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Heart failure: an historical perspective

Roberto Ferrari*, Cristina Balla, and Alessandro Fucili

Chair of Cardiology and LTTA Centre, University Hospital of Ferrara, Ferrara, Italy. Maria Cecilia Hospital, GVM Care and Research, E.S. Health Science Foundation, Cotignola, Italy

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The story of heart failure (HF) traces a path from the oldest records of human healing practices several millennia ago, winding through various changing models of physiology, sickness and health. It passes through today's landscape of neurohormonal modulation, device therapy, and assist devices, towards a future of therapies, some in development today, some as-yet unimagined, based on pathophysiological insights yet to come. This review attempts to follow the path and notes the traces left by earlier travellers, as well as the therapeutic improvements made possible by the developments in our understanding of HF that followed from their successes and failures. As we focus on pathophysiology, transplantation and mechanical assist devices will be treated more cursorily. Likewise, as this is a history of the development of modern (sometimes 'Western' although more properly 'global' or 'scientific') medicine, alternative therapies are not discussed in this paper.

Ancient times

It is believed that the oldest identified case of decompensated HF is the remains discovered in a plundered tomb in the Valley of the Queens by the Italian Egyptologist Ernesto Schiaparelli. The remains date back over 3500 years and are now housed in the Egyptian museum in Turin, Italy. They belonged to an Egyptian dignitary named Nebiri who lived under the reign of the 18th dynasty Pharaoh Thutmose III (1479–24 BC). Andreas Nerlich, a pathologist from Munich, Germany, examined the histology of the lungs and described the presence of pulmonary oedema, likely due to 'heart failure', as histochemical staining of lung tissue ruled out other diseases as cause of 'fluid in the air spaces of the lung', including tuberculosis, granulomas, or microbacterial infections.[1]

The Egyptians knew of a number of other components of HF too, such as cardiac hypertrophy.[2] Coronary atherosclerosis, a common cause of HF, has also been found in several Egyptian mummies.[3] The Egyptians were not alone: on the other side of the world, in China, 'the Yellow Emperor's Classic of Internal Medicine' discussed dropsical swellings as early as 2600 B.C.[4]

Descriptions of what could have been HF occur in Greek and Roman texts, although oedema, dyspnoea and anasarca, the most common manifestations described in these texts, could be attributed to other causes than HF.[5] Hippocratic corpus describes rales '*When the ear is held to the chest, and one listens for some time, it may be heard to see the inside like the boiling of vinegar*'[6] (translation by A. Katz).[5] He also discussed a rather modern way to drain this fluid through a hole drilled in the ribcage.[7] However, at that time, there seem to have been no understanding about why the fluid had accumulated.[5]

Subsequently, the centre of medical science returned to Egypt, and more specifically to Alexandria where Erophilus and Erasistratus performed human dissections and experiments. They recognized that the heart contracts but believed that the arteries contained air and that blood was confined to the veins. Even Galen, a Greek physician who lived in the Roman Empire during the second century failed to understand the role of the heart as a pump for the blood and thought it was just a source of heat. He almost certainly described atrial fibrillation (AF) and indeed palpated the arterial pulse, a technique that had been used for prognosis millennia earlier by the Egyptians.[8] However, Galen believed that the pulse was transmitted by the arterial walls rather than by blood flowing through the lumen.[9]

*Corresponding author. Tel: +39 0532 239882, Email: fri@unife.it

Again, the ancient Europeans were not alone in discussing cardiovascular pathology. The medieval Arab scholar Ibn Sina, known to the West as Avicenna (980–1037), had a reputation as an authority on heart disease. His treatise entitled 'Kitab al-Adviyt-al-Qalbiye' or 'The book on drugs for cardiac diseases' discusses therapies for difficulty in breathing, palpitation, and syncope. Widely used in the West in a Latin translation in the 14th century, the treatise remains in the Galenic tradition of humours.[10,11]

The view that the primary function of the heart was to distribute heat by pumping air made it difficult to establish a link between cardiac function and dyspnoea or anasarca, The turning point came in 1628 when William Harvey clearly described circulation and provided the basis for understanding the haemodynamic abnormalities in HF.[12] A few years later, a description of HF due to tamponade and to mitral stenosis became available.[13,14] In the mid-18th century, Lancisi noted that valvular regurgitation leads to ventricular dilatation, but he appreciated that the ventricle cavity does not enlarge in aortic stenosis.[15] He also suggested that the dilatation weakens the heart. Subsequently, several scientists described the existence of cardiac hypertrophy, both eccentric and concentric, and the existence of acute and chronic HF as well as the role of adaptive and maladaptive changes in the failing heart. All of this was evaluated at the bedside by palpation, percussion, and auscultation, and eventually confirmed by autopsy, as Röntgen did not discover x-rays until 1895.[16–18] Distinction between the various forms of cardiac enlargement continued into the 20th century. A turning point occurred in 1918 when E.H. Starling[19] published his 'Law of the Heart'. The demonstration that increasing end-diastolic volume enhances cardiac performance caused much surprise, scepticism and confusion as it contradicted the 19th century view that dilatation weakened the heart.

Achievements in the 1940s-60s

Our understanding of HF was significantly advanced in the 1940s and 1960s by the introduction of cardiac catheterisation[20] and cardiac surgery.[5] This allowed the characterisation of many forms of structural heart disease, both rheumatic and congenital. However, these advances did not solve the clinical and aetiopathological challenges posed by HF because ischaemic heart disease, hypertension and dilated cardiomyopathies were emerging as major causes of HF. In the decades before the 1980s, the only attempt to explain the changes occurring in HF was related to the back/forward theories and treatment was based on bed rest, inactivity and fluid restriction. On the pharmacological side, only digitalis and diuretics were prescribed, and HF research often concentrated more on the kidney than on the heart.[5] With the description of 'Families of Starling Curves' by S.J. Sarnoff[21] the idea of contractility came about, based on the possibility of shifting from one curve to another, and the 'contractile' state of the heart became a major regulator of cardiac performance. Despite the difficulties in measuring contractility—which was subject to two decades of heated controversy—the view prevailed that contractility is reduced in patients with chronic HF and that increasing it would be positive.[22] Research was concentrated on understanding the cause of low contractility in HF. Thus, the role of energy starvation and abnormal calcium movement gained rapid popularity and stimulated efforts to develop inotropic drugs that were more powerful than digitalis. The idea was quite logical as ejection fraction (EF) correlates with survival. Therefore, increasing the EF should increase survival. However, all clinical trials of inotropic drugs were stopped prematurely because the agents did more harm than good and none had a positive effect on survival.[23,24] A few years later, cardiac glycosides were also found not to improve survival in patients with HF in sinus rhythm.[25]

If the wider public took notice of cardiology in the 1960s is was in December 1967, as Christian Barnard conducted the first orthotopic heart transplant at Groote Schuur hospital in Cape Town, South Africa. The 1960s was also the decade that saw the emergence of LV assist devices (LVADs), beginning in 1961 when Dennis and co-workers uses a roller pump to assist the left ventricle: a cannula was placed through the septum into the left atrium, and blood was returned to the femoral artery.[26,27] Today, a large number of LVADs are in use and their place in the management of HF is well established, mostly as bridging therapy to heart transplantation.[28]

From the mid-1970s, the availability of vasodilators provided a means to reduce afterload in order to increase cardiac efficiency and cardiac output in HF.[29] As with the positive inotropes, it was thought that vasodilators would increase EF, decrease ventricular diastolic pressure and improve cardiac energetics, all effects that would be advantageous in HF. However, when the first large randomized clinical trial in HF, the Vasodilator-Heart Failure Trial (V-HeFT I), was conducted by J. Cohn and others in 1986, it showed that, despite short-term haemodynamic improvement, afterload reduction alone could prolong survival.[30] Despite these initial promising results, it soon emerged that the long-term benefits of vasodilators were not related to their haemodynamic effects and a series of trials showed that patients treated with these agents were at greater risk of developing worsening HF and mortality than those treated with placebo.[31–34]

From the pathophysiological point of view, at this time Starling's law of the heart and the neuroendocrine response to HF were still considered compensatory mechanisms. But something was about to change.

The 1980s change of direction: HF becomes a neuroendocrine disease

In the 1980s, the idea that nature would provide humans with different mechanisms to counteract HF already seemed quite optimistic. Indeed, it was Peter Harris who questioned such a way of thinking, based on the assumption that nature intervenes only to allow the survival of the species.[35] Harris, along with others including one of the present authors (R.F.), speculated that the neuroendocrine response to HF determined in Western patients, treated with diuretics, vasodilators and inotropes may be misleading, as the therapy itself was known to induce a neuroendocrine response. The great difficulty of measuring the real response to HF in untreated patients resulted in an expedition to India where in the early 1980s it was still possible to

find untreated patients with severe HF being admitted to hospitals. We could demonstrate that neuroendocrine activation indeed occurs in untreated HF and that this is the same response as occurs after exercise, vasodilation and even untreated acute MI.[36-40] We concluded that it is a stereotyped response which could be set in motion any time that blood pressure or cardiac output are reduced or are insufficient to maintain the body's needs. The response is very useful for humans and mammals in order to overcome short-term and acute stressful conditions. For mammals, it helps to avoid bleeding and to hunt, which of course are two pre-requisites for the survival of the species.[35] However, in HF, blood pressure and cardiac output are reduced over long time periods. Therefore, the neuroendocrine response is chronically activated, with deleterious consequences as the persisting increase in catecholamines of the renin-angiotensin system (RAS) damages the function and structure of myocytes.

Apart from the physiopathological understanding, the real importance of the work conducted in India was that it gave rise to a new way of understanding and treating HF which became a *neuroendocrine* disease rather than a *heart* disease. As a consequence, angiotensin converting enzyme inhibitors (ACEIs) and beta-blockers were successfully introduced as a treatment for HF. ACEIs reduce the risk of death and hospitalisation in all patients with HF with reduced ejection fraction (HFrEF), regardless of the severity of the symptoms.[41] Beta-blockers paradoxically improve EF, eliminate symptoms and decrease the risk of mortality and hospitalisation.[42] Both classes of drugs reduce remodelling of the failing ventricles[43] and appear to be beneficial regardless of aetiopathogenesis, race, sex etc.

Later, another class of drugs joined the family of anti-neuroendocrine activation drugs: mineral corticoid receptor antagonists (MRA). The beneficial prognostic effect of MRAs has been shown on top of therapy with ACEIs and beta-blockers.[44] The story then continued with the development of the angiotensin receptor blockers (ARBs). The addition of these drugs to standard HF therapy has been shown to further reduce hospitalisation.[45] Interestingly, already at this early stage of neuroendocrine research, it was thought that atrial natriuretic peptide could be helpful for HF because of its vasodilator capacity.[46] However, the peptide appears to have limited effect on modulating the pathophysiology of HF[47] and it has not been shown in human studies to modify cardiac structure, function or survival. [48]

Putting it all together, the neuroendocrine story is full of successes and caused great changes; from vasodilators to anti-RAS drugs; from positive inotropes to negative inotropes, such as beta-blockers which, paradoxically, in HF have become the ideal positive inotrope as they increase EF without increasing oxygen consumption.

The following years explain the HF 'paradoxes'

The impact of these pharmacological changes such as beta-blockers, ACEi and MRAs did alter the national story of the disease progression and the way to view it. In the 1990s, HF was no longer a disease but a 'syndrome', a Greek word meaning 'going together'. Going together because the heart is just the beginning of the disease which then spreads to the periphery, involving the neuroendocrine and neurohormoral (cytokine) systems[49] as well as the peripheral muscles, greatly contributing to symptoms such as dyspnoea and fatigue[50] and, of course, the kidneys and even the gut, which when hypo-perfused can develop bowel oedema and release endotoxin-induced harmful cytokines.[51,52]

The first paradox is that whilst there has been a remarkable reduction in occurrence and an improvement of prognosis in almost all heart diseases over the last decades, this has not happened with HF. There are two main reasons for this paradox: (i) HF is the consequence of the success brought about by reperfusion (either with thrombolysis or angioplasty) in the treatment of acute myocardial infarction[53] and (ii) we now recognize that HF can exist even in the presence of normal ejection fraction (HFpEF). Recognition of HFpEF has largely contributed to the increased diagnosis of HF. HFpEF itself can also be considered a paradox: an impairment of left ventricular (LV) function was considered a pre-requisite for HF. HFpEF reinforces the view that the periphery matters in HF. In fact, two opposite mechanisms distinguish these two categories of HF: in HFPEF the problem starts from the periphery (hypertension, metabolic syndrome etc.) and spreads to the heart.[53] In HFrEF, the problem starts in the heart (infarction or an infection) and then spreads to the periphery. This leads to the opposite phenotype: in HFrEF the ventricle is hypertrophic (eccentric) and large; in HFpEF it is hypertrophic (concentric) and small.

As mentioned above, another paradox relates to beta-blockers being the ideal positive inotropes. There are several reasons for this. First, the relationship between frequency (heart rate) and force (contraction) is altered in HF. The force of healthy papillary muscle increases proportionately to the increase in heart rate. In contrast, in HF the relationship becomes negative, i.e. contraction decreases in response to increased heart rate. As a result, in HF, increasing heart rate coincides with a reduction of EF and vice versa.[54] Beta-blockers in HFrEF reduce the heart rate and thus increase EF, preventing or even reversing remodelling. This has been confirmed by two clinical studies of ivabradine, a specific inhibitor of the I_f current in the sinoatrial node. In these studies, selective heart rate reduction with ivabradine added to beta-blockers further reduced remodelling and improved EF.[55-57] Heart-rate reduction also decreases energy expenditure (which is increased by positive inotropes) as shown by higher energy phosphate availability.[58] In addition to slowing the heart rate, beta-blockers reduce negative effects of catecholamines on the myocytes and favourably improve the balance between hypertrophy and apoptosis which is at the molecular basis of remodelling.[59,60]

The 1990s addresses the benefit of devices in HF

The recognition that ventricular arrhythmias are responsible for much of the sudden deaths in HF patients lead to the introduction of implantable cardioverter—defibrillators (ICDs) in the first decade of the 21st century. Today

these devices are invaluable in preventing arrhythmia-related mortality.[28] Later, the function of ICDs was upgraded to resynchronising the contraction of the ventricles (CRT), which enhances ventricular contractility, diminishes secondary mitral regurgitation, reverses ventricular remodelling and sustains the improvement in EF.[61] Today, indications for CRT therapy can be very precise and personalized, taking advantage of the latest imaging technologies.[62] Technological developments are continuously providing new advances in LV assistance such as implant-based multi parameter telemonitoring[63] and chronic vagal stimulation.[64] Furthermore, wireless implanted devices that monitor heart function at a distance are already a reality.

In the 2000s, HF turns into molecular biology, genetics and stem cells.

Already in 1987, molecular and genetic science moved to centre stage in cardiology.[65] Only 3 years later the first molecular cause of a familial cardiomyopathy, a missense mutation in the cardiac beta-myosin heavy chain gene was reported.[66] It is hoped that one day the replacement of faulty genes with correct copies delivered by viral vectors might be a useful therapeutic tool for HF. This is already possible in both hypertrophic and some dilated cardiomyopathies with gene therapy targeted to improve abnormal calcium cycling. A newly discovered type of regulation termed epigenetics[67] has recently been identified as another important possible therapy for HF. Linked to epigenetics is the concept of micro RNAs (miRNAs). These are small non-coding RNA segments that regulate gene transcription and protein formation by silencing the messenger RNA, and are deeply involved in HF. Pre-clinical research into miRNAs has shown the influence of these molecules on calcium cycling, ventricular hypertrophy and HF.[68] In addition, miRNAs could be useful biomarkers for severity of HF and need of transplantation.

Substantial hope was also given to stem cell therapy for HF.[69] It was thought that implantation of stem cells which could differentiate in cardiomyocytes into injured hearts could regenerate the myocardium and its perfusion and improve cardiac function. Bone marrow contains different stem cells and it is not hard to acquire. Autologous bone marrow-derived mono nuclear cells called endothelial progenitor cells were considered first for therapeutic purposes. However, the results were mixed and despite a positive meta-analysis, the approach has not yet found routine use.[70-72] Thereafter, mesenchymal stem cells harvested by adipose tissue by liposuction was considered. Unfortunately, however, when obtained from HF patients, the function of these stem cells is already compromised [73] Research has now moved to autologous stem cells injected into patients with reduced LV function. The efficacy of this technology is under investigation.[70] It seems, however, that the best cell type, progressing method and administration route, dose, timing and more importantly efficacy remain to be determined.

An alternative approach currently being explored is the chemical decellularizing of a human heart while preserving its three-dimensional architecture and vascularity, generating a structurally intact decellularized extracellular matrix (dECM). The dECM preserves anisotropic cardiac mechanical properties, patent macro and microvasculature, and competent valves. Initial studies indicated that cardiomyocytes seeded onto a human ECM exhibit calcium dynamics and impulse propagation, which suggest that they form functional intercellular connections.[74] Whether the process can be taken all the way to the manufacture of a human heart graft will be clear in the future.

HF today

The latest developments in HF research and therapy are not limited to devices and cellular biology but also extend to new pharmacological treatments. The excellent results in HFrEF from the PARADIGM -HF study, in which a dual angiotensin receptor and neprilysin inhibition (ARNi) with sacubitril/valsartan (LCZ696) significantly improved prognosis compared with treatment with the ACEi enalapril, indicate that there is room for further development in terms of control of neuroendocrinal activation.[75] The PARADIGM-HF trial is a breakthrough in HFrEF treatment as it is the first time in nearly 30 years that a new drug, an ARNi, performed better than the classical ACEi. The engineered ARNi molecule containing two active agents (sacubitril/valsartan), not simply two drugs in one pill, might result in a completely new and efficacious molecule, opening the scope for exploring further interesting avenues.

As sketched out above, much has happened throughout the history of HF but much still needs to happen. HF therapy can be divided into three areas, that for HFrEF, HFpEF and for acute HF (AHF), respectively. Most of the medical successes have been in the treatment of HFrEF and the other two areas present large unmet needs for pathophysiological insights and improved therapies.

In HFpEF our therapeutic armoury lags far behind that for HFrEF. In HFpEF the heart responds to hypertension, metabolic syndrome and other factors by increasing wall thickness with preserved contractile force. From this follows that HFpEF presents with different challenges to HFrEF, notably how to reverse pressure overload-induced cardiac hypertrophy.[76] We are still waiting for the drug or therapy that can address unmet treatment needs for patients with HFpEF.

Sacubitril/valsartan is currently being investigated in HFpEF. Phase II trial data with sacubitril/valsartan indicate that the ARNi reduces nt-proBNP and left-atrial size in patients with HFpEF.[77] The on-going PARAGON-HF mortality/morbidity trial will reveal the efficacy and safety of ARNi compared with valsartan in this indication.

In AHF treatment has thus far aimed to reduce acute symptoms and stabilize the patient[78] and the early history of HF sketched out above was largely about AHF, focusing on symptomatic treatment. Already the ancient Egyptians aimed to 'cause emptying' using concoctions of elderberry, wormwood and other herbal preparations.[79] The practice of bloodletting has been around for at least five thousand years [80] and was particularly popular for dyspnoea.[81]

Today treatment of AHF predominantly target the inerent haemodynamic crisis. When initiated early, diuretics, supplemental oxygen, vasodilators and inotropic agents improve the shortness of breath, pulmonary crackles and peripheral oedema typical of AHF.[78,82,83] Yet, beyond stabilising patients' haemodynamic and respiratory functions

we are still struggling to improve long-term prospects for patients with AHF. A patient hospitalized with acute decompensation runs an approximately one-in-three risk of being rehospitalized or dead within 60–90 days of discharge.[84,85] These numbers have changed little over the decades,[86] even as the management of HFrEF kept recording major successes as discussed above.

The road to improved pharmacotherapies for acute HF is littered with promising compounds that failed in large-scale randomized clinical trials, although the conceptual foundation for their use appeared sound at the outset. None reduced long-term mortality after hospital discharge.[87-90] We are still struggling with the link between acute symptomatic relief, provided by a number of currently available treatments, and long-term risk reduction, which is not achieved with any agent used in AHF at present.

There is optimism that ongoing research to address unmet treatment needs in AHF will pay off. The RELAX-AHF trial with serelaxin, a recombinant peptide of the human relaxin-2 hormone that occurs naturally in humans, presented promising results in 2013. In this phase II/III trial, continuous infusion of serelaxin for 48 hrs within 16 hrs of presenting to the hospital improved dyspnoea, signs and symptoms of congestion, and initial length of hospital stay.[91] In addition, a safety end point analysis found a 37% reduction in all-cause mortality at 180 days with serelaxin compared with placebo ($P = 0.028$) primarily from a reduction in cardiovascular (CV) mortality and sudden death.[91,92] A reduction in CV mortality with serelaxin had previously been reported in the Phase II Pre-RELAX-AH study.[93] If not a chance finding, this would represent the first time a drug has shown a positive effect on long-term mortality in acute HF. Confirmation of these findings awaits the completion of the on-going RELAX-AHF 2 trial, which is several times larger than RELAX-AHF and sufficiently powered to detect an effect on mortality.[94]

Other drugs may share the limelight with serelaxin in coming years. Among names to look out for are ularitide, a synthetic natriuretic peptide currently in Phase III (the TRUE-AHF trial; NCT01661634) or the 4th-generation calcium-channel blocker clevidipine which has been targeted at patients with AHF and SBP $>$160 mm Hg.[95] Nicorandil, a hybrid compound of a potassium-channel opener and NO donor first introduced in the late 1980s, has been tried in AHF in recent years with beneficial short-term effects on symptoms and echocardiographic variables.[96] But inconclusive long-term outcomes such as rehospitalizations.[97] More compounds are in early development and some of these will surely make headlines as research moves on.

Conclusion

HF is a disease of our time, known since ancient times. It is due to become even more prevalent with the increased ageing of populations worldwide. It will put a further strain on healthcare systems in terms of increased morbidity, mortality and cost. And the huge challenge remains how to improve prospects for patients with HFpEF or AHF. Yet there is reason for optimism. Compared with earlier eras, today's HF physician has a vastly expanded range of options and a long history of medical knowledge to draw on. Medical research has never been so intense as today or so well-informed, helped not only by past successes but also by insights from failures.

Despite the long history of HF we still know relatively little. It is a revolutionary disease. We live in a modern, technological revolution which aims to replace failing cardiomyocytes by gene or stem cell therapy. The electronic revolution helps us monitor heart function at a distance using wireless devices. New approaches in terms of population data mean that registries are replacing trials all over the world and the big data approach means that the patient experience is central to the research. But is this a real revolution? Or have these different research approaches always existed? Looking back at the work of many scientists both in clinical and basic science who have provided so many ideas and consequently corrected so many mistakes we have to congratulate them. It is their inspiration and their dispassionate studies that have changed our knowledge and the way we view and treat HF. It is their perseverance that makes the future of HF management full of further possibilities.

We are sure that the HF story will never end and personally feel honoured to be part of it.

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