Enhanced peripheral vasoconstrictor response and increased thromboxane A2 synthesis after the cold pressor test in patients with angina at rest

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ABSTRACT Peripheral vascular resistance (PVR) and thromboxane A2 (TxA2) synthesis after the cold pressor test were investigated in different subsets of patients with angina (10 with stable effort angina, 36 with resting angina [24 in an active phase and 12 in an inactive phase], and five with Prinzmetal's variant angina) and in 41 control subjects of equivalent age and risk factors. Left ventricular end-diastolic pressure, ejection fraction, extent of coronary angiographic lesions, and baseline PVR were not significantly different among the various patient groups. In all patient groups, except those with variant angina, the cold pressor test resulted in a higher increase in PVR than in the control subjects (p < .001 for all groups). In patients with variant angina the vasoconstrictor response was increased only in proximity (about 1 hr) to ischemic attacks. In patients with active resting angina the vasoconstrictor response was on the average four times longer than that in patients with effort angina and with inactive resting angina (p < .001). This exaggerated vasoconstrictor response was associated with elevated TxA2 resting levels in plasma and with increased TxA2 synthesis after the cold pressor test. A linear relationship was found between the area of the vascular response and the area of TxA2 production after the cold pressor test in patients with active resting angina (r = .87, p < .001). The increased TxA2 synthesis and the inappropriate increase of peripheral vascular response to sympathetic stimulation revert back to normal in the inactive phase. These alterations might contribute to the occurrence of inappropriate vasoconstriction and of the abnormal vascular responsiveness to various stimuli frequently found in patients with unstable angina.


SPONTANEOUS anginal attacks at rest have often been found to be associated with relative increases in heart rate and arterial blood pressure, which precede the onset of pain or ST segment depression in many patients1–7 and may play an important role in triggering and/or worsening myocardial ischemia. Because of the increases in heart rate and/or blood pressure before the onset of pain or ST segment depression, it has been suggested that angina at rest may be caused by an autonomically mediated sympathetic discharge with consequent increases in systemic vascular resistance.8 Furthermore, continuous monitoring of patients has shown that with continuing pain there is a tendency toward a secondary sympathetically induced increase in arterial blood pressure and heart rate, which can trigger a feedback mechanism increasing myocardial oxygen demand.2,5,8 Thus, in anginal patients the vascular responsiveness both to resting sympathetic flow and to reflexively increased sympathetic activity may play an important role in the occurrence and/or worsening of myocardial ischemic attacks.

Sympathetic activation is able to induce thromboxane A2 (TxA2) synthesis by vessel wall.9 Because of its direct vasoconstrictor activity, TxA2 is reported to potentiate the vasoconstrictor effect of norepinephrine and angiotensin II10,11 and thus might play a role in an abnormally enhanced vascular response to sympathetic stimulation.

The aim of this study was therefore to investigate peripheral vascular responsiveness to sympathetic stimulation such as the cold pressor test in different subsets of anginal patients and to correlate peripheral vascular responses to TxA2 production.

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Methods

Selection of patients and control subjects. From November 1981 to August 1983, 51 inpatients (37 men and 14 women ages 36 to 63 years) suffering from stable effort angina (n = 10), resting angina (n = 36), and Prinzmetal’s angina (n = 5) were studied. Four patients among those with resting angina had had a previous myocardial infarction (more than 6 months before the study). Because of the experimental procedure, patients with associated peripheral vascular disorders of the lower limbs were not enrolled in the study.

Angina was diagnosed on the basis of typical chest pain and supported by electrocardiographic evidence at rest and on exercise, Holter monitoring (Del Mar Avionics, Mod. 668, Irvine, CA), and coronary angiography (performed in 44 of 51 patients, 32 with resting angina, seven with stable effort angina, and five with Prinzmetal’s angina). On Holter recordings, we considered a transient planar or downsloping ST segment depression of at least 0.2 mV occurring 80 msec or longer after the end of QRS and lasting at least 1 min in consecutive beats12 significant for myocardial ischemia. Coronary angiography was performed by the Judkins or Sones technique and the occurrence and severity of coronary lesions evaluated from at least three projections was assessed both according to a semiquantitative method (score A) as previously described13 and according to the method of Genini14 (score B). Left ventricular end-diastolic pressure and ejection fraction were evaluated by left heart catheterization.

Stable effort angina was diagnosed according to the following criteria: (1) typical anginal pain during effort and no anginal attacks at rest, (2) absence of ischemic attacks at rest during a 3 day Holter monitor recording, and (3) stable ischemic threshold during at least three bicycle ergometric tests performed in the week preceding the study. We considered patients with resting angina those found to have ischemic attacks at rest or resting angina associated with effort angina, who showed ST segment elevation or depression during the attacks. Patients with resting angina were subdivided into two groups: patients with active disease and patients with inactive disease. Patients who had had no ischemic attacks at rest, symptomatic or asymptomatic (Holter monitoring on alternate days), during the week preceding the study were considered to have inactive disease. All the other patients were considered to have active disease. According to these criteria, 12 patients had inactive and 24 had active resting angina. Twelve of the 24 patients with active disease were again studied several weeks later when they were in the inactive phase. These patients were maintained on nitrates as they were during the first examination in the active phase.

Prinzmetal’s angina (variant angina) was defined as angina at rest associated with transient ST segment elevation and good tolerance to exercise (bicycle ergometric test).

The four groups of patients were not significantly different in age (F = .03), sex, body weight (F = .14), plasma cholesterol levels (F = .26), blood pressure (F = .69), and smoking habits. No patient suffered from diabetes. Patients stopped or discontinued all other therapy at least 1 week before study except nitrates, which were last administered at least 4 hr before the investigation. This period of time is beyond the duration of any possible prostanoid-stimulating activity of these drugs.15 No statistically significant differences were found among the various groups of patients regarding left ventricular end-diastolic pressure and ejection fraction (F = .29 and .43, respectively).

Each group of patients with ischemic heart disease was compared with a suitable group of control subjects. Forty-one controls were selected among inpatients so that age (F = .05), sex, body weight (F = .13), plasma cholesterol levels (F = .43), blood pressure (F = .36), and smoking habits did not significantly differ from those of the four patient groups. The control subjects had normal electrocardiograms at rest and nonsignificant electrocardiographic responses to ergometric exercise stress testing and Holter monitoring, and they were not affected by cardiovascular disease, diabetes, hyperthyroidism, or other diseases that could jeopardize the prognosis in the following 5 years. Neither controls nor patients affected by ischemic heart disease took aspirin or other cyclooxygenase-inhibiting drug during the 10 days preceding the study. They all abstained from methylxanthine and alcoholic beverages, and those who smoked abstained from tobacco for 24 hr before and during the study. All patients and control subjects gave informed consent.

Design and experimental procedure. To check a possible circadian rhythm of vascular resistance, in preliminary investigations we studied the time course of vascular response to the cold pressor test every 2 hr during the day (from 8 A.M. to 8 P.M.) for 2 consecutive days. This investigation was performed on each of the first two subjects enrolled in each of the experimental groups. In control subjects and in patients with effort and resting angina, the vascular response did not vary among the various measurements. In contrast, in patients with variant angina the vascular response to the cold pressor test was markedly different in the various measurements. Therefore in the final experimental design the vascular response to the cold pressor test was tested twice a day (between 8 and 9 A.M. and 6 and 7 P.M.) for 2 consecutive days in all subjects (except those with variant angina) and the vascular response to the cold pressor test was expressed as the mean of the results obtained in the four tests.

To validate the wide fluctuations in vascular response found in patients with variant angina, this group of patients was compared with a group of five patients with active resting angina and with a group of five control subjects matched for sex, age, body weight, plasma cholesterol levels, blood pressure, and smoking habits. All these subjects were studied by measuring peripheral vascular resistance (PVR) every 2 hr (from 8 A.M. to 8 P.M.) for 2 consecutive days and the pattern of the single measurements was considered.

Blood sampling for TxB2 assay was performed in all subjects only during the two morning tests (8 A.M.) and the mean of the two measurements was presented in the results. Moreover, to rule out the possibility that plasma TxB2 changes after the cold pressor test were caused by platelet activation, TxB2 was also measured on the third day, 1 hr after administration of 10 mg/kg iv aspirin (as lysine acetylsalicylate), which is able to completely inhibit TXA2 formation by platelets but does not affect plasma TxB2 levels.9 However, during this sympathetic stimulation PVR was not measured because prostacyclin inhibition by aspirin increases vascular response to the cold pressor test.9

Evaluation of the vascular response to the cold pressor test. Vascular response to the cold pressor test was investigated by measuring changes of lower limb vascular resistance. Sym pathetic stimulation was induced by a modified cold pressor test.10 Cold application lasted 2 min.

Patients lay in the supine position in a quiet and comfortable room at 22° C for at least 30 min before cold application. It was essential that the patients were quiet and relaxed. Patients were monitored by electrocardiographic recordings during sympathetic stimulation and arterial blood pressure was measured every 30 sec for the duration of the investigation. PVR was calculated by the formula: resistance = mean arterial pressure / blood flow and expressed in arbitrary units.6–18 Mean arterial pressure was calculated by the formula: diastolic pressure + 1/3 pulse pressure. Blood pressure was measured by a Riva-Rocci sphygmomanometer, taking phase V of Korotkoff sounds as an index of diastolic pressure. The blood flow (ml/100 ml tissue/min) was measured by strain-gauge plethysmography19–21 with an SU4 Periflow 4 Janssen Scientific Instruments, Beerse,
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Belgium). Reported values were the average of five consecutive readings. Each measurement was automatically made by the plethysmograph, which, synchronized with the electrocardiogram, occluded veins for 3 beats and released them for 2. PVR was measured every 30 sec for 14 min after cold application. The basal value was the average of four values obtained before cold application.

For blood sampling, a 16-gauge Teflon catheter needle with a three way stopcock was inserted in the antecubital vein and sterile saline solution was infused continuously at a low flow rate through the catheter to prevent clotting. After each blood sampling, saline was also briefly flushed to wash the catheter. Blood samples for basal values were obtained when the subjects appeared to be relaxed, but not sooner than 15 min after venipuncture. Blood samples for TxB2 assay were drawn before, during (beginning at 100 sec) and at 4 and 10 min after the beginning of cold application.

TxA2 assay. TxA2 was assayed as its stable derivative TxB2 by radioimmunoassay according to the method of Gränsström et al.22 Samples for TxB2 assay were drawn without venous stasis directly into cold polypropylene syringes containing 10 μg/ml phenylphosphon in 0.037 M EDTA (4.5 ml/0.5 ml) to avoid the formation of cyclooxygenase-mediated arachidonic acid metabolites by platelets during handling of the samples.22 TxB2 was assayed in platelet-poor plasma (obtained by centrifugation at 3800 g for 30 min at 4°C) with a commercial kit (American Biomedical Technologies, Esslingen, West Germany). By this method, 10 pg TxB2/ml of platelet-poor plasma was the lowest detectable amount. The intra-assay and interassay variation coefficients were 8.7% and 10.4%, respectively. Cross-reactivity of TxB2 antibody, evaluated in the radioimmunoassay system by measuring the inhibition of the binding of labeled TxB2, caused by various prostaglandins and related substances, was 0.18% with PGD2, less than 0.05% with PGF2α, less than 0.05% with 6-keto-PGF1α, less than 0.05% with PGE2, and less than 0.05% with 12-HETE. In previous investigations, suitable methods were developed to ascertain that TxB2 assayed by radioimmunoassay was exclusively TxB2.9

Statistical analysis. Results are given as mean ± SD. The statistical analysis was performed with the following tests: the Wilcoxon rank sum test for paired and unpaired data, the linear regression, and the one-way analysis of variance. For the analysis of the relationships among coronary angiographic lesions, vascular response, and TxA2 production, the areas delimited by the curves and baseline levels of PVR and TxA2 increase were calculated by computer (GPS4; General Processor, Italy).

Results

Vascular response to sympathetic stimulation. Baseline PVR (figure 1) and left ventricular function, as evaluated by the left ventricular end-diastolic pressure and ejection fraction at rest, did not differ significantly among the various groups of patients and control subjects.

All patients experienced pain in the foot immersed in ice water. Three patients (two with active resting angina and one with variant angina on only one occasion) reported chest pain or other uncomfortable symptoms during cold stimulation. Only these three patients had ST segment changes indicating myocardial ischemia. Blood pressure and double product values increased significantly during cold application in all patients, but in patients with active resting angina blood pressure and double product were significantly higher (table 1).

PVR increased significantly in all subjects during the cold pressor test (p < .001 for each group, figure 1), but remarkable differences in elevation and in its time course were observed among the different groups of patients. In the individual control subjects the duration of the increase in PVR varied from 2.5 to 5.5 min from the beginning of cold application. Three and a half minutes from the beginning of the cold pressor test the mean values of PVR did not differ from the baseline values. In patients with effort and inactive resting angina, there was a greater significant increase in PVR than in the respective control groups (70.1 ± 3.1 vs 51.7 ± 2.9 arbitrary units for effort angina and 73.7 ± 4.2 vs 59.6 ± 3.2 arbitrary units for inactive resting angina; p < .001 for both groups); PVR returned to pretest values in the same period (figure 1). In patients
TABLE 1
Mean values of PVR, blood flow, and mean arterial pressure (MAP) observed in resting conditions (R) and at the point of their maximal increases (M)

<table>
<thead>
<tr>
<th></th>
<th>PVR (arbitrary units)</th>
<th>Blood flow (ml/100 ml tissue/min)</th>
<th>MAP (mm Hg)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Active resting angina (n = 24)</td>
<td>R 26.8 ± 4.2</td>
<td>3.7 ± 0.5</td>
<td>101.4 ± 8.9</td>
<td>9,402 ± 1,079</td>
</tr>
<tr>
<td></td>
<td>M 78.2 ± 6.7</td>
<td>1.7 ± 0.1</td>
<td>128.7 ± 8.2</td>
<td>15,580 ± 1,264</td>
</tr>
<tr>
<td>B. Inactive resting angina (n = 12)</td>
<td>R 30.1 ± 2.5</td>
<td>3.4 ± 0.1</td>
<td>100.7 ± 9.2</td>
<td>8,970 ± 800</td>
</tr>
<tr>
<td></td>
<td>M 73.8 ± 4.2</td>
<td>1.7 ± 0.1</td>
<td>123.0 ± 8.1</td>
<td>12,941 ± 633</td>
</tr>
<tr>
<td>C. Effort angina (n = 10)</td>
<td>R 30.8 ± 4.0</td>
<td>3.4 ± 0.3</td>
<td>99.2 ± 10.5</td>
<td>9,140 ± 644</td>
</tr>
<tr>
<td></td>
<td>M 70.1 ± 3.1</td>
<td>1.7 ± 0.2</td>
<td>120.7 ± 10.9</td>
<td>12,657 ± 511</td>
</tr>
<tr>
<td>D. Pooled controls (n = 36)</td>
<td>R 27.9 ± 3.2</td>
<td>3.6 ± 0.3</td>
<td>98.6 ± 8.0</td>
<td>8,989 ± 863</td>
</tr>
<tr>
<td></td>
<td>M 54.1 ± 5.0</td>
<td>2.3 ± 0.2</td>
<td>120.8 ± 7.7</td>
<td>12,045 ± 685</td>
</tr>
</tbody>
</table>

Resting values: No significant differences for all the groups.
Maximal values: PVR = A vs C, A vs D, B vs D, C vs D; p < .001; A vs B: p < .05; B vs C: NS. Blood flow = A vs D, B vs D, C vs D: p < .001; A vs B, A vs C, B vs C: NS. MAP = A vs D: p < .001; A vs B, A vs C: p < .05; B vs C, B vs D, C vs D: NS. Double product = A vs B, A vs C, A vs D, B vs D: p < .001; C vs D: p < .005; B vs C: NS.

with active resting angina cold application induced significantly higher peak values of PVR than in the control subjects (78.2 ± 6.7 vs 52.2 ± 4.5 arbitrary units; p < .001) and the increase of PVR was longer lasting (from 10 to 13.5 min) than in control subjects and in patients with inactive resting angina and effort angina (figure 1). This behavior of PVR was found consistently and was independent of any temporal relationship to the ischemic attacks. The mean PVR values returned to baseline only 12.5 min after the beginning of sympathetic stimulation and the last value significantly different from that in control subjects was found 10.5 min from the beginning of the cold pressor test (figure 1).

In patients with variant angina the vascular response to sympathetic stimulation was found to differ greatly in the various measurements during the two day period of observation. In some measurements vascular response was not different from that in control subjects unaffected by ischemic heart disease, whereas in others it was higher and longer lasting. More precisely, 41 of 70 measurements in the five patients were altered because the vascular response to the cold pressor test was higher and overall longer lasting and the return to baseline values took place 11.2 ± 1.9 min from the beginning of sympathetic stimulation. However, this longer-lasting vascular response was observed only when sympathetic stimulation occurred in close proximity to ischemic attacks (about 1 hr). When stimulation did not occur in close proximity to ischemic attacks, PVR returned to baseline values in the same time as in the healthy control subjects (5.2 ± 0.7 and 4.9 ± 0.7 min, respectively).

**TxB2 levels in plasma.** In patients with active resting angina, baseline plasma TxB2 levels were significantly higher than those in control subjects (48.0 ± 14.7 vs 23.4 ± 8.4 pg/ml; p < .001) and those in patients with inactive disease and with effort angina (p < .001 for both groups, figure 2). In contrast, no significant differences could be found between patients with inactive resting angina and effort angina and between these groups and their respective control subjects (26.6 ± 10.7 vs 23.1 ± 6.1 pg/ml and 21.9 ± 5.4 vs 22.6 ± 6.5 pg/ml). Cold application was associated with a prompt elevation of plasma TxB2 levels in all subjects, but marked differences were found between patients with resting angina and the other groups (figure 2). In patients with active resting angina, peak TxB2 levels after the cold pressor test were significantly higher than those in patients with inactive resting angina and effort angina. In these last two groups of patients the cold pressor test–induced increase in TxB2 level was not significantly higher than the increase induced in the control subjects. The TxB2 increase in patients with active resting angina was not related to their higher baseline levels because the absolute increase in TxB2 concentration was significantly greater (42.7 ± 31.7 vs inactive disease 17.4 ± 15.0 pg/ml, p < .001, and vs effort angina 22.7 ± 19.6 pg/ml, p < .001). Moreover, in many patients (13 of 24) peak TxB2 levels were reached 4 min instead of 2 min after cold application.
sympathetic stimulation was only irregularly paralleled by abnormal TxA₂ formation. Finally, in all groups of subjects plasma TxB₂ levels were not significantly affected by aspirin either before or after the cold pressor test (figure 4).

**Relationship between vascular response to the cold pressor test and TxA₂ production.** To investigate a possible relationship between vascular response and TxA₂ synthesis after the cold pressor test, the area under the PVR curve was plotted against the area under the TxB₂ curve. A significant linear relationship was found in patients with active (r = .87, p < .001) and inactive angina (figure 3).

In only two of five patients was cold application followed by marked elevation in plasma TxB₂ levels similar to that in patients with active resting angina. This increase in TxA₂ formation after the cold pressor test was associated with a higher and longer lasting increase in PVR. In the other three patients TxB₂ variations after the cold pressor test were not different from those in the control subjects even though the concomitant vascular response to sympathetic stimulation was significantly increased and longer lasting in four of six measurements. Thus in patients with variant angina the alteration of vascular response to

**FIGURE 2.** Plasma TxB₂ levels after the cold pressor test in patients with ischemic heart disease (●) and in control subjects (○). *p < .01; **p < .005; ***p < .001 vs basal values.

**FIGURE 3.** Plasma TxB₂ levels after the cold pressor test in patients with variant angina (▲), their respective control subjects with resting angina (●), and in the healthy control subjects (○).
resting angina \( (r = .79, p < .001) \). No significant relationship was found in patients with effort angina \( (r = .30, p = \text{NS}) \) or in the control subjects \( (r = .11, p = \text{NS}) \) (figure 5).

**Discussion**

These findings indicate that peripheral vascular response to the cold pressor test is increased in anginal patients as compared with control subjects, and especially in patients with active angina at rest, who showed a more markedly elevated and, above all, longer vasoconstrictor response than the other groups of patients. The increased vascular response was observed in all measurements in patients with classic
angina, whereas it was found only in close proximity to ischemic attacks in patients with variant angina.

The abnormal vascular responsiveness observed in anginal patients does not seem to be caused by drugs, since all patients were on nitrates only, which are known to induce vasodilatation and, probably, to stimulate PGI₂ synthesis without interfering with sympathetically induced reflex vasoconstriction. In addition, the pattern of the vascular response was different in the different groups of patients.

The exaggerated vasoconstrictor response to sympathetic stimulation found in patients with active angina at rest does not seem to be a consequence of differences in coronary lesions or of enhanced sympathetic tone resulting from repeated ischemic attacks or from differences in left ventricular function. No relationship was found between the presence and severity of coronary angiographic lesions and prolonged vasoconstrictor response to sympathetic stimulation. Similarly, left ventricular end-diastolic pressure and ejection fraction both in patients with active angina at rest and in those with variant angina were not significantly different.

**FIGURE 5.** Relationship between vascular response to the cold pressor test and TxA₂ production (areas under the curves) in patients with active resting angina, inactive resting angina, effort angina, and their respective controls. The areas under the TxA₂ response curve and the vascular resistance response curve are represented on the x and y axes, respectively. a.u. = arbitrary units.

**FIGURE 6.** PVR in patients with active resting angina studied again in the inactive phase (n = 12) before, during, and after the cold pressor test. ● = active phase; ○ = inactive phase.
from the control subjects and from patients with effort angina and inactive angina at rest. Moreover, a normal baseline sympathetic tone in patients with active angina at rest is suggested by the absence of any difference in baseline PVR among these patients and the other groups. In addition, normal baseline plasma catecholamine levels have been reported in anginal patients. It is also very unlikely that the increased vascular responsiveness of patients with active angina at rest was a direct consequence of the ischemic attacks. In fact, although the daily number of ischemic attacks in these patients was not different from that of patients with variant angina, the altered vascular response to the cold pressor test was always present independently of the occurrence of ischemic attacks, whereas in patients with variant angina the response to the cold pressor test was increased only in close proximity to the ischemic attack (about 1 hr before).

The markedly longer-lasting vasoconstrictor response to the cold pressor test found in patients with active angina at rest was associated with a significant elevation of TxB2 levels in plasma both before and after cold application. Moreover, a good correlation was found between vasoconstrictor response and TxA2 formation after the cold pressor test. The increased levels of TxB2 represent true levels of plasma TxB2 because the presence of phenoprophen in anticoagulant for blood sampling and administration of aspirin do not allow TxA2 formation by platelets. There is much evidence that human arteries and veins of some vascular beds are able to synthesize TxA2 and that sympathetic stimulation is able to induce prostaglandin synthesis both in vivo and in vitro. TxA2 as well as cyclic endoperoxides of arachidonic acid modulate Ca2+ entry and Ca2+ release from intracellular stores. Thus the increased TxA2 could play a role in the mechanism(s) of increased vascular responsiveness to different stimuli found in patients with active angina at rest.

The long-lasting vasoconstrictor response and the increased TxA2 formation after the cold pressor test seem to be specific to the activity of angina and not a common feature of coronary artery disease. This is suggested both by the lack of differences in the presence and severity of coronary angiographic lesions between patients with active angina at rest and patients with inactive angina and by the observation that in the 12 of 24 patients with active angina restudied when they were in inactive phase, the abnormal prolongation of vasoconstrictor response and the increased TxA2 formation found at the first observation reverted and were not different from the control observations.

The alteration of vascular response to cold stimulation observed in patients with variant angina does not seem to be accounted for by disordered prostaglandin synthesis. TxA2 formation after the cold pressor test was significantly altered only in two of five patients. However, the number of the observations is too small, therefore precluding any conclusion.

From the present data, since the coronary circulatory response was not studied, it cannot be inferred whether the prolonged increase of PVR after the CPT observed in patients with active angina at rest also involves the coronary bed. An inappropriate coronary vasoconstrictor response to the cold pressor test has frequently been found in patients with coronary artery disease. In any case, subthreshold (usually ineffective) stimuli could cause spontaneous myocardial ischemic attacks in patients with active resting angina because of their peripheral vascular hyperresponsiveness through increased myocardial oxygen consumption.

References

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**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>2 min</th>
<th>4 min</th>
<th>10 min</th>
</tr>
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<tbody>
<tr>
<td>Active phase</td>
<td>50.1 ± 15.7</td>
<td>74.0 ± 29.0</td>
<td>89.6 ± 43.4</td>
<td>56.8 ± 21.9</td>
</tr>
<tr>
<td>Inactive phase</td>
<td>29.0 ± 9.2</td>
<td>42.6 ± 16.7</td>
<td>40.5 ± 16.5</td>
<td>30.2 ± 9.3</td>
</tr>
</tbody>
</table>

All values of the inactive phase are statistically different from those of active phase for at least p < .01.


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