

# Heart Failure – New Insights

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**ABSTRACT:** Ten years ago we published a review updating current knowledge on heart failure. We summarized that heart failure is a neuro-humoral and inflammatory syndrome, and that pro-inflammatory cytokines are involved in cardiac depression and in the complex syndrome of heart failure. We suggested that understanding the role of these cytokines may enable us to reverse cardiac depression and heart failure. Now we know that there are several mechanisms involved in this syndrome, including inflammation, nitric oxide-dependent pathways, apoptosis, reactive oxygen species, and mitochondrial energy metabolism. This review will focus on the up-to-date mechanistic aspects of heart failure, including clinical trials that have contributed to our better understanding of this entity.

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**KEY WORDS:** heart failure, endothelial dysfunction, reactive oxygen species

For more than 10 years heart failure was regarded as a complex cascade of chronic inflammatory reactions that cause gradual cardiac depression and the syndrome of heart failure [1]. Heart failure is the final step in different cardiovascular pathologies such as ischemic heart disease, hypertension and valvular heart disease. The reduced ejection fraction is the hallmark of chronic systolic dysfunction and is related to an increased volume in the left ventricle.

Diastolic heart failure, caused by old age, hypertension and sometimes by other etiologies like restrictive and infiltrative cardiomyopathy, is best defined as elevated end-diastolic pressure in a chamber of normal size. Diastolic dysfunction contributes to symptomatic heart failure, especially in elderly patients or patients with a history of hypertension [2].

During March-April 2003, 4102 consecutive patients hospitalized in internal medicine and cardiology departments in Israel were recorded. Their age was 73 ± 12 years and 57% were male patients. Seventy-five percent had hypertension, 50% had diabetes mellitus type 2, 59% had dyslipidemia, 82% had coronary artery disease, 33% had chronic atrial fibrillation, 41% had renal failure, and 49% were anemic. Mortality rates were 4.7% in-hospital, 7.6% at 30 days, 18.7% at 6 months and 28.1% at 12 months. Multiple logistic regression analysis revealed that increased 1 year mortality rate was associated with New York Heart Association class III–IV (odds ratio 2.07, 95% confidence interval 1.78–2.41), age (for 10 year

increment) (OR 1.41, 95% CI 1.31–1.52), renal failure (1.79, 1.53–2.09), anemia (1.50, 1.29–1.75), stroke (1.50, 1.21–1.85), chronic obstructive pulmonary disease (1.25, 1.04–1.50) and atrial fibrillation (1.20, 1.02–1.40). This nationwide heart failure survey indicated a high risk of long-term mortality and the urgent need for more effective management strategies for patients with heart failure discharged from hospitals [3].

The symptoms of heart failure are predominately those of congestion, fatigue, and organ system dysfunction, related to inadequate cardiac output in response to stress. Vascular and neuron-endocrine mechanisms are important players and should be addressed and discussed; however, our focus in this review will be on inflammatory mechanisms, nitric oxide-dependent pathways, and energy balance, which may shed some light on the mystery of the heart failure syndrome and the high morbidity and mortality rates.

## MOLECULAR, CELLULAR AND INFLAMMATORY MECHANISMS

### REACTIVE OXYGEN SPECIES

Experimental and clinical heart failure trials documented an increased production of reactive oxygen species, like superoxide, hydrogen peroxide, and hydroxyl radicals. Recent studies found different sources of increased ROS production in the failing heart, including NAD(P)H and xanthine oxidase, dysfunctional nitric oxide synthase, and the mitochondrial electron transport chain [4]. ROS are involved in the deterioration of patients with heart failure and studies have demonstrated the important role of the antioxidant effects of statins on cardiac hypertrophy and on vascular dysfunction in this population. Based on that notion the CORONA trial was planned to study the antioxidant effects of statins (rosuvastatin) on cardiac function in patients with heart failure. Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic heart failure, although the drug did reduce the number of cardiovascular hospitalizations [5].

One of the major consequences of high ROS levels in heart failure is its effect on endothelial dysfunction, secondary to endothelial nitric oxide synthase-derived nitric oxide inhibition that reacts with superoxide to form toxic peroxynitrite [6]. Clinical studies found that among heart failure patients

ROS = reactive oxygen species  
 OD = odds ratio  
 CI = confidence interval

with severe endothelial dysfunction and reduced nitric oxide availability, the worse the endothelial dysfunction the worse the clinical outcome [7].

#### INFLAMMATION

The past decade has provided increasing evidence that vascular inflammation is involved in the clinical deterioration of patients with heart failure, with increased production and enhanced release of pro-inflammatory cytokines, activation of the complement system, production of autoantibodies, and over-expression of the major histocompatibility complex class II molecules, as well as activation of vascular cellular adhesion molecules that perpetuate the inflammatory state.

Patients with heart failure have high levels of tumor necrosis factor- $\alpha$  in their blood, and soluble TNF $\alpha$  receptors 1 and 2 serve as prognostic markers in this population [8]. TNF $\alpha$  has a direct effect on cardiomyocytes and down-regulates sarcoplasmic reticulum proteins, inhibits contractility and induces apoptosis.

Two large clinical studies were conducted with TNF $\alpha$  blockers: The first one, RENAISSANCE (Randomized Etanercept North American Strategy to Study Antagonism of Cytokines), used etanercept.

The second used infliximab. Both of them directly antagonized TNF $\alpha$  but did not prove to have any clinical benefit by causing TNF $\alpha$  blockade [9]. One of the explanations for the lack of response to etanercept was that it was a highly selective TNF $\alpha$  inhibitor, formed by the dimerization of the soluble component of the TNF receptor-1 linked to the constant region of the human immunoglobulin. This component has no cross-reaction with any known cytokine, and the highly selective nature of this compound could well be one of its disadvantages [8,9]. Another argument was that the immune system is redundant and other pro-inflammatory cytokines that are increased in heart failure (like interleukin 1, interleukin 6, and transforming growth factor- $\beta$ ) can participate and substitute for the absence of TNF $\alpha$  in etanercept-treated patients. Following this concept, there are now at least two forms of non-specific immunomodulatory strategies under investigation: the intravenous gamma globulin and immunoadsorption.

There are two randomized trials with IVIG in heart failure patients: The first trial, IMAC (Intervention in Myocarditis and Acute Cardiomyopathy) comprised 62 patients with recent-onset cardiomyopathy and an ejection fraction of less than 40%. They were randomized to receive high dose IVIG or placebo for 2 days. In this study the placebo group

improved its ejection fraction from 23% to 42% in 6 months, and there was no real benefit in the IVIG treatment [10]. The second study comprised 40 patients with left ventricular ejection fraction of less than 40%. They were treated for 6 months on a monthly basis with IVIG. The ejection fraction increased from 26% to 31% in the treated patients, with no significant change in the placebo group [11]. This study proved the beneficial effects of IVIG in heart failure.

Extracorporeal immunoadsorption has been known for about 20 years but only recently attracted the attention of physicians. Immunoadsorption is capable of eliminating huge amounts of immunoglobulins from the patient's circulation with minimum side effects known for plasmapheresis. Simple removal of immunoglobulins from the circulation does not necessarily result in stopping the immune process. Repeated treatment cycles with adequately processed plasma vol-

umes must be used to overcome redistribution of pathological autoantibodies. Extensive immunoadsorption is mandatory in order to achieve an effect on the humoral immune system. Nevertheless, the almost complete elimination of immunoglobulin G results in a severe humoral immune deficiency and clinicians must be aware of any infectious complication when classical immunological screening fails.

The technique of immunoadsorption was examined for 5 days in 34 end-stage heart failure patients with high serum anti- $\beta$ 1 antibodies. The left ventricular ejection fraction improved from 22% to 38%, with improvement in end-systolic and end-diastolic volumes, and with disappearance of the anti- $\beta$ 1 antibodies even 3 months after the treatment [12]. Even though these two immunological approaches have proved to be beneficial they are still not in clinical routine use.

#### INTERLEUKIN-6

Patients with heart failure have high levels of IL-6. IL-6 is considered a strong prognostic marker for morbidity and mortality of patients with heart failure and in patients after acute myocardial infarction [13]. It was recently demonstrated that the IL-6-gp130-Janus kinase (JAK)-STAT signaling cascade in patients with end-stage heart failure is altered at each level in the human failing heart. At the receptor level, there is an enhanced expression and activation of gp130 (tyrosine phosphorylation). The expression of JAK2 (the signaling molecule) and the signaling molecule of the IL-6-gp130 cascade (STAT3) are severely reduced in failing hearts. Activation of STAT3 via the gp130 receptor system is essential for cardiac hypertrophy and for cytoprotection in cardiomyocytes subjected to ischemia or to toxic stress.

### Heart failure is a multi-factorial syndrome that is dependent on inflammation, reactive oxygen species, endothelial function, and energy

TNF $\alpha$  = tumor necrosis factor- $\alpha$   
IVIG = intravenous immunoglobulin

IL = interleukin

STAT3 is required to protect the heart from ischemia and reperfusion injury and from myocardial infarction [14]. Taken together the IL-6-gp130-STAT3 signaling cascade in human failing hearts is deregulated at all levels. Gp130 and its mediator STAT3 play a key role in cardioprotection and preserve cardiac function. It now seems that high IL-6 levels in heart failure are protective rather than detrimental with respect to gp130 signaling.

#### ADHESION MOLECULES

Activation of integrins by different ligands in the extracellular matrix (e.g., collagen, fibronectin, laminin) starts activation of intracellular pathways through integrin-bound proteins. Melusin is a muscle-specific protein that interacts with the integrin  $\beta$ 1 cytoplasmic component. Melusin is required to promote adaptive hypertrophy in response to mechanical stress, and a deficiency in melusin caused an early onset of cardiac dilation and dysfunction after pressure overload [15]. On the other hand, over-expression of melusin reduced ventricular dilation in response to pressure overload and resulted in a prolonged compensatory hypertrophy [16].

### Understanding the basic mechanisms may help us develop new treatments based on new mechanistic insights

#### APOPTOSIS

Apoptosis is involved in heart failure. Heart failure is characterized by a very low but abnormal level of myocyte apoptosis that persists for months to years. The apoptosis rate is estimated to be 0.08% to 0.25% in patients with dilated cardiomyopathy (compared with a rate of 0.001–0.002% in healthy hearts) [17]. Transgenic mice (to caspase 8) had a tenfold increase in the rate of apoptosis compared with normal mice, which was associated with dilated cardiomyopathy and a high rate of mortality. Treatment with a caspase inhibitor (started before cardiac decompensation) prevented dilatation and attenuated cardiac decompensation, preventing dilation and inhibition of cardiac function in procaspase-8 transgenic mice. These effects of caspase inhibition always correlated with inhibition of cardiomyocyte death, suggesting that the major benefit of this treatment results from inhibiting apoptosis [18].

A recent study investigated the effect of apoptosis on end-stage heart failure. Myocardial samples were taken from the hearts of 36 patients who underwent cardiac transplantation and from 11 normal hearts that served as a control group. Apoptosis was evaluated histochemically, biochemically, and by a combination of histochemical analysis and confocal microscopy. It was found that the heart failure samples had a 232-fold increase in myocyte apoptosis. These myocardial samples from the end-stage heart failure patients also

demonstrated other evidence of accelerated apoptosis, such as DNA strand breaks in myocyte nuclei with chromatin condensation and fragmentation. This study demonstrated that programmed cell death accompanies heart failure and may be an important mechanistic factor in the progression of myocardial failure and dysfunction [19].

#### ENERGY, OXIDATIVE STRESS AND THE MITOCHONDRIA IN HEART FAILURE

In order to support contractile activity the heart needs energy. This energy comes from a daily synthesis of around 30 kg of ATP in the mitochondria via oxidative phosphorylation [20]. Catabolism of exogenous substrates such as fatty acids, glucose, pyruvate, lactate and ketone bodies generates most of the reduced compounds that are necessary for mitochondrial electron transport. Ninety percent of the ATP requirement is met by the catabolism of free

fatty acids via  $\beta$ -oxidation in the mitochondria, increasing the ATP yield. In heart failure there is a low ratio between phosphocreatine and ATP [21]. A low ratio between phosphocreatine and ATP correlates with clinical symptoms and predicts mortality better than left ventricular ejection fraction [22]. The reasons for the low ratios in heart failure are still unknown and are most probably multifactorial. However, there is evidence of mitochondrial dysfunction in both the cardiac and the skeletal muscle of heart failure patients. Defects were found in the creatine kinase energy transport system, including decreased activity of total creatine kinase and the mitochondrial isoform in the human myocardium and in the skeletal muscle of heart failure patients.

There are other mitochondrial changes in heart failure, including a decrease in mitochondrial number, an increased oxidative stress due to elevated levels of free fatty acids, and increased tissue hypoxia [23]. The increased free fatty acid level found in heart failure patients is a result of adipose tissue lipolysis due to an increased sympathetic drive. It has been shown that high plasma free fatty acid levels are detrimental to the heart and increase oxygen consumption. Decreased myocardial oxygen efficiency could result also from inefficiency of fatty acid oxidation, which is responsible for more oxygen consumption per ATP synthesized. In heart failure patients, further loss of cardiac efficiency could result from mitochondrial uncoupling, with protons re-entering the mitochondrial matrix independent of ATP synthesis [24]. Excessive uptake of free fatty acids may also decrease levels of the insulin responsive glucose transporter (GLUT) 4 and may lead to lipid accumulation and myocardial insulin resistance. An insulin-resistant state further impairs the metabolic flexibility of the failing heart, depleting glycogen reserves and

limiting the capacity for work, particularly under hypoxic conditions. Therefore, lowering plasma levels of free fatty acids may improve the cardiac efficiency and contractile function of the failing heart. The PPAR- $\gamma$  agonist rosiglitazone improves hepatic and peripheral insulin sensitivity and lowers plasma glucose and free fatty acid levels. However, a meta-analysis of 42 clinical studies revealed that rosiglitazone therapy increased the risk of myocardial infarction and death from cardiovascular causes in diabetic patients. The cause is unknown but may be related to the many genes that are up-regulated in response to PPAR- $\gamma$  activation [25]. Impaired blood flow in heart failure can add stress of tissue hypoxia in the peripheral musculature and in the heart itself. The transcriptional factor hypoxia-inducible factor-1 induces changes in gene transcription of genes that encode proteins involved in adaptation to hypoxia. The cardiac metabolic response to hypoxia is considered to adopt a fetal metabolism, in which carbohydrates predominate as substrates for energy metabolism [26]. Cardioprotective effects of hypoxic adaptation might therefore include improved efficiency of the failing heart, with a switch toward glycolysis and glucose oxidation, and restriction of myocardial fatty acid uptake. It is suggested that late in the process of heart failure, substrate metabolism is insufficient to support cardiac function because the hypoxic heart can no longer oxidize fats and may develop insulin resistance.

In tissue hypoxia low availability of oxygen, the final receptor of mitochondrial electron transport, results in electron accumulation as the complexes become highly reduced. Several studies suggested that ROS generation is enhanced in heart failure because of electron leak from the respiratory chain. Prolonged oxidative stress in the failing myocardium results in damage to mitochondrial DNA, further ROS generation, accumulation and cellular injury leading to functional decline. Mitochondria are both the source and the target of a cycle of ROS-mediated injury in the failing heart. Based on these data there must be a strategy to protect the heart against the oxidative stress, which would likely be through modulation of mitochondrial electron transport. A recent study in which heart failure patients were treated with vitamin C, an antioxidant, demonstrated an improvement in their endothelial function but not in skeletal muscle energy metabolism [27]. Angiotensin-converting enzyme inhibitors also protected mitochondrial function in a rat model of heart failure. It is believed that their tissue effects (decreased oxidative stress and improved endothelial function) occur through activation of intracellular signaling cascades that stimulate mitochondrial biogenesis and improve energy metabolism. No modification of myocardial oxidative capacity, oxidative enzymes or energy transfer enzymes has been reported in exercising rats with experimental heart failure. However, an improvement has been demonstrated in the skeletal muscle

oxidative capacity with increased mitochondrial density following training in heart failure patients, with an improvement in heart failure symptoms like exercise intolerance and chronic fatigue [28].

## ENDOTHELIAL CELLS, ENDOTHELIAL FUNCTION AND ENDOTHELIAL PROGENITOR STEM CELLS IN HEART FAILURE

### ENDOTHELINS

Endothelial cells secrete peptides that control vascular homeostasis. These peptides, called the family of the endothelins, are produced in a variety of tissues where they act as modulators of vasomotor tone, cell proliferation, and hormone production. There are three members in this family: endothelin-1, endothelin-2 and endothelin-3.

Endothelin-1 is the only peptide that is produced in endothelial cells, but it is also produced in vascular smooth muscle cells. Stimuli like hypoxia, ischemia and shear stress induce the transcription of endothelin-1 messenger RNA and the synthesis and secretion of endothelin-1 within minutes [29]. Plasma endothelin-1 is cleared mostly by the lungs during first passage, and 75% of its secretion is toward the vascular smooth muscle side of the cells, where it binds to specific receptors on muscle cells and causes vasoconstriction. It is secreted like a paracrine rather than an endocrine hormone. Plasma endothelin-1 measurements were found to correlate with the severity of congestive heart failure and may have a prognostic value. The human endothelin-1 gene is on chromosome 6, and the sequence of the mature peptide is coded for in the second exon.

Endothelin-2 is produced in the kidneys and intestine, with smaller amounts produced in the myocardium, placenta and uterus. No specific function was found for endothelin-2 so far. Endothelin-3 circulates in the plasma but its source is unknown. It was found in high concentration in the brain and may have an important role in neuron and astrocyte proliferation and development. It is also found in the lung and in the kidneys [30].

### ENDOTHELIN RECEPTORS

There are two receptors (A and B) that bind all three endothelins. The receptors are members of the super-family of receptors linked to guanine-nucleotide-binding (G) proteins.

- *Type A endothelin receptors*: Endothelin-A receptors have 10 times more binding affinity for endothelin-1 than endothelin-3. These receptors are expressed on vascular smooth muscle cells and on cardiac myocytes. These receptors mediate mainly the vasoconstrictor action of endothelin-1. The vasoconstriction is related to the ability to stimulate phospholipase C, which leads to the

formation of inositol-1,4,5-triphosphate and diacylglycerol. This stimulation increases the intracellular calcium concentration that leads to vasoconstriction. Nitric oxide shortens the duration of vasoconstriction by accelerating the return of intracellular calcium to its basal concentration. Endothelin-1 (through endothelin-A receptors) inhibits the activation of chloride channels and therefore suppresses the pro-arrhythmic effects of catecholamines. It also inhibits the activation of calcium channels (L-type) and activates potassium channels; both these activities decrease the electrical excitability of the heart [31].

- *Type B endothelin receptors*: They are expressed mainly on endothelial cells and to a much lesser extent on vascular smooth muscle cells. They bind endothelin-1 and endothelin-3 with similar affinity and can mediate the actions of either peptide. Activation of these receptors has similar effects as those of endothelin-A receptor activation. However, they are linked to inhibitory G proteins that lead to inhibition of cyclic AMP generation and activation of the Na<sup>+</sup>-H<sup>+</sup> antiporter. Endothelin-3 binds to endothelin-B receptors and may cause vasodilation, probably secondary to increased production of NO and prostacyclin and the activation of potassium channels [32].

#### PHYSIOLOGY OF ENDOTHELINS

Angiotensin II, arginine vasopressin, thrombin, high density and low density lipoproteins, and insulin all stimulate the production of endothelin-1, which mediates the effects of vasoactive peptides and growth factors. In contrast, the vasodilators NO and prostacyclin inhibit the production of endothelin-1 through a common mechanism involving the generation of cyclic guanosine monophosphate. Atrial natriuretic hormone also inhibits the production of endothelin-1. They all inhibit endothelin-induced vasoconstriction. The belief is that the vasodilator and anti-growth effects of NO may be related to inhibition of the production and action of endothelin-1 [33].

#### PATHOPHYSIOLOGY OF ENDOTHELINS

Plasma endothelin-1 concentrations are elevated two- to fourfold in patients with congestive heart failure. The 1 year mortality rate after myocardial infarction correlates with plasma endothelin-1 levels. When endothelin-1 is infused to animals there is a significant increase in vascular resistance and cardiac depression that may explain the manifestations of heart failure. High endothelin-1 levels seen in severe heart failure may cause bronchospasm through endothelin-A

receptors expressed on pulmonary bronchial smooth muscle cells, contributing to respiratory distress, a classic symptom in severe heart failure [34,35].

Bosentan is a competitive antagonist of endothelin-1 at the endothelin-A and endothelin-B receptors. It was recently demonstrated that in patients with systolic heart failure and secondary pulmonary hypertension, bosentan did not have any beneficial effects and the treatment was discontinued because of increased adverse events [36].

#### ENDOTHELIAL FUNCTION IN HEART FAILURE

Endothelium-dependent NO-mediated vasodilation in response to hormonal agonists and shear stress is inhibited in the skeletal muscle and coronary and pulmonary circulations of patients with heart failure compared to healthy subjects. The endothelial dysfunction in heart failure is attributable to decreased activity of the endothelial nitric oxide synthase,

increased degradation of nitric oxide by reactive oxygen species, and a decreased responsiveness of the vascular smooth muscle. Endothelial dysfunction is also associated with reduced exercise hyperemia and impaired functional

### **New approaches based on these new insights may open new directions of management and research – like physical therapy, nitric oxide enhancer therapy, exercise, immunological therapy – which may change the present clinical outcome**

capacity [34]. A clinical study that examined biomarkers of endothelial function in the arterial systemic circulation by measuring flow-mediated dilation in the brachial artery and in the pulmonary circulation by exhaled nitric oxide production during sub-maximal exercise found that impaired vascular endothelial function, as evidenced by decreased flow-mediated dilation in the brachial artery and decreased exhaled NO production, are associated with increased mortality risk in patients with heart failure. Flow-mediated dilation was used as an indirect biomarker of endothelial function that is partly dependent on shear stress-induced release of NO. Flow-mediated dilation is also regulated by local prostaglandin production, by the effects of local metabolic conditions on hemoglobin-NO interactions, and by systemic effects related to inflammation, sympathetic activation, and deconditioning. Flow-mediated dilation in the brachial artery is closely associated with endothelium-dependent vasomotion in the coronary circulation and is associated with pro-inflammatory and prothrombotic changes in endothelial cells. In patients with heart failure the decreased exhaled NO may be related to decreased diffusion of NO from the lower airways or a reduced production of NO in the lower respiratory tract. Increased mortality in association with decreased exhaled NO could be related to autonomic dysregulation of ventilation during exercise, progressive right ventricular dysfunction in response to increased pulmonary vascular resistance, or other hemodynamic factors associated with

NO = nitric oxide

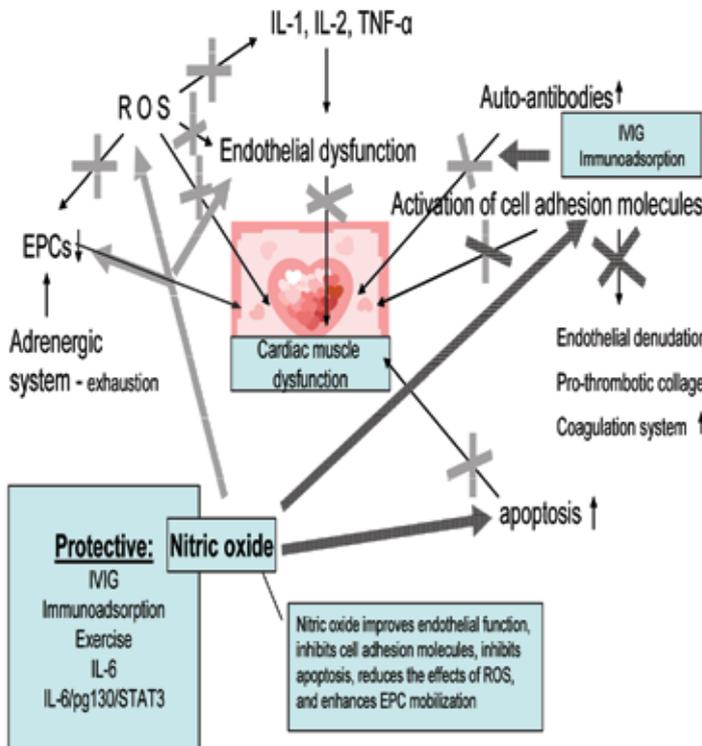
decreased aerobic capacity [35]. Another study evaluated the endothelial function, endothelial integrity and biochemical biomarkers in the blood of 30 patients with heart failure and found that patients with heart failure had a threefold increase in circulating endothelial cells in the blood (which is a novel technique to assess the disruption of endothelial integrity), a fivefold increase in the level of brain natriuretic peptide, a poorer flow-mediated dilation (a decrease of sixfold) and high levels of von Willebrand factor. In the entire cohort of 50 subjects, there were modest inverse correlations between flow-mediated dilation and von Willebrand factor, circulating endothelial cells, and brain natriuretic peptide. There was also a positive correlation between circulating endothelial cells and von Willebrand factor. The impaired endothelium-dependent vasodilation may explain the abnormal vasoconstriction that is the hallmark of heart failure. The increased number of circulating endothelial cells raises the possibility that other parts of the vascular bed are also involved and there is a denudation of vascular endothelial cells. It also means that the endothelial damage in heart failure is generalized. Endothelial denudation also exposes the underlying pro-thrombotic collagen that forms the sub-endothelial layer, and activation of the coagulation system may explain

the excess of thromboembolism risk that is associated with heart failure [37] [Figure 1].

**ENDOTHELIAL PROGENITOR STEM CELLS AND HEART FAILURE**

The bone marrow-derived EPCs originate from hematopoietic stem cells, which are positive for CD34. Circulating EPCs home to sites of neovascularization and differentiate into endothelial cells. EPCs and CD34+ cells increase in patients with endothelial damage, after vascular trauma, and after acute myocardial infarction [38]. A prospective clinical study enrolled 26 patients with heart failure (16 patients had mild heart failure and 10 had severe heart failure with an acute exacerbation), and 22 healthy volunteers served as the control group. The ratio of CD34+ cells to 1000 white blood cells in patients with mild heart failure was higher than that in the control group. However, the ratio of CD34+ to 1000 white blood cells in patients with severe heart failure was significantly lower than that in the control group or in the mild heart failure group. Injury to the heart causes hematopoietic progenitor cells to migrate to sites of damage and to undergo progenitor cell differentiation. This mechanism may explain the increase in CD34+ cells in patients with mild heart failure. Others found a decrease in hematopoiesis in the bone marrow of mice with heart failure. In severe heart failure, suppressed bone marrow function may lead to inhibition of CD34+ stem cells production and mobilization. It could be that in advanced cases of heart failure there is an exhaustion of progenitor cells, and this phenomenon may explain the biphasic bone marrow pattern that was demonstrated in this study [39]. Heart failure is characterized by peripheral and myocardial tissue ischemia, which results in release of angiogenic factors and enhancement of mobilization of stem cells from the bone marrow to the peripheral blood. EPCs in the peripheral blood may serve as a pool (reservoir) for progenitor cells that are used to repair damaged endothelium [39]. It could be that in the first stages of heart failure when there is still a strong adrenergic stimulation there is a relatively larger pool of endothelial progenitor stem cells “ready to go” secondary to enhanced production and mobilization of endothelial stem cells from the bone marrow to the peripheral blood, so that they will be available on time and ready to repair the damaged vascular bed. After a certain time (which may be individual) there is a process of exhaustion of the immune system and the inflammatory system, with a decrease in the adrenergic drive and a decreased stimulation to transfer stem cells from the bone marrow to the peripheral blood [Figure 1].

Figure 1. Schematic description of events in heart failure



**SUMMARY**

Heart failure syndrome is a mystery. It is now more evident that vascular inflammation and endothelial function, together with endothelial cells and endothelial progenitor stem cells as

EPC = endothelial progenitor stem cell

well as the mitochondria all play active roles in the fight against myocardial deterioration and damage – but somehow – without success.

Heart failure is a cardiovascular syndrome that is increasing in incidence and prevalence, and a better understanding of the mechanisms of heart failure may enable us to find a better cure and improve the prognosis. Will it be a better understanding of the mitochondrial energy metabolism or a better insight into the inflammatory systems; will it be the ability to manipulate the immunological system or to enhance self-production of endothelial progenitor stem cells, or maybe stem cell transplantation? Which one of these approaches will open the door to long-term success in the fight against heart failure? This enigma has yet to be solved.

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