Alpha-Adrenergic Coronary Vasoconstriction in Humans

I read with interest the study of Jensen et al. (1) and the accompanying editorial (2). Jensen et al. demonstrated the abundance of the $\alpha_{1D}$-adrenoceptor subtype on the mRNA and by radioligand binding on the protein level in epicardial coronary arteries of explanted healthy and diseased human hearts. This information is novel and potentially important for the development of more specific $\alpha$-adrenoceptor blockers to treat hypertension and/or prostate hyperplasia. The accompanying editorial correctly emphasizes the importance of studies in human rather than animal tissue. The original study and the editorial, however, do not acknowledge the limitations of the in vitro nature of the study. Specifically, no information on the morphological and/or functional status of the analyzed coronary arterial segment with respect to its underlying atherosclerosis is provided. In fact, mRNA and radioligand binding of an adrenoceptor in vitro are one thing, but their functional contribution to coronary blood flow in vivo is a different thing. The original study and the editorial do not acknowledge that: 1) coronary blood flow in humans is tightly regulated by redundant mechanisms such that $\alpha$-adrenergic vasoconstriction has little impact under physiological conditions; and 2) microvascular $\alpha_2$-adrenoceptors are of greater importance than epicardial $\alpha_1$-adrenoceptors, particularly in the presence of coronary stenoses (3). The functional importance of $\alpha_2$-adrenergic coronary vasoconstriction was first demonstrated in dogs (4,5) and subsequently confirmed in humans in relevant clinical settings such as percutaneous coronary intervention (6–9). Thus, in the context of $\alpha$-adrenergic coronary vasoconstriction, the “in vivo over in vitro” may outweigh the “human over animal” preference; studies in dogs are particularly suited because their coronary vascular $\alpha$-adrenoceptor distribution is largely identical to that of humans (5,6). The original study and the editorial contrast human only to mouse and rat tissue. Clearly, studies in humans in vivo are preferable, notably with respect to polymorphisms (7) and also feasible with current imaging modalities (3).

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REFERENCES


Reply

We appreciate Dr. Heusch for calling attention to our paper (1) and for his generous praise.

We do, however, disagree with some comments in his letter. His letter says that we do not acknowledge the distinction between $\alpha_2$-adrenergic receptors (ARs) (microvascular) and $\alpha_1$-ARs (epicardial coronaries), the fact that $\alpha$-vasoconstriction is limited to arteries with coronary artery disease, and that $\alpha_2$-mediated coronary vasoconstriction is more important than $\alpha_1$-mediated.

In fact, in our introduction, we state: “The $\alpha_1$-ARs constrict primarily epicardial coronary arteries and large arterioles, whereas $\alpha_2$-ARs act mostly on the coronary microcirculation. Stimulation of $\alpha_1$-ARs by endogenous catecholamines produces little constriction of normal coronary arteries, but causes pronounced vasoconstriction in coronary arteries with atherosclerotic endothelium” (1). In making these statements, we cite Dr. Heusch’s group (references 3 and 6 in his letter).

In addition, in his reference 6, $\alpha_1$- and $\alpha_2$-agonists appear to reduce coronary blood flow to a similar extent in patients with coronary artery disease (Figs. 3 and 5 in Baumgart et al. [2]), suggesting similar $\alpha_1$- and $\alpha_2$-mediated effects in humans.

Furthermore, his letter also states that no information is provided “on the morphological and/or functional status of the analyzed coronary arterial segment with respect to its underlying atherosclerosis.” On the contrary, we did analyze $\alpha_1$-AR subtype mRNAs according to the presence or absence of coronary artery disease, as determined by coronary angiography and direct observation, and found no significant differences (Fig. 5A in Jensen et al. [1]).

We do agree fully that in vivo coronary physiology is most important. In this regard, it is highly pertinent that the $\alpha_{1D}$
subtype causes coronary vasoconstriction in mice (3,4), reinforcing our point that α₁-subtype expression is similar in the mouse and human heart and that mouse models can be relevant to human disease. We also believe that our identification of α₁D as the major α₁-AR subtype in human coronaries (1) and α₁A and α₁B as the major subtypes in human myocardium (5) will facilitate much more precise studies with agonists and antagonists in large animals and humans.

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Determinants of Raised Pulse Pressure in Women

Cecelja et al. (1) conclude that increased wave reflection, not arterial stiffness, determines pulse pressure, including central pulse pressure (cPP), in women. They base this conclusion on regression analysis showing that the ratio of femoral to aortic diameter (DFA) [assumed an index of central-peripheral artery discontinuity and hence of wave reflection]] was a significant determinant of pressure augmentation (ΔPaug) whereas pulse wave velocity (PWV [a measure of arterial stiffness]) was not. However, from Table 3 in their article (1), it appears that DFA accounts for only ~2% of variation in ΔPaug. In contrast, PWV accounts for 30% of variation in P1.

In analysis of the contribution of P1 and ΔPaug to variance in cPP, the relative contributions (for the whole cohort) were 22% and 76%, respectively. We therefore calculate that PWV contributes 6.6% and DPA 1.5% to cPP variance. From Figure 2 (1), P1 contributes about two-thirds of total cPP (for the whole cohort). For the whole group, the proportional contribution to cPP, therefore, is ~0.7% for wave reflection and 20% for arterial stiffness (assuming PWV and DPA are indeed appropriate surrogates and using results from Table 3 [1]).

These analyses suggest an entirely opposite conclusion to the authors. We believe their data are actually consistent with the proposition that arterial stiffness, not wave reflection, is the major determinant of both cPP and its variation in this cohort of women; a lack of association between PWV and T1 is also consistent with this interpretation.

Perhaps the "simple approach" adopted by Cecelja et al. (1) to assessing reflected pressure is overly simplistic. The authors could not formally decompose central blood pressure into forward and reverse going waves (via reflection coefficient or wave-intensity analysis), and there are problems using central T1 to delineate forward and reverse going waves:

1. P1 only represents the full magnitude of ejection wave if any reflected wave arrives after the peak (i.e., T1 is a local minimum rather than an inflection point). Peak ejection pressure would otherwise be lost under the reflected component.
2. ΔPaug does not correspond to the magnitude of any reflected wave; even a small reverse going wave arriving early in ventricular ejection will produce an inflection point interpreted as a large ΔPaug, similarly, a large wave arriving late may result in a small ΔPaug. Reflection site and PWV predominantly determine ΔPaug, not the magnitude of the reflected wave.
3. It is well demonstrated that estimated central T1 obtained by transfer function techniques is unreliable in representing true central inflection point (2,3).

Among women ≥60 years of age, Cecelja et al. (1) observed a small influence of aortic diameter on P1 with no effect of DFA, supporting that aortic stiffness and diameter (4) rather than wave reflection are important in determining PP in this age group in whom it is an important predictor of cardiovascular risk.

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REFERENCES


Reply

We thank Drs. Cameron and Dart for their interest in our work (1). The main finding of our study was that augmentation pressure...