35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Noninvasive Assessment of Left Ventricular Force-Frequency Relationships by Measuring Carotid Arterial Wave Intensity during Exercise Stress

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Abstract— **Background: Evaluation of the contractile state of the left ventricle during exercise is important in drawing up a protocol of cardiac rehabilitation. It has been demonstrated that color Doppler- and echo tracking-derived carotid arterial wave intensity is a sensitive index of global left ventricular (LV) contractility.**
Objectives: We assessed the feasibility of measuring carotid arterial wave intensity and determining force-frequency (contractility-heart rate) relationships (FFR's) during exercise totally noninvasively.
Methods: We measured carotid arterial wave intensity with a combined color Doppler and echo tracking system in 15 healthy young male volunteers (age 20.8 ± 1.3 years) at rest and during exercise. FFR's were constructed by plotting the maximum value of wave intensity (WD_1) against heart rate (HR).
Results: WD_1 increased linearly with an increase in HR. The goodness-of-fit of the regression line of WD_1 on HR in each subject was very high (r^2 0.67 ~ 0.91, $p < 0.0001$ respectively). The slope of the WD_1-HR relation ranged from 0.31 to 1.52 [m/s^3(beat/min)].
Conclusions: A global LV FFR can be generated in healthy young volunteers with an entirely noninvasive combination of exercise and wave intensity. These data should show the potential usefulness of FFR in the context of cardiac rehabilitation.

Introduction

Evaluation of the changes in contractile state of the left ventricle during exercise is an important, and as yet not easy, goal in the procedure for cardiac rehabilitation. The positive inotropic effect of increasing the frequency of contraction in isolated cardiac muscles has been known as Bowditch effect or staircase phenomenon. The positive inotropic effect of increased heart rate (HR) produced by pacing also has been demonstrated in healthy human subjects, which has been called the force-frequency relationship (FFR) [1]. In conventional methods of obtaining FFR's, the maximum rate of LV pressure rise (Peak dP/dt) measured with a catheter-tipped micromanometer was used as an index of cardiac contractility, and atrial pacing was used to change heart rate (Peak dP/dt - HR relation) [1, 2]. It has also been reported that the FFR is significantly affected in hearts with a variety of diseases [2-5]. It has also been demonstrated that the Peak dP/dt-HR relation is markedly enhanced (the slope is increased) during exercise compared with during pacing in normal hearts, but the enhancement is limited in diseased hearts [1, 2]. In spite of its potential for evaluating cardiac function during exercise, Peak dP/dt-HR relation has not been widely used because of its invasive nature.

We have reported that carotid arterial wave intensity (WI) measured with a combined system of color Doppler and echo tracking is a sensitive index of global LV contractile function (Fig.1) [6, 7].

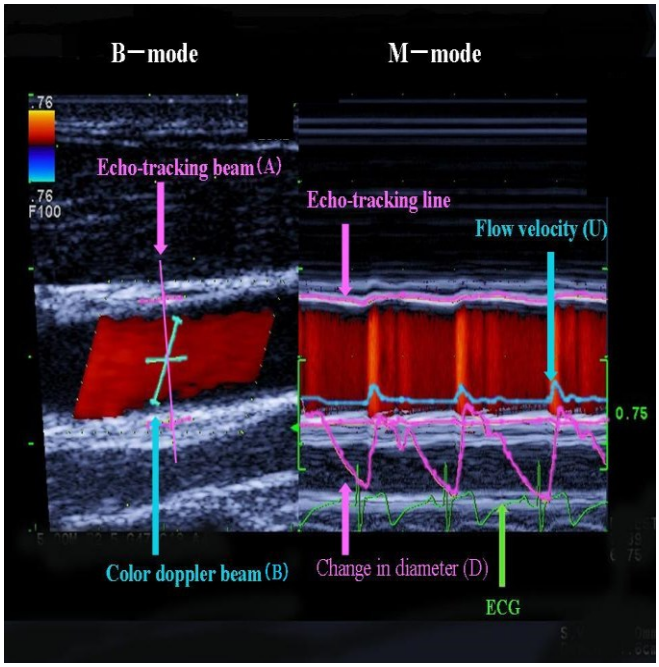

Figure 1. Simultaneous measurements of diameter-change waveforms and blood flow velocity. View on the monitor during the measurements. Left: Color-Doppler / B-mode long-axis view of the common carotid artery. Lines A and B indicate the ultrasonic beam for echo tracking and for blood flow velocity measurement, respectively. By setting the tracking positions displayed as small pink bars on the echo-tracking beam (line A) to arterial walls, echotracking automatically starts. The blood flow velocity averaged along the Doppler beam (line B) crossing the artery was measured using range-gated color-Doppler signals. Right: The diameter-change waveforms, which are calculated by subtracting the distance to the near wall from that to the far wall, and the velocity waveforms are displayed on the M-mode view.

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In this study, we assessed the usefulness of WI to measure LV contractility and FFR's during exercise, and evaluated the feasibility of an entirely noninvasive method for demonstration of the global LV FFR.

Methods

Definition of wave intensity in terms of diameter change

Wave intensity (WI) is a hemodynamic index, which is defined as

$$WI = (dP/dt)\,(dU/dt), \quad (1)$$

where dP/dt and dU/dt are the derivatives of blood pressure (P) and velocity (U) with respect to time, respectively. The maximum value of WI during a cardiac cycle (W_1) significantly correlates with Peak dP/dt (or max dP/dt) [6].

In our method of obtaining carotid arterial WI, carotid diameter-change waveform was used as a surrogate for carotid pressure waveform [7, 8]. Using diameter-change waveform directly, we can also define a wave intensity (WD) as

$$WD = (1/D)\,(dD/dt)\,(dU/dt). \quad (2)$$

WD is obtained by measuring U and D without measuring upper arm pressure (Fig. 2), which is easier to perform during exercise.

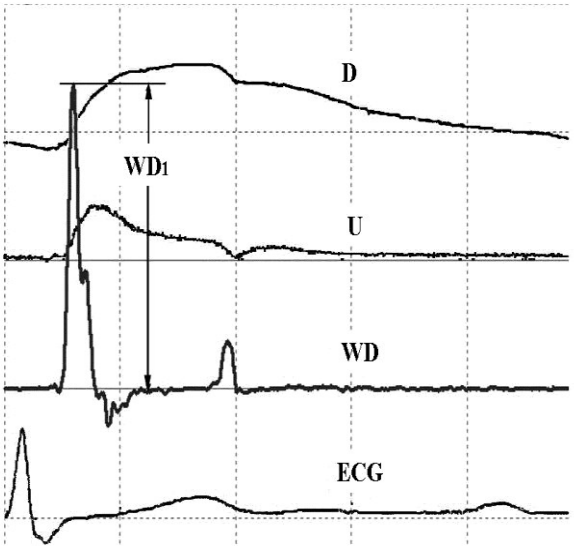

Figure 2. Representative recordings of diameter (D) and blood flow velocity (U), and calculated wave intensity (WD) obtained from the common carotid artery of a normal human.WD is the wave intensity defined by using D as WD = (1/D) (dD/dt) (dU/dt).

The definition of the stiffness parameter (β) gives the relation

$$(1/D)\,(dD/dt) = (1/\beta P)\,(dP/dt). \quad (3)$$

Therefore,

$$WD = (1/\beta P)\,WI. \quad (4)$$

Hence, the maximum value of carotid arterial WD during a cardiac cycle (WD_1) correlates with the maximum value of WI (W_1) (Fig. 3). Therefore WD_1 correlates with Peak dP/dt as W_1 does. The details of the method of measurements were described elsewhere [7].

Subjects

We studied 15 healthy male volunteers (mean age 20.8 ± 1.3 years, age range 19 – 23 years) (Table 1). We obtained informed consent from all the subjects. Approval from the Ethics Committee of Himeji Dokkyo University was obtained before study initiation.

Protocol

Subjects were asked to refrain from caffeine, alcohol, and exercise during 24-hour period before test.

Before the measurements of WD_1 and HR, the subjects lay down in the supine position for 10minutes. The location to be measured was the common carotid artery at about 2cm proximal to the carotid bulb. We used scanning in the long axis view, and obtained a B-mode image of a longitudinal section of the artery (Fig. 1 left). With the B- and M-mode scans displayed simultaneously on a split screen, the echo-tracking system tracked the vessel wall movements to

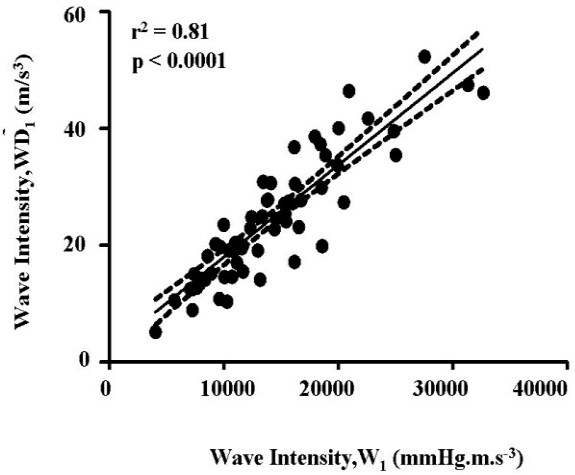

Figure 3. Relationship between the maximum values of WD (WD_1) and WI (W_1). Pooled data obtained from 67 subjects (age range 19 to 24 years).

produce displacement waveforms of the anterior and posterior artery walls (Fig. 1 right). This gave the diameter-change waveforms [7].

After the measurements of WD_1 and HR at rest, gradual bicycle exercise was performed starting at an initial workload of 20 W and lasting for 2minutes; thereafter, the workload was increased stepwise by 20 W at 1-minute intervals. Electrocardiogram was continuously monitored.

The criteria for the endpoint included increase of heart rate to [(220-age) × 0.8 (bpm)], and achievement of maximum fatigue or the impossibility of continuing exercise. We measured WD_1 and HR during the exercise.

Statistical analysis

The obtained data are presented as mean ± SD. Correlation between WD_1 and HR was assessed by the linear regression method before and during exercise. A value of $p < 0.05$ was considered statistically significant.

Results

The baseline data from the subjects are shown in Table 1.WD_1 increased linearly with an increase in HR (Fig. 4). The goodness-of-fit of the regression line of WD_1 on HR in each subject was very high (r^2 0.67 ~ 0.91, $p < 0.0001$, respectively).

Table 1.Baseline characteristics of the subjects.

	age [years]	height [cm]	weight [kg]	BMI [kg/m]	HR at rest [bpm]	WD_1 at rest [m/s3]
1	23	171	64	21.9	65	28
2	23	171	64	21.9	74	32
3	21	175	62	20.2	61	10
4	21	163	55	20.7	84	23
5	21	170	60	20.8	74	19
6	20	172	65	22.0	65	21
7	21	173	54	18.0	82	9
8	19	175	63	20.6	78	18
9	21	171	87	29.8	73	22
10	22	172	66	22.3	74	23
11	19	177	71	22.7	61	9
12	19	160	56	21.9	88	50
13	19	180	69	21.3	62	19
14	21	173	70	23.4	62	22
15	22	170	60	20.8	79	17
mean	20.8	171.5	64.4	21.9	72	22
SD	1.327	4.773	7.847	2.4	9	10

BMI : Body Mass Index, HR: Heart Rate, WD_1: The maximum value of wave intensity WD.

The slope of the WD_1-HR relation ranged from 0.31 to 1.52 [m/s^3 (beat / min)].

Discussion

The basic property of the force-frequency effect to progressively enhance myocardial contractility as heart rate increases is markedly augmented due to β-adrenergic stimulations induced by exercise in normal hearts. However, significant impairment of exercise-induced amplification of the FFR is observed in diseased hearts. Therefore, one would expect the diversity of responses of the FFR to β-adrenergic stimulations induced by exercise affords increased sensitivity for detection of contractile impairment.

One group has used exercise echocardiography to demonstrate FFR's nonivasively[9].However, in contrast to the present study, their index (systolic blood pressure/ end-systolic volume) was a rarely used and unvalidated index of contractility [10] .

Several other groups have used tissue Doppler-derived isovolumic acceleration (IVA) during exercise, and presented FFR curves [10-12]. However, IVA is a parameter of regional myocardial contractility of LV wall, and not necessarily represents the global contractile state of the left ventricle. Indeed, values of IVA vary considerably according to the region of interest of left ventricular wall. In some cases, IVA obtained from the mid lateral wall is more than 50% greater than that obtained from the basal anterior wall [13] .

In addition, the IVA-HR relation during exercise is not linear [10] , in contrast to the linear WD_1-HR relation. It is always easier to characterize a linear relation than to characterize a nonlinear relation.

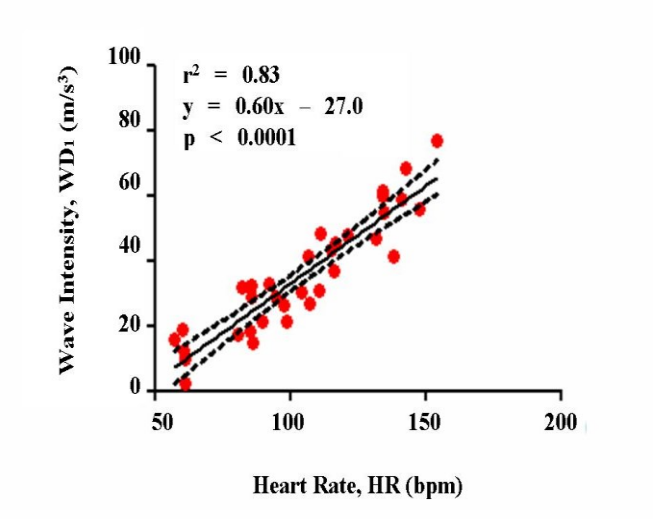

Figure 4. The FFR (WD_1-HR relation) obtained from a representative subject.

Limitations

Although the WD_1-HR relation depends on age, our study subjects only ranged from 19 to 23 in age. We should enroll a greater number of subjects to be divided into age groups in future study. The final goal of our study is to apply the force-frequency relation in practicing cardiac rehabilitation. However, we did not enroll patients with heart diseases in the present feasibility study.

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