The new frontiers of therapy in congestive heart failure: brainstorming among internists, cardiologists and interventional electrophysiologists

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CARDIAC REMODELING: A STORY OF CELLULAR LIFE (HYPERTROPHY) AND DEATH (APOPTOSIS)

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In post-infarct, an early phase of remodeling can be identified within the first hours after infarction in the site of necrosis; this results in scar formation and ventricular expansion at various levels and it must be actually considered a positive event.

There is also a late phase of remodeling in non-necrotic remote zones that results in further dilation and ventricular dysfunction. This must be actually considered a negative event since it influences the progression to heart failure.

The late remodeling is characterized by the presence of both hypertrophic cells – as a tentative of repair – and apoptotic cells within fibrotic zones.

Stretch of vital myocytes – due to morphological modifications in close-by necrotic myocytes – causes release of hormones and cytokines that induce changes at the gene level with re-expression of the embryonic phenotype thus affecting the death-life cycle.

Introduction

The pathophysiology of heart failure is changing. Several years ago, the attention was focused on "the central role of the periphery" mainly looking at neuroendocrine alterations, reduced oxygen and flow to skeletal muscles, physical deconditioning due to reduced activity, cachexia due to malnutrition, and altered metabolism of skeletal muscle cells. Today, there is a re-evaluation of the role of the "center": we speak of "the central role of the center" in the progression to heart failure.

Progression towards failure

After a *primum movens* at the cardiac level, which involves several causes for the disease, the progression towards the real syndrome goes through a series of alterations at different levels and organs. The first modifications occur at the molecular level and determine on the one hand hypertrophy and/or apoptosis of myocytes and, on the other hand, proliferation of extracellular matrix. All these changes are characterized by a trend of myocytes to return to the embryonic phenotype, with expression of genes and proteins typical of the fetal life. The final result is a modification of the energy used during contraction and a lower number of vital myocytes due to apoptosis and increased fibrosis. Some authors believe that the aim of this phenomenon is self-support or an adaptive response, but these interpretations are not free from criticisms.

With progression of these alterations, there is also a progression from the "cellular" to the "organ" dimension – the so-called "cardiac remodeling" – which leads to cardiac malfunctioning with inevitable reduction of pump function and blood pressure. This phenomenon represents the signal for the start of a series of impairments typically characterized by a neuroendocrine response with the ultimate target to maintain blood pressure. The acknowledgement for a positive finality of the neuroendocrine response is no longer acceptable especially after the clinical results with new drugs, such as ACE-inhibitors, beta-blockers, and aldosterone inhibitors that contrast the effects of the renin-angiotensin-aldosterone and sympathetic systems, typically activated in heart failure. Neuroendocrine alterations influence not only the periphery but also the center, i.e. the heart itself.

Once the systemic balance is reached, cardiac failure involves all the other organs of the body: peripheral muscles, kidneys, lungs, endothelium, brain, etc., and gains the "sad" recognition of "syndrome".

But, as it usualyy happens, schematizations are too rigid and do not correspond to reality, neither biological nor pathological, where rigidity, by definition, is not "accepted", nor "violated".

Molecular remodeling

Molecular remodeling may be included in a wide perspective that involves life/death cycle. Life is part of a program, and, therefore, also death can be programmed, i.e. apoptosis. The two aspects – *life* and *death* – are complementary, the first not existing without the second. This concept may appear paradoxical in a social context but it is quite common in a biological context, where "cycles" are essential and in *continuum*, as seasons progress over the years. In the organism, the different types of cells follow their cycles of life and death: hemopoietic system, skin cells, endothelial cells, etc.

There are established "rules" for this cycle: a lymphocyte lives for 8 hours, it dies regularly and constantly by apoptosis; a red cell dies after 12 days, and so on. This aspect is not only fascinating from the intellectual point of view but it is also full of significance in the perspective of developing new techniques in molecular biology to intervene at the gene level, and therefore in view of the possibility of influencing the life/death cycle[1].

We must keep in mind that adult myocytes are extremely specialized cells: they do not replicate and therefore they do not show a close cycle of life and death (Fig. 1). This is not true for embryonic myocytes that, still growing, possess a cycle of life and death and therefore they replicate and die by apoptosis (Fig. 2).

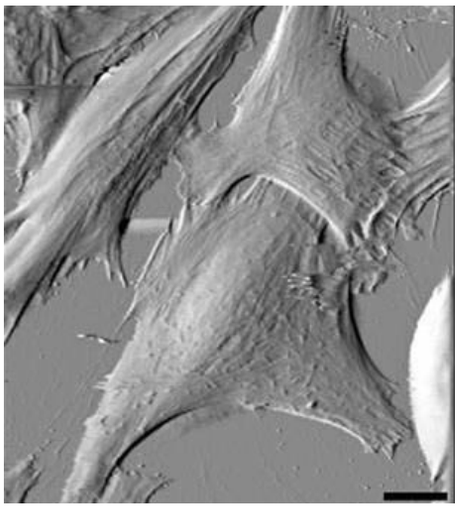

Figure 1. *Adult myocyte is a terminal cell, it does not have a cycle of life and death, it does not normally duplicate and does not undergo apoptosis. It encounters necrosis.*

From a "dynamic" point of view, the passage from fetal to neonatal and adult lives, considering the important function of ventricles – in particular the left one – leads to a series of phenomena similar to those observed in compensatory hypertrophy.

After birth, DNA synthesis immediately diminishes, as does cellular mitosis, suggesting that in adult myocytes the phenomenon of cellular growth may develop "predominantly" via hypertrophy. Please note that we said "predominantly", not "exclusively"! The new acquisitions in basic cardiology, preceded by human histology, indicate that a cellular mitotic activity still exists in myocytes after birth. However, the true significance of a limited mitosis observed in bioptic samples of failing patients is not known yet, and, in fact, growth stimuli lead to hypertrophy in adult myocytes.

Another phenomenon that characterizes the passage from fetal to adult life is the disappearance of atrial natriuretic peptide granules and other contractile proteins from the ventricles[2-7].

Determinants of embryonic phenotype

One important question at this time is certainly "How and by which mechanisms do genetic pathways of embryonic life reactivate in pathological conditions?". The answer is not simple at all, but it goes through two concepts recently developed in cellular physiology. These are a) myocytes may produce autonomously, although at a low level, endocrine agents, such as hormones and cytokines that act in an autocrine/paracrine way on surrounding myocytes, b) myocytes represent the sensor to couple a mechanic stimulus to a molecular biological event, such as the release of endocrine agents.

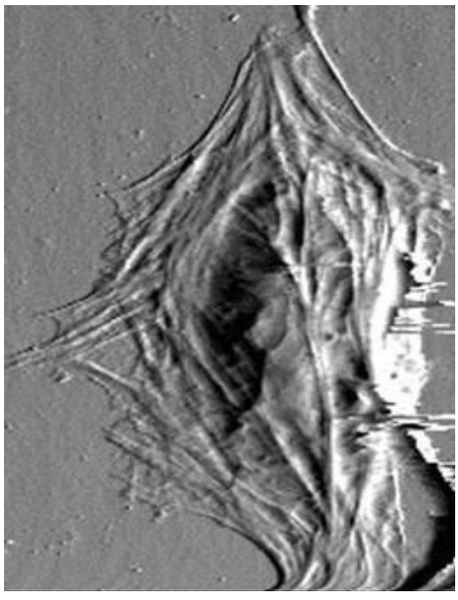

Figure 2. *The genetic program of embryonic myocyte foresees the life/death cycle, the myocyte duplicates and dies of apoptosis.*

Let us see what happens at molecular levels after an acute myocardial infarction. An intracoronary thrombus is an extraordinary event and certainly not welcome to the myocytes that are deprived of oxygen, essential for energy production and therefore for their life. Myocytes die of necrosis: an accidental death with immediate release of intracellular compounds that determine inflammation. In the meantime, myocytes increase their intracellular calcium level and myofilaments respond with hypercontraction: myocytes shrink. From the histopathological point of view, it is not astonishing to find that necrosis is characterized by bands of hypercontraction and cytomyolysis. At the clinical level, these alterations result in a reduction of ventricular compliance and/or increase in end-diastolic ventricular pressure.

This series of events alters the geometry of myocytes quite in advance with respect to that of ventricles, as shown in figure 3. Myocytes, from the typical rod shape, shrink into a spherical shape with hypercontracted myofilaments, typical of irreversible necrosis (Fig. 4). This happens in a few seconds; it causes release of intracellular compounds and determines stretch of surrounding myocytes that are not necessarily necrotic. Stretch of sarcolemma in viable myocytes (mechanical stimulus) causes release of hormones and cytokines (molecular biological event) which, through a cascade of autocrine and/or paracrine mechanisms, determine nuclear modifications responsible for re-expression of embryonic proteins.

This mechanism perpetuates itself by involving firstly vital myocytes surrounding the necrotic zone, and then remote myocytes. It constitutes the molecular language through which the myocytes communicate among themselves and react, in a stereotyped manner, with the re-programming of embryonic genes to a stressful event such as necrosis.

Doing so, the damage induced by myocardial infarction is not limited to the ischemic and/or necrotic zone, but it spreads also to the non-ischemic and viable areas of the ventricle producing the so-called late remodeling.

Phases of post-infarct remodeling

From the clinical point of view, it is important to specify the subsequent phases of post-infarct remodeling: an early and a late phase.

The *early* phase starts in the infarct zone and is represented, at the molecular level, by necrosis itself and subsequent inflammation with fibroblasts activation and scar formation. The ventricular wall grows thinner, it becomes rigid, it looses the capacity of contracting and it offers less resistance to the endoventricular pressure. The ventricle may dilate and post-infarct aneurysm may represent the ultimate consequence of a series of events. In the clinical setting, early remodeling depends on the entity, degree and extension of myocardial injury. Scar formation is however a positive and a repairing event. Early remodeling is to be considered a cardioprotective event, not a phenomenon to contrast but, on the contrary, to favor.

The other phase of remodeling is the *late* one that, in some patients, may involve still viable remote zones of the ventricle. Late remodeling is clinically characterized by increasing ventricular dilation, alteration of geometry of the chamber and progression to cardiac failure. Late remodeling does not occur in all patients, but only in a percentage ranging between 30 to 50%. It is generally associated with large infarcts that involve the anterior wall of the left ventricle, but it may also represent a consequence of right infarcts. Late remodeling is not considered a positive event. Late remodeling, and consequent ventricular dilation, may either develop just after myocardial necrosis, or much later, in terms of months or years, either progressively or with peaks of acute events with-

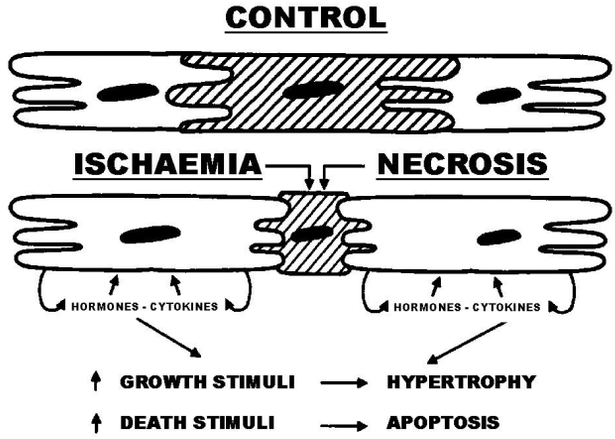

Figure 4. *Schematization of the consequences of geometry alteration in viable myocytes following necrosis of surrounding myocytes.*

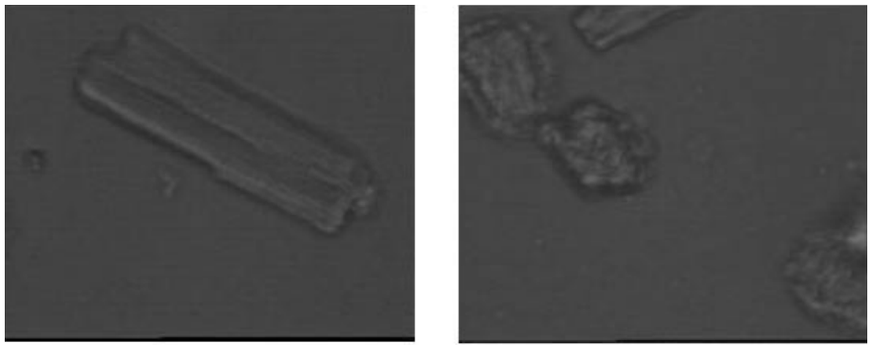

Figure 3. *Viable* (left) *and dead* (right) *cardiac myocytes isolated from an adult rat heart.*

in periods of relative stability. At the moment, besides infarct size, we do not have any markers to tell us which patients with myocardial infarction will develop cardiac remodeling. The process of remodeling is also influenced by genetic and molecular factors, and by the presence of recurrent ischemia and hypertension. This second and late phase of remodeling affects the progression towards cardiac failure, and, therefore, must be prevented and treated. Some classes of drugs have been found to be useful, e.g. ACE-inhibitors, beta-blockers, and aldosterone inhibitors. Reperfusion of ischemic zones still viable and resynchronization of ventricular contraction indicate interesting ways of non-pharmacological treatment of remodeling. Cellular transplantation by stem cells also represents the future.

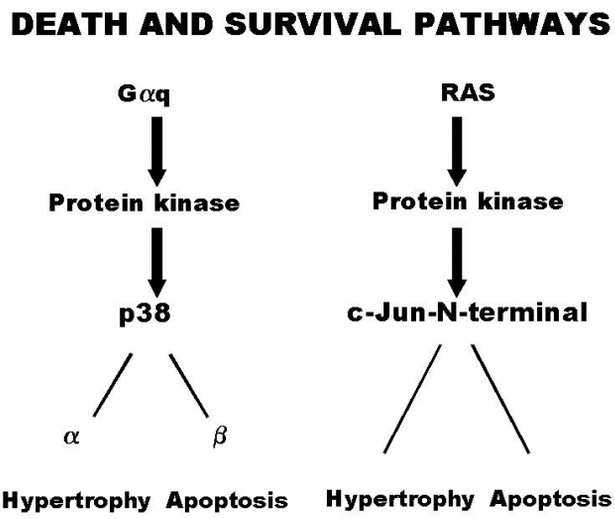

Figure 5. *Cellular mediators involved in apoptosis and hypertrophy.*

Cardiac failure as a discrepancy between hypertrophy and apoptosis: two opposite phenomena deriving from the same signal

Myocytes – as well as all the other cells in the organism – show complex but yet undisclosed systems that regulate the cell destiny: the so-called "death and survival pathways". These molecular pathways are activated during the embryonic life, they remain quiescent during the adult life, and are activated under pathological conditions, such as the post-infarct late remodeling, or remodeling activated by pressure overload (hypertension or aortic stenosis) or volume overload (valve failure). Activation of one of these pathways may cause either apoptosis or, by intrinsic reasons due to the fact that the myocyte is a terminal cell, hypertrophy. Surprisingly, activation of a cascade of intracellular mediators may stimulate and/or inhibit one or the other pathway (Fig. 5). The discovery of these pathways is relatively recent and opens to new pathophysiological perspectives, still unknown in the cardiology setting but yet already studied in immunology and oncology.

The progressive reduction of contractility that characterizes cardiac failure could be the consequence of alteration of one or more specific mediators, released at the local level resulting in an intracellular physiological activation of both these pathways. The final result depends on the balance between apoptosis and hypertrophy, such that a limited degree of hypertrophy with no excess apoptosis will lead to a compensatory and beneficial state for the myocardium, whereas an excess of growth or death can be extremely damaging and contributing to the progression to cardiac failure. In analogy with carcinogenesis, cardiac failure can be seen as a progressive, complex and multifactorial process that involves physiological and molecular mediators that activate, induce, inhibit or suppress the two fundamental pathways of cell destiny: life and death.

A good example of such effects comes from oncology: approximately 15% of patients with breast cancer treated with herceptin – an antibody that binds to ErbB2 and therefore induces apoptosis in neoplastic cells – develop cardiac failure with idiopathic dilated cardiomyopathy at fast onset, similar to that obtained in the mouse with mutation of gp130. It is likely that herceptin activates apoptosis also at the cardiac level, a process extremely useful to contrast breast cancer, but not necessarily for myocytes. This new "perception" of cardiac failure opens to new possible therapeutic treatments.

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IS IT POSSIBLE TO PREDICT THE SYNERGISTIC BENEFIT OF COMBINED EFFECTIVE DRUGS IN CONGESTIVE HEART FAILURE?

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During the last two decades, congestive heart failure (HF) has become one of the widest medical, epidemiological and economical problems of the western world.

Treatment of HF was initially based on digoxin and diuretics, the advent of ACE-inhibitors and subsequently of beta-blockers and aldosterone receptor blockers has changed the natural history of HF improving morbidity and mortality.

The success in treating HF with the blockade of two neurohormonal systems led in the last years to the hypothesis that a more complete neurohormonal blockade could add beneficial effect on prognosis of HF and numerous agents have been tested. The addition of these neurohormonal modulator agents to the traditional tailored therapy, actually composed by ACE-inhibitors, beta-blockers and possibly aldosterone, seems to have harmful results.

It is not clear whether there is a role for a much more complete neurohormonal antagonism in the treatment of heart failure. The modulation of neurohormonal systems other than renin-angiotensin-aldosterone and adrenergic systems has to be further investigated.

The careful evaluation of etiologic variables, clinical data and instrumental parameters combined with a strict control of co-morbidities may help in selecting the better approach for HF treatment in the single patient.

During the last two decades, congestive heart failure (HF) has become one of the widest medical, epidemiological and economical problems of the western world.

Until the 1980s no effective treatment for HF had shown to reduce mortality and the traditional agents were inotropes (digoxin) and diuretics.

Nowadays the knowledge of HF pathophysiology allow us to state that in congestive HF there is a chronic activation of the sympathetic nervous system and of the renin-angiotensin-aldosterone system that brings to a persistent neurohormonal stimulation carrying adverse hemodynamic effects and myocardial and vascular remodeling. In the 1980s this hypothesis and the evidence of hemodynamic changes such as an increased preload and afterload brought to the introduction of vasodilators in the therapy of HF. The first drug that demonstrated an effect on mortality was the angiotensin-converting enzyme (ACE)-inhibitor enalapril. The results of the CONSENSUS trial led to more research through the neurohormonal hypothesis, saving lives was emotive and this new class of agents was effective in reducing symptoms and mortality[1]. Anyway, even after the introduction of ACE-inhibitors the prognosis of HF patients continued to be poor and a large number of new drugs were developed and examined. Phosphodiesterase inhibitors such as milrinone and enoximone, calcium antagonists such as amlodipine, dopamine agonists such as ibopamine and other vasodilators such as flosequinan were tested in many clinical trials but no one was able to reduce mortality even if some agents demonstrated symptoms relief and an increase in exercise tolerance[2].

In the 1990s a traditionally contraindicated class of agents, beta-blockers, demonstrated a reduction of mortality in HF when added to an "optimized therapy" with ACE-inhibitors and with or without digoxin. Many trials testing non selective beta-blockers, as carvedilol that is a $beta_1$, $beta_2$-antagonist, or selective beta-blockers such as metoprolol or bisoprolol, $beta_1$-antagonists, have been conducted in the last years demonstrating their safety and an important added value in reducing mortality (from 30 to 35%) in both mild and advanced HF and in reducing hospitalizations[3,4].

The success in treating HF with the blockade of two neurohormonal systems led in the last years to the hypothesis that a more complete neurohormonal blockade could add a beneficial effect on the prognosis of HF.

Aldosterone receptor blockade has been tested for reducing the activation of the renin-angiotensin-aldosterone system during ACE-inhibitor treatment; only one large trial evaluated spironolactone (the RALES study) in patients with advanced HF demonstrating a reduction in mortality and morbidity of quite 30%[5]. It should be remarked that in this trial only a minority of patients assumed beta-blockers, so we do not have a clear information on the additional value of aldosterone receptor blockade to a tailored therapy with ACE-inhibitors and beta-blockers. Further studies will evaluate the role of spironolactone in HF when added to an optimized therapy.

In this evolving scenario of neurohormonal blockade the evidence that ACE-inhibitors can block incompletely the production of angiotensin II and the introduction in the clinical practice of a new class of agents, the angiotensin II receptor blockers (ARBs), has brought to the hypothesis that ARBs could provide a more complete effect in neurohormonal modulation. Many trials have been conducted testing ARBs versus ACE-inhibitors or ARBs on top of ACE-inhibitors.

In 1997 a first trial conducted with losartan compared to captopril in patients with HF (ELITE) demonstrated that ARB might be more effective than an ACE-inhibitor, where subsequent studies as ELITE II failed to confirm this previous positive results. Subsequently the Val-HeFT trial showed that valsartan can be effective in patients intolerant to ACE-inhibitors; moreover by adding an ARB to an ACE-inhibitor the hospital admissions are reduced; afterwards these results ARBs began to be used as an alternative to ACE-inhibitors in intolerant patients or as an add on therapy in patients with advanced HF who were intolerant to beta-blockers or with hypertension despite a complete therapy[6,7]. A recent

well conducted trial (CHARM) evaluating different strategies of use in HF of candesartan showed interesting results: this ARB showed benefit in patients taking optimized ACE-inhibitor therapy reducing the relative risk of cardiovascular death and hospital admission; moreover this trial firmly established that patients intolerant to ACE-inhibitors should be given an ARB.

In the setting of the neurohormonal hypothesis, ongoing researches are testing agents that block other overactive systems in advanced HF as endothelin antagonists, vasopeptidase and cytokine inhibitors.

The earliest small studies of endothelin receptor blockers were interesting, they demonstrated an improvement in hemodynamic parameters; however other large studies did not confirm these results. Endothelin antagonists such as bosentan in the REACH-1 and ENABLE trials, enrasentan in the ENCOR trial and tezosentan in the recent RITZ-4 trial demonstrated no improvement in mortality or HF hospitalization and in some cases a worse prognosis[8].

Also etanercept and infliximab, two tumor necrosis factor-alpha antagonists, that theoretically could improve HF, failed to show a benefit when tested in clinical trials[9].

Omapatrilat is a vasopeptidase inhibitor that block both ACE and neutral endopeptidase, reducing not only the production of angiotensin II but increasing concentrations of bradykinin, natriuretic peptide and endothelin. In the OVERTURE trial no clear additional benefit for HF patients was documented in the omapatrilat group[10].

Recently the preliminary results of ACTIV in Congestive HF trial have been presented; this study evaluated the effect of tolvaptan, a vasopressin 2 antagonist, in persistent HF: no significant effect on morbidity and mortality has been observed, but tolvaptan seems active in reducing body weight and in increasing sodium plasma levels.

These failures are probably due to the selection of unimportant targets, incorrect doses or to an adverse effect caused by excessive blockage; for example omapatrilat may cause a resistance to endogenous natriuretic peptide and causes, also, an increase in plasma endothelin that is a substrate of neutral endopeptidase neutralizing in this way some possible benefits.

Another agent recently tested in HF is moxonidine, an imidazoline agent acting as a centrally sympatholytic agent; the MOXCON trial was stopped because of a higher mortality rate in the group treated with moxonidine; following investigation demonstrated an important reduction of norepinephrine levels[11].

All these results suggest that the aim of a more complete neurohormonal blockade may be harmful in HF; maybe we have to realize that there is a limit to a multiple neurohormonal antagonism and we have to search for other therapeutic options. However, we need further information about these specific agents, their dosages and targets before a clear definition of their role in HF treatment.

The excessive blockage of the adrenergic system with bucindolol in the BEST trial has been proposed as a possible reason for the unsuccessful mortality results of this trial; these outcomes are in contrast with the findings of other beta-blocker trials. However, these findings may be due to the greater number of African-Americans and severe HF patients enrolled in this study. Pharmacogenetics is trying to determine the role of genetic variants in individual responses to drugs; in the last years many data have been published about the genetic polymorphisms of proteins that have important effects on the efficacy of many cardiovascular drugs. The response to ACE-inhibition and to $beta_2$-antagonists is related to polymorphisms of ACE and ADRB2 gene, respectively[12]. Potentially pharmacogenetics could provide clinicians useful tools for the identification of the right drug and dose for the single patient.

Nowadays cardiac resynchronization therapy is opening new possibilities in the treatment of HF: it improves left ventricular function without increasing global oxidative metabolism; it actually reduces oxygen consumption improving myocardial efficiency. Oxidative metabolism of the interventricular septum increases relatively to the lateral wall; therefore there is a significant decrease in catecholaminergic activation, so cardiac resynchronization therapy can be included in the group of therapies acting on neurohormonal activation and considered not only a mechanical treatment.

There is no doubt that the combination therapy with ACE-inhibitor and beta-blockers is the mainstay of HF therapy; diuretics, mostly in patients with fluid overload, and digoxin have still a role in the therapy of HF, even if digoxin has no effect on mortality but only in reducing hospitalization. Spironolactone must be administered in patients with advanced HF, particularly if there is fluid overload. ARBs should be considered for all the patients who are intolerant to ACE-inhibitors. New information about the role of beta-blockers will come from the analysis of the CARMEN trial that evaluated HF patients treated with carvedilol, enalapril and carvedilol plus enalapril. Preliminary data suggest that there is not any significant difference in all-cause mortality in the three treatment groups; combination therapy is very effective in reducing left ventricular diameters compared with the enalapril alone therapy; the effects of carvedilol therapy were not significantly superior to enalapril alone or inferior to the combined therapy[13].

From the analysis of the results of randomized clinical trials ACE-inhibitors, beta-blockers and aldosterone produce a significant effect in terms of mortality and morbidity in patients with the dilatative hypokinetic model of HF. The careful evaluation of etiologic variables, such as ischemic versus non-ischemic dilated cardiomyopathy, and of clinical data, such as heart rate, blood pressure and ventricular arrhythmias, and of instrumental parameters, mainly derived from echocardiography, combined with a strict control of co-morbidities may help in selecting the better approach to HF treatment in the single patient.

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THE UNITARY PERSPECTIVE OF THE INTERNIST

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Introduction

In many countries general internal medicine specialists have been the mainstay of medical care, even if the last two decades has seen a shift to a subspecialization, with a weakening of the role of the generalist. Ironically this happened at a time when the underlying trend in the population of hospital in-patients has been towards complex, multisystem disorders requiring medium and long-term care, rather than patients with single system disease for whom rapid investigation and treatment by procedural specialists are appropriate[1]. The main differences between these two approaches to care lie in their knowledge, skills and attitude to patient management. Generalists' skills are predominantly non-invasive and their approach to the investigation and management of patients with chronic and/or multidisciplinary problems is holistic. Specialists have knowledge in depth and apply a reductionist approach and often invasive skills, to a single discipline. The debate on the role of the two disciplines has tended to focus on the differences between them, rather than looking at ways in which health care services can utilize and share the strengths of both. Congestive heart failure (CHF) is an appropriate example of chronic condition, where these figures can work together to improve the outcome of their patients. The target of the management of these patients should be a multidisciplinary approach, since such a policy should represent optimum use of the complementary skills of these professional groups[2].

In the field of CHF the unitary perspective of the internist is of special value for the simultaneous presence of multiple chronic conditions and comorbidities that interact each other producing a complex and challenging clinical dynamic process.

Heart failure epidemiology

CHF is a common clinical diagnosis representing the final pathway of several different disease processes affecting the cardiovascular system. The incidence and prevalence of CHF are progressively increasing; trends are related to increasing age of the population as well as to improved survival of patients with myocardial infarction and hypertension. It is estimated that more than 3 million individuals in the United States are affected by CHF, with 500 000 to 700 000 new cases diagnosed each year[3-5].

National estimates for the United States suggest that heart failure affects 1.5-2.0% of the total population and as much as 6-10% of the elderly[6]. The population-based estimate from this source indicates an increase in prevalence in men from 8 per 1000 at age 50-59 years to 66 per 1000 at age 80-89 years[7]. Furthermore, annual hospitalizations due to CHF increased from 570 000 to 2 280 000 between 1970 and 1991. CHF is the number 1 hospital discharge diagnosis for persons aged > 65 years[8-10].

Comorbidity

In CHF comorbidity is due to cardiac or non-cardiac diseases. Both influence the management, the quality of

life, the rate of rehospitalization, the incidence of cardiovascular events and prognosis of the patients. In 1998 Brown and Cleland[11] showed that 13.2% of admissions to hospitals due to CHF were associated with acute myocardial infarction, 7.3% with angina or chest pain, 11.8% with chronic airways obstruction, 8.3% with chronic or acute renal failure, and 5.3% had had a stroke, 15.4% had atrial fibrillation; diabetes was a common concomitant condition.

In a recent Italian survey patients admitted in hospital for CHF showed a very high prevalence of comorbidity (70.2%); the most frequent associated diseases were chronic obstructive pulmonary disease (41.3%), diabetes mellitus (28.4%), anemia (13.9%), renal dysfunction (8.4%), and thyroid disease (6.4%). Also in this study comorbidity affected the length of stay (11.4 ± 7.7 days in patients with comorbidity vs 9.9 ± 7.4 in patients without comorbidity, $p = 0.01$) and in-hospital mortality (6.4 vs 3.8%, $p = 0.016$).

Lien et al.[12] in a retrospective study (116 patients, median age 86 years, range 65-98 years with an established diagnosis of CHF during their hospital admission) showed that only 28% of patients were admitted for worsening symptoms which could be attributed to CHF and none of the patients had CHF as their only medical problem. In fact comorbidities included chest diseases (30%), incontinence (29%), cerebrovascular diseases (26%), musculo-skeletal problems (41%). Barthel index for activities of daily living score was ≤ 16/20 in 35%. Mental state questionnaire score was < 7/10 in 38%. Ninety percent were taking four or more different medications. More than one third were on psychotropic drugs.

Braunstein et al.[13] showed in a recent study that nearly 40% of hospitalized patients with CHF had ≥ 5 non-cardiac comorbidities, and this group accounted for 81% of the total in-patient hospital days experienced by all CHF patients. The risk of hospitalization and potentially preventable hospitalizations strongly increased with the number of chronic conditions (both $p < 0.0001$). After controlling for demographic factors and other diagnoses, comorbidities (Table I) including chronic obstructive pulmonary disease/bronchiectasis, renal failure, diabetes, depression, and other lower respiratory diseases (all $p < 0.01$) were consistently associated with remarkably increased risk for CHF-preventable and all-cause preventable hospitalizations and mortality, In addition non-cardiac comorbidities negatively affected outcomes of patients with CHF (Table II).

Table I. Twenty most common non-cardiac chronic disease conditions for patients aged ≥ 65 years with congestive heart failure (n = 122 630).

Chronic disease defined by the CCS code	% Prevalence (n=)
Essential hypertension	55 (67 211)
Diabetes mellitus	31 (38 175)
COPD and bronchiectasis	26 (32 275)
Ocular disorders (retinopathy, macular disease, cataract, glaucoma)	24 (29 548)
Hypercholesterolemia	21 (25 219)
Peripheral and visceral atherosclerosis	16 (20 027)
Osteoarthritis	16 (19 929)
Chronic respiratory failure/insufficiency/ arrest or other lower respiratory disease excluding COPD/bronchiectasis	14 (17 610)
Thyroid disorders	14 (16 751)
Hypertension with complications and secondary hypertension	11 (13 732)
Alzheimer's disease/dementia	9 (10 839)
Depression/affective disorders	8 (9371)
Chronic renal failure	7 (8652)
Prostatic hyperplasia	7 (8077)
Intravertebral injury, spondylosis, or other chronic back disorders	7 (8469)
Asthma	5 (6717)
Osteoporosis	5 (6688)
Renal insufficiency (acute and unspecified renal failure)	4 (5259)
Anxiety, somatoform disorders, and personality disorders	3 (3978)
Cerebrovascular disease, late effects	3 (3750)

CCS = clinical classification system; COPD = chronic obstructive pulmonary disease. From Braunstein et al.[13], modified.

The best approach is the combined one

Whether patients with CHF should be treated by cardiologists or generalists or by consultation between the two is still matter of debate[14]. Although generalists provide better overall care, they lack the specialized training and experience of cardiologists[15-18]. Cardiologists, on the other hand, provide better specific CHF care[19-24]. However, little is known about the quality of primary care provided by cardiologists. Studies have demonstrated that consultation between generalists and specialists is associated with superior quality of care[25]. Responses from cardiologists might include increased vigilance to conditions that complicate care, reorganized practices to reduce access barriers and improved communications with other providers when quality of comprehensive care seems suboptimal. In the US Medicare responses might include multidisciplinary disease management teams, explicit payment for care coordination and new case-mix-adjusted reimbursement strategies that reward cardiologists for recognizing and referring, when necessary, patients with inappropriately treated non-cardiac conditions. It is reported that an improved survival associated with cardiologist care and a mixture of general practitioner and cardiologist care compared with general practitioner care and the pattern of out-patient care may therefore be important for the survival of patients with CHF. In a recent study Ahmed et al.[26] confirmed that the collaboration between generalists and cardiologists improves the processes of CHF care. This collaboration was associated with reduced CHF readmission rates,

Table II. Association of non-cardiac comorbidity with ambulatory care-sensitive congestive heart failure hospitalization among Medicare beneficiaries with congestive heart failure (n = 122 630).

Condition	Risk ratio (95% CI)	
	Unadjusted	Adjusted*
Chronic renal failure	1.91 (1.83-1.99)	1.43 (1.36-1.50)
Acute and unspecified renal failure	1.83 (1.74-1.93)	1.18 (1.11-1.25)
Hypertension with complications or secondary hypertension	1.82 (1.76-1.88)	1.51 (1.45-1.56)
Lower respiratory disease, failure or insufficiency	1.57 (1.52-1.63)	1.34 (1.30-1.39)
COPD/bronchiectasis	1.49 (1.45-1.53)	1.40 (1.36-1.44)
Diabetes mellitus	1.41 (1.37-1.44)	1.33 (1.29-1.37)
Essential hypertension	1.31 (1.28-1.35)	1.23 (1.20-1.27)
Asthma	1.31 (1.23-1.39)	1.05 (1.00-1.11)
Anxiety, somatoform disorders, and personality disorders	1.22 (1.14-1.31)	1.15 (1.07-1.23)
Peripheral or visceral atherosclerosis	1.19 (1.15-1.23)	1.08 (1.04-1.11)
Depression/affective disorders	1.16 (1.10-1.21)	1.11 (1.05-1.16)
Thyroid disorders	1.05 (1.01-1.09)	1.04 (1.00-1.08)
Chronic back disorders	1.01 (0.96-1.06)	1.00 (0.95-1.06)
Osteoarthritis	1.01 (0.97-1.05)	1.01 (0.97-1.05)
Cerebrovascular disease, late effects	0.98 (0.91-1.07)	0.91 (0.84-0.98)
Ocular disorders	0.98 (0.95-1.01)	0.96 (0.93-0.99)
Prostatic hyperplasia	0.93 (0.88-0.99)	0.92 (0.86-0.97)
Osteoporosis	0.91 (0.86-0.97)	0.93 (0.87-0.99)
Hypercholesterolemia	0.90 (0.87-0.93)	0.84 (0.81-0.87)
Alzheimer's disease/dementia	0.82 (0.78-0.86)	0.81 (0.77-0.85)

CI = confidence interval; COPD = chronic obstructive pulmonary disease. * adjusted for patient race, age (65-69, 70-74, 75-79, 80-84, > 85 years) and gender, primary caring provider type (cardiologist, generalist, non-cardiac specialist), patient's county of residence per capita hospital beds, total physicians and cardiovascular specialists. From Braunstein et al.[13], modified.

without significant differences in mortality rates. These results suggest that the impact of collaborative care on the functional status and quality of life of patients with CHF should be prompted and spread.

Perspectives

Although a generalist perspective has always been important in health care, this broader view has become imperative in the face of the changing epidemiology of illnesses in industrial societies. Chronic conditions, not acute diseases are now the most common problems in health care and for these diseases the goals of care are to enhance functional status, minimize distressing symptoms, cope with the psychosocial stresses of disability, and prolong life through secondary prevention. In chronic illness, care of the whole person is of paramount importance.

The article by Starfield et al.[27] makes evident the virtue of generalism in the care of patients with chronic illness. Most patients with chronic illnesses do not have a single, predominant condition. Rather, most have comorbidity, the simultaneous presence of multiple chronic conditions and the comorbidities interact to produce complex and challenging clinical dynamics. Furthermore the medications for one condition have adverse effects that worsened another condition. What is needed is a model of care that addresses the whole person and integrates care for the person's entire constellation of comorbidities. This generalist approach does not deny the value of specialty care, which can offer expertise and unique services to the care of patients with chronic illness.

Fulfilling the promise of this approach, however, will test the resourcefulness of primary care clinicians and health care systems. The issue of comorbidity highlights the intricacy of primary care and the complexity of providing holistic care. A major challenge to medical generalism is the difficulty of measuring health status and clinical outcomes at a "general" level – that is, at the level of the whole person rather than at the level of the component diseases of patients with cardiac disease. The common presence of multiple comorbidities renders single disease outcomes inadequate for evaluating the quality of a generalist-oriented model of care that simultaneously addresses all of the conditions affecting a patient's health[28].

The generalist's approach stresses a central role for the primary care clinician as the coordinator and integrator of specialty care and other referral services, working in partnership with the patient and other health care personnel to optimize overall physical functioning, mental health, and well-being. The conceptual and pragmatic logic of a generalist's approach to the care of patients with chronic illness is compelling and represents a major challenge for health systems.

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