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Chapter 2

Pathophysiology in Heart Failure

Kaan Kırali, Tanıl Özer and Mustafa Mert Özgür

Additional information is available at the end of the chapter

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Abstract

Heart failure syndrome is defined as the inability of the heart to deliver adequate blood to the body to meet end-organ metabolic needs and oxygenation at rest or during mild exercise. Myocardial dysfunction can be defined as systolic and/or diastolic, acute or chronic, compensated or uncompensated, or uni- or biventricular. Several counter-regulatory mechanisms are activated depending on the duration of the heart failure. Neurohormonal reflexes such as sympathetic adrenergic system, renin-angiotensin cascade, and renal and peripheral alterations attempt to restore both cardiac output and end-tissue perfusion. An adequate stroke volume cannot be ejected from the left ventricle, which shifts the whole pressure-volume relationship to the right (systolic failure). Adequate filling cannot be realized due to diastolic stiffness, which shifts the diastolic pressure-volume curve upward without affecting the systolic pressure-volume curve (diastolic failure). Left ventricular heart failure is the dominant picture of heart failure syndrome, but the right heart can develop isolated failure as well. Biventricular failure is mostly an end-stage clinical situation of the heart failure syndrome. More recently, the rise in the incidence of right ventricular failure can be seen after the implantation of a left ventricular assist device. This chapter clarifies and presents pathophysiologic alterations in heart failure syndrome.

Keywords: heart failure, systolic dysfunction, diastolic dysfunction, myocardial stiffness, ventricular dilatation, neurohormonal, renin-angiotensin, norepinephrine

Heart failure is an epidemic contributing considerably to the overall cost of health care in developed and also developing countries. Heart failure syndrome (HFS) is the currently accepted term describing a systemic disease affecting several organs, creating high morbidity and mortality rates due to the heart's inability to supply oxygenated blood, including metabolites, to end organs and peripheral tissues (**Table 1**) [1]. Acute event or acute refractory form

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of chronic heart failure can be fatal, whereas chronic prognosis is characterized by terminal congestive heart failure symptoms. The failing heart strives to balance "preload" and "afterload" for compensation of impaired contractility and to deter the development of congestion using a myriad of mechanisms.

(1) Activated feedback signals from peripheral reflex circuit
a. Inflammation
b. Anabolic blunting (proteolysis)
c. Insulin resistance (>50% reducing normal anabolic responses)
d. Oxygen radical accumulation
(2) Global metabolic imbalance (increased catabolic/anabolic imbalance)
(3) Systemic dysregulation of several hormonal pathways
(4) Multi-organ dysfunction (hyperbilirubinemia, uremia, anemia, hypoalbuminemia, etc.)
(5) Development of sarcopenia and cachexia

Table 1. Heart failure syndrome as a multisystem disease.

1. Left heart failure

Left heart failure (LHF), with any structural and/or functional cardiac abnormalities, is a complex clinical state characterized by left ventricular pump dysfunction and related clinical symptoms (dyspnea, fatigue, exercise intolerance, etc.), including signs of volume overload (pulmonary crackles, peripheral edema, etc.) [2]. All steps of energy extraction, transfer, and utilization are affected, with metabolic failure being the important underlying pathophysiologic mechanism causing first myocardial and then systemic decompensation [3]. The pathophysiologic state perpetuates the progression of the failure, regardless of the precipitating event via several compensatory mechanisms. Compensatory mechanisms exist on every level of this scenario to restrain the clinical symptoms via correction of the global imbalance between the catabolic and anabolic status; however, they can lead to further myocardial deterioration and worsening HFS.

The most important classification of LHF is dependent on whether the left ventricular ejection fraction (LVEF) is reduced or preserved. The standard relationship between intracavitary volume and pressure values is affected in heart failure, and left ventricular pressure-volume curves change according to the failure type (**Figure 1**). In systolic LHF, an adequate stroke volume cannot be sustained due to reduced ventricular systolic contractile function, which shifts the whole pressure-volume relationships to the right. In diastolic LHF, an adequate filling cannot be realized due to diastolic stiffness (poor ventricular compliance, impaired relaxation, worsened end-diastolic pressure), which shifts the diastolic pressure-volume curve upward; however, the systolic pressure-volume curve does not change.

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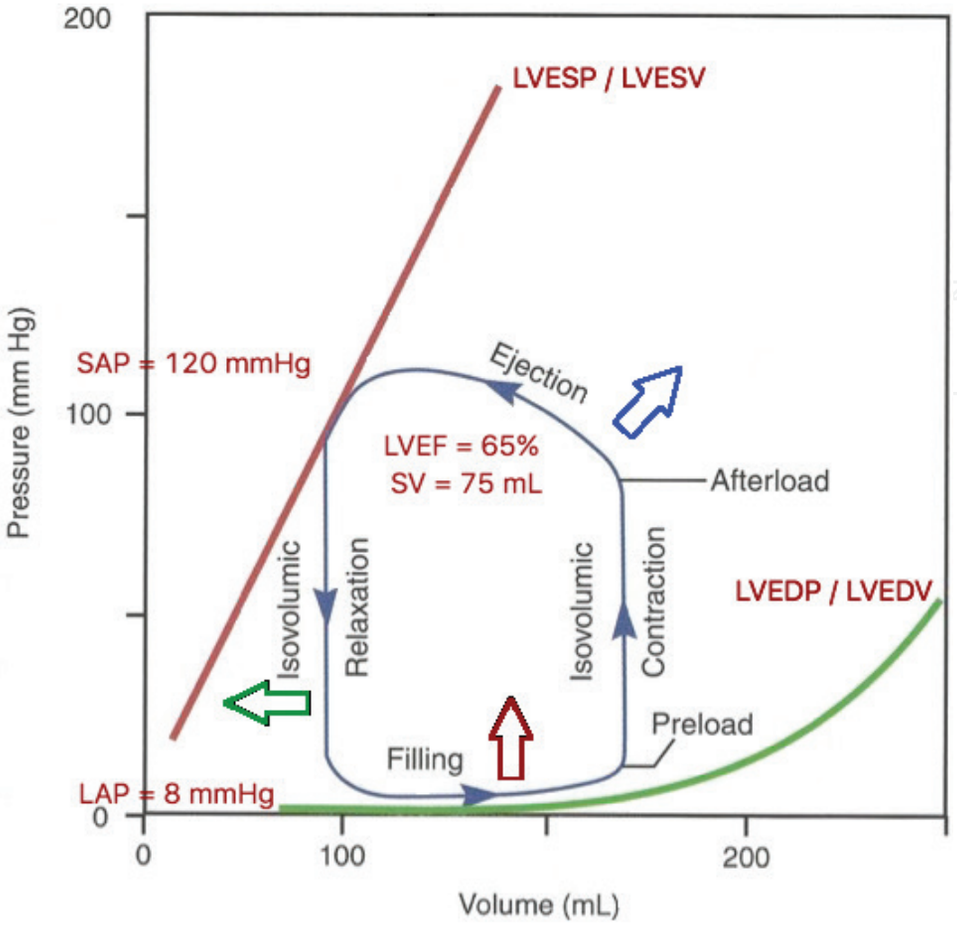


Figure 1. Left ventricular pressure-volume relationships: the green line represents the diastolic pressure-volume relationship, and the red line represents the end-systolic pressure-volume relationship. Both curves are shifted to the right in dilated CMP (blue arrow), to the left in hypertrophic CMP (green arrow), and only diastolic curve is shifted upward in restrictive CMP (red arrow). CMP, cardiomyopathy; LAP, left atrial pressure; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESP, left ventricular end-systolic pressure; LVESV, left ventricular end-systolic volume; SAP, systolic aortic pressure; SV, stroke volume.

From asymptomatic to symptomatic stages, several counterregulatory mechanisms are activated (**Table 2**). First, inadequate stroke volume induces sympathetic nervous system activation, which increases cardiac contractile frequency and strength. This chronotropic effect leads to enhancement of total stroke volume per minute via increasing heart rate frequency, but this positive effect is reversed after tachycardia reaches a threshold of 140–150 beats/min (**Figure 2**). The next step is the augmentation of intravascular volume via neurohormonal system activation, which results in increasing intravascular volume, enlarging ventricular chambers, and improvement in myocardial fiber tension [4]. The inotropic effect via the Frank-Starling mechanism increases myocardial contraction power, but this positive effect reverses after the sarcomere length reaches the upper limit of 2.2 μm (**Figure 3**). At this stage, no physiologic mechanism can improve the contractility, stroke volume, and cardiac decompensation, and the left ventricle (LV) undergoes progressive alterations from reversible cellular to irreversible myocardial remodeling. The heart is a self-renewing

organ, characterized by an increase in myocyte turnover rate during pathological stress, especially in heart failure. The turnover mechanism becomes overwhelmed by a faster loss of myocytes, and this unfavorable imbalance causes the progression of ventricular remodeling during heart failure.

(a) Activation of neurohormonal systems
(b) Increasing preload to help to sustain cardiac performance
(c) Myocardial cell regeneration and apoptosis
(d) Myocardial hypertrophy and/or ventricular dilatation
(e) Compensation of symptoms
(f) Irreversible myocardial remodeling
(g) Decompensation of clinic status
(h) End-stage multi-organ dysfunction

Table 2. Step-by-step counterregulatory actions during ventricular failure.

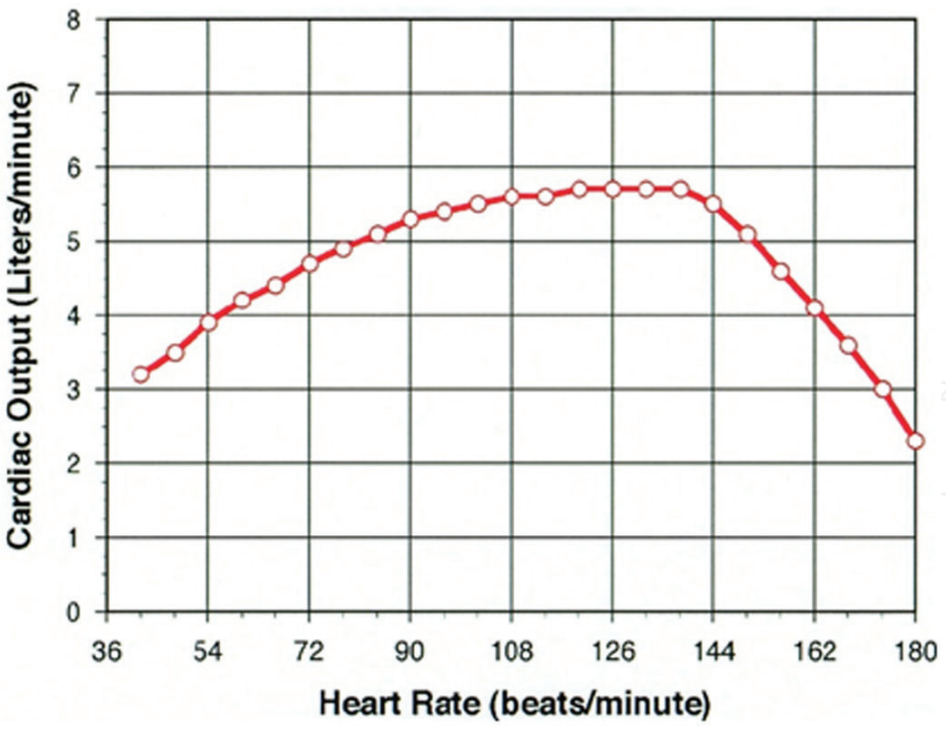


Figure 2. Relationship between cardiac output and heart rate (chronotropy; Bowditch effect).

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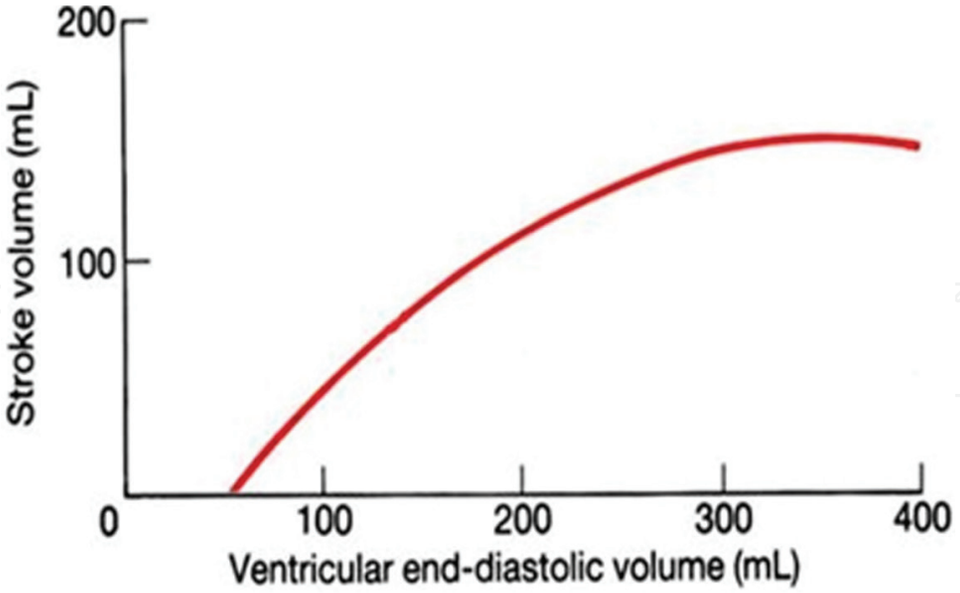


Figure 3. Relation between cardiac output and left ventricular filling (inotropy; Frank-Starling effect).

1.1. Morphological changes

Any of the cardiac pathology causing myocardial dysfunction results in abnormal myocyte growth, with a resultant cascade of gene activation stimulating cardiac remodeling. The hallmarks of cardiac remodeling are myocardial cell hypertrophy and cardiac dilatation with increased interstitial matrix formation. This compensatory mechanism to preserve contraction capability shifts to a maladaptive process after a cutoff level and contributes to the worsening of heart failure during myocardial degenerative progression. Progressive necrotic, apoptotic, or autophagic myocyte loss may contribute to worsening cardiac dysfunction and left ventricular remodeling. Changes within the extracellular matrix such as fibrillary collagen synthesis and degradation, loss of collagen struts, and collagen cross-linking characterize subsequent myocardial adaptation during cardiac remodeling. Cardiac fibroblasts are transformed into myofibroblasts and migrate into the area surrounding injured tissues to secrete collagen and restrict the injured site by scar formation (myocardial fibrosis).

Extracellular matrix requires myocytes to take appropriate position during the cardiac cycles and allows the opening of capillary vessels. Cardiac mitochondria are the main structure to generate energy, in the form of adenosine triphosphate (ATP), through oxidative phosphorylation and to continue cardiac function. Therefore, mitochondrial dysfunction is the major determinant for the development of heart failure via activation of cell death caused by excessive production of reactive oxygen radicals. In the early stage of left ventricular hypertrophy, the number of cardiac myocytes with preserved cellular organization increases; however, they are larger than normal due to the growing number of myofibrils and mitochondria, as well as the large size of the mitochondria and nuclei. Myocytes also increase autophagic

activity in order to maintain ATP levels, to sustain contractile function during these demanding nutritional and energy-consuming phases. Mitophagy is a critical mitochondrial quality control mechanism in myocytes, whereas damaged mitochondria and autophagosomes are selectively sequestered and broken down. This process helps to prevent oxidative damage or myocardial stress under baseline conditions, whereas impaired or dysregulated mitophagy is a major contributor to the development and progression of heart failure [5]. Inhibiting autophagy reduces ATP levels and exacerbates remodeling, whereas enhancing autophagy mitigates remodeling and cardiac dysfunction. The hemodynamic and neurohormonal alterations cause an increase in cytosolic calcium entry, which augments myocardial contractility; on the other hand, it impairs the lusitropic effect and leads to increased myocardial energy consumption resulting in further reduction of cardiac function.

Long-standing hypertrophy disrupts cellular organization, such as enlarged nuclei with myofibril displacement. Additionally, some collagen lytic enzymes (matrix metalloproteinase) activated by neurohormonal substances can create progressive degradation of extracellular matrix. In late stages, the pathologic progress is characterized by myocytolysis, a disruption of sarcomeres and Z-bands. In the chronic phase, some components increase and cause myocyte death, creating perivascular fibrosis within intramuscular vessels. This process causes fibrillary collagen to fill the place of dead myocytes. Ultimately, the disruption of mechanical power by the damaged myocytes becomes detrimental, and the left ventricular wall becomes thinner and dilated.

1.2. Neuroendocrine changes

The pathophysiology of LHF is characterized by hemodynamic abnormalities resulting in autonomic nervous system imbalance and neurohormonal activation. Alterations in receptor activation cause an autonomic imbalance with increased sympathetic activity and diminished vagal activity, both of which may have profound effects on cardiac function and structure. Neurohormonal alterations act as a complex and combined compensatory mechanism to support and maintain tissue perfusion during the HFS (**Table 3**). However, these neurohormonal responses become maladaptive due to uncontrollable activation and promote progression of heart failure. The main sympathetic neurohormones are norepinephrine (noradrenaline) and angiotensin II, which act in an autocrine (myocardial synthesis) and paracrine (endocrine synthesis) manner.

1.2.1. Autonomic nervous system

Sympathetic (adrenergic) and parasympathetic (cholinergic) nerve systems are controlled by the central nervous system and are in balance in healthy individuals, where sympathetic activation is lower at rest, as well as in the normal heart [6]. Baroreceptors at the aortic arch and carotid sinuses, as well as mechanoreceptors at the cardiopulmonary tract, sense arterial wall tension and produce afferent signals resulting in a significant increase of excitatory (sympathetic) impulses via norepinephrine or inhibitory (parasympathetic) impulses via acetylcholine (**Figure 4**). Chemoreceptors at the peripheral vessels and metaboreceptors in the muscles sense acid-base balance and oxygenation of the blood and produce afferent signals resulting in a significant increase of sympathetic stimulation (the excitatory impulse). Mechanical and

chemical changes like hypoxia, hypotension, or acid-base imbalance are sensed by receptors, creating a feedback cascade to maintain cardiovascular homeostasis. In the case of heart failure, the first response of sympathetic nervous system activation is the increasing release and decreasing uptake of norepinephrine at the adrenergic nerve endings. In response, the parasympathetic receptor activity becomes dysfunctional by the increased sympathetic stimulation, which in turn leads to increasing systemic vascular resistance and heart rate.

(1) Sympathetic nervous system

(2) Renin-angiotensin system

(3) Neurohormonal alterations of renal function

  (a) Arginine vasopressin

  (b) Natriuretic peptides

(4) Neurohormonal alterations in the peripheral vasculature

  (a) Vasoconstrictors

    (i) Endothelin

    (ii) Neuropeptide Y

    (iii) Urotensin II

    (iv) Thromboxane A_2

  (b) Vasodilators

    (i) Nitric oxide

    (ii) Bradykinin

    (iii) Adrenomedullin

    (iv) Prostaglandins (PGI_2 and PGE_2)

    (v) Adipokines

(5) Remodeling factors

  (a) Tumor necrosis factor

  (b) Soluble ST2

  (c) Growth differentiation factor (GDF)-15

  (d) Gelectin-3

(6) Interleukin activation

(7) Anabolic metabolism dysfunctions

  (a) Insulin resistance

  (b) Growth hormone resistance

  (c) Anabolic steroid resistance

Table 3. Neuroendocrine responses.

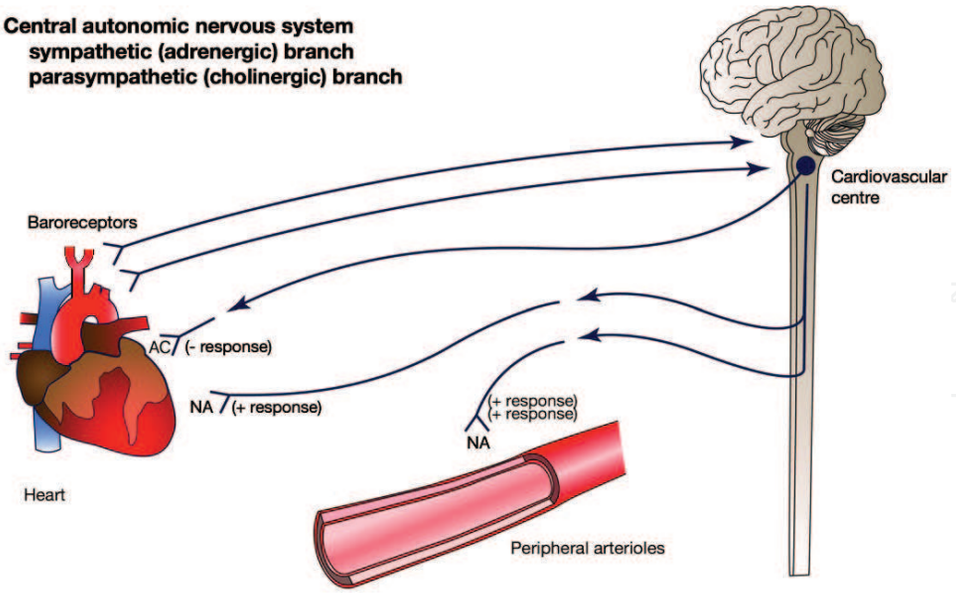


Figure 4. Autonomic nervous system function.

In the HFS, sympathetic stimulation affects several key organs to maintain cardiac output, especially the heart, the kidney, and the peripheral vasculature. Increased sympathetic activity (1) augments ventricular contractility and heart rate to sustain stroke volume, (2) stimulates efferent arteriole vasoconstriction and proximal tubular sodium reabsorption to improve ventricular preload, and (3) leads to systemic vasoconstriction and enhanced venous tone to increase systemic vascular resistance and blood pressure. Alternatively, alterations in autonomic function are broadly associated with both increased cardiovascular and, in many cases, all-cause mortality in humans. Norepinephrine is a potent adrenergic neurotransmitter and increases three to four times more than the normal level in HFS. This process has opposed effects: acute excretion or lower level of norepinephrine is associated with improvement of cardiac function; however, higher levels are associated with worsening of the HFS [7]. α-Adrenergic receptors are present in vascular smooth muscle much more so than in cardiac myocytes; however, only α^1-subtype receptors demonstrate significant density in myocardium, and their numbers increase modestly in heart failure, which leads to myocyte hypertrophy. Stimulation of these receptors in cardiac myocytes by norepinephrine induces myocyte growth and hypertrophy and reproduces fetal isoforms of contractile proteins. β-Adrenergic receptors consist of β^1 subtype and are present in more than 80% in the heart. This system plays a critical role in modulating cardiac performance, specifically inotropy, chronotropy, and lusitropy. However, chronically elevated stimulation of the sympathetic system has detrimental repercussions in HFS (cardiac β-adrenergic desensitization). Ongoing adrenergic stimulation reduces the β-adrenergic receptor, particularly β^1 concentrations in the myocardium (downregulation). This causes an increased expression of β-adrenergic receptor kinase inhibiting β-receptor (both β^1 and β^2) activation by phosphorylating them (functional desensitization).

1.2.2. Renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system is a secondary compensatory mechanism that maintains intravascular volume and vascular resistance. This system is activated later in heart failure due to renal hypoperfusion, decreased sodium in the macula densa of the distal tubule, increased sympathetic stimulations (β^1 adrenergic activity), and diuretic therapy. The system is very sensitive and is activated with the extrication of renin from the juxtaglomerular apparatus. Renin is responsible for the conversion of angiotensinogen to angiotensin I (inactive decapeptide), and angiotensin I is then converted to angiotensin II (active octapeptide) by angiotensin-converting enzyme. The majority of angiotensin-converting enzyme (>90%) is found in tissues, with the rest located in the circulation. The activity of angiotensin-converting enzyme increases during heart failure with increased expression of myocardial form. Two opposing receptors are present; renin receptor type 1 and renin receptor type 2. Activation of type 1 receptors leads to cell growth, causing the release of norepinephrine from sympathetic nerves, either directly or indirectly. This in turn decreases lusitropy, increases afterload by inducing the release of aldosterone from the adrenal cortex indirectly and contributes to the increase of intravascular volume directly by promoting tubular reabsorption of sodium. Furthermore, this stimulates water intake by increasing thirst. The activation of type 2 receptors leads to the inhibition of cell growth, vasodilatation, and natriuresis. On the other hand, atrial natriuretic peptide (ANP) inhibits the release of renin.

Excessive production of angiotensin II can lead to fibrosis of several organs, especially the heart and kidneys, and can also induce cellular proliferation of cardiac fibroblasts and the rate of myocyte apoptosis. Aldosterone has similar actions with unfavorable effects of angiotensin II. Aldosterone provokes hypertrophy and fibrosis within the vasculature and myocardium, resulting in ventricular stiffness, endothelial cell and baroreceptor dysfunction, and the inhibition of norepinephrine uptake.

1.2.3. Renal neuroendocrine alterations

The most adverse outcome of HFS is increased salt and water retention by the kidneys, which results in the worsening of heart failure. Regulation of the fluid balance of the body is primarily managed by body fluid osmolality and changes in plasma volumes [8]. This is a normal pathway that is observed in non-failed hearts due to excessive intake of sodium, but it is a detrimental pathway in heart failure. Decreasing plasma volume or blood pressure is perceived as tissue hypoperfusion, which then stimulates specialized baroreceptors, and in turn activates several neurohormonal pathways that produce hypoperfusion of the tissues. Inadequate perfusion of the kidney and other organs results in adverse impulses that increase vasopressor response via angiotensin II, aldosterone, and norepinephrine production. This central response increases arginine vasopressin secretion, which regulates free water clearance and plasma osmolality. All of these responses try to prevent tissue hypoperfusion. Additionally, they can aggravate the process of heart failure and cause cardiac remodeling. Treatment modalities against any kind of heart failure syndrome can cause hyponatremia, which occurs as either depletional or delusional [9].

The natriuretic peptides provide the most important counterregulatory effect of the neurohormonal system via increasing excretion of sodium and water. Atrial (ANP) and B-type (BNP) natriuretic peptides are produced primarily in response to myocardial stretch due to pressure or volume overload: ANP from the atrial wall and BNP from the ventricular wall. Both peptides are responsible for vasodilatation, natriuresis, diuresis (inhibition of renin and aldosterone cascade), and inhibition of vascular smooth muscle proliferation. The third (C-type) natriuretic peptide released from endothelial cells results in vasodilatation and inhibits endothelin but does not promote natriuresis. These peptides increase during heart failure or decompensated situations, but they can also be used to guide heart failure therapy [10]. Both biomarkers are influenced by other factors such as obesity, arrhythmia, anemia, sepsis, pulmonary embolism, etc.

1.2.4. Peripheral neuroendocrine alterations

The main goal of the body is to preserve brain and cardiac circulation throughout the HFS via decreasing blood flow to peripheral tissues and visceral organs. The increased sympathetic adrenergic stimulation of the peripheral arteries causes arteriolar vasoconstriction for the maintenance of arterial pressure and vasoconstriction of the peripheral veins to increase venous return. Counterregulatory vasodilator responses result in vasodilatation of the peripheral vasculature to prevent aggressive overload of the circulatory system. Loss of the endothelium-mediated vasodilatory responsiveness in HFS causes the inability of counterregulatory and/or control of sympathetic adrenergic activation, which subsequently exacerbates heart failure, cardiac remodeling, and symptoms.

1.2.5. Anabolic metabolism alterations

Insulin is the strongest anabolic stimulatory signal via activation of transcription factor 4, which is complementary to the general amino acid control pathway. In heart failure, the anabolic efficiency of insulin decreases more than 50%. As a principal metabolic feature of heart failure, increased insulin resistance impairs functional capacity of the heart and muscles and worsens heart failure via impaired metabolic efficacy, tissue fibrosis, apoptosis, and lipotoxicity. Growth hormone or insulin-like growth factor 1 causes an anabolic signal rise; however, it cannot prevent cachexia. Anabolic steroid metabolism is also impaired in HFS.

Anabolic failure of the body occurring during long-standing heart failure appears with different clinical signs (**Table 4**). Skeletal muscle is the largest amino acid storage pool in the body, and its atrophy is the first clinical sign for cardiac cachexia (proteolysis). Adipose tissue is actively affected by different lipolytic signals, whereas insulin resistance blocks activation of lipogenic enzymes (lipolysis). Osteopenia or osteoporosis can develop in higher stages of the disease. This catabolic/anabolic imbalance leads to tissue wasting, weight loss, and ultimately cardiac cachexia (body weight loss > 6% in < 1 year), which is the worst and gravest prognosis of the HFS. Iron deficiency is another important metabolic dysfunction that occurs secondary to blood loss, malnutrition, inflammation (hepcidin dysfunction), and impaired synthesis of bioactive heme, and it impairs enzymatic electron transfer activities in the body with or without anemia.

1. Proteolysis
2. Lipolysis
3. Osteolysis
4. Cardiac cachexia
a. Hypoalbuminemia
b. Anemia
c. Impaired glucose tolerance
d. Inflammation
e. Anorexia
5. Iron deficiency
6. Hyperuricemia

Table 4. Clinical presentation of imbalanced catabolic status in heart failure.

1.3. Left ventricular remodeling

Reversible or irreversible left ventricular failure (LVF) results in left ventricular remodeling via complex changes of cardiac myocytes and nonmyocyte components of the myocardium (**Table 5**) [11]. Treatment of reversible pathologies affecting the heart can reverse this process and maintain the anatomohistologic structure. Irreversible pathologies lead to progressive loss of myofilaments and contractile function, as well as alterations in excitation-contraction coupling, fatal arrhythmias, and desensitization of ß-adrenergic signaling. This type of left heart failure impacts the development of left ventricular hypertrophy, in that pressure overload or myocardial accumulation causes concentric hypertrophy with increased left ventricular wall stiffness, with or without left ventricular thickening. However, volume overload also causes eccentric hypertrophy with dilation of the left ventricular wall, with or without thinning. A progressive loss of connectivity of the collagen network causes progressive left ventricular dilatation, but it preserves the structural integrity of the heart. A change in left ventricular shape from an elliptical form to a spherical form creates increasing wall stress and mechanical energy, which results in left ventricular dilatation and wall thinning. This progressive dilatation causes pull-apart pathology of the papillary muscles resulting in significant mitral regurgitation from the inability of the valve leaflets to coapt. In addition, myocardial fibrosis results in arrhythmia and/or sudden death.

The heart anatomically consists of a single, intertwined muscle band. The muscle fibers, both inside and out, achieve maximum contractile performance by making a 60° angle from each other. This angle increases when a stretching occurs, as in heart failure, and the elliptical shape of the heart mutates into a spherical shape, which decreases stroke work and volume significantly. The oblique arrays of apical fibers create 60% LVEF with 15% fractional shortening, while transverse arrays can create just 15% LVEF. When the arrays of myocardial fibers are unbalanced from any cause, the contractile performance of the heart will be affected (**Table 6**). The enlargement of myocardial cells alters left ventricular shape and function.

Systolic dysfunction disrupts emptying of the ventricular chamber and decreases stroke volume, whereas volume overload increases left ventricular end-diastolic pressure. Diastolic dysfunction reduces the filling capacity of the LV due to myocardial stiffness, despite the relatively preserved contractile performance and ejection fraction. Each type of cardiomyopathy has one or both dysfunctional processes. Dilated cardiomyopathy is characterized by impaired systolic function, with enlargement of cardiac chambers, whereas hypertrophic cardiomyopathy is depicted by a smaller ventricular cavity due to a hypertrophic myocardium. Restrictive cardiomyopathy occurs secondarily from diastolic dysfunction and exhibits normal chamber size.

(1) Structural alterations
(a) Ultrastructural remodeling
(b) Mitochondrial remodeling
(c) Extracellular matrix remodeling
(d) Metabolic remodeling
(2) Electrophysiologic alterations
(a) Action potential remodeling
(b) Excitation-contraction coupling remodeling
(c) Repolarization remodeling
(3) ß-Adrenergic receptor signaling alterations

Table 5. Myocardial remodeling.

(a) Myocardial infarction causes loss of contraction and subsequent to fibrosis of affected heart muscle, which breakdowns the array of myocardial fibers due to stretching of myocardial fibers
(b) Valvular and/or congenital heart diseases leading to biventricular volume overload derange the array of myocardial fibers due to ventricular dilatation
(c) Cardiomyopathies and the intrinsic disorders of the myocardium may cause a breakdown of the array of myocardial fibers due to both mechanisms

Table 6. Pathophysiologic changes in different etiologies.

2. Right heart failure

The right ventricle (RV) is not a mirror image of the LV and has its own anatomy, circulation, physiology, and hemodynamics. The RV consists of separated inlet (receives blood from the right atrium) and outlet (funnels blood into the pulmonary artery) portions and has a crescent-shaped structure with a concave free wall and convex interventricular septum (IVS) [12]. It is relatively thin walled with the muscle mass of the RV being relatively less than that

of the LV (about 1/6). However, the RV can eject almost an equal stroke volume as the LV into a lower afterloaded (low pressure-low resistance) and highly compliant pulmonary circuit with a more complex contractile mechanism, but with lower stroke work than the LV (25% of the left ventricular stroke work). The dominant movements of the RV include longitudinal shortening, pressing of the free wall against the septum, contraction of the IVS, and a "wringing" action of the LV (**Table 7**). Right heart failure (RHF) is defined as persistent signs and symptoms of right ventricular dysfunction (RVD) in the absence of LVF, cardiac tamponade, ventricular arrhythmias, and/or pneumothorax.

1. Longitudinal/twisting motion (septal contraction)	80%
Interventricular septum shares fibers with both ventricles	
LV maintains 20–40% RV contractile function	
2. Transverse motion (free wall contraction)	20%
3. Traction of the RV free wall at the points of binding to the LV	

Table 7. Right ventricular contractile functions.

2.1. Pathophysiology of right heart failure

Right-sided heart failure has been accepted as an eventual consequence of left-sided heart failure (the LV as guilty and the RV as victim), and the RV has been largely ignored as a passive conduit or a bystander chamber for several decades [13]. The International Right Heart Foundation Working Group describes a comprehensive definition of RHF: "A clinical syndrome due to an alteration of structure and/or function of the right heart circulatory system that leads to suboptimal delivery of blood flow (high or low) to the pulmonary circulation and/or elevated venous pressures—at rest or with exercise" [14]. The definition of RHF represents a dysfunction of any components that constitute the right heart circulatory system, from systemic veins (post-systemic capillaries) to the pulmonary artery (pre-pulmonary capillaries). Right ventricular failure (RVF) can develop most commonly secondarily to left-sided HFS, but some specific etiologic pathologies result in isolated right-sided HFS (**Table 8**) [15]. The well-known etiologic reasons of RVF are pulmonary arterial hypertension (PAH) with or without LHF, LVF, or implantation of a left ventricular assist device (LVAD).

Pulmonary arterial hypertension (PAH) is seen in almost all RHF scenarios and occurs as a consequence of chronic left heart pathologies, chronic lung diseases, pulmonary embolism, or any pathology affecting the distal pulmonary vascular bed. Pressure overload caused by pre- or post-capillary dynamics starts the "RVD and RVF" vicious circle (**Figure 5**). The hemodynamic definition of PAH type is critical to determine the appropriate treatment modality. Pulmonary hypertension is a common complication of LHF and the diagnosis of PAH-related hemodynamic parameters (**Table 9**). The main differentiation between pre- and post-pulmonary types is pressure gradients between both sides of the pulmonary capillaries, whereas the diastolic pressure gradient has more prognostic value due to lesser dependence of stroke

volume and loading conditions [16]. The threshold level of the transpulmonary pressure gradient (TPG) to discriminate between pre- and post-capillary PHT should be 12 mmHg. The diastolic pulmonary gradient (<5 mmHg) combined with the systemic blood pressure and cardiac output is superior to the TPG for determining the differential diagnosis between pulmonary vascular disease, high output or high left heart filling state, and sepsis.

1. Pressure overload
a. Left-sided HFS (most common cause)
b. Primary pulmonary hypertension
c. Pulmonary embolism
d. RVOT obstruction and/or peripheral pulmonary stenosis
2. Volume overload
a. Tricuspid regurgitation
b. Pulmonary regurgitation
c. Atrial septal defect and/or anomalous pulmonary venous return
d. Coronary artery fistula into right chambers
e. Carcinoid syndrome
3. Ischemia and infarction
4. Intrinsic myocardial process
5. Arrhythmogenic RV dysplasia
6. Chronic lung diseases

Table 8. Etiology of right heart failure.

Right ventricular failure has a specific pathophysiologic algorithm (**Figure 6**). Increased afterload due to pressure overload of the pulmonary circulation prolongs the systolic contraction of the RV. On the other hand, the RV is able to tolerate an increased preload due to volume overload. In the early phase of RVF, wall thickening and enhanced contractility are the first important responses of pressure overload, which creates an adaptive remodeling with concentric hypertrophy and preserved right ventricular function. In chronic, higher afterload states even though myocardial contractility is advanced, the right pump functions decrease proportionally, and contractile dysfunction occurs later in the process. This remodeling process is sustained by the contribution of neurohormonal, genetic, and molecular components. Meanwhile, the RV dilates to provide adequate stroke volume, but this counter effect leads to tricuspid annular dilatation, valve coaptation defect, and eventually significant tricuspid regurgitation. This process triggers a maladaptive remodeling, which causes eccentric hypertrophy and deteriorated right ventricular function. In the beginning of diastole of the LV, the RV is contracting, and the IVS moves leftward causing ventricular dyssynchrony. Ventricular dyssynchrony accelerates right heart and biventricular failure with several fatal complications such as arrhythmia, hepatorenal failure, protein-losing enteropathy, and cardiac cachexia. Myocardial ischemia or infarction of the RV is not a significant factor for heart

failure as it is in LVF, because the right ventricular free wall is supplied by a single coronary artery, whereas the IVS and the rest of the RV have the benefit of left-sided collateral blood flow, which protects the RV against ischemia.

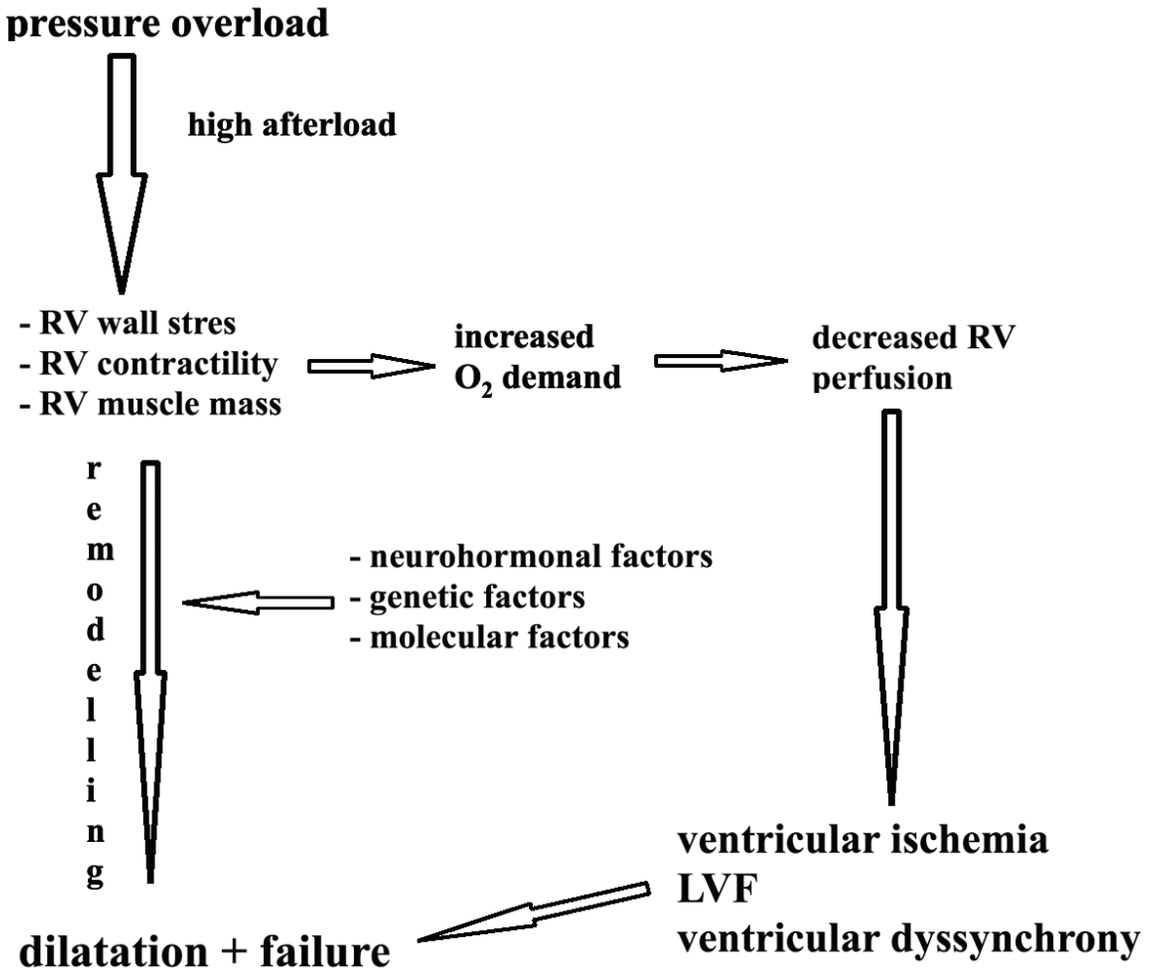


Figure 5. Pathophysiological changes caused by pulmonary hypertension on the right heart.

2.2. Transition of left heart failure to right heart failure

The main cause of RHF is PAH related to an intolerable afterload increase in pulmonary circulation due to LHF and is associated with elevated left ventricular filling pressure, severe mitral regurgitation, and impaired left atrial compliance secondary to a dilated LV. Therefore, LHF is the most common (65–80%) reason for PAH (group 2 PAH) [17]. Sudden elevation of the left heart and consequently pulmonary circulatory pressure increases endothelial permeability causing fluid infiltration into alveolar and interstitial spaces. Pulmonary edema is one of the first signs of acute left HFS, although decreased permeability in the chronic stage of LHF does not cause pulmonary congestion. Significant overloading of the pulmonary arterial vasculature leads to mechanical, neurohormonal, and molecular changes in the pulmonary vasculature system. Destructive neurohormonal changes cause the desensitization of the pulmonary vascular bed against vasodilator agents (nitric oxide, natriuretic peptides, etc.) and excretion of

vasoconstrictor agents (endothelin-1, etc.). Vasoconstriction is the net response of the pulmonary vasculature system to sustain and maintain the right heart stroke volume. If this process cannot be treated or resolved, long-standing PAH will cause reactive structural changes and interstitial fibrosis in the pulmonary vasculature, specifically in the small pulmonary resistance arteries, and will result in increasing pulmonary vascular resistance (PVR) [18]. The next step of this maladaptive process is pulmonary arteriolar remodeling, which includes thickening of the alveolar-capillary membrane, medial hypertrophy, intimal and adventitial fibrosis, and luminal occlusion in small pulmonary arterioles. Arterial resistance and compliance in the lung are determined by the small pulmonary resistance vessels, in contrast to the systemic circulation determined by the aorta. The last stage after irreversible PVR is remodeling of the right heart and organs behind the RV. Maladaptive remodeling of the RV is similar to that of the LV in that there is an increase in myocardial fibrosis, dilatation, wall thinning, tricuspid insufficiency, and contractile failure (**Figure 6**) [19]. Pulmonary hypertension associated with left heart disease is a significant predictor for rehospitalization and mortality [20].

	LVEF	RVEF	CVP (RAP)	mPAP	PCWP (LVEDP)	TPG	DPG	PVR
Normal	Normal	Normal	<10 mmHg	<15 mmHg	<10 mmHg	<10 mmHg	<5 mmHg	<2 WU
Precapillary (PVD)	Normal	Decreased	>15 mmHg	≥25 mmHg	≤15 mmHg	>12 mmHg	>7 mmHg	>3 WU
Post-capillary (LHF)	Decreased	Normal	>15 mmHg	≥25 mmHg	>15 mmHg	≤12 mmHg	<7 mmHg	<3 WU
Combined	Decreased	Decreased	>15 mmHg	≥25 mmHg	>15 mmHg	>12 mmHg	>7 mmHg	>3 WU
Irreversible PAH	Decreased	Decreased	>15 mmHg	≥25 mmHg	>15 mmHg	>15 mmHg	>10 mmHg	>6 WU

CVP, central venous pressure; DPG, diastolic pulmonary gradient; LHF, left heart failure; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVD, pulmonary vascular disease; PVR, pulmonary vascular resistance; Rap, right atrial pressure; RVEF, right ventricular ejection fraction; TPG, transpulmonary gradient.

Table 9. Pulmonary hypertension types.

Increased filling pressure of the right heart chambers reflects back to the systemic venous system and affects visceral and peripheral tissues. The left HFS with low systemic perfusion pressure and elevated PVR contributes to this process and aggravates organ dysfunction. The liver is the most affected organ in RHF via congestive hepatopathy. Cardiac hepatopathy is a clinical entity with signs and symptoms of elevated hepatic biomarkers approximately twice the upper limit of normal: aspartate aminotransferase > 100 U/L, alkaline phosphatase > 200 U/L, and serum bilirubin > 2 mg/dL [21]. Increased elevation of the right atrial pressure and/or severe tricuspid regurgitation implies increased hepatic venous pressure causing hepatic circulatory failure, hepatic congestion, and hepatic ischemia. In the early phase, sinusoidal congestion with hemorrhagic necrosis and hepatocyte degeneration dominates the reversible silent clinical status. Chronically elevated right heart pressures disrupt hepatic venous return and consequently hepatic arterial circulation, so that decreased hepatic oxygen and

nutrient delivery results in hepatocellular necrosis, fatty changes, and fibrosis. The congested and hypoxic liver cannot work properly, and, ultimately, cardiac cirrhosis develops, which is characterized by hepatic insufficiency such as portal hypertension, coagulation abnormality, biliary malfunctions, and other metabolic dysfunctions.

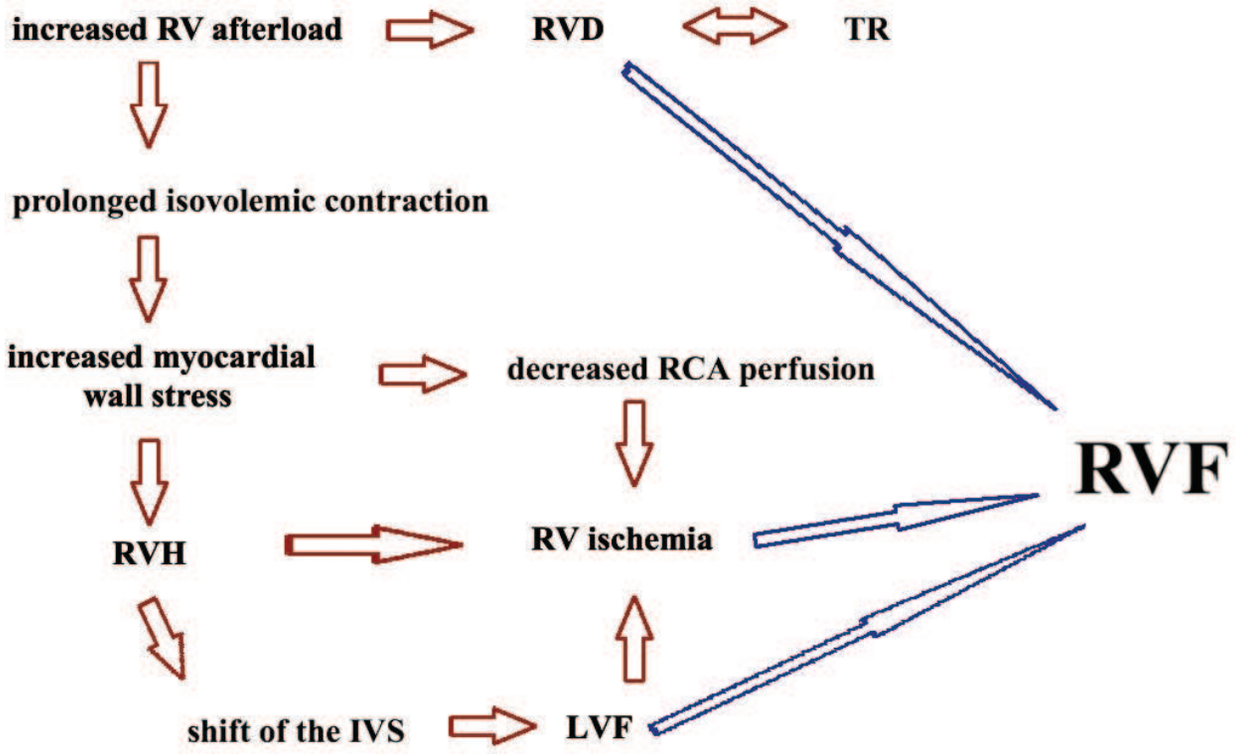


Figure 6. RVF pathophysiology. IVS, interventricular septum; LVF, left ventricular failure; RCA, right coronary artery; RV, right ventricle; RVD, right ventricular dysfunction; RVF, right ventricular failure; RVH, right ventricular hypertrophy; TR, tricuspid regurgitation.

3. Right ventricular failure after left ventricular assist device implantation

End-stage HFS requires mechanical uni- or biventricular circulatory support, but isolated LVAD implantation covers the majority (>90%) of treatments. Uni- or biventricular failure can be treated only by LVAD implantation. This therapy has several indications (**Table 10**). Currently, more LVADs have been implanted as destination therapy in advanced LVF with both advantages and disadvantages. The main intention of LVAD therapy is to provide support to the failing LV, allowing for improved stroke volume that ultimately promotes peripheral tissue perfusion. Furthermore, the LVAD improves right ventricular function due to unloading of the LV and consequently the RV [22]. The most serious complication of LVAD therapy can be a newly developed or continued deterioration of RVF as pathophysiologic sequela, which worsens postoperative mortality and morbidity, end-organ dysfunction due to severe congestion (coagulopathy, malnutrition, renal and hepatic dysfunctions, edema, ascites, etc.),

hospitalization durations, and success of bridge to transplant therapy. The classification of RVF after LVAD implantation is described by The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and is associated with increased perioperative mortality, prolonged length of stay, and worse survival even after cardiac transplantation (**Table 11**) [23]. The definition of serious RVF after LVAD implantation must be very clear, because it needs to be treated by heart transplantation or mechanical circulatory support (**Table 12**) [24]. Post-implant RVF can occur beyond the immediate postoperative period or later, and it significantly impacts survival after LVAD implantation because it is a progressive condition. Early post-implant RVF results in worse survival and is predicted by greater preoperative tricuspid incompetence [25]. Prolonged RVF for more than 2 weeks is associated with adverse outcomes, with the incidence of moderate or severe RVF necessitating right or biventricular ventricular assist device placement after LVAD implantation ranging between 10 and 40% [26].

1. Bridge to transplantation (BTT)
2. Bridge to candidacy for transplantation (BTC)
3. Destination therapy (DT)
4. Bridge to recovery (BTR)

Table 10. LVAD indications.

1. Mild
a. Post-implant inotropes, inhaled nitric oxide, or intravenous vasodilators not continued beyond post-op Day 7 after LVAD implant
2. Moderate
a. Post-implant inotropes, inhaled nitric oxide, or intravenous vasodilators continued beyond post-op Day 7 and up to post-op Day 14 after LVAD implant
b. CVP or right atrial pressure >16 mm Hg
3. Severe
a. Prolonged post-implant inotropes, inhaled nitric oxide, or intravenous vasodilators continued beyond post-op Day 14 after LVAD implant
b. CVP or right atrial pressure >16 mmHg
c. Need for RVAD at any time after LVAD implant

CVP, central venous pressure; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; RVAD, right ventricular assist device; RVF, right ventricular failure.

Table 11. INTERMACS definition of post-implant RVF (severity scale).

Right ventricular output determinants such as preload, afterload, and contractility are deranged in RVF after LVAD implantation (**Table 13**). Post-implant RVF is multifactorial and includes leftward shifting of the IVS, suboptimal RV afterload reduction, and RV myocardial dysfunction. Echocardiography is the primary imaging modality for monitoring cardiac function, filling and contraction behaviors, and device malfunctions [27].

1. Need for intravenous inotrope and pulmonary vasodilator therapy > 14 days
2. Need for RVAD implantation
3. Hemodynamic parameters
   a. CVP > 16 mmHg
   b. CVP/PCWP > 2/3
   c. PVR > 2 Wood units
   d. MAP < 55 mmHg
   e. CI < 2 L/min/m^2
   f. Inotropic support > 20 U
   g. MVS < 55%
   h. HR > 100 / min
4. Laboratory parameters
   a. Bilirubin > 2 mg/dL
   b. Creatinine > 2 mg/dL
   c. AST > 80 IU/L
   d. Albumin < 3 g/dL
5. Echocardiographic parameters
   a. TAPSE < 7.5 mm
   b. RAD > 5 cm
   c. RVEDD > 3.5 cm
   d. RVEF < 30%

AST, aspartate aminotransferase; CI, cardiac index; CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure; MVS, mixed venous oxygen saturation; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAD, right atrial diameter; RVAD, right ventricular assist device; RVEDD, right ventricular end-diastolic diameter; RVEF, right ventricular ejection fraction; RVF, right ventricular failure; TAPSE, tricuspid annular plane systolic excursion.

Table 12. Definition of serious RVF.

Increased preload (volume overload) causes the RV to fail due to the overstretching of the right ventricular myocardium. Improved left-sided forward flow with mechanical unloading in conjunction with perioperative transfusions of blood products suggests that increased venous return to the RV can be well tolerated. However, excessive fluid transfusions can aggravate RVF due to the effect of the Frank-Starling mechanism, exacerbation of tricuspid regurgitation, reduction of septal contribution, and ventriculo-arterial uncoupling. The main echocardiographic findings are a leftward shift of the interatrial septum, distension of the RV, worsening of tricuspid regurgitation, and plethora.

Despite the benefit of the LVAD decompressing the LV and reducing pulmonary overload significantly, it is not successful in every situation due to irreversibility of PAH, which is the main determinant for irreducible afterload. Reverse remodeling of the pulmonary vasculature can

potentially occur with continued unloading, and, unlike heart transplantation, elevated PVR is not able to predict post-implant RVF. The second reason is continuity of preoperative significant mitral regurgitation due to untouched strategy, which cannot be improved and results pulmonary congestion though implantation of LVAD postoperatively. Because the RV has a very different myocardial structure than the left side and is very sensitive to acute change in afterload, any limited or huge failure of afterload decreasing causes significant post-implant RVF due to ineffectiveness of Frank-Starling mechanism on the right heart.

Improvement of right ventricular contractility after LVAD implantation is a predictor for positive outcomes; however, if the right ventricular systolic function does not improve, there are several risk-scoring algorithms that can be used to help predict the need for biventricular support [28]. Excessive leftward shift of the IVS due to volume overload and/or aggressive LV decompression may decrease septal contribution to right ventricular contraction causing mechanical dyssynchrony and elevation of right ventricular work. The main echocardiographic findings of post-implant RVF are decreased tricuspid annular plane systolic excursion (TAPSE < 7.5 mm), reduced right ventricular fractional area change (RVFAC < 35%), increased RV/LV ratio (>0.75), and septal akinesia. Severe unloading of the LV affects left ventricular contraction, depending on it right ventricular systolic function. In normal heart, the left ventricular contraction supplies roughly one half and septal contraction one quarter of the right ventricular ejection function. Prevention and treatment of RVF can be provided with the maintenance of the ejection function of the LV.

1. Preload
a. Increased left ventricular output and venous return (approximately 100%)
b. Excessive administration of blood products and fluids
2. Afterload
a. Maintenance of pulmonary arterial hypertension
b. Respiratory problems
3. Contractility
a. Overstretched cardiac myofibrils (decreasing stroke volume)
b. Aggravated annular dilatation and tricuspid regurgitation
c. Impaired ventricular interdependence (left ventricular failure)
d. Dyssynchronism of interventricular septum (noncontractible and/or leftward shift of the septum)

Table 13. Determinants leading to RVF after LVAD.

Author details

Kaan Kırali[1, 2*], Tanıl Özer[1] and Mustafa Mert Özgür[1]

*Address all correspondence to: imkbkirali@yahoo.com

1 Department of Cardiac Transplantation and Ventricular Assist Device, Kartal Koşuyolu YIEA Hospital, Istanbul, Turkey

2 Department of Cardiovascular Surgery, Faculty of Medicine, Sakarya University, Sakarya, Turkey

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