


**Myocardial α1-Adrenergic Receptor Stimulation**

Regarding the recent article in *Circulation* by Landzberg et al. in particular their reference to the nonresponsiveness of heart failure patients to the α1-adrenergic receptor stimulation by phenylephrine, it is noteworthy that the heart rate of patients in heart failure was significantly higher than that of normal subjects receiving the same dose of the α1-adrenergic agonist. It has been shown that increases in heart rate reduce the α1-adrenergic stimulation of contractility induced by α1-agonists in isolated myocardial preparations. In our previous article on α1-adrenergic effects on contractility induced by methoxamine, we showed the same effect in intact human subjects when heart rate was increased by atropine or pacing. It is surprising that the authors do not refer to the different heart rates in their heart failure patients as an explanation for their findings.

In the “Discussion” section of their article, Landzberg et al. commented that in our experiments “ phenotamine did not significantly diminish the effect of methoxamine on Emax, suggesting that α1-adrenergic receptor stimulation may not have been responsible for the observed effect” of this drug. In fact, we mentioned that although the average slope of the end-systolic pressure (ESP)/dimension (ESD) relation (m) was not modified, the expected effect of phenotamine on m values was observed in three of the five subjects who received this drug. Moreover, in all subjects, the ESDs at each level of ESP attained during constant methoxamine infusion were larger after phenotamine, an observation clearly suggesting that phenotamine antagonized the inotropic effect of methoxamine.  

Landzberg et al. also state that we “failed to demonstrate an α1-adrenergic receptor–mediated positive inotropic response to systemic administration of phenylephrine,” when, in fact, we did not use phenylephrine in our experiments. What we did provide evidence for was the existence of an α1-adrenergic receptor–mediated positive inotropic response to methoxamine, because the m values during methoxamine infusion were significantly higher than those obtained during the infusion of angiotensin II, and this effect was not blocked by propranolol and was, as mentioned above, reduced by phenotamine. In addition, we clearly showed that this inotropic effect was attenuated or abolished with increases in heart rate induced by atropine or cardiac pacing. We feel that our previous communication did represent the first available evidence in favor of a positive inotropic effect mediated by α1-adrenergic receptors in the human heart and that the article by Landzberg et al provides valuable evidence in support of such a positive inotropic effect.

**References**


**Reply**

Drs. Curiel and Perez-Gonzalez have raised a salient point regarding the role of heart rate in determining the response to α1-adrenergic receptor stimulation. In vitro studies, it has often been noted that the contractile response to α1-adrenergic receptor stimulation is less at high (versus low) frequencies of stimulation. For example, the contractile response to α1-adrenergic receptor stimulation in guinea pig ventricle is greater at a stimulation frequency of 1 Hz than at 2.5 Hz. However, these frequencies of stimulation are far removed from the physiological range, and it is not known whether changes in heart rate within the physiological range affect the contractile response to α1-adrenergic receptor stimulation in vitro or in situ.

We agree that the observations in the study by Curiel et al suggest that a positive inotropic effect may have occurred with systemic methoxamine administration. However, the critical test of this conclusion, the ability to block this effect with a specific α1-adrenergic receptor antagonist (phenotamine), was not statistically significant. Therefore, conclusions regarding the contractile effect of methoxamine were necessarily indirect and based on assumptions that cannot be validated. The role of heart rate in determining the response to methoxamine is likewise difficult to interpret. The substantial reflex-mediated decrease in heart rate that occurred during systemic methoxamine and angiotensin II infusions in the study of Curiel et al reinforces a point we made in our article, namely, that the direct hemodynamic effects of infused agents such as methoxamine, as well as their secondary reflex-mediated effects on autonomic outflow to the cardiovascular system, complicate the interpretation of such studies. It is for this reason that we felt that infusion of phenylephrine directly into the coronary artery (thereby largely avoiding systemic hemodynamic effects) was necessary.

We regret that at one point in our article when referring to the study of Curiel et al, we inadvertently stated that they used phenylephrine. Please note that during the major discussion of that article, the use of methoxamine was correctly cited. We believe that the important observations of Curiel, Perez-Gonzalez, and colleagues are complementary to ours, and together, these studies support the conclusion that α1-adrenergic receptor stimulation has a direct inotropic effect in human hearts in situ.

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