examine the variability in transient ischemia that occurs during daily activity, as Benhorin et al. and others have demonstrated (1,7,8). Benhorin et al. (1) incorrectly describe our submaximal exercise as one in which the work load increases gradually (3). In fact, in three of the studies, after determination of effort tolerance, the patients exercised at a fixed work rate that elicited ~70% of the peak heart rate attained during the Bruce protocol (3–5). This is similar to that in which many patients engage during cardiac rehabilitation exercise as well as during daily activities. Our data show that the ischemic threshold varies under these exercise conditions. Thus, the conclusions of Benhorin et al. (1) can only be applied to the specific protocols used.

In conclusion, although the study by Benhorin et al. (1) demonstrates a similarity in the ischemic threshold between two specific test protocols, it is clear that the ischemic threshold is not fixed under all circumstances. Indeed, Benhorin et al. (1) have shown that the ischemic threshold during ambulatory activity differs sharply from that seen with either the Bruce or the Davidson protocol.

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Reply

We thank Garber et al. for their comments on our recent publication in the Journal (1).

In our study we elected to compare the results of the Bruce and the modified Davidson exercise protocols because these are two common protocol prototypes, differing mainly in their work load increase rate, and our results are naturally mainly applicable to exercise protocols that are similar to those we used.

On the other hand, Garber et al. (2) compared the ischemic thresholds during an "incremental" versus a "fixed work load" submaximal exercise test and documented a significantly lower ischemic threshold during the latter than during the former. Despite the lower ischemic threshold during the fixed work load protocol, this protocol provoked ischemic electrocardiographic changes only in 85% of those patients who exhibited ischemic changes during the "incremental" exercise protocol. Moreover, more patients (82%) remained asymptomatic during this protocol than during the incremental protocol (52%).

The significant difference in the ischemic threshold between ambulatory monitoring and exercise testing that was documented in our study (1) is strengthened by the findings of Garber et al. (2) and, indeed, it seems that a "fixed work load" exercise protocol simulates better regular daily activity than an "incremental" exercise protocol.

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Angiogenesis and Low Molecular Weight Heparin

I read with interest the article by Quyyumi et al. entitled the "Angiogenic Effects of Low Molecular Weight Heparin in Patients with Stable Coronary Artery Disease: A Pilot Study" (1). Initially, I was most intrigued by the title, which was even reprinted as a "teaser" on the cover of the Journal itself as "Angiogenesis and Low Molecular Weight Heparin." After carefully reading the study, I was disappointed to find that there were no data to support the authors' title, which implies that they had actually induced the growth of new coronary blood vessels in patients with angina.

The term "angiogenesis" was coined by A. T. Hertig (2) in 1935 when he described the development of new blood vessels in the placenta. This topic has been more recently discussed in detail by Folkman and Klagsbrum (3) in their 1987 review of angiogenic factors. Quyyumi et al. found in their study that low molecular weight heparin, when administered daily for 4 weeks, along with an exercise program tended to lessen stress-induced ischemia in patients with angina compared with placebo plus exercise. However, without presenting any data to suggest that there was actual growth of new coronary blood vessels in humans, the authors have no justification to use the very specific term "angiogenic" in their title.

Another concern involves the confounding heterogeneity of their small patient groups. The large standard deviations of the baseline functional data, such as the results of treadmill exercise (Table 2), make it highly unlikely that a statistically significant difference would be seen among groups, even if there truly was a difference in the degree of baseline ischemia—a so-called type II statistical error. For example, the pretreatment mean duration of ischemic episodes monitored at baseline by ambulatory ST segment monitoring in the heparin group (n = 10) was 112 ± 105 versus 171 ± 171 min in the placebo group (n = 13). There is a real suggestion that the placebo group may have had much more severe baseline ischemia compared

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