

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Cardiomyocyte and Heart Failure

Shintaro Nakano, Toshihiro Muramatsu,
Shigeyuki Nishimura and Takaaki Senbonmatsu

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/47772>

1. Introduction

In recent years, outcome of therapy in patients with heart failure is going up. Many clinical trials have demonstrated that renin angiotensin aldosterone system inhibitors and β -blockers have functional roles in stabilizing and /or reversing cardiac remodeling via suppression of the excessive activation of renin angiotensin aldosterone and the adrenergic nervous system. Additively, the cardiac resynchronization therapy and ventricular assist device therapy also achieve remarkable success in heart failure therapy. Conversely, in many counties that come up against an elderly society, heart failure is a looming public health problem. Therefore, much further advancement of heart failure therapy and decrement of patients with heart failure are one of most important assignments in the medical services. In this chapter, we describe the recent topics of heart failure including 1,molecular basis of cardiomyocyte, 2,mechanisms of progression in heart failure, 3,renin angiotensin aldosterone system and heart failure, 4, β -adrenergic receptor and heart failure, 5, non-drug treatment and heart failure, 6,heart transplantation and heart failure, 7,Cardiac regeneration and heart failure.

2. Molecular basis of cardiomyocyte

The heart is a highly organized tissue and consists of ventricular or atrial cardiomyocytes, pace maker cells, Purkinje cells, vasculature, and connective tissue. The ventricular cardiomyocytes are columnar shaped cells of 20 μ m in diameter and 60-140 μ m in length, while the atrial cardiomyocytes are ellipsoidal shaped cells of 5 μ m in diameter and 10-20 μ m in length (Table 1). The ventricular cardiomyocytes occupies approximately 50% of the heart weight, and 2-4 billion of them make up the human left ventricle. Approximately 50% of the cell volume in an individual contracting cardiomyocyte is made up of myofibrils and 25% of the cell volume is occupied by mitochondria. The remainder consists of nucleus, sarcoplasmic reticulum (SR), and the cytosol (Fig 1). Myofibril is the rodlike bundle that

	Ventricular myocyte	Atrial myocyte	Purkinje cells
Shape	columnar	ellipsoidal	Long and broad
Length μm	60-140	10-20	150-200
Diameter μm	20	5	35-40
T-tubules	Pleasantful	Rare or none	Absent
	Mitochondria and sarcomeres abundant		

Table 1. Characteristics of cardiac cells

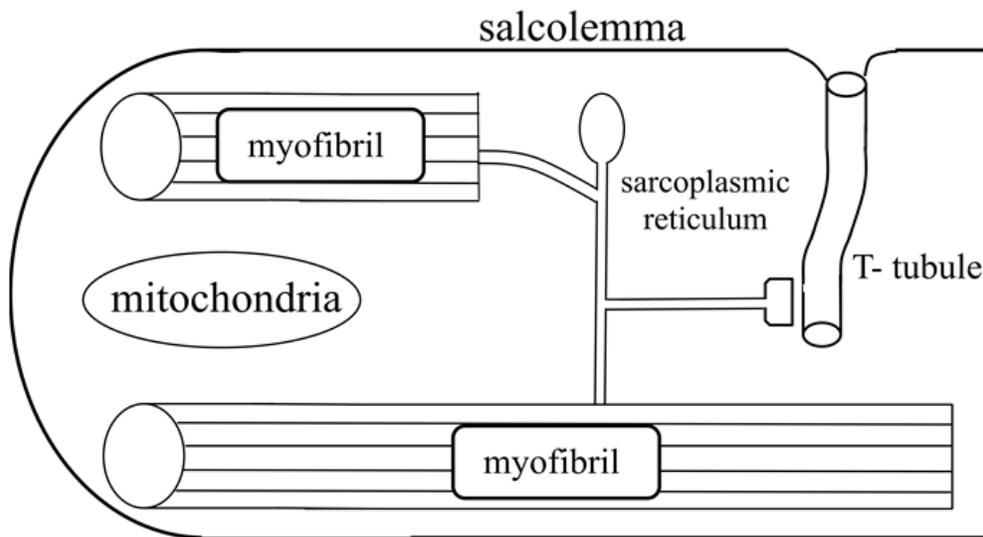


Figure 1. Ventricular cardiomyocyte

forms the contractile elements within cardiomyocytes. As one of the specialized structures of the cardiomyocyte, there is the sarcolemma, which is a coalescence of the plasma membrane proper and the basement membrane. The sarcolemma is composed of a lipid bilayer, which contains hydrophilic heads and hydrophobic tails. This structural fabric allows the sarcolemma to regulate the interactions with the intracellular and extracellular environment. The transverse tubular system (T-tubules) is specialized organo-parts of cardiomyocyte in the sarcolemma. The T-tubules are invagination of the sarcolemma into the cardiomyocyte, and they form a barrier between the intracellular and extracellular space. When electrical action potential reaches T-tubules, the wave of depolarization induces Ca^{2+} influx into the cardiomyocyte through the voltage-sensitive L-type Ca^{2+} channel of the T-tubules. This leads to Ca^{2+} discharge of the sarcoplasmic reticulum into cytosol resulting in contraction of the heart. Thus, the T-tubules are important structural components in the excitation-contraction coupling system described later. Myofibril is composed of actin thin filament, myosin thick filament and titin, which stabilizes myosin at the Z-line (Fig 2). The cardiomyocyte has aggregation of myofibrils and the fundamental contractile unit within the cardiomyocyte is the sarcomere, which has a length of 1.8 μm in the systole and 2.2 μm in the diastole. Other than myofibril, the contractile apparatus contains tropomyosin, the troponin complex. Myosin has a filamentous tail and a globular head region that contains the site for actin binding. Actin has 2 forms G and F. F-actin is the backbone of the thin filament, while G-actin works

as a stabilizing protein. Using ATP, the G-actin interacts with the myosin globular head leading to the crossbridge formation and sarcomere shortening. Tropomyosin lies on the side of actin for rigidity to thin filament. The troponin complex, also present in the thin filament, is composed of troponin C, I and T. These proteins regulate crossbridge formation. In the systole, an increased Ca^{2+} binding to the troponin C leads to the actin-myosin interaction resulting in initiating crossbridge formation. The troponin I and T suppress actin-myosin interaction in decreased Ca^{2+} of the diastole. The previous report indicates that cTnT1, isoform of troponin T that is not expressed under normal heart, is induced expression level in heart failure [1]. Ca^{2+} is the fundamental ion for evoking the excitation-contraction coupling complex (Fig 3). Upon the wave of depolarization, the voltage-sensitive L-type Ca^{2+} channel of the T-tubules opens and allows Ca^{2+} influx. This rapid but small Ca^{2+} influx causes activation of large amounts of Ca^{2+} release from the ryanodine receptor (RyR2) on the sarcoplasmic reticulum. Finally, cytosolic Ca^{2+} level changes from 100 nmol/L to 10 $\mu\text{mol/L}$ in concentration. Ten $\mu\text{mol/L}$ of Ca^{2+} also binds to the troponin C. Active relaxation of the cardiomyocyte is dependent on the function of the sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA2a in the heart). For each 1 mol of ATP hydrolyzed, 2 mol of Ca^{2+} is transported back into the sarcoplasmic reticulum. Phospholamban (PLB) regulates the function of SERCA2a. Additionally, the $\text{Na}^+/\text{Ca}^{2+}$ exchanger on the plasma membrane removes Ca^{2+} from cytosol. Human heart excretes 1 ton of blood in a day. Therefore, cardiomyocytes are required to maintain high level of ATP. Usually, the heart produces 6kg of ATP in a day. To produce high level of ATP, fatty acid and glucose are expended as substrates of ATP.

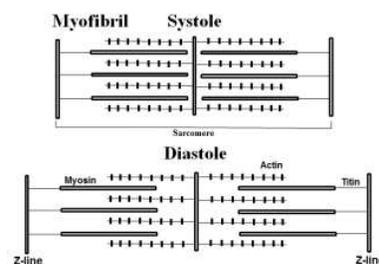


Figure 2.

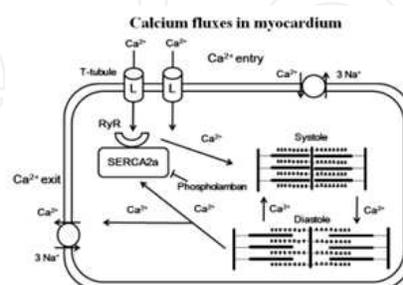


Figure 3. Calcium fluxes in myocardium

3. Mechanisms of progression in heart failure

Heart failure is observed as a progressive disorder that is initiated after an index event. This index event contains myocardial infarction, sustained hypertension, severe arrhythmia, viral

infection, stressed environment, or a genetic disease. Finally, the index event damages the cardiomyocytes resulting in loss of function or collapses in the pumping of the heart. Heart failure is clearly a major clinical and a public health problem. Despite the recent innovations in treating heart failure and its predisposing conditions, it still remains highly prevalent and lethal due to increasing life spans across the cultures. It is estimated that nearly 23 million people have heart failure worldwide. Elderlies consist of 80% of the total heart failure population, and the morbidity prevalence of heart failure in the elderly is over 1%. This epidemiological study clearly indicates that human heart failure is an age-related disorder. Heart failure evokes the overexpression of biologically active molecules that are capable of exerting deleterious effects on the heart and circulation [2]. Under this pathological environment, the compensatory mechanisms induce activation of the adrenergic nervous system and renin angiotensin system, which is termed “neurohormonal alternation” in heart failure. These systems are responsible for maintaining cardiac output through increased retention of salt and water, peripheral arterial vasoconstriction, and increased contractility and activation of inflammatory mediators, which are responsible for cardiac repair and remodeling. Although sustained neurohormonal alternation is interpreted to be the key to disease progression, there is an increasing clinical evidence to suggest against it. Cardiac hypertrophy has two basic patterns to respond to hemodynamic overload (Fig 4). Pressure overload induces concentric hypertrophy, which shows a thick appearance, whereas volume overload induces eccentric hypertrophy, which displays an elongated appearance. Cardiac hypertrophy induces alterations in the biological phenotype of the cardiomyocyte, which in turn reactivates fetal genes that are normally not expressed [3]. The reactivation of these fetal genes is associated with a decreased expression of a number of genes that are normally expressed in the adult normal heart. This may contribute to the contractile dysfunction that develops in the failing heart. During heart failure, the progressive cardiomyocyte loss may also contribute to cardiac dysfunction and left ventricular remodeling through necrotic, apoptotic or autophagic cell death pathways.

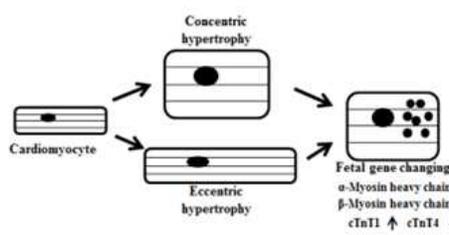


Figure 4. Process of ventricular remodeling

3.1. Heart failure with a normal ejection fraction

Now heart failure with a normal ejection fraction (HF_{nl}EF) is a common term of cardiologists, because it is possible that the prevalence of HF_{nl}EF has increased over time, leading to more widespread recognition. However, in the 20th century, existence of such patients with HF_{nl}EF had not been considered. The term HF_{nl}EF has been used in current management guidelines. Although consensus of HF_{nl}EF seems to be building toward use of EF higher than 50% to designate HF_{nl}EF, the approach to patients with borderline reduction

in EF (EF of 40 to 50%) adds to the complexity of the classification [4]. Numerous epidemiologic studies and national registers have defined the prevalence of HFnlEF in various heart failure populations and have documented a prevalence of 50% to 55% [5]. The prevalence of heart failure increases with age and is similar in men and women. The prevalence of heart failure with reduced EF increases with age but is more common in the men than in women at any age, whereas the prevalence of HFnlEF increases even more dramatically with age more than heart failure with a reduced EF and is much more common in women than in men at any age [6]. Most large contemporary studies have suggested that all-cause mortality for HFnlEF is similar to that of heart failure with reduced EF [13]. Meanwhile, there are minimal differences in heart failure readmission rates between morbidity of patients with HFnlEF and with heart failure with a reduced EF [7]. Patients with HFnlEF have been shown to have pathophysiologic characteristics similar to those of heart failure patients with a reduced EF, including severely reduced exercise capacity, neuroendocrine activation, and impaired quality of life [8]. Since LV structure and function are altered by age, gender, and cardiovascular disease in absence of heart failure, understanding of the pathophysiologic mechanisms in HFnlEF dictates a clear understanding of LV diastolic and systolic function and the manner under physiological and pathological conditions. So there are wide-ranging abnormalities in extracardiac, whole heart, extracellular matrix, cardiomyocyte and myofilaments as mechanisms of particular current or emerging clinical interests in HFnlEF.

4. Renin angiotensin aldosterone system and heart failure

The renin–angiotensin system (RAS) plays pivotal roles in the regulation of the cardiovascular system under normal and pathological conditions (Fig 5) [9]. Renin is released from the juxtaglomerular cells in the kidney, and cleaves the N-terminal end of circulating angiotensinogen, which is synthesized in the liver, to form the biologically inactive decapeptide angiotensin I (Ang I). Angiotensin-converting enzyme (ACE) cleaves 2 amino acids from Ang I to the biological active octapeptide Angiotensin II (Ang II). Ang II binds to two major G-protein coupled receptor (GPCR) subtypes, AT₁ and AT₂. Although both the AT₁ and AT₂ receptors are expressed in the human myocardium, expression level of the AT₂ receptor is less than half the level of the AT₁ receptor. Cellular localization of the AT₁ receptor in the heart is most abundant in nerves distributed in the myocardium. The AT₂ receptor is localized more highly in the fibroblasts and the interstitium. Activation of the AT₁ receptor evokes vasoconstriction, cell growth, aldosterone secretion, and catecholamine release with strong effects on cardiac hypertrophy and congestive heart failure (Table 2). In contrast, accumulating evidences show that the function of the AT₂ receptor is vasodilation, the inhibition of cell growth, and bradykinins release (Table 2) [17]. However, the opposite functions of the AT₂ receptor against the AT₁ receptor have not yet reached the consensus. Senbonmatsu et al. reported that the AT₂ receptor binds to promyelo cycticleukemia zinc finger protein (PLZF), which is a transcription factor, and its subsequent translocation into the nucleus, where it up-regulates the p85 α regulatory subunit of phosphoinositide 3-kinase (PI3K) resulting in the development of cardiac hypertrophy similar to the AT₁ receptor (Fig

6) [10,11]. Since PLAF selectively expresses in the heart but not in the kidney or the vascular, the AT₂ receptor may have dual effects depending on the cell components.

It has been thought that RAS plays as the dual manners. One way is that RAS works as the neuroendocrine system and thus acts on the heart in an endocrine manner, which is termed “the circulating RAS” (Fig 5, Right side). The other way is that Ang II is synthesized directly within the myocardium and thus acts in an autocrine and paracrine manner, which is termed “the tissue or local RAS” (Fig 5, Left side). The accumulating evidences suggested that the pathologic states may be mediated by mainly the local RAS [12]. However, the local RAS still remains an enigma because renin is secreted from only the juxtaglomerular cells in the kidney. What supplies renin in the local RAS? Plasma concentration of prorenin, which is a precursor of renin, is about 10 folds of that of renin because of expressions in various tissues. However, prorenin does not display protease activity in the plasma because the enzymatic cleft is covered by the prosegment, and is not converted to active renin in the plasma. Recently, the (pro)renin receptor ((P)RR) was discovered [13]. (P)RR binds both renin and prorenin [14]. Although the binding of renin to (P)RR may increase its catalytic activity, the binding affinity between (P)RR and renin is lower than that of (P)RR and prorenin [15]. The binding of prorenin to (P)RR evokes conformational change of prorenin resulting in the renin activity without removal of its prosegment (Fig 7). This nonproteolytic activation of prorenin may contribute to the activation of the local RAS. In addition to the enzymatic activity, prorenin has been shown to provide other (P)RR-mediated effects. The binding of prorenin to (P)RR induces the activation of intracellular signaling, including the p38 MAP kinase-HSP27 cascade, the PI3K pathway and the ERK 1/2 pathway; these effects occur independently of Ang II [16]. Coincidentally, the direct renin inhibitor, aliskiren is available in clinics and basic scientific experiments.

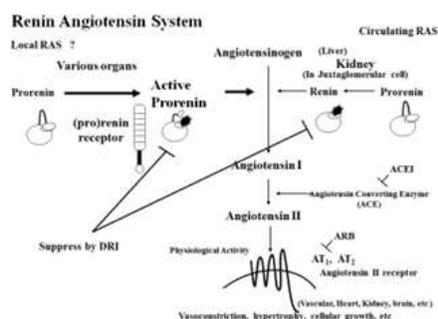


Figure 5. Renin Angiotensin System

RAS is activated in patients with heart failure. The presumptive mechanisms for RAS activation in heart failure include renal hypoperfusion; decreased filtered sodium reaching the macula densa in the distal tubule; and increased sympathetic stimulation of the kidney, leading to increased renin (Fig 8) [17]. RAS has several important actions that are critical for the maintenance of circulatory homeostasis. However, sustained activation of RAS is maladaptive and leads to fibrosis of the heart, kidney and other organs. Activated RAS also leads to worsening neurohormonal activation by enhancing the release of norepinephrine (NE) and stimulating the adrenal cortex to produce aldosterone. The sustained expression of

aldosterone also exerts harmful effects by provoking hypertrophy and fibrosis within the vasculature and the myocardium. Thus prolonged activation of RAS contributes to reduced vascular compliance and increased ventricular stiffness. Hence, the drugs, which counteract the excessive activation of RAS and the adrenergic nervous system, hold potential for a power to relieve the symptoms of heart failure with a depressed left ventricular function by stabilizing and/or reversing cardiac remodeling. From the last decade of the 20th century, many clinical trials have been performed for evidence of efficacy of RAS inhibitors against patients with heart failure.

Physiological Function and Regulation of Angiotensin Receptors

	AT ₁	AT ₂
Affinity	Ang II > Ang III > Ang I	Ang III > Ang II > Ang I
Antagonist	ARBs	PD123319, CGP42112A
Structure	359 amino acids, GPCR 42 kDa	363 amino acids, GPCR 41 kDa
G-Protein	Gq β	Gi, Gs?, Not?
Signaling	PLC activation RAS/ERK JAK2/STAT	PLZF activation Phosphatase activation Kinin/NO/cGMP
Function	Growth Stimulation	Growth Stimulation? Suppression?

Table 2. Physiological Function and Regulation of Angiotensin Receptors

AT₂ signaling Mediated with PLZF

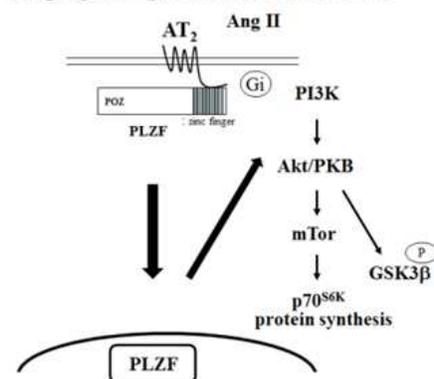


Figure 6. AT₂ signalling Mediated with PLZF

Physiology of (pro)renin receptor and prorenin.

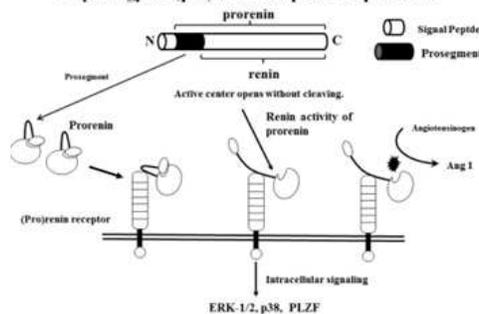


Figure 7. Physiology of (pro)renin receptor and prorenin

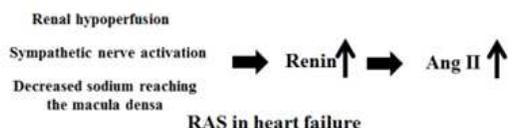


Figure 8.

4.1. Angiotensin converting enzyme inhibitor and heart failure

ACEIs should be used in symptomatic and asymptomatic patients with reduced left ventricular function, because there is overwhelming evidence of ACEI to heart failure. ACEIs suppress the production of Ang II through inhibition of ACE. ACEIs also have diverse effects independent of RAS inhibition in contrast to other RAS inhibitors. This is because ACEIs cleave carboxyl-terminal dipeptides of various oligopeptides such as angiotensin (Ang) I, kinins, Ang (1-7) or matrix metalloproteases (MMPs) (Fig 9). In Blood Pressure Lowering Treatment Traialists' Collaboration (BPLTTC) suggested that ACEIs but not ARBs hold evidence of blood pressure-independent effects on the risk of major coronary disease events [18]. Thus it is thought that ACEIs have superior benefits to other RAS inhibitors due to their cardioprotective effects. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), which recruits patients with New York heart association (NYHA) class IV heart failure shows that ACEIs treatment is tremendously advantageous in severe heart failure [19]. ACEIs also exhibit efficacy for patients with mild to moderate heart failure [20, 21]. In the Vasodilator in heart failure II (V-HeFT-II) trial, enalapril had significantly lower mortality than that of the combination of hydralazine plus isosorbide dinitrate, which does not directly suppress neurohormonal system, despite weaker blood pressure lowering the effects of enalapril [22]. These observations of clinical trials support that ACEIs have the power to improve the natural history in a patient with broad range of reduced left ventricular function through several mechanisms including blood pressure lowering, suppression of neurohormonal system, and RAS independently cardioprotective effects. ACEIs should be initiated in low doses, followed by increments in each dose if lower doses have been well tolerated. Usually, titration is achieved by doubling the dosage every 3 to 5 days. The dose of ACEIs should be increased until the doses used are similar to those that have been shown to be effective in clinical trials or permissibly maximum dosage in each country. Higher doses of ACEIs are more effective than lower doses in preventing hospitalization because of suppression of the sustained activated RAS in patients with heart failure. ACEIs should keep being used for patients with reduced left ventricular function for reasons other than severe hypotension, severe renal dysfunction or high potassium retention associated with ACEIs treatment. The side effects of ACEIs that are related to kinin potentiation include a nonproductive cough, which is in about 10% of patients, and angioedema, which is in 1% of patients. For patients who cannot tolerate ACEIs taking because of the cough or angioedema, ARBs are the next recommended line of therapy. Patients intolerant to ACEIs because of hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. The combination of hydralazine and an oral nitrate should be considered to the latter patients.

4.2. Angiotensin II receptor blocker and heart failure

ARBs are well tolerated in patients who are intolerant of ACEIs treatment because of the development of nonproductive cough, angioedema or skin rash. Under such conditions, ARBs should be used in symptomatic and asymptomatic patients with reduced left ventricular function who are ACEI-intolerant for reasons other than hyperkalemia or renal insufficiency. Although the target of ACEIs and ARBs is the inhibition of the AT₁ receptor, their mechanisms are different. ACEIs suppress Ang II production, while ARBs interfere the activation of the AT₁ receptor leading to an unlocking of the negative feedback of RAS, which results in an increment of the RAS peptides. The increased renin, Ang I, Ang II may evoke an unblocked AT₁ receptor by ARB. Therefore, high-dose ARBs appear to be better than low-dose ARBs for treating patients with heart failure. The question of high-dose versus low-dose ARB clinical outcomes was evaluated in the Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan (HEAAL) trial [23]. However, this study showed that treatment with high-dose losartan was not associated with a significant reduction in the primary endpoint of all-cause death or admission for heart failure when compared to that of low-dose losartan. Although ARBs are as effective as ACEIs in some clinical trials, ARBs does not cap ACEIs in a direct comparison of ACEIs versus ARBs trails. In the Losartan Heart failure Survival Study (ELITE-II), losartan was not associated with improved survival in older heart failure patients when compared to captopril, but was significantly better tolerated [24]. In the Valsartan in Acute Myocardial Infarction Trail (VALIANT), losartan was not as effective as captopril on all-cause mortality in post myocardial infarction patients who developed left ventricular dysfunction associated with signs of heart failure, while valsartan was shown to be non-inferior to captopril on all-cause mortality [25]. Hence, the general consensus is that ACEIs remain as the first-line drug for the treatment of systolic heart failure, while ARBs are strongly recommended for ACE-intolerant patients.

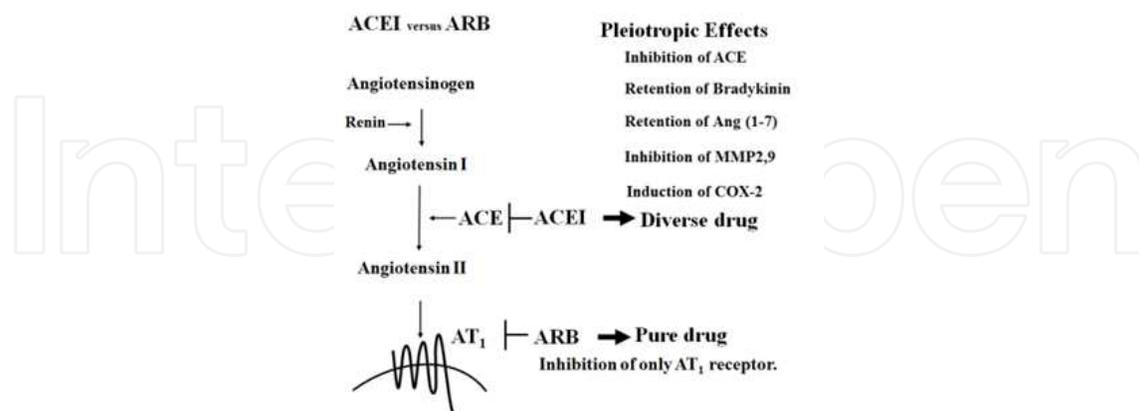


Figure 9.

4.3. Direct renin inhibitor and heart failure

Direct renin inhibitor, aliskiren, is the 3rd RAS inhibitor and it is available in clinics since the 21th century. Aliskiren is an orally active renin inhibitor and is a competitively non-peptide

inhibitor that binds to the active site in cleft of renin instead of angiotensinogen. Since renin is the limiting protease of RAS, aliskiren may be a rationalized RAS inhibitor in three RAS inhibitors. In the Aliskiren Observation of Heart Failure Treatment (ALOFT) study in patients with NYHA class II to IV heart failure. NT-pro BNP was significantly lower in patients who were randomized to aliskiren when compared to placebo [26].

4.4. Aldosterone blocker and heart failure

We already described that ACEIs is the first-line drug for patients with heart failure. Although ACEIs may transiently decrease aldosterone secretion, long-term usage of ACEIs rapidly return of aldosterone to levels similar to those before ACEIs. This is termed “aldosterone breakthrough”. The predictable mechanism of aldosterone breakthrough is that RAS takes a detour through the tissue chymases but not ACE. The results of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EMPHASIS-HF) study, which recruits patients with NYHA class II heart failure and an ejection fraction of no more than 35% to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy, displays that the administration of an aldosterone blocker is an available drug in patients with severe heart failure [27]. The dose of aldosterone blocker should be increased until the doses used are similar to those that have been shown to be effective in clinical trials or permissibly maximum dosage in each country. Patients should be counseled to avoid high potassium-containing foods. Potassium levels and renal function should be rechecked within 3 days and again, 1 week after initiation of an aldosterone blocker.

5. β -adrenergic receptor and heart failure

In the cardiomyocyte, β -adrenergic receptors dominate, and NE evokes increment of heart rate and contractile force, while in the arterioles, NE has predominantly vasoconstrictive effects acting through postsynaptic α_1 -receptor. In addition, NE stimulates presynaptic α_2 -receptors to invoke feedback inhibition of its own release, thereby modulating excess release of NE. Predominant β -adrenergic receptors are β_1 subtype in the cardiomyocyte, while most non-cardiac receptors are β_2 . The left ventricle of the human heart also expresses β_2 -receptors that are about 20% of the total β -receptor population, whereas the atria express β_2 -receptors about 40% of total population. The cardiac β_1 -receptors are colligated stimulatory G protein G_s , which is a component of the G protein-adenylyl cyclase system. However on the contrary, the cardiac β_2 -receptors are colligated both G_s and the inhibitory G protein G_i . Therefore, the intracellular signaling of β_2 -receptors remains controversially. Hypothetically, β_2 -receptors are more strongly coupled to G_s under normal conditions, but this coupling is weakened and the coupling to G_i is strengthened under heart failure. The percentage of β_2 -receptors in the left ventricle during heart failure is up to double because of β_1 -receptor downregulation. The β_2 -receptors may modulate the total valance of the adrenergic receptor system. Upon NE stimulation, the activation of G_s -adenylyl cyclase system is initiated as the positive inotropic effects in the cardiomyocyte. NE stimulation induces the molecular change in β_1 -receptors, leading to the binding of GTP to α_s subunit of G_s . The dissociated GTP- α_s subunit of G_s from β_s , γ_s subunits stimu-

lates adenylyl cyclase resulting in the formation of cAMP from ATP. cAMP activates cAMP-dependent protein kinase A (PKA). PKA plays important roles as phosphorylation of various key proteins and enzymes. PKA is locally bound to A-kinase anchoring protein (AKAP), which induces phosphorylation of a sarcolemmal protein p27 leading to increased entry of calcium ion through increased opening of the voltage-dependent L-type calcium channels in the sarcolemma. This small influx of calcium ion through the L-type calcium channels is a trigger of phosphorylation of the ryanodine receptor resulting in greater and more rapid rise of intracellular free calcium ion concentration. High concentration of the intracellular calcium ion increases calcium-troponin C interaction with deinhibition of tropomyosin effect on actin-myosin interaction. Thereby, increased rate and number of cross bridges interacting with increased myosin ATPase activity are amplified. Finally the heart procures increased rate and peak of force development. The increased relaxant effect is the consequence of increased PKA-mediated phosphorylation of phospholamban. Increased phosphorylation of troponin I also help desensitize the contractile apparatus to calcium ions. Sustained β receptor stimulation rapidly induces the activity of the β -agonist receptor kinase (β ARK1), G protein-coupled receptor kinase (GRK2). β ARK1- GRK2 increases the affinity of the β receptor for another protein family, arrestins, which cause the dissociation. β -arrestin is scaffolding and signaling protein that links to one of the cytoplasmic loops of the GPCR coupled β adrenergic receptor, lessening activation of adenylyl cyclase to inhibit the function of this receptor. Furthermore, β -arrestin switches the agonist coupling from G_s to G_i [28].

In heart failure, activation of the sympathetic nervous system is one of the most important adaptations. This occurs early in the course of heart failure. This activation is accompanied by a concomitant withdrawal of parasympathetic tone. This imbalance results in a resultant loss of heart rate and variability and increased peripheral vascular resistance in patients with heart failure. As a result of the increase in sympathetic tone, there is an increase in circulating levels of NE, a potent adrenergic neurotransmitter. The elevated levels of circulating NE result from a combination of increased release of NE from adrenergic nerve endings, and its consequent "spillover" into the plasma, with reduced uptake of NE by adrenergic nerve endings. In patient with moderate heart failure, the coronary sinus NE concentration exceeds the arterial concentration, indicating increased adrenergic stimulation of the heart. However, as heart failure progresses, there is a significant decrease in the myocardial concentration of NE. The mechanism responsible for cardiac NE depletion in severe heart failure is not clear and may relate to an exhaustion phenomenon resulting from the prolonged adrenergic activation of the cardiac adrenergic nerves in heart failure. For this reason, β -blocker therapy represents a major advance in the treatment of heart failure patients with reduced left ventricular function. Although there are a number of potential benefits to blocking all three receptors that are β_1 , β_2 and α_1 , the blocking of β_1 -adrenergic receptor display most of the deleterious effects of sustained sympathetic activation. Three β blockers have been shown to be effective in reducing the risk of death in patients with chronic heart failure [29-31]. Sustained -release metoprolol succinate and bisoprolol both competitively block the β_1 -adrenergic receptor, and carvedilol competitively blocks the α_1 -, β_1 - and β_2 -adrenergic

receptor. β -blockers should be initiated in low doses followed by gradual increments if low doses have been well tolerated. The dose of β -blockers should be increased until the doses used are similar to those that have been shown to be effective in clinical trials or permissibly maximum dosage in each country. However, the dose titration of β -blockers should proceed no sooner than at 2-week intervals, because the initiation and/or increased dosing of these agents may lead to worsening fluid retention because of the abrupt withdrawal of adrenergic support to the heart and circulation. Therefore, it is important to optimize the dose of diuretics before starting of β -blockers.

6. Non-drug treatment and heart failure

Other than internal and surgical therapies, there are implantable devices including the cardiac resynchronization therapy (CRT) or left ventricular assist device (LVAD) for the management, monitoring and assisted circulation in heart failure. Patients with severe heart failure may require the non-drug treatments for the purpose of surviving or facilitating the process of heart transplantation. 6-1, Cardiac resynchronization therapy (CRT) and heart failure.

Delays in interventricular or intraventricular electrical activation cause marked abnormalities in the sequence of global and segmental right and left ventricular activation, and impair mechanical performance. In patients with moderate to severe heart failure colligating wide QRS, a significant improvement was demonstrated an increase in exercise duration, and quality of life [32]. CRT was associated with reverse remodeling of left ventricular resulting in improved EF, dimensions and volume, and reduced mitral regurgitation. Moreover, CRT reduced the risk of complications and death among patients with moderate or severe heart failure owing to left ventricular systolic dysfunction and cardiac dysynchrony, and this effect was not limited to ischemic heart disease. The combination of Implantable cardiac defibrillator (ICD) and CRT (CRT-ICD) in addition of optimal medical therapy has resulted in a 39% reduction in heart failure hospitalization and a 36% reduction in mortality in comparison with ICD alone [33]. CRT also has led to a degree of improvement in left ventricular volume and EF in patients with mild heart failure similar to that in patients with severe heart failure [34]. CRT reduced mortality and hospitalizations among asymptomatic or mildly symptomatic heart failure patients [52]. Hence, recent clinical trials are directed toward focus on delaying progression of heart failure in asymptomatic or less symptomatic patients.

6.1. Ventricular assist device (VAD) and heart failure

Timely referral for mechanical circulatory support (MCS) evaluation and appropriate implantation depends on familiarity with recent advances in pump design and clinical outcomes. The expansion of durable left ventricular assist device (LVAD) options for patients with advanced heart failure came just as the significant shortage of donor hearts was becoming apparent. In the U.S., according to the Centers for Medicare and Medicaid Services, implant strategies are divided into four groups; such as bridge to transplant (BTT),

bridge to candidacy (BTC), destination therapy (DT), and Bridge to recovery (BTR). In contemporary thinking, the dichotomous decision of either a bridge to transplantation or destination therapy is no longer tenable, and one could consider mechanical circulatory in the context of a "bridge to decision"[35]. Evolving pump design has driven clinical progress. After the invention of a smaller high-speed, rotary impeller pump with a single moving part, continuous-flow VADs with enhanced durability and near-silent operation became available. The transition from pulsatile technology toward continuous flow has been remarkably swift, and this rapid rise of continuous flow has made improved survival and performance [36, 37]. Pump complications, such as stroke, bleeding and infection, remain substantial risks. Embolic strokes appear more common than hemorrhagic strokes with all device designs. The Heartmate II has relatively low thrombotic risk provided patients are on an anticoagulation regimen that features an antiplatelet agent such as aspirin along with warfarin with an international normalized ratio (INR) goal of 1.5 to 2.0 [38]. Infection related to LVAD is reported 11-20%. The importance of infections in the VAD patient prompted the creation of a comprehensive set of guidelines and definitions [39].

Another pump development is miniaturization along with less invasive surgery. INTERMACS profiles have been developed to define clinically important differences in the severity of disease among patients with advanced heart failure [40]. Sicker subset of INTERMACS profile has been consistently associated with higher perioperative mortality. This trend will prompt the application of implantation of mechanical circulatory support to less sick heart failure patients in earlier stage. Adequate right ventricular function is necessary for proper LVAD function. Right heart failure after LVAD implant results in up to a 6-fold increase risk of death and is a major contributing factor in prolonged hospitalizations [41]. Right ventricular failure (RVF) results in persistently elevated venous pressure and insufficient LVAD preload, which occurs in 6 to 35% of LVAD recipients [41]. In DT setting, in addition to a right ventricular assist device (RVAD) support, biventricular ventricular assist device (BiVAD) support with two continuous flow devices has been reported [42]. However, if RVF persists and long-term RV support is required, then the total artificial heart (TAH) is an option for those patients who are eligible for transplant. The TAH offers full circulatory replacement therapy for patients with irreversible biventricular failure. Freedom Driver, one of the smaller-sized TAH may allow discharge from hospital, and is undergoing investigation [43].

7. Heart transplantation and heart failure

Heart transplantation (HT) is indicated for those with chronic progressive heart failure despite optimal therapy, or with cardiogenic shock requiring mechanical support or high-dose inotropes. Heart failure patients with adult congenital heart disease are also taken into consideration for HT [44]. Various organizations for HT in the world have updated the waiting list of HT candidates to ensure an equitable system of donor organ allocation under the shortage of donor hearts. Cardiopulmonary exercise (CPX) is routinely used in the determination of candidacy for cardiac transplantation [45, 46]. In the presence of beta-blocker, a cutoff for peak VO₂ of <14ml/kg/min should be used to guide listing (Class I) [47]. Right

ventricular failure (RVF) and pulmonary hypertension (PH) are factors that prompt to reconsider suitability for waiting list. PH and elevated pulmonary vascular resistance (PVR) should be considered as relative contraindications to cardiac transplantation when the PVR is greater than 5 Woods units or the pulmonary vascular index is 6 or the transpulmonary gradient exceeds 16 to 20 mm Hg. If the systolic pulmonary arterial pressure exceeds 60 mmHg in conjunction with any of the aforementioned three variables, the risk of RVF and early death is increased [48]. For those with irreversible pulmonary pressures, a combined heart-lung transplant is a therapeutic choice.

Advances in post-transplant care have improved outcomes in older patients. A follow-up of HT recipients >65 years of age demonstrated survival rates comparable to those of younger patients [49]. Although the Patients older than 70 years have also been reported to have acceptable outcome with presumably less donor organ rejection, usually alternate-type program or permanent mechanical support should be pursued [50]. Active or recent malignancy is a contraindication to HT due to limited survival rates. However, pre-existing neoplasms may be treatable with chemotherapy to induce remission. Therefore it is essential to assess each patient as to their risk of tumor recurrence.

Diabetes with end-organ damage other than nonproliferative retinopathy or poor glycemic control with glycosylated hemoglobin (HbA1C) greater than 7.5 despite optimal effort is a relative contraindication for transplant. It is reasonable to consider the presence of irreversible renal dysfunction (eGFR greater than 40ml/min) as a relative contraindication for HT. Obese patients with BMI > 30 kg/m² demonstrated nearly twice the 5-year mortality [51]. Therefore for this population, weight loss should be mandatory before listing for HT. Other comorbidity includes cirrhosis, peripheral vascular disease, addictions (tabacco, excessive alcohol) [52]. Psychosocial evaluation is mandatory before listing-up for HT. Immunologic evaluation is also needed. Immunocompatibility testing including ABO blood group typing, human leukocyte antigen and antibody screening should be completed. Panel-reactive antibody (PRA) test, which can identify the presence of circulating anti-human leukocyte antigen (HLA), and should be performed preferably by flow cytometry [53]. In France, single center data reported that actuarial survival rates were 75%, 58%, and 42% at 5, 10, and 15 years, respectively [54]. In Netherland, comparable survival rate was reported with the overall 1-, 5-, 10- and 15-year survival was respectively 77%, 67%, 53% and 42% [55]. Recent advance in HT technology along with surrounding circumstances has disclosed further issues to revise. The proposed challenges in this regard include optimization and individualization of immunosuppressive therapies, expansion and optimization of the donor and recipient candidate population, characterization of comorbidities, and understanding of antibody mediated rejection [56]. Late outcomes in the HT population remain poor with a median cardiac allograft survival of 11 years, a statistic that has not improved in over a decade [57]. The major causes of late morbidity and mortality are chronic kidney disease, cardiac allograft vasculopathy (CAV), and malignancy [46]. The dosing of calcineurin inhibitor (CNI), cyclosporine or tacrolimus, a purine synthesis inhibitor such as mycophenolate mofetil, and corticosteroids, which have a narrow therapeutic index, is typically based on the weight and renal function of a patient. A key research priority should be to develop

clinical trials that evaluate how CNI sparing and elimination approaches (CNI-free immunosuppression). Better understanding of individualized immunologic characteristics is a key component to perform proper immunosuppressive therapy.

8. Cardiac regeneration and heart failure

Since usually heart failure results from deficiency of the cardiomyocyte, heart regeneration may become the prospective therapeutic technology of heart failure through regenerating lost cardiomyocytes to recovery of cardiac function. However, from the 19th century to the early 20th century, there had been the consensus that indicates that the heart is an organ incapable of regeneration [58]. Ventricular hypertrophy had been caused by enlargement rather than proliferation of the cardiomyocyte. From '60s, the investigators have opened up the milestone articles that display the evidence of heart regeneration of the human adult heart [59]. Pathologically hypertrophied heart demonstrates the evidence of cardiomyocyte proliferation when the heart weight exceeds 450g that contains about 210g of myocardium [60]. To evaluate cardiomyocyte proliferation, biochemical measurement of tissue DNA content and fluorescent analysis of individual nuclear DNA content associated with histopathology have been employed [61]. Most human cardiomyocyte nuclei are polyploid by the onset of puberty. In response to pathological overloads, human cardiomyocytes commonly reinitiate DNA synthesis without nuclear division [62]. Human cardiomyocytes seem to remain mononucleated throughout life. Thus, DNA synthesis is common in the adult human heart. Although this cannot be equated to cardiomyocyte proliferation, the measurement of cardiomyocyte DNA content is useful for investigation of heart proliferation. Using these methods, researchers have displayed that the cardiomyocyte nuclear number is steady at ~2 billion, which is reached at about 2 months of age, in the range of heart weight from 50g to 350g [63]. However, there is a linear increase in nuclear number, reaching 4 billion cardiomyocyte nuclei in hypertrophied hearts, which are weighting 700-900g. Since the number of non-cardiomyocytes such as fibroblasts and vascular cells increases linearly with heart weight throughout life, these results indicate that cardiomyocyte renewal occurs during pathological hypertrophy in the adult human heart [60, 64]. In 2009, there was definitive evidence of regeneration of the human heart. Employing ¹⁴C, generated by nuclear bomb tests during the Cold War, infiltrate nuclear and label the DNA of dividing cells, the age of the cardiomyocyte composing the human heart was performed [65]. Mathematical modeling suggested that cardiomyocyte renewal was age-dependent, 1% of human cardiomyocytes were renewed at the age of 20, and this rate was reduced to 0.45% at the age of 75. About 45% of the cardiomyocytes would be predicted to be renewed over a normal human life on the basis of this kinetics. Most of the cardiac regeneration studies focused on the proliferation of existing cardiomyocytes, and were not designed to detect cardiomyocytes formed from progenitor cells or not. To determine whether such progenitor cells contribute to cardiomyocyte renewal, the genetic fate-mapping experiment was performed using transgenic mice [66]. This system allowed the authors to distinguish between cardiomyocyte renewal from existed cardiomyocytes via proliferation and cardiomyocyte renewal from progenitor cells. The adult mammalian heart shows that heart regeneration depends on replenishment by cardiomyogenic progenitor cells than on re-

placement by cardiomyocyte proliferation. Thus, these human and rodent heart studies provide strong evidence for plasticity in the adult human heart. Although actually cardiomyocyte regeneration from progenitor cells probably occurs in the human heart, it seems to be a very slow process different from that of the zebrafish, which rapidly promotes cardiac regeneration through cardiac proliferation, besides ageing is associated with the loss of ~ 1g /of myocardium per year in the absence of specific heart disease [67].

Stem cell biology is one of frontier areas of biomedical research including regeneration medicine. In the latter part of 20th century, bone marrow stem cell (BMCs) transplantation was gotten a lot of attention as a next regeneration medicine, however, the accumulating evidences indicate that BMC do not work by directly differentiating into new cardiomyocytes. In the 21th century, the existence of several types of cardiac stem cells has been reported. Cardiac stem cells display cell surface markers as c-kit positive, Sca-1 positive, Abcg2 positive, cardiosphere-derived cells (CDCs) positive and islet-1 positive respectively [68]. These cells can be isolated and differentiated into fully mature cardiomyocytes that express contractile proteins, generation of calcium transients and respond to β -adrenergic stimulation. However, their abundant presence in the adult human heart and their capacity to engraft, regenerate myocardium leading to improving of cardiac function does not reach the sufficient evidence as the consensus. In fact, clinical trials using CDCs and c-kit positive cells are underway in California, Louisville and Kentucky respectively. Embryonic stem cells (ESC) and induced pluripotent stem cells (iPS) are able to generate any cell type in our body. They have a tremendous potential for regeneration associated with obvious problems such as immune rejection, the carcinogenic potential. Therefore, they are a potentially inexhaustible supply of the human cardiomyocytes. IPS was originally generated by the reprogramming of adult somatic cells by the forced expression of up to four stem cell related transcription factors, which is termed "Yamanaka factors". So the cardiomyocytes from any pluripotent stem cell type are immature and lack the expression profile, morphology and function of the adult ventricular cardiomyocyte. Therefore, the cardiomyocytes from patient-derived iPS cells may play a normal cardiac function. Human ESC-derived cardiomyocyte express early cardiac transcription factors such as NKX2.5, as well as the expected sarcomeric proteins, ion channels, connexins and calcium-handling proteins. They show similar functional properties to those reported for cardiomyocytes in the developing heart, and undergo comparable mechanisms of excitation- contraction coupling and neurohormonal signaling [69, 70]. Human iPS-derived cardiomyocytes show a very similar phenotype [71, 72]. Furthermore, these cells have shown to engraft in infarct mouse, rat, guinea pig and pig heart, forming islands of nascent, proliferating human myocardium within the scar zone [73, 74]. Furthermore, two research groups achieved directly reprogrammed cardiomyocyte from somatic cells [75, 76]. These results may be one of most important evidences of cardiac regeneration employing pluripotent stem cell. Final goal of these biochemical tools will depend on the long-term engraftment of regenerative cells.

9. Summary

We described recent topics of the heart failure in basic and clinical field. To materialize applicable conditions responding to an elderly society, therapeutic, economic or Social security

problems associated with heart failure have to be gotten fixed. Thereby, the research system close linkage between basic and clinic is important to prevent and remedy heart failure in the elderly societies.

Author details

Shintaro Nakano, Toshihiro Muramatsu, Shigeyuki Nishimura and Takaaki Senbonmatsu
Division of Cardiology, International Medical Center, Saitama Medical University, Saitama, Japan

Takaaki Senbonmatsu
Department of Pharmacology, Saitama Medical University, Saitama, Japan

Acknowledgement

We thank Ayumi Hara for secretarial assistance.

10. References

- [1] Nassar R, Malouf NN, Mao L, et al. (2005) cTnT1, a cardiac troponin T isoform, decreases myofilament tension and affects the left ventricular pressure waveform. *Am J Physiol Heart Circ Physiol.* 288: H1147-56.
- [2] Mann DL, Bristow MR. (2005) Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation.* 111: 2837-2849.
- [3] Lowes BD, Gilbert EM, Abraham WT, et al. (2002) Myocardial gene expression in dilated cardiomyopathy treated with beta-blocking agents. *N Engl J Med.* 346: 1357-1365.
- [4] Redfield MM, Jacobsen SJ, Burnett JC Jr, et al. (2003) Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA.* 289: 194-202.
- [5] Hogg K, Swedberg K, McMurray J. (2004) Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol.* 43: 317-327.
- [6] Ceia F, Fonseca C, Mota T, et al. (2002) Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. *Eur J Heart Fail.* 4: 531-539.
- [7] Bhatia RS, Tu JV, Lee DS, et al. (2006) Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med.* 355: 260-269.
- [8] Kitzman DW, Little WC, et al. (2002) Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA.* 288: 2144-2150.
- [9] de Gasparo M, Catt KJ, Inagami T, et al. (2000) International union of pharmacology. XXIII. The angiotensin II receptors. *Pharmacol Rev.* 52: 415-472.
- [10] Senbonmatsu T, Saito T, Landon EJ, et al. (2003) A novel angiotensin II type 2 receptor signaling pathway: possible role in cardiac hypertrophy. *EMBO J.* 22: 6471-6482.

- [11] Wang N, Frank GD, Ding R, et al. (2012) Promyelocytic Leukemia Zinc Finger Protein Activates GATA4 Transcription and Mediates Cardiac Hypertrophic Signaling from Angiotensin II Receptor 2. *ProS One*. In press.
- [12] Iwai N, Shimoike H, Kinoshita M. (1995) Cardiac renin-angiotensin system in the hypertrophied heart. *Circulation*. 92: 2690-2696.
- [13] Nguyen G, Delarue F, Burckle C, et al. (2002) Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest*. 109: 1417-1427.
- [14] Ichihara A, Hayashi M, Kaneshiro Y, et al. (2004) Inhibition of diabetic nephropathy by a decoy peptide corresponding to the "handle" region for nonproteolytic activation of prorenin. *J Clin Invest*. 114: 1128-1135.
- [15] Batenburg WW, Krop M, Garrelds IM, et al. (2007) Prorenin is the endogenous agonist of the (pro)renin receptor. Binding kinetics of renin and prorenin in rat vascular smooth muscle cells overexpressing the human (pro)renin receptor. *J Hypertens*. 25: 2441-2453.
- [16] Saris JJ, 't Hoen PA, Garrelds IM, et al. (2006) Prorenin induces intracellular signaling in cardiomyocytes independently of angiotensin II. *Hypertension*. 48: 564-571.
- [17] Timmermans PB, Wong PC, Chiu AT, et al. (1993) Angiotensin II receptors and angiotensin II receptor antagonists. *Pharmacol Rev*. 45: 205-251.
- [18] Turnbull F, Neal B, Pfeffer M, et al. (2007) Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. *J Hypertens*. 25: 951-958.
- [19] (1987) Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med*. 316: 1429-1435.
- [20] Pfeffer MA, Braunwald E, Moye LA, et al. (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. 327: 669-677.
- [21] Torp-Pedersen C, Kober L. (1999) Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction. TRACE Study Group. *Trandolapril Cardiac Evaluation*. *Lancet*. 354: 9-12.
- [22] Rector TS, Johnson G, Dunkman WB, et al. (1993) Evaluation by patients with heart failure of the effects of enalapril compared with hydralazine plus isosorbide dinitrate on quality of life. V-HeFT II. The V-HeFT VA Cooperative Studies Group. *Circulation*. 87: VI71-VI77.
- [23] Konstam MA, Neaton JD, Dickstein K, et al. (2009) Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet*. 374: 1840-1848.
- [24] Pitt B, Poole-Wilson PA, Segal R, et al. (2000) Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. *Lancet*. 355: 1582-1587.

- [25] Pfeffer MA, McMurray JJ, Velazquez EJ, et al. (2003) Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med.* 349: 1893-1906.
- [26] McMurray JJ, Pitt B, Latini R, et al. (2008) Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail.* 1: 17-24.
- [27] Pitt B, Remme W, Zannad F, et al. (2003) Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 348: 1309-1321.
- [28] Baillie GS, Sood A, McPhee I, et al. (2003) beta-Arrestin-mediated PDE4 cAMP phosphodiesterase recruitment regulates beta-adrenoceptor switching from Gs to Gi. *Proc Natl Acad Sci U S A.* 100: 940-945.
- [29] Waagstein F, Bristow MR, Swedberg K, et al. (1993) Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. *Lancet.* 342: 1441-1446.
- [30] CIBIS-II Investigators and Committees. (1999) The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 353: 9-13.
- [31] Poole-Wilson PA, Swedberg K, Cleland JG, et al. (2003) Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet.* 362: 7-13.
- [32] Abraham WT, Fisher WG, Smith AL, et al. (2002) Cardiac resynchronization in chronic heart failure. *N Engl J Med.* 346: 1845-1853.
- [33] Adabag S, Roukoz H, Anand IS, et al. (2011) Cardiac resynchronization therapy in patients with minimal heart failure: a systematic review and meta-analysis. *J Am Coll Cardiol.* 58: 935-941.
- [34] Bleeker GB, Holman ER, Steendijk P, Boersma E, van der Wall EE, Schalij MJ, Bax JJ. (2006) Cardiac resynchronization therapy in patients with a narrow QRS complex. *J Am Coll Cardiol.* 48: 2243-2250.
- [35] Felker GM, Rogers JG. (2006) Same bridge, new destinations rethinking paradigms for mechanical cardiac support in heart failure. *J Am Coll Cardiol.* 47: 930-932.
- [36] Kirklin JK, Naftel DC, Kormos RL, et al. (2011) Third INTERMACS Annual Report: the evolution of destination therapy in the United States. *J Heart Lung Transplant.* 30: 115-123.
- [37] Slaughter MS, Rogers JG, Milano CA, et al. (2009) Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med.* 361: 2241-2251.
- [38] Boyle AJ, Russell SD, Teuteberg JJ, et al. (2009) Low thromboembolism and pump thrombosis with the HeartMate II left ventricular assist device: analysis of outpatient anti-coagulation. *J Heart Lung Transplant.* 28: 881-887.
- [39] Hannan MM, Husain S, Mattner F, et al. (2011) Working formulation for the standardization of definitions of infections in patients using ventricular assist devices. *J Heart Lung Transplant.* 30: 375-384.
- [40] Stevenson LW, Pagani FD, Young JB, et al. (2009) INTERMACS profiles of advanced heart failure: the current picture. *J Heart Lung Transplant.* 28: 535-541.

- [41] Fitzpatrick JR 3rd, Frederick JR, Hsu VM, et al. (2008) Risk score derived from pre-operative data analysis predicts the need for biventricular mechanical circulatory support. *J Heart Lung Transplant*. 27: 1286-1292.
- [42] Kirklin JK, Naftel DC, Kormos RL, et al. (2010) Second INTERMACS annual report: more than 1,000 primary left ventricular assist device implants. *J Heart Lung Transplant*. 29: 1-10.
- [43] Jaroszewski DE, Anderson EM, Pierce CN, et al. (2011) The SynCardia freedom driver: a portable driver for discharge home with the total artificial heart. *J Heart Lung Transplant*. 30: 844-845.
- [44] Simmonds J, Burch M, Dawkins H, et al. (2008) Heart transplantation after congenital heart surgery: improving results and future goals. *Eur J Cardiothorac Surg*. 34: 313-317.
- [45] Mudge GH, Goldstein S, Addonizio LJ, et al. (1993) 24th Bethesda conference: Cardiac transplantation. Task Force 3: Recipient guidelines/prioritization. *J Am Coll Cardiol*. 22: 21-31.
- [46] Costanzo MR, Augustine S, Bourge R, et al. (1995) Selection and treatment of candidates for heart transplantation. A statement for health professionals from the Committee on Heart Failure and Cardiac Transplantation of the Council on Clinical Cardiology, American Heart Association. *Circulation*. 92: 3593-3612.
- [47] Mehra MR, Kobashigawa J, Starling R, et al. (2006) Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates--2006. *J Heart Lung Transplant*. 25: 1024-1042.
- [48] Butler J, Stankewicz MA, Wu J, et al. (2005) Pre-transplant reversible pulmonary hypertension predicts higher risk for mortality after cardiac transplantation. *J Heart Lung Transplant*. 24: 170-177.
- [49] Zuckermann A, Dunkler D, Deviatko E, et al. (2003) Long-term survival (>10 years) of patients >60 years with induction therapy after cardiac transplantation. *Eur J Cardiothorac Surg*. 24: 283-291.
- [50] Blanche C, Blanche DA, Kearney B, et al. (2001) Heart transplantation in patients seventy years of age and older: A comparative analysis of outcome. *J Thorac Cardiovasc Surg*. 121: 532-541.
- [51] Lietz K, John R, Burke EA, et al. (2001) Pretransplant cachexia and morbid obesity are predictors of increased mortality after heart transplantation. *Transplantation*. 72: 277-283.
- [52] Radovancevic B, Poindexter S, Birovljev S, et al. (1990) Risk factors for development of accelerated coronary artery disease in cardiac transplant recipients. *Eur J Cardiothorac Surg*. 4: 309-313.
- [53] Kobashigawa J, Mehra M, West L, et al. (2009) Report from a consensus conference on the sensitized patient awaiting heart transplantation. *J Heart Lung Transplant*. 28: 213-225.
- [54] Roussel JC, Baron O, Perigaud C, et al. (2008) Outcome of heart transplants 15 to 20 years ago: graft survival, post-transplant morbidity, and risk factors for mortality. *J Heart Lung Transplant*. 27: 486-493.

- [55] Tjang YS, van der Heijden GJ, Tenderich G, et al. (2008) Survival analysis in heart transplantation: results from an analysis of 1290 cases in a single center. *Eur J Cardiothorac Surg.* 33: 856-861.
- [56] Shah MR, Starling RC, Schwartz Longacre L, et al. (2012) Heart transplantation research in the next decade—a goal to achieving evidence-based outcomes: national heart, lung, and blood institute working group. *J Am Coll Cardiol.* 59: 1263-1269.
- [57] Stehlik J, Edwards LB, Kucheryavaya AY, et al. (2010) The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult heart transplant report—2010. *J Heart Lung Transplant.* 29: 1089-1103.
- [58] Karsner HT, Saphir O, Todd TW. (1925) The State of the Cardiac Muscle in Hypertrophy and Atrophy. *Am J Pathol.* 1: 351-372.1.
- [59] LINZBACH AJ. (1960) Heart failure from the point of view of quantitative anatomy. *Am J Cardiol.* 5: 370-382.
- [60] Adler CP, Costabel U. (1975) Cell number in human heart in atrophy, hypertrophy, and under the influence of cytostatics. *Recent Adv Stud Cardiac Struct Metab.* 6: 343-355.
- [61] Herget GW, Neuburger M, Plagwitz R, et al. (1997) DNA content, ploidy level and number of nuclei in the human heart after myocardial infarction. *Cardiovasc Res.* 36: 45-51.
- [62] Adler CP, Friedburg H. (1986) Myocardial DNA content, ploidy level and cell number in geriatric hearts: post-mortem examinations of human myocardium in old age. *J Mol Cell Cardiol.* 18: 39-53.
- [63] Adler CP. (1975) Relationship between deoxyribonucleic acid content and nucleoli in human heart muscle cells and estimation of cell number during cardiac growth and hyperfunction. *Recent Adv Stud Cardiac Struct Metab.* 8: 373-386.
- [64] Grajek S, Lesiak M, Pyda M, et al. (1993) Hypertrophy or hyperplasia in cardiac muscle. Post-mortem human morphometric study. *Eur Heart J.* 14: 40-47.
- [65] Bergmann O, Bhardwaj RD, Bernard S, et al. (2009) Evidence for cardiomyocyte renewal in humans. *Science.* 324: 98-102.
- [66] Hsieh PC, Segers VF, Davis ME, et al. (2007) Evidence from a genetic fate-mapping study that stem cells refresh adult mammalian cardiomyocytes after injury. *Nat Med.* 13: 970-974.
- [67] Kikuchi K, Holdway JE, Werdich AA, et al. (2010) Primary contribution to zebrafish heart regeneration by gata4(+) cardiomyocytes. *Nature.* 464: 601-605.
- [68] Carvalho AB, de Carvalho AC. (2010) Heart regeneration: Past, present and future. *World J Cardiol.* 2: 107-111.
- [69] Kehat I, Kenyagin-Karsenti D, Snir M, et al. (2001) Human embryonic stem cells can differentiate into myocytes with structural and functional properties of cardiomyocytes. *J Clin Invest.* 108: 407-414.
- [70] Zhu WZ, Santana LF, Laflamme MA. (2009) Local control of excitation-contraction coupling in human embryonic stem cell-derived cardiomyocytes. *PLoS One.* 4: e5407.
- [71] Zhang J, Wilson GF, Soerens AG, et al. (2009) Functional cardiomyocytes derived from human induced pluripotent stem cells. *Circ Res.* 104: e30-e41.

- [72] Zwi L, Caspi O, Arbel G, et al. (2009) Cardiomyocyte differentiation of human induced pluripotent stem cells. *Circulation*. 120: 1513-1523.
- [73] Laflamme MA, Chen KY, Naumova AV, et al. (2007) Cardiomyocytes derived from human embryonic stem cells in pro-survival factors enhance function of infarcted rat hearts. *Nat Biotechnol*. 25: 1015-1024.
- [74] Fernandes S, Naumova AV, Zhu WZ, et al. (2010) Human embryonic stem cell-derived cardiomyocytes engraft but do not alter cardiac remodeling after chronic infarction in rats. *J Mol Cell Cardiol*. 49: 941-949.
- [75] Ieda M, Fu JD, Delgado-Olguin P, et al. (2010) Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. *Cell*. 142: 375-386.
- [76] Efe JA, Hilcove S, Kim J, et al. (2011) Conversion of mouse fibroblasts into cardiomyocytes using a direct reprogramming strategy. *Nat Cell Biol*. 13: 215-222.