Clinical Pathology and Treatment of Renin-Angiotensin System

1. Usefulness of Blocking of the Renin-Angiotensin System in Treatment of Chronic Heart Failure

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In the last 30 years, the concept of chronic heart failure (CHF) has changed. Before the 1970s, the fundamental pathophysiology of CHF was thought to be volume-overload, and thereby the first line of drugs for CHF included digitalis and diuretics. In the 1970s, numerous experimental and clinical studies of cardiac function brought about the change in the concept of CHF that the main pathophysiology of CHF is regarded as pump failure and an increase in the afterload. In accordance with the concept change, positive inotropic agents and vasodilators became widely used. As is well known however, the positive inotropic agents did not improve survival but rather worsened it. In 1987, CONSENSUS study (1) for the first time disclosed the usefulness of the ACE inhibitor, enarapril; it improves survival of severe CHF compared with placebo. Also the V-Heft trail (2) proved that ACE-inhibitors have a more beneficial effect on cardiac function and survival than the so-called vasodilator, hydralaradine. This finding, together with many clinical studies, proves that blocking of the renin angiotensin system (RAS) improves cardiac function, left ventricular remodeling and survival.

In the 1980s, numerous humoral factors, such as the natriuretic peptide family, all of which regulate cardiovascular homeostasis, were discovered and their receptors were also cloned. Moreover, development of their blockers or the mice overexpressing or lacking the gene encoding cardiovascular hormone has provided a better understanding of the molecular mechanism of the development and progression of CHF.

Cardio-Stimulating and Cardio-Protective Hormones

Cardiac homeostasis is balanced by two systems which counteract each other. One is the cardio-stimulating system, such as RAS and the sympathetic nervous system, and the other is the cardio-protective system, such as the natriuretic peptide system. When cardiac pumping function is reduced, RAS and the sympathetic nervous system are activated to preserve cardiac output by their positive inotropic and chronotropic actions, to maintain perfusion pressure to vital organs by constricting arterioles, and to increase extracellular volume by stimulating aldosterone secretion. Over-activation of cardio-stimulating hormones augments afterload and cardiomyocyte injury by Ca2+ overload, and thereby leads to the vicious cycle of heart failure. In contrast, ANP and BNP, cardio-protective hormones, counteract with cardio-stimulating hormones through their vasodilating, diuretic and natriuretic actions and inhibitory actions of aldosterone secretion. As illustrated in Fig. 1, in healthy or normal condition, cardio-stimulating hormones and cardio-protective hormones are balanced, and at the early stage of CHF, as cardio-protective hormones are activated in response to activation of cardio-stimulating hormones, two systems are still equilibrated. As CHF is advanced, however, cardio-protective hormones cannot be augmented to the level counteracting cardio-stimulating hormones, which results in the vicious CHF cycle.

Why are cardio-protective hormones equally activated to cardio-stimulating hormones even in the advanced CHF? It is possible that the reason for the inappropriate activation of cardio-protective hormones is fundamentally related to the fact that we homosapiens are terrestrial animals. After animals were born in the sea, about four hundred million years ago, animals who would have the system for the sodium storage in the body, could come onto land. That system is certainly RAS. It is likely, therefore, that the genomes of terrestrial animals are programmed to easily activate genes encoding the proteins related to RAS. This would be a reasonable theory as to why we easily suffer from CHF.
Imbalance of Cardio-Stimulating and Cardio-Protective Hormones Is a Cause of Heart Failure

To elucidate whether or not the imbalance, per se, of cardio-stimulating and cardio-protective hormones causes CHF, several kinds of genetic engineered mice over-expressing RAS-related genes, or lacking genes encoding cardio-protective hormones or their receptors, have been developed. In rats over-expressing murine renin genes, whose hypertension with around 200 mmHg of systolic blood pressure was treated by calcium channel blocker in combination with β-blocker, systolic blood was decreased to blood pressure similar to normal control rats, but left ventricular hypertrophy was not improved completely. In contrast, when the rats were treated with an angiotensin receptor antagonist, left ventricular hypertrophy was completely inhibited (3). Next, mice lacking the gene encoding GC-A, a common receptor for ANP and BNP, whose cardio-protective actions were down-regulated, showed high blood pressure and left ventricular hypertrophy with interstitial fibrosis without any experimentally induced left ventricular stress, such as aortic banding or myocardial infarction. Double knockout mice, which were generated by crossing GC-A knockout mice with AT1a knockout mice, showed normal blood pressure and normal left ventricular size without interstitial fibrosis (Fig. 2). Moreover, pharmacological blockade of AT1a signaling by AT1 selective angiotensin receptor blocker also decreased blood pressure to the normal level and improved cardiac remodeling corresponding to normal heart (4). When acute myocardial infarction was developed by ligating coronary artery, survival and post-infarct ventricular remodeling including interstitial fibrosis were worse in GC-A knockout mice than in wild type mice (5).

These findings suggest that absolute or relative activation of cardio-stimulating hormones in comparison with cardio-protective hormones induces left ventricular hypertrophy and fibrosis, thereby resulting in heart failure. In other words, inhibiting cardio-stimulating hormones by angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and/or β blockers is the essential for the treatment of heart failure.

Clinically, How Do We Diagnose an Imbalance of Cardio-Stimulating and Cardio-Protective Hormones?

Recently, activation of RAS in CHF is like common sense among cardiologists. For the treatment of CHF, we use RAS inhibitors, such as ACE inhibitors or ARBs as the first line drugs. In this context, the clinical monitoring of RAS activation is very helpful for the physician to optimize the dose and duration of RAS inhibitors. In CHF both systemic and local (cardiac) RASs are activated, whose activating profile is somewhat different from each other. At the early stage of CHF, cardiac RAS is activated earlier than the systemic one, and the advanced stage of CHF, systemic RAS surpasses the
local one. In contrast, when the CHF is treated, systemic RAS activation is decreased rapidly, but local RAS activation remains at a high level until CHF is completely improved (Fig. 3) (6). To treat CHF well, both systemic and cardiac RASs should be inhibited by RAS inhibitors. In this context, how is it possible for physicians know which RAS is activated by clinical parameters? For systemic RAS, reduced renal flow and activation of renal sympathetic nerve activity stimulate renin release from JG cells in the kidney. Renin then generates angiotensin I from angiotensinogen, ACE cleaves angiotensin I to angiotensin II and finally angiotensin II stimulates aldosterone secretion from zona glomerulosa cells in adrenal cortex. Thus, the high levels of the plasma renin activity and plasma aldosterone concentration are markers for the activated systemic RAS. On the other hand, although mRNA of renin, angiotensinogen, ACE and aldosterone synthase are up-regulated in failing hearts, their up-regulation is not sufficiently high to increase the circulating levels of renin angiotensin II and aldosterone. In the failing heart, increased angiotensin II works to stimulate BNP expression as a paracrine fashion, which results in the elevation of plasma BNP level. The plasma BNP level is a surrogate marker for cardiac RAS (Fig. 4). It is, therefore, clinically important that physicians treat CHF patients by monitoring not only the plasma renin activity and plasma aldosterone level but also the plasma BNP level, and physicians dose-up or keep RAS inhibitor until plasma BNP level is decreased substantially.

Figure 5 shows the change of plasma markers for CHF in a 38-year-old man with decompensated DCM. On admission, laboratory examinations showed a plasma renin activity of 38 ng/hr, plasma aldosterone concentration of 2670 pg/ml and plasma BNP level of 1070 pg/ml at the absence of ACE inhibitor or ARB, indicating extreme secondary aldosteronism due to CHF. We started treatment with alacepril and furosemide, but replaced alacepril with losartan because of drug-induced liver dysfunction. Losartan decreased the plasma aldosterone concentration rapidly but could not relieve the symptoms related to the low output syndrome without a significant decrease in plasma BNP level. Cardiac function was kept low and cardiomegaly was persistent. After failure of add-on therapy of β blocker, enarapril was administered additionally. The combination therapy of losartan and enarapril dramatically decreased the plasma aldosterone level, and then carvedilol was successfully added on. After that, the patient’s symptoms were improved and the plasma BNP level was further decreased to below 100 pg/ml with a gradual increase of ejection fraction from 22% to 41%, and cardiomegaly disappeared. From this case, we learned the following two points. First, during the treatment there exists a time lag between the decrease in plasma aldosterone and BNP levels, which clearly indicates the time lag between inactivation of systemic and cardiac RAS. Second, keeping the plasma BNP level low is very important for the improvement of CHF, thus physicians should try to keep it low by optimizing the dose of RAS inhibitors.

**AT1 Receptor as a Stretch Receptor**

Recently Zou et al (7) in at Chiba University discovered that AT1 receptor is a sensor for stretch. Earlier, in vitro studies indicated that stretch itself stimulates hypertrophic responses, such as an increase in leucine uptake, ERK acti-
vation and upregulation of ANP mRNA expression, the mechanism by which stretch rapidly increased angiotensin II production and stimulated AT1 signaling. And this stretch-induced hypertrophic response was almost completely inhibited by ARB. However, Zou et al (7) have shown that stretch can stimulate AT1 signaling without production of angiotensin II in cultured myocytes isolated from angiotensinogen knockout mice hearts. Moreover, transverse aortic banding induces left ventricular hypertrophy in mice lacking the angiotensinogen gene, which was blocked by an inverse agonist for AT1 receptor, candesartan.

**Conclusion**

In CHF, although both systemic and local RASs are activated to preserve cardiac output and perfusion pressure to vital organs, too much activation leads to the vicious cycle of CHF and unfavorable results. Clinical and experimental studies have proved that inhibition of RAS improves cardiac function and the prognosis of CHF. Recently AT1 receptor is activated by stretch itself without the ligand. Further studies are necessary to certify the pharmacological and clinical characteristics of inverse agonists for AT1 receptor in CHF treatment that differs from Ace inhibitor or AT1 receptor blocker without inverse agonistic activity.

**References**


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