Letters to the Editor

Editor's Note

Due to communication problems, several Letters to the Editor were misplaced and were not published in a timely fashion. We became aware of this recently when one of the authors contacted us as to the publication status. We have gathered those letters together and are now publishing them in this issue. In general, we believe that the letters and the replies are self explanatory. We apologize for this delay.

The CHARM of a Paradox

The paradox in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) study (1) needs to be explained if low brachial systolic pressure is perceived by physicians as a contraindication to the use of arterial dilator drugs such as nitrates, carvedilol, and candesartan in systolic heart failure. Meredith et al. (1) extended results of previous studies (AHeFT [African-American Heart Failure Trial (2)] and COPERNICUS [Carvedilol Prospective Randomized Cumulative Survival (3)]) in showing that an arterial vasodilator was at least as effective in trials of cardiac failure for improving outcomes in patients with systolic blood pressure (SBP) <100 mm Hg (whose left ventricular ejection fraction averaged 25%) as in those with normal or high SBP and without appreciable risk of causing symptomatic hypotension.

The paradox arises from exclusive consideration of brachial rather than central pressure (4) and from assuming that effects of dilator drugs on high-resistance arterioles dominate over effects on low-resistance conduit arteries. Arterial vasodilator drugs such as nitroglycerin reduce wave reflection (5,6) and "trap" reflected pressure waves in the peripheral circulation so that they do not summate with central systolic pressure, with this differentially reduced compared with brachial SBP (4,6). In patients with a low left ventricular ejection fraction and the ventricle contracting weakly and acting (in engineering terms) as a "pressure source" (6,7), reduction in aortic and left ventricular systolic pressure leads to increased left ventricular ejection from the heart (6,7). Such an increase in stroke volume can maintain or increase SBP in patients with cardiac failure due to systolic dysfunction.

The paradox described by Meredith et al. (1) is explicable. It explains why drugs that dilate muscular arteries and reduce wave reflection are very effective for reducing systolic pressure in hypertension when the heart is contracting normally (i.e., as a flow source) (6,7) and for increasing cardiac output in patients with heart failure when the heart's contraction is weakened, and it acts as a pressure source (6,7).

Consideration of blood pressure, cardiac output, and peripheral resistance is insufficient to explain the function of the pulsating heart and blood vessels. These comments are offered without any criticism of the excellent work of Meredith et al. (1).

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Please note: Dr. O'Rourke is the founding director of AtCor Medical, Sydney, Australia, maker of a pulse-wave analysis system.

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Cardiac Resynchronization in Mildly Symptomatic Heart Failure and Asymptomatic Patients

I read with interest the results of the REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) trial in the paper by Linde et al. (1). The trial concluded that cardiac resynchronization therapy, in combination with optimal medical therapy, reduces the risk of heart failure hospitalization and improves ventricular structure and function in New York Heart Association functional class I and II patients with previous heart failure symptoms. I think that it is worth noting that the studied population was composed of patients having significantly prolonged QRS duration (average 156 ms) as well as quite severe

dilated left ventricular end-diastolic dimensions (average 70 mm). Hence, one should be careful when considering these results in the heart failure patients of New York Heart Association functional classes I and II.

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Redox Regulation of Post-Prandial Vascular Endothelial Dysfunction

Prophylactic Benefits of High-Intensity Exercise

Tyldum et al. (1) elegantly demonstrated that an acute bout of high-intensity interval exercise (HIE) provides superior prophylaxis against post-prandial vascular endothelial dysfunction compared with an isocaloric bout of continuous moderate-intensity exercise. The post-prandial maintenance of brachial artery flow-mediated vasodilation was attributed to an enhanced mobilization of antioxidants into the systemic circulation, which was shown to be exercise-intensity dependent. The authors speculated that by neutralizing lipemia-induced oxidative stress, HIE preserved endothelial function subsequent to an increase in vascular nitric oxide (NO) bioavailability. Given the limited assessment of free radical metabolism, I would like to raise some additional points for consideration and indeed proffer an alternative interpretation at least for their metabolic findings.

The authors referred to our study, which documented an exercise-induced mobilization of lipid soluble antioxidants into human skeletal muscle (2). Within the context of their observed HIE-induced increase in (blood borne) total antioxidant status, this was taken as evidence that "acute [HIE] exercise tends to tip the pro- and antioxidant balance in favor of increased antioxidant status." However, this interpretation is incorrect because multiple biomarkers of free radical–mediated lipid peroxidation, end point determinants of oxidative stress (regardless of the antioxidant response), were shown to increase markedly. Thus, the exercise-induced mobilization of antioxidants into both muscle and blood serves to limit, although clearly not terminate, oxidative stress, which, despite the body's best (antioxidant) efforts, ultimately prevails.

Furthermore, increased vascular lipid free radical formation does not necessarily translate into reduced endothelial NO bioavailability (3). Whether the observed elevation in total antioxidant status illustrated in Figure 2 of Tyldum et al. (1) (≈150 μmol compared with the continuous moderate-intensity exercise trial, which, in contrast, was characterized by impaired endothelial function) was sufficient to outcompete "inactivating species" such as superoxide ($O_2^{\cdot-}$ + $NO^{\cdot}$ → $ONOO^-$, k = ≈10^9 M/s) to liberate an "additional" pocket of (endothelial) NO is also from a thermodynamic standpoint questionable given the pharmacological concentrations of (for example) ascorbate required to achieve such an effect (>1 mM, which equates to roughly 20-fold the ambient plasma concentration). Finally, I would argue that it is the rate of antioxidant depletion that is more important than the absolute baseline concentration because it likely reflects the dynamics of consumption due to the sacrificial scavenging of free radicals. Thus, if anything, the HIE (and indeed the continuous moderate-intensity exercise) group exhibited a blunted antioxidant response compared with the control (no exercise) group.

Is it conceivable, given that the antioxidants were confined to the intravascular space, that the exercise intensity-dependent elevation in plasma total antioxidant status does not represent a priming of the body's endogenous antioxidant defenses but is merely a hemoconcentration artifact subsequent to plasma volume loss (4), further perpetuated by food intake? As little as 30 s of high-intensity exercise has been shown to depress plasma volume for as long as 24 h into recovery, which, incidentally, was associated with increased oxidative stress despite the blood's best efforts to elevate retinol and α-tocopherol (5). Although the superior cardioprotection afforded by HIE is indeed a fascinating and truly novel finding, further research is required to establish whether this is due to altered redox homeostasis.

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