Product of Heart Rate and First Heart Sound Amplitude as an Index of Myocardial Metabolic Stress During Graded Exercise

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Background: The double product (DP) breakpoint of heart rate (HR) and systolic blood pressure has been identified as coincident with anaerobic threshold (AT), but there are no simple methods for measuring cardiac metabolic stress (CMS) during an exercise test. It was hypothesized that the DP of HR and the amplitude of the first heart sound (AHS1) (DP-AHS1) would reflect CMS, and thus, the breakpoint in the DP-AHS1 (DPBP-AHS1) could be an alternative method for determining AT.

Methods and Results: Subjects (age range, 18–73 years) were recruited to perform a graded exercise test on a cycle ergometer with continuous monitoring of DP-AHS1, with left ventricular pressure (LVP; experiment 1, Ex1), plasma catecholamine and blood lactate (experiment 2, Ex2) and gas exchange (experiment 3, Ex3). Ex1: in all subjects there was a strong correlation between AHS1 and LVdP/dtmax (r=0.94–0.98), and between the DP-AHS1 and the triple product of HR, LVdP/dtmax, and max LVP (r=0.98–0.99). Ex2: DP-AHS1 was strongly correlated with adrenaline (r=0.97–1.00) and lactate (r=0.96–1.00) levels in all subjects. Ex3: there was a strong correlation between DPBP-AHS1, AT and maximum oxygen consumption.

Conclusions: The present simple measure of DP-AHS1 can reflect plasma adrenaline and lactate levels during graded exercise testing. Further, DPBP-AHS1 is a surrogate marker of AT and a good index of functional aerobic capacity. (Circ J 2013; 77: 2736–2741)

Key Words: Anaerobic threshold; Catecholamine; Heart sound; Left ventricular pressure; Physical exertion

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The threshold or “breakpoint” phenomenon that occurs in AT and DP during a graded exercise test is related to increased plasma catecholamine level. The rapid rise in plasma catecholamine level also causes an increase in myocardial oxygen demand (MOD) by increasing both HR and SBP. Furthermore, animal studies have shown that following adrenaline injection, the recorded amplitude of the first heart sound (AHS1) exhibits a similar increase to that of the early systolic wave of the first derivative of left ventricular pressure (LVdP/dtmax), a major determinant of MOD. Several studies have also reported continuous measurement of AHS1 during a graded exercise test. Thus, if AHS1 accurately reflects LVdP/dtmax, it may be used in place of SBP for the calculation of DP.
In the present series of studies, we (1) evaluated the relationship between AHS1 and LVdP/dtmax during graded exercise test; (2) examined the relationship between the product of HR and AHS1 (DP-AHS1) and plasma adrenaline during graded exercise test; and (3) evaluated the ability to determine DP-AHS1 and its relationship to aerobic capacity. We hypothesized that DP-AHS1 (product of HR and AHS1) would reflect MOD, and thus, the breakpoint in the product of HR and AHS1 (DPBP-AHS1) could be an alternative method for determining AT. AHS1 provides an available, inexpensive technique that could be continuously monitored during graded exercise.

Methods

Study Design

The present study was divided into 3 separate experiments. Experiment 1 examined the relationship between DP-AHS1 and MOD during a graded exercise test. Experiment 2 examined the relationship between DP-AHS1 and plasma adrenaline, noradrenaline, and blood lactate during graded exercise. Experiment 3 examined the reproducibility and inter-observer variability of DP-AHS1, and assessed the relationship between DPBP-AHS1, AT, and VO2max. All procedures, including the invasive protocols, were approved by the ethics committee of Fukuoka University, and informed consent was obtained from each volunteer after a detailed explanation of the study, including the risks and any potential discomfort associated with the procedures.

Participants

Healthy adults (age range, 18–73 years) were recruited for the 3 experiments. Due to the invasive nature of investigations, we recruited subjects from co-authors in experiment 1 and students in experiment 2. The subjects in experiment 3 were middle-aged to elderly because they are the target group of exercise testing. Mean ± SD participant age, body weight, and height are given in Table. All participants presented to the laboratory at least 1 h before the experiment and relaxed while seated for >30 min. An electrically braked cycle ergometer (Lode Rehcor, Groningen, Netherlands) was used to perform the exercise tests in all experiments. In order to determine the breakpoint, we chose the ramp test in experiments 1 and 3. To determine the relationship between DP-AHS1, plasma adrenaline and blood lactate level, we used the graded test in experiment 2.

Heart Sound Measurement

External phonocardiograms were obtained using an acceleration-type heart sound microphone (MA-300; Fukuda Denshi, Tokyo, Japan) with a high pass filter of 18 dB/octave and a normal frequency cut-off of 50 cycles/s. The microphone was positioned at the upper part of the sternum for ease of placement, greater stability and less respiratory variations of AHS1 during exercise. An electrocardiograph (ECG) with a CM5 electrode was used to simultaneously monitor and continuously record during exercise. Outputs of the phonocardiogram were downloaded to a personal computer using waveform-processing software (Chart 5; AD Instruments) via Powerlab (AD Instruments). The sampling rate was set at 1 kHz. The peak amplitude during the first 140 ms from the R wave was defined as the AHS1.

Table. Subject Physical Characteristics

|                | Experiment 1 | Experiment 2 | Experiment 3-1 | Experiment 3-2 |
|----------------|--------------|--------------|----------------|----------------|
| n (M/F)        | 7 (7/0)      | 12 (12/0)    | 25 (20/5)      | 23 (8/15)      |
| Age (years)    | 31.0±4.0     | 22.0±3.0     | 21.0±2.0       | 57.0±11.0      |
| Height (cm)    | 172.9±5.6    | 174.4±4.4    | 170.1±6.9      | 160.3±7.4      |
| Weight (kg)    | 66.3±6.7     | 70.0±10.6    | 63.5±8.3       | 73.6±12.8      |

Data given as mean ± SD.

Experiment 1

We advanced a 4-F pigtail catheter (SPC-454D; Millar Instruments, Houston, TX, USA) via the radial artery and placed it so that the pigtail tip lay at the distal LV apex. After 1 min of unloaded cycling at 60 rpm, the workload was increased at a slope of 30 W/min until volitional fatigue.

LVP, ECG, and phonocardiogram outputs were simultaneously sent to a personal computer using waveform-processing software via Powerlab. HR, AHS1, LVP, and LVdP/dtmax were continuously measured and means calculated at every consecutive 10 beats. The double product of HR and AHS1 (DP-AHS1) and the triple product (TP) of HR, LVdP/dtmax, and LVP, which is widely used as the index of MOD, were calculated.

Experiment 2

Participants presented to the laboratory at 08:00 hours after fasting overnight. Prior to the exercise test, indwelling catheters were placed in the antecubital veins. After 4 min of unloaded cycling at 60 rpm, the workload was increased by 15 W every 2 min until the rating of perceived exertion (RPE) reached 17.

Blood samples were obtained during the last 30 s of every stage from the indwelling catheter for catecholamine analysis and from the earlobe for lactate analysis. Blood samples from the indwelling catheter were placed in a heparinized tube containing EDTA. The separated plasma samples were stored at −80°C until analysis. Plasma catecholamine concentration was determined by high-performance liquid chromatography. Blood samples from the earlobe were collected in 20-μl capillary tubes and immediately mixed with a lysing stabilizing agent in a vial. Blood lactate was analyzed using Biosen 5030 (EKF Industrie, Elektronik, Barleben, Germany).

Experiment 3

After 4 min of 10-W cycling at 60 rpm, the workload was increased with a slope of 15 W/min. Twenty-five subjects participated in 2 sessions (test 1 and test 2) ≤1 week apart in order to observe day-to-day reproducibility of the DP-AHS1 (experiment 3-1).

For this experiment, participants performed the ramp test until reaching RPE=18. Twenty-three subjects performed the ramp test until volitional fatigue to observe the relationship between DPBP-AHS1, AT and VO2max (experiment 3-2). For experiment 3-2, respiratory gas analysis was conducted using the mixing chamber method to evaluate the volume of expired air, and the O₂ and CO₂ fraction was continuously analyzed on mass spectrometry (ARCO-1000; Arco Systems, Chiba, Japan). Blood samples were collected at 3 min, 5 min, and immediately after exercise to determine lactate level. VO2max was defined as a...
Figure 1. Recording of electrocardiogram and phonocardiogram in 1 subject during cycling at rest, 45W, 60W, 75W, 90W, 105W, and 120W.

Figure 2. Representative data of the product of heart rate (HR) and the amplitude of the first heart sound (HR×AHS1), triple product, AHS1 and first derivative of the left ventricular pressure (LVdP/dtmax) against workload for 1 subject. DPBP, double product breakpoint.
plateau of \( \dot{V}O_2 \) or maximum blood lactate >8 mmol/L.\(^1\) Three blinded investigators assigned AT using the V-slope method.\(^2\)

**Statistical Analysis**

Pearson’s product-moment correlation was used to assess the relationship between 2 parameters. Reproducibility from the 2 successive tests was assessed with Pearson’s product-moment correlation and the mean difference±SD. Interobserver variability was assessed using mean coefficient of variance±SD among 3 investigators. All analyses were conducted using Excel 2010 (Microsoft, Redmond, WA, USA). All data are reported as mean±SD. P<0.05 was considered statistically significant.

**Results**

**Experiment 1: AHS1 and LVdP/dt\(_{\text{max}}\), and DPBP-AHS1 and TP**

Representative data of AHS1 changes from control (arbitrary units) to graded exercise intensities are presented in Figure 1. We were able to measure AHS1 without any difficulty during exercise in all experiments. In all participants, there were very high positive correlations between AHS1 and LVdP/dt\(_{\text{max}}\) (0.94–0.98; average, 0.97) and between DP-AHS1 and TP (arbitrary units; 0.97–0.99; average, 0.98). Representative data for TP and DP-AHS1 response vs. cycle workload for 1 participant is shown in Figure 2. Both measures are expressed as a ratio of rest because they are showing the relative stress in the heart against resting level. TP demonstrated the threshold phenomenon, with a sharp increase above a certain level of exercise intensity, and increased by more than 10-fold from rest to maximum exercise in all participants. We detected a clear breakpoint in the DP-AHS1 as well as for TP at submaximal workload during graded exercise in all participants. DPBP-AHS1 was almost identical to the breakpoint of TP (Figure 3).

The average and SD of DPBP-AHS1, the breakpoint of TP and peak workload were 83.2±24.4, 85.7±24.4 and 217.2±32.6 W, respectively.

**Experiment 2: DP-AHS1, Plasma Adrenaline, and Blood Lactate**

DP-AHS1 as a ratio of the resting value and the plasma adrenaline, and blood lactate plateau of \( \dot{V}O_2 \) or maximum blood lactate >8 mmol/L.\(^1\) Three blinded investigators assigned AT using the V-slope method.\(^2\)

![Graph](image1.png)

**Figure 3.** Relationship between the breakpoint of the double product (DPBP) of heart rate and the amplitude of the first heart sound (DPBP-AHS1) and the breakpoint of the triple product (TP).

![Graph](image2.png)

**Figure 4.** Product of (○) heart rate (HR) and the amplitude of the first heart sound (HR×AHS1) and (●) plasma adrenaline concentration during graded exercise as a function of workload. Each point represents mean±SE (n=12).
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Discussion

A novel finding of this study was the observation that DP-AHS1 (the product of HR and AHS1) mirrored the TP (the product of HR, LVdP/dtmax, and LVP) and plasma catecholamines during graded exercise test. Further, we found that DPBP-AHS1, which can be easily determined, reflects functional aerobic capacity. AHS1 was previously reported to increase in parallel to LVdP/dtmax with injection of adrenaline in rodents. As expected, we found that AHS1 was highly correlated with LVdP/dtmax during exercise. During exercise, HR, SBP, and LVdP/dtmax are significant determinants of MOD. Our prior work and that from other studies has demonstrated that the DP of HR and SBP, which is a widely used index of cardiac oxygen demand, rapidly increases above LT and AT in patients with CAD, as well as in healthy subjects. As expected, TP started to increase more above a certain level of exercise during graded exercise test. In line with this observation, DP-AHS1, which represents 2 major determinants of cardiac oxygen demand, had an identical threshold phenomenon. AHS1 itself also seems to be the breakpoint (Figure 2), but AHS1 is a marker of LVdP/dtmax, which is only 1 determinant of MOD as an inotropic factor, thus we prefer to use the DP together with HR, which is representative of a chronotropic factor.

The physiological mechanisms behind the abrupt increase in TP may be related to an increase in cardiac contractility induced by β-adrenergic stimulation during exercise. The abrupt increase in adrenaline increased the DP, especially in AHS1. We observed a strong correlation between the DP-AHS1 and plasma adrenaline, suggesting causal effects of β-adrenergic stimulation on the increase in DP-AHS1. We surmise that DPBP-AHS1 reflects the effects of the increase in sympathetic nervous activity as well as circulating catecholamines on myocardial oxygen consumption.

The test–retest correlation for DPBP-AHS1 was similar to the higher value reported for AT and DPBP. The reproducibility of DPBP-AHS1 determined by the relative difference between the test and retest was also comparable to the AT. We also found that the interobserver variability of DPBP-AHS1 was as good as that for AT. The correlation between DP-AHS1 and VO2max and AT was high, while the correlation coefficient between DPBP-AHS1 and VO2max was comparable to that between AT and VO2max (r=0.88).
nally, the much greater changes in AHS1 compared with SBP make it simple to detect DP-AHS1. Given that AHS1 can be determined automatically with software, it is easy to monitor the product of HR and AHS1 during the test.

Study Limitations
AHS1 decreases in association with a reduction in the rate of intraventricular pressure development or in the conditions that cause the atrioventricular valves to close prior to ventricular systole. Thus, DPBP-AHS1 might not be detected in those with congestive heart failure in whom cardiac contractility is impaired, and in those with valvular heart disease in whom the AHS is low. The validity of DP-AHS1 in cardiac patients requires further study. Signal noise is also a disadvantage with regard to the present technique of measuring heart sounds, particularly during treadmill exercise. But we have been able to successfully measure AHS1 during exercise on a cycle ergometer without any difficulty, as well as measure AHS1 immediately after exercise on an intermittent treadmill protocol.

Conclusions
The product of HR and AHS1 mirrors cardiac oxygen demand and exhibits a threshold phenomenon during graded exercise, which may reflect a catecholamine-induced increase in β-adrenergic activation. These data suggest that DPBP-AHS1 may be a valid and useful surrogate marker of AT, which may be used to determine functional capacity and the appropriate level of exercise training.

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