from Servier. Dr. Pedersen served on the advisory board for Roche Diagnostics in 2012 for a special issue of Lung Cancer Screening. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The DLCST (Danish Lung Cancer Screening Trial) trial was funded in full by a governmental grant by the Danish Ministry of Health and Prevention from 2004 to 2011. Danish Lung Cancer Screening Trial [DLSCT]; NCT00496977.

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Letters to the Editor

The Way to Determine Coenzyme Q

Coenzyme Q (CoQ, ubiquinone) is a lipophilic molecule present in all cells, located mainly in the inner mitochondrial membrane. It is composed of a redox active benzoquinone ring conjugated to an isoprenoid chain. The length of the chain differs among species; in humans, it contains predominantly 10 isoprenoid units (CoQ_{10}). The synthesis of this chain shares the mevalonate pathway with cholesterol and dolichol biosynthesis (1), in which 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-Co A) reductase is a key enzyme and target for statins. CoQ shuttles electrons from complex I and complex II, to complex III of the mitochondrial respiratory chain. It also functions as a lipid-soluble antioxidant, and is involved in multiple aspects of cellular metabolism, including pyrimidine nucleotide biosynthesis and beta-oxidation of fatty acids (1).

Recently, Larsen et al. (2) studied the role of simvastatin on skeletal muscle of patients with hypercholesterolemia. This work indicates that simvastatin compromises glucose intolerance and decreases insulin sensitivity, and also indicates a decrease of coenzyme Q_{10} (CoQ_{10}) in human skeletal muscle. However, these results are based on an analytical mistake because the authors have confused the lipid antioxidant CoQ_{10} with the encoded protein by the *COQ10B* gene. *COQ10B* encodes for a mitochondrial protein that does not participate in CoQ_{10} biosynthesis and apparently contributes to CoQ_{10} function in respiration (3).

Their paper claims the changes of CoQ_{10} are caused by simvastatin, but the authors have analyzed the expression of Coq10b peptide using the antibody ab41997 (Abcam, Cambridge, United Kingdom), included in their Figure 6, that should not be confused with the lipid CoQ_{10} content. The analysis of CoQ_{10} is carried out in hexane-ethanol extracts by a high-performance liquid chromatography system with a C18 reversed-phase column and an electrochemical detector (4). This approach has previously demonstrated that statin drug–related myopathy is associated with a mild decrease in muscle CoQ_{10} concentration (5). The overall work of Larsen et al. (2) is not invalidated by this comment, but the results on CoQ_{10} levels should be revised.

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Reply

We appreciate the comment from Dr. Navas regarding our recent report on simvastatin's effect on skeletal muscle (1).

We agree with Dr. Navas that the coenzyme Q–binding protein COQ10 homolog B (COQ10B) was measured. As Dr. Navas writes in his letter, COQ10B is essential to the function of coenzyme Q10 (CoQ10) in regard to mitochondrial respiration (1). In a paper by Barros et al. (2), it is suggested that COQ10B in yeast is binding coenzyme Q6 (CoQ6), which is necessary for CoQ6 to transport electrons in the electron transport chain, which subsequently leads to the transport of electrons and production of ATP (2). CoQ6 is present in yeast and bacteria, and is equivalent to CoQ10 in humans (3). Previously, it has been reported that statin treatment decreases the amount of CoQ10 in skeletal muscle (4), and in combination with the results from our present report observing a reduced content of COQ10B (1), this indicates that statin treatment has a similar effect on CoQ10 and COQ10B.

COQ10B is essential for electron transport in the mitochondrial electron transport chain, and therefore, we believe that our conclusion in the report is valid, as Dr. Navas also writes in his letter.

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Sex Differences and Arterial Stiffness

Die Methode ist Alles

We are concerned about methods used by our esteemed colleagues, Coutinho et al. (1), and question their conclusion, based on higher characteristic impedance (Z_c) and lower total arterial compliance (TAC), that the aorta and large elastic arteries of women are stiffer than those of men. Both calculated Z_c and TAC relate volume to pressure without scaling. The aorta of a child is small. With growth, Z_c decreases and TAC increases, but this cannot be interpreted as lower stiffness because arteries become more, not less, stiff with age (2). Likewise, small animals have higher Z_c and lower TAC than larger animals. Because there are systematic differences in weight and height between male and female adult cohorts (2), the (smaller) females will appear to have stiffer arteries (i.e., higher Z_c and lower TAC) than men if not appropriately scaled for body size. When appropriately scaled to aortic cross-sectional area in Table 1 of Coutinho et al. (1), Z_c in males ($172 \times 10\ cm^2 = 1{,}720$ dynes $\cdot$ s $\cdot$ cm^{-3}) and in females ($211 \times 8.3 = 1{,}751$ dynes $\cdot$ s $\cdot$ cm^{-3}) are virtually identical. With the same scaling, TAC also appears identical.

Scaling is used elsewhere in the authors' data analysis, but not consistently. Smaller echo dimensions in females are consistent with smaller body size (Table 1 [1]). Height and weight are not provided in the table, text, or online appendix.

The authors' Table 1 (1) contains many anomalies that ought be considered and explained. Amplification of the pressure wave between the central and peripheral sites is 3%, not 5%, in males, and −3%, not zero, in females. Both values are much lower than measured invasively (2). Mean pressure, calculated as (brachial diastolic blood pressure $\times$ 2 + systolic blood pressure) $\div$ 3 (data supplement [1]), is 93, not 97, mm Hg for males and 92, not 98, mm Hg for females. Values for left ventricular (LV) outflow tract diameter must be centimeters, not millimeters (i.e., 2.3 cm male, 2.0 cm female). Taper in diameter of 55% in males (35.6/23.0) and 63% for females (32.6/20.0) over a length of <5 cm between the LV outflow tract and site of aortic diameter measurement (which we do not challenge) must create secondary flow and turbulence in the aorta (2). There is concern also on the low value of pressure amplification compared with those in the authors' reference 9 (1) and in the paper by Safar et al. (3) in the same issue of the *Journal*.

The authors are highly respected clinical investigators and colleagues, and may not be aware of the aforementioned anomalies, if their data were analyzed in an outside center without adequate technical scrutiny. We have not been able to trace the source of the quoted "NIHem" on the Internet. We need stress in papers such as this, Carl Ludwig's dictum: "Die Methode ist Alles" (2).

Differences in arterial hemodynamics between adult males and females do exist, but can be attributed to shorter body length with earlier return of wave reflection, and hence, greater aortic pressure augmentation in females (the authors' Table 1). Such greater pressure augmentation accounts for impaired LV relaxation and the higher prevalence of diastolic heart failure in females (2). In this, we certainly agree.

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Please note: Prof. O'Rourke is the Founding Director of AtCor Medical and significant shareholder.

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Reply

We thank Drs. O'Rourke and Safar, on behalf of all the authors, for their interest in our paper (1). They highlight the importance of "scaling" for aortic size, given the known inverse relationship between aortic diameter and characteristic impedance (Z_c) (2). The multivariable models presented in our study (1) adjusted for aortic diameter as a measure of body size and demonstrated that women had higher Z_c even after adjusting for aortic size. The augmentation index (AIx) was indeed higher in women than men in our study, but was not associated with left ventricular diastolic function or ventricular–arterial coupling. In our cohort of older, predominantly hypertensive participants, increased proximal aortic