For the baseline volume, $V_n$, the relationship between left ventricular volume and circumference is

$$4) V_n = qC_n^3$$

where $q$ is a shape factor related to the (arbitrary) shape of the end-diastolic left ventricle (e.g., for a sphere $q = \frac{4}{3} \pi \frac{1}{d_2}$). The model also assumes that at end-diastole the wall thickness is a small fraction of the mean ventricular radius, then,

$$5) V = qC^3 = qSC'C'$$

so that, using 3) and 4)

$$6) V/V_n = S^3 = (C/C_n)^3$$

and from 2) and 6)

$$7) P(C) = a_1 + a_2 C + a_3 C^2 + a_4 C^3 + a_5 C^4 + \ldots$$

Using a Davidson-Fletcher-Powell nonlinear function minimization algorithm, the function 7) is fit to the observed control pressure-volume relationships. The output of this computer subprogram is a set of estimates of the three parameters $a_1$, $a_2$, and $a_3$. Using these parameters in 7), the analysis program computes the predicted pressure at each actually observed cubed circumference, using the minimum cubed circumference observed in the control period as $C_n$, the baseline circumference. The squared difference between this predicted pressure and the end-diastolic pressure actually observed gives an estimate of the variance of the observed pressures about the predicted pressure-volume curve, when summed over all points observed in the control period. A similar procedure gives the estimated variance about the same predicted pressure-volume curve in each ischemic period. The ratio of the estimated ischemic variance about the predicted pressure-volume curve to the control variance about the same curve yields the statistic $F$, which is used to test the hypothesis that the ischemic pressure-volume observations come from the same underlying pressure-circumference curve as that generated from the control observations. Thus, it can be inferred that ischemia does not alter any of the parameters $(a_1, a_2, a_3)$ which characterize the predicted pressure-volume relationship. Consequently, the parameters characterizing the pressure-volume relationship $(a_1, a_2, a_3)$ must remain unaltered by ischemia. Since left ventricular end-diastolic volume stiffness is determined by these parameters, it is concluded that end-diastolic volume stiffness is unaltered by ischemia.

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Heart Rate and Arterial Blood Pressure during Exercise in Patients with Angina Pectoris

Effects of Training and of Nitroglycerin

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SUMMARY

In 29 patients with typical exertional angina pectoris, intra-arterial systolic blood pressure (SBP), heart rate (HR), and the rate-pressure product ($RPP = HR \times SBP \times 10^{-2}$) were continuously recorded during repeated bouts of leg or arm exercise. Development of chest pain was independent of the workload and occurred at a fairly constant value of RPP, of HR, and of SBP in each patient for a given type of exercise, but the pain threshold values for all three variables were consistently higher during arm exercise than during leg exercise. The reproducibility of the pain threshold values was assessed for leg exercise. The variation, based on individual coefficients of variation, ranged from 1.3% to 13% (group mean, about 6%). There was no significant difference between the SBP values obtained by the traditional, noninvasive cuff technique and the values during intra-arterial monitoring.

In 25 patients a physical training program of an average of three months increased the maximal amount of work (watt × sec) performed before onset of pain by 100%. The most conspicuous effect of training on cardiac function was a 10% reduction of HR at a given workload, SBP being unchanged. Over-all, the data suggest that the increased exercise capacity caused by training could be accounted for by the reduction in the relation between RPP and external workload. The improvement in exercise capacity resulting from training was on the same level of magnitude as the 90% increase obtained in 11 untreated patients after administration of 0.25 to 0.50 mg of nitroglycerin sublingually prior to exercise. In contrast to the finding after training, nitroglycerin administered to subjects increased HR by 10%, but reduced SBP by 13%, RPP remaining unchanged. Therefore to explain the effect of nitroglycerin on exercise capacity additional economizing changes in myocardial performance (e.g., reduction of heart volume) are required.

IT IS WELL DOCUMENTED that most patients with angina pectoris on exertion develop an increased exercise capacity from a period of physical training. After training the patients are able to exercise for longer time at a given workload or sustain a higher workload before pain develops. The main reason for the increased exercise capacity is assumed to be a reduced myocardial oxygen consumption ($MV\bar{O}_2$) at a given total body oxygen consumption ($VO_2$). In patients with coronary artery disease, as well as in young healthy subjects, $MV\bar{O}_2$ can be estimated from the heart rate (HR) and the systolic blood pressure (SBP) or the product of these variables — the so-called rate-pressure product (RPP). Accordingly, anginal pain — which is supposed to reflect an insufficient myocardial oxygen supply in relation to the oxygen requirements — occurs at a fairly constant RPP threshold value in the individual patient both when provoked by exercise and when provoked by other situations which increase HR and SBP. Physical training reduces HR and often also SBP at a given $MV\bar{O}_2$ and thus in the trained state longer time and/or higher workloads can be reached before the critical RPP threshold value at which pain is elicited occurs. In addition a higher
anginal threshold for RPP has been observed after training, adding further to the improved exercise tolerance.\textsuperscript{5, 6}

The aim of the present study is to analyze further the relation between the onset of angina and the work of the heart during different types of exercise and to compare the effect of training and of nitroglycerin on this relationship.

Materials

Twenty-nine male patients, mean age 55 yrs, range 44--66 yrs, with exertional angina pectoris were studied. The diagnosis was based on a typical history and on the results from an exercise test including recording of the ECG and blood pressure by sphygmomanometer and on an evaluation of the effect of nitroglycerin on exercise performance. Clinically significant ST-segment depression (19 patients) or T-wave changes (7 patients) appeared in all but three patients during exercise, and all patients responded favorably to nitroglycerin. The patients were clinically stable. The duration of angina pectoris varied from three to 96 months (average, 31 months). Eight of the patients had suffered from one documented myocardial infarction and one patient had had three myocardial infarctions. On the average 25 months had elapsed from the last infarction to the initiation of this study. Eleven patients had angina only on exertion; seven also had attacks at rest but only rarely; seven patients regularly suffered from attacks of chest pain at rest, in four of whom the symptoms were typical of nocturnal angina. No patients had symptoms of cardiac decompensation indicated by edema or dyspnea at rest. One patient received digitalis and diuretics and four patients, who had been treated with a beta-receptor blocking agent for several months prior to their admittance, continued this medication during the study. The remaining 24 patients had received no antianginal drug other than nitroglycerin, which was taken when necessary. Before initiating the study the patients' informed consent was obtained.

Procedure and Methods

Exercise Tests

About a week prior to the study, a routine upright bicycle ergometer test was performed involving ECG recording and measurement of blood pressure with a sphygmomanometer. The lowest workload which provoked angina between 3 and 5 min after the start of exercise was determined as well as the highest load the patient could sustain for at least 1 min before onset of pain.

The baseline study with measurement of intra-arterial blood pressure during exercise was performed in the morning with the patient in the fasting state. Using the Seldinger technique, a catheter was inserted in the brachial artery and the tip advanced about 15 cm proximally. If arm exercise was included in the protocol, the femoral artery was cannulated and the tip of the catheter was placed in the abdominal aorta. The patient rested for 30 min after catheterization and resting values for ECG and blood pressures were obtained with the patient in the supine position.

An example of the protocol for the exercise tests is shown in figure 1. All patients exercised on the bicycle ergometer at three to four different workloads in the upright position.

Twelve patients performed two arm exercise periods (cranking) and 17 of the patients repeated one of the leg loads twice. Prior to the start of the last of these exercise periods 0.25 to 0.50 mg of nitroglycerin was administered sublingually. During all exercise bouts the patients were instructed to indicate the slightest sensation known to lead to an anginal attack. Exercise was continued until development of an unmistakable anginal attack. Practically all exercise periods were completed within five min. Between the exercise periods the patients rested on the ergometer at least 5--10 min after the pain had disappeared.

Post-training studies were performed according to exactly the same protocol as the pretraining studies in each patient. If pain was not provoked within 5 min at a given workload, exercise was stopped in order to allow repeated exercise bouts without exhausting the patients.

Leg exercise was performed on an electrically braked bicycle ergometer (Elema-Schönander). Arm exercise was performed on a mechanically braked ergometer (Monark, Sweden) modified for this type of exercise performed in the sitting position. Intra-arterial blood pressures and ECG in three precordial leads (V₁, V₄, V₅) were recorded continuously throughout the study. Arterial catheters were connected to an Elema-Schönander EMT 35 pressure transducer. Pressures were recorded on a direct writing recorder (Elema-Schönander, Mingograph 81). Both in the supine and upright position manometer zero was set at the mid-thoracic point of the anteroposterior plane at the fourth sternocostal joint. Throughout the study frequent calibrations were performed by water standards of reference corresponding to 50 and 100 mm Hg.

From the pressure tracings heart rate (HR) and arterial systolic blood pressure (SBP) were derived and the product $HR \times SBP \times 10^{2}$, the rate-pressure product (RPP),\textsuperscript{18} was calculated. In 11 patients the plasma volume was measured before and after training using $^{111}$I-labeled human albumin. Total blood volume was derived from the plasma volume and the hematocrit corrected for an average body hematocrit ratio of 0.91.

Training Program

All patients were invited to participate in a supervised training program and 25 completed such a program. The patients came to the laboratory daily, or three times a week, for training sessions lasting about one hour. The training included intermittent exercise on bicycle ergometer; exercise periods of normally 5 min duration were interrupted by resting periods of approximately the same duration. Four to six such periods were carried out on each training day. The workloads were individually tailored so that chest pain or discomfort normally occurred at the end of the 5 min period. In some patients nitroglycerin was used during the training sessions in order to allow sufficiently high workloads to obtain a training effect.

As exercise tolerance increased during the training period, workloads were augmented in order to maintain approximately the same relative work intensity. The duration of the total training program depended on their progress in working capacity and on their possibility to get time off from occupational work. On the average the patients completed 38 training sessions within a period of three months.
Statistics

Standard deviations were calculated using the formula \( \text{sd}^2 = \Sigma (x-\bar{x})^2/(N-1) \) and the Student \( t \)-test for paired observations has been used when applicable. The coefficient of variation was calculated as the standard deviation in percent of the mean value \((\text{sd} \times 100/\bar{x})\).

Results

Control Study: Pain Threshold Values For RPP, HR and SBP

Intra-arterial Blood Pressure Measurement. In each patient the variation of RPP at the onset of angina pectoris for the repeated exercise bouts at different workloads was calculated. In the pretraining tests performed with an indwelling catheter the coefficient of variation varied from 1.4%-13.0% among the 29 patients, the group mean value being 6.2\% \pm 3.31\% (SD). The corresponding anjinal threshold for HR varied from 1.3%-11.2% with a group mean value of 6.2\% \pm 2.74\% (SD), while the variation of the SBP value at the onset of pain ranged from 1.9%-9.7% with a group mean value of 4.9\% \pm 3.03\% (SD). The RPP, HR, and SBP values at the anjinal threshold value were reproducible with the same degree of assurance.

Sphygmomanometric Blood Pressure Measurement. In 16 patients the anjinal threshold for RPP, HR, and SBP from the preliminary exercise test, in which sphygmomanometric SBP measurements were used, were compared to corresponding values derived from the studies involving intra-arterial SBP recording. Rate-pressure product at the onset of pain was on average 195 \pm 7.08 (standard error, SE) obtained with cuff pressures, while the value based on direct intra-arterial measurement of SBP was 201 \pm 7.51 (SE). The difference between values obtained from the two methods was not statistically significant. The reproducibility of the anjinal threshold for RPP did not differ significantly between the two methods. The coefficients of variation being 5.3\% \pm 3.00\% (SD) vs. 5.6\% \pm 2.91\% (SD) for direct and indirect measurements of SBP, respectively. The effect of an indwelling catheter did not significantly change SBP values measured during the exercise test performed (174 mm Hg \pm 5.72 [SE] with catheter, vs. 170 \pm 5.33 [SE] without catheter). By contrast HR at the onset of angina was slightly lower during the exercise tests performed without catheterization (112 beats/min \pm 3.56 [SE], vs. 119 beats per min \pm 4.71 [SE], \( P < 0.05 \)).

Effects of Training

Exercise Capacity. The training program effect on the response to exercise varied in the different patients. In the post-training study six patients carried out 5 min of exercise without angina at all the workloads which provoked pain...
within 5 min in the pretraining study. Six other patients did experience pain after training, but only at the highest workload. Five patients noted angina at two or three loads, while the remaining eight patients continued to have angina at all workloads after training.

If pain was provoked at a given workload after training, the time to onset of pain was usually prolonged. Three patients, however, complained of angina after reduced or unchanged duration of exercise at one of the workloads, and in one patient the time to onset of pain was unchanged or reduced at all workloads. In each patient the total energy (in watt \( \times \) sec) produced before the onset of pain was calculated for each exercise period. To evaluate the effect of training the maximal pre- and post-training values were used. Group means and individual values are shown in figure 2. After training the patients could on average produce double the amount of energy before pain was provoked. In ten patients after training the maximal product of working time and workload was achieved at a workload which did not provoke angina pectoris within the five min exercise period. Several of these patients were certainly able to exercise longer or at a higher workload. Thus in these patients the real increase in exercise capacity induced by training is somewhat underestimated. The 15 patients, in whom the maximal energy production continued to be limited by chest pain after training, increased the amount of energy (in watt \( \times \) sec) produced before onset of pain by an average of 74% of the pretraining maximum.

RPP, HR, and SBP. The finding that the patients were able to exercise longer at a given workload before pain was elicited could be related mainly to the fact that after training RPP increased less in proportion to the workload. Individual values from the pretraining study for RPP, HR, and SBP at the onset of pain were compared to the corresponding post-training values measured after the same duration of exercise at identical workloads. The group means and individual values (all workloads) are shown in figure 3. After training at the time for onset of pain in the pretraining study there was an almost 10% reduction in RPP which resulted from a reduction in HR whereas SBP remained practically unchanged.

The group means for the RPP, HR, and SBP anginal threshold values did not change significantly in response to training (fig. 4). However, nine patients tolerated a higher RPP and showed an increase of 108% in amount of work (in watt \( \times \) sec) accomplished before angina. In seven patients with reduced RPP at onset of angina the increase in amount of work before angina was only 51%. In the six patients who were not limited by angina pectoris in the post-training exercise tests, the highest measured RPP value exceeded the pretraining threshold value by 21%, but this difference was not significant. The amount of watt \( \times \) sec these patients produced during 5 min of exercise at the highest workload after training was 154% greater than the maximal energy production they achieved before onset of angina in the control study.
Resting HR and Blood Volume. After training resting HR was reduced from 83 beats/min to 79 beats/min or 5.3% (P < 0.05, N = 25). This reduction corresponded to 41% of the decrease seen during exercise. The blood volume increased from 5131 ml to 5326 ml or 4% (N = 11). This change did not reach statistical significance.

Comparison of Arm Exercise and Leg Exercise

During arm exercise before training one of the 12 patients so studied did not experience angina at either workloads. In the remaining 11 patients the RPP threshold was clearly higher during arm exercise than during leg exercise (fig. 5). Both HR and SBP were higher during arm exercise than during leg exercise at the onset of angina. Nine of these patients were studied during arm exercise both before and after leg training. In five of them after training the time to onset of pain was increased at the same workload or pain was not provoked within 5 min. The average increase in working time at a given load was 110%. In the remaining four patients the working time to pain was essentially unchanged after training.

Rate-pressure product during arm exercise (measured at the time for onset of pain in the pretraining arm exercise test) was 263 before training of the leg muscles and 255 after (NS). The corresponding values for HR decreased from 142 beats/min to 130, P < 0.01, whereas SBP increased by 15 mm Hg from 185 mm Hg to 200 mm Hg. The change in SBP was not statistically significant, however.

Effects of Nitroglycerin

Figure 6 shows the effect of nitroglycerin during leg exercise on RPP, HR, and SBP measured at the time for onset of pain at the same workload performed without administration of nitroglycerin. As seen, nitroglycerin increased HR and decreased SBP whereas no significant change was seen in the group mean value for RPP. In five patients pain continued to occur within 5 min of exercise after nitroglycerin. The difference between mean RPP at the onset of pain, 226 as compared to 216 without nitroglycerin, was not significant. For the 11 patients studied in this way administration of nitroglycerin increased total energy expenditure during leg exercise by an average of 90%.

Nine of these patients participated in the training program. In the pretraining study after nitroglycerin was given these patients exercised on average 259 sec before angina was provoked. After training, without nitroglycerin, the patients exercised 194 sec at the same workloads before angina. The increase in working time obtained by nitroglycerin in these patients was not significantly greater than the increase caused by training.

Rate-pressure product measured at the time for onset of pain in the control study was 195 after nitroglycerin and 190 after training at identical workloads. This difference was not significant. After nitroglycerin HR was 137, vs 118 after...
training. Systolic blood pressure was 144 mm Hg after nitroglycerin and 162 mm Hg after training. Both differences were statistically significant ($P < 0.01$).

Discussion

Robinson who originally demonstrated that the onset of anginal pain occurs at a relatively constant RPP value in each patient, used a correction for variations in systolic ejection time when it was considered necessary. Several later investigators have consistently corrected for the ejection time by using as an index of $\text{MVO}_2$ either the triple product (TP) of SBP, HR, and ejection time, or the tension-time index (TTI) (area under systolic arterial pressure curves times HR).

In the present study the simple product of HR and SBP (RPP) was employed because we determined in the first 11 patients studied that the reproducibility of the pain threshold for RPP was the same as for TTI and because $\text{MVO}_2$ has been shown to correlate better to RPP or HR alone than to TTI in young healthy subjects exercising in the upright position.

For clinical purposes the use of RPP instead of TP or TTI has the advantage that this index of $\text{MVO}_2$ can be readily obtained by noninvasive SBP measurement. In terms of repeatability there was in this study no difference between the RPP when SBP was measured intraarterially or by the cuff technique. SBP was the same with the two methods, but heart rate was somewhat higher in the study performed with indwelling catheters.

Redwood and coworkers studied the influence of variations in the exercise protocol on the reproducibility of the anginal threshold for TP. They found elevated TP threshold values at so-called "supramaximal" workloads, which provoked pain after about 1.40 min of exercise. On the basis of this finding they recommended the use of exercise periods of at least 3 min duration. In the present study we wanted to assess the constancy of the RPP threshold for angina provoked at different workloads and after different durations of exercise. As a consequence in each patient one or more exercise period was performed at workloads which were "supramaximal" according to the definition of Redwood et al. However, individual RPP anginal threshold values varied only 5–6% on the average both when direct and indirect SBP measurements were used. In only three of the patients the RPP at the onset of pain increased with increasing workload. In these patients the average coefficient of variation for the anginal threshold was 10%.

In consequence, determination of RPP at the onset of pain during repeated exercise periods of different intensity and duration can be used to confirm the diagnosis of angina pectoris and to evaluate the effect of therapeutic interventions. That pain occurs at fairly constant RPP independent of the workload underlines that $\text{MVO}_2$ and not total body VO₂ limits the exercise capacity in these patients.

The finding that the RPP threshold value was higher during arm exercise than during leg exercise in the same patient probably reflects the fact that RPP does not take into account another important determinant of $\text{MVO}_2$, the end-diastolic volume. A smaller stroke volume during arm exercise is presumably associated with a smaller end-diastolic left ventricular volume and thus a given RPP corresponds to a lower $\text{MVO}_2$ in this situation. Accordingly, angina is provoked at lower values for HR and SBP during leg exercise in the supine position, where the heart volume is known to be greater than during leg exercise in the upright position. It should be mentioned, however, that Wahren and Bygdemann found the same RPP at the onset of pain during arm exercise as during leg exercise. This discrepancy cannot be explained as the experimental set-up in the two studies was essentially the same.

Training increased the exercise tolerance in most patients. This was assessed from the increase in amount of exercise performed before pain was provoked so that both the workload and the interval of time it could be sustained were taken into account. Nevertheless, this does not give a complete picture of the improvement obtained by training. Both before and after training the onset of pain was defined as the moment the patient felt the slightest sensation or discomfort in the chest. However, many of the patients reported that the pain was less severe and developed more slowly after training, allowing the patient to continue exercising longer after the onset of angina. We did not attempt to quantitate the patients’ indications of the severity of anginal pain in any systematic way.

The reduction in HR at a given workload and time was the most consistent objective effect of training seen in this study, and it was the main factor responsible for the improved relationship between the myocardial pressure work and the total body energy expenditure (fig. 3). The physiological mechanism which causes the training bradycardia is still not well understood. In young healthy subjects HR response during exercise with trained muscles was compared to HR response during exercise with nontrained muscles and the results suggested that two different factors contribute to the reduction in HR induced by training. The first seems to be intimately associated with a general reduction of the sympathetic drive at a given submaximal workload related to local adaptations in the trained muscles. The other is a lowering of the basal HR setting which may be attributed to a direct training effect on the heart or other central circulatory changes.

It could be expected that training effects on the peripheral vascular system predominated in patients with heart disease. The relative contributions of central and peripheral changes to the reduction in HR during exercise may be estimated from the ratio between the fall in resting HR and the HR reduction observed during exercise with trained muscle groups. After leg training during leg exercise this ratio is 0.60–0.80 in young healthy subjects as compared to 0.20–0.30 in previous studies of coronary artery disease patients.

In the present study this ratio averaged 0.41. In this context it should be noted, however, that the exercise HR values from the present study were measured after only a few minutes of exercise — an interval during which HR still shows a relatively steep rise.

After training of the leg muscles during heavy exercise with nontrained arm muscles, young healthy subjects show a significant increase in SBP as compared to the pretraining value as well as an increase in cardiac output. This was interpreted as a primary improvement in myocardial performance induced by training. In only three of the angina pectoris patients so studied here did training of the leg muscles result in an increase in SBP during heavy arm exercise. This could be taken to indicate that, in contrast to nor-
mal subjects, direct training effects on myocardial function play a minor role in improving response to exercise in patients with coronary artery disease.

The RPP pain threshold value, determined on the basis of the mean value for the entire group, was not increased after training in the present study. This is in contrast to the findings in two previous reports. In our study it was evident, however, that patients who showed an increase in RPP at the onset of pain in response to training had the greatest increase in exercise capacity. The patients who had unchanged or reduced exercise capacity after training often had a lower RPP pain threshold.

It is as yet not clarified whether the ability to sustain higher values for the product of SBP and HR before pain is provoked is due to improved myocardial oxygen supply or to possible additional economizing effects on myocardial function. It is in this context conceivable that after training these patients exercise with a smaller left ventricular end-diastolic volume in the upright position. Other explanations for improvements seen after training could be improved myocardial oxygen supply or oxygen extraction because of increased vascularization, increased content of oxidative enzymes in myocardial muscle cells, or a shift to the right of the oxy-hemoglobin dissociation curve, but none of these effects have been demonstrated in coronary artery disease patients (cf. ref. 23).

This study suggests that the potency of training and nitroglycerin are almost equal in augmenting the exercise tolerance in patients with angina pectoris. The increase in total amount of work performed before the onset of pain was almost the same with the two different interventions. Rate-pressure product measured at the time of onset of pain in the control study was also essentially the same after training as after nitroglycerin. However, it should be noted that the same RPP values may reflect different values for myocardial blood flow and oxygen uptake in the two situations. Training changes RPP primarily by reducing HR, while nitroglycerin reduces SBP but increases HR. A reduction in HR may enhance myocardial blood flow by prolonging the diastole and thus the time for perfusion of the left ventricle. In contrast with the reduction in blood pressure seen after nitroglycerin, regions in which further reduction in resistance to flow is not possible could actually be even less well perfused in the face of the associated rise in heart rate. However, such possible adverse effects on myocardial perfusion and the extra costs in MVO₂ caused by the higher HR seem to be more than counterbalanced by the reduction in over-all MVO₂ caused by the fall in SBP and left ventricular volume.¹⁴

About 10% elevation of the RPP anginal threshold value has been observed in previous studies as an effect of nitroglycerin. Rate-pressure product at the onset of pain was unchanged after nitroglycerin in this study. This disagreement between the present and previous findings may be explained by variations in the individual responses among the relatively small numbers of patients included in the different investigations.

No treatment has so far been proven to influence life expectancy in coronary artery disease. Thus the efficacy of a therapeutic approach can still be judged only from the symptomatic effect. Increased exercise capacity is the appropriate indicator of symptomatic improvement as far as exertional angina pectoris is concerned. The above results have confirmed that physical training is efficient in increasing the exercise capacity in most patients with exertional angina pectoris, and they suggest that the “long-term” effects of training be equal to the very short-term effects of nitroglycerin in this respect. Furthermore training is a sound approach from a physiological point of view and may imply several psychological advantages as compared to drug administration and surgery. For practical reasons training may not be feasible in all patients who could be expected to improve from it, but it is in our opinion of sufficient value to be incorporated in the clinical routine as a supplement to both medical treatment and to surgery and to deserve continuous attention in clinical research.

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Heart rate and arterial blood pressure during exercise in patients with angina pectoris.
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