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.1,2 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.3 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 the myocardium. Most angiotensin II functions in the myocardium.

The cardioprotective action of ACE inhibitors and AT1R blockers depends on the expression level of myocardial AT1R, and AT1R 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.7 More recent studies in human heart failure have shown downregulation of AT1R,8-14 either without changes8-12 or with an increase13,14 in AT1R numbers. Measurement of AT1R and AT2R numbers has been analyzed using ligand-binding assays based on membrane fractions from cardiac tissue. Cell type-specific expression patterns of AT1R and AT2R have not yet been defined in failing human hearts.

An important new study of cardiac AT,R density in failing human heart appears in the present issue of Circulation Research. Serneri et al15 isolated myocytes as well as membrane fractions from failing human hearts and found that AT,R density did not change in failing myocytes but decreased in cardiac membrane fractions. This suggests that myocytes remain in endstage failing hearts as potential targets for angiotensin II–mediated effects and that AT,R is selectively downregulated in nonmyocyte cells. Serneri et al15 report that stretch-activated signals attributable to ventricular filling pressure inhibited downregulation of AT,R in myocytes but not in nonmyocytes. In fact, stretching of myocytes from neonatal rat hearts, but not that of fibroblasts, was shown to upregulate AT,R expression.16 Thus, myocytes maintain AT,R numbers even in the failing stage, supporting the efficacy of ACE inhibitors and AT,R blockers in this pathological state.

Serneri et al15 demonstrate that the progression of heart failure is closely associated with a progressive increase in cardiac angiotensin II formation and a strong correlation with the increasing end-diastolic stress. Conversion of angiotensin I to angiotensin II, ACE, and angiotensinogen mRNA levels were significantly increased in failing heart samples, whereas chymase expression did not change. Interestingly, Serneri et al15 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 present mainly in the interstitial region of failing hearts. These findings suggest that in the failing heart stage, angiotensin II is 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.13 AT,R expression was highly localized in fibrous regions, and AT,R was localized in both myocytes and nonmyocytes.13 Serneri et al15 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.15 Thus, it seems that the main target of

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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(Circ Res. 2001;88:861-863.)
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Circulation Research is available at http://www.circresaha.org

See related article, pages 961–968
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 AT1R blockers, although angiotensin II is known to induce myocyte hypertrophy and interstitial fibrosis associated with fibroblast proliferation.

Cardiac insulin–like growth factor-1 (IGF-1) and endothelin-1 (ET-1) play a critical role in supporting cardiadaptive response to hemodynamic overload. Human compensatory hypertrophy attributable to aortic valve disease is associated with an increased myocyte formation of IGF-1 in volume overload and IGF-1 and ET-1 in pressure overload.

Cardiac production of these growth factors is positively related to myocardial contractility. Serneri et al. 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 ET-1 in response to angiotensin II.

Recent evidence suggests that local angiotensin II through AT1R activates the transcription factor nuclear factor-kB, thereby promoting expression of numerous genes, including various cytokines and adhesion molecules. Such AT1R-mediated transcriptional systems might be impaired in failing myocytes, and novel transcriptional factors could be generated. Because AT1R 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

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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