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EDITORIAL COMMENT

A ($Alpha_1$-Adrenergic Receptors), B (Blocking $Alpha_1$-Adrenergic Receptors), C (Catecholamines)

On the Road to Heart Failure*

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Heart failure (HF) after myocardial infarction (MI) is the result of a myriad of cellular processes that ultimately culminate in a critical decline in contractile function and circulating blood volume. A central regulator of these cellular processes are classes of G protein–coupled receptors in the heart, $alpha_1$-adrenergic receptors (α1-ARs) and β-adrenergic receptors (β-ARs). Because both classes of receptors are activated by catecholamines, which are chronically elevated after cardiac injury, their direct downstream responses, cross-talks, and compensatory effects play a central role in determining the extent of the injury and the disease outcome. Although the role of β-ARs in HF has been extensively studied, the role of α-ARs in HF has not been explored as much, in part because of their lower expression levels.

In the healthy myocardium, the α1A-ARs and α1B-ARs are expressed in cardiomyocytes, whereas the α1D-ARs are primarily expressed in coronary arteries. α1-ARs couple to Gαq and activate phospholipase Cβ1, leading to an increase in inositol triphosphate and diacylglycerol, ultimately resulting in intracellular calcium release and activation of protein kinase C.[1] Interestingly, cardiac fibroblasts that make up >50% of myocardial cells do not express any of the α1-ARs. In the failing myocardium, in humans, although β-AR expression is down-regulated and they do not function adequately, α-AR expression and activity slightly increases.[2] In this setting, the α1-ARs have increased importance in generating the combined required positive inotropy when the β-AR responses are attenuated.

Gain-of-function studies in mice show that the beneficial effects of α1-ARs include: 1) physiological hypertrophy, mediated via protein kinase D, extracellular signal–regulated protein kinases 1/2, and histone deacetylases[2]; 2) early and late ischemic preconditioning, mediated via activation of protein kinase C, heat shock proteins, and induction of inducible nitric oxide synthase; 3) increased myocyte survival postinjury via extracellular signal-regulated protein kinase activation and via transcription factors GATA binding protein 4 and nuclear factor of activated T cells; and 4) positive inotropy in the left ventricle and right ventricle (RV) postinjury via alterations in L-type Ca^{2+} channel currents, Na^{+}/H^{+} exchanger, and myofilament Ca^{2+} sensitivity.[1] Conversely, mice lacking either α1A-ARs or α1B-ARs or both in the myocardium are hypotensive, have reduced response to α1-AR agonists, and have smaller hearts at birth, respectively, indicating their importance not only in the adult heart postinjury but also developmentally.

In this issue of *JACC: Basic to Translational Science*, Zhang et al[3] have shown that mice lacking α1A-ARs specifically in cardiomyocytes (cmAKO) had exaggerated remodeling, ventricular dysfunction, and compromised cardiomyocyte biomechanical

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adaptability that resulted in a significantly higher mortality rate 2 weeks' post-MI compared with wild-type control mice. The pathologic cause of the increased mortality in cmAKO mice was ventricular rupture. The authors further discovered that the ventricular rupture was a result of cardiomyocyte necroptosis and not apoptosis, which was receptor-interacting protein kinase 1 (RIP1)-RIP3-mixed lineage kinase domain-like protein (MLKL) mediated.

Loss of a large number of cardiomyocytes after MI is one of the most significant factors that contribute to pathobiology. In the acute phase, massive cell loss post-MI is usually attributed to apoptosis via reactive oxygen species-induced DNA damage and cytochrome C release from mitochondria or via tumor necrosis factor-α. Beyond apoptosis in the initial acute phase, the cellular loss has been attributed to autophagy, mediated by the formation of autophagosomes, or is chaperone mediated or lysosomal, and finally, necroptosis mediated by the formation of necrosomes containing RIP3 and MLKL. The temporal distribution of the aforementioned processes ranges from 2 hours' post-MI to 12 weeks' post-MI. However, there is an overlap between them as the injury moves from the acute to the chronic phase. In the cmAKO mouse model, Zhang et al[3] had to limit their investigations to 3 days' post-MI due to exaggerated mortality 5 days' post-MI. Immunoblotting results indicated a 2-fold higher expression of RIP1 and RIP3 and an 8-fold increase in MLKL in the border zone. No differences were observed in the levels of cleaved caspase 8 and cleaved poly(ADP-ribose) polymerase-1, indicating necroptosis and not apoptosis as the prevalent cell death pathway in cardiomyocytes lacking α1A-ARs.

As reported by Nakaoka et al,[4] the α-AR agonist phenylephrine is cardioprotective by inducing Akt-1-mediated autophagy. Although not investigated in the present study by Zhang et al,[3] it would be important to know if autophagy was altered at baseline in the cmAKO mice that predisposed the heart to exaggerated responses or if it becomes altered after injury, resulting in drastically accelerated pathologic processes. As previously stated, α1-ARs, and specifically α1A-ARs, play an important role in ischemic preconditioning.[2] Therefore, in addition to the role of necroptosis and autophagy, lack of α1A-ARs could also potentially affect ischemic preconditioning, leading to accelerated and excessive cardiac damage post-MI.

In the healthy myocardium, α1-AR stimulation generates positive inotropy in the left ventricle and negative inotropy in the RV. However, in HF, the negative inotropy in the RV switches to positive as a compensatory effect.[2] A key question is whether α1A-ARs specifically mediate this switch. In its absence, does this switch not happen, leading to accelerated contractile decline 3 days' post-MI? Alternatively, it could also be argued that the inotropy switch does indeed happen in the RV, but the compromised biomechanical properties of the myocardium at baseline simply cannot keep up with the combined increased inotropy, leading to rupture.

Alteration of cardiomyocyte metabolism is another aspect that can potentially play an important role in early mortality in cmAKO mice. It is known that α1-AR increases glucose uptake in the heart, and α1A-AR specifically mediates this glucose uptake via activation and translocation of glucose transporter 1/4.[5] In addition, α1-AR plays a role in glucose oxidation, which becomes important in ischemic recovery. In the absence of the α1A-AR, these processes might already be disrupted at baseline as well as after injury.

Similar to this study, Yeh et al[6] also investigated the role of α1A-ARs post-MI but in a global α1A-AR knockout model. In this study too, there is approximately 60% mortality in the α1A-AR knockout mice in the first week post-MI, but the remaining 40% of mice survived up to 4 weeks. At baseline, these mice had slight cardiac hypertrophy and increased p38, a pro-inflammatory and pro-apoptotic regulator, indicating the hypertrophy was more pathologic than physiological. Interestingly, the cardiac-specific cmAKO hearts did not display baseline hypertrophy but did have >70% higher biaxial tensile stretch, rendering them biomechanically compromised and predisposed to rupture.[3] Therefore, in both studies, the absence of α1A-ARs had pathologic effects at baseline, clearly indicating their importance.

In addition to their cmAKO mouse model, Zhang et al[3] describe a single-center retrospective clinical study, which highlighted that patients who underwent a percutaneous coronary intervention after MI and subsequently used α-blockers had a significantly higher mortality rate after 3 years. As has been observed in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack *Trial*), the use of the α_1-blocker doxazosin for hypertension increased the incidence of HF to a point at which that arm of the trial had to be discontinued.[2] Similarly, in V-HeFT (Vasodilator-Heart Failure *Trial*), the patient cohort that received the α_1-blocker prazosin as a vasodilator had a trend toward a higher mortality rate.[2] In addition to being detrimental in the heart, α-blockers might potentially have a detrimental effect on brain functions, as it has been shown that α1A-ARs and α1B-ARs are expressed in the hippocampus,

amygdala, cortex, and thalamus; they also play a significant role in neurogenesis, spatial working memory, memory consolidation, general cognition, and age-related cognitive decline, thus extending their importance in dementia-related diseases.[5] In addition to their effects on cardiac metabolism, α1-ARs regulate gluconeogenesis in the liver and kidney and glucose uptake in white and brown adipose tissue.[5] Therefore, exposure to α-blockers potentially disrupts multiple organ metabolism. Given such significant and diverse roles played by α1-ARs, the use of α-blockers warrants much more caution.

Taken together, Zhang et al[3] show the significant role of α1A-ARs in the heart post-MI in a mouse model, and how blocking them via α-blockers in patients, significantly contributes to the pathobiology on the road to HF. Overall, this interesting study sheds new light on these minor yet powerful catecholamine receptors in the heart, and time will tell us the translational significance of these studies.

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REFERENCES

1. O'Connell TD, Jensen BC, Baker AJ, Simpson PC. Cardiac alpha1-adrenergic receptors: novel aspects of expression, signaling mechanisms, physiologic function, and clinical importance. *Pharmacol Rev*. 2013;66(1):308–333.

2. Jensen BC, O'Connell TD, Simpson PC. Alpha-1-adrenergic receptors in heart failure: the adaptive arm of the cardiac response to chronic catecholamine stimulation. *J Cardiovasc Pharmacol*. 2014;63(4):291–301.

3. Zhang J, Sandroni PB, Huang W, et al. Cardiomyocyte alpha-1A adrenergic receptors mitigate postinfarct remodeling and mortality by constraining necroptosis. *J Am Coll Cardiol Basic Trans Science*. 2024;9(1):78–96.

4. Nakaoka M, Iwai-Kanai E, Katamura M, Okawa Y, Mita Y, Matoba S. An alpha-adrenergic agonist protects hearts by inducing Akt1-mediated autophagy. *Biochem Biophys Res Commun*. 2015;456(1):250–256.

5. Perez DM. Current developments on the role of α_1-adrenergic receptors in cognition, cardioprotection, and metabolism. *Front Cell Dev Biol*. 2021;9:652152.

6. Yeh CC, Fan Y, Xu Y, Yang YL, Simpson PC, Mann MJ. Shift toward greater pathologic post-myocardial infarction remodeling with loss of the adaptive hypertrophic signaling of alpha1 adrenergic receptors in mice. *PLoS One*. 2017;12(12):e0188471.

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