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observed by others in patients with coronary artery disease undergoing dobutamine-stress (2). However, the PET technique enabled us to detect very early changes in myocardial blood flow before these clinical signs of ischemia eventually developed. Since we know that the presence of clinical signs of ischemia are inconsistent, subjective and variable in the same patient, we decided to focus on quantifiable, regional measures of myocardial blood flow.

In contrast to Dr. Langobardi's statement, there are data about the anti-ischemic effect of quinapril on clinical variables of myocardial ischemia in patients with coronary artery disease. Bussmann et al. (3) have previously reported the results of a randomized, double-blind, cross-over study of 16 men with coronary artery disease receiving oral quinapril or placebo. They were able to show that quinapril (10 mg) lead acutely, and after two weeks of treatment, to a significant reduction in the extent of ST depression during exercise electrocardiogram.

Taken together these data indicate that quinapril has an anti-ischemic potential. However, we agree with Dr. Langobardi and have this clearly stated in our paper, that we do not treat myocardial blood flow values but patients with coronary artery disease. Therefore, the unique, anti-ischemic potential of quinapril in the treatment of patients with coronary artery disease must be substantiated in large clinical trials. From our data quinapril seems to be a promising choice for such studies.

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Pressure Relaxation of the Left Ventricle and Filling Pressures

We read with great interest the article by Senzaki et al. (1). In a careful study, the authors contrasted various methods for assessing the time constant tau of left ventricular (LV) pressure decay. They observed that pressure relaxation consistently deviated from a monoexponential (ME) decay in dilated cardiomyopathy and concluded that this deviation induced inaccuracies in the interpretation of the time constant tau. They proposed that the use of the hybrid-logistic (HL) method (2) resulted in more consistent data fits in various heart diseases.

The manuscript by Senzaki et al. yields important novel information on the analysis of LV pressure decay by focusing on the goodness of fit. Pressure decay is the best reflection of myocardial relaxation so far (3). Impaired myocardial relaxation will interfere with LV filling and result in elevated end-diastolic pressure (4). Senzaki et al. did not discuss the information that LV pressure decay might provide on incomplete myocardial relaxation and, as a consequence, on increased end-diastolic pressure. From a clinical and physiological point of view, it appears to us that this issue is at least as important as the goodness of fit.

We compared the ME method with the HL method. Single beat aortic clamping was performed in healthy hearts from dogs and rabbits (4). Leg elevation and phenylephrine administration were performed in coronary surgery patients (5). The goodness of fit was improved by the use of the HL-method in accordance to the paper under scrutiny. In these experimental and clinical studies, load dependence of LV pressure decay was less pronounced with the HL-method, but still was present and even highly significant. Changes in end-diastolic LV pressure induced by increasing cardiac load were closely correlated with relaxation rate, assessed both by the ME and HL methods (4,5). Of note, the ME method provided a better prediction of changes in end-diastolic pressure than did the HL method. The predictive value of the ME method was confirmed in more than 120 coronary surgery patients subjected to leg elevation (6).

Senzaki et al. suggested that increased load dependence of pressure decay in congestive heart failure, as was observed in dogs by Ishizaka (7) and in patients by Eichhorn (8), would not have been observed if these authors would have used the HL method. However, it should be noted that Ishizaka (7) not only reported increased load dependency of pressure decay (ME method) in cardiomyopathic hearts but also an upward shift of the diastolic pressure-volume loops. Eichhorn showed in a subsequent study (9) that load dependency of relaxation could predict the chronic response to a beta-adrenergic blocking agent and decreased in parallel with decreases in LV filling pressures.

Independently from its mathematical limitations and drawbacks, the ME time constant of LV pressure decay remains a good predictor of load-dependent changes of diastolic LV pressures. For this reason the previous reports on increased load dependence of pressure decay in cardiac overload and in diseased hearts keep for us their scientific and clinical value.

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REPLY

Dr. Leite-Moreira and colleagues raise important issues regarding relations between chamber loading, relaxation and end-diastolic pressure (EDP). They argue that load-induced relaxation changes importantly determine chamber EDP. Since the monoexponential-derived (ME) time constant better correlates with EDP than does an alternative hybrid-logistic (HL) parameter, they contend that this supports use of the former. Our study (1) also reported links between ME relaxation time constants and EDP; however, this was more attributable to mathematics, as changes in EDP for whatever reason (real or arbitrary) altered ME relaxation estimates even when the pressure decay waveform was unchanged. This was particularly true in depressed hearts due to systematic deviation of the ME model from actual pressure decline, and this same behavior largely explained apparent enhanced load-sensitivity of relaxation in such hearts.

There are many determinants of EDP: notably, intrinsic chamber stiffness and volume loading, extrinsic forces from the right heart and pericardium, atrial-ventricular interactions, and relaxation. However, for the last to affect EDP it must be very prolonged or the heart rate must be particularly fast, because otherwise there is sufficient time to complete relaxation during filling. Reported correlations between EDP and ME-relaxation rates do not imply a physiologic cause and effect dependence. For example, in one study (2) leg raising induced a 5 ms prolongation in relaxation, yet, relative to the constant heart rate of 90 min^{-1}, this change was small and hard to link to the EDP rise. On the other hand, preload increase with leg raising should elevate EDP and, thereby, raise the lower-range cutoff pressure for data subjected to relaxation analysis. As we showed (1) this alone can amplify apparent relaxation changes based on the ME model. Such behavior is particularly anticipated with depressed basal function observed in the prior study (2), but would be blunted by use of the HL model (1). In this sense, the improved EDP prediction by ME-tau changes noted by the authors may be more mathematical in origin.

In other studies of normal rabbit and canine hearts, coelevation of EDP with relaxation rate was observed only at very high afterloads from single-beat aortic clamping (3). Such nonphysiologic loading is different from the volume and pressure changes we and others employed (1,4,5). Here EDP rise could also be explained by increased end-systolic volumes with aortic occlusion, diminishing restoring forces that contribute to pressure decay (6). Also, the pressure at the onset of filling (that is, left atrial pressure) increases, which can elevate diastolic pressures at any relaxation rate (7). Similar maneuvers performed in isolated hearts in which the pressure at the onset-of-filling was constant revealed minimal EDP change (8).

Correlations between upward or downward diastolic PV-curve shifts or EDP and relaxation rate does not require physiologic causality. As we showed (1), this can largely stem from discrepancies between the decay-model indexing relaxation and actual pressure decline. These mathematical issues predict the stronger correlations between ME-decay and load-dependent changes in EDP that the authors note. Our analysis suggests caution when interpreting such data. Further studies testing these links with more targeted and selective manipulations are still needed to better separate the math from the physiology.

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