Importance of the Design of an Exercise Protocol in the Evaluation of Patients with Angina Pectoris

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SUMMARY
The severity of angina and the effects of therapeutic interventions in patients with coronary artery disease have been assessed by determining changes in both exercise performance and the triple product (TP) of heart rate, systolic pressure, and ejection time occurring at angina. However, the validity of conclusions based on such changes is uncertain since the effects of different exercise protocols on these variables have not been determined. Twelve patients with angina were studied during upright bicycle exercise; repeated bouts of exercise using a standard protocol of 20-w increments every three minutes produced no consistent changes in TP at angina. When exercise began 20 to 60 w above the work load of the standard protocol that produced angina, exercise capacity was reduced (average 1'40 vs. 4'40, P < 0.001), and triple product at angina exceeded control anginal values (average 4,840 vs. 4,150, P < 0.001). In the control studies nitroglycerin (TNG) and carotid sinus nerve stimulation (CSNS) enabled patients to exercise to a higher level, although the triple product at angina was unaltered. However, at the higher work load TNG and CSNS exerted only minimal effects on exercise capacity, indicating that if the work load is excessive, a reduction in myocardial oxygen consumption produced by a therapeutic intervention may be comparatively minor so that a potentially salutary effect would be masked. We conclude that work loads causing angina in less than three minutes cannot reliably be used for studying the effects of therapy. However, if progressive work loads are chosen which cause angina in the control studies in three to six minutes, exercise capacity and triple product at angina provide important information about the efficacy and mechanism of action of a therapeutic intervention.

Additional Indexing Words:
Bicycle ergometer     Myocardial oxygen consumption     Tension-time index
Rate-pressure product     Nitroglycerin     Carotid sinus nerve stimulation
Ejection time

Exercise is frequently used in the evaluation of patients with angina pectoris in order to determine the role of various therapeutic interventions in the treatment of this symptom. Patients commonly perform some standardized form of exercise with either the bicycle ergometer or motor-driven treadmill, and the duration of exercise is utilized to assess the effects of a therapeutic intervention. As knowledge accumulated regarding the determinants of myocardial oxygen consumption (MVO₂), it became apparent that the tension-time index and rate-pressure product provided an approximation of MVO₂. By means of such indices, it has been inferred...
that angina occurs during exercise at a relatively constant level of MV\(\text{O}_2\) in each patient. Thus, exercise testing has been employed to evaluate the efficacy of a therapeutic intervention both in terms of changes in exercise capacity and in terms of changes in the level of MV\(\text{O}_2\) associated with the development of ischemic pain.

It is a basic assumption in exercise studies of angina that changes in exercise capacity and indices of MV\(\text{O}_2\) are due to alterations brought about by the therapeutic intervention under test. However, it is not known what effect the exercise protocol itself has on these variables. It is also unclear whether differences in the design of exercise protocols affect their ability to uncover changes in exercise performance.

Accordingly, we studied the reproducibility of results in patients with angina pectoris using a standard exercise protocol and analyzing the effects of changes in this protocol on exercise performance, on the indices of MV\(\text{O}_2\) at which angina occurred, and on our ability to determine whether therapeutic interventions had succeeded in altering exercise performance. In addition, in order to evaluate the reliability of measurements of arterial pressure and ejection time made from a peripheral artery, we compared pressure pulse tracings simultaneously obtained from the central aorta and brachial artery at rest and during exercise.

**Methods**

Twelve patients were studied (table 1). Their ages ranged from 30 to 60 years (average 50 years). All gave a typical history of exertional chest pain present from 9 months to 18 years. Nine of the 12 patients had had one or more attacks of documented myocardial infarction in the past, as evidenced by characteristic electrocardiographic and enzyme changes. The presence of major coronary arterial disease was demonstrated in all patients by selective coronary arteriography.

The patients were brought to the exercise laboratory on at least two separate days prior to the definitive studies. They were exercised upright on a constant load bicycle ergometer calibrated in watts and pedaled steadily at about 45 rpm. In these preliminary trials exercise capacity was assessed by increasing the workload by 20 w every three minutes until the onset of angina, at which time patients stopped exercising. Repeated bouts of exercise were performed with 15-minute rest periods intervening until exercise performance was reproducible. The electrocardiogram was monitored continuously, using the manubrial-C\(_5\) (CM\(_4\)) bipolar lead with one electrode over the manubrium sterni and the other in the V\(_5\) position.

On the day of the definitive investigations, the patients were studied in the fasting state. No premedication was given. A 75-cm catheter (no. 5 Elecath) with end and side holes was introduced by Seldinger technique into the left brachial artery under local anesthesia and advanced under fluoroscopic control until its tip lay in the descending part of the aortic arch. In addition, in six patients a 4-inch no. 20 Teflon catheter was also introduced into the right brachial artery by Seldinger technique for peripheral arterial pulse recordings. Both catheters were connected to Statham 23Db pressure transducers, and arterial pressures were recorded on a multichannel direct-writing recorder. Manometer zero was set at 10 cm below the sternal angle. Recordings were taken continuously at 0.25 mm/sec paper speed with 50 mm/sec recordings at half-minute intervals for measurement of the heart rate and ejection time (onset of rise of pressure pulse to the incisura, in seconds). The product of heart rate (beats/min), systolic arterial pressure (mm Hg), and ejection time (sec), subsequently termed the *triple product*, was calculated and used as an approximate index of MV\(\text{O}_2\).

During the definitive studies the load on the bicycle was increased by 20 w every three minutes until angina occurred; the initial work level was chosen so that each patient experienced angina during the second level (three to six minutes of exercise). This exercise protocol will henceforth be referred to as the standard protocol.

The response to exercise with the standard protocol and the changes in exercise performance and the indices of MV\(\text{O}_2\) at angina caused by modifications in the standard protocol were studied as follows:

1. In order to test the reproducibility of exercise when no therapeutic intervention was employed, patients performed three or more serial bouts of exercise with the standard protocol of 20-w increments every three minutes with intervening rest periods of at least 15 minutes.

2. The effects of placebo were studied by comparing the exercise response after placebo
Table 1

Clinical Data on Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of symptoms</th>
<th>Previous myocardial infarction</th>
<th>ECG</th>
<th>LV cine</th>
<th>Coronary angiography*</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.K.</td>
<td>49</td>
<td>M</td>
<td>18 months</td>
<td>No</td>
<td>Normal</td>
<td>Normal</td>
<td>Stenosis of left circumflex and LAD</td>
<td>TNG</td>
</tr>
<tr>
<td>A.M.</td>
<td>59</td>
<td>M</td>
<td>7 yr</td>
<td>Yes</td>
<td>Old diaph MI</td>
<td>Normal</td>
<td>Triple vessel disease</td>
<td>Propranolol, digitalis, TNG</td>
</tr>
<tr>
<td>J.W.</td>
<td>52</td>
<td>M</td>
<td>5 yr</td>
<td>No</td>
<td>LVH</td>
<td>Normal</td>
<td>Triple vessel disease</td>
<td>TNG</td>
</tr>
<tr>
<td>H.G.</td>
<td>48</td>
<td>M</td>
<td>18 months</td>
<td>Yes</td>
<td>Old anterolateral and posterior MI</td>
<td>Poorly contracting LV</td>
<td>Triple vessel disease</td>
<td>TNG</td>
</tr>
<tr>
<td>P.D.</td>
<td>46</td>
<td>M</td>
<td>7 yr</td>
<td>Yes</td>
<td>Ischemic ST changes</td>
<td>Paradoxical movement apex; akinesia anterolateral wall</td>
<td>Triple vessel disease</td>
<td>TNG</td>
</tr>
<tr>
<td>O.H.</td>
<td>61</td>
<td>M</td>
<td>12 yr</td>
<td>Yes</td>
<td>Old anterior MI</td>
<td>Poorly contracting LV; akinetic apex</td>
<td>Triple vessel disease</td>
<td>TNG, diuretic, CSNS</td>
</tr>
<tr>
<td>B.L.</td>
<td>61</td>
<td>M</td>
<td>8 yr</td>
<td>Yes</td>
<td>Old diaph MI</td>
<td>Poorly contracting LV; akinetic apex</td>
<td>Triple vessel disease</td>
<td>TNG, diuretic, CSNS</td>
</tr>
<tr>
<td>J.N.</td>
<td>60</td>
<td>M</td>
<td>10 yr</td>
<td>Yes</td>
<td>Old anterior MI</td>
<td>Normal</td>
<td>Triple vessel disease</td>
<td>CSNS</td>
</tr>
<tr>
<td>F.C.</td>
<td>53</td>
<td>M</td>
<td>18 yr</td>
<td>Yes</td>
<td>Old diaph MI</td>
<td>Normal</td>
<td>Triple vessel disease</td>
<td>CSNS</td>
</tr>
<tr>
<td>L.G.</td>
<td>30</td>
<td>M</td>
<td>2½ yr</td>
<td>Yes</td>
<td>Old diaph MI, old anterior MI</td>
<td>Poorly contracting LV</td>
<td>Triple vessel disease</td>
<td>TNG</td>
</tr>
<tr>
<td>D.L.</td>
<td>35</td>
<td>M</td>
<td>3 yr</td>
<td>Yes</td>
<td>Old diaph MI</td>
<td>Dyskinesia diaph wall</td>
<td>Total occlusion RCA; stenosis obtuse marginal Stenosis LAD; stenosis left circumflex</td>
<td>TNG</td>
</tr>
<tr>
<td>C.S.</td>
<td>48</td>
<td>M</td>
<td>18 months</td>
<td>No</td>
<td>Ischemic ST changes</td>
<td>Normal</td>
<td>Methyldopa, orinase</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MI = myocardial infarction; LVH = left ventricular hypertrophy; CSNS = electrical stimulation of carotid sinus nerves; LAD = left anterior descending coronary artery; RCA = right coronary artery; TNG = nitroglycerin; LV cine = left ventricular cineangiogram; diaph = diaphragmatic.

*Stenosis and triple vessel disease refer to areas of narrowing in excess of 75%.
with exercise when no placebo was given, the
order of the two exercise bouts being randomized.

3. In order to determine whether the work load
and triple product at which angina occurred
could be influenced by the duration of exercise
performed at subanginal levels, patients exercised
under conditions of the standard protocol, and
results were compared with those obtained when
exercise was started at a level 20 w lower than
the initial level in the standard bouts; the load
again was increased by 20 w every three minutes
until angina occurred. The order of the two bouts
of exercise was randomized.

4. We studied the effects on exercise performance
and triple product at angina of a
"supramaximal" work load, that is, a load 20 to 60
w greater than that required to precipitate angina
in the standard exercise bouts. Exercise capacity
and triple product were also determined at these
higher work loads after sublingual nitroglycerin
and electrical stimulation of the carotid sinus
nerves.

5. To compare the results of small increments
in exercise intensity with those obtained when
large increments were employed, the standard
protocol was altered so that although the work
load was still increased 20 w per three minutes,
this increase was achieved by 3- to 4-w
increments every half minute instead of abrupt
20-w increments every three minutes as in the
standard protocol.

6. Lastly, the patients exercised continuously
at work loads 20 to 40 w below the level at which
they had experienced angina in the standard
studies. This protocol was employed to determine
whether heart rate, blood pressure, and ejection
time reached constant levels during prolonged
bouts at subanginal work loads or whether these
determinants of MVO₂ continued to be affected
by the duration as well as the intensity of exercise.

Results

Exercise Performance*

1. Nine patients performed repeated bouts
of exercise using the standard protocol of 20-w
increments every three minutes. As shown in
figure 1, exercise capacity for any particular
individual changed relatively little; in no
instance did this alter more than 70 seconds
during the serial exercise trials. An analysis of
variance performed on these data, however,
revealed a small tendency for exercise capacity
to increase with successive exercise trails.
An increase averaging 21 seconds was demonstrable
during the second exercise bout
(\( P < 0.05 \)). A trend toward further increase in
exercise capacity was seen during subsequent
exercise trials, but this tendency was not
statistically significant. The triple product of
blood pressure, heart rate, and ejection time at
the onset of angina was unchanged for any
particular individual throughout the course of
the exercise trials (fig. 2). No trend toward
change was evident on analysis of variance
using the triple product data.

2. There was no significant difference in
time to angina and triple product at angina
between exercise with no prior treatment and
exercise with placebo when the order of the
untreated and placebo-treated exercise bouts
was randomized.

3. When exercise was begun at a level 20 w
lower than that used at the start of the
standard protocol and the intensity increased
by 20 w every three minutes, the triple
product at angina and the exercise level at
which angina occurred again did not differ

*Numbers correspond to those used in "Methods" section so as to facilitate identification of the specific experimental protocol employed in each problem under question.
Effects of serial exercise on triple product at angina. The triple product of systolic pressure (SP), heart rate (HR), and ejection time (ET) is on the vertical scale and the time at which the serial bouts of exercise were performed on the horizontal scale. For each patient the closed circles showing the values of triple product at angina are connected by solid lines.

significantly from the values obtained when the standard protocol was employed (fig. 3). Thus, patients developed angina at the same work load regardless of the work load at outset provided they exercised for longer than three minutes.

4. When patients exercised at loads 20 to 60 w above the level at which they developed angina in the control studies, exercise performance, as anticipated, was markedly reduced (average 1'40" vs. 4'40", P < 0.001), but triple product at angina exceeded control anginal values (average 4,840 vs. 4,150, P < 0.001) (fig. 4). When the standard exercise protocol was used, it was readily apparent that nitroglycerin and carotid sinus nerve stimulation enabled the patients to exercise to a higher level (fig. 5). However, at the higher work loads imposed during the supramaximal exercise studies, angina occurred so rapidly that it was far more difficult to appreciate any beneficial effects resulting from the administration of nitroglycerin or carotid sinus nerve stimulation.

5. When the work load was increased more gradually than in the standard protocol (3 to 4 w per 30 seconds), the level at which angina occurred and the triple product at angina were unchanged from values obtained when the work load was raised by 20-w increments every three minutes.

6. Three of five patients who exercised continuously at work loads which were between 20 and 40 w below the level at which they had experienced angina in the control

**Figure 2**

**Figure 3**

Effects on exercise capacity of reducing the initial work load. Each pair of vertical bars represents the results of two exercise bouts in each patient. The stippled bar represents values obtained during the standard protocol; the striped bar represents values obtained when exercise was begun at a level 20 w lower than in the standard protocol. The bottom of each bar represents the work load at the start of exercise; the top the work load at angina. The order in which the two exercises were performed was randomized. In each patient the work load at which angina occurred was identical for the two bouts.

**Figure 4**

Effect of "supramaximal" exercise bouts on exercise capacity and triple product. (Left) The duration of exercise to angina during control exercise using the standard protocol compared in each patient with the duration of exercise to angina using the supramaximal work load (see text). (Right) Triple product at angina during control exercise compared in each patient with triple product at angina using the supramaximal work load. Mean differences are indicated by the open circles on either side of each panel.

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bouts had no angina despite pedaling for over 12 minutes. The other two patients eventually reported angina, but this was not until one had exercised for 11.5 minutes and the other nearly 8 minutes. In the three patients who did not develop angina, a steady state was reached by about the fourth minute of exercise, the triple product remaining below the critical value at which angina occurred (fig. 6). In the two patients who eventually developed angina, the triple product slowly increased as exercise proceeded until it reached the critical value at which angina occurred.

Central and Peripheral Arterial Pulse Recordings

The brachial arterial systolic pressures at rest and during exercise were consistently higher than those recorded simultaneously from the aorta (fig. 7a). However, the increments that occurred from rest to exercise as measured in the aorta differed from those measured in the brachial artery in an unpredictable manner (fig. 7b). There was no correlation between either the absolute values of ejection time measured centrally and peripherally (fig. 7c) or between the direction of changes that occurred as a result of exercise (fig. 7d). In light of these findings, all values of systolic pressure and ejection time used to assess different exercise protocols and therapeutic interventions were obtained from central aortic pressure tracings.

Electrocardiographic Changes

With the CM5 lead for ECG monitoring, 9 of 12 patients demonstrated S-T segment abnormalities either at rest or on exercise. Three of 12 showed no S-T segment abnormalities. In these three, S-T changes were not
The results of this investigation demonstrate the practicability of studying the effects of an acute therapeutic intervention in patients with angina pectoris when an appropriate exercise protocol is employed. With our protocol serial exercise trials resulted in only minor changes in exercise capacity. No statistically significant changes in exercise capacity were detectable after the second exercise. In addition, serial exercise testing did not result in significant change in the triple product at angina for any given patient. Thus, it is reasonable to assume that any substantial changes in exercise capacity or triple product at angina which occur when this protocol is employed are due to the effect of the interposed treatment. Since small changes in exercise capacity occurred during the second exercise (average increase from the first bout was 21 seconds), additional assurance that all possible errors in interpretation are eliminated would be obtained if an initial warm-up exercise were employed.

Several factors probably contributed to the reproducibility of the results. First, all patients underwent several preliminary trials to familiarize themselves with bicycle exercise and the laboratory environment. These preliminary trials also enabled us to determine the work load at which angina occurred before the definitive experiments were performed. Second, adequate time (15 minutes) was allowed for recovery from each exercise bout. Third, progressive increments in exercise intensity were employed with the starting level chosen to ensure that angina occurred between the fourth and sixth minutes. This eliminated the possibility of the patient becoming fatigued if exercise were to proceed for too long a period before angina occurred. It also eliminated the difficulty in interpreting the effects of an intervention when angina was precipitated too soon after the start of exercise. Finally, we used a constant load bicycle ergometer. This bicycle also has a relatively large inertial component, especially helpful in minimizing the effects of sudden changes in pedaling speed that may inadvertently occur. Although the influence of the specific characteristics of the redwood
the bicycle employed in such studies is unknown, it is likely that this factor may be of importance and that careful testing of any different system should be undertaken before similar reproducibility of results is assumed.

While placebo therapy for angina pectoris has been estimated to give symptomatic improvement in about 39% of patients on continuous treatment and improvement in exercise performance after placebo also has been demonstrated in chronic drug studies, acute studies comparing the results of control and postplacebo exercise have failed to demonstrate any significant difference induced by placebo. The results of the present investigation, in which the order of exercise with and without placebo was randomized, confirm these latter findings. It would appear, therefore, that when an intervention is being tested for its therapeutic efficacy in patients with angina, an acute study would be more reliable and reproducible (if the characteristics of the intervention permit) than a chronic study in which many other variables are necessarily introduced.

In evaluating the causes responsible for changes in the exercise capacity of patients with angina pectoris, it is important to distinguish between an improvement in the circulatory response to exercise and an improvement in myocardial oxygen delivery. Systolic pressure, heart rate, and ejection time are among the major determinants of myocardial oxygen consumption and are thus important factors relating to the onset of angina. Robinson showed that angina occurred at reproducible levels of the product of heart rate and systolic pressure regardless of the work load imposed, and he therefore suggested that this product is an approximate index of myocardial oxygen consumption. This conclusion implies that when exercise performance improves in association with an increase in the rate-pressure product at the onset of angina, an augmentation in myocardial oxygen delivery probably is responsible for the improved exercise response. In contrast, if angina occurs at a higher intensity of exercise but rate-pressure product at angina is unaltered, then a more efficient circulatory response to exercise presumably is responsible for enhanced performance. Although changes in ejection time did not occur ordinarily, Robinson noted that after nitroglycerin, ejection time consistently changed, and with this intervention, the product of heart rate and systolic pressure corrected for the change in ejection time gave a better correlation with angina than the product of rate and pressure alone. The results of the present study confirm these findings and further serve to emphasize that when an attempt is being made to assess the effects of a therapeutic intervention on the level of MVO2 necessary to precipitate angina, all three variables must be considered.

An index of MVO2 incorporating blood pressure, heart rate, and ejection time still ignores changes due to alteration in ventricular size and in inotropic state, both major determinants of MVO2. The constancy of the triple product at angina in our own studies (except during supramaximal exercise, which may produce a transient disequilibrium between myocardial oxygen supply and demand) and in similar studies by Robinson suggests that alterations in exercising ventricular size and inotropic state may be safely ignored in the context of the interventions studied. During other circumstances, particularly those which are likely to alter greatly the exercising ventricular size or inotropic state, the possible influence of such changes on MVO2 must be carefully assessed.

Peripheral arterial systolic pressures have been employed in the calculation of the rate-pressure product or one of its variations in several studies of exercise performance in patients with angina pectoris. While our results indicate that the error introduced by using peripheral rather than central systolic pressures is small, a considerable error will result in assuming that the peripheral ejection time bears a constant relationship to the ejection time measured in the central aorta. The disparities between aortic and brachial arterial ejection times can be attributed to distortion of the pressure wave as it travels peripherally so that a trough in this wave has
little temporal relationship to the incisura of the aortic pressure tracing.\textsuperscript{18}

Our data emphasize the importance of utilizing increasing work loads individualized for each patient, rather than a single work load for the evaluation of all patients with angina. If the level used is below that necessary to cause angina and evokes a steady-state triple product response close to the critical level for ischemia (e.g., fig. 5, 50 w), only slight changes in the conditions of the experiment, possibly unrelated to the effects of any therapeutic intervention, could cause a long delay in the onset of pain. On the other hand, if the level used is considerably above that necessary to evoke angina in a given patient (e.g., a supramaximal level), the critical level of $\text{MV}_\text{O}_2$ necessary to precipitate ischemic pain may be exceeded so rapidly that any change in exercise performance caused by a therapeutic intervention could be difficult to identify. This is illustrated in figures 8 and 9. When our standard exercise protocol is employed, changes in exercise performance induced by nitroglycerin and carotid sinus nerve stimulation are clearly demonstrable. However, when the patient exercises at a work load which for him produces excessively high myocardial oxygen demands (fig. 8, 120 w; fig. 9, 80 w), the reduction in $\text{MV}_\text{O}_2$ produced by the therapeutic interventions is relatively minor; thus, their potentially salutary effects are masked. Studies employing a fixed work load protocol for all patients will risk having some patients exercising at excessively low or high work loads relative to their individual capacities, thus biasing the results for or against a particular therapeutic maneuver.

Figures 8 and 9, representative of the results found in the other patients, also demonstrate

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure8.png}
\caption{Comparison between the effects of nitroglycerin on exercise performance and triple product using the standard protocol and a "supramaximal" work load. Triple product is on the vertical scale and the time of exercise in minutes on the horizontal scale. Using the standard protocol, patient E.K. pedaled for three minutes at 40 w and then for 2.5 minutes at 60 w before having angina at 5.5 minutes (solid line to the right). At an initial work load of 120 w, angina occurred at just over one minute (solid line to the left). With the standard protocol nitroglycerin enabled him to pedal eight minutes to 80 w (interrupted line to the right), but at a work load of 120 w, the time to onset of angina was only slightly delayed when compared with the value attained at 120 w before therapy (interrupted line to the left). Both with and without nitroglycerin, the triple products at angina with the high work load were greater than the triple products at angina using the standard protocol.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure9.png}
\caption{Comparison between the effects of electrical stimulation of the carotid sinus nerves on exercise performance and triple product using the standard protocol and a "supramaximal" work load. The format is the same as in figure 8. Using the standard protocol, patient O.H. experienced angina at 40 w, exercising for 5.5 minutes. At a work load of 80 w, angina occurred at 1 minute and 40 seconds. With the standard protocol carotid sinus nerve stimulation enabled the patient to exercise seven minutes to 60 w (interrupted line), but at a work load of 80 w, the time to onset of angina was minimally delayed compared with the value attained at 80 w before stimulation. As in figure 8, the triple product at angina with the high work load exceeded the value using the standard protocol.}
\end{figure}
that the triple product after both nitroglycerin and carotid sinus nerve stimulation is lower both at rest and at any given exercise work load. If the triple product is a reasonable index of $\text{MVO}_2$, these findings would suggest that nitroglycerin and carotid sinus nerve stimulation improve exercise capacity primarily by reducing the rate of increase of myocardial oxygen demands rather than by augmenting myocardial oxygenation or increasing the patient's pain threshold. Such reasoning also implies that the increased intensity of exercise the patient can perform after nitroglycerin or carotid sinus nerve stimulation is probably not deleterious since the oxygen demands of the myocardium produced by the greater work loads probably do not exceed the oxygen demands produced by the lesser work loads in the control studies. In contrast, the triple product at the onset of angina is considerably increased when supramaximal levels of exercise are performed. The mechanism responsible for this triple product overshoot is uncertain. It is possible that a lag period occurs between the onset of ischemia and the patient's ability to recognize the resulting sensation as pain. Thus, because of the rapid increase in $\text{MVO}_2$ during such strenuous exercise, the patient may be unaware of the presence of ischemia until myocardial oxygen demands appreciably exceed the critical level at which angina is experienced. This finding suggests that sudden strenuous exercise associated with rapid rises in heart rate and/or blood pressure may be potentially harmful in a patient with angina pectoris because, under these circumstances, myocardial oxygen demands may far outstrip myocardial oxygen supply before the patient is warned by pain. A gradual increase in the intensity of activity, however, would not appear to engender the same risk since it would permit adequate time for recognition of the onset of ischemic pain and thereby minimize the possibility that a sudden and excessive increase in $\text{MVO}_2$ might occur.

We also found that both the intensity of exercise resulting in the precipitation of angina and the triple product at which angina occurs were unaffected either by substituting small for large increments in exercise intensity or by having the patient begin exercise 20 w lower than the level used in the standard protocol (fig. 3). In the latter situation exercise is merely prolonged an additional three minutes before the onset of angina. If long bouts of exercise are regularly employed, however, incidental factors such as fatigue may limit exercise performance and therefore complicate interpretation of the results. Consequently, it is preferable to adjust the work load so that patients have angina after three to six minutes of exercise in the control bouts since, when this is done, any improvement or deterioration in performance induced by therapy should be readily apparent.

The finding that the work load required to precipitate angina is constant regardless of the amount of preceding exercise performed at submaximal work loads suggests that for a given patient there is a stable relationship between a particular work load and its associated steady-state triple product (and, presumably, its myocardial oxygen cost). Thus, the work load which provokes angina results in a critical triple product, which for that particular patient results in myocardial ischemia. All antecedent submaximal work loads, always associated with subcritical triple products, fail to produce ischemia and therefore do not influence the onset of angina. Nitroglycerin and carotid sinus nerve stimulation appear to act by altering the relationship between work loads and their resultant steady-state triple product rather than by altering the critical triple product associated with angina.

The constancy of work load at angina for any particular patient suggests that in the evaluation of patients with angina pectoris due to coronary artery disease, measurement of work load during a standardized exercise test may be helpful in defining the restriction imposed by the angina. Patients may therefore be described as having 40-w angina or 80-w angina and so on, these levels determined by using our standard protocol. This functional classification would also add to the clinical
evaluation of the progress of the disease and more accurately describe the response to various therapeutic measures imposed.

While the conclusions of this study are based on data obtained from exercise performed in the upright position on the bicycle ergometer, it would be expected that similar conclusions would apply to protocols employing other methods of exercise evaluation, including the motor-driven treadmill. We prefer the bicycle ergometer since it causes less interference in electrocardiographic and hemodynamic recordings than treadmill exercise. It should be emphasized, however, that when the effects of an intervention on the triple product at angina are being assessed, the same mode of exercise should be used since preliminary findings in our laboratory indicate that at angina, heart rate, blood pressure, ejection time, and their product may be different with different types of exercise.

References
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