Endothelium-Dependent and -Independent Perfusion Reserve and the Effect of L-Arginine
on Myocardial Perfusion in Patients With Syndrome X

To the Editor:

We read the recent article by Bøttcher et al1 with interest. Unfortunately, the authors do not discuss their findings in the light of a previous study by our group.2 This study is quite relevant to their work and was published in Circulation 5 years ago. In our experiment, we also used positron emission tomography to measure myocardial blood flow (MBF) at rest and after the administration of intravenous dipyridamole in patients with syndrome X (n = 29) and in a substantial control group (n = 20). Our principal finding was that no significant differences existed between patients and controls with respect to myocardial blood flow (Figure 1). With a broader range of controls, Bøttcher et al’s corresponding figure (Figure 2) would probably not be distinguishable from ours.

Although Bøttcher et al’s data are quite consistent with ours in a number of respects, their interpretation of the data is perplexing. For example, on 2 occasions in the article, they state that basal MBF was elevated; however, their table shows that no significant difference was found for basal MBF between their patients and the age-matched controls. It is then suggested that an accumulation of adenosine in the extravascular component (caused by patchily distributed prearteriolar constriction or inadequate dilatation) offers a unifying hypothesis for the generation of pain and for the ECG changes observed. In our study, there were no demonstrable relationships among MBF, chest pain, or the dipyridamole-induced ECG changes; the clinical use of theophylline has been, for the most part, disappointing.

Although ultimately the authors offer “differences in patients’ characteristics” and the “heterogeneous nature of the disorder” as an explanation for discrepancies with other studies in the literature, more fruitful avenues for research on this topic, other than MBF, deserve attention (for example, Cannon’s3 recent work).

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Response

We thank Drs Rosen and Camici for their interest in our article. They raise several issues regarding the interpretation of our findings.

We acknowledge that a reference to their previous article could have been made. An important difference exists between the control group used in their study and the one in our study. Rosen et al’s population consisted of patients undergoing angiography due to atypical chest pain symptoms. The angiography and the ensuing exercise test were normal. In contrast, our control group consisted of healthy subjects with no chest pain symptoms. The difference is nicely illustrated in the figures provided by Rosen and Camici. In the control group of Rosen et al’s study, several controls have extremely low hyperemic flow values. This was not the case in our study. We hypothesize that some of the controls in Rosen et al’s
study may have subdetectable disease, which “dilutes” the difference in hyperemic blood flow between the patients and controls. Like Rosen et al, we did not find any difference in basal blood flow between the syndrome X patients and the age-matched control group. However, in the group B controls, resting perfusion was lower than that observed in the syndrome X patients. Because the 2 groups were not matched, we did not elaborate on this finding. Compared with the age-matched controls, the important finding is—as explicitly written in our article—reduced coronary blood in patients with syndrome X seems to be caused by a reduction of the increase in blood flow after dipyridamole and not by elevated basal myocardial blood flow.

The ECG changes referred to in our study occurred during exercise testing and not during dipyridamole administration, which rarely causes ECG changes even in severely ischemic patients. Regarding the effect of aminophylline treatment, several newer studies have documented an effect on at least some parameters.1,2

We agree with Rosen and Camici that measures other than myocardial perfusion may contribute to the understanding of the severe chest pain symptoms experienced by this patient group. Although the majority of the patients do not show metabolic or functional evidence of myocardial ischemia,3–5 ~40% have impaired coronary flow reserve.5 The mechanisms underlying this abnormality are not known, and it was the aim of our study to evaluate this particular point.

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