Editorial Comment

New Insight of Angiotensin II Receptor Blocker Treatment in Cardiac Dysfunction Using Angiotensin-Converting Enzyme 2–Deficient Mice

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Angiotensin-converting enzyme (ACE) 2 was simultaneously identified in 2000 by two research groups (*1*, *2*), and its amino-terminal domain shares approximately 40% sequence identity with ACE. ACE2 is able to cleave both angiotensin (Ang) I and Ang II to Ang-(1–9) and Ang-(1–7), respectively. Ang-(1–7) is known to potentiate the vasodilatory effects of bradykinin, stimulate nitric oxide and prostaglandin release, and antagonize the actions of Ang II. It has also been highlighted as a new player in the renin-angiotensin system (RAS).

At least three lines of ACE2-deficient mice have been generated by different research groups (*3*–*5*). Interestingly, there are significant differences in some of the reported phenotypes of these distinct lines, especially with regard to their cardiovascular physiology. These differences are considered to be induced by the genetic background of the mouse strains, suggesting that the roles of ACE2 in the cardiovascular system may be more complicated than we understand at present.

In this issue of *Hypertension Research*, Nakamura *et al*. examined the role of Ang II receptor blocker (ARB) in age-associated cardiac function in ACE2-deficient mice (*6*). They have demonstrated that ARB, candesartan, prevents the development of the cardiac dysfunction observed in ACE2-deficient mice *via* inhibition of Ang II type 1 (AT_1) receptor signaling, which is accelerated by excess of serum Ang II. Interestingly, the beneficial effect of candesartan was not induced by apparent histological changes, such as the prevention of interstitial fibrosis and myocyte hypertrophy. To our knowledge, this is the first report to demonstrate the beneficial effect of ARB on age-dependent cardiac dysfunction in ACE2-deficient mice.

The present study by Nakamura *et al*. (*6*) used ACE2-deficient mice that were based on a C57BL/6 background (*3*). These mice, like another ACE2-deficient strain based on a mixed background of C57BL/6 and 129/SvEv (*4*), exhibit no significant increase in interstitial fibrosis with age, in contrast to wild-type mice. However, in the same mouse strain, Yamamoto *et al*. showed an increase in interstitial and perivascular fibrosis by pressure overload with transverse aortic constriction (TAC) (*3*). Candesartan was also able to prevent such TAC-induced histological changes (*3*), indicating that blockade of AT_1 receptor signaling may prevent ACE2-dependent cardiac dysfunction with or without histological change.

In failing human hearts, ACE2 expression is reported to be increased (*7*). An increase in ACE2 is considered to play a protective role in the early stages of heart failure by elevating Ang-(1–7) levels. In contrast, overexpression of ACE2 in cardiac myocytes caused changes in cardiac conductivity, resulting in arrest and sudden death (*8*). A loss of ACE2 could impair cardiac function, and the level of ACE2 expression may be pivotal for cardiac protection. This paradigm may be similar to Ang II type 2 (AT_2) receptor signaling in the heart,

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where AT_2 receptor function is reported to vary depending on Ang II receptor binding proteins (*9*). Both processes are potentially overlapping counter-regulatory components of the RAS. Therefore, as speculated by Nakamura *et al*. (*6*), the role of counter-regulatory systems in the RAS should depend on the balance between the ACE–Ang II–AT_1 receptor axis and the ACE2–Ang-(1–7)–Mas axis in the maintenance of cardiac function. To date, although ACE2 may prevent cardiac dysfunction, it is not possible to establish the appropriate level of ACE2 in the heart to act as a beneficial effector for heart failure. Further investigation is necessary to explore the role of the pathophysiological function of ACE2.

Several new players in the RAS, including ACE2, are at the center of emerging therapeutic approaches to preventing multiple organ damage. Nakamura *et al*. (*6*) provide timely new insight into the role of ACE2 by linking it to cardiac function, and they provide the basis for potential therapeutic benefit in the form of cardiac protection through an ARB-mediated blockade of the RAS.

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