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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References

1. Benhorin J, Pinsker G, Moriel M, Gavish A, Tzivoni D, Stern S. Ischemic threshold during two exercise protocols and during ambulatory electrocardiographic monitoring. J Am Coll Cardiol 1993;22:671–7.
2. Carleton RA, Siconolfi SF, Shafique M, Bouchard P. Delayed appearance of angina pectoris during low level exercise. J Cardiac Rehabil 1983;3:141–8.
3. Garber CE, Carleton RA, Camaione DN, Heller GV. The threshold for myocardial ischemia varies in patients with coronary artery disease depending on the exercise protocol. J Am Coll Cardiol 1991;17:1256–62.
4. Heller GV, Ahmed I, Tilkemeier PL, Barbour MM, Garber CE. Comparison of chest pain, electrocardiographic changes and thallium-201 scintigraphy during varying exercise intensities in men with unstable angina pectoris. Am J Cardiol 1991;68:569–74.
5. Heller GV, Ahmed I, Tilkemeier PL, Barbour MM, Garber CE. Influence of exercise intensity on the presence, distribution and size of thallium-201 defects. Am Heart J 1992;123:909–16.
6. Pupita G, Kaski JC, Galassi AR, et al. Ischemic threshold varies in response to different types of exercise in patients with chronic stable angina. Am Heart J 1989;118:539–44.
7. Deanfield JE, Maser A, Selwyn AP, et al. Myocardial ischemia during daily life in patients with stable angina. Lancet 1983;2:753–8.
8. Schang SJ, Pepine CJ. Transient asymptomatic S-T segment depression during daily activity. Am J Cardiol 1977;39:396–402.

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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References

1. Benhorin J, Pinsker G, Moriel M, Gavish A, Tzivoni D, Stern S. Ischemic threshold during two exercise testing protocols and during ambulatory electrocardiographic monitoring. J Am Coll Cardiol 1993;22:671–7.
2. Garber CE, Carleton RA, Camaione DN, Heller GV. The threshold for myocardial ischemia varies in patients with coronary disease depending on the exercise protocol. J Am Coll Cardiol 1991;17:1256–62.

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