PROGNOSTIC VALUE OF ECHO-DERIVED PEAK CARDIAC POWER OUTPUT-TO-LEFT VENTRICULAR MASS COMPARED TO CARDIOPULMONARY EXERCISE TESTING IN PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION

Relatore
Chiar.mo Prof. Mario Marzilli

Candidato
Giulia Elena Mandoli

Anno Accademico 2013/2014
Alla mia famiglia
ABSTRACT

Background. Peak cardiac power output (peak CPO) at exercise echocardiography showed to be closely related to peak VO2 at cardiopulmonary exercise testing (CPET). To gain further perspective in the evaluation of left ventricular (LV) remodeling in myocardial hypertrophy, the peak cardiac power output-to-LV mass (peak CPOM), a measure of the rate at which cardiac work is delivered with respect to the potential energy stored in LV mass, was recently introduced.

Aim. To compare the value of peak CPOM with CPET variables in the prognostic stratification of patients with chronic stable heart failure (HF) due to LV dysfunction.

Materials and methods. 115 patients with chronic stable HF (mean LV EF% 0.31±0.6) underwent CPET and exercise echocardiography. The two tests were performed within 7 days according to standard symptom-limited exercise protocols. Peak CPOM was calculated as the product of a constant (K=2.22 x 10^{-1}) with cardiac output (CO) and the mean arterial pressure (MAP) divided by LV mass (M) to convert the units to watts/100 g: CPO = K × CO (l/min) × MAP (mmHg) × M^{-1}(g). Patients were followed-up for the composite end point of all-cause mortality or hospitalization for HF.
Results. There were 16 deaths and 21 hospitalizations for worsening HF during a mean follow-up of 24 months. At ROC analyses, the areas under the curve for the composite end point were greater for peak CPOM (AUC=0.82) and VE/VCO2 (AUC=0.76), followed by CPO (AUC=0.75), peakVO2 predicted (AUC 0.72), VO2 (AUC =0.69), LV EF (AUC=0.69) and NYHA class (AUC=0.68). At the multivariate logistic regression analysis, peak CPOM was the most powerful predictor of outcome (p <0.0001). The Kaplan-Meier analysis revealed that survival free from HF-hospitalization at 24 months was 83% in patients with a peak CPOM >0.60 watts/100 g, while it was 29% in those with a peak CPOM ≤0.60 watts/100 g (p <0.0001, Logrank: 34.1).

Conclusion. The assessment of LV ratio power-to-mass by the echo-derived peak CPOM can provide additional insights in the prognostic stratification of patients with HF.
INDEX

1 HEART FAILURE ...........................................................................................................7

1.1 Epidemiology ............................................................................................................8

1.2 Clinical classification .................................................................................................9

1.3 Aetiology and risk factors .........................................................................................11

1.4 Physiopathology of heart failure .............................................................................14

1.4.1 The neurohormonal model ...............................................................................15

1.4.2 Cardiac hypertrophy and left ventricular remodeling .....................................20

1.4.2.1 The meaning of hypertrophy ......................................................................24

1.4.2.2 Structural alterations of the myocardial architecture ..................................26

1.4.2.3 The relationship between myocardial hypertrophy and heart failure .......31

2 THE HEART AS A PUMP ............................................................................................37

2.1 Cardiac work ............................................................................................................40

2.1.1 Pressure-Volume Diagram ..............................................................................43

2.1.2 The ventricular elastance .................................................................................47

2.2 Cardiac power .........................................................................................................50

2.3 Myocardial efficiency ..............................................................................................51

2.4 Peak cardiac power output-to-left ventricular mass (CPOM) .............................53

3 AIM OF THE STUDY ....................................................................................................56

4 MATERIALS AND METHODS....................................................................................57

4.1 Population of the study ...........................................................................................57

4.1.1 Exclusion criteria ..............................................................................................57

4.2 Echocardiography ..................................................................................................58

4.3 Exercise echocardiography .....................................................................................59

4.4 Cardiopulmonary exercise testing (CPET) ............................................................60

4.5 End Points of Event-Free Survival .........................................................................61

4.6 Statistical Analysis ..................................................................................................61

5 RESULTS ......................................................................................................................63

5.1 Characteristics of the study patients .......................................................................63

5.2 Time-independent analyses of event-free survival .............................................66

5.3 Time-dependent analyses of event-free survival ................................................70

6 DISCUSSION ...............................................................................................................75

6.1 Limitations ...............................................................................................................81

7 CONCLUSIONS ..........................................................................................................83
8 BIBLIOGRAPHY .................................................................................................................. 85

Index of figures ....................................................................................................................... 91

Index of tables ........................................................................................................................ 91

List of abbreviations ................................................................................................................ 92
1 HEART FAILURE

Over the years many definitions of heart failure (HF) have been given. The historically-recognized definition is the one conveyed by Braunwald in his essay: “The heart failure is a pathophysiological state, in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues, or in which the heart can do it at the expense of an increase of the filling pressure. The inability of the heart to satisfy the tissue needs can be due to an inefficient or insufficient filling and/or to an abnormal contraction and following emptying”.¹ The same author defines the heart failure also under a clinical point of view as “a syndrome that affects those patients who, because of hereditary or acquired alterations of the heart structure or the heart function, develop a constellation of clinical symptoms (dyspnoea and asthenia) and signs (oedema and wheeze) that lead to frequent hospitalizations, to a decrease of the quality of life and to a minor life expectancy”.² When a symptomatology due to an organ dysfunction turns up, we can start talking about decompensated heart failure.

In 2013 AHA guidelines for the Management of Heart Failure, HF is defined as “a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood”.

1.1 Epidemiology

The heart failure has been defined as an epidemic but its real epidemiology is complex because of the several factors that interact in a complicated way to influence its prevalence and incidence. Some manifestations, above all the early and the organ-specific ones, can be difficult to diagnose precisely. The intrinsic ambiguity led to the definition of various criteria used in epidemiological studies, such as the ones used by the Framingham Heart Study, those used by Cardiovascular Health Study or by the European Society of Cardiology.

Every year 670,000 new cases of heart failure are diagnosed. Some studies have demonstrated how the incidence, adapted for gender and age, has been steady in the last years, whereas the prevalence turns out to be increased from the 70s thanks to the increase of survival of the patients affected. The prevalence, specifically, increases with age and in particular it mainly enhances over the age of 65. Even though the relative incidence is minor in women, they form more than the half of cases due to the superior life expectancy. Furthermore the combination between an ageing of the world population and a demographic increase will lead to a reduplication of the population over 65 years old, so the most exposed category, and consequently to a further increase of individuals affected by heart failure.
It is evaluated that there are about 23 millions of people in the world affected by heart failure nowadays.\textsuperscript{9}

For what concerns the death rate, despite of the improvement of both diagnostic techniques and therapeutic options, the heart failure still remains a deadly clinical syndrome. According to the Framingham Heart Study, the mortality at 30 days increases up to 10\%, at a year up to 20-30\% and at 5 years up to 45-60\%.\textsuperscript{7}

\textbf{1.2 Clinical classification}

The heart failure can be functionally divided into:

- High-output heart failure
- Low-output heart failure.

The high-output heart failure is characterized by a volumetric overload, with a consequent increase of the ventricular diastolic pressure, but with a stroke volume chronically elevated.

With “high-output” we usually refer to a value > 8 litres/minute or as a cardiac index > 3.9 l/min/m\textsuperscript{2}.\textsuperscript{10} According to some authors, the same definition would be improper because the heart is inherently normal and able to generate a high stroke volume; others, instead, have highlighted that, anyhow, it is a condition that occurs only with in presence of underlying cardiac illnesses.\textsuperscript{11} A chronic high-output condition can be associated to cardiac dilatation and hypertrophy,
persistent tachycardia and valvular abnormalities: these are conditions that can all culminate into the development of heart failure. From a pathophysiological point of view, the main problem in the high-output form is linked to the presence of reduced peripheral vascular resistances that are caused by a phenomenon of widespread vasodilation or by the presence of an arterial-venous shunt.

Both these conditions can determine a drop in systemic arterial pressure, a peculiarity of low-output heart failure. Nonetheless this condition leads to a sympathetic activation, to an offsetting increase of the cardiac output and to a neurohormonal activation (included RAS and vasopressin); this process may cause hydrosaline retention and decompensated heart failure. Therefore the hydrosaline retention, that ensues a neurohormonal reaction similar to that in the systemic hypotension, occurs in both the low- and high-output, but in the first case is due to the reduced cardiac output, while in second one to a decrease of the peripheral vascular resistances (see Figure 1.1).  

The main causes of this kind of heart failure include chronic anaemia, thyrotoxicosis, presence of a systemic arterio-venous fistula, Paget’s disease.

In Western countries, the prevalence is much lower if compared to the low-output heart failure, characterized by a decreased cardiac output.
1.3 Aetiology and risk factors

In recent years, attention has been focused on the distinction between heart failure with reduced ejection fraction (HErEF, less than 40%) and heart failure with preserved ejection fraction (HEpER, more than 40-50%). In order to define the preserved ejection fraction-form, many criteria have been proposed, which include: clinical signs and symptoms of heart failure, evidence of preserved or normal left ventricular ejection fraction and evidence of abnormalities in left ventricle with diastolic dysfunction that can be determined by Doppler-echocardiography or cardiac catheterization. Studies
demonstrated that the incidence of HFpEF is increasing and a great portion of hospitalized patients shows this variant; they are mainly older women with a history of arterial hypertension\textsuperscript{14}, but at the base there are frequently obesity, CAD, diabetes mellitus, atrial fibrillation, and hyperlipidaemia, as well.\textsuperscript{15} Patients who show a left ventricular systolic dysfunction typically have some elements of diastolic dysfunction.\textsuperscript{16}

Despite of the difference between the two aetiologies, there are many points in common. In industrialized countries, the main cause (60-75\%) of heart failure is coronary artery disease, including both ischemia and acute myocardial infarction, in both genders. Studies have shown that within 7-8 years following a myocardial infarction, more than one third of patients will develop heart failure, especially those individuals affected by a left ventricular dysfunction that had already been detected at the time of the acute event.\textsuperscript{17} So having a positive anamnesis for AMI enhances exponentially the probability of developing heart failure during life and it is not surprising that, given the close association between coronary artery disease and heart failure, a lot of atherosclerosis risk factors are also risk factors for the development of the second one.

In the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry, ischemia was pointed out
as the main cause of hospitalization in patients with heart failure and also the principal responsible for hospital death rate in the same patients.\textsuperscript{18}

Another important risk factor for heart failure is arterial systemic hypertension, responsible for the appearance of a pressure overload in the left ventricle. In the cohort of patients from the Framingham study, 75\% of patients had a history of AHT.\textsuperscript{19} In previous studies, it had already been highlighted how AHT also doubles the risk of developing heart failure in men and even triples in women.\textsuperscript{20} There is a correlation between the magnitude of ATH and the risk of the disease since the greater is the elevation of blood pressure, the greater the risk of developing heart failure is. The probability of fatal events in patients with BP $\geq 160/90$ mmHg is twice that of those with BP $<140/90$ mmHg.\textsuperscript{19}

The pressure overload can be equally caused by an obstructive valvular disease.\textsuperscript{21}

Also diabetes mellitus, which is a pathology whose prevalence is nowadays in a remarkable increase, and insulin-resistance are linked to the development of heart failure, above all in the female sex, where the risk increases 5 times than in the healthy population.\textsuperscript{22} Furthermore diabetes correlates to a worse prognosis if heart failure occurs: the Olmsted cohort has shown that the 5-year
survival of patients suffering from both heart failure and diabetes was only 37% compared to 46% of patients with heart failure but without diabetes.\textsuperscript{23}

Elevated cholesterol levels are a known risk factor for atherosclerotic vascular disease so they can be also correlated with heart failure. Although elevated concentrations of total cholesterol are not a strong predictor of the onset of heart failure, an increase in the ratio between total cholesterol and HDL are associated with a high risk of development of the pathology.\textsuperscript{24}

We must not forget the role of cigarette smoking: tobacco use remains the main avoidable cause of disease and premature death in the United States of America. The current smokers have a higher risk of developing heart failure compared to non-smokers and ex-smokers. The CASS (Coronary Artery Surgery Study) shows that smoking is independently associated with an increased risk of heart failure by 47%.\textsuperscript{25}

1.4 Physiopathology of heart failure

Heart failure can be seen as a progressive disease that is to realize from the moment when an index event leads to a damage of the heart muscle, with a consequent loss of function of cardiomyocytes or to a disruption of the ability of the myocardium to generate force with inability of the heart to contract normally. Regardless of the nature of the pathogenic cause, the common
feature of each of these index events is that all lead to a decrease in the pumping function of the heart.

In response to the event that brings to an alteration of the systolic function of the left ventricle, some compensatory mechanisms trigger and precipitate, ultimately, in compensated (then mostly asymptomatic at the clinical level) heart failure at first and finally decompensated.

1.4.1 The neurohormonal model

The first compensatory mechanisms that the body puts in place are those included in the “neurohormonal model”, which comprises the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. Numerous studies, carried out in the second half of the 90s, have shown that heart failure progresses because of an overexpression of biologically active molecules that determine a deleterious effect both on the heart itself and on the circulation. Actually it is emerged that a high proportion of classical neurohormones, primarily norepinephrine and angiotensin II, is not produced only at the level of the neuroendocrine system and so it acts in an endocrine way on the heart, but it is also synthesized within the myocardium itself, and then it acts in an autocrine and paracrine way.
For what concerns the activation of the sympathetic nervous system, this is a phenomenon that develops early during the evolution of heart failure and it is associated with a parallel reduction of the parasympathetic tone. In standard conditions, inhibitory afferent fibres coming from the baroreceptors of the arch of aorta and from the carotid sinus as well as from the cardiopulmonary mechanoreceptors, are responsible of the inhibition of the sympathetic tone whereas the input coming from muscular metaboreceptors and from peripheral chemoreceptors, is the primary stimulus to sympathetic efflux; in patients with heart failure, instead, the inhibitory sign decreases to the detriment of the increase of excitatory tone and this causes a generalized growth of the sympathetic stimulation and in a weakening of the parasympathetic one (see Figure 1.2). This process determines a loss of the variability of the heart rate and an increase of the peripheral vascular resistances.²⁸
Consequently to the increase of the sympathetic tone, there is an increase of circulating levels of noradrenaline (NA) as a result of both its increased synthesis and reduced reabsorption from the nerve endings. In patients with heart failure in the early stages, we can find circulating norepinephrine at 2-3 times higher levels than the normal values. With the progression of the disease, instead, there is a marked reduction in the levels of this neurohormone as a result of a phenomenon of “exhaustion” following the prolonged activation of the cardiac sympathetic nerves but also the reduced activity of myocardial tyrosine-hydroxylase, which is the speed-limiting
enzyme in the synthesis of noradrenaline. As a proof of this process, performing a myocardial scintigraphy using MIBG (Metaiodobenzylguanidine, normally taken up by adrenergic nerve terminals) marked with iodine-131, we can see that the uptake does not occur in a normal way, which indicates a compromised reabsorption of NA.\textsuperscript{30}

In the presence of high concentrations of norepinephrine, the stimulation of the sympathetic receptor $\beta_1$ in cardiomyocytes plays an inotropic and chronotropic positive effect with a consequent increase in cardiac stroke volume, while the stimulation of $\alpha_1$ vascular receptors causes peripheral vasoconstriction. This is a mechanism that tries to compensate the inability of the heart to perfuse the peripheral organs but actually increases the energy requirements of the myocardium itself and thus aggravates ischemia under conditions of already-reduced oxygen concentrations, which can even lead to sudden cardiac death.\textsuperscript{31}

Differently from the sympathetic nervous system, the components of the renin-angiotensin-aldosterone system are activated at a later time. It seems that the leading cause of the induction of this system lies in the renal hypoperfusion, which derives from the reduced cardiac output.

The main hormone of the activation cascade is the angiotensin II (AG-II), which, at short term, plays a homeostatic role on circulation but at a long term has harmful effects, since it determines the development of interstitial fibrosis
not only at cardiac level but also at renal and many other organs; moreover it may cause a worsening of the neurohormonal activation due to an increased release of noradrenalin and to the stimulation of the adrenal cortex, causing the secretion of aldosterone. The latter one, as the AG-II, supports firstly the circulation by promoting sodium reabsorption in the kidney, but in time induces hypertrophy and fibrosis in the myocardium and blood vessels with reduced compliance and increased ventricular stiffness; in addition it determines baroreceptoral and endothelial dysfunction and reduces the reuptake of norepinephrine with further worsening of heart failure.\textsuperscript{32} Not to be forgotten the fact that the activation of RAAS causes, in the last instance, marked hydrosaline retention, one of the most significant aspects from a clinical point of view of heart failure.

In order to thwart the activity of these vasoconstrictors neurohormones, some mechanisms of counter-regulation trigger.

In patients with heart failure we can record high levels of prostaglandin E\textsubscript{2} and prostacyclin I\textsubscript{2}, which act through a vasodilator mechanism and counteract the hydrosaline retention.

The natriuretic peptides, including the atrial natriuretic peptide (ANP) and the brain natriuretic peptide (BNP), are secreted by heart chambers in relation to the transmural pressure, often consequent to the increased hydrosaline retention, largely contributing to the maintenance of the pressure-volume
homeostasis. In fact, they act at renal level by promoting the excretion of water and sodium and inhibiting the release of renin and aldosterone, on vessels with a vasodilating effect, as well as on many organs with an anti-fibrotic effect. Therefore we can easily understand how, above all in the early phases of heart failure, their role is important to prevent a quick worsening of the condition due to vasoconstrictor neurohormones. In advanced heart failure, however, because of many still-obscure reasons, their action seems to be weakened, leaving plenty of time and space to the RAAS activity. Nevertheless the close relationship between the plasmatic concentrations of these peptides and the cardiac load, led to their use as cardiac-health markers with diagnostic and prognostic applications in a variety of illnesses that affect the cardiovascular system; in particular the BNP and its N-terminal fragment (NT-pro-BNP) – that despite of its biological helplessness, it is secreted in a same molar quantity than the first one – have been valued for their use in the management of heart failure and, in part, in its diagnosis as well, even though their concentrations are influenced also by the age and the possible presence of renal comorbidity.

1.4.2 Cardiac hypertrophy and left ventricular remodeling

At a long term, the maintenance of the neurohormonal imbalance in favour of vasoconstrictor hormones, as well as the pathogenic cause underlying the heart failure, leads to the development of cardiac hypertrophy.
A hypertrophy is an increase of cell size with a consequent increase of the organ size. This increase in volume is correlated to an increased synthesis of the structural components of a cell. The hypertrophy can be either physiologic or pathologic, and at the base there is an increased functional demand or a specific hormonal stimulus.\textsuperscript{36}

The cardiomyocyte is generally considered as a cell with terminal differentiation that has lost its ability to divide, thus an increase of the mechanical load of the heart does not cause an increase in the number of cells (hyperplasia), but just a hypertrophy. The number of blood vessels and their relationship with the number of the cells remain unchanged. The increase in the mechanical work caused by pressure or volume overload or by trophic signals increases the synthesis of proteins, the amount of proteins in each cell, the number of sarcomeres and mitochondria, the size and mass of myocytes, therefore lastly the size of the heart.\textsuperscript{37}

Furthermore the kind of hypertrophy reflects the nature of the stimulus. We can classically distinguish two kinds of hypertrophy:

- **Eccentric hypertrophy**: by this we mean the increase of the number of sarcomeres for serial affixing (see Figure 1.3 and 1.4). Fibres turn out to be longer and the ventricular chamber turns out to be bigger. This volume enhancement is obtained without fibre stretching, namely
without an increase of preload in sense of an increase of strain, scilicet as the detente of sarcomere. With this process, the heart can be even doubled in volume while the end-diastolic pressure is normal. This adaptation is impossible to have with the dilatation mechanism. The eccentric hypertrophy intervenes as a compensation in volume overloads, namely when the heart has to increase, a lot and chronically, the ventricular load without elevating the pressure and the heart rate.

- **Concentric hypertrophy**: by this, instead, we mean the increase in the number of sarcomeres for parallel affixing (see figure 1.3 and 1.4). The fibre is therefore thicker and the volume of the ventricular chamber does not change while the wall is thickened. Thus the ventricular mass increases and so the mass/volume ratio. Sometimes the thickening takes place towards the interior of the chamber that will be then reduced in volume. The concentric hypertrophy always involves unfavourable consequences for the cardiac dynamics, for example: it increases the distance between the capillary vessels and the centre of the fibre, therefore it creates a certain cellular hypoxia in some areas which leads to a loss of contractility; it increases the fibrous component and thus increases the average stiffness of myocardial tissue, and consequently decreases the compliance of LV; bridges of connection between the fibres develop. In conclusion, in hypertrophy concentric, the fibre
distensibility decreases given that, to equal diastolic pressure, the force that stretches the fibre is lower (by the law of La Place). This kind of hypertrophy represents the compensation mechanism of chronic pressure overloads such as in aortic stenosis and in arterial hypertension. It is better to discern this form from the concentric remodeling, in which the mass/volume ratio has increased without a mass increasing (thus the volume is reduced).  

Figure 1.3 The concentric and eccentric hypertrophy can be distinguished through the orientation with which the sarcomeres are added.
1.4.2.1 The meaning of hypertrophy

The force-velocity and pressure-output curves show an inverse relationship between the ability to develop force and the one to shorten. This inverse relationship has its foundation in biochemistry and thermodynamics of the contraction. From these considerations, derives that the maximum power (obtainable from the product of the pressure for the output or, in case of fibre, from the product of the force for the shortening velocity) can occur only at an average level of force or pressure. Practically the heart always tries to place itself into a certain condition in order to work at the highest power, and so the
compensation mechanisms tend to keep the contraction force – namely the diastolic and systolic stress – constant.

When a chronic overload interferes, the compensation is given by the hypertrophy or by the concentric remodeling that work precisely, standardizing the systolic stress. From the law of La Place we know that

\[ T = \frac{pR}{2h} \] (where \( T \) = parietal tension, \( p \) = pressure, \( R \) = radius, \( h \) = parietal thickness) thus to keep the stress constant, if \( p \) increases (systolic overload) the \( R/h \) ratio must decrease. This is obtained through the concentric hypertrophy, which models the heart in order to increase the thickness without changing, or even diminishing, the radius. If the radius enhances (volume overload), instead, the thickness must increase a bit, because the \( R/h \) ratio must be constant.

The constancy of the \( R/h \) ratio or its equivalent’s one, perhaps more used, mass/volume is therefore necessary to ensure the optimization of the contraction force. If this contraction force is normal (diastolic stress), the hypertrophy is “adequate”. In the normal pressures field, the hypertrophy is appropriate when the mass/volume ratio is equal to 1 or when \( R/h < 4 \). The optimal mass/volume ratio is equal to 0.8% and if this value is in default, the hypertrophy is “inadequate”. This is a characteristic of failing hearts, at least potentially, because they act in suboptimal zone for an excess of afterload.
Eventually, if the hypertrophy is excessive and so the systolic stress is decreased, the hypertrophy is called “inappropriate”.$^{38}$

1.4.2.2 *Structural alterations of the myocardial architecture*

Several studies have demonstrated how the cardiomyocytes hypertrophy causes some modifications of the myocyte biological phenotype that follow the reactivation of a group of genes that are normally not-expressed after birth. The reactivation of these foetal genes, the so-called *foetal genetic program*, is also accompanied by the reduced expression of genes normally expressed in the adult heart. The stimuli for the myocyte genetic reprogramming include the stretch-strain of the myocyte itself, neurohormones (such as NA, AGII), the inflammatory cytokines (such as the endothelin) and the reactive oxygen species, ROS, (for example superoxide, NO). These stimuli act locally inside the myocardium where they exert autocrine and paracrine effects, as well as at systemic level where they produce endocrine effects.

The beginning phase of cardiomyocytes hypertrophy is morphologically characterised by increases in number of myofibrils and mitochondria, as well as by the enlargement of mitochondria and of nuclei: the cell overall looks bigger although with a subcellular organisation still preserved. As the
hypertrophy advances, instead, mitochondria increase in number and new contractile elements are added in some confined areas of the cell itself.

When subjected to long-term hypertrophy, cells thus show a clear subversion of the cellular architecture such as markedly enlarged nuclei with greatly-lobulated membranes, associated with displacement of adjacent myofibrils with loss of the normal recording of Z-bands. Eventually, the late stage of hypertrophy is characterized by the loss of the contractile elements (myocytolysis) with marked disruption of the Z-bands and severe subversion of the normal sarcomeres parallel arrangement, associated with dilation and increased tortuosity of the T-tubules (see Figure 1.5).
Figure 1.5 Histopathology of hypertrophy
A. The beginning phase of cardiac hypertrophy is morphologically characterized by the increase in number of myofibrils and mitochondria and in volume of mitochondria and nuclei. Myocelles are larger than the normal ones but the cellular organization is mostly preserved.

B. At a more advanced phase of hypertrophy, cells increase preferentially the volume or the number of little specific organs such as the mitochondria and we can observe the addition of new contractile elements in some cellular areas that lead to a cellular ultrastructure and borders abnormality; the surrounding cells can have variously increased in volume.

C. Cells that are subjected to a long-term hypertrophy show obvious abnormalities of the molecular structures such as markedly enlarged nuclei with greatly-lobulated membranes, that cause displacement of adjacent myofibrils and so the alteration of the normal recording of Z-bands.

D. Eventually, the late stage of hypertrophy is characterized by the loss of the contractile elements, marked disruption of the normal sarcomeres parallel arrangement, fibrous tissue deposition and dilation and tortuosity of the T-tubules.2

One of the main problems of a heart that undergoes a hypertrophic programme is linked to the proliferation of the connective tissue component that accompanies the cardiomyocytes hypertrophy and, in a last instance, leads to the development of interstitial fibrosis. In fact, besides the increase of muscle mass, strictly speaking, cardiac hypertrophy also concerns the
proliferation of non-myocyte elements, in particular fibroblasts, and the deposition of the extracellular material.\textsuperscript{43} This aspect is found primarily in the ventricles with pathological hypertrophy, whereas in physiological hypertrophy is marginal and therefore we tend to think that this is exactly the crucial difference between the pathological hypertrophy and the athlete’s heart.\textsuperscript{44}

As demonstrated a long time ago, it is possible to observe cardiac fibrosis in many conditions, in presence of both volumetric and pressure overload; in these circumstances, we observe a thickening of the fibrillar collagen and a remodeling of extracellular matrix up to the disappearance of myocardial fibrosis, which, when is in excess, markedly contributes to the ventricular dysfunction.

In the chronic pressure overload, the structural remodeling of the interstitial component of the LV wall does not regard, however, only the collagen accumulation. Particular importance is in fact covered by modifications that affect the collagen architecture. In animals suffering from pressure-overload hypertrophy, it was demonstrated a pathological alignment of collagen fibrils, the so-called \textit{cross-hatching}.\textsuperscript{45} These alterations have been reported also in men, where collagen fibrils have been pinpointed and these had an increased thickness with marked cross-hatching. In patients with aortic stenosis, this
particular interstitial remodeling turns out to be associated to a decrease in the ejection fraction and an increase in diastolic rigidity.\textsuperscript{46}

It seems that at the base of the whole process there is – again – the angiotensin II and aldosterone activity.

When the increase in ventricular mass is not due only to the myocyte hypertrophy but also to the interstitial fibrosis, some alterations of the nutrition of the myocardial tissue, that depend on an organic and functional transformation in a pathological sense of the coronary circulation, may occur. In the end, the association between fibrosis, increase of the intercapillary distance and decrease of the capillary density may contribute to compromise coronary reserve in these subjects.

Just about the vascular aspect of hypertrophy, it is known that in the hypertrophic heart, compared to the increase muscular mass, the number of capillaries decreases per unit area. Moreover, the increase in dimension of myocytes, to which follows a reduction of the cellular volume/surface ratio, determines an increase of oxygen diffusion distance from blood to myocytes. Thus the hearts is in a condition of altered mass/vascular supply ratio, to which the development of myocardial hypoperfusion may follow. In the peculiar hypertrophy of the athlete’s heart, instead, we cannot observe any trophic disorders of cardiomyocytes.
In addition to the structural component, also functional factors contribute to limit the coronary reserve. It seems that a reduced ability of self-regulation of the coronary circle may contribute to the limitation of the coronary reserve of hypertrophic heart.\textsuperscript{47}

Recently attention has been focused on the modification of the endothelial response to the variations of coronary flux and in particular on a reduced synthesis of releasing factors of endothelial origin, such as the NO, and the overproduction of vasoconstrictor substances, such as the endothelin-1, that may be the cause of an increase on vascular resistances. The increase of MVO\textsubscript{2} seems to contribute to alter the demand/offer ratio to the myocardial cell, above all at a subendocardial level, where – during the cardiac cycle – higher tension apply.\textsuperscript{48}

1.4.2.3 The relationship between myocardial hypertrophy and heart failure

As already said, it is now established that cardiac hypertrophy, even though it arises as adaptive process, at a certain point it comes to acquire the characteristics of a pathological phenomenon that leads to biomolecular, biochemical and morphological alterations of myocardium. When the hypertrophy gets inadequate, a sequence of events starts happening, and, through the expansion and the progressive deterioration of ventricular function, it may lead to the development of heart failure.\textsuperscript{49} At the base of the
functional hypertrophic LV deterioration there are many causes such as an altered cellular energy balance, the loss of contractile elements due to necrosis or apoptosis, modifications of the extracellular matrix and a reduced myocardial function that follows the expression of typical genes of foetal heart.

The role of myocardial hypertrophy in heart failure pathogenesis is possibly crucial; the presence of a hypertrophy in hearts with chronic dysfunctions is almost detectable in a constant way. Nowadays, however, any kind of mechanisms able to provide a convincing explanation of the process that leads from the hypertrophy to heart failure has been proved. In the context of a cardiac disease, hypertrophy can be seen as an intermediate stage between the initial myocardial damage and subsequent irreversible myocardial failure. Probably in the evolutionary history of hypertrophy, the overlap of alterations of the structural components of myocytes related to parietal stress, of myocardial nutrition and of intervention of biochemical factors related to the overload but also to the basic pathogenic cause, will lead to a shift from adaptive to pathological hypertrophy.

In the 60s, Meerson and colleagues,\textsuperscript{50} relying on studies conducted on rabbits, defined the phases in which the evolution from hypertrophy to left ventricular failure consists. The first stage corresponds to the initial myocardial injury,
which can be derived from the underlying presence of an overload or it can be the primary cause of the overload of the remaining healthy myocardium itself; later a condition of stable hyperfunction establishes, followed by a stage of exhaustion and fibrosis. This sequence is observable in conditions of acute hemodynamic overload, in which a temporary and initial impairment of the ventricular function turns up, followed by an usually-prolonged period of return to normality and it finishes with an evolution into cardiac disease; in the majority of valvular illnesses and in arterial hypertension conditions, the first stage is hardly recognisable because the overload establishes gradually.

On experimental laboratory preparations, it is possible to record how, in response to an acute overload, an asynchronous synthesis of contractile proteins occurs, as well as an abnormal genesis of subcellular structures, besides to an inadequate increase of the capillary network and a deposition of abnormal quantities of connective tissue. Moreover, in the isolated and working heart of rats subjected to the effects of acute pressure overload, it was observed a significant increase of the heart weight, reflecting the presence of myocardial oedema, associated to a quick and marked depression of the ventricular function. By analysing the ultrastructural data, it turned out a significant increase of the interstitial space, combined with signs of cellular necrosis, mitochondrial alterations and fragmented and disoriented myofibrils. Furthermore, the excess of interstitial fluid can determine an impairment of
the myocardial perfusion through the increase of the diffusion distance of oxygen and the extravascular compression of microcirculation.

In the following phase of stable hyperfunction (stage II), the ventricular hypertrophy represents a compensatory phenomenon to the elevated load due to the high parietal stress. As already said, as long as the hypertrophy is able to balance the hemodynamic load, while maintaining the wall stress, it is called «adequate hypertrophy». At this stage, the myocardium is able to function normally, developing high isometric tensions and supporting an increased mechanical work for extended periods, even months or years. However, this incessant overload may lead to exhaustion of the capacity of myocytes to synthetize, to intracellular accumulation of calcium, to alteration of the balance of myocardial oxygen and to interstitial remodeling. At this stage, it can already be demonstrated the presence of reactive fibrosis and small areas of reparative fibrosis localized mainly in the subendocardial area; this is a prerequisite for the transition to structural changes that accompany the development of inadequate hypertrophy. Probably myocyte apoptosis may play an important role in the progression to myocardial failure, as well.

Eventually, the next phase of exhaustion and progressive cardiosclerosis (stage III) denotes the final stage, in which the muscular cells present degenerative phenomena, they can come across death and can be substituted by fibrotic tissue. The clinical manifestations of heart failure are the consequence of the progressive myocardial damage that occurs in the face of
a state of non-compensatory hypertrophy. From an ultrastructural point of view, we can see myocellular injuries that include: magnification and deformation of nuclei, disorganization of the structure of sarcomeres, proliferation of T tubules, accumulation of lipofuscins and glycogen. In more advanced stages, the most obvious change is the decrease of the myofilaments until the demise of sarcomeres which can cause cell death and later the progressive replacement by fibrous connective tissue.

The prevalence of sclera-regressive processes seems to lead to phenomena of tissue remodeling, because of the increase of interstitial fibrous component and through the alteration of the relationship between myofibrils and connective microcirculation. An extensive subendocardial reparative fibrosis is now a known event and amply histologically demonstrated.

It is important to underline how in compensatory hypertrophy (with a high mass/volume ratio), the evolution is generally favourable in a short term period; instead when there is a kind of non-compensatory form (with a low mass/volume ratio), the evolution of the disease is unfavourable from the beginning. An unfavourable mass/volume ratio in a hypertrophic ventricle helps to diminish the ability of heart to pump blood and so increases the parietal stress; these phenomena, in turn, affect the neuroendocrine activation and therefore the perpetuation and the aggravation of the vicious circle.
In patients suffering from idiopathic dilated cardiomyopathy of recent onset, it was observed that the ones that had an elevated mass/volume ratio survived better and had a minor number of hospitalizations during the follow-up. In patients with ventricular dilatation and a low mass/volume ratio, in which the parietal stress was permanently high despite of the presence of a ventricular hypertrophic response, instead, the evolution of the illness tended to be unfavourable because of the presence of an inadequate hypertrophy. Nonetheless, at a long term even the compensatory hypertrophy, which initially is a mechanism of adaptation to the overload, has the tendency to evolve towards the myocardial insufficiency.

In front of a patient suffering from myocardial hypertrophy or from heart failure is thus important to evaluate the characteristics of the left ventricular chamber, above all the mass, the volume and the cardiac output, in order to define the entity of the reserve of the ventricle itself to pump blood compared to the potential energy stored in the ventricular mass. Determining the ability of the ventricle to develop work, both in basal conditions and under stress, is a key prognostic factor as well as the foundation of therapy which is then administered to the same patient.
2 THE HEART AS A PUMP

The heart can be compared to a pressure generator, or a pump, put at the beginning of a system of conducts within which blood flows and where blood comes to, after having flowed the entire circulatory system.\textsuperscript{51} The heart, in fact, getting the contractile energy from the chemical energy coming from the scission of high-energy-of-hydrolysis phosphates, supplies potential energy (volume energy) to a volume of blood. The arterial pressure represents the mechanical manifestation of the cardiac contraction.

The hydraulic pumps are operating machines that, converting the mechanical energy into hydraulic energy, determine the passage of liquid substances from a lower energetic level to a higher one; they transform the mechanical energy (usually provided by an electrical engine) into hydraulic energy, generally in the form of potential energy.

In particular, we can compare the heart to a volumetric pump because it develops its action through the alternation of filling and emptying of a closed volume. In practice, volumetric pumps consist in a cylinder of a variable capacity, so that, when the pump is placed in communication with the container from which the liquid comes from, the volume increases, while the volume decreases when the pump is in communication with the container in
which the liquid flows. In the volumetric machines field, those who are alternative, are characterised by chambers in which the liquid remains stuck for a long or a short period of time, experiencing, in that period of time, an increase in energy; the chambers are sometimes set in communication, through valves, to the conduct, to which are linked, and, as a consequence, a back-and-forth movement is created above the liquid by the moving surface.52

The functioning of the cardiac pump is similar to the suction-delivery pump (see Figure 2.1), whose description dates back to the I century B.C. by Vitruvius: by raising the piston of this pump, we form a depression in the inferior chamber that leads to the opening of the outlet valve; by lowering the piston, afterwards, the pressure in the cylinder increases and determines the opening of the discharge valve and the passage of the liquid in the upper chamber.53
The ventricular pump is formed by muscular fibres in a circular and longitudinal arrangement and by a net of connective support: this particular conformation let the transfer of energy form the walls towards its content. The ventricular muscular fibres contraction, that has the task to generate potential energy, is spent partially to win the forces that oppose to the emptying and partially to move a volume of high-pressured blood equal to the systolic stroke volume.

The ventricular chamber is comparable to a camber that sets in communication a low-pressured system with a high-pressured one. Recently, relying on a theory according to which the myocardium would be formed by a
single muscular band, bent to form some spirals that form the ventricular chambers, permitted to interpret the function of the ventricular pump comparing it to a pump formed by a cylinder in which a piston slides: the most external loop would represent the cylinder walls, the most internal one, instead, the piston.\textsuperscript{54, 55, 56}

Similarly we can consider the cardiac valves as the ones present in the mechanical pump because they open up when the pressure in the upstream chamber becomes higher than the downstream one, both for an increase in the upstream pressure (as for semilunar valves) and for a decrease in the downstream pressure (as for the atrio-ventricular valves). The closure instead happens when there is a pressure gradient that drives the blood back, with a greater speed the greater is the velocity of the blood stream.

2.1 Cardiac work

As it emerges from one of the basis of classical physics, the equality between work and energy, it turns out that the cardiac pump has to develop work to assure to blood the energy necessary to the circulation. The myocardial contraction energy is transferred to the blood contained in the ventricular chamber through a force exerted through the movement of the endocardial surface. The energy developed is then directed, thanks to the cytoskeleton
endosarcomerical proteins, before to the cardiomyocyte and then to the fibres and to myocardial walls.

The left ventricle, at each beat, performs a work called pressure-volume systolic work or external work, evaluable through the formula:

\[ W = (p_{Ao} - p_{Ra}) \times SV \]

In which \( p_{Ao} \) is the aortic medium pressure, \( p_{Ra} \) is the right-atrium medium pressure and \( SV \) is the stroke volume. If we consider the right-atrium pressure as negligible, the formula can be approximated to:

\[ W = \text{arterial medium pressure} \times SV \]

The unit of measurement is the work one:

\[ \text{Pascal} \times m^3 = \frac{\text{Newton}}{m^2} \times m^3 = \text{Newton} \times m = \text{Joule} \, . \]

As we can infer form the formula, the cardiac work process considers the attribution of an energy, under a pressure energy form, at each cardiac cycle, to a volume of blood that is pushed in the circulatory system, gaining over the forces that every time thwart.\textsuperscript{57}
There are actually some limits to this valuation, mainly coming from the assumption of a constant pressure during the process of the systolic pressure. To evaluate better the expulsion work we must consider the ventricular pressure at each instant of the ejection phase (instead of the arterial medium pressure) and the volume variation at each moment of the ejection phase (instead of total variation). Therefore, given that the pressure and the volume change continuously during the cardiac cycle, the work done by the ventricle is more rightly expressed as the summation of the elementary works done at each instant of the contraction:

\[
W_s = p_1 dV_1 + p_2 dV_2 + p_3 dV_3 \ldots p_n dV_n = \int_{V_d}^{V_s} p_s dV
\]

In this formula \( W_s \) is the systolic work, \( V_d \) and \( V_s \) are respectively the end-diastolic and end-systolic volumes, \( dV \) is the elementary volume and \( p_s \) the systolic ventricular pressure.

We must then recall the existence of an acceleration work: the blood expelled from the ventricle has got a component of kinetic energy and one of potential energy that, respectively, leads it to accelerate and gain over the systemic vascular resentences.\(^{58}\)
At each cardiac cycle the energy necessary to the development of the pump function does not regard only the external work, rather indeed this represents only a minor quota of the energy that is used, but the majority is utilized to put and keep in tension the myocardial fibres: we talk about *internal work*. This one cannot be quantified in mechanical terms but it has got a remarkable metabolic relevance because it partly depends on the myocardial consumption of oxygen.

The chemical energy included in nutrients (glucides, lipids and proteins) and stored in high-energy phosphoric bonds, it is after mostly transformed in heat and it is dissipated by heart after having been used to the development of the internal work; eventually the remaining part is used to guarantee the blood sliding into the vessels.

2.1.1 Pressure-Volume Diagrams

To represent the totality of the energy generated by the ventricle during a cardiac cycle, we can use a pressure-volume diagram, like the one in Figure 2.2:
Figure 2.2 Pressure-Volume diagram of the left ventricle during the cardiac cycle.

A diagram like this shows the mutual relationships that subsist between ventricular pressures and volumes during the cardiac cycle, allowing to analyse the dynamic of the left ventricle and the filling and ventricular ejection ratios. The sequence, which must be observes anticlockwise, of the phases shown by the diagram begins in end-diastole, when in the left ventricle there is a low-pressure condition but the volume is elevated. The ascendant deflection follows, and this represents the isovolumetric contraction of the ventricular myocardium, in which an increase in the internal chamber-pressure occurs, while the volume is unaltered (closed valves). We then observe a movement leftwards of the diagram in the ejection phase, in which,
with the opening of the semilunar valves, the emptying of the ventricular chamber begins, with a consequent decrease in volume while the pressure is unvaried. In the descendant portion of the diagram, that indicates the isovolumetric diastole, we realize how the pressure decreases, whereas the volume is constant: it is the isovolumetric diastole, which begins when the semilunar valves close and the ventricular fibres start stretching. In the end, to re-join to the starting point, we can detect a movement rightwards of the diagram: this corresponds the ventricular filling from the opening of the atrio-ventricular valves, in which the internal chamber-volume enhances and this is accompanied by a slight pressure increase.

In this same diagram, instead, the internal work can be depicted as the pressure-volume area inside the descendant part of the graphic (isovolumetric diastole) and the intercept on the work axis (see Figure 2.3).
The summation of the external and internal cardiac work constitutes the total mechanical energy index of each heartbeat.\textsuperscript{61}

There is a linear relationship between the total cardiac work and the myocardial consumption of oxygen.\textsuperscript{62} Given that the size of the pressure-volume area of internal work increases with the volume, when we go and determine the functional characteristics of the left ventricle, it is essential to consider the position in which it operates along the axis of the volumes, above all in case of dilated and hypokinetic ventricles that, while developing a low-
pressure-volume work, set a very high energy expenditure related to the amount of internal work in relation to the high ventricular size.

The area under the diastolic portion of the pressure-volume curve represents the work done by the blood to fill the ventricular chamber, stored as elastic energy in the myocardial walls and then returned in the systolic phase.

The pressure-volume diagrams are included between two curvilinear relationships between pressure and volume: the end-diastolic pressure-volume relationship (EDPVR) and end-systolic pressure-volume relationship (ESPVR). The first one is drawn through the junction between end-diastolic points of each loop square (it is necessary to measure the pressure-volume relationships under different load conditions) and has got curvilinear trend, derived from the passive non-linear properties of ventricular chamber; the second curve can be described, instead, by joining the end-systolic points and looks like a straight line. In each recording of a pressure-volume diagram, the end-systolic point falls on the ESPVR and end-diastolic point on the EDPVR curve.

2.1.2 The ventricular elastance

In order to evaluate the ventricular inotropic situation independently form the pre-load and post-load, we estimate the so-called ventricular elastance, which
is defined as the pressure variation that corresponds to a certain change of the ventricular chamber’s volume, calculable as the relationship between pressure and volume in end-systole in different load situations. It conveys some indications about the ventricular stiffness. It reaches the peak during end-systole and it is a time-independent quantity.

The formula obtained in the experimental environment to estimate the elastance is this one:

\[ E(t) = \frac{p(t)}{V(t) - V_0} \]

in which \( E(t) \) is the elastance (in mmHg) in time \( t \) from the beginning of the contraction, \( p(t) \) and \( V(t) \) are the instant pressures and the volume in the \( t \) instant respectively, while \( V_0 \) is the ventricular volume – at pressure equal to 0 – in systole. The slope of this straight line is identified with the maximum elastance value (\( E_{max} \)), which is the ratio between the end-diastolic pressure and the end-systolic volume (\( p_{ED}/V_{ES} \)); in clinical researches, anyway, the \( E_{max} \) value is usually approximated through the estimation of the end-diastolic elastance (\( E_{ES} \)), represented by the inclination of the ESPVR curve which is
usually a roughly straight line and not very sensitive to cardiac load-dependent factors.

In human beings, the elastance values can be determined by measuring repeatedly the ventricular pressures and volumes in end-systole in condition of changeable load: crescent values of post-load determine consensual increases of the pressure and volume in end-systole.

If inotropism varies, the slope of the elastance straight line changes. In fact, after a positive inotropic stimulus (for example after catecholamine administration), the developed end-diastolic pressure and the systolic stroke volume increase, the end-diastolic volume decrease, the ejection work enhances and this is clear from the modification of pressure-volume loop. Consequently, the ventricular elastance straight line moves upwards and leftwards. On the other hand, a decrease of inotropism determines a reduction of the slope of the straight line (see Figure 2.4).65, 66
Figure 2.4: Change of the left ventricle pressure-volume diagram after the administration of catecholamine.

### 2.2 Cardiac power

After analysing the ability of heart to perform work, it is important to know the velocity in which this work is done, like in every mechanical system. The concept of work, in fact, leaves aside the one of time, so it can be done indifferently either in a long period of time or in a short one, although this may lead to different effects. Since the heart work is formulated, as we said before, in terms of pressures and volumes \( W = p \cdot \Delta V \), the cardiac power \( P \) can be calculated as:
\[ P = p \frac{\Delta V}{t} \]

so as the product of the pressure and the flux. During physical exercise, the ratio between the heart power and the weight of the organ is similar to those of mechanical pumps.\(^{67}\)

2.3 Myocardial efficiency

Since the heat production represent the effect of energetic transformation that triggers form the liberation of chemical energy from the exergonic combustion of carbonic combustibles in presence of oxygen, we can express the cardiac pump efficiency as:

\[
\text{Myocardial efficiency} = \frac{\text{external work}}{MVO_2}
\]

In which \(MVO_2\) is the myocardial oxygen consumption. At a normal heart, it is attributed an average efficiency of 25\%, but, since most of the energy that is consumed in the cardiac cycle is directed to the conduct of reactions that are independent of the contractile process, the efficiency of the contraction is undoubtedly higher than the one estimated. The efficiency of the ventricular contraction was quantified at around 30\%, very similar to that of a mechanically propelled machine.\(^{68,69}\)
Recent studies have provided a clearer picture about the mechanoenergetic effects of ventricular hypertrophy. In particular, it was shown that the myocardial oxygen consumption increases in response to the increased metabolic demand that follows the high workload being put on the ventricle that leaves unchanged but efficiency although it has been observed a non-significant reduction. The work of ejection in hypertrophy does not change but the work developed per gram of tissue is disproportionately depressed in relation to changes in MVO$_2$. Therefore the apparent normalization of oxygen consumption per unit of weight induced by the hypertrophy occurs at the expense of the mechanical efficiency. Actually, these alterations are not reproducible in presence of myocardial hypertrophy that follows an aortic stenosis or arterial hypertension and this underlines the complexity of the various adaptive processes that occur with the hypertrophy that follows several pathogenic causes. Similarly, in the context of an appropriate hypertrophy, such as in the athlete’s heart, cardiac efficiency is normal.

An altered myocardial efficiency represents, thus, an important prognostic factor in failing heart that lets us to evaluate how much, with the same mass increase, the myocardium is able to develop external work also compared with the oxygen consumption (fundamental aspect when the heart failure comes for a previous ischaemic heart disease).
2.4 Peak cardiac power output-to-left ventricular mass (peak CPOM)

There is still room to improve prognostic stratification of high-risk outpatients with heart failure (HF). Prognostication of HF patients is based on readily available information that includes symptom severity (usually NYHA functional classification), left ventricular (LV) ejection fraction and natriuretic peptides. However, none of these parameters provide nuances of cardiac pump and circulatory system performance. Exercise stress echocardiography may endow with additional insights for prognostication of these patients.  

Cardiac power output (CPO), which is the product of mean arterial pressure (MAP) and cardiac output (CO), is a measure of cardiac energy delivery. This parameter has shown a great ability to predict outcome in a broad spectrum of cardiac disease both at rest and during exercise. Echo-derived peak CPOM is a variable that couples peak CPO with LV mass at peak exercise or during maximal inotropic stimulation. Since it is a measure of the rate at which cardiac work is delivered with respect to the potential energy stored in LV mass, it provides information about the rate at which potential energy is transformed into useful work.

Power-to-weight ratio is a measure that is widely applied to mechanical engines to compare the performance of vehicles, aircrafts and other mobile power sources. This ratio represents a measure of actual performance of any energy source or any engine. It is also used as the index of performance of a
vehicle as a whole by the ratio between engine power and its weight (less frequently its mass) to give rise to a parameter that is independent from the size of the vehicle.

Every pump has its own maximum performance, which denotes its pumping capacity. Cardiac pumping capacity can be defined as the cardiac power output achieved by the heart during maximal stimulation. It represents the recruitable reserve available that is expected to be proportional to the number of contractile units of the myocardium. Similarly to any mechanical engine, an index that relate peak LV power output and LV mass, such as peak CPOM, may be considered as measures of LV pumping capacity. Indeed, it allows us to evaluate the relationship between recruited myocardial muscle mass and the power of the left ventricle at maximum workload.

In view of the fact that normal heart muscle grows to match the workload imposed on it, the mass of the ventricular wall depends on the chronic load with which it is confronted. Therefore, a stronger ventricle with a greater muscular mass will contract to a higher LV power output under stimulation. Since cardiac power output is the product of cardiac output (CO) and blood pressure (BP), the myocardium grows when either its CO or its BP is augmented. The physiological example of the former is the increase in LV mass in athletes. When the integrity of myocardial structure is compromised owing to myocyte loss, interstitial fibrosis and scarring, a disproportion
becomes apparent between maximal peak CPO and LV mass and this leads a decrease of peak CPOM.\textsuperscript{84}

Recently, peak CPOM has proved to be an independent predictor of outcome in patients with advanced HF.\textsuperscript{85}

Cardiopulmonary exercise testing (CPET) is a valuable and accurate tool for risk stratification of HF patients, among several CPET variables peak VO\textsubscript{2},\textsuperscript{86} VE/VCO\textsubscript{2} relationship and their combination have been identified as predictors of prognosis,\textsuperscript{87,88} and they are used for timing of heart transplantation and ventricular assist device implantation. However, gas exchange measurements are only indirect measures of cardiac function and sometimes cannot properly reflect the status of cardiac pump and circulatory system performance. It is interesting to know whether the assessment of peak CPOM during exercise testing may be comparable to CPET parameters to risk stratify HF patients. Hence, the present study was designed to compare the value of peak CPOM and CPET in the prognostic stratification of patients with chronic HF.
3 AIM OF THE STUDY

Prognostication of HF patients is based on readily available information that includes symptom severity (usually NYHA functional classification), left ventricular (LV) ejection fraction and natriuretic peptides. However, none of these parameters provide nuances of cardiac pump and circulatory system performance. Exercise stress echocardiography may endow with additional insights for prognostication of these patients.

The present study was designed to compare the value of peak CPOM, a variable that couples the peak CPO with LV mass at peak exercise or during maximal inotropic stimulation with cardiopulmonary exercise testing (CPET) variables in the prognostic stratification of patients with heart failure with reduced ejection fraction (HFrEF) due to LV dysfunction.
4 MATERIAL AND METHODS

4.1 Population of the study

This study included a total of 115 subjects (91 men and 24 women) with heart failure with reduced ejection fraction (HFrEF) [LV ejection fraction (EF) \( \leq 40\% \)] and clinically stable enrolled at the Cardiovascular Diseases Unit 1, Cardiothoracic department, Cisanello Hospital, Pisa.

4.1.1 Exclusion criteria

The exclusion criteria were heart failure secondary to valvular heart disease, presence of aortic regurgitation, peripheral artery disease limiting the capability of performing exercise stress test and reduced exercise tolerance attributable to myocardial ischemia. The 115 study patients with HFrEF were under oral treatment with angiotensin converting-enzyme inhibitors or angiotensin II receptor blockers (95%), loop diuretics (78%), and beta blockers (72%), anti-aldosterone drugs (58%) and digoxin (21%). Beta blockers were withheld at least 48 hours before the test.
4.2 Echocardiography

All patients underwent an ultrasound examination at baseline and during bicycle semi-supine exercise using an Acuson Sequoia C256 ultrasound instrument (Siemens, Mountain View, California) equipped with a 3.5-MHz transducer and harmonic imaging.

Prior to exercise, a complete echocardiographic and Doppler examination was performed with the subject in left lateral supine position. The standard parasternal long-axis view as well as the three standard apical four-chamber, two-chamber and long-axis views were acquired optimizing gain setting, sector angle and depth. LV end-diastolic and end-systolic volumes were calculated according to the biplane Simpson’s rule. The LV mass index was determined by using the M-mode method according to the recommendations of the American Society of Echocardiography. The LV outflow tract anteroposterior diameter was measured in the parasternal long-axis view and the LV outflow tract area was calculated as πr² (cm²). The LV stroke distance (cm) was measured tracing the outer edge of the most dense (or brightest) portion of the spectral aortic tracing recorded from the apical 5-chamber view, with the PW Doppler sample volume positioned about 5 mm proximal to the aortic valve. Doppler tissue imaging longitudinal velocities were recorded with the sample volume placed at the junction between the septal and lateral LV wall and the mitral annulus in the 4-chamber view and peak early
myocardial wave (e’) velocities were measured. The ratio of mitral E peak velocity and averaged e’ velocity (E/e’) was calculated. Patients with more than mild mitral regurgitation were selected according to the vena contracta method.

4.3 Exercise echocardiography

Symptom-limited graded bicycle semi-supine exercise was performed at an initial workload of 20 watts lasting for one minute; thereafter the workload was increased stepwise by 10 watts every minute. A 12-lead electrocardiogram and blood pressure determination were performed at baseline and every minute thereafter.

At baseline and during each exercise level, Doppler-derived cardiac output at LV outflow tract, heart rate and arterial systolic blood pressure (BP) and diastolic BP (by cuff sphygmomanometer) were measured. Mean BP was estimated as follows: diastolic BP + 1/3 (systolic BP – diastolic BP). Stroke volume was calculated as stroke distance x LV outflow tract area and cardiac output as stroke volume x heart rate. Great care was taken to assure patient hold breathing at each acquisition time and to acquire three consecutive Doppler tracings. All measures were averaged over three consecutive cycles.
Peak CPOM was calculated as the product of a constant \((K=2.22 \times 10^{-1})\) with cardiac output \((CO)\) and the mean arterial pressure \((MAP)\) divided by LV mass \((M)\) to convert the units to watts/100 g: 
\[
CPO = K \times CO \text{ (l/min)} \times MAP \text{ (mmHg)} \times M^{-1} \text{ (g)}. 
\]

### 4.4 Cardiopulmonary exercise testing (CPET)

Incremental CPET was conducted on an electrically braked cycle ergometer (Ergoline, Milano, Italy), recording standard measurements \((VO_2, VCO_2, V_E/VCO_2, \text{ heart rate and ECG, oxygen saturation, O}_2 \text{ pulse, peak VO}_2, \text{ breath frequency, Bf, and pulmonary ventilation, VE, by ZAN Ferraris CardioRespiratory software})\) according to ATS/ERS guidelines.\(^{93}\) All subjects performed CPET wearing a mask containing a pneumotachograph, connected to the software.

Cardiac and breathing reserves were calculated during incremental CPET as following: a) maximum predicted values \((220 - \text{ years of age})\) - maximum heart rate achieved during CPET; b) \((\text{FEV}_1 \text{ pre-test x 40})\) - VE max achieved during CPET.\(^{94}\)

Constant load CPET was performed at 80% of the maximal workload achieved during the incremental CPET. Before each constant load CPET, a forced flow-volume loop was recorded (pretest \(\text{FEV}_1\)) and a rest Inspiratory
Capacity (IC) was measured; afterward, at 1 min intervals during each test and at 2 min intervals after the end of exercise, IC manoeuvres were still collected, in order to assess for the presence of dynamic hyperinflation. As maximum value of VO2 reached at the end of constant load CPET, we chose the mean value of VO2 measured over the last 30 s of loaded exercise.95

Exercise echocardiography and cardiopulmonary exercise testing were performed within 7 days according to standard symptom-limited exercise protocols.

4.5 End Points of Event-Free Survival

For event-free survival analyses, observation began on the date of index exercise stress echocardiography. End points were all-cause mortality and cardiac events (cardiac mortality or hospitalization for worsening heart failure). Event-free survival data were obtained through follow-up of patients and verified through local authority registry and hospital records.

4.6 Statistical Analysis

Data are presented as mean ±SD for continuous variables and as percentages for categorical variables. Continuous variables were compared using paired-
samples and independent-samples Student’s $t$ test. Categorical variables were compared by means of the $\chi^2$ test.

Time-independent associations between variables and outcomes were assessed using receiver operating characteristic (ROC) curve analysis and logistic regression. Statistical comparison of ROC curves was performed using the method of paired ROC curves of Hanley and McNeil. Cox proportional-hazard regression analysis was used to identify predictors of outcome in time-dependent analysis. Kaplan-Meier curves were constructed and log-rank tests were used to test for differences between event-free survival curves. The likelihood ratio test was used to compare different multivariate Cox models by taking into account the different number of variables used in each model and to explore the incremental prognostic value of power/mass ratio over established clinical and echocardiographic prognostic variables. The log likelihood and the overall model $\chi^2$ (i.e., that calculated by testing the hypothesis that all regression coefficients for the variables in the model are identically zero) were calculated for each model. The probability level was $p < 0.05$ for all data examined.
5 RESULTS

5.1 Characteristics of the study patients

The study population comprised patients with heart failure that were in New York Heart Association (NYHA) class I or II (n=85) and NYHA class III or IV (n=30).

They were followed-up for a mean period of 24±22 months. Sixteen patients (14%) died due to various causes and twenty-one patients (18%) were hospitalized for worsening heart failure. During the follow up, implantable cardioverter defibrillators (ICD) were implanted in 17 patients (15%) and cardiac resynchronization therapy (CRT) systems in 4 patients (3.5%).

Patients’ characteristics are summarized in Table 5.1.

Mean LV EF at peak exercise was 28±6% in patients with events and 32±6% in subjects with no events (p-value=0.0021). Instead, mean cardiac output was 7.5±3.3 L/min in the group of patients with events and 9.7±2.8 L/min in the other group (p=0.0003). Peak CPO was between 0.9 and 2.7 W in hospitalized and/or dead patients and between 1.5 and 3.7 W in patients with no events, with a p-value of 0.0003. Peak CPOM was found to be 0.58±0.25 W/100 g in patients with events while 0.94±0.24 W/100 g in the others, with a p-value <0.0001.
From cardiopulmonary test, resulted that peakVO$_2$ was $15\pm4$ in patients with events and $18\pm5$ ml/(mg*min) in the control subjects, respectively $57\pm18$ and $70\pm18$% of predicted with a $p$-value of 0.0007. O$_2$ pulse was $11\pm4$ in patients with events and $12\pm4$ 100 ml/(beat*kg) in patients with no events. Finally, peak VE/VCO2 resulted $38\pm6$ in the first group and $32\pm6$ L/L in the second group of subjects with a $p$-value <0.0001.
### Table 5.1: Characteristics of the study patients. Group 1 includes patients with combined event hospitalization for HF + all-cause death; group 2 comprises patients with no events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n=37)</th>
<th>Group 2 (n=78)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61±12</td>
<td>62±11</td>
<td>ns</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>81</td>
<td>79</td>
<td>ns</td>
</tr>
<tr>
<td>NYHA class III-IV (%)</td>
<td>49</td>
<td>24</td>
<td>0.0092</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>28±5</td>
<td>27±4</td>
<td>ns</td>
</tr>
<tr>
<td>CRT (%)</td>
<td>41</td>
<td>15</td>
<td>0.0029</td>
</tr>
<tr>
<td>ICD (%)</td>
<td>62</td>
<td>19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PeakVO2 (ml/(kg*min))</td>
<td>15±4</td>
<td>18±5</td>
<td>0.0007</td>
</tr>
<tr>
<td>VO2 predicted (%)</td>
<td>57±18</td>
<td>70±18</td>
<td>0.0004</td>
</tr>
<tr>
<td>O2pulse (100 ml/(beat*kg))</td>
<td>11±4</td>
<td>12±4</td>
<td>0.027</td>
</tr>
<tr>
<td>peak VE/VCO2 (L/L)</td>
<td>38±6</td>
<td>32±6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Circulatory power</td>
<td>1941±964</td>
<td>2853±1377</td>
<td>0.0004</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>28±6</td>
<td>32±6</td>
<td>0.0021</td>
</tr>
<tr>
<td>LV E/e' ratio</td>
<td>15±9</td>
<td>11±5</td>
<td>0.0013</td>
</tr>
<tr>
<td>Peak CO (L/min)</td>
<td>7.5±3.3</td>
<td>9.7±2.8</td>
<td>0.0003</td>
</tr>
<tr>
<td>Peak CPO (W)</td>
<td>1.8±0.9</td>
<td>2.6±1.1</td>
<td>0.0003</td>
</tr>
<tr>
<td>Peak CPOM (W/100 g)</td>
<td>0.58±0.25</td>
<td>0.94±0.34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Digoxin (%)</td>
<td>32</td>
<td>16</td>
<td>0.042</td>
</tr>
<tr>
<td>ß-blockers (%)</td>
<td>67</td>
<td>78</td>
<td>ns</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>97</td>
<td>71</td>
<td>0.0011</td>
</tr>
<tr>
<td>ACE-inhibitors (%)</td>
<td>91</td>
<td>93</td>
<td>ns</td>
</tr>
<tr>
<td>Anti-aldosterone drugs (%)</td>
<td>78</td>
<td>50</td>
<td>0.0031</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or as percentages.

Legend: BMI = Body mass index; CRT = Cardiac resynchronization therapy; EF = ejection fraction; ICD = Implantable cardioverter defibrillator; LV = left ventricular; peak CO = peak Cardiac output; peak CPO = peak Cardiac power output; peak CPOM = peak Cardiac power output-to-left ventricular mass.
5.2 Time-independent analyses of event-free survival

Results of ROC analysis for outcome prediction are shown in Table 5.2 and 5.3. For compound “death+hospitalization” events, among all variables, peak CPOM showed the largest area under the curve (AUC=0.816). A value of ≤0.60 watt/100 g was identified as the best cut-off value, showing 70% of sensitivity and 85% of specificity for the prediction of events. After peak CPOM, peak VE/VCO2 has the second largest area under the curve (AUC=0.757); a value of >32 L/L was found to be the best cut-off, with a sensitivity of 80% and a specificity of 60%. Similarly, for death events only, CPOM showed the largest area under the curve (AUC=0.795); the best cut-off resulted to be ≤0.60 watt/100 g in the same way, showing 75% of sensitivity and 77% of specificity.

Figure 5.1 displays the comparison of ROC curves of peak CPOM and LV ejection fraction for compound events and death events. Statistically significant differences between the areas under the curve were apparent in both cases between peak CPOM with respect to LV ejection fraction.

Results of univariate and multivariate logistic regression are shown in Table 5.4. Although a number of variables were associated with the risk of events,
stepwise multivariate analysis showed that the only independent predictor was peak CPOM (overall model p<0.0001).

Table 5.2 ROC curve analysis for death + hospitalization events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Area under the curve</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class III-IV</td>
<td>0.676</td>
<td>0.582 to 0.760</td>
<td>0.0004</td>
</tr>
<tr>
<td>EF</td>
<td>0.692</td>
<td>0.599 to 0.775</td>
<td>0.0002</td>
</tr>
<tr>
<td>Peak CO</td>
<td>0.737</td>
<td>0.647 to 0.815</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak CPO</td>
<td>0.751</td>
<td>0.661 to 0.827</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak CPOM</td>
<td>0.816</td>
<td>0.733 to 0.882</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PeakVO₂</td>
<td>0.691</td>
<td>0.598 to 0.774</td>
<td>0.0003</td>
</tr>
<tr>
<td>VO₂ predicted</td>
<td>0.718</td>
<td>0.626 to 0.798</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak VE/VCO₂</td>
<td>0.757</td>
<td>0.677 to 0.832</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Legend: EF = ejection fraction; peak CO = peak Cardiac output; peak CPO = peak Cardiac power output; peak CPOM = peak Cardiac power output-to-left ventricular mass.

Table 5.3 ROC curve analysis for death events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Area under the curve</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class III-IV</td>
<td>0.598</td>
<td>0.503 to 0.689</td>
<td>0.1651</td>
</tr>
<tr>
<td>EF</td>
<td>0.735</td>
<td>0.644 to 0.813</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak CO</td>
<td>0.698</td>
<td>0.605 to 0.780</td>
<td>0.0181</td>
</tr>
<tr>
<td>Peak CPO</td>
<td>0.704</td>
<td>0.611 to 0.785</td>
<td>0.0156</td>
</tr>
<tr>
<td>Peak CPOM</td>
<td>0.795</td>
<td>0.710 to 0.865</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PeakVO₂</td>
<td>0.720</td>
<td>0.629 to 0.800</td>
<td>0.0026</td>
</tr>
<tr>
<td>VO₂ predicted</td>
<td>0.714</td>
<td>0.622 to 0.794</td>
<td>0.0094</td>
</tr>
<tr>
<td>peak VE/VCO₂</td>
<td>0.723</td>
<td>0.631 to 0.803</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Legend: EF = ejection fraction; peak CO = peak Cardiac output; peak CPO = peak Cardiac power output; peak CPOM = peak Cardiac power output-to-left ventricular mass.
Figure 5.1 ROC curves comparing peak LV ejection fraction and peak CPOM for the prediction of adverse events “death + hospitalization” (above) and “death” events (below) at follow-up.
Table 5.4 Univariate and Multivariate logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wald</td>
<td>P-value</td>
</tr>
<tr>
<td>EF</td>
<td>8.20</td>
<td>0.0042</td>
</tr>
<tr>
<td>Peak CO</td>
<td>11.91</td>
<td>0.0006</td>
</tr>
<tr>
<td>Peak CPO</td>
<td>15.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak CPOM</td>
<td>24.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>peakVO₂</td>
<td>9.98</td>
<td>0.0016</td>
</tr>
<tr>
<td>VO₂ predicted</td>
<td>10.13</td>
<td>0.0013</td>
</tr>
</tbody>
</table>

Legend: EF = ejection fraction; peak CO = peak Cardiac output; peak CPO = peak Cardiac power output; peak CPOM = peak Cardiac power output-to-left ventricular mass.
5.3 Time-dependent analyses of event-free survival

In time-dependent analyses, when the patients were divided using the cut-off value of LV ejection fraction (EF) of 30% identified by ROC analysis, differences in the event-free survival probability were observed ($p=0.0005$, Logrank: 12), as shown in figure 5.2. Subjects with an EF >30% had an event-free survival at 24 months of 80%, and those with an EF ≤30% of ≈50%.

Considering the peak CPO instead, when the patients were divided using the cut-off value of 1.90 Watt identified by ROC analysis, significant differences in the event-free survival probability were observed ($p<0.0001$, Logrank: 24.5), as shown in figure 5.2. Subjects with a peak CPO >1.90 watt had an event-free survival at 24 months of 82%, and those with a peak CPO ≤1.90 watt of ≈40%.

In addition, when the patients were divided in two groups using the cut-off value of peak CPOM of 0.60 watt/100 g identified by ROC analysis, significant differences in the event-free survival probability were observed ($p<0.0001$, Logrank: 34.1), as we can see in figure 5.2. Subjects with a peak CPOM >0.60 watt/100 g had an event-free survival at 24 months of 8%, and those with a peak CPOM ≤0.60 watt/100 g of 29%.

With regard to the parameters of the cardiopulmonary exercise testing, in time-dependent analyses we can observe differences in the event-free survival
probability dividing patients into two groups with peakVO2 cut-off value of 14 ml/kg/min (p=0.0037, Logrank: 4.8) identified by ROC analysis (figure 5.2). Subjects with a peakVO2 >14 ml/kg/min had an event-free survival at 24 months of 77% and those with a peakVO2 ≤14 ml/kg/min, a free-event survival of ≈45%.

If we consider only all-cause death events, in time-dependent analyses, when the patients were divided using the cut-off value of LV EF of 30% identified by ROC analysis, significant differences in the survival probability were observed (p=0.0009, Logrank: 10.9), as shown in figure 5.3. Subjects with a EF >30% had a survival probability at 24 months of 90%, and those with a EF ≤30% of ≈70%. Instead, considering the peak CPO, if we divide subjects using 1.90 watt as cut-off value, identified by ROC analysis, differences in the survival probability were observed (p=0.0021, Logrank: 9.4), as shown in figure 5.3. Subjects with a peak CPO >1.90 watt had a survival probability at 24 months of 88%, and those with a CPO ≤1.90 watt of ≈65%. Regarding peak CPOM, when the patients were divided using the cut-off value of peak CPOM of 0.60 watt/100 g identified by ROC analysis, significant differences in the survival probability were observed (p<0.0001, Logrank: 19.8), as we can see in figure 5.3. Subjects with a peak CPOM >0.60 watt/100 g had a survival probability at 24 months of 91%, and those with a peak CPOM ≤0.60 watt/100 g of ≈55%. Finally, in time-dependent analyses, dividing subjects
using the cut-off value of peakVO2 of 14 ml/kg/min identified by ROC analysis, significant differences in the survival probability were observed ($p=0.0058$, Logrank: 7.6), as shown in figure 5.3. Subjects with a peakVO2 $>14$ ml/kg/min had a survival probability at 24 months of $\approx$90%, and those with a peakVO2 $\leq 14$ ml/min/kg of 63%.
Figure 5.2 Comparison between Kaplan-Meier event-free survival curves for EF, peak VO2, peak CPO, peak CPOM
Figure 5.3 Comparison between Kaplan-Meier survival curves for EF, peak VO2, peak CPO, peak CPOM
6 DISCUSSION

In our findings, it can be demonstrated, in line with previous studies, how peak CPOM is an extremely useful parameter in prognostic stratification of patients with HF with reduced ejection fraction. By subjecting patients to exercise echocardiography, we calculated peak CPOM as the product of a constant \((K=2.22 \times 10^{-1})\) with cardiac output (CO) and the mean arterial pressure (MAP) divided by LV mass (M) to convert the units to watts/100 g:

\[
CPO = K \times \frac{CO \text{ (l/min)} \times MAP \text{ (mmHg)} \times M^{-1}(g)}{100}.
\]

Prognostication of HF patients is based on readily available information that include symptom severity (usually NYHA functional classification), left ventricular (LV) ejection fraction and natriuretic peptides. However, none of these parameters provide nuances of cardiac pump and circulatory system performance. Exercise stress echocardiography may endow with additional insights for prognostication of these patients.\(^{75}\)

Beginning in the mid-1990s, consensus guidelines recommended the application of the CPET to supplement other clinical data in the management of patients with HF.\(^{87}\) In fact the CPET allows, by subjecting the patients to an effort, to assess the response of cardiorespiratory system to exercise and therefore stratify the prognosis according to the degree of compromise emerged.
Most investigators have found that peakVO2 (calculated as the ratio of cardiac output and arteriovenous oxygen difference) is the best CPET indicator of prognosis in patients with heart failure. This well-established variable can be thought of as integrating a number of factors which determine the severity of heart failure and the degree of functional limitation including cardiac reserve, skeletal muscle function, pulmonary abnormalities, and endothelial dysfunction. PeakVO2 correlates poorly with haemodynamic factors measured at rest which is consistent with the fact that these resting parameters do not reflect functional reserve. There is, however, a good correlation between maximum cardiac output and peakVO2. The measurement of peak VO2 was first described by Webber and colleagues as a method for characterising cardiac reserve and functional status in heart failure. Subsequently peakVO2 has been shown by a number of investigators to be of prognostic significance, with lower peak VO2 predicting mortality and the need for cardiac transplantation (peak VO2 is currently one of the most important criteria to select patients for a heart transplant but also for a LVAD implantation). Attempts have been made to use percentage of predicted peakVO2 to improve the prognostic power of this measure. Percentage of predicted peak VO2 may account for factors such as age, sex, and muscle mass which may have a significant impact on peakVO2.
In our study, statistical analysis confirmed the important role of cardiopulmonary exercise testing peakVO2 in the prognostic stratification of patients with advanced HF. Subjects with a peakVO2 <14 ml/kg/min had a particularly impaired prognosis.

It is well known that exercise intolerance is one of the main manifestations of HF, varying directly with the severity of the disease. However, it is important to highlight how maximal oxygen consumption during cardiopulmonary testing depends not only on cardiovascular factors: many other pathological conditions (obesity, respiratory diseases, muscular diseases etc.)98,99 as well as cardiovascular deconditioning (poor fitness)100 can likewise lead to values in the CPET parameters, especially in peakVO2, which overlap with those of patients with heart failure; in addition it does not consider the influence of LV remodeling and provides only an indirect assessment of left ventricular exercise function.

Therefore, peakVO2 cannot prescind from exercise echocardiographic parameters to give a complete and correct assessment of the ability of the left ventricle to perform its function of pump.

Peak cardiac power output (peak CPO), which is the product of mean arterial pressure (MAP) and cardiac output (CO) at the peak of the exercise, is a measure of cardiac energy delivery, reflecting the power developed from the left ventricle.76 Roul and colleagues101 were the first group to evaluate the
prognostic value of peak CPO during maximal exercise testing. In many following studies, this parameter has shown a great ability to predict outcome in a broad spectrum of cardiac disease both at rest \cite{102, 78, 79, 80} and during exercise.\cite{103, 81}

The echo-derived parameter peak CPOM (which reflects the number of watts that are developed by 100 g of LV mass) allows us to evaluate the relationship between recruited myocardial muscle mass and the power of the left ventricle at maximum workload. It can give information about the rate at which potential energy stored in left ventricular mass is transformed into useful work. This parameter in fact, by coupling peak exercise LV power output, which incorporate BP and flow response of the cardiovascular system to exercise, and LV mass is an integrated measure of LV pumping capability. Dini and colleagues \cite{85} recently proved that peak CPOM is an independent predictor of outcome in patients with advanced HF. The concept behind this index is that a stronger ventricle with greater muscular mass will contract to higher LV power output under stimulation. An increase in LV size is fundamental to the ability to generate a large stroke volume.\cite{104} Although abnormal pump function plays a major role in determining both pathophysiology and prognosis in patients with heart failure, also changes over time in LV size and structure are important in disease progression and outcomes.\cite{89} Transition to failure is accompanied by progressive LV cavity
enlargement and decline in the mass/volume ratio despite an increase in LV mass. We also know that left ventricular enlargement can help maintaining stroke volume despite reduced contractile function, and this has been considered a compensatory response.\textsuperscript{86} Therefore, in patients with heart failure, beyond the classic parameters used, as the ejection fraction, it is important to establish to what degree LV remodeling may be considered compensatory or maladaptive and this can simply be implemented using echocardiography at rest and during exercise. In the evolution of cardiac remodeling we can observe how when the recruitable power output per unit of left ventricular mass reduces because of progressively decreasing ability of the myocardium to generate force to overcome the load, left ventricular function rapidly deteriorates.\textsuperscript{91} We must also consider that, in the process of cardiac remodeling, besides changes in the architecture of ventricular myocytes, there is a proliferation of the connective tissue component that accompanies the cardiomyocytes hypertrophy and, in a last instance, leads to the development of interstitial fibrosis. Finally when the increase in ventricular mass is not due only to the myocyte hypertrophy but also to the interstitial fibrosis, some alterations of the nutrition of the myocardial tissue, that depend on an organic and functional transformation in a pathological sense of the coronary circulation, may occur.
For this reason, it has been hypothesized that the combination of severely reduced LV performance at maximum workload and increased LV mass reflects an adverse ventricular remodeling process that might have an impact on the risk stratification of patients with heart failure with reduced ejection fraction. A reduced peak CPOM is likely to reflect all LV morphological changes we have analysed.

LV ejection fraction is the most frequently used index of cardiac function, but it may not accurately reflect myocardial contractility, and it provides little prognostic information in patients with advanced heart failure. The interpretation of an ejection fraction <35% in a patient in NYHA class I with mild LV dilation may be quite different from that of an individual with class III symptoms associated with a severely dilated left ventricle. Both ejection fraction decreases reflect LV chamber remodeling despite relative preserved stroke volume. However, in one instance, compensatory LV remodeling dominates this decline, with a near normal residual myocardium capable of providing adequate cardiac reserve. In the other case, the entire LV myocardium is depressed, with little reserve pumping capacity. These two situations may look similar when assessed by conventional measures, such as LV ejection fraction or wall motion score index, but are very different by alternative approaches, such as cardiopulmonary testing or hemodynamically derived cardiac power output.
In order to ensure a correct and complete prognostic stratification of patients with heart failure with reduced ejection fraction, which takes account of all aspects which we have discussed, the best option is to submit the subjects both to exercise echocardiography and cardiopulmonary test so as to combine their results and get a full metabolic and cardiorespiratory profile of the patients.

This study demonstrates how the parameter peak CPOM can represent an surplus value in the stratification of patients with heart failure with reduced ejection fraction, in addition to the criteria that are classically used in these patients, as the ejection fraction or the NYHA class. Furthermore, when peak CPOM is combined with CPET parameters, the prognostic stratification of the patients results more accurate and complete.

6.1 Limitations

Certain limitations to this analysis need to be mentioned. First, we did not include several articles potentially duplicating data, which may in turn have caused other information to be unintentionally excluded, although most clearly contained redundant information.

Although three-dimensional imaging is the most accurate way to measure LV mass by echocardiography, M-mode methods are in current use in clinical
practice and suggested by the American Society of Echocardiography.\textsuperscript{1} Nevertheless, the calculation of LV mass on the basis of two-dimensional and three-dimensional echocardiography is to be recommended, especially in deformed and/or remodeled ventricles.\textsuperscript{75,107} The assessment of LV outflow tract diameter for the calculation of forward stroke volume during exercise may sometimes be problematic, especially in repeated examinations. Therefore, the measurement of LV outflow tract diameter was performed only at rest and assumed not to change in response to exercise, as suggested by the American Society of Echocardiography.\textsuperscript{76} On the other hand, the assessment of LV stroke distance is recognized to be a simple, rapid, and reliable measure even in the context of a stress test and allows serial evaluations for multiple comparison.

By design, the CPX score focuses primarily on the ventilator gas exchange response to exercise and does not include other clinical markers of risk in HF. There are other CPET responses that predict risk, particularly oscillatory breathing,\textsuperscript{108,109} which were not included in the score.

In this study, the confounding effect of cardiac medications on outcome was not considered. Finally, the number of patients included in this study was rather small for risk stratification; but, this was the first comprehensive study that tested the value of these new indices in patients with heart failure, and our findings are intended to be preliminary.
7 CONCLUSIONS

None of the currently available variables for prognostic stratification of patients with HFrEF is sufficiently significative and, at the same time, none of these provides information on pump function of the heart under stress. Exercise stress echocardiography may endow with additional insights for prognostication of these patients.\textsuperscript{75}

PeakVO2 is considered the best CPET indicator of prognosis in patients with heart failure. Our study confirmed the important role of cardiopulmonary exercise testing peakVO2 in the prognostic stratification of patients with advanced HF. Subjects with a peakVO2 <14 ml/kg/min had a particularly impaired prognosis. However, the peak VO2 value depends not only on cardiovascular factors: many other pathological conditions (obesity, respiratory diseases, muscular diseases etc.)\textsuperscript{98,99} as well as cardiovascular deconditioning (poor fitness)\textsuperscript{100} can likewise lead to values in the CPET parameters, which overlap with those of patients with heart failure; in addiction it does not consider the influence of LV remodeling and provides only an indirect assessment of left ventricular exercise function.

LV ejection fraction is the most frequently used index of cardiac function, but it may not accurately reflect myocardial contractility, and it provides little prognostic information in patients with advanced heart failure.
Echo-derived peak CPOM allows to evaluate the relationship between recruited myocardial muscle mass and the power of the left ventricle at maximum workload. It can give information about the rate at which potential energy stored in left ventricular mass is transformed into useful work. Dini and colleagues recently proved that CPOM is an independent predictor of outcome in patients with advanced HF and it is likely to reflect the LV morphological changes in maladaptive remodeling. In our study CPOM resulted to have the greater statistical significance in the prognostic stratification of patients with HFrEF.

In order to ensure a correct and complete prognostic stratification of patients with HFrEF, which takes account of all aspects which we have discussed, the best option is to submit the subjects both to exercise echocardiography and cardiopulmonary test so as to combine their results and get a full metabolic and cardiorespiratory profile of the patients.

In conclusion, this study demonstrate how the echo-parameter peak CPOM can represent a surplus value in the stratification of patients with HFrEF, in addition to the criteria that are classically used in these patients, as the ejection fraction or the NYHA class. Furthermore, when CPOM is combined with CPET parameters, the prognostic stratification of the patients results more accurate and complete.
8 BIBLIOGRAPHY


35. Lorena Maries, Ioan Manitiu. *Diagnostic and prognostic values of B-type natriuretic peptides (BNP) and N-terminal fragment brain natriuretic peptides (NT-pro-BNP).* Cardiovasc J Afr. 2013 October; 24(7): 286–289.


Bonow R, Mann D, Zipes D, Libby P Malattie del cuore di Braunwald Ed.9, 2012, Capitolo 25, pagg 515-516


Meerson FZ. On the mechanism of compensatory hyperfunction and insufficiency of the heart. Cor Vasa. 1961;3:161–177


87. Jonathan Myers , PhD, Ross Arena, PhD, Frederick Dewey, BA,Daniel Bensimhon, MD, Joshua Abella, D, Leon Hsu, BS,Paul Chase, MEd, Marco Guazzi, MD, PhD, and Mary Ann Peberdy, MD. A cardiopulmonary exercise testing score for predicting outcomes in patients with heart failure. American Heart Journal 2008; 156
89. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18: 1440-63.
98. Richard V. Milani, MD; Carl J. Lavie, MD; Mandep R. Mehra, MD. Cardiopulmonary Exercise Testing: How Do We Differentiate the Cause of Dyspnea? Circulation July 27, 2004
Index of figures

Figure 1.1 Diagram illustrating the mechanisms by which various pathological conditions can lead to high-output heart failure .................................................................11
Figure 1.2. Image illustrating the comparison between the normal balance between sympathetic and parasympathetic tone, and the alterations that occur in a patient suffering from heart failure ...............17
Figure 1.3 The concentric and eccentric hypertrophy can be distinguished through the orientation with which the sarcomeres are added ........................................................................................................23
Figure 1.4 Scheme of cardiac and cellular remodeling, that occurs in response of the hemodynamic overload depending on the nature of the provoking stimulus .........................................................24
Figure 1.5 Histopathology of hypertrophy .................................................................................28

Figure 2.1 Suction – delivery pump ......................................................................................39
Figure 2.2 Pressure-Volume diagram of the left ventricle during the cardiac cycle ....................44
Figure 2.3 Representation the external cardiac work and of the internal cardiac work in the pressure-volume of the left ventricle during the cardiac cycle .................................................................46
Figure 2.4 Change of the left ventricle pressure-volume diagram after the administration of catecholamine .................................................................................................................50

Figure 5.1 ROC curves comparing peak LV ejection fraction and peak CPOM for the prediction of adverse events “death + hospitalization” (above) and “death” events (below) at follow-up ..............................................68
Figure 5.2 Comparison between Kaplan-Meier event-free survival curves for EF, peak VO2, peak CPO, peak CPOM ..............................................................................................................73
Figure 5.3 Comparison between Kaplan-Meier survival curves for EF, peak VO2, peak CPO, peak CPOM ...............................................................................................................................74

Index of tables

Table 5.1: Characteristics of the study patients ...........................................................................65
Table 5.2 ROC curve analysis for death +hospitalization events ..................................................67
Table 5.3 ROC curve analysis for death events ..........................................................................67
Table 5.4 Univariate and Multivariate logistic regression ............................................................69
List of abbreviations

$AG-II = \text{Angiotensin II}$

$AMI = \text{Acute Myocardial Infarction}$

$ANP = \text{Atrial Natriuretic Peptide}$

$BNP = \text{Brain Natriuretic Peptide}$

$ATH = \text{Arterial Hypertension}$

$AUC = \text{Area Under the Curve}$

$BMI = \text{Body Mass Index}$

$BP = \text{Blood Pressure}$

$CAD = \text{Coronary Artery Disease}$

$CO = \text{Cardiac Output}$

$CPET = \text{Cardiopulmonary Exercise Testing}$

$CPO = \text{(peak) Cardiac Power Output}$

$CRT = \text{Cardiac Resynchronization Therapy}$

$EF = \text{Ejection Fraction}$

$EDPVR = \text{End-Diastolic Pressure-Volume Relationship}$

$ESPVR = \text{End-Systolic Pressure-Volume Relationship}$

$h = \text{Parietal thickness}$

$HF = \text{Heart Failure}$

$HEpER = \text{Heart Failure with preserved Ejection Fraction}$

$HErEF = \text{Heart Failure with reduced Ejection Fraction}$

$ICD = \text{Implantable Cardioverter Defibrillators}$

$LV = \text{Left Ventricle}$

$M = \text{Mass}$

$MAP = \text{Mean Arterial Pressure}$

$MIBG = \text{Metaiodobenzylguanidine}$

$MVO2 = \text{Myocardial oxygen consumption}$

$NA = \text{Noradrenaline}$

$NYHA = \text{New York Heart Association}$

$NO = \text{Nitric Oxide}$

$P = \text{Power}$

$p = \text{Pressure}$

$R = \text{Radius}$

$RAAS = \text{Renin-Angiotensin-Aldosterone System}$

$ROC = \text{Receiver operating characteristic}$

$ROS = \text{Reactive Oxygen Species}$

$SD = \text{Standard Deviation}$

$SV = \text{Stroke Volume}$

$T = \text{parietal Tension}$

$t = \text{Time}$

$Vd = \text{End-diastolic Volume}$

$Vs = \text{End-systolic Volume}$

$W = \text{Work}$