Renin-Angiotensin System in Human Failing Hearts

Message From Nonmyocyte Cells to Myocytes

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The survival benefit conferred by angiotensin-converting enzyme (ACE) inhibitors in patients with heart failure has led to an intense interest in the mechanisms underlying the action of angiotensin II. However, ACE inhibition therapy does not completely block angiotensin II production, and in some patients angiotensin II remains elevated, in part because of the conversion of angiotensin I to angiotensin II by chymase activity. The main two receptors for angiotensin II, AT1 receptor (AT1R) and AT2 receptor (AT2R), are present in the myocardium. Most angiotensin II functions in the cardiovascular system are mediated by AT1R. AT2R has anti-AT,R effects, such as negative chronotropic action or inhibition of interstitial fibrosis, which may play a protective role in development of heart failure. Presently, no therapeutic agents that specifically act on AT2R are approved for clinical trials. However, AT,R blockers are available that could shunt the activity of the cardiac renin-angiotensin system toward selective stimulation of beneficial AT2R. Two separate clinical approaches (ELITE-II and RESOLVD) compared ACE inhibitors with AT,R blockers in patients with heart failure. No significant differences were observed in the beneficial effect of these two classes of agents, and the cardioprotective role of AT2R remains to be determined.

The cardioprotective action of ACE inhibitors and AT,R blockers depends on the expression level of myocardial AT,R and AT,R in patients with heart failure. The first study to examine these levels in human myocardium found no significant changes in total angiotensin II receptor numbers between failing and nonfailing hearts. More recent studies in human heart appear in the present issue of Circulation Research. Serneri et al isolated myocytes as well as myocardial ACE inhibitors in patients heart failure samples, whereas chymase expression did not change. Interestingly, Serneri et al also showed that ACE and angiotensinogen mRNAs in the nonfailing hearts were expressed only in trace amounts, whereas their expression was notably enhanced in failing hearts and exclusively localized in nonmyocyte cells. Angiotensin II protein was expressed only in trace amounts, whereas their expression was notably enhanced in failing hearts and exclusively localized in nonmyocyte cells. Angiotensin II protein was present mainly in the interstitial region of failing hearts. These findings suggest that in the failing heart stage, angiotensin II was actively processed and released from nonmyocyte cells present in the interstitial regions, leading to the activation of AT,R and AT,R that exists in myocytes as well as nonmyocytes. AT,R and AT,R densities in failing myocytes are <10% of cardiac membrane fractions, suggesting that the receptors are dominantly present in nonmyocyte cells. We have shown using autoradiography that receptors for angiotensin II are localized in fibrous regions rather than in myocardium, and a similar distribution pattern was observed in both nonfailing and failing human hearts. AT,R expression was highly localized in fibrous regions, and AT,R was localized in both myocytes and nonmyocytes. Serneri et al also report that the main fraction of angiotensin II receptors in failing hearts is included in nonmyocyte cells, whereas their expression in myocytes is much less (10% to 20%) than those in nonmyocytes. Thus, it seems that the main target of
angiotensin II is nonmyocyte cells (mainly fibroblasts) and the effect on myocytes might be less than that on fibroblasts. Perivascular fibrosis of microcoronary arteries occurs in the initial phase of cardiac remodeling, which leads to the decrease in coronary blood flow followed by myocardial ischemia. Inhibition of perivascular fibrosis by blocking angiotensin II–mediated action is likely a main mechanism responsible for cardioprotective action of ACE inhibitors or AT,R blockers, although angiotensin II is known to induce myocyte hypertrophy17 or interstitial fibrosis associated with fibroblast proliferation.18

Cardiac insulin–like growth factor-1 (IGF-1) and endothelin-1 (ET-1) play a critical role in supporting cardiac-adaptive response to hemodynamic overload. Human compensatory hypertrophy attributable to aortic valve disease is associated with an increased myocyte formation of IGF-1 in vivo in volume overload and IGF-1 and ET-1 in pressure overload.19 Cardiac production of these growth factors is positively related to myocardial contractility.19 Serneri et al.15 additionally demonstrate that angiotensin II induces IGF-1 and ET-1 synthesis by human isolated nonfailing myocytes and that failing myocytes are selectively unable to produce appreciable amounts of IGF-1 and ET-1 in response to angiotensin II stimulation, not withstanding the similar density and binding capacity of angiotensin II receptors. Platelet-derived growth factor synthesis via AT,R was preserved in failing myocytes,15 angiotensin II receptors. Platelet-derived growth factor synthesis via AT,R was preserved in failing myocytes,15 angiotensin II receptors. Platelet-derived growth factor synthesis via AT,R was preserved in failing myocytes,15 angiotensin II receptors. Platelet-derived growth factor synthesis via AT,R was preserved in failing myocytes,15 angiotensin II receptors. Platelet-derived growth factor synthesis via AT,R was preserved in failing myocytes,15 suggesting a specific impairment of the pathways leading to IGF-1 and ET-1 formation. Although Serneri et al.15 could not define the mechanisms responsible for the incapacity of failing myocytes to produce IGF-1 and ET-1, some signaling pathways via AT,R may be interrupted or novel intervening molecules may be generated in failing myocytes to affect the signal transduction.

Recent evidence suggests that local angiotensin II through AT,R activates the transcription factor nuclear factor-kB, thereby promoting expression of numerous genes, including various cytokines and adhesion molecules.20 Such AT,R-mediated transcriptional systems might be impaired in failing myocytes, and novel transcriptional factors could be generated.21 Because AT,R on myocytes is not downregulated in failing human hearts, the long-lasting excessive angiotensin II formation can mediate detrimental effects on overloaded or failing myocytes, including depression of contractility or impaired relaxation. Thus, the defective response of failing myocytes to angiotensin II stimulation may reside either in intracellular signal transduction pathways or in transcription factors. However, specific studies are required to investigate cellular functions or biochemical machinery of failing myocytes and nonmyocytes in response to angiotensin II.

References


Key Words: angiotensin II ■ angiotensin receptor ■ human heart ■ heart failure ■ angiotensin-converting enzyme
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Circ Res. 2001;88:861-863
doi: 10.1161/hh0901.091204

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