Chapter 10
Evolutionary Paradigms in Cardiology: The Case of Chronic Heart Failure

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Lay Summary In this chapter, attempts are made to use an evolutionary perspective for understanding heart failure (HF), a major issue in cardiology and the endpoint of most of cardiovascular diseases (CVDs) including myocardial infarction, arterial hypertension or valve diseases. Evolutionary medicine takes the view that illness is linked to incompatibilities between the environment in which humans currently live and their genome, which has been shaped by several environmental conditions during biological evolution. Chronic HF occurs after a long period of adjustment of the heart to the new working conditions imposed by CVD (e.g. atherosclerosis). Such an adjustment has been possible due to an ancient, widespread and evolved cellular response to physical forces, called mechanotransduction. Mechanotransduction renders the maximum cardiac contraction slower and more efficient under increased load. From an evolutionary perspective, the heart fails firstly because the adaptive process reaches its own limits. In addition, the anthropogenic increase in lifespan and the accompanying ageing have contributed a new dimension, cardiac fibrosis, that aggravates cardiac function and is one of main biological marker for HF.

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10.1 Introduction

Evolutionary medicine and evolutionary cardiology take the view that illness is linked to incompatibilities between the environment in which humans currently live and their genome which has been shaped by successive environmental conditions during biological evolution [1–6]. In this chapter, we described some conspicuous elements of evolutionary medicine in cardiology that concern the ultimate step of most of CV diseases, namely HF.

In developing countries, CVDs represent one of the leading causes of mortality and morbidity [7, 8]. In the past, CVD mainly originated from infections including valve heart diseases (also called Bouillaud disease), due to severe septic sore throat, endocarditis and myocarditis. In recent decades, both the increase in lifespan and the first epidemiological transition fully modified the medical landscape. The incidence of infections progressively disappeared; instead, within the field of CVD, the clinical consequences of both arterial hypertension and atherosclerosis became predominant.

The first epidemiological transition occurred at the beginning of the twentieth century and was mainly a consequence of a better control of infections. It resulted in a substantial drop of neonatal mortality and the beginning of the global increase of lifespan. A transition occurred in the latter half of the twentieth century and was characterized by an increase in non-transmissible age-related diseases [9, 10]. Presently, to prevent CVD, controlling infections have become less important than controlling new cardiac risk factors, such as sedentary behaviours, obesity, tobacco smoking, air pollution and diet (sugar, fat and salt). These new risks are strongly associated with low socio-economic status in high-income populations.

It is a common misunderstanding to pool all CVD together, and it is important to clarify this issue. From a clinical and aetiological point of view, CVD is a heterogeneous group. For example, clinical manifestations of atherosclerosis, such as myocardial infarction, have little in common with infection-related valve diseases, or congenital heart diseases. As a result, cardiology covers a heterogeneous physio-pathological field of investigations, from fully inherited monogenic diseases, such as hypertrophic cardiomyopathy, to the clinical manifestations of atherosclerosis, which largely depends on behaviour and environment. Consequently, it is impossible to provide the same evolutionary approach to such a wide variety of diverse conditions, and integrating the relevant evolutionary paradigm in cardiology training is far from being achieved, or, even, properly conceived, even by cardiologists!

In this chapter, we illustrate how cardiologists can make use of evolutionary thinking for improving the diagnostic and treatment of chronic HF. In most CVD, HF develops after a long period of compensatory adjustment, and the heart finally fails and does not perform a normal cardiac output and the corresponding normal oxygenation of peripheral tissues (this is the definition of heart failure, HF) [11]. HF is a syndrome, with several causes, which, we argue, indicates the endpoint of an adaptive process. Although we have restricted our approach to chronic HF, other cardiac conditions can be informed by evolutionary thinking, such as arterial hypertension [12, 13] or atherosclerosis ([11], See also Chap. 11).

10.2 The Myocardial Tissue Response to Cardiac Overload as an Adaptation: Research Findings

Cardiac and skeletal or smooth muscle functioning is based upon mechanics and creates movement against gravitational force. The muscle is a thermodynamic machine achieving maximum economy according to the thermodynamics law [14]. Not surprisingly, the permanent modifications of mechanical conditions by CVD, such as myocardial infarction or valve disease, will modify muscle economy (see Box 10.1). The myocardial tissue response to this change in economy is an activation of a very ancient adaptive process, called mechanotransduction, which is the cellular response to mechanical forces.

Box 10.1 Economy and Mechanotransduction in Muscle Physiology
According to the thermodynamic principles, economy is improved when more force is produced for less heat dissipated. In a muscle, when the heat produced per g of developed tension is reduced, the system becomes more efficient. In other words, a car is more economic when it dissipates less heat and utilizes less energy as gasoline, for the same distance, the same speed and the same load. With the same motor, for the same distance, an overloaded car will immediately have a worse economy. In the heart, the motor is the contractile apparatus, and when the load is increased, the contractile apparatus has to be modified by an appropriate gene reprogramming to recover a normal economy. Foetal gene reprogramming has been selected during evolution to modify the cardiac protein content and renders the contractile apparatus more efficient [29, 31].

From a thermodynamic point of view, living cells are dissipative systems with low entropy that funnel energy into their own production and reproduction [11], and any drop in economy imposed by an environmental pressure has to be readjusted to allow the cells to survive and reproduce. This is the basis of mechanotransduction in muscles that have to permanently produce force against gravitation. As shown in Fig. 10.1, mechanotransduction is mainly composed of two complexes that allow continuity in the transmission of the force signal to the chromosomes: (i) at the external membrane level, ion channels and the adhesion protein/integrin complex and (ii) at the nuclear membrane level, the linker of the nucleoskeleton and cytoskeleton complex.

Chronic HF indicates the limits of this adaptive process and occurs after a long period of adjustment. Acute HF is something different, and it frequently occurs as an exacerbating episode during the course of chronic HF, but can also be a totally unexpected event occurring on a normal heart, such as acute failure after a massive pulmonary embolism: the heart fails because it does not have enough time to develop any compensatory process [11]. From a therapeutic point of view, in acute HF, it is urgent to save the patient by a rapid activation of contractility, and several

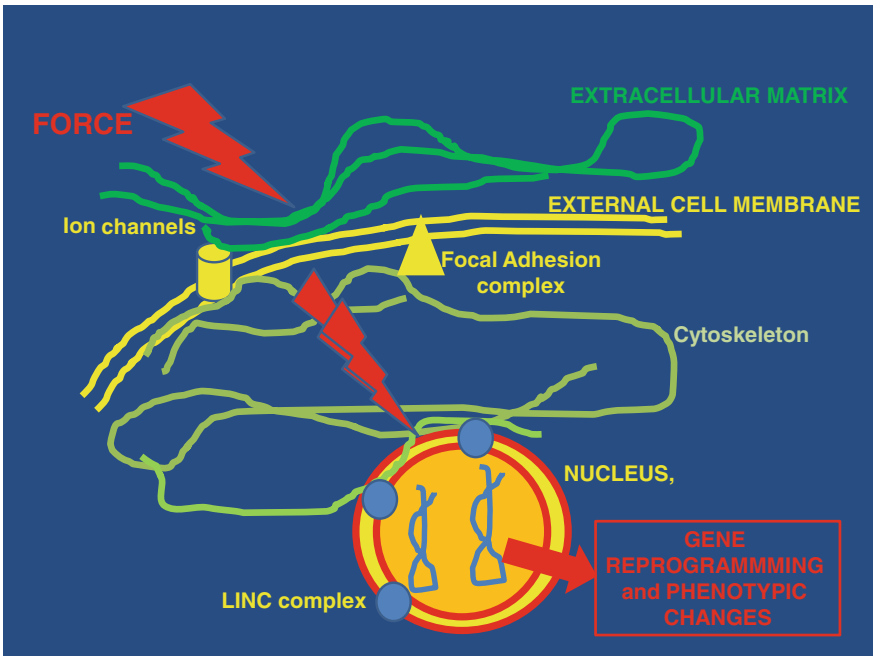

Fig. 10.1 Mechanotransduction. The general mechanism summarized above has been transmitted throughout evolution from the common ancestors of yeasts and humans [19–21]. The nucleus, which is the defining feature of eukaryotic cell, is tightly integrated into the structural network of the cell through a LINC complex. During evolution, LINC was essential for a broad range of cell functions, including meiosis and cell movements. Recent articles showed that the same LINC complex did also probe its mechanical environment, especially within the heart [22]. The mechanical continuity is assumed by several junctions from extracellular matrix to nucleus and allows forces to propagate relative long distances within the cells. (i) Physical forces act on the extracellular matrix and, by so doing, activate several ion channels and the adhesion proteins/integrin dimer complex, which transmits the signal to the cytoskeleton (actin and microtubules). (ii) Mechanosensing is enabled by protein conformations that accommodate the applied force. (iii) Finally, the transduction of the signal to chromatin through the nuclear membrane was performed by the LINC complex. Chromatin rearrangements result in a release of transcriptional factors and a gene reprogramming with specific phenotypic responses. For space limitations, the mechanism of the transmission of the force through the external membrane was not detailed (see [19])

inotropic drugs are fully indicated. By contrast, the adaptive process that occurs during chronic HF is characterized by a reduction of the contractile capacity of the heart, and inotropic drugs are usually not indicated; instead, the therapy is based on drugs which lower the cardiac load.

Several adaptations account for such a long-time preservation of the myocardial economy under mechanical overload. They are likely to be consequences of a foetal gene reprogramming and include cardiac hypertrophy, the reduction of V_{max} and the accompanying decrease in heat produced per g of tension that all allow the tissue to

recover a normal economy. The failure of these adaptive processes to compensate anymore for the changes in working conditions constitutes a crucial determinant of HF. The same adaptive processes are also observed in exercise-induced cardiac and skeletal muscle hypertrophy. Nevertheless, in these physiological conditions, mechanical overload is not permanent (even professional athletes train only a few hours a day!) and failure does not happen.

Other components—the senescent process first, but also ischaemia, diabetes and obesity—have been superimposed on this basic process and render HF a more complicated issue. The most important of the biological determinants that limits the adaptive process is myocardial fibrosis, a multi-factorial marker of increasing electrical cardiac heterogeneity, diastolic stiffness and systolic dysfunction [11, 15]. In developing countries, the most important cause of HF is myocardial ischaemia due to coronary atherosclerosis. The wound healing response of the myocardium after myocardial infarction involves both the infarcted area and the non-infarcted ventricle. Reparative fibrosis is organized as a scar and is surrounded by reactive fibrosis. Consequently, ischaemia adds a new detrimental component to the general process of adjustment. The same is true for diabetes, which is equally fibrogenic (see details and references in [16]).

We will discuss below evolutionary paradigms that are essential for understanding the pathophysiology of HF and the limits of the adaptive process. HF involves three important and fully interrelated evolved processes or traits, namely mechanotransduction, the development of myocardial anatomical structures and ageing [15–17].

10.2.1 Mechanotransduction: An Evolutionary Legacy

Mechanotransduction is the cellular responses to physical forces (Fig. 10.1), and, in cardiovascular medicine, is involved at two levels: (i) in the heart, hypertrophy and the transcriptional modifications of the myocardium are the first responses of the tissue to mechanical overload and (ii) in the arterial wall, a transduction process is initiated in endothelial cells by the mechanical forces of the arterial lumen, the so-called shear stress, that will either contribute to atherogenesis (i.e. formation of abnormal fatty or lipid masses in arterial walls), or modify the arterial wall stiffness during hypertension, two major contributors of HF.

10.2.1.1 Mechanotransduction During Evolution: The General Process

The general process of mechanotransduction (Fig. 10.1) has been described in nearly every tissue, including skeletal muscle, lungs, ears, skin (touch), nerves, liver and kidney and in any eukaryotes, mammals and plants [18–22]. It has several basic features that are all linked to the evolution of life. The various genetic components

and pathways involved in mechanotransduction have been favoured by natural selection during the evolutionary history of living species, as it enabled organisms to adjust to one of the most important variables of the environment, namely physical forces. Like every crucial biological pathway (another good example is circadian clocks), it is not surprising that many different components and sub-mechanisms involved with mechanotransduction involve load-bearing sub-cellular structures, such as plasma membrane itself (the phospholipid layer is sensitive to force), plasma membrane proteins (the stretch-sensitive ion channels or various cell adhesion complexes sense force), cytoskeleton (the widespread deformations of elastic cytoskeletal components are at the origin of several models of mechanotransduction), extracellular matrix components (as fibronectin or collagen) or the different constituents of the contractile apparatus itself [19–21]. Such a complexity is clearly a signature of the "tinkering" process during evolution [23].

Mechanotransduction can roughly be divided into three interrelated steps ([19, 20], Fig. 10.1): (i) the cellular response to forces is a rapid process enabled by mechanotransmission and consistent with the direct effects of mechanical overload in the heart [24]; (ii) mechanosensing generates protein folding that accommodates to physical forces, but the proteins involved are usually specific to a given tissue; (iii) the mechanoresponse influences general transcriptional networks that are not specifically force-dependent, and several different mechanisms have recently been documented [21, 22, 25]. The final result is a gene reprogramming and a modification of the myocardial phenotype with major physiological consequences.

Mechanotransduction itself may be also considered as one example, amongst several, of a broader phenomenon, called phenotypic plasticity, and, as such, is based on quantifiable reaction norms, i.e. on the relationships between phenotype and environmental factors for a given genotype [17, 26]. The genotype permitting such a "reaction norm" has been selected for by natural selection because it increased the ability of individuals to survive and reproduce in variable environments. Here, the CV diseases (e.g. atherosclerosis) create new environmental conditions imposed on the heart [16, 17].

10.2.1.2 Heart Failure: When Adaptive Plasticity Reaches Its Limits

Cardiac muscle sensors that have been selected for sense movements (cyclic as well as stable) and a special attention have recently been focused on the passive elastic elements of the sarcomere, the basic contractile unit of a muscle, such as the titin molecule which is a long "passive" molecule that runs from one end of the sarcomere to another and which may sense stress during diastole. Several mutations (especially on the titin kinase) have recently been discovered and shown to be involved in HF. Research suggests that the elastic protein titin kinase could play a decisive role in the deleterious process of cardiac dilatation, a crucial determinant of HF. Further, the same observation has been made concerning the active components of the sarcomere: it has been shown that in muscles, mechanotransduction is using a specific mechanotransmission pathway through its contractile apparatus. Then, the

above-described general process of mechanotransduction has been modified and adapted to this particular tissue throughout evolution [21, 27].

The **mechanoresponse** to cardiac overload is both a quantitative and qualitative gene reprogramming. The final results are adaptive modifications of the cardiac structures, which allow the heart to function normally in these new working conditions [15–17]. The heart hypertrophies and the maximal contraction velocity of the muscle (V_{max}) becomes lower. Foetal gene reprogramming was first proposed in our group as a global molecular explanation of this mechanoresponse [16, 28, 29]. Foetal gene reprogramming was probably the only alternative available to deal with increased load during cardiac evolution [16, 30]. It simultaneously includes (i) a global activation of gene expression leading to cardiac hypertrophy, (ii) the re-expression or the increased expression of genes normally expressed during foetal life, such as those coding for the slow isoform of myosin [28] and for the brain natriuretic peptide (BNP) and (iii) the blunted expression of genes which are not expressed during the foetal life. The corresponding proteins include membrane components, such as enzymes regulating the calcium transient [29] and a potassium channel regulating the action potential duration. The latter accounts for the enlargement of the QT interval on the electrocardiogram (the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, representing electrical depolarization and repolarization of the ventricles), a marker of cardiac remodelling which is familiar to clinicians (references in [16]) (Table 10.1).

This foetal reprogramming is an adaptive process for several reasons [16]. First, cardiac hypertrophy normalizes the wall stress (according to the Laplace law) and multiplies the contractile units. The changes in contractile and membrane proteins account for a lower V_{max} that adapts the myocardial economy to the new loading conditions [15, 16, 31]. The same relationship does also exist in skeletal muscles and explains why red and white skeletal muscles have, in phylogeny, different shortening velocity [30]. Second, other changes in gene expression also contribute to adjustment. Three of them are widely utilized in clinical practice as biomarkers for HF: the plasma levels of the atrial natriuretic factor (ANF) and the brain natriuretic peptide (BNP), and the QT interval duration. In normal conditions, ANF forms small grains in atria and is physiologically regulated by water availability. Mechanical overload induces the ventricular expression of genes coding for ANF and is responsible for the enhanced plasma levels of ANF. BNP, which plays a similar role in homeostasis control, is normally expressed in both atria and ventricles, and its plasma level is enhanced by cardiac mechanical overload. In practice, BNP is a more sensitive biomarker for mechanical overload and is now widely adopted in clinical practice. ANF and BNP are both diuretic agents, and the enhancement of the production of urine is adaptive because it reduces the load of the heart. An enhanced level of BNP indicates cardiac overload but, sensu stricto, is not a marker of HF, as generally believed, because the definition of HF also includes functional signs. Another frequently forgotten direct marker of the adaptive process is the lengthening of the QT interval on the ECG and, its electrophysiological equivalent, the lengthening of the action potential duration. The increased QT interval and action potential durations are well-documented

Table 10.1 Foetal programme re-expression during cardiac remodelling

	Changes in gene expression	Phenotypic consequences Physiological and practical applications
Global increased expression	Collagen, contractile proteins, channels … with activation of pre-existing or imported stem cells	Cardiac hypertrophy, increased contractile units and improved wall stress
Genes re-expressed	Myosin isoform (slower)	Reduction of V_{max} and the accompanying normalization of myocardial economy
	General anaerobic switch	Better recovery period after the contractile event
	Ventricular expression of the atrial natriuretic factor (ANF) and increased brain natriuretic peptide (BNP)	Diuresis and reduction of the preload. BNP is the most widely utilized biomarker for cardiac mechanical overload and HF
Genes whose expression is blunted	Calcium ATPase of sarcoplasmic reticulum (SERCA2)	Increased relaxation time, participates in the slowing of contraction
	Early transient K^+ current, I_{tO}	Increased action potential duration, and QT duration on the ECG, a marker of cardiac remodelling, participates in the slowing of contraction
	Adrenergic and muscarinic receptors	Decreased heart rate variability and reduced response to exercising
	Myoglobin	Anaerobic switch and better recovery period

Phenotypic consequences and practical applications (from Refs. [16, 17])

characteristics of the hypertrophied heart, and, as components of the slowing of the contraction velocity, are adaptive.

Economy is indeed crucial to any tissue and especially to a tissue in charge of a mechanical function such as muscles (Box 10.1). To quantify the economy of this system, the energy flux and mechanical performances have been simultaneously measured on experimental models of cardiac overload in Alpert's group, and by so doing, they have demonstrated that the adaptive process mainly involves an improvement of energy utilization rather than one of energy production [31] (Fig. 10.2). In other words, the diminution of V_{max} is a beneficial event allowing the heart to contract at a normal energy cost. The same rationale also applies to other muscles [30].

The slowing of V_{max} is an evolutionary process by which a muscle can adapt economy to a wide range of load. Such a pheno-conversion is a non-specific response of the genome to any modification in the loading conditions. Depré et al. [32], for example, had developed a model of ventricular unloading in rats by

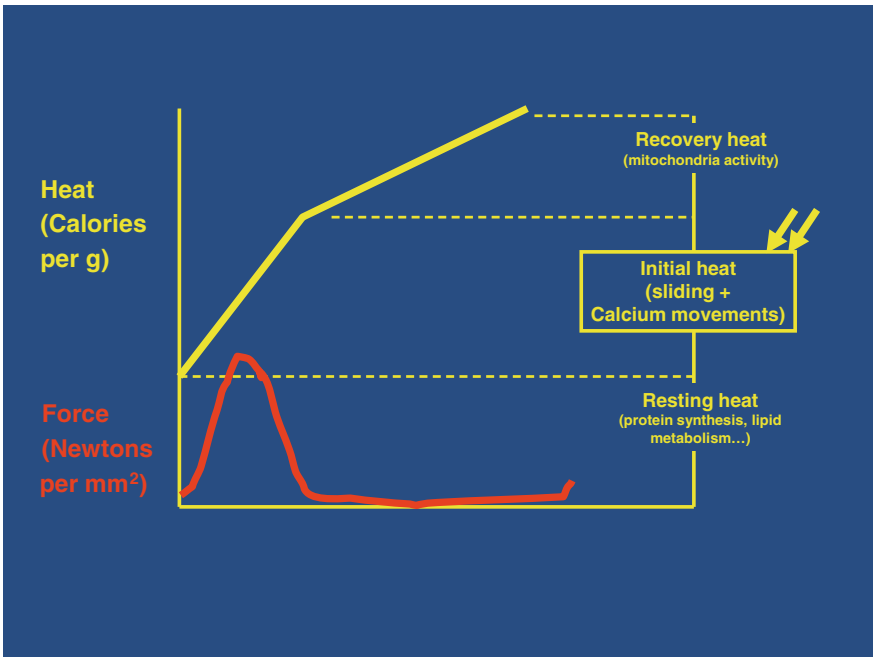

Fig. 10.2 Cardiac economy. For the cardiac muscle, economy is a central determinant of adaptation to new loading conditions. Heat production is measured on isolated papillary muscles of the heart during force development in normal conditions. Three types of heats are shown as follow: resting heat produced by the different cellular synthesis; initiation heat produced during the force development; and recovery heat, which indicates the process of recovery of energy. Initial heat is the only one that is reduced during chronic cardiac overload in hypertrophied heart (*arrows*). From a thermodynamic point of view, such a reduction in heat production indicates that an adaptive process has occurred in order to normalize muscle economy and that, in addition, the process results from changes in energy utilization at the levels of both the sliding mechanism (mainly the contractile proteins) and the calcium movements (enzymes and ion channels in charge of intracellular calcium movements) (see Box 10.1) (Adapted from Alpert and Mulieri [31])

heterotopic cardiac transplantation and showed that the foetal isoforms were all re-expressed, whereas the "adult" isoforms were downregulated.

From a physiological point of view, the degree of mechanical overload parallels both cardiac hypertrophy and myocardial economy. Such a relationship is familiar to cardiologists and constitutes the basis of a clinical diagnostic. From a therapeutic point of view, during chronic cardiac overload (the situation is different in acute HF, as explained previously), any inotropic intervention is basically deleterious since it goes against the adaptive process that has been selected for during thousands years of evolution. To conclude, at the beginning, cardiac remodelling is not a disease per se but the physiological response of the heart to a CVD. HF indicates the limits of this physiological adaptive process and is a disease. It is worth noting that mechanotransduction is also involved in two other CVDs fully related to HF, arterial hypertension [12, 13] and atherogenesis [33, 34].

10.2.2 Development and Myocardial Structure

The cardiac structure itself strongly depends on embryogenesis. The anatomical description, initially proposed by Torrent-Guasp et al. [35] for the heart, is crucial for understanding HF. The same helical cardiac structure is found in humans, horses, oxen, sheep, dogs, pigs, cats and rabbits and also chicken, lissamphibians, chelonians, fish and sharks. This means that at least tetrapod possesses the same basal cardiac morphology (we here used the systematic classification of Lecointre [36]). Data concerning cardiac morphology and the torsion process in clades living before tetrapod are not, for the moment, well documented [37–40].

The primitive heart evolves from a singular tube in chordate ancestor, into a dual pumping chamber with separate right and left sides [37, 40, 41]. The complex structure of the heart (a triple figure-eight spiral band with three S-shaped helixes) correlates with the conventional embryologic development [40, 42]. Recent investigations have indeed led to a better understanding of how the 3D force-producing cellular behaviours are regulated during bending [41, 43].

Cardiac morphology includes two simple loops that start at the pulmonary artery and end in the aorta. The so-called contractile band is responsible for a spiral horizontal basal loop that surrounds the two ventricular cavities, with a change in direction causing a second spiral and giving rise to the double helical structure of the ventricular mass. Such a “rope structure” does explain why cardiac contraction is indeed more analogous to a mop torsion than to a balloon contraction. Such a torsion mechanism of the ventricles has likely been selected for because it improves the efficiency of ejection and allows an active suction during cardiac filling [40, 41] (Fig. 10.3).

Such a complex helicity is an evolved feature that is significant for cardiac functioning. In turn, the impairment of systolic torsion observed during the early stages of cardiac overload is an important determinant of HF [42]. The detailed analysis of such a complexity through recent advance in cardiac imaging provides new prognostic indicators in cardiology [42], and cardiac torsion is now frequently used as a prognosis index. Age also induces modifications of the ventricular twist, which can be measured in vivo [44].

10.2.2.1 Ageing

One of the major new conditions accounting for the symptoms of HF is ageing and the accompanying fibrosis [45, 46]. The senescent processes are responsible for the recent emergence of age-related non-transmissible chronic diseases including the clinical manifestations of atherosclerosis, as well as many cancers, and neuro-degenerative diseases [8]. Ageing are new partners in the present medical landscape, and the role of the senescent cell is determinant in the development of age-associated diseases [46]. Ageing results from the improvement of hygiene,

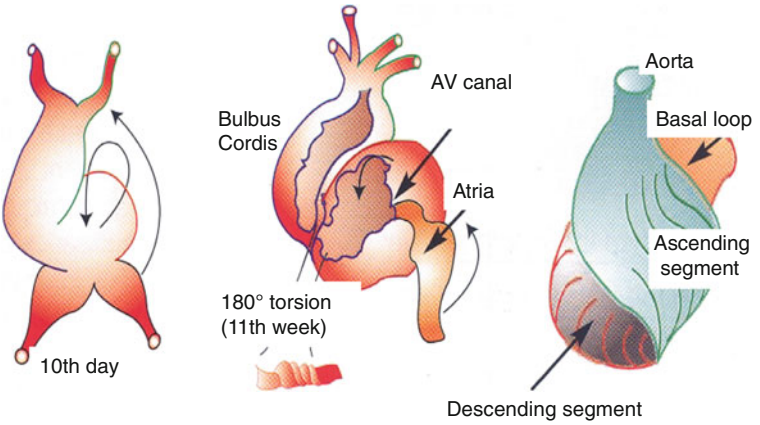

Fig. 10.3 Embryologic development of cardiac ventricles. At ten days, the torsion of the tubular heart begins. At eleven weeks, a 180° torsion happens which finally results in the final two loop rope structures of the adult heart (rearranged using data from [35]). The process exists in every tetrapod, and the torsion structure improves the efficiency of cardiac contraction, which becomes analogous to the torsion of a mop. Measuring the cardiac torsion provides information of cardiac contractility and the prognosis of HF

nutritional status and medical sciences, which are all the consequences of human activity; ageing in humans has clearly an anthropogenic origin. At this scale, such a process has never been experienced in any living species during the history of life and has nothing to do with the variations in ageing rates across species, which have been reported so far.

In 2016, HF represents the endpoint of most CVD. Average lifespan reaches 80 years in most developed countries, and because the main cause of the CV manifestations is atherosclerosis, HF is mainly observed in aged persons with ischaemic heart disease. Both ischaemia and HF generate myocardial fibrosis, thereby increasing myocardium heterogeneity and stiffness [16, 45]. Fibrosis is actually the main biomarker for HF [16, 46]. From an evolutionary perspective, the heart fails while attempting to maintain a normal cardiac output firstly because the adaptive process has its own limits.

10.3 Implications for Policy and Practice

Several CVDs can be understood within an evolutionary framework. Here, we focuses on chronic HF, a leading cause of morbi-mortality and the endpoint of most CVD including ischaemic heart diseases, arterial hypertension and valve diseases.

Chronic HF occurs after a long period of adjustment of the heart to the new working conditions imposed by CVD (e.g. atherosclerosis). Cardiac hypertrophy

and the slowing of the maximum shortening velocity (Vmax) are the main components of this adaptive process. Hypertrophy is adaptive by both increasing the number of contractile units and reducing the wall stress. The slowing of V_{max} is adaptive by normalizing cardiac muscle economy. Such an adjustment has been made possible by an ancient, widespread and evolved cellular response to physical forces, called mechanotransduction. Mechanotransduction renders the cardiac contractions slower and more efficient under increased load. From an evolutionary perspective, the heart fails firstly because the adaptive process reaches its own limits. In addition, the anthropogenic increase in lifespan and the accompanying ageing have contributed to a new dimension, cardiac fibrosis that aggravates cardiac function and is one of the main biological markers for HF. To conclude, at the beginning, cardiac remodelling is not a disease per se but the physiological response of the heart to a CV disease. HF indicates the limits of this physiological adaptive process and is a disease.

Evolutionary thinking has practical consequences for the diagnostic and treatment of HF.

New diagnostic biomarkers cardiac hypertrophy, the lengthening of the QT interval duration on ECG and the slowing of Vmax are clinical markers for adaptation. In addition, BNP plasma level is a routine biomarker for HF in clinical practice. Its increase is the result of foetal reprogramming, and as a diuretic factor, BNP participates to the adaptive process by reducing cardiac load.

The helical cardiac structure has been shaped by embryo development in every tetrapod, and systolic torsion impairment observed during the early stages of cardiac overload is an important prognostic factor for HF. Attempts to quantify cardiac torsion were proposed to measure cardiac performances instead of the ejection fraction that is currently utilized by clinicians.

As a new perspective on the treatment and from an evolutionary perspective, the major goal of the treatment of chronic HF is to improve muscle economy and a positive inotropic effect is not indicated in chronic HF (as opposed to acute HF). The major goal of therapy is then to reduce the load either by suppressing the cause (e.g. by treating a valve disease or hypertension), or by reducing the loading conditions (e.g. with anti-aldosterone drugs, converting enzyme inhibitors or diuretics).

The present modifications of the medical landscape render HF a more complicated disease. Any evolutionary thinking has to include a new crucial factor, namely the age-associated cardiac fibrosis, which renders the heart stiffer both mechanically and electrically heterogeneous. Cardiac fibrosis is a consequence of the activity of the aged cell, and ageing itself results from the recent anthropogenic enhancement of lifespan. Cardiac fibrosis is presently an important determinant of HF both in clinical and in experimental condition.

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Glossary

Atheroma and Atherosclerosis	Lipid accumulation in arterial wall intima, media and sometimes adventitia, leading to foam cells and an important inflammatory reaction. The process leads to arterial stenosis and angina pectoris. Ultimately, atherosclerotic plaques are formed, and plaque rupture within arterial lumen causes thrombosis and myocardial infarction (or brain stroke). The disease is multi-factorial and involves numerous genetic and environmental factors
Cardiac remodelling	Qualifies changes that result in the rearrangement of normally existing structures. Cardiac remodelling includes cardiac hypertrophy, foetal gene reprogramming and fibrosis
Fibrosis	An increased concentration and mass of extracellular matrix components, mainly collagen
Foetal gene reprogramming	Gene reprogramming is essential for any organ facing new environmental conditions, such as pressure or volume overload in the heart. For the heart, the only alternative programme available is the foetal programme (see Table 10.1). For the skeletal muscle, an additional programme is also possible and re-expressed, the embryonic programme. Most elements of these two reprogramming phenomena are adaptive … by chance (see discussion in Ref. [30])
Heart failure	The heart fails when it cannot assume anymore the normal oxygenation of peripheral tissues by a normal output [11, 14, 15]
Inotrope	Agent that increases cardiac force and contractility. Calcium itself is the physiological inotrope, but is not utilized as a drug. Major drugs having an inotrope effect include digitalis, digoxin, several

	adrenergic agents and calcium sensitizers. Most of them have additional pharmacological effects. Digitalis, for example, is also a diuretic, and this is why digitalis is still prescribed in certain conditions of chronic HF by clinicians
Maximum contraction velocity of the unloaded cardiac muscle	See V_{max}
Mechanotransduction	The cellular responses to mechanical forces. The process is essential in physiologic homeostasis and for embryonic development and is present in nearly every cell and living species. One essential piece of the transduction is the linker of nucleoskeleton ad cytoskeleton (LINC) complex, which exists from yeasts to humans (Fig. 10.1). LINC was initially a determinant of several basic cellular processes such as meiosis, nuclear shaping and chromosome organization. As such, the complex has preserved its general architecture throughout evolution before being able to act as an essential component of mechanotransduction [21]. In the switch-like models of mechanotransduction, applied forces are instantaneously transmitted to load-bearing structure and induce conformational changes in mechanosensitive proteins, including those from the LINC complex. Mechanotransduction is sensitive to cyclic and steady stretch, vibration, stress and pressure through different pathways and plays, for example, a role in hearing, the inflation/deflation of the lungs and touch sensation, and in many diseases including cancer, osteoporosis, myopathies and muscular dystrophies [19, 20]
Sarcomere	Contractile unit of the myofibril. It includes two main filaments (thin and thick). The sliding of these filaments is the basis of muscle contraction. Sarcomere proteins include actin, myosin, titin and

	the troponin components and participate in mechanotransduction both as a sensor and as an actor
Shear stress	Force component applied tangentially to the surface of a material (the luminal side of a vessel wall), which tends to cause deformation. In vascular physiology, shear stress depends on blood content, pressure and turbulences. It is a major atherogenic component. Arterial hypertension also increases shear stress
Stiffness	Pressure per volume change, a physical measurement of the rigidity of vessels or of the cardiac cavity
V_{max} or maximum contraction velocity of the unloaded cardiac muscle	Physiological measurement commonly made on isolated papillary muscle indicating the maximal contractile capacity of the heart. In phylogeny, V_{max} correlates with the ATPase activity of the main contractile protein, myosin. Such a correlation is usually considered as the biochemical explanation to explain the differences between fast (white) and slow (red) muscles [30]

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