A New Look at the Heart in Heart Failure

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Chairmen:
G. Breithardt, Münster, Germany
F. Zannad, Nancy, France
P. Adragão, Lisbon, Portugal

Abstracts
Dear colleagues,

It is a great pleasure to welcome you to the International Symposium "A New Look at the Heart in Heart Failure" which will present the most recent findings and concepts in the management of heart failure. The survival and prognosis of heart failure patients remain poor and are even worse than of most forms of cancer. The eminent role of peripheral mechanisms underlying the development and progression of heart failure has been identified over the last decade. Pharmacotherapy based on these concepts has significantly improved prognosis.

Very recent interest has concentrated on the performance of the heart itself which, besides its disturbances in signal transduction and contraction of individual myocytes, may show major overall derangements of ventricular performance due to abnormal contraction patterns. Therefore, newer approaches like "cardiac resynchronization therapy" appear promising as adjunctive therapy for selected patients.

Let's take a new look at the heart in heart failure by joining an internationally renowned faculty that will discuss the present day pathophysiology and management of heart failure.

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Pathophysiology of heart failure:
Forget about the heart: The role of peripheral mechanisms

The endocrine response to heart failure

Two sets of neurohormones, with opposing effects, are activated in congestive heart failure (CHF). The vasoconstrictor hormones like catecholamines, angiotensin I, endothelin are antinatriuretic and anti-diuretic and generally, have growth-promoting properties. The vasodilator hormones; (atrial natriuretic peptides CGRP etc) are natriuretic and diuretic and have antimitogenic effects. Noradrenaline, the renin-angiotensin-aldosterone system (RAAS) and the atrial natriuretic peptides have been well studied and, in some circumstances, used for making clinical and therapeutic decisions.

Despite the activation of these systems with opposing actions, it is clear that in CHF the natriuretic and vasodilator effects of atrial natriuretic peptides are clearly overwhelmed by baroreceptor-mediated influences that lead, through activation of the sympathetic and RAAS systems, to vasoconstriction and salt and water retention.

The majority of studies on the neuroendocrine response to CHF have been made in patients already treated with diuretics, digitalis, ACE inhibitors and vasodilators. The data obtained are important for treated patients referred daily to hospital and/or CHF clinics. From the pathophysiological point of view, however, such data are elusive as treatment itself may affect the mechanisms being studied. We therefore, report neurohormone measurements in untreated patients with water retention and reduced renal blood flow.

Recently the role of tissue vs plasma neuroendocrine activation and of neurohumoral vs neurohormonal activation has been recognised and lead to the important concepts that

1. acute myocardial infarction can no longer be considered as a regional disease: The localised activation of the sympathetic and RAAS systems is in fact responsible for the spreading of the injury from the necrotic to the viable myocytes, the so called remodeling process leading to hypertrophy and apoptosis of the myocytes. This may not explain the anti-remodeling effect of the ACE inhibitors and beta-blockers.

2. in severe heart failure tumor necrosis alpha and several cytokines are abnormally elevated and may contribute to the progression of the disease.
The swinging pendulum
Roberto Ferrari (Ferrara, I), Bernard Swynghedauw (Paris, F)
Pathophysicsiology of heart failure:
Forget about the heart: The role of peripheral mechanisms

Peripheral circulation, skeletal muscle and cachexia

For patients with chronic heart failure (CHF) symptoms at rest or during low intensity exercise (like slow walking) are of relevance – cardiac output or left ventricular ejection fraction (LVEF) at rest are not performance limiting. Understanding the periphery is a major step towards understanding shortness of breath and fatigue in CHF patients.

Reduced peripheral blood flow only in part is a consequence of abnormal cardiac output, but more importantly it is a consequence of endothelial dysfunction and dominant vasoconstriction. When tissues are under-perfused ischemia and hypoxia can develop, which can contribute to:

- impaired oxidative metabolism and reduced exercise capacity,
- impaired insulin sensitivity (of the skeletal musculature),
- increased permeability of the gut for bacterial endotoxin,
- increased production of inflammatory cytokines (in any tissue), and
- apoptosis, tissue wasting (in muscle, fat and bone tissue), and general cachexia.

The best marker of poor peripheral perfusion, inflammation and metabolic abnormalities is serum uric acid (independent of kidney function and diuretic dose). It has been discussed that the causal link is via xanthine oxidase derived free oxygen radicals. Recently, we have concluded a placebo controlled, double blind, cross-over study of the effect of the xanthine oxidase inhibitor allopurinol on peripheral blood flow in hyperuricemic CHF patients. Allopurinol therapy for one week improved endothelial function and vasodilator capacity in arms and legs. Also, a marker of free radical production (allantoin) was reduced by allopurinol therapy. The changes in endothelial function directly related to the degree of uric acid reduction, not to the degree of allantoin change. Therefore, uric acid may also have direct damaging effects in CHF patients.

Leg muscle atrophy occurs early in CHF – muscle tissue is replaced by fat tissue and no general weight loss can be found. This loss of musculature may be due to disuse atrophy. The amount of leg musculature very closely relates to peak oxygen consumption in CHF patients. In patients with advanced CHF muscle wasting becomes more severe and more global (e.g. it also affects the arms). Muscle wasting in advanced CHF appears to be due to a hormonal and immunological catabolic / anabolic imbalance. Consequently, anti-inflammatory (i.e. anti-catabolic) or direct pro-anabolic therapies may be indicated in CHF patients with proven metabolic abnormalities.

The latter may be particularly relevant for patients with cardiac cachexia (definition: >6% weight loss in previous 6 months to 3 years). Using this definition we found the prevalence of cardiac cachexia in CHF to be 12 to 14% [SOLVD, ELITE II]. The cumulative incidence of cardiac cachexia in mild to moderate CHF is 10% in 1 year and 26% in 2 years [ELITE II]. Higher age, female sex, NYHA class and high serum uric acid levels (but not body mass index and LVEF) predict future weight loss in CHF. ACE inhibitors (enalapril, ELITE II) and beta blockers (carvedilol, COPERNICUS) can prevent weight loss in CHF patients, but do not reverse cachexia. No specific therapy for patients with cardiac cachexia exists. We have data suggesting that heart transplantation [but not therapy with a left ventricular assist device] can prolong life in patients with cardiac cachexia. New therapeutic trials in CHF should focus on high risk subgroups like on patients with cardiac cachexia.

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Clinical and Experimental Research

Publications
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The swinging pendulum
Roberto Ferrari (Ferrara, I), Bernard Swyngedauw (Paris, F)
Myocardial fibrosis as a result of an exaggerated accumulation of collagens type I and III has been reported in the myocardium of patients with cardiac diseases like ischemic heart disease and hypertensive heart disease. It has been proposed that the excess of myocardial collagen seen in these conditions is the result of both increased collagen synthesis and decreased collagen degradation. Recent experimental and clinical findings suggest that a number of humoral factors as e.g. transforming growth factor, angiotensin II and aldosterone play a critical role in such alterations of cardiac collagen metabolism.

Myocardial fibrosis has been proposed to alter cardiac performance, namely diastolic function. In fact, accumulation of collagen fibers within the myocardium is mainly responsible for an increase in intrinsic myocardial stiffness that may alter left ventricular diastolic properties and the pattern of left ventricular filling. The clinical relevance of myocardial fibrosis is given by two considerations: 1) it has been estimated that 30 to 45% of heart failure patients exhibit diastolic dysfunction with preserved systolic function and 2) studies performed in large populations of patients with congestive heart failure reported that the prognosis for patients with diastolic heart failure was poor.

Thus, management of cardiac patients must focus also on interventions aimed to detect and target myocardial fibrosis. The available data on the use of biochemical and/or echocardiographic methodologies to address excessive accumulation of collagen fibers in the myocardium are promising. On the other hand, preliminary data suggest that the goal of reducing myocardial fibrosis is achievable in patients with cardiac diseases like hypertensive heart disease treated with specific agents namely those drugs interfering with the renin-angiotensin-aldosterone system. Collectively, these findings set the stage for larger trials wherein non-invasive measures and reparative strategies of myocardial fibrosis could prove useful to either prevent or ameliorate heart failure.
The swinging pendulum
Javier Díez (Pamplona, E), Angelo Auricchio (Magdeburg, D)
Pathophysiology of heart failure:
Back to the heart

Dys-synchrony, segmental kinetics, and valvular incompetence

Cardiac contraction normally occurs in a spacially and temporally uniform manner, so that all portions of the wall more-or-less contract synchronously. Dys-synchrony, such as occurs with intraventricular conduction delay, is disadvantageous to the heart for several reasons. First, the heart is inefficient, suffering from reduced ejection despite similar or even increased metabolic costs. Second, there is abnormal regional loading placed on the heart that may alter its function and arrhythmogenicity. Third, global end-systolic volumes are increased raising wall stress to the entire ventricle. Dys-synchrony can also result in abnormal valvular function since papillary muscle contraction no longer occurs with proper timing relative to atrial contraction.

Recent studies in animals and humans have comprehensively demonstrated how dys-synchrony alters regional and global function. Magnetic resonance tagging methods have provided detailed 3-dimensional geometric maps delineating the effects of abnormal activation pattern. In hearts with underlying systolic dysfunction due to cardiomyopathy, dys-synchrony has particularly adverse effects on function since many of the normally available reserve mechanisms are no longer active or are severely compromised.

Re-synchronization by means of left or bi-ventricular pacing has been found to improve the timing of regional contraction, reduce mitral regurgitation, and enhance chamber systolic function. This improvement can be substantial, with nearly 40% increase in cardiac output, and 25-35% elevation in the maximal rate of pressure rise (dp/dtmax). In clinical studies, these effects combine to improve chamber efficiency, enhancing systolic function to levels achievable with 15-25µg/kg/min of dobutamine but with a net decline in myocardial oxygen consumption. Such changes do not require a significant reduction in mitral regurgitation, but might be further amplified in individuals in which this problem is also present.

We have recently developed novel echo-contrast methods to quantify dys-synchrony directly before and after pacing therapy. These data indicate that dys-synchrony is reduced by nearly half with single-point pre-excitation (LV or Bi-v), in association with improved ejection fraction. Furthermore, the level of mechanical dys-synchrony appears to be the most direct predictor of mechanical response to pacing therapy.
The swinging pendulum
Javier Díez (Pamplona, E), Angelo Auricchio (Magdeburg, D)
Pathophysiology of heart failure:
Back to the heart

Atrial and ventricular instability in heart failure

About one half of the deaths in patients with heart failure (HF) are sudden (mostly due to ventricular arrhythmias (VA), Ventricular tachycardias (VT), degenerating in ventricular fibrillation (VF) or immediate VF). Other dysrhythmias in HF include mainly, atrial fibrillation and sustained and non sustained VT.

Many factors predispose to the genesis of dysrhythmias such as ischemia, structural alterations as fibrosis and myocardial scaring, and humoral factors. Reentrant mechanisms, after depolarizations and trigger activities significantly contribute to arrhythmogenesis. Alterations in K currents leading to action potential prolongation and increased dispersion of depolarization play a significant role. In addition alterations in ventricular mechanics produce electrophysiological changes ( electromechanical feedback) that increase vulnerability to VA because the acute stretch of ventricles produces shortening of the action potential and VA after depolarizations.

A number of non invasive methods allow stratification of the risk of VA in HF, unfortunately most of these methods have a high negative predictive value but a lower positive predictive value. The fact that there is no formal marker for the risk of sudden cardiac death is due to the diversity of HF etiologies, the complexity of arrhythmias mechanisms and the difficulties in identifying sudden cardiac death.

Therapy of supraventricular arrhythmias, mainly atrial fibrillation is complex in HF. Class I antiarrhythmic drugs are contraindicated and the other remaining options are class II (especially sotalol) and Class III drugs (especially amiodarone). In some cases, non pharmacological methods such as ablation and pacing (or defibrillation) must be considered.

The treatment of VA is also difficult. A potential role may exist for beta-blocking agents and amiodarone. However the use of ICD is increasingly recommended after the results of several controlled trials. Moreover, recent data suggest that a better survival is observed in patients treated with ICD when low ejection fraction is present. Many studies are currently on-going to determine the value of this therapy modality in prophylactic indications.
Pathophysiology of heart failure: 
Back to the heart

What is wrong with positive inotropic drugs: 
Lessons from basic science and clinical trials

Chronic mechanical overload (CMO) changes genetic expression and modifies myocardial performances to adapt muscle economy to new environmental conditions. The improved hemodynamic status is obtained by reexpressing the foetal programme which slowers the maximum shortening velocity and impairs adrenergic system. In other words, the most characteristic structural changes that occurs in CMO is the expression of a number of genes that finally slowers the cardiac cycle both at rest and during exercising, and the physiological response of the genome to CMO is the development of a permanent negative inotropic state. Then, from a basic point of view, the prescription of inotropes in chronic heart failure, HF, goes against the physiological process of adaption. In addition: (i) any inotropic effect enhances oxygen consumption; (ii) the only inotrope that exists is Ca\(^{2+}\) and every inotropic drugs increase available Ca\(^{2+}\) or renders troponin C more sensitive to Ca\(^{2+}\), and simultaneously Ca\(^{2+}\) has a potent arrhythmogenic effect.

Why, despite these limitations, are inotropes still prescribed and, still in development in drug companies departments? The main, and probably unique, reason is that every inotropic drug has other targets which counterbalance the deleterious effects of the drug. Digitalis augments baroreceptor discharge sensitivity, diuresis, and is a bradycardic agent. Vesnarinone, calcium-sensitizers, phosphodiesterase inhibitors have additional vasodilatory effects. Large trials in patients with sinus rhythm have confirmed such equivocal actions. Every new inotrope that has been fully studied so far has deleterious effects. Digitalis is an exception. PROVED and RADIANCE have concluded that digoxin withdrawal resulted in a significant worsening of symptoms. DIG have concluded that digoxin has not influence in all-cause or CV mortality, nevertheless is significantly reduced the risk of hospitalisation for HF, specially in the advanced stages.

Finally, as the list of drugs (ACE, Beta-blockers and spironolactone) that reduce mortality and morbidity increases, the use of a family of drugs that, from a basic and clinical point of view, is unlikely to modify mortality, will inevitably restrict digitals prescription after that of others whose efficiency is well-documented and discourage further research in a hopeless field.

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The swinging pendulum
Javier Díez (Pamplona, E), Angelo Auricchio (Magdeburg, D)
Pathophysiology of heart failure: The burden of heart failure

Heart failure: Burden to the patient, burden to society

It has almost become a cliche to say that chronic heart failure (CHF) is a major public health problem but that is what it is. CHF combines a high prevalence with a terrible burden of symptoms and morbidity, all of these contributing to a huge societal cost. To compound the problem, patients with CHF live only a short time and, though CHF predominantly affects the elderly, it is still a cause of significant premature loss of life. All in all, a terrible burden to both patients and society.

To give some examples, CHF has a prevalence of 1-3% in the overall population, rising to around 10% in the very elderly. Several studies now show that CHF impairs quality of life more than almost any other chronic medical problem. Patients are willing to trade a high proportion of their remaining life for symptom relief. Numerous reports have documented the ever increasing numbers of hospital admissions due to CHF, the major driver of the cost of this condition. In most countries CHF accounts for around 5% of all medical admissions and is the commonest cause of admission to a medical ward in patients > 65 years of age. The resultant cost of CHF is of the order of 2% of total health care expenditure. There is also a substantial financial imposition on patients and their families. The most striking consequence of CHF is, however, its impact on longevity. A recent population study has shown that patients having a first hospital admission for CHF have a 5 year mortality of 75% (compared to much better survivals for similar patients with almost all forms of cancer or acute myocardial infarction).

Things are improving - a little - but much, much more needs to be done.

References
How do heart failure patients die?

Death is determined by a continuum of events with progressive deterioration among the patients that do not die suddenly. Approximately 90% of heart failure patients die of cardiovascular causes such as progressive heart failure, arrhythmia and ischaemic events. Current treatment strategies prolong life expectancy in the heart failure population, but have done little to alter the mode of death.

Clinicians are familiar with the various patterns of progression in heart failure. The process of remodeling is a central mechanism leading to continuous deterioration whereas myocardial infarction and arrhythmia contribute to the stepwise progression of heart failure and increases the risk of sudden death.

Evaluating the mode of death requires a thorough understanding of the critical events prior to death. Once an ischaemic event occurs, ischaemia remains the dominant reason for subsequent hospitalisation and death. Most heart failure patients experience multiple preterminal events. Precipitating factors such as myocardial infarction or arrhythmia and the presence of comorbidity usually contribute to the clinical picture. Heart failure patients may die from pneumonia or thromboembolic events due to confinement to bed during periods of decompensation and hospitalisation.

The most accurate data on death mode in patients with heart failure is obtained from the large randomised trials. However, several issues complicate the interpretation of these data. The study population is highly selected and the terminology such as “heart failure” and “sudden death” is not based on aetiology. Autopsy has revealed the presence of an acute ischaemic event in approximately 50% of sudden deaths and in 35% of the overall deaths among patients with ischaemic heart failure. The proportion of acute coronary events is related to the aetiology of the heart failure. Another major problem in interpreting the results of the large randomised trials is the divergence in the definitions used to describe mode of death; there are no uniformly accepted guidelines for endpoint committees in their adjudication process.

An accurate description of the mode of death is important in our attempts to elucidate the mechanisms operative in the heterogeneous heart failure population. Clinicians, pathologists, drug regulation agencies and the pharmaceutical industry have different needs in this regard. The establishment of a simple, clinically relevant classification system remains the major challenge if the current confusion is to be resolved.
Management of heart failure: Clinical trials in heart failure: A story full of success and failure

Issues of study design: Patient, endpoint and drug selection

Before designing a new study, the first and most important question is for the clinicians to define their target population i.e. the patients for whom they have a need for improving the management, as well as the therapeutic objective i.e. the expected main clinical benefit. Selection of eligibility criteria, choice of end points and study design will then be tailored to fit the question.

The availability of drugs which reduce mortality in heart failure patients such as ACE inhibitors, beta-blockers etc, makes it more and more difficult to launch new mortality studies with new drugs. If improvement of 10-20% are deemed clinically relevant, several thousands of patients have to be enrolled. Thus, investigators are tempted to look for alternative study designs which would require smaller sample sizes for example using surrogate endpoints.

Often, so-called ‘surrogate’ outcomes are used instead of clinical outcomes, because these are supposed to allow trials to be just as informative but to be of shorter duration and smaller sample size. However, diverging effects on intermediate outcomes and mortality have been observed with several drugs in cardiology. For example, phosphodiesterase inhibitors while effective on symptoms at short term, significantly increased total mortality.

Equivalence trials may seem attractive for the evaluation of new molecules of a pharmaceutical class which has already been shown effective in specific indications like beta-adrenoceptor antagonists and angiotensin converting enzyme inhibitors.

However, before deciding to embark in such a trial design investigators should be aware of the limitations of such an approach. Perhaps the main problem lies in the needed sample size. A clinically relevant and realistic interval of equivalence should be set and a reasonable statistical power given. Thus, again the sample size may as large as for a superiority trial.

Finally, the present availability of several effective treatments on hard endpoint in heart failure patients will lead to new questions about their appropriate combinations and not systematically their addition, with the need for new studies of strategies and more innovative designs.

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Publications
Publications and abstracts. Lectures at National and International Conferences, Congresses and Symposia.
Make the patient feel better and live longer
Mario C. Deng (New York, USA), Edoardo Gronda (Milan, I)
Management of heart failure:
Clinical trials in heart failure: A story full of success and failure

Established evidence-based drug therapy in heart failure

Recent results of well-designed clinical trials established evidence-based medicine in the treatment of congestive heart failure (CHF). Formerly, treatment of CHF was based on diuretic therapy (its long-term benefit is still not proven) and on digitalis which benefits symptoms, but not by decrease in mortality [DIG]. Since then, the paradigms of CHF has shifted from a cardio-centric and hemodynamic view to a systemic neuroendocrine disease. Evidence-based medicine requests that clinical benefits should be evaluated by hard endpoints, i.e. morbidity and mortality. "Soft" intermediate endpoints like hemodynamic improvement are not always associated with quality of life and/or survival benefit.

ACE inhibitor therapy demonstrated benefit in all forms of CHF with systolic dysfunction, whether asymptomatic [SOLVD prevention], symptomatic [SOLVD treatment], severe [CONSENSUS] or in post-myocardial infarction [SAVE, AIRE, TRACE]. Strong evidence established this treatment as the cornerstone of drug management of CHF, as far as it is used at proper optimal dose (ATLAS).

Angiotensin II receptor blockers (ARB) have challenged but not equated ACE inhibitors (ELITE I + II). VALHEFT has shown that the combination of valsartan, ACE inhibitor and/or beta-blocker was not beneficial. CHARMS is currently investigating the effects of candesartan in three ways: vs an ACE inhibitor in patients with preserved left ventricular function, vs placebo in patients intolerant to ACE inhibitors and on top of ACE inhibitors in all other patients. In the meantime, it is advised to continue to use ACE inhibitors as initial therapy for CHF. In patients with documented intolerance to ACE inhibitors (about 10-20% of patients with heart failure), ARBs may be useful as a substitute to block the renin angiotensin aldosterone system (RAAS).

The RALES trial has proven that aldosterone’s deleterious effects may be independent from the stimulation of RAAS which can not be suppressed by ACE inhibitors and/or ARBs and include, beyond Na+ and water retention, cardiac fibrosis and autonomic dysfunction. A new class of drugs arose: Selective Aldosterone Receptor Antagonists (SARAs).

Beta-blocker trials have also challenged “classical pathophysiology” as they have been proven to provide additional quality of life and survival benefit on top of conventional therapy in mild to moderate [CIBIS II, MERIT-HF, Carvedilol trials], as well as in severe stable CHF (COPERNICUS).

New therapeutic avenues have been explored like Endothelin Antagonists (REACH, ENABLE), Dual ACE and NEP Inhibitors (OVERTURE), Vasopressin Antagonists, Adenosine Agonists.

Diastolic heart failure is still being paid little attention (CHARM), and so is advanced-decompensated HF (RUSSLAN, LIDO). Clinical trials also address preventive therapy, especially in hypertension and LV hypertrophy (LIFE), acute MI and HF (EPHESUS, CAPRICORN, VALIANT). Negative trials with Inotropes, PDE inhibitors (VEST, PRIME), Antiadrenergics (MOXCON), Xamoterol, Vasodilators (FIRST), Flosequinan (VEHEFT II), Calcium antagonists (PRAZE) and more recently TNF-alpha-receptor antagonists (RECOVER, RENAISSANCE) contributed to progress as positive ones.

Finally, research is needed to hasten the implementation of trial results into clinical practice. Education and implementation programs should be designed in order to fight ignorance, incredulity and inaction, the three main reasons of doctors’ non-compliance with guidelines.

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Clinical and Experimental Research
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Publications
Make the patient feel better and live longer
Mario C. Deng (New York, USA), Edoardo Gronda (Milan, I)
Management of heart failure: 
Emerging therapies - Drugs and genes

New drugs for heart failure: What to expect from the ongoing trials?

Current guidelines suggest that all patients with chronic heart failure (CHF) should be treated with ACE-inhibitors and betablockers and that use of spironolactone should be limited to patients with more severe CHF.

Recently VALHEFT showed that Valsartan, an Angiotensin Receptor Blocker (ARB), reduces morbidity and mortality in patients with CHF treated with one of the two ACE-inhibitors or betablockers, or with none of them. Adding Valsartan to patients treated with both drugs did not provide any further beneficial effect. The CHARM trial is testing the effect of candesartan in three different populations of patients with CHF:

• patients with depressed EF, already on treatment with ACE-inhibitors (added CHARM);
• patients with depressed EF, intolerant to ACE-inhibitors (alternative CHARM);
• patients with preserved EF, treated or not with ACE-inhibitors (preserved CHARM).

The "added CHARM" and the "alternative CHARM" will be able to confirm the VALHEFT results; in particular, "alternative CHARM", differently from VALHEFT has the adequate size to define the role of ARBs in patients who can not tolerate ACE-inhibitors. "Preserved CHARM" is focusing the attention on patients never tested in preceding studies.

Other two lines of research are ongoing in patients with CHF, testing the effects of new drugs interacting with the neurohormonal system: neutral endopeptidase inhibitors (NEP) and endothelin receptor antagonists (ERA).

In patients with CHF, the influence of vasoconstrictor systems is increased while the role of vasodilator system is diminished. Patients with CHF can be rationally managed either by decreasing the activation of endogenous vasoconstrictor systems (i.e. by inhibition of ACE) or by inhibition of the breakdown of vasodilator factors (i.e. by inhibition of NEP) or preferably by exerting both actions. Omapatrilat is a new compound able to exert both actions, being a NEP inhibitor with ACE-inhibition activity. The OVERTURE trial is assessing the benefit/risk profile of this compound in patients with symptomatic CHF.

Finally, ERAs are now under investigation both in patients with acute heart failure than in the chronic treatment of those with CHF.

A comprehensive framework of the effects of all these compounds will be available in the next couple of years.
Make the patient feel better and live longer
Mario C. Deng (New York, USA), Edoardo Gronda (Milan, I)
Management of heart failure:
Emerging therapies - Drugs and genes

Cardiac reparation: Fixing the heart with genes, cells and new vessels

Angiogenesis, gene therapy and cell-based interventions are among the newest treatment modalities which have been proposed to improve the outcome of patients with ischemic heart disease and, more specifically, heart failure. The complexity of gene dysregulation involved in heart failure casts some doubt about the clinical efficacy of single targeted gene therapies. However, an important spin-off of progress in genetics should be a better understanding of the molecular mechanisms of heart failure and the subsequent design of appropriately targeted drug interventions.

Both experimental and clinical data have now established the ability of angiogenic growth factors to stimulate the development of new blood supply of functional significance and, although several issues still need to be addressed, therapeutic angiogenesis yet stands as a promising means of ameliorating ischemic symptoms. There is also a bulk of experimental evidence that implantation of contractile cells into fibrous post-infarction scars can allow them to regain some functionality. Although preliminary clinical data are still scanty, they tend to support this concept and raise serious hopes that cellular transplantation can find its place among strategies designed to ameliorate heart failure. Indeed, angiogenesis, gene therapy and cell-based interventions should be viewed as complementary approaches whose combination might improve the still dismal outlook of patients with severe ischemic heart disease.

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Make the patient feel better and live longer
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Cardiac resynchronization therapy has been recently proposed as a supplemental treatment of drug-refractory congestive heart failure.

This new therapy aims to improve quality of life and exercise capacity, in patients selected on the basis of dilated cardiomyopathy and cardiac asynchrony. In this particular heart failure population, the expected benefits depend on careful placement of the leads, particularly that responsible for left ventricular pacing. In practice, the choice of optimal left ventricular lead placement associated with the best hemodynamic changes is often an individual compromise taking into account the highly variable coronary sinus anatomy. Prior to the implant, echocardiography and more precisely tissue Doppler imaging investigation, may be helpful to identify the ideal left ventricular pacing site, based on the late activated segmental contraction, which in most of the cases turns out to be the mid lateral wall.

Complications observed during left ventricular lead implantation remain low, consisting mainly of phrenic nerve stimulation and coronary sinus perforation in < 1%, and should further decrease with the use of new instrumentation dedicated to the procedure.
Make the patient feel better and live longer
Helmut Klein (Magdeburg, D), Pedro Adragão (Lisbon, P)
Management of heart failure: Emerging therapies: Cardiac resynchronisation therapy (CRT)

Technical aspects of cardiac resynchronisation therapy (I)

Biventricular pacing allows significant haemodynamic improvement in most patients with chronic heart failure (CHF) and intraventricular conduction delay, especially left bundle branch block. Growing experiences indicate that the pacing site and the atrioventricular/intraventricular delay seem to be crucial to obtain short-term and long-term improvement of left ventricular function, although prospective evaluations are still lacking.

In patients with left bundle-branch block, the mid-lateral and mid-posterolateral wall of the left ventricle have been identified as the region where the latest activation occurs. Therefore, the lateral and posterolateral veins are supposed to be the most effective pacing sites. Prospective evaluation could provide information to draw conclusion about the efficacy of different pacing sites. On the other hand, further improvement in lead technology are expected to facilitate transvenous access and stable positioning at different areas of the left ventricle.

The importance of an appropriately timed atrial contraction in ventricular loading is well established, since the prolongation of AV interval, that commonly occurs in CHF patients, provokes a reduction of the LV active filling, a shortening of the passive diastolic filling and the onset of a ventriculo-atrial gradient thus initiating diastolic mitral regurgitation. AV delay optimization can limit these deleterious haemodynamic effects, although the influence of the AV delay seems to be less important than the pacing site. It is commonly accepted that the optimal AV delay is the shortest AV delay, which allows a complete ventricular filling, and is usually determined under echocardiographic guidance. At rest, a mean AV delay close to 100-120 msec, with significant interindividual variation, has been determined as the optimal interval for the majority of patients with atrio-biventricular pacing; increasing rates at exercise and VDD modality may require shorter atrioventricular delays. Finally, a short AV interval can also reduce mitral valve regurgitation.

New generation biventricular devices are equipped with two separated channels for RV and LV lead, thus allowing to vary the interventricular paced-timing (VV interval) and to select different energy levels. The opportunity to anticipate the LV activation and to obtain a “predominant left fusion beat” can provide relevant haemodynamic benefits even from a non-optimal LV site. Moreover, the management of technical problems, such as the presence of diaphragmatic stimulation is facilitated by the regulation of RV and LV energy-output from separated channels.

In conclusion, growing opportunities to choose among many different leads and devices allow us really to “ tailor” biventricular stimulation in every heart failure patient, thus providing increasing chances to obtain a desirable clinical outcome.

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Make the patient feel better and live longer
Helmut Klein (Magdeburg, D), Pedro Adragão (Lisbon, P)

Technical aspects of cardiac resynchronisation therapy (II)

Biventricular pacing has recently been proposed as an adjuvant therapy to optimal medical treatment in patients with drug-refractory heart failure due to chronic left ventricular (LV) systolic dysfunction and intraventricular conduction delay. This new technique requires pacing the LV effectively, permanently and safely.

Our experience (August 1994 - February 2000) has demonstrated the technical feasibility, with acceptable pacing thresholds and long-term results of transvenous LV pacing with the lead inserted into a tributary vein of the coronary sinus. LV lead implantation was attempted in 116 patients (mean age 67 years, mean NYHA class 3±0.5, mean LV ejection fraction 22±6%, mean QRS duration 185±26ms). The overall implantation success rate was 88% (n=102), with a “learning curve”: a progressive increase from 61% in the early experience to 98% in the last year. The rate of acute and late LV lead dislodgement decreased from 30% in the early experience to 11% since 1999. The rate of implantation failure and of lead-related problems has considerably decreased with the growing experience and the availability of new and specific leads and tools, such as “over the wire” leads.

Positioning of the RV and LV leads is often crucial to achieving permanent and effective resynchronisation, and the optimal configuration is somewhat difficult to predict before implantation and may be compromised by the coronary sinus anatomy. So, programming pacing polarity and pulse amplitude independently on each ventricular port or programming the intraventricular delay may be helpful in the postoperative period to optimise therapy delivery. In some patients, especially those with permanent atrial fibrillation and intrinsic AV conduction, permanent biventricular capture may require recently available algorithms to avoid spontaneous or fusion beats.

Safety is obviously a key point for the future of this new therapeutic modality. Experience to date has shown low rates of coronary sinus thrombosis (and when necessary, successful explantation without adverse events) and low incidence of pro-arrhythmic effects and a few suspected sudden deaths. Conversely, some preliminary data coming from the early experience suggest that cardiac resynchronisation may have a preventive effect on ventricular arrhythmias.

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Clinical and Experimental Research

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Management of heart failure: Emerging therapies: Cardiac resynchronisation therapy (CRT)

ICDs with or without CRT: Multiple therapies in a single device

Sudden cardiac death is a major threat to patients with advanced heart failure accounting for about 50% of all deaths in this patient population. It is undoubted that the ICD is highly effective in reducing mortality from sudden death and recent data suggest that the benefit is more substantial in patients with severely depressed left ventricular function. Many of the patients with impaired left ventricular function suffer from some degree of heart failure and 20-40% of heart failure patients have ventricular conduction disturbance, depending on the underlying disease. It is estimated that 10% of heart failure patients may benefit from cardiac resynchronization therapy (CRT).  

In one retrospective analysis of an unselected ICD population 7-13% of patients were considered suitable for additional CRT, depending on the criteria used. However, the question frequently arises which patient with a CRT device needs ICD backup. Some early data suggest a reduction of ventricular tachyarrhythmias with CRT, which may be explained by a more efficient pump action leading to a reduction in sympathetic tone triggering arrhythmias.

While there is presently no indication for an ICD in all patients with advanced heart failure suitable for CRT, studies evaluating the benefit of the ICD in this setting are currently ongoing. One trial, the COMPANION trial, performed in the USA, compares the influence of best conventional (medical) treatment to CRT with or without ICD backup on mortality. Another trial, the PACMAN study, performed in Europe, investigates the influence of CRT on functional capacity, with the ICD implanted as a backup when indicated by currently accepted guidelines. The results of these studies may help to clarify the role of CRT in severe heart failure in conjunction with ICD backup.

References


Make the patient feel better and live longer
Helmut Klein (Magdeburg, D), Pedro Adragão (Lisbon, P)
Management of heart failure: Emerging therapies: Cardiac resynchronisation therapy (CRT)

Results of the first decade of CRT

Despite recent advances in pharmacological therapy as well as in interventional cardiology, heart failure (HF) remains a disabling disease with high morbidity and mortality. It is therefore clear that new therapeutic options are needed for treatment of HF. Ventricular dysfunction and ventricular dilatation, a hallmark of HF, are frequently associated with atrial and ventricular conduction delays. By its nature, pharmacological treatment is unable to correct conduction delays and the negative mechanical effects on ventricular function generated by such conduction disturbances. In contrast, cardiac resynchronisation therapy (CRT) has been successfully used in patients with HF and ventricular conduction delay. 3-D electro-anatomical mapping has shown that CRT restores: 1) synchronous activation of the left ventricle, by removing the mechanical delay between the septum and the left free lateral wall; 2) resynchronizes the timing of activation of both right and left ventricle; 3) optimizes the atrioventricular filling. These effects result in major improvements of stroke volume, ventricular contractility, and reduction of diastolic and systolic mitral insufficiency. Cardiac efficiency and myocardial oxygen consumption has also been improved by CRT, and always to a larger extent when compared with inotropic drugs.

Three small, but randomized trials [PATH-CHF, MUSTIC, and MIRACLE] have reported similar short- and mid-term improvements of functional class, exercise capacity, and quality of life of patients with HF, chronically paced with resynchronization devices. The significant symptomatic benefits have also been confirmed in a large European registry – the CONTAK registry, including more than 1000 patients followed up to 6 months after CRT. Moreover, a direct reset of the neurohumoral status, assessed by norepinephrine plasma level, BNP and cytokines, has been shown to occur shortly after commencing CRT. Recordings of the resting heart rate, heart rate variability and heart rate profile during exercise testing have also shown changes compatible with increases in parasympathetic activity and reductions in sympathetic activity. CRT has also been shown to initiate a reverse remodeling process with a significant reduction of the ventricular volume at 6 months after implantation. Finally, all trials - PATH-CHF, MUSTIC, MIRACLE and CONTAK-CD - have consistently reported lower hospitalization rates and number of deaths when CRT has been used. Two major ongoing trials, COMPANION and CARE-HF, are currently investigating whether CRT reduces mortality and morbidity.

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Management of heart failure:
Emerging therapies: Cardiac resynchronisation therapy (CRT)

Going into the next decade:
Morbidity/mortality trials in the field of CRT

Cardiac resynchronisation therapy has evolved as a new therapeutic option for patients with left ventricular dysfunction and congestive heart failure. In selected patients with broad QRS complexes presenting a left bundle branch block pattern, bi-ventricular pacing leads to improvement in left ventricular performance, especially in the presence of preexisting marked asynchrony of left ventricular contraction. Synchronous activation of the left ventricle by bi-ventricular pacing leads to acute improvements in performance that has been shown to be sustained in the great majority of cases and that is accompanied by improvement in symptoms, increase in walking distance, and less need for hospitalisations.

In the era of evidence-based medicine, decision making concentrates on hard end points like mortality which, for good reasons, has almost become a dogma for randomised therapeutic trials. However, the aim of medicine is not only to prolong life but, first of all, to reduce suffering from disease, i.e. in the setting of heart failure to improve exercise capacity and reduce symptoms. This end has now been well documented by several studies that used cardiac resynchronisation therapy in patients already on optimal drug therapy like the PATH-CHF trial or MUSTIC.

The specificity of cardiac resynchronisation therapy is evidenced by its lack of effect in patients with relatively minor increases in QRS width despite the presence of a left bundle branch block pattern. The degree of asynchrony of left ventricular contraction and the amount of myocardial scarring (e.g., previous myocardial infarction) are important parameters that determine the response rate. Echocardiographic studies have identified parameters of left ventricular contraction that reflect the mechanisms underlying the improvement in hemodynamics (e.g., reduction in left ventricular volume or acute improvement in atrioventricular plane displacement).

The improvements in hemodynamics are not due to a positive inotropic effect of pacing but by elimination of an unsynchronised and, thus, energy wasting contraction pattern. Indeed, it has even been demonstrated that cardiac resynchronisation therapy even reduces (instead of increasing) left ventricular energy requirements.

Overall, there is now sufficient evidence that cardiac resynchronisation therapy even reduces (instead of increasing) left ventricular energy requirements.

Going into the next decade:
Morbidity/mortality trials in the field of CRT

Cardiac resynchronisation therapy has evolved as a new therapeutic option for patients with left ventricular dysfunction and congestive heart failure. In selected patients with broad QRS complexes presenting a left bundle branch block pattern, bi-ventricular pacing leads to improvement in left ventricular performance, especially in the presence of preexisting marked asynchrony of left ventricular contraction. Synchronous activation of the left ventricle by bi-ventricular pacing leads to acute improvements in performance that has been shown to be sustained in the great majority of cases and that is accompanied by improvement in symptoms, increase in walking distance, and less need for hospitalisations.

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Overall, there is now sufficient evidence that cardiac resynchronisation therapy has beneficial effects on left ventricular performance that translates into benefits for the patients. Still, its potential to prolong life, needs further evaluation. As heart failure most often coexists with an increased risk of ventricular arrhythmias and an increased prevalence of atrial fibrillation, the relative role of different treatment options that could be incorporated into a single device (i.e. biventricular pacing, ventricular defibrillation and atrial preventive or overdrive pacing) needs to be determined. Therefore, mortality trials that address the effect of cardiac resynchronisation therapy on total mortality but also on arrhythmic mortality and mortality from heart failure, are needed to place this new mode of therapy into the framework of all available therapeutic options.
Make the patient feel better and live longer
Helmut Klein (Magdeburg, D), Pedro Adragão (Lisbon, P)
How to tailor therapy to the individual patient:

Polypharmacy in the treatment of chronic heart failure: ACE-inhibitors, beta-blockers and other drugs

Chronic heart failure (CHF) is an increasing world-wide problem, with significant morbidity and mortality. In the last decades, several agents have been developed that decrease the progression of this syndrome, and large-scale clinical trials have proven the applicability and efficacy of these drugs. Especially, the use of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers has been proven beneficial, resulting in a decline of symptoms and a decrease of various “hard” cardiovascular end-points, including mortality. These drugs are generally combined with “standard” treatment of CHF, consisting of diuretics, with or without digoxin.

The patients that were eligible for these trials usually were highly selected, and only stable, younger patients without additional co-morbidity were included. Indeed, the results obtained from these trials cannot be extrapolated automatically to all patients with CHF. In general practice, a different population is usually observed than that reported in the trials, consisting of more elderly and female patients, who may also be taking a variety of other drugs. Not all these patients will therefore benefit similarly from these drug regimens, since efficacy and safety may vary, especially in the elderly. Moreover, in CHF patients with more advanced disease, the physician may face difficulties to titrate ACE-inhibitors and beta-blockers to optimal doses, if tolerated at all. As a result, one often has to choose between one agent or the other.

In recent years a large number of new drugs has been developed for the treatment of CHF, but in most of these drugs only short-term benefit could be shown, and as a result, the majority has not gained a place in CHF. In many of these so-called “negative” drug trials, pharmacological interactions played a crucial role. This may be particularly relevant in the elderly, who may react differently to drugs, and develop side-effects in response to polypharmacy.

This article will deal with aspects of optimal drug treatment in patients with CHF, and focus on the possible problems that can occur in combining the various drugs. A hierarchy in drugs is proposed, in which the starting point is the assumption of a central role for early and widespread use of ACE-inhibitors and beta-blockers.
“Ready to wear” or “tailor-made” therapy?
Jose Luis López Sendón (Madrid, E), Luc Piérard (Liege, B)
How to tailor therapy to the individual patient:

**Cardiac resynchronisation therapy: When and for whom?**

Dilated cardiomyopathy, ischaemic or idiopathic, is often associated with electrical conduction disturbances. Based on observational studies which focused on modification of atrioventricular (AV) timing the current ACC/AHA Guidelines for pacemaker implantation recommend dual chamber (DDD) pacing with a short AV delay for patients with symptomatic, drug refractory dilated cardiomyopathy with a prolonged PR interval when acute haemodynamic studies have demonstrated a haemodynamic benefit of pacing.

More recently cardiac resynchronisation therapy (CRT) by left or biventricular stimulation has evolved as a new therapy for patients with advanced heart failure (HF) and intraventricular conduction defects, particularly left bundle branch block (LBBB). The acute haemodynamic benefit of left ventricular (LV) based pacing is almost invariably superior to standard DDD pacing, although not all patients show improvement. Chronic CRT has been investigated in prospective trials but long term follow up data to inform accurate patient identification, timing of implantation and the effect of CRT on clinical outcomes is still limited; prediction of response to CRT remains poorly characterised.

Current data suggest that CRT may benefit patients with ischaemic or idiopathic dilated cardiomyopathy, in NYHA Class III/IV despite optimal medical therapy who display wide QRS complexes of LBBB type (≥150 msec) and LV systolic dysfunction (ejection fraction <35%). Echocardiographic LV diastolic diameter <70mm and LVDP/dt max ≤700mmHg/sec may be additional predictors of response. Optimisation of AV timing is mandatory to maximise benefit. Non responders may be predicted by a normal QRS width or RBBB-type conduction delay, extreme LV dilation, a low value of pre-implant aortic velocity-time integral with significant mitral regurgitation regardless of QRS width, and failure to respond to CRT by 6 months post-implant.

CRT can improve symptoms, exercise tolerance and quality of life in severe HF. Early data suggest CRT may reduce the frequency of ventricular tachy-arrhythmias in HF patients with implanted defibrillators, may provide a ‘bridge-to-transplant’, and may improve prognosis.

New technology promises sophisticated device-based monitoring of chronic CRT therapy. Large, prospective randomized controlled trials are required to evaluate the precise role of CRT in HF, how to optimize pacing site and programming and to refine the identification of patients who will gain most benefit.

**References**


“Ready to wear” or “tailor-made” therapy?
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How to tailor therapy to the individual patient:

End-stage heart failure: Which options?

The syndrome of heart failure has assumed epidemic proportions worldwide. For advanced heart failure, novel medical therapies including comprehensive neurohormonal blockers targeting the renin-angiotensin and adrenergic system, and cardiac surgical interventions improving pump function, ischemia, and arrhythmias, have become available during the last decades.

Their introduction into medical practice requires continuous evaluation of evidence according to established criteria, distinguishing between experimental procedures, expert consensus, or evidence by one or more large randomized clinical trials. While the role of angiotensin-converting enzyme inhibitors, beta-blockers, and spironolactone in advanced heart failure therapy has been established in randomized clinical trials, observational data support the use of cardiac surgical interventions including revascularization, mitral valve repair, left ventricular geometry restoration, mechanical circulatory support devices, antiarrhythmic devices and cardiac transplantation. The potential of gene therapy, cell transplantation, and xenotransplantation is being explored at the experimental level.

In order to effectively translate evidence-based management protocols into practice, comprehensive heart failure centers with expertise in all aspects of medical and surgical advanced heart failure care continue to evolve worldwide.
“Ready to wear” or “tailor-made” therapy?
Jose Luis López Sendón (Madrid, E), Luc Piérard (Liege, B)
A New Look at the Heart in Heart Failure

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