impairment in ability of the heart to pump sufficient amounts of blood into the circulation during systole that is, left ventricular systolic dysfunction. Echocardiography is most often employed to assess left ventricular systolic function, an ejection fraction of <40% indicating impaired left ventricular systolic function. Heart failure can also occur in patients with normal left ventricular systolic function in whom higher filling pressures are needed to obtain a normal end-diastolic volume of the left ventricle, so called heart failure with preserved left ventricular ejection fraction or ''diastolic'' heart failure.

Despite progress in reducing HF related mortality, hospitalizations for HF remain frequent and rates of readmissions continue to rise.

The early symptoms recognition is also really challenge for the future. There is a need for an increase in awareness among the general population where the burden of the disease is often under evaluated.

A leading problem is also the recurrent hospitalisations, which are due to cardiovascular and non-cardiovascular causes. The need for a multidisciplinary approach and a comprehensive characterization of predictors of readmission in patients with HF is imperative and must integrate the impact of multimorbidity related to coexisting conditions.

New models of patient-centered care that draw on community-based resources to support HF patients with complex coexisting conditions are needed to decrease hospitalizations. Predicting the prognosis (''prognostication'') in an individual patient with HF is instrumental in the decision to initiate or refrain from possible interventions. The prognosis-for example, 5 year survival-of a particular patient is usually made implicitly on the basis of patient characteristics and available (for example, biochemical, haemodynamic, echocardiographic or electrocardiographic) measurements. By means of multiple logistic regression and receiver operating characteristic (ROC) analyses a prognostic model or simplified score can derived, that can aid physicians in stratifying patients according to their prognosis.

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An Alogorithm for Medical Treatment of HFrEF

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For decades, heart failure was treated with diuretics and digoxin, and this did not change until the late eighties. In 1987 it was shown that ACE-inhibitors can reduce mortality by 20% in patients with severe congestive heart failure.(!) After this ACE-inhibitors have become the cornerstone of the treatment of heart failure with reduced ejection fraction (HFrEF) and have substantially improved clinical outcome in these patients. After this, beta-blockers have shown tremendous additional value. Although beta-blockers were originally contra-indicated in patients with HFrEF, several large randomized controlled trials need to be stopped prematurely due to overwhelming efficacy.(2,3) In fact, the effects of beta-blockers on the reduction in mortality and morbidity in patients with HFrEF are even greater compared with beta-blockers. In the meantime, it appeared that digoxin had no additional benefit in reducing mortality in these patients, and were slowly used less often over the years. During a long period of time. all patients with HFrEF were routinely treated with diuretics, beta-blcokers and ACE-inhibitors. In 1999, one trial showed that mineralocorticoid receptors could further improve survival and reduce the risk for hospital readmissions, but this trial was only done in severe HFrEF patients and only 10% used a beta-blocker. (4)Therefore, it took another decade, before final strong proof became available that MRAs were also effective in patients with milder HFrEF on top of a beta-blocker.(5) From this time on, until now, ACE-inhibitors (or alternatively angiotensin receptor blockers), beta-blockers and MRAs have become the cornerstone of the treatment of HFrEF. The increased clinical use of these therapies have resulted in a dramatic improvement of the outcomes of these patients. In 2010, another group of drugs became available for HFrEF; the so called If channel inhibitors.(6)These agents reduced heart rate and had shown to reduce the combined endpoint of cardiovascular death and/or heart failure hospitalization.

However, the drug only works in patients in sinus rhythm with a heart rate >70 bpm, despite optimal up titration of beta-blockers, and is therefore only suitable for a minority of patients.

Recently, there was a major breakthrough about a novel class of drugs: the angiotensine receptor neprilysin inhibitors.(7) These agents block the angiotensin II receptor, but also inhibitor the breakdown of natriuretic peptides, and this dual mechanism show to be overwhelmingly superior to ACE-inhibitors in reducing mortality and or heart failure hospitalization. This study rocked the solid believe that ACE-inhibitors would always remain to be the cornerstone of the treatment of heart failure. The position of the ARNIs remains to be established. The PARADUIGM-HF study was performed in patients that were already on an ACE-inhibitor, and was given at the background of beta-blockers and MRAs. Also, the trial was performed in patients with elevated natriuretic peptides and/or a recent heart failure hospitalization (a high risk subgroup of HFrEF patients) . Whether this drug is also effective in lower risk patients still needs to be established. Nevertheless, FDA and EMA have already p[provided a broad indication for the use of ARNIs. The future will learn us how this novel drug will be taken up by the doctors that take care of heart failure patients.

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The Centre And The Periphery: Mechanisms In HFpEF

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The term *"diastolic HF"* was first coined to reflect the leading pathophysiologic factor believed to cause the syndrome – left ventricular diastolic dysfunction. In the landmark study by Zile et al, abnormalities in left ventricular relaxation and compliance were uniformly demonstrated in 47 cases of HF despite a normal ejection fraction. However, population-based studies also showed that left ventricular diastolic dysfunction was present in a large proportion of community-based adults without HF, and that patients with *"systolic HF"* were even more likely to have moderate/severe diastolic dysfunction compared to patients with so-called *"diastolic HF"*. Nonetheless, progression of left ventricular diastolic dysfunction was found to be a major mechanism distinguishing HFpEF from age-, sex- and body size-matched healthy controls and hypertensive individuals without HF in the general community.

Other mechanistic studies challenged the concept that HFpEF was a uniform syndrome of *"diastolic HF"*. These studies described various abnormalities beyond diastolic dysfunction, including abnormal ventricular-arterial coupling with exercise, impaired systemic vasodilator reserve, chronotropic incompetence, myocardial contractile dysfunction despite a normal ejection fraction, left atrial dysfunction, pulmonary hypertension with intrinsic pulmonary vascular disease, endothelial dysfunction, and volume overload (related to extra-cardiac causes such as obesity, chronic kidney disease, or anemia). It is possible that each of these mechanistic studies selected a specific subset of patients with HFpEF; indeed evidence is mounting that HFpEF is not a single homogeneous syndrome, but is rather a heterogeneous condition consisting of several pathophysiological sub-types. It has in particular been proposed that three subtypes of HFpEF patients exist: those with exercise induced diastolic dysfunction, those with chronic volume overload and those with associated right HF and/or pulmonary hypertension.

The importance of recognizing the heterogeneity of the pathophysiology in HFpEF is highlighted by the fact that a *"one size fits all"* approach for clinical trials in HFpEF has been disappointing and that treatments directed at HFpEF as a large undifferentiated group have failed to improve outcomes. Understanding the heterogeneity of HFpEF and improved phenotypic characterization of mechanistic sub-types might therefore allow the design of more targeted HFpEF clinical trials.

Most recently, a new paradigm has been put forward based on observation of specific myocardial structural and functional changes observed in HFpEF. This paradigm emphasizes the role of a pro-inflammatory state with widespread endothelial dysfunction, leading to reduced nitric oxide (NO) bioavailability in cardiomyocytes, reduced myocardial cyclic guanosine 3', 5'-monophosphate (cGMP) content and low protein kinase-G activity (PKG). The central role of the NO-cGMP-PKG pathway is described in this paradigm: Endothelial dysfunction has been shown to be highly prevalent and independently predictive of survival in HFpEF, suggesting that it plays a major role in the pathophysiology of HFpEF. Endothelial dysfunction occurs in diabetes and hypertension, both important risk factors for HFpEF, and causes oxidative stress with high levels of reactive oxygen species which interfere with NO production in endothelial cells. This leads to reduced NO bioavailability to adjacent cells such as cardiomyocytes. cGMP is the second messenger that plays a role in various key physiologic pathways, including cardiovascular homeostasis, cellular growth and contractility, and inflammation. Guanylate cyclases are enzymes that catalyze the conversion of guanosine-5'-triphosphate to cGMP. Membrane-bound particulate guanylate cyclase (pGC) serves as a receptor for natriuretic peptides, whereas soluble guanylate cyclase (sGC) acts as a receptor for NO. Subsequently, cGMP effectors include cGMP-dependent protein kinases, such as PKG. The disruption of the NO–cGMP-PKG signalling pathway can therefore explain the development of concentric LV remodelling, increased stiffness of the cardiomyocyte through hypo-phosphorylation of titin, and increased collagen deposition in HFpEF.

Progress has been made in the understanding of the pathophysiology of this condition, and there is increasing emphasis on therapeutic strategies aimed at altering specific signalling pathways. It is critical for future clinical trials to ensure a proper characterization of the phenotype of patients to be tested. Several novel approaches appear promising in pre-clinical or early clinical studies, but need to be tested in properly designed clinical trials.

Acute Heart Failure: What we still need

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Acute heart failure (AHF) is a pandemic as it represents the most common reason for hospital admission in the elderly.

Patients developing AHF have significant symptoms and signs of fluid congestion and an unacceptably high level of morbidity and mortality. Over 20% patients who develop AHF die within 6 months of admission and over 30% are re-admitted to hospital.

Although half of those patients have preserved left ventricular systolic function, almost 10% of cases require inotropic therapy due to severe systolic dysfunction and are often refractory to the existing medical therapies. Despite its prevalence and dire outcome, there has been little progress made in the last 2-3 decades in the medical therapy treatment of AHF. The management of patients is still primarily based on drugs that improve symptoms but have a neutral if not a negative effect on prognosis, while several novel agents tested by clinical trials have failed to provide improvement of mid or long-term outcome.

Advanced heart failure: what can we do

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Heart failure (HF) is pandemic and its prevalence is increasing around the world. While therapeutic advances have greatly improved the clinical course of HF patients, currently available treatment strategies are palliative rather than curative. A consequence of the growing number of HF patients and their longer survival has been a substantial increase in the population with advanced disease. It is estimated that ~10% of HF patients have advanced disease and that this group accounts for up to 30% of HF hospitalizations. Most importantly, advanced HF is associated with a marked reduction in survival with some surveys reporting up to 50% mortality at 1 year.

Not surprisingly, a disproportionate share of healthcare costs are allocated to the care of patients with advanced HF. Given the substantial impact that advanced heart failure has on patients, their families and health care systems, well-defined strategies are needed to help manage this complex and high-risk group of patients.

A variety of clinical characteristics and tests are useful in defining the patient's status and determining whether or not they have advanced HF[1]. These include persistent dyspnea or weakness that limit ability to perform activities of daily living or to walk 1 block without stopping (i.e. NYHA Class IV), repeated HF hospitalizations, progressive deterioration in renal function or reduction in serum sodium levels, cachexia, inability to tolerate ACEIs or beta blockers, and frequent ICD shocks. Risk scores, biomarkers (e.g. natriuretic peptides) and specialized tests (e.g. cardiopulmonary exercise testing) can also be helpful in determining whether or not a patient has advanced HF.

Once standard therapy including drugs and devices have been optimized and the diagnosis of advanced HF is confirmed, a variety of options should be considered.

These include consideration of the following:

- Heart transplantation
- Mechanical circulatory support systems (including ventricular assist devices and the total artificial heart)[2]
- Palliative and hospice care[3]
- Experimental therapies (including gene transfer and stem cell therapy)

Although heart transplantation provides the most definitive cure for advanced HF, the number of donor hearts available limits this option to a relatively small number of patients. Mechanical circulatory support (MCS) has proved to be an effective therapy that can be used either as a bridge to transplant or as destination therapy[2]. With improvement in design, the number of MCS devices being implanted has grown dramatically over the past few years. Persistence of device related infection, bleeding complications and pump thrombosis has stimulated efforts to develop safer and more effective devices.

Palliative care is a medical specialty that focuses on relieving pain and discomfort and providing emotional support for patients and their families[3]. It enhances communication between the healthcare team and the patient and it helps support family members and transitions of care to hospice. There is evidence that palliative care reduces costs and is associated, paradoxically, with an improvement in survival.

In addition to these approaches a variety of new strategies are being assessed including gene transfer and stem cell therapies. Gene transfer for HF involves delivery of a gene to the heart that leads to increased production of molecules that can help correct derangements in cardiac function[4]. A variety of new delivery systems and genetic targets are being developed for gene transfer. However, despite promising early results, none of these have yet been shown to favorably affect outcomes in HF patients[5]. Adequate delivery of genes to the myocardium in the complex biologic milieu of advanced HF remains a major problem that has limited success in this field.

Further research in this and other promising areas is needed in order to provide new effective therapies for the growing population of advanced HF patients.

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