Angiotensins and the Heart
Is Angiotensin-(1–7) Cardioprotective?
Jan Wysocki, Lisa Wilsbacher, Daniel Batlle

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Left ventricular hypertrophy is the most common cardiac complication of hypertension. Although the initial adaptations associated with cardiac hypertrophy are compensatory, ultimately abnormal ventricular function including diastolic dysfunction (impaired relaxation) and often heart failure may develop.¹ Activation of the renin–angiotensin system and its main effector peptide angiotensin II (Ang II), acting on the Ang II type 1 receptor, has been considered an important part of the cascade leading to left ventricular hypertrophy and cardiac fibrosis.¹,² Recent work, however, examining the effects of Ang II infusion using cardiomyocyte and vascular smooth muscle-specific Ang II type 1 receptor knockouts suggests that the hypertension-induced increase in afterload, rather than direct Ang II–Ang II type 1 receptor signaling in the heart, is the key factor that promotes hypertrophic responses.³ The renin–angiotensin system peptide Ang-(1–7), which is generated from Ang II by the action of carboxypeptidases, such as ACE2,³ exhibits actions that are mainly opposite to those of Ang II, including vasodilatory and antifibrotic effects.³

In this issue, Machado de Almeida et al⁴ report a series of interesting observations that suggest that in an Ang-(1–7) transgenic line, TGR(A1–7)3292, there is cardioprotection from deoxycorticosterone acetate (DOCA)–salt induced hypertension which is independent of blood pressure. The latter conclusion is not unexpected considering the strong evidence against an antihypertensive effect of Ang-(1–7): (1) acute infusions of supraphysiologic concentrations of this peptide do not lower blood pressure in mice,¹ (2) a 4-week continuous infusion of Ang-(1–7) did not decrease blood pressure in DOCA-treated Sprague-Dawley (SD) rats,⁵ (3) acutely Ang-(1–7) does not attenuate the hypertensive effect of infused Ang II, and a blocker of the Mas receptor also does not worsen the blood pressure response to infused Ang II,³ and (4) the antihypertensive effects of an Ang II antagonist are not altered by the concomitant administration of the Ang-(1–7) receptor blocker.⁷ Notwithstanding these observations, the rat transgenic TGR(A1–7)3292 used displayed an attenuated hypertensive response to DOCA, and appropriate experiments were performed to show that the observed cardioprotective effects were not found in control animals with hydralazine-induced attenuated blood pressure levels.⁵ Previous studies have shown cardioprotective effects of Ang-(1–7).⁵,⁶,⁹ The question then arises: how does Ang-(1–7) act directly on cardiomyocytes to reduce hypertrophic responses?

Machado de Almeida et al⁴ examines this question in detail using the DOCA hypertension model in SD control and TGR(A1–7)3292 rats by investigating cardiomyocyte-specific molecular pathways that are associated with hypertrophy and diastolic dysfunction. As expected, SD rats treated with full-dose DOCA (SD-DOCA) developed hypertension, and echocardiography revealed concentric left ventricular hypertrophy and impaired relaxation. In addition, cardiomyocytes isolated from SD-DOCA rats expressed increased levels of cardiac stress markers; furthermore, Ca²⁺ homeostasis was disturbed in SD-DOCA cardiomyocytes with reduced peak Ca²⁺ transients and reduced expression of sarcoplasmic reticulum Ca²⁺-ATPase 2, which mediates the rapid reuptake of cytosolic Ca²⁺. However, the rate of Ca²⁺ reuptake, which is prolonged in the settings of diastolic dysfunction and decreased sarcoplasmic reticulum Ca²⁺-ATPase 2a activity, was not reported. Similar to their previous results,⁴ TGR(A1–7)3292 rats treated with DOCA demonstrated an absence or attenuation of several echocardiographic hypertrophic changes when compared with baseline TGR(A1–7)3292 rats; importantly, however, left ventricular posterior wall and interventricular thickness were similar in TGR(A1–7)3292 and SD rats at baseline despite a 20% lower body weight in TGR(A1–7)3292 rats. Sarcoplasmic reticulum Ca²⁺-ATPase 2 protein levels and phospholamban signaling pathways were preserved in TGR(A1–7)3292-DOCA rats when compared with SD-DOCA rats.⁵ The relative differences between SD and SD-DOCA versus TGR(A1–7)3292 and TGR(A1–7)3292-DOCA rats overall support a protection from cardiac hypertrophy and diastolic dysfunction in TGR(A1–7)3292-DOCA rats.

As noted above, the authors administered hydralazine to 1 group of SD-DOCA rats and reduced DOCA dose to a second group of SD rats to match the blood pressure in TGR(A1–7)3292-DOCA rats. Despite attenuated blood pressure increase, SD-DOCA-hydralazine rats displayed more significant echocardiographic markers of cardiac hypertrophy than TGR(A1–7)3292-DOCA rats, and both SD-DOCA-hydralazine and SD-low-DOCA demonstrated diastolic dysfunction.

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Interestingly, cardiomyocytes isolated from SD-DOCA-hydralazine rats elicited a high peak transient Ca\(^{2+}\) that was similar to TGR(A1–7)3292-DOCA rats but was in contrast to the low peak transient Ca\(^{2+}\) in SD-DOCA; however, one would expect the SD-DOCA and SD-DOCA-hydralazine groups to be similar to each other and different from TGR(A1–7)3292-DOCA, given diastolic dysfunction in both SD control groups. Likewise, levels of phosphorylated phospholamban, which stimulates sarcoplasmic reticulum Ca\(^{2+}\) ATPase 2 and promotes normal diastolic function, were similar between SD-DOCA-hydralazine and TGR(1–7)3292-DOCA rats, and significantly higher than in SD-DOCA rats; one would expect decreased phosphorylated phospholamban in SD-DOCA-hydralazine rats, given the presence of diastolic dysfunction. These incongruous results require additional investigation to better understand the mechanism of improved echocardiographic diastolic function only in TGR(1–7)3292-DOCA rats when compared with SD-DOCA and SD-DOCA-hydralazine rats.

What role does attenuated fibrosis play in the cardiac protection mediated by Ang-(1–7)? Although the current study focused on cardiomyocytes, fibroblasts can bind Ang-(1–7) in vitro to reduce collagen expression.\(^6\) Consistent with these data, chronic Ang-(1–7) infusion in SD-DOCA rats attenuated interstitial and perivascular collagen deposition\(^6\) and Ang-(1–7) coinfusion with Ang II prevented both hypertension-induced cardiac interstitial fibrosis and cardiomyocyte hypertrophy.\(^11\) Furthermore, the previous study of TGR(A1–7)3292 DOCA-treated rats found attenuated expression of collagen types I and III that accompanied the improvement of cardiac function.\(^8\) Therefore, one could assume that the beneficial cardiac effects in the current study were not limited solely to improved myocyte function, but potentially to fibrosis reduction as well.

What other cardiomyocyte pathways might contribute to the cardioprotective effects of Ang-(1–7)? Cardiac effects of Ang-(1–7) are mediated by the Mas receptor through various signaling pathways, including autotoids, mitogen-activated protein kinases/ERK, AKT, nicotinamide adenine dinucleotide phosphate oxidase, transforming growth factor-β1, epidermal growth factor receptor, and nuclear factor-κB activity.\(^12\) Interestingly, Machado de Almeida et al.\(^5\) found both elevated Mas receptor protein levels and increased phosphoERK (activated mitogen-activated protein kinases/ERK) only in SD-DOCA cardiomyocytes, whereas phosphoERK was reduced in TGR(A1–7)3292-DOCA cardiomyocytes; these observations do not fit a model of increased plasma Ang-(1–7) and Mas receptor activation as the mechanism of cardioprotection. Moreover and unexpectedly, their previous study in TGR(A1–7)3292 DOCA-treated rats revealed normal plasma Ang-(1–7) but increased local cardiac Ang-(1–7), and the mechanism underlying this phenomenon remains unknown.\(^5\)

Several other issues deserve comment. The transgene used to generate TGR(A1–7)3292 rats consisted of a fusion protein containing the human renin signal peptide followed by the Fc portion of mouse IgG, then the prosegment of human prorenin, containing the human renin signal peptide followed by the Fc portion of mouse IgG, then the prosegment of human prorenin, and finally the cyatriphus promoter with the intention to generate Ang-(1–7) in all tissues, but the transgene only expressed in testes and generated a 2-fold increase in plasma Ang-(1–7) levels.\(^13\) It is unclear whether control SD rats used in this study were littermates of TGR(A1–7)3292 rats; if not, some effects in TGR(A1–7)3292 rats, including smaller size and potentially the attenuated DOCA-induced blood pressure rise, may be because of founder effects rather than increased plasma Ang-(1–7). Moreover, levels of this peptide were not reported in this study, and therefore it is uncertain if the observed effects are directly related to increased levels of circulating and local cardiac Ang-(1–7). Experiments using a blocker of the Mas receptor would have provided important insight into the role of Ang-(1–7) because increased Mas receptor level in SD-DOCA rats but unchanged Mas receptor level in TGR(1–7)3292-DOCA rats is difficult to interpret mechanistically. Finally, confirmation of the current results using alternative hypertension models would add strength to the molecular mechanisms outlined in this study; thoracic artery constriction would be a better model, as it non-pharmacologically increases ventricular afterload. Looking ahead for therapeutic application, it remains uncertain whether exogenous Ang-(1–7) or Mas receptor agonists will replicate the cardioprotection observed in the transgenic Ang-(1–7) model studied by Machado de Almeida et al.,\(^5\) but such studies in hypertensive models are clearly worthy of consideration.

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Disclosures

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