Ratio of exercise and recovery systolic blood pressure integrals in prediction of coronary artery disease

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ABSTRACT

Aim This study was performed to determine whether the ratio \( Q = \frac{A}{B} \) of area A under the curve of exercise systolic blood pressure (SBP) increase and area B under curve of recovery SBP decrease is predictive of angiographic coronary artery disease (CAD).

Methods Patients who performed exercise testing and subsequently underwent coronary angiography, within three months, were analyzed in this study. According to angiographic report, patients were divided in three groups: without disease or with stenosis less than 50% (group 1), significant (group 2), and severe (group 3). Severe disease was defined as left main, three-vessel or two-vessel disease with involvement of proximal left anterior descending artery.

Results There were 137 patients included in this study (age 59 ± 10, 70% male). Group 1 included 57%, group 2 included 30%, and group 3 included 13% of patients. Mean values of the Q ratio were 2.72 ± 0.9, 1.74 ± 0.76, 1.01 ± 0.38 in groups 1, 2 and 3, respectively. By means of robust discrimination analysis, statistically significant difference between groups 1, 2 and 3 in values of the ratio Q \( (p < 0.001) \) was found.

Conclusion The ratio of exercise SBP increase and recovery SBP decrease areas under the curve suggests severity of CAD.

Key words: systolic pressure, area under curve, exercise test, coronary angiography, coronary artery disease
INTRODUCTION

In exercise testing, electrocardiogram (ECG) changes are traditionally analyzed in prediction of the coronary artery disease (CAD). Unfortunately, sensitivity and specificity of these changes are not high (1). In searching for markers of higher sensitivity and specificity, systolic blood pressure (SBP) changes have received attention of investigators. Recovery time after exercise test has been merely devoted to observing patient, rather than exploiting its diagnostic utility. However, reports regarding recovery only ST segment depression emerged (2) and so have analyses of recovery only SBP (3).

Since the first report that delayed SBP recovery after exercise is predictive for CAD (4), different ratios of SBPs have been investigated to express delayed recovery (3-8). Closest thought to our analyzing is the use of recovery ratios only, investigated by McHam et al. (3). In our study we propose analysis of SBP change in different mathematical approach. Measure of delayed recovery expressed as ratio of SBPs at two time points (e.g. at 3 vs. 1 minute of recovery or at 3 minute of recovery vs. peak-exercise) is imprecise, and is substituted in our study by calculation of area under the curve of SBP change (mathematical term integral). Area size is a measure of all pressure differences (i.e. each SBP value achieved during exercise or recovery minus starting SBP) and duration of exercise or recovery. So new time point (recovery time) is introduced, when SBP in recovery demotes to starting value. Ratio (Q) of areas enables comparison of areas A (patients with different areas B (i.e. different exercise duration and different starting and peak-exercise SBP values).

SBP is central circulatory parameter, whose maintenance is superordinated to all regulatory mechanisms. Demand ischemia profoundly subordinates all these mechanisms to its self-termination. Therefore, SBP changes are related to ischemia. Thus, analysis of areas under SBP curve during and after exercise test should show the relation to CAD severity.

We intend to prove that ratio (Q = A/B) of exercise and recovery areas under SBP curve are predictive for any significant CAD as well as severe disease. In Figure 1 illustrates the hypothesis.

PATIENTS AND METHODS

Study population samples

We analyzed patients who performed exercise testing, and subsequently underwent coronary angiography, within three months. Indications for coronary angiography were clinically suspected CAD, previous myocardial infarction and evaluation after percutaneous coronary interventions. Exclusion criteria were: congestive heart failure, cardiomyopathy, valvular heart disease, atrial fibrillation/flutter, coronary artery bypass graft, clinically evident peripheral arterial disease (PAD), failure to increase SBP by at least 10 mm Hg, starting SBP above 170 mm Hg, starting diastolic blood pressure exercise time less than 5 minutes. The reasons for the last exclusion criterion were the insufficient number of blood pressure (BP) measurements and SBP changes were very small.

The study was approved by local ethical committee.

Exercise testing

The Bruce protocol was used for treadmill testing (9). Within each stage, exercise BP measurements were performed once. Blood pressures were measured by indirect arm-cuff column

Figure 1. Hypothetic ratio of areas under the curve in three groups of patients. Patients with CAD respond with delayed SBP recovery i.e. increased area under the recovery SBP curve. The ratio of the areas A (red) and B (blue) decreases with disease severity.
sphygmanometry and BP values were rounded to every 5 mmHg. Heart rate (HR) was continuously available. Recovery time was defined as time needed for SBP to demote to the starting value. Recovery BP was measured at 1, 2, 3, 5, 7, 9, 11, 13 and 15 minutes of recovery. When SBP demoted to starting value the BP measurements were usually stopped. If these measurements were not available the patient was not included. Medications were obtained from medical documentation with special attention to beta-blocker dosage.

Indications for the test termination were limiting clinical symptoms (angina, equivalent angina and dyspnea), ST segment depression of 2 mm, ventricular tachycardia and exaggerated SBP over 230 mmHg.

**Area calculation**

Area under curve of exercise SBP increase is the area A. The area under curve of recovery SBP decrease is the area B. Each area is influenced by exercise/recovery duration and SBP changes (i.e. exercise/recovery SBP value minus starting SBP value). A coordinate system was formed, where abscissa denotes time and 1 centimeter represents 1 minute and ordinate denotes SBP and 1 centimeter represents 10 mmHg. The areas were calculated in square centimeters by counting square millimeters. Ratio of areas (Q = A/B) enables a comparison between the area B patients and different areas A (i.e. different exercise duration and different starting and peak-exercise SBP values).

**Coronary angiography**

According to the coronary angiography report, the patients were divided into three groups.

Group 1 (insignificant or no CAD): any coronary artery or major branch < 50% or no CAD; one chronic total occlusion (CTO) (except for proximal left anterior descending artery (pLAD)) + stenosis < 50%.

Group 2 (significant CAD): any coronary artery or major branch > 50%; any one CTO + stenosis > 50 % (no pLAD involvement); proximal LAD CTO; not included in the group 3 nor in the group 1.

Group 3 (severe CAD): left main > 50%; three-vessel disease (if all three proximal segments involved then stenoses > 50%, if no proximal left anterior descending (pLAD) involvement then all stenoses > 70%); two-vessel disease (if pLAD > 70% and other vessel proximal segment > 70% or proximal LAD > 70% + major diagonal branch or middle LAD > 70%); two proximal chronic total occlusions (CTO) (one is pLAD); one proximal CTO + pLAD stenosis > 70%; any two CTO + pLAD > 50%.

**Statistical analyses.**

Basic characteristics and peak exercise values were expressed in mean ± standard deviation values. Differences among the groups were analyzed by the ANOVA test. A robust discrimination analysis was used to assess the significance of differences in baseline characteristics, peak-exercise values and values A, B and Q between groups 1, 2 and 3. Sensitivities, specificities, positive value and negative predictive value were calculated using standard definitions, separately for any CAD (group 2 and 3 compared to group 1) and severe disease (group 3 compared to the group 2). The values of P <0.01 were considered statistically significant.

**RESULTS**

There were 137 patients included in this study (mean age 59 ± 10 years; range 34-84 years; 70% male). The most common reasons for the test termination were fatigue (45%), onset of angina (34%), exercise SBP >230 mm Hg (5%), 2 mm ST depression without angina (11%) and achievement of maximal HR for age (5%). No angiographic
CAD or stenosis <50% was noted in 57% of patients (group 1), significant CAD in 30% (group 2) and severe CAD in 13% (group 3). In the Table 1, there are baseline and exercise characteristics of three groups of patients. Subjects in the groups 2 and 3 were older, less likely to be female, more likely to be taking antihypertensive medications and had higher resting SBP and HR. Resting diastolic BP was only higher in the group 2. Exercise characteristics (i.e. peak-exercise values) of patients are nearly the same SBP, higher diastolic BP in groups 2 and 3, lower HR and rate-pressure product in the groups 2 and 3.

Mean values and standard deviations of the areas A, B and Q ratios in the groups 1, 2 and 3 are shown in Figure 2 and Table 2. As shown in Figure 2, there is a tendency of smaller areas A, larger areas B and lower ratios Q in groups 1, 2 and 3. By means of the robust discrimination analysis, there is a statistically significant difference between the groups 1, 2 and 3 in values of area B and ratio Q (p < 0.001). Difference between the groups 1, 2 and 3 in the values of the area A is statistically non-significant (p = 0.028).

Sensitivity, specificity, positive predictive value and negative predictive value were calculated for different ratios Q in the range from 0.75 to 2.5 separately for any CAD and severe disease. Any...
CAD includes both groups 2 and 3. Severe disease is in the group 3 only and it is compared to group 2. Sensitivity and specificity of highest values for same ratio Q (i.e. Q = 2) for any CAD are 80%. Sensitivity and specificity of the highest values for same ratio Q (i.e. Q = 1.25) for severe disease are 76%. Sensitivities and specificities were calculated for different ratios Q as shown in Figure 3, in range from 0.8 to 2.5 separately for any CAD and severe disease. Positive value and negative predictive value were calculated for different ratios Q as shown in Figure 4, in range from 0.75 to 2.5 separately for any CAD and severe disease. For ratio Q = 2 calculated positive value and negative predictive value were 77% and 86%, respectively. For ratio Q = 1.25 calculated positive value and negative predictive value were 51% and 89%, respectively. Alternative form of expressing results as shown in Figure 5 is distribution of ratios Q in the coordinate system where abscissa and ordinate denote areas A and B, respectively.

### DISCUSSION

Decline of HR and SBP in recovery is faster in subjects in group 1 than in groups 2 and 3. There are two extreme forms of delay: with SBP augmentation (further increase above peak-exercise in recovery) followed by sudden decline and no augmentation but a long gradual decline. Furthermore, we observed that beta-blockers mitigated not only peak-exercise SBP, HR and rate-pressure product (10), but recovery values as well. In the groups 2 and 3, no augmentation was observed in patients on beta-blockers and their recovery area B was smaller than in patients taking no beta-blocker therapy with CAD of similar severity.

Beyond time point, when SBP demoted to the starting value (defined as the late recovery phase), SBP is expected to be bellow the starting value and HR is maintained the same. However, we observed that in patients on beta-blockers (in groups 2 and 3), SBP during late recovery was near the starting value and HR was slowly but apparently increasing.

Demand ischemia (e.g. intermittent claudications) induces metaboreflex. Skeletal muscle receptors (and their associated afferent fibers) are stimulated chemically representing afferent arm of metaboreflex (11, 12). Efferent arm is a sympathetic response via adrenal medulla neurons (circulating adrenaline) and sympathetic efferents on systemic resistance arteries (noradrenaline) and arterioles (although after reduction of adenosine and lactate). There is a similarity with cardiac muscle (e.g. demand ischemia - exertion angina in CAD or

Table 2. Mean values and standard deviations of areas A, B and ratios Q in groups 1, 2 and 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>26.06 ±</td>
<td>22.95 ±</td>
<td>18.14 ±</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>15.93 ±</td>
<td>14.47 ±</td>
<td>11.64 ±</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>10.58 ±</td>
<td>14.97 ±</td>
<td>19.36 ±</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>6.02 ±</td>
<td>9.81 ±</td>
<td>12.64 ±</td>
<td></td>
</tr>
<tr>
<td>Q</td>
<td>2.72 ±</td>
<td>1.74 ±</td>
<td>1.01 ±</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>0.91 ±</td>
<td>0.76 ±</td>
<td>0.38 ±</td>
<td></td>
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Figure 4. Positive (PPV) and negative (NPV) predictive values of different ratios Q for any and severe CAD (any CAD includes group 2 and 3, severe CAD includes group 3 only)

Figure 5. Distribution of ratios Q in three groups of patients

All patients are divided in groups 1 (blue), 2 (yellow) and 3 (red). Each point has a coordinate X (area A - in square centimeters) and coordinate Y (area B – in square centimeters). Slopes of three lines (blue, yellow and red) are mean values of Q⁻¹ in groups 1, 2 and 3, respectively (the patients in higher group have a larger recovery area for the same exercise area)
aortic stenosis). Sympathetic drive could be responsible for SBP augmentation and delayed recovery in general. Increase in exercise SBP is achieved by cardiac output increase (health) or by arterial vasoconstriction (disease) (11). The same thing is with delayed SBP recovery, mediated through vasoconstriction and increased level of circulating catecholamines. In recovery, HR declines because of parasympathetic predominance (although less rapidly in patients than in healthy subjects). Therefore, cardiac output could not be responsible for SBP augmentation. Further evidence is study by Rozanski et al. (13), where end-systolic volume (ESV), end-diastolic volume (EDV), HR and SBP were measured at rest, peak-exercise and recovery. They proved that in patients with CAD, in recovery there is an isolated ESV decrease, while EDV is equal to the resting value. Since ventricular loading is not reduced (EDV same; SBP increased) the ejection fraction (EF) increase was associated with an increased supply/demand ratio and catecholamine stimulation. In accordance with the study by Pfisterer et al. (14) who observed the attenuated EF increase in patients on beta-blockers, we observed in same patients the response with attenuated SBP augmentation. Increase in recovery EF Rozanski et al. (13), associated with highly significant stenoses and viable myocardium. Our observations regarding augmentation are in accordance with these findings.

Our further observation is related to an excluded patient with angiographically severe PAD. Among them, we investigated those without coronary artery stenoses and echocardiographically determined normal EF. They responded with recovery SBP augmentation and Q was 0.29 (recovery surface 3.5 times larger than exercise surface; the worst measured value with coronary arteries was Q = 0.5).

Another problem of stenoses detection by this calculation is explained in this example. We observed an extreme example, patients with 99% stenosis of proximal right coronary artery, with no ECG changes and no angina during the 12-minute exercise, only the history of atypical pain on strenuous exertion. In the study by Kimchi et al. (15), as well as the study by Pfisterer et al. (14), a rare phenomenon of EF increase in CAD patients during exercise was analyzed, which is probably related to the above mentioned example. Whether this is a form of warm up (or walk through) angina remains to be determined. Mechanisms under investigation are different (collaterals, not necessarily angiographically visible, vasodilatation, altered oxygen consumption, preconditioning and stunning) (16, 17), time dependent and related to previous training (18, 19). Although warm up is related to an increased ischemia threshold in the second, following exercise, in this example it is related to the ischemia threshold not correlating with a degree of stenosis in the first exercise in the previously trained patients. Obviously, the same highly significant stenoses produce ischemia in a wide range including an extreme lack ischemia.

There are several limitations of this study. Each exercise test was performed once, therefore reproducibility of ratio was not tested. In regard to warm up effect and variability of demand ischemia with stenoses of similar severity, reproducibility and sensitivity require further studies. Delayed recovery besides in CAD was observed in PAD and is probably present in other disease states. Specificity awaits for studies especially related to particular disease states separately and in combination. The subject of this study was limited to the relevant role of beta-blockers. Further investigation on a larger, representative sample of CAD patients is needed for the analysis of subgroups specifically related to beta-blockers. By measurement of BP at intervals of 1 minute maximal augmented SBP value was most likely missed. Continuous meas-

Figure 6. Shape of recovery areas in different groups of patients Patients with augmented SBP in recovery have a different slope in recovery, still areas are larger than in healthy subjects. In relation to the patients on beta-blocker therapy it is observed that augmentation of SBP is attenuated or absent. Furthermore, HR (green line) throughout the late recovery has a tendency of gradual increase in same patients.
urement or more BP measurements will not only increase precision of the ratio, but will also reveal shape of the area B. In conclusion, delayed SBP recovery has already been shown as an independent correlate of angiographically severe CAD. Our findings suggest that the ratio of exercise and recovery areas under SBP curve correlate with angiographic severity of CAD. Thus, measurement of that ratio can be used as an additional method in prediction of angiographic CAD severity.

REFERENCES


