with the heparin group, and this therefore may skew the results considerably.

The demographic data in Table 1, which are not reported to be statistically different, are cause for concern. For example, only 1 (10%) of 10 heparin-treated versus 5 (38%) of 13 placebo-treated patients have a history of a previous myocardial infarction. A previous infarction causes maximal collateral development (4,5), and therefore the potential for improved collateral flow may be markedly diminished with any drug treatment or exercise program. The large preponderance of postinfarction patients in the placebo group would tend to bias the results in favor of heparin treatment.

The modest differences in the statistically significant results in the two groups after treatment may have no practical significance. Moreover, the authors state in the Results section that there were differences caused by heparin treatment when they were not actually statistically different. For example, with radionuclide ventriculography, "A decrease (2.5 ± 4.2%) in left ventricular ejection fraction with exercise at baseline was converted to a mean increase after 4 weeks of dalteparin sodium therapy ($p = 0.09$)." In the Discussion section, *nonsignificant* differences in exercise-induced left ventricular dysfunction between the two groups are touted to demonstrate the virtues of heparin treatment.

This study suggests a beneficial effect of low molecular weight heparin on myocardial ischemia that needs verification (as they plan) in larger patient groups. However, the mechanism(s) by which this salutary effect occurs is not defined by this study. Low molecular weight heparin may help open preformed collateral channels, but unfortunately there were only indirect measures of coronary collateral flow studied, and certainly nothing to document the occurrence of coronary angiogenesis. Alternatively, heparin may provide a positive effect through its anticoagulant action in capillaries, or it might decrease oxygen demand (wall stress or ventricular contractility were not measured), dilate existing larger coronary vessels or even function by activating lipoprotein lipase in capillaries to increase triglyceride breakdown and increase free fatty acid levels. This effect has been shown to increase ventricular function with no increase in myocardial oxygen demands (5–8).

In a future study, the addition of more direct clinical measures of coronary flow, such as thallium ventriculography at rest and exercise, coronary arteriography to visualize collateral flow changes (collateral intensity score) or even positron emission angiocardiography, would document whether low molecular weight heparin treatment increased collateral flow. However, a more formidable task will be to prove that this drug promotes or modulates actual angiogenesis in humans.

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Reply

Robinson objects to the use of the term "angiogenesis" in the title of our study (1). Previous studies, using different animal models, have demonstrated that the combination of heparin and ischemia resulted in angiogenesis, that is, either an increase in size and thus function of preformed collateral vessels or new vessel growth (2,3). Our study was designed not to prove angiogenesis in the human heart but to investigate whether this putative action on collateral vessel growth of heparin compounds in combination with ischemia resulted in a clinically significant functional improvement in patients with ischemia.

We agree that there is no possible way of demonstrating true new vessel growth in a living human heart. Although it is suggested that improvement in angiographic collateral index would provide more convincing evidence for angiogenesis, it is well known that angiography does not demonstrate collateral vessels <200 μm, it is a poor measure of collateral function and is likely to be an inadequate measure of subtle changes in the size of existing collateral vessels (4). Thallium scintigraphy has similar drawbacks because it is not a quantitative measure of blood flow. Positron emission tomography would provide quantitation of regional myocardial blood flow, but we believed that in a pilot study neither this expensive modality nor repeat cardiac catheterization to examine the collateral index would be justified unless we could first demonstrate a functional improvement.

Robinson suggests that the modest improvement observed may be of "no practical significance." It must be pointed out, however, that improvement in the duration of exercise to ischemia by 2 min, to chest pain by 2.3 min and the 35% reduction in ischemia during ambulatory monitoring in the treated group is not trivial and compares with the improvement observed with conventional antianginal regimens. Although Robinson suggests, on the basis of the ambulatory monitoring data, that the placebo group may have had more severe ischemia, it should be remembered that the exercise duration to ischemia was in fact slightly longer in the placebo group. He also suggests that the improvement in left ventricular function might be due to changes in lipids. This, however, does not explain why ischemia measured as ST segment depression during exercise or Holter monitoring also improved.

To overcome the shortcomings of using any one functional index of myocardial ischemia in patients with coronary artery disease, we resorted to three different tests: treadmill exercise testing, ambulatory ST segment monitoring and exercise radionuclide ventriculography. Multivariate analysis was performed to detect whether the preselected five variables derived from these tests as indirect indexes of collateral function improved with dalteparin sodium administration, even when individually these were not statistically different because of the small number of patients and the heterogeneity among the patients. The other purpose of this *pilot* study was to elucidate what the size of the population would have to be in a full-scale definitive study, given the variability of patients with coronary artery disease.

As previously, the improvement seen in our patients is most likely, but certainly not definitively, due to an increase in collateral

function, and we believe that the study serves as a useful preliminary step to examine this novel approach for treatment of myocardial ischemia.

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