our model brady- and tachyarrhythmias and hypotensive episodes were managed with little or no help after the early training was completed. Since no serious complications occurred during any procedure, we cannot comment on the ability of the physician assistant to deal with these but would anticipate a high level of able participation.

While it is true that clinical practice and research can be combined, the amount of research that can be performed will be importantly influenced by the amount of time spent in clinical care. Our article creates no imperative for others to do what we have done. It simply suggests an option and we believe that it is best to leave it to the discretion of individual academicians to allocate their time rather than decide for them.

The physician assistant in this project had become skilled in the evaluation and management of patients with heart disease during the previous 6 years. The training protocol in the catheterization laboratory was not significantly different from that provided to fellows. She performed the third coronary arteriogram that she saw. The article describes all patients.

The time saving to the cardiologist results when the physician assistant performs procedures that would have been performed by the cardiologist, not simply by substituting a physician assistant for a fellow.

Our fellowship program is dedicated to producing academic cardiologists and is small. We have 6 or 7 fellows, of whom 3 or 4 cover the clinical services for the University and VA hospitals while the remainder engage in research. Performing all 1,600 catheterizations in these 2 hospitals would distort the fellows' training.

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30 November 1987

An Echo-Dense Mass in the Pericardial Space as a Sign of Left Ventricular Free Wall Rupture During Acute Myocardial Infarction

In the May 1, 1987 *Journal*, Knopf et al[1] reported the presence of an echo-dense mass in the pericardial space as a sign of left ventricular free wall rupture during acute myocardial infarction. I do not agree with their sentence "An echo-dense area due to organized thrombus has not been previously reported with myocardial rupture during acute myocardial infarction." In 1985 we reported a case of rupture of the free wall of the right ventricle diagnosed by 2-dimensional echocardiography.[2] Echocardiographic examination revealed an intrapericardial thrombus associated with a fissure of the inferior wall of the right ventricle. Other European reports enumerated in a recent article[3] also described such a sign of free wall rupture.

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17 November 1987

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Tissue Plasminogen Activator and Selective Coronary Vasodilation

It is generally accepted that the beneficial effects of tissue plasminogen activator (TPA) for recanalization of thrombotically occluded coronary arteries is based on its capacity for local, clot-specific fibrinolysis.[1,2] Unlike streptokinase and urokinase which, indirectly and directly respectively, result in conversion of plasminogen to plasmin (the enzyme that hydrolyzes fibrin) both within the general circulation and at the site of thrombus formation, TPA achieves thrombolysis by attraction of circulating plasminogen to the site of the fibrin clot and converting it to plasmin locally.[3] In addition to its fibrinolytic effect, plasmin is known to mediate the conversion of prekallikrein (from the α-2-globulin fraction of plasma) to kallikrein with the latter subsequently mediating the conversion of kininogen to bradykinin.[4] Bradykinin has been shown to be a powerful vasodilator of coronary (and other) arteries,[4–6] which is believed to be mediated at least in part by endothelial-derived relaxing factor.[7] It would therefore seem highly appropriate to explore the feasibility of increasing the effectiveness of TPA at sites of acute threatening coronary occlusion by maximizing the effect of bradykinin at these sites.

Under physiologic conditions bradykinin is kept in check by inactivation at the endothelial cell level by kininase II, which has been shown to be identical with angiotensin converting enzyme (peptidyl dipeptidase).[8,9] Further study is necessary to confirm whether diminishing the effect of angiotensin converting enzyme by treatment with an inhibitor similar to captopril[10] might augment the recanalization by TPA of thrombotically occluded arteries by reducing the inactivation of bradykinin by adjacent intact endothelium. It may be argued that systemic vasodilation in the face of myocardial ischemia is not without risk. However, this must be weighed against the potentially grave consequences of acute coronary occlusion.

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Adi Kurgan, MD, PhD
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17 November 1987

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Blood Pressure Changes Above and Below the Anaerobic Threshold

In the June 1987 issue of the *Journal* (59:1342–1344), Spence et al reported that the systolic blood pressure (BP) response was greater above the anaerobic threshold than it was below the anaerobic threshold of progressively increasing bicycle ergometry. Diastolic BP rose below the anaerobic threshold, but fell above the anaerobic threshold. Use of time as an index of physical work, as employed by Spence et al, is acceptable only if oxygen consumption increases in the same incremental manner. This criterion was not met in the study. The proper variable to correlate with BP is oxygen consumption, since this variable represents the metabolic work that the body is performing during exercise. Time does not represent metabolic work. We used the material provided by the authors in Table I and regressed oxygen consumption on systolic and diastolic BP. The following lines are formed.

Systolic BP = $43.2 \times VO_2 + 124.5$,

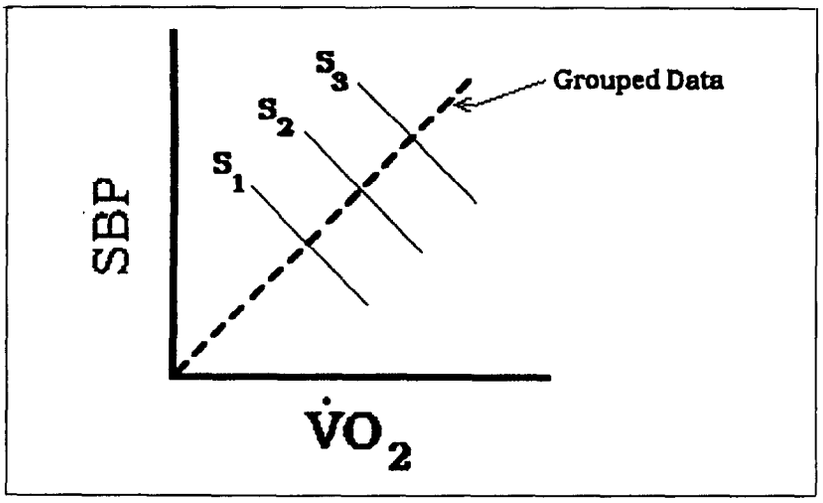

FIGURE 1. Hypothetical slope.

below anaerobic threshold
Systolic BP = 27.4 × VO_2 + 150.9, above anaerobic threshold
Diastolic BP = 9.6 × VO_2 + 82.3, below anaerobic threshold
Diastolic BP = −5.3 × VO_2 + 100.0, above anaerobic threshold.

Since the slope of the line formed for systolic BP below anaerobic threshold is greater than that above the anaerobic threshold, we conclude that systolic BP increases more rapidly for a given increase in oxygen consumption below the anaerobic threshold than above this point. This is the opposite of the authors' conclusion, which employs time as a measure of work. Using time as the independent variable, the authors arrive at the same conclusion for diastolic BP as we do using oxygen consumption as the independent variable.

The nonlinear response of BP above and below the anaerobic threshold of progressive bicycle ergometry is not a new observation. We found similar results, using oxygen consumption as the independent variable.[1] In this study, we showed that mean arterial BP increases below the anaerobic threshold, but does not increase further above the anaerobic threshold. If mean arterial BP is computed in the article by Spence et al, the following lines are obtained.

MAP = 20.8 × VO_2 + 96.3, below anaerobic threshold
MAP = 5.6 × VO_2 + 117.0, above anaerobic threshold.

Consequently, these authors showed less of an increase in mean arterial pressure (MAP) above the anaerobic threshold, as well.

The precise cause and effect relations of cardiovascular and vasopressor hormone responses to the "anaerobic threshold" are poorly defined. We believe that this point should be assessed when doing an exercise prescription because it represents a significantly different hormonal and cardiovascular milieu.

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Paul M. Zabetakis
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23 November 1987

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REPLY: We appreciate the comments made by Gleim and Zabetakis regarding our report on the relation of BP to anaerobic metabolism.[1] Using grouped data, Gleim and Zabetakis indicate that the regression equations of systolic BP as a function of oxygen consumption demonstrate a greater slope below anaerobic threshold than above. This finding is not relevant to the relation between systolic BP and oxygen consumption for an individual subject. Their use of our grouped data confuses the effect of differences *among* subjects' levels for a given variable with the effect of changes *within* subjects for any variables. It is possible to conceive of situations in which the slope of the relation between variables for each subject is negative, while the slope or relation across subjects is positive (Figure 1 illustrates this notion).

Therefore, the finding of differences in slopes of systolic BP before and after anaerobic threshold is—and must be—based on the analysis of the individual subject's regression equations that we performed (see page 1343 of our article). The grouped data presented in our report illustrate a trend and are not appropriate for reanalysis. It is not possible to present all individual subject data in a condensed published report. Since we do not make a statement relating BP to oxygen consumption, the conclusion presented by Gleim and Zabetakis is not an opposite finding, as they state, but a different one.

When analyzing the rate of change of a variable that is related to a discrete event, it is tenable to relate this variable to time. We adjusted time for each subject to examine BP as related to a common physiological event—anaerobic threshold. Not only is time easily conceived by the investigator and reader alike, but time and workload are both relevant to the observed effects on systolic BP. Because workload increased linearly with time for each individual subject and because oxygen consumption increases with increasing workload, time may be used to characterize both the workload and oxygen consumption. In fact, we found correlations between time and oxygen consumption of 0.96 and 0.98 before and after anaerobic threshold, respectively.

The equation used by Gleim et al[2] for approximating MAP (MAP = 2/3 diastolic BP + 1/3 systolic BP) is questionable during conditions of increased heart rate. Because elevated heart rate is accompanied by a disproportionately shortened diastole, the temporal relation of systole and diastole change.[3] Thus, the mean arterial BP calculations should account for temporal changes in the cardiac cycle at higher heart rates. Since the pressure waveform may change shape as a function of heart rate, the simplified approximation to the BP curve offered by the equation may also vary in accuracy.

Our study protocol differed substantially from that of Gleim et al in several ways: (1) on average our subjects were 20 years older; (2) our study population included 25 subjects in contrast to their 8 subjects; (3) the subjects in our study were exercised to a submaximal endpoint; and (4) our study group included both hypertensive and normotensive subjects, all of whom had previously demonstrated a hypertensive response to exercise and reproduced this response during anaerobic metabolism.

The nonlinear response of BP under 2 conditions of metabolism, indeed, is new information—from both the earlier report of Gleim et al and our study. There are many indicating that systolic and mean arterial BP responses are progressively elevated and essentially linear as a function of graded exercise, heart rate, cardiac output and oxygen consumption. In the introduction to our report we cited a sample of these studies.

We agree with Gleim and Zabetakis that BP may respond differently under 2 metabolic conditions and, thus, is an important consideration in prescribing exercise in a clinical setting.

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Houston, Texas
16 December 1987

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