Elevated plasma levels of angiotensin II have been identified as a key determinant of cardiac hypertrophy and congestive heart failure. Angiotensin II signaling mediates its biological actions in part by altering intracellular sarcolemmal reticulum/endoplasmic reticulum calcium stores and voltage-dependent L-type Ca$^{2+}$ channels. Calcium concentration is directly involved in cardiac excitation–contraction coupling and plays a central role in intracellular signaling pathways. Because calcium is the physiological activator of the contractile proteins, chronic elevations of cardiac angiotensin II–altered calcium handling have been postulated to underlie the calcium overload and contractile dysfunction after myocardial infarction. Kamp and Helll have suggested involvement of protein kinase A (PKA) and protein kinase C (PKC) pathways in the modulation of intracellular calcium stores and contractility. This is consistent with the reported ability of angiotensin II to promote cardiac hypertrophy via the phosphoinositide 3-kinase (PI3K)/Akt-dependent pathway. In this regard, PI3K transduces extracellular signals into cellular function by regulating activity of several genes downstream of angiotensin II type 1 receptor (AT$_1$R). Based on sequence homology and substrate preference, 8 members of the PI3K family have been identified. The most widely studied isoforms of the PI3K family include PI3K$_{{\alpha}}$ and PI3K$_{{\gamma}}$, which regulate a variety of biological actions, including L-type calcium channel activity and genes associated with cell growth and survival.

Although chronic angiotensin II stimulation reportedly leads to cardiac remodeling, metabolic alterations, and fibrosis, little is known of the acute phase effects of angiotensin II on cardiomyocyte contractility. By definition, inotropy relates to alterations in contractile force generation independent of sarcomere length. It is mainly dictated by changes in activator calcium for excitation-contraction coupling, sensitivity of myofibrillar proteins to free intracellular calcium, changes in activator calcium for excitation-contraction coupling, independent of sarcomere length. It is mainly dictated by changes in calcium concentration. Angiotensin II infusion increased vascular resistance with a corresponding decrease in coronary artery flow rate after 5 minutes of angiotensin II stimulation, with return to baseline levels after 8 minutes. Because coronary vascular resistance can directly influence cardiac function and could possibly underlie the observed biphasic response to angiotensin II (early decline at 5 minutes, followed by an increase in ventricular pressure after 8 minutes), Liang et al further showed that angiotensin II-induced biphasic response of +dP/dt$_{max}$ persisted even after ventricular myocyte were treated with the potent vasodilator P1075. This indicates that the negative inotropic effect was not attributable to the vasopressor actions of angiotensin II on coronary flow. Moreover, in isolated ventricular myocytes, angiotensin II produced a decrease in L-type Ca$^{2+}$ current. A similar biphasic response in cell shortening was also observed after angiotensin II treatment. Interestingly, angiotensin II-induced cell shortening was abrogated when cells were pretreated with the AT$_1$R blocker irbesartan, verifying the involvement of AT$_1$Rs in angiotensin II-mediated effects on myocyte contractility. The altered contractile response by angiotensin II coupled with a decrease in L-type Ca$^{2+}$ currents provided a novel mechanism to explain how angiotensin II negatively regulates cardiac inotropy acutely.

In addition, Liang et al showed that the negative inotropic actions of angiotensin II were largely abolished in PI3K$_{{\alpha}}^{-/-}$ but not in PI3K$_{{\gamma}}^{-/-}$ hearts, whereas the positive inotropic actions of angiotensin II observed in the PI3K$_{{\alpha}}^{-/-}$ hearts were similar to that in wild-type controls. In regard to the negative regulation of cardiac inotropy, the importance of PI3K$_{{\alpha}}$ and not of PI3K$_{{\gamma}}$, though unproven, may be explained in part by differential coupling of the AT$_1$R to different isoforms of PI3K and subsequent L-type calcium channels in response to acute vs chronic angiotensin II stimulation. Because glycogen synthase
kinase-3 beta (GSK3β) is a part of the PI3K pathway, Liang et al further explored the possibility that GSK3β may be involved in the angiotensin II signaling axis. Interestingly, mice genetically ablated for GSK3β (GSK3β−/−) demonstrated a similar response to angiotensin II as did wild-type controls, excluding the involvement of GSK3β in this pathway. Similarly, angiotensin II had no apparent effect on p47phox (a subunit of NADPH oxidase) knockout hearts, suggesting that increased reactive oxygen species production is not involved in the acute phase decline in myocardial contractility by angiotensin II. Notably, PKC inhibition blocked both the positive and the negative inotropic actions of angiotensin II, suggesting that PKC likely impinges on L or more signaling pathway downstream of angiotensin II to regulate cardiac inotropy. This dual action of PKC may explain earlier reports demonstrating the ability of PKC to elicit both positive and negative inotropic effects on myocardial function. Taken together, the work by Liang et al highlights an interesting mechanism that may explain acute vs early chronic effects of angiotensin II on myocyte contractility.

Although the report by Liang et al linking early vs late inotropic effects of angiotensin II to PI3Kα and PKC is conceptually novel, the underlying mechanisms that account for this differential inotropic effect remains unclear. From this study, it appears that PI3Kα is required for the observed early negative inotropic effect of angiotensin II, but the question regarding how angiotensin II switches from the acute negative inotropy to the late positive inotropy remains unanswered. For instance, it is unclear why inhibition of PI3Kα abrogated the acute negative inotropic effect of angiotensin II but failed to mitigate the late effect. If we assume both actions on inotropy are differently regulated by angiotensin II (ie, acute early versus chronic), then what is the underlying mechanism that switches the early vs late effects? Another interesting finding of the study highlights that PKC inhibition completely blocks both the positive and the negative inotropic actions of angiotensin II, hinting to the possibility that PKC is a key regulator/effecter of inotropy by angiotensin II. If PKC is in fact playing a central role, then it is unclear how it can regulate these 2 divergent and opposing effects of angiotensin II on contractility. What is the mechanism that causes the transition from negative to positive inotropy? Because multiple PKC isoforms (PKC-ε, PKC-β1/2, and PKC-Δ) exist, with each linked to different pathological conditions, it would be important to know which of the PKC isoforms mediates the angiotensin II-induced effects on inotropy actions or, for that matter, whether equivalent angiotensin II–PI3K signaling pathways are functional in the diseased myocardium, such as the hypertrophied or failing heart. Nevertheless, the authors provide new important information regarding the signaling pathways linking angiotensin II to L-type calcium channels and cardiac contractility. The findings of the present study implicate that PI3Kα is a key transducer of intracellular signals elicited by angiotensin II. This may prove useful in designing novel therapeutics to improve cardiac performance in individuals with increased circulating angiotensin II levels as seen after acute myocardial infarction.

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None.

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Negative Inotropy by Angiotensin II Is Mediated via Phosphoinositide 3-Kinase Alpha—Protein Kinase C-Coupled Signaling Pathway

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