

# Are Clinical Heart Failure and Ejection Fraction Always Connected?

Federico Cacciapuoti\*

*Internal Medicine - II Faculty of Medicine - University of Naples, Italy*

**Abstract:** Left Ventricular Ejection Fraction % (LVEF%) is an hemodynamic index indicative for left ventricular function. Its numeric value can be obtained by different methods, such as two- or three-dimensional echocardiography, cardiac catheterization, and Nuclear Medicine-methods. It depends not only on myocardial contractility but also on preload and afterload, as well as heart rate and left ventricular distensibility.

Normal LVEF% is recorded in patients with diastolic heart failure. On the contrary, in patients with systolic heart failure, values of LVEF% <40% usually are found. That generally is connected with clinical symptoms of congestive failure. Nevertheless, a mismatch between low LVEF% and congestive signs can be evident in some forms of systolic HF. That may happen in patients with slowly progressive reduction of systolic left ventricular function. In this occurrence, determining factors of LVEF% can mutually balance each other, through in presence of reduction of one or more determinants. In addition, in some valvular cardiac incompetences, as aortic and mitral insufficiency or in congenital heart disease, such as intra-ventricular and intra-atrial defects, LVEF% can be preserved, also in presence of signs of inadequate peripheral perfusion. Conclusively, LVEF% is an useful hemodynamic parameter, that is not always indicative of left ventricular function concerning the peripheral perfusion.

**Keywords:** Ejection fraction, systolic and diastolic heart failure, symptoms of congestive HF, aortic and mitral incompetences.

## INTRODUCTION

Left ventricular ejection fraction% (LVEF%) is the amount of blood pumped by left ventricle at each heart beat [1]. Value major than 50% indicates an adequate peripheral perfusion and vice-versa, value lower than 40-45% discloses a condition of low perfusion. LVEF% consists of two phases: the first is named the filling period and happens in diastole. The second phase corresponds to the emptying time, and occurs in systole. Its measurement is equal to the ratio between (end-diastolic LV volume – systolic LV volume) and end-diastolic LV volume %, according to the following formula:

$$E.F\% = \frac{(\text{diastolic LV volume} - \text{systolic LV volume}) \times 100}{\text{diastolic LV volume}}$$

Its value depends on:

### A) Stroke Volume

It is the blood volume ejected during systole per beat, and is obtained from the formula:

$$SV = \text{End Systolic Volume (ESV)} - \text{End Diastolic Volume (EDV)}$$

SV multiplied by the Heart Rate (HR) is equal to the Cardiac Output (CO).

### B) Cardiac Output

Cardiac Output (CO) corresponds to the volume of blood being pumped by the left ventricle/min [2]. It is measured in  $\text{dm}^3 \text{min}^{-1}$  ( $1 \text{ dm}^3 = 1000 \text{ cm}^3$ ) and comes from to the formula:

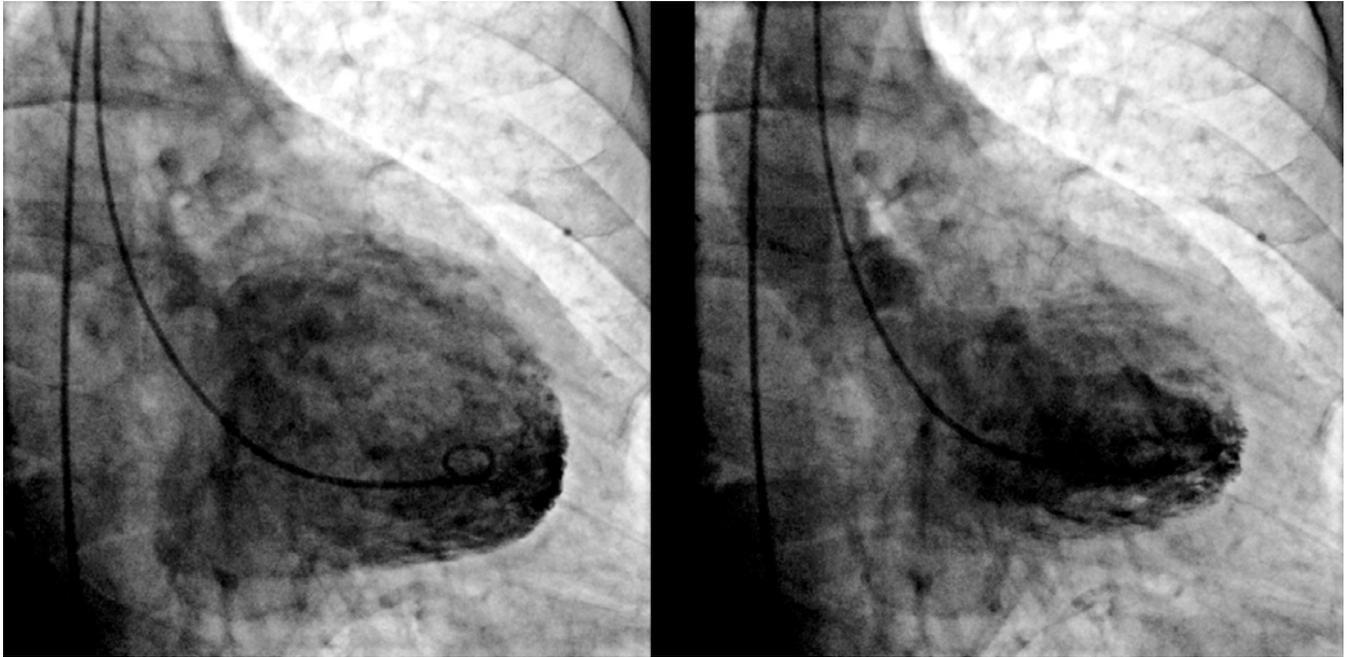
$$\text{Cardiac Output} = SV \times HR$$

There are many methods for invasively measuring CO, including direct cardiac catheterization and indirect methods such as the Fick principle, assuming that the rate of oxygen consumption is a function of the rate of blood flows and the rate of oxygen pick up by the red blood cells.

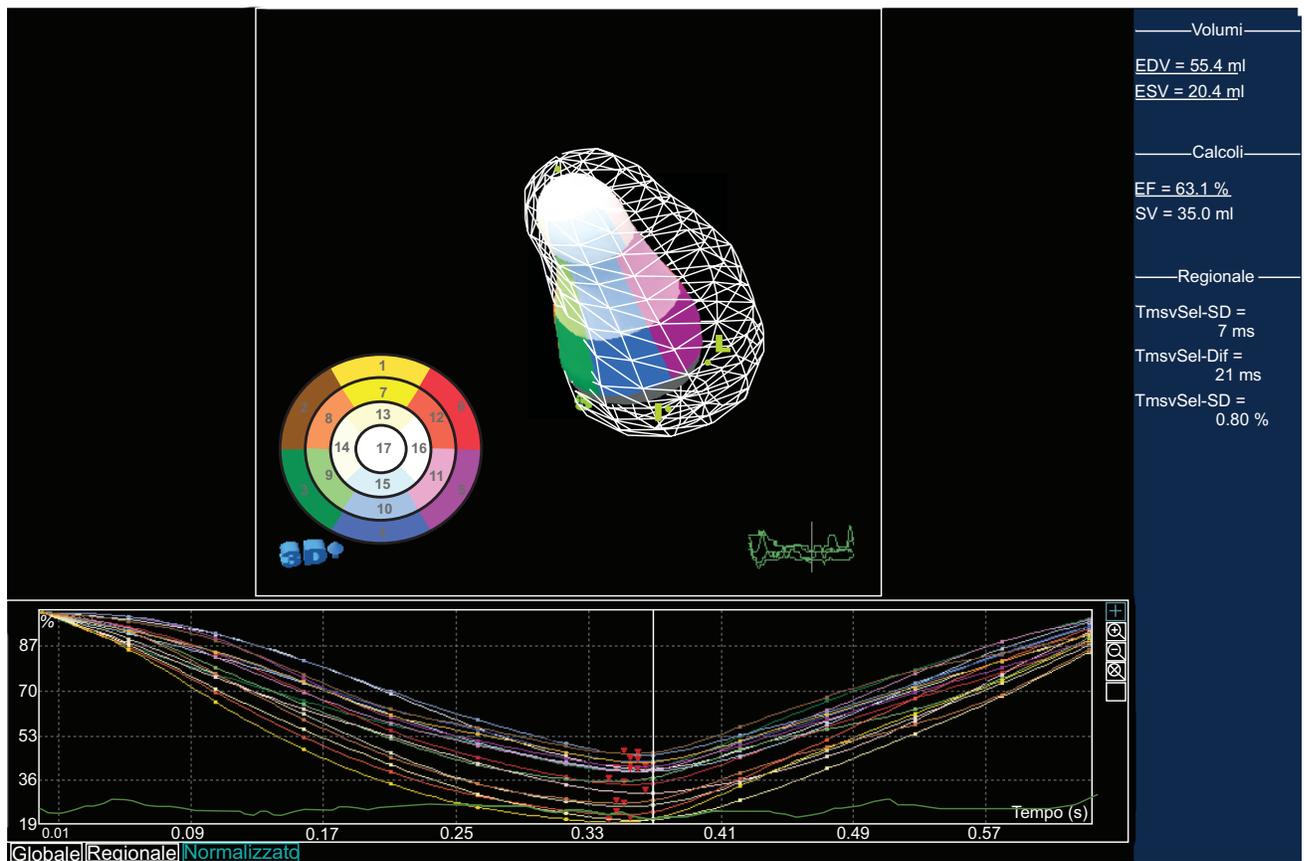
### Measurement of Ejection Fraction

2-D echocardiographic measurements of E.F%. happens means by the Simpson's rule and the area-length methods [3]. The most commonly used is the biplane disks-method (modified Simpson's rule). The value between 55% and 75% corresponds to normal LVEF%, whereas the value = / < 40% indicates a low LVEF%. LVEF% obtained by echocardiography was significantly lower than this obtained by cardiac catheterization (Fig. 1). More recently, three-dimensional echocardiography was also employed (Fig. 2). This method allows to obtain results almost similar to that provided by nuclear medicine, considered as "gold standard" [4,5]. The nuclear method is SPECT test like the MUGA (MUltiple Gated Acquisition) scan [6] (Fig. 3). In addition, nuclear stress test (gated SPECT) [7]; cardiac resonance imaging (MRI) [8] and computer tomography (CT) can be used.

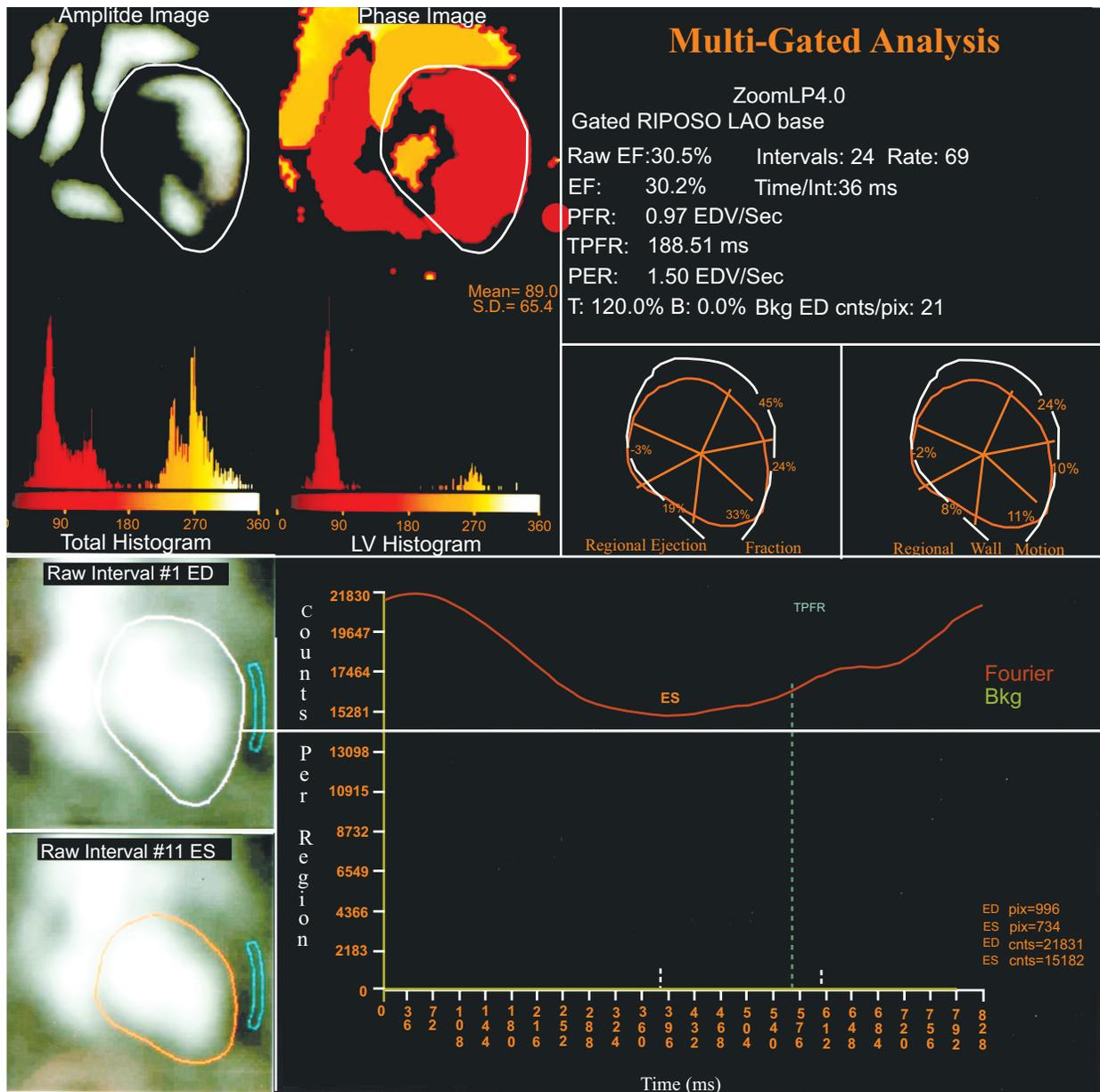
\*Address correspondence to this author at the Cattedra di Medicina Interna, Facoltà di Medicina e Chirurgia, Seconda Università di Napoli, Piazza L. Miraglia, 2, 801238- Napoli, Italy; E-mail: fulviocacciapuoti@alice.it



**Fig. (1).** LV angiography obtained in diastole (left) and in systole (right).



**Fig. (2).** Three dimensional echocardiography-Left ventricular volumes (EDV, ESV) measurement, with determination of stroke volume (SV) and global and segmental ejection fraction % (EF%), obtained totally and by dividing all myocardial walls in 17 segments.



**Fig. (3).** Multi-Gated Analysis of LV with regional ejection fraction% and regional wall motion are illustrated. Amplitude and phase images of LV are also reported. Finally, counts per region referred to time in diastole (ED) and systole (ES) are shown.

**Determinants of Ejection Fraction**

- 1) **Contractility.** It is the ability of the cardiac fibers to contract at a given fiber length, in absence of any changes in preload and/or in afterload [9]. Changes in contractility (or inotropy) produce significant changes in E.F. Contractility results from the binding between thick filaments (myosin) and thin filaments (actin). In turn, the degree of binding depends on the concentration of calcium ions in the cytosol. The most important regulators of contractility are the autonomic nerves.
- 2) **Preload.** It is affected by venous blood pressure and the rate of venous return. These conditions produce stretching of left ventricle in diastole after atrial contraction and passive ventricular filling . It is also in-

fluenced by venous tone [10]. Preload is related to the strength of myocardial contraction means by the Frank-Starling law [11]. Increased venous return increases ventricular filling and therefore preload, which is the initial stretching of the cardiac myocytes.

Pre-load can be calculated as:

$$(LVEDP \times LVEDR)/2h$$

where: LVEDP=Left Ventricular End Diastolic Pressure; LVEDR=Left Ventricular End Diastolic Radius (measured at the ventricle’s midpoint); h=thickness of the ventricle. This calculation is based on the law of Laplace.

- 3) **Afterload.** This term is used to mean tension produced by LV to contract. But, afterload can also be described as the resistance against which the left ventri-

cle ejects. It is also the wall stress or tension that develops in the ventricular myocardial wall during systole. Afterload is determined by arterial tone and blood arterial pressure. It varies with arteriolar resistance too [12]. An increased after-load includes: arterial systemic hypertension and aortic valve disease (aortic stenosis and aortic insufficiency).

- 4) *Heart Rate*. This parameter plays an important role in maintaining an adequate cardiac output when intrinsic contractility fails or cardiac output decreased [13].
- 5) *Distensibility*. It is the ability to stretch ventricular walls in order to LV receive the amount of blood that will be pumped in the next systole [14]. It depends on plasticity, hysteresis, viscosity, thickness and composition of the ventricular wall.

### Heart Failure

Heart Failure (EF) is a clinical syndrome associated with the impaired peripheral perfusion [15]. This condition may happen during ventricular emptying phase, in filling phase or in both phases. Two modes of LV function respectively induce primary systolic and diastolic HF. The main mechanisms responsible for two forms of LVHF are reported in Fig. (4). There are considerable similarities between two entities both in pathophysiological and clinical profile.

PATHOGENESIS OF HEART FAILURE
<ul style="list-style-type: none"> <li>• <u>Diastolic HF</u></li> <li>↑ <i>altered LV relaxation</i></li> <li>↑ <i>inability to fill LV</i></li> </ul>
<ul style="list-style-type: none"> <li>• <u>Systolic HF</u></li> <li>↑ <i>altered pump function of LV</i></li> <li>↑ <i>inability to LV empty</i></li> </ul>

**Fig. (4).** Hemodynamic mechanisms inducing two types of HF.

### Diastolic HF

Some studies demonstrated that in approximately 40% of the patients with HF, left systolic function is well preserved [16]. This entity was also termed “diastolic HF”. It can be defined as clinical syndrome characterized by the symptoms of heart failure, preserved ejection fraction, and abnormal diastolic function. Vasan and Levy proposed some diagnostic criteria for define the diastolic HF. They require the presence of an abnormal LV relaxation, dependent on reduced diastolic distensibility and/or increased diastolic stiffness; and preserved or lightly reduced LVEF% [17]. Concentric left ventricular hypertrophy is characteristic of diastolic HF. In this state, myocyte width is increased more than the length and sarcomeres are deposited in parallel, inducing the wall thickness increase. That is due the increased myocyte protein synthesis. A decreased degradation of myocyte protein also occurs. Conditions that cause these abnormalities are: thickening and/or stiffening of ventricular walls, invasion of the heart muscle by foreign substances or fibrous tissue, pericardial effusion, constrictive pericarditis. All these reduce the passive distensibility of the ventricular walls. In aged individuals, LV distensibility may be diminished by myocardial

infiltration with various substances happening in some degenerative diseases, such as amyloidosis. Another factor that affects diastolic distensibility is the deterioration of the myocardial active relaxation process, dependent on the reduction of calcium ions entered in troponin sites during systole. Prior data suggest that patients who have heart failure with preserved ejection fraction are mostly older, prevalently belonging to female sex and having an history of systemic hypertension.

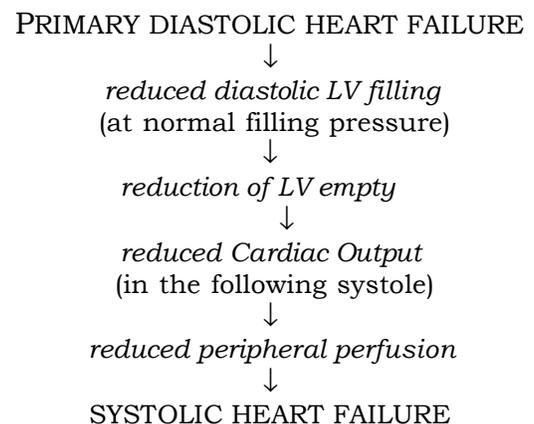
### Systolic HF

In systolic HF, the primary defect is an impaired ability of the heart to contract. The myocardium is weakened, and the resultant impairment of contractility leads to reduced cardiac output. In addition, systolic HF usually shows an E.F.<50% and is associated with eccentric left ventricular hypertrophy. This condition is dependent on increased myocyte length/width ratio and the sarcomeres are deposited in series with rising of left ventricular volumes for impairment of slide of thin filaments on thick filaments [18,19].

The different behavior of LVEF% in two forms of HF depends on the different changes of ventricular dimensions, induced by the changes of LV contractility or distensibility respectively.

Diastolic heart failure can travel to systolic heart failure, for a reduction in LV filling and its reduced empty, with following decrease of cardiac output at following systole (Fig. 5). In these occurrences, total HF occurs, with clinical signs of congestive HF and reduction of LVEF%.

### Shift from diastolic to systolic HF



**Fig. (5).** Main events favouring the shift from diastolic to systolic heart failure.

Whether or not there are substantial differences in mortality and morbidity among symptomatic patients with systolic and diastolic HF remains controversial. In the Helsinki Aging Study, the 4-year mortality was 43% for the patients with preserved systolic function and 54% for those with reduced LVEF% [20]. In the Cardiovascular Health Study, the mortality rate was higher in symptomatic patients than in those with preserved systolic function [21]. In patients with severe clinical HF, mortality appears to be higher in those with reduced LVEF% than in patients with preserved systolic function [22].

## Causes of HF Progression

Some mechanisms activated in response to failing heart and an attempt to restore the previous cardiac healthy state, are reported in succession (Fig. 6). Nevertheless, these only temporary act, but progressively make worse HF until its non-reversibility.

MECHANISMS ACTIVATED BY HF
• <i>LV Remodeling</i>
• <i>Imbalance SNS/PSNS</i>
• <i>RAAS Activation</i>
• <i>Endothelin</i>
• <i>Nitric Oxide</i>
• <i>Activation of NPS</i>
• <i>Left Atrial Remodelling</i>
• <i>Immune System</i>

Fig. (6). Mechanisms activated by heart failure.

- 1) *LV Remodeling*. Besides the changes of myocyte's length/width ratio and the sarcomeres deposition (in series or in parallel), changes in the extracellular matrix and abnormalities of collagen synthesis and degradation occur in both types of HF. Abnormalities of activation of matrix metalloproteinases (MMPs) and their endogenous inhibitors (TIMPs) are described. Increased MMPs/TIMPs ratio, with increased MMPs or decreased TIMPs, favors adverse remodeling [23]. Increased plasma levels of MMPs are directly associated with systolic HF [24]. Plasma levels of TIMPs are inversely related to systolic function and LV hypertrophy [25]. Finally, serum levels of amino-terminal propeptide of Type III procollagen (PIIINP) were found to be elevated in patients with dilated cardiomyopathy [26]. In addition, myocyte loss, either by ischemic necrosis or apoptosis (programmed cell death), occurs in both types of HF [26].
- 2) *Activation of the Sympathetic Nervous System*. Attention has turned to the sympathetic nervous system and its deleterious effects on cardiovascular apparatus in patients with HF. Sympathetic Nervous System (SNS) increases its activity, through an imbalance of two systems: Sympathetic/Parasympathetic Nervous System in favour of the first, by *feed-back* mechanism. SNS increases plasma levels of vasoconstricting and volume-expanding hormones, but also counter-regulatory hormones. The net hemodynamic effects are vasoconstriction, increased blood volume, increased heart rate and myocardial contractility [27]. In the short term, these activations are compensatory and maintain perfusion of vital organs. In the long time, however, they lead decompensation, accelerating myocardial damage and increasing morbidity and mortality. On the other hand, SNS activation also induces some ventricular arrhythmias [28], further favouring the morbidity and mortality in these patients.
- 3) *Renin-Angiotensin-Aldosterone System (RAAS)*. An early study performed in 1981 demonstrated the RAAS is activated in response to edematous heart failure [29]. Its serum levels normalize after resolution of the edema by treatments with diuretics and/or digitalis. RAAS effects, mediated by Angiotensin II, consist in systemic vasoconstriction, Aldosterone release, and renal sodium resorption [30]. On the other hand, Angiotensin II facilitates cardiac remodeling by inducing growth-related substances. It has also cardiotoxic effects and interacts with other neurohormones, worsening HF [31].
- 4) *Others*
  - Endothelin. Increased vasoconstriction and reduced vasodilation are a short term compensatory mechanisms in HF. The elevated vasoconstrictor tone is caused by the activation of Sympathetic Nervous System, by release of neurohormones like angiotensin II, catecholamines, and vasopressin. The endothelium is also involved in the increase of vascular tone, by releasing a variety of vasoactive substances. In HF, there is an imbalance between the diminished release or the inactivation of vasodilators and increased production or reduced inactivation of potent vasoconstrictive substances, such as endothelin-1. In addition to the vasoconstrictor effect, endothelin-1 also possesses anti-natriuretic and anti-mitogen properties [32]. An endothelial dysfunction connected to raised plasma levels of brain natriuretic peptide (BNP), was also described. The inverse relation exists between plasma BNP and flow-mediated dilatation (expression of normal function of endothelium), indicative of prevalent vasoconstrictive effect and prothrombotic tendency typical of HF [33]. The wide spectrum of action of the endothelin system gives at the endothelium an interesting target for clinical future researches.
  - Nitric Oxide. It is a molecule with two controversial effects depending on the dose. Small doses are beneficial, with vasodilatory effect, and protecting against foreign invaders. On the contrary, in high doses it induces the formation of peroxynitrite, a cytotoxic agent, and contributes to HF. Three nitric oxide synthase (NOS) isoforms exist and can be expressed in the heart. Among these, inducible nitric oxide synthase (iNOS) is prevalently involved in HF, and is positively correlated with its severity. In fact, it interferes with vasomotor tone, further increasing the vasoconstriction of HF [34].
  - Atrial Natriuretic Peptide (ANP). It is a circulating peptide with natriuretic, diuretic, and vasorelaxing properties secreted from the atria. Its level is increased in HF, related to increased atrial pressure and plasma levels have been correlated with survival [35]. ANP also appears to inhibit the RAAS and reduce central sympathetic outflow. For all these reasons, the system may have a key role in maintaining a compensated state of HF.
  - Left Atrial Remodeling. Left atrium is a muscular chamber located between pulmonary circulation and

left ventricle, acting by modulating LV filling and so, the amount of the blood pumped in the great circulation during the following systole. The increase of LVEDP favored by the fluid overload present in HF, causes atrial stretch and dilation. This condition is transiently counterbalanced by endocrine (ANP synthesis and secretion) and neuro-regulatory (control of sympathetic activity) responses. But, the progressive left atrial remodeling contributes to the progression of asymptomatic left ventricular systolic dysfunction to symptomatic heart failure [36].

- **Immune System.** In response to injury in the heart muscle cells that occurs when the heart fails, the immune system releases immune factors, as pro-inflammatory cytokines; activation of the complement system; and production of autoantibodies, intended to protect these areas. Several lines of evidence support a role of immune mechanisms in the pathogenesis of HF. But these proteins can cause inflammation and other damages and are involved in cardiac depression and in the progression of HF.

The origin of the immune activation in patients with HF is still unknown. However, two hypotheses have been proposed. One suggests that the wall's edema leads to bacterial translocation with endotoxin release and immune activation. The second suggests that the heart in HF is the main source of cytokines, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and other proinflammatory cytokines (interleukin-1 and-6) [37].

#### **Exercise in HF**

Exercise intolerance, evident in HF, is defined as the reduced ability to perform activities that involve dynamic movement because of symptoms or fatigue. But, ergoreflex activation induced by the dynamic exercise can also be favourable in decompensate patients. The benefits of exercise training in these patients include an improvement in exercise tolerance assessed not only by exercise duration but also by peak  $\text{Vo}_2$  [38-41]. The majority of studies, however, have shown minimal or no changes in LVEF%. Benefits have also been reported in muscle structure and physiological response to exercise, such as improvements in endothelial function, catecholamine spillover, and oxygen extraction [42]. But, despite these beneficial effects, advanced age, heart disease, and intensity of the exercise can affect the results obtained. The Agency for Healthy Care Policy and Research Guidelines on Cardiac Rehabilitation recommended exercise training for patients with chronic stable HF [43]. Although an improvement in exercise capacity after exercise training seems to be mainly related to peripheral adaptations, some studies have suggested a favorable effect on myocardial adaptations as well as on the outcome of exercise-induced coronary vessel adaptation. Nevertheless, because agreement on a universal exercise prescription for this population does not exist, an individualized approach is recommended. Exercise training guidelines for these patients should be followed as provided in the AHA Standards [44]. Duration of exercise should include an adequate warm-up period. Further, it is recommended that patients with HF continue to remain active either in a formal exercise program or one at home for an indefinite period of time.

#### **Low LVEF% without Clinical Symptoms of HF and Vice Versa**

In diastolic HF, LVEF% is normal or slightly reduced without signs of circulatory failure. On the contrary in systolic HF, usually LVEF% significantly reduced with clinical symptoms of hypo-perfusion. This indicates that LVEF% revealing the adequacy of left ventricular systole to perfusion of the peripheral organs in these patients. Nevertheless in some cases of systolic HF with low values of LVEF%, the symptoms of failure may be absent. That may happen when systolic left ventricular failure slowly occurs. In these occurrences, reduced LVEF% is counterbalanced by one or more factors affecting global LV function. In other words, the ability of the heart to function as pump seems to be dependent on the complex relationship among the determinants of LV function, such as heart rate, pre-or-after-load, ventricular compliance, LV contractility and distensibility. One factor responsible for HF may mutually influence each other till to a certain extent. In addition, the factors long worsening HF but temporarily ameliorative of this state may also intervene to induce a mismatch between LVEF% and clinical symptoms dependent on systolic HF.

On the contrary, if the blood is pumped in different directions instead of in the peripheral organs alone, LVEF% can be uncoupled with an adequate perfusion. In these occurrences, the patient might have normal LVEF% and symptoms of congestive heart failure at the same time. That happens because a share of blood pumped out LV moves from LV to another cardiac chamber, but is unable to be entirely utilized for peripheral oxygenation. This hemodynamic condition occurs in some valvular diseases, such as the aortic and mitral incompetences. In these diseases, LVEF% cannot be used to assess LV function. Specifically, in aortic valvular regurgitation, the blood flow, pumped out by LV in systole, takes two directions: a part normally reaches the peripheral organs, a part (ineffective) returns back in the left ventricle during diastolic phase ("caput mortuum"), through the aortic valvular insufficiency. Corrected LVEF (c.E.F.), or the amount of blood reaching to the peripheral organs (effective for the oxygenation), rather total LVEF is the true LVEF [45,46]. In mitral regurgitation, a share of blood flows towards the aorta and a share back returns in the left atrium (ineffective) during the ventricular systole. Forward E.F. (f.E.F.) is a new hemodynamic index useful for peripheral perfusion [47]. Similar hemodynamic changes also happen in tricuspid and pulmonary regurgitation and in atrial and ventricular septal defects. In these diseases, the ratio:  $(\text{LVEDV} - \text{LVESV})/\text{LVEDV}$  is  $>50\%$ , but the amount of blood really reaching the peripheral organs is c.E.F or f.E.F only. In these conditions, the clinical signs of an inadequate peripheral perfusion and  $\text{LVEF} > 50\%$  can be present at the same time.

#### **CONCLUSIVE REMARKS AND THERAPEUTICAL IMPLICATIONS**

In the steady state, diastolic HF shows a normal value of LVEF% ( $>50\%$ ), with very few or without signs of heart failure. Instead, systolic HF is usually characterized by congestive clinical symptoms matching with low LVEF% ( $<40\%$ ). But, when systolic HF slowly occurs, low LVEF% can be uncoupled with congestive symptoms. In addition, in some cardiac valvular diseases and septal defects, a mis-

match between LVEF% (normal) and peripheral congestion (present) can be found. These different pictures demonstrate that, the LVEF% value not always indicates the adequacy of peripheral perfusion, as commonly previously believed. This concept produces considerable differences in the treatment of two forms of HF. In presence of congestive symptoms, diuretics remain the principal therapy in both systolic and diastolic HF. Angiotensin-receptor blocking agents (ARBs) and ACE-inhibitors (ACEIs) were also employed for reduce the progression towards reverse remodeling whether in systolic HF or in diastolic form [48,49]. In severe systolic HF, Aldosterone antagonists can improve symptoms and quality of life. These therapeutic agents also substantially decrease mortality in these patients [50]. Inotropic drugs as digitalis, will be employed in systolic HF, in presence of congestion signs only. On the contrary, in diastolic HF statin therapy has been recently employed to reduce the morbidity and mortality, even if the mechanism of this beneficial effect remains still unclear [51]. In this connection, prospective controlled studies will be required. The differences between diastolic and systolic HF are also important for non-pharmacologic interventions, such as cardiac resynchronization therapy (CRT). This has been reported to improve prognosis for patients with refractory systolic HF. But, it has not been shown to be of benefit in diastolic HF [52]. Finally, LV assist devices producing reverse remodeling by increasing collagen cross-linking and myocardial stiffness, can be of benefit in patients with systolic HF [53].

Conclusively, these remarks indicate that EF% habitually is an useful hemodynamic parameter for predict the effectiveness of peripheral perfusion and the adequacy of HF treatments. But, in some cases its value not corresponds to the ventricular function and vice versa, with important prognostic and therapeutic implications.

## REFERENCES

- [1] Braunwald E. Normal and abnormal myocardial function. In: Fauci AS, Braunwald E, Isselbacher KJ, Eds. Harrison's principles of internal medicine. New York: NY-Mc Graw-Hill 1998; pp. 1278-86.
- [2] Guyton AC, Jones CE, Coleman TG. Graphical analysis of cardiac output regulation. Circulatory physiology: cardiac output and its regulation. Philadelphia W.B. Saunders & Co: USA 1973; p. 237.
- [3] Schiller NB, Shah PM, Crawford M, *et al.* Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of two-dimensional echocardiograms. J Am Soc Echocardiogr 1989; 2: 358-67.
- [4] Qin JJ, Jones M, Shiota T, *et al.* New digital measurement methods for left ventricular volume using real-time three-dimensional echocardiography: comparison with electromagnetic method and magnetic resonance imaging. Eur J Echocardiogr 2000; 1: 96-104.
- [5] Kondo C, Fukushima K, Kusakabe K. Measurement of left ventricular volumes and ejection fraction by quantitative gated SPET, contrast ventriculography and magnetic resonance imaging: a meta-analysis. Eur J Nucl Mol Imaging 2003; 30: 851-8.
- [6] Germano G, Kiat H, Kavanagh PB, *et al.* Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. J Nucl Med 1995; 36: 2138-47.
- [7] Yoshioka J, Haswgawa S, Yamaguchi H, *et al.* Left ventricular volumes and ejection fraction calculated from quantitative electrocardiographic-gated <sup>99m</sup>Tc-tetrofosmin myocardial SPECT. J Nucl Med 1999; 40: 1693-8.
- [8] Hoffmann R, von Bardeleben S, Ten Cate F, *et al.* Assessment of systolic left ventricular function: a multi-centre comparison of cineventriculography, cardiac magnetic resonance imaging, unenhanced and contrast-enhanced echocardiography. Eur Heart J 2004; 17: 218-23
- [9] Brusaert DL, Sonnenblick EH. Cardiac muscle mechanics in the evolution of myocardial contractility and pump function: problems, concepts, and directions. Prog Cardiovasc Dis 1973; 16: 337-61.
- [10] Ranklin LS, Moss S, Grossman W. Alterations in preload and ejection phase indices of left ventricular performance. Circulation 1975; 51: 910-5.
- [11] Schneider NS, Shimanoshi T, Amano A, Matsuda T. Mechanism of the Frank-Starling law: a stimulation study with a novel muscle contraction model that includes titin and troponin I. J Mol Cell Cardiol 2006; 41: 522-36.
- [12] Covell JW, Pouleur H, Ross Jr J. Left ventricular wall stress and aortic input impedance. Fed Proc 1980; 39: 202-7.
- [13] Yoshikawa T, Baba A, Akaishi M, *et al.* Neurohumoral activations in congestive heart failure: correlations with cardiac function, heart rate variability, and baroreceptor sensitivity. Am Heart J 1999; 137: 666-71.
- [14] Booth DC, Wisenbonght T, Smith M, De Maria AN. Left ventricular distensibility and passive elastic stiffness in atrial septal defect. JACC 1998; 12: 1231-6.
- [15] Hunt SA, Abraham WT, Chin MH. *et al.* ACC/AHA 2005 guideline update for diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines (writing committee to update the 2001 guidelines for the evaluation and management of heart failure) developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005; 112: e154-e235
- [16] Brusaert DL, Sys SU, Gillebert TC. Diastolic failure: pathophysiology and therapeutic implications. J Am Coll Cardiol 1993; 22: 318-25.
- [17] Vasani RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation 2000; 101 (17): 2118-21.
- [18] Carabello BA. Concentric versus eccentric remodeling. J Card Fail 2002; 8(Suppl 6): S58-S63
- [19] Vasani RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based study cohort. J Am Coll Cardiol 1999; 33: 1948-55.
- [20] Kupari M, Lindross N, Irvanainen AM, *et al.* Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study. J Intern Med 1997; 24: 187-94.
- [21] Gottlander JS, McClelland RL, Marshall R, *et al.* Outcome of congestive heart failure in elderly persons: influence of ventricular systolic function. The Cardiovascular Health Study. Ann Intern Med 2002; 137: 631-9.
- [22] Lenzen MJ, Scholte OP, Reimer WJ, *et al.* Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. Eur Heart J 2004; 25: 1214-20.
- [23] Spinale FG. Matrix metalloproteinases: regulation and dysregulation in the failing heart. Circ Res 2002; 90(5): 520-30.
- [24] Sundstrom J, Evans JC, Benjamin EJ, *et al.* Relations of plasma total TIMP-1 levels to cardiovascular risk factors and echocardiographic measure: the Framingham Heart Study. Eur Heart J 2004; 25: 1509-16.
- [25] Rossi A, Ciccoira M, Golia G, *et al.* Amino-terminal propeptide of type III procollagen is associated with restrictive mitral filling pattern in patients with dilated cardiomyopathy: a possible link between diastolic dysfunction and prognosis. Heart 2004; 90: 650-4.
- [26] De Marco T, Chatterjee K, Rouleau JL, Parmley WW. Abnormal coronary hemodynamics and myocardial energetics in patients with chronic heart failure caused by ischemic heart disease and dilated cardiomyopathy. Am Heart J 1988; 115: 809-15.
- [27] Mancina G. Neurohumoral activation in congestive heart failure. Am Heart J 1990; 120: 1532-7.
- [28] Meredith IT, Kent RL, Jennings GL, Esler MD. Evidence of a selective increase in cardiac sympathetic activity in patients with sustained ventricular arrhythmias. N Engl J Med 1991; 325: 618-24.
- [29] Dzau VL, Colucci WS, Hollenberg NK, Williams GH. Relation of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure. Circulation 1981; 63: 645-51.
- [30] Hirsch AT, Pinto YM, Schunkert H, Dzau VJ. Potential role of the tissue renin-angiotensin system in pathophysiology of congestive heart failure. Am J Cardiol 1990; 66: 22D-30D.

- [31] Kabour A, Henegar JR, Janiki JS. Angiotensin II (AII)-induced myocyte necrosis: role of the AII receptor. *J Cardiovasc Pharmacol* 1994; 23: 547-53.
- [32] Sutsh G, Barton M. Endothelin in heart failure. *Curr Hyper Rep* 1999; 1: 62-8.
- [33] Chong AY, Blann AD, Patel J, Freestone B, Hughes E, Lip YH. Endothelial dysfunction in congestive heart failure: relation of flow-mediated dilation to circulating endothelial cells, plasma indexes of endothelial damage, and brain natriuretic peptide. *Circulation* 2004; 110: 1794-8.
- [34] Starling RC. Inducible nitric oxide synthase in severe human heart failure: impact of mechanical unloading. *JACC* 2005; 45: 1425-7.
- [35] Brandt RR, Wright RS, Redfield MM, Burnett JC Jr. Atrial natriuretic peptide in heart failure. *Am Coll Cardiol* 1993; 22(Suppl A): 86A-92A.
- [36] Karayannis G, Kitios G, Kotidis H, Triposkiadis F. Left atrial remodeling contributes to the progression of asymptomatic left ventricular dysfunction to chronic symptomatic heart failure. *Heart Fail Rev* 2008; 13: 91-8.
- [37] Torre-Amione G. Immune activation in chronic heart failure. *Am J Cardiol* 2005; 95: 3-8.
- [38] Belardinelli R, Georgiou G, Cianci G, *et al.* Exercise training improves left ventricular diastolic filling in patients with dilated cardiomyopathy: clinical and prognostic implications. *Circulation* 1995; 91: 2775-84.
- [39] Hambrecht R, Niebauer J, Fiehn E, *et al.* Physical training in patients with heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *J Am Coll Cardiol* 1995; 25: 1239-49.
- [40] Callaert-Vegh Z, Wenk M, Goebbels U, *et al.* Influence of intensive physical training on urinary nitrate elimination and plasma endothelin-1 levels in patients with congestive heart failure. *J Cardiopulm Rehabil* 1998; 18: 450-7.
- [41] Camnista LB, Davidoff R, Picard MH, *et al.* Moderate-high intensity exercise training after myocardial infarction: effect on left ventricular remodeling. *J Cardiopulm Rehabil* 1999; 19: 373-80.
- [42] Pina IL, Apsein CS, Gary JB, *et al.* Exercise and heart failure: a statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention. *Circulation* 2003; 107: 1210-25.
- [43] US Department of Health and Human Services. Agency for Health Care Policy and Research. Clinical Practice Guideline No. 17: Cardiac Rehabilitation. Washington DC: Agency for Health Care Policy and Research; October 1995. AHCPR Publication No. 96-0672.
- [44] Flechter GF, Balady GJ, Amsterdam EA, *et al.* Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation* 2001; 104: 1694-740.
- [45] Itaya R, Kubota T, Todaka K, Sugimachi M, Sunagawa K, Nakamura M. Corrected ejection fraction-a new predictor of ventricular function in patient with aortic and/or mitral regurgitation. *Proc 54<sup>th</sup> meeting. Jpn Circ J* 1990; 54: 759.
- [46] Abd-el-Aziz A, Frere AEFH, Khalil TS, Mansour KS, Abd-el-Amid AF, Abd-el-Barry KH. Study of the value of corrected ejection fraction in the evaluation of left ventricular function in patients with mitral or aortic regurgitation. *Angiology* 2000; 51: 555-64.
- [47] Tabayashi K, Endo M, Sadahiro M, *et al.* Assessment of left ventricular function in patients with mitral regurgitation: value of the forward ejection fraction. *Tohoku J Exp Med* 1988; 155: 355-61.
- [48] Kober L, Torp-Pedersen C, Carlsen JE, *et al.* A clinical trial of the angiotensin-converting enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med* 1995; 333(25): 1670-6.
- [49] Yusuf S, Pfeffer MA, Swedberg K, *et al.* Effects of candesartan in patients with chronic heart failure and preserved left ventricular ejection fraction: The CHARM Preserved Trial. *Lancet* 2003; 362 (9386): 777-81.
- [50] Pitt B, Zannad F, Remme WJ, *et al.* For the randomized Aldactone evaluation study investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; 341: 709-11.
- [51] Fukuta H, Sane DC, Brucks S, Little WC. Statin therapy may be associated with lower mortality in patients with diastolic heart failure. A preliminary report. *Circulation* 2005; 112: 300-3.
- [52] Abraham WT, Fisher WG, Smith AI, *et al.* Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002; 346: 1845-53.
- [53] Kltz S, Foronjy RF, Dickstein ML, *et al.* Mechanical unloading during left ventricular assist device support increases left ventricular collagen cross-linking and myocardial stiffness. *Circulation* 2005; 112: 364-74.

Received: October 01, 2009

Revised: October 30, 2009

Accepted: November 10, 2009

© Federico Cacciapuoti; Licensee *Bentham Open*.

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.