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Do Acute Changes in Heart Rate by Isoproterenol Affect Aortic Stiffness in Patients with Hypertension?

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Background : Increased aortic stiffness is a independent risk factor of cardiovascular disease in patients with hypertension. Acute changes of the heart rate (HR) have been reported not to affect the aortic stiffness in pacing. However, it is unknown whether acute changes in HR caused by sympathomimetics can affect the aortic stiffness in patients with hypertension. We investigated the effect of acute changes in HR produced by isoproterenol on the aortic stiffness in 17 hypertensive patientss (mean age: 59±9 years).

Methods : All vasoactive drugs were discontinued at least 3 days before the study. The carotid-to-femoral pulse wave velocity (PWV) was measured by the foot-to-foot method. The pulse waves were recorded at the baseline and at every increase of HR by 5 to 10 bpm with a gradual increase of the dose of isoproterenol. The blood pressures and HR were measured simultaneously. For the analysis, HR, PWV, compliance (C), and compliance index (Ci) were converted as percent changes (△) from the baseline values. Percent changes of the parameters of the aortic stiffness, i.e., △PWV, △C, and △Ci, were grouped by every 10% increase in △HR.

Results : There was no significant difference among groups in △PWV, △C and △Ci (p>0.05 for each of the group). The regression analysis showed no significant correlation of △HR with △PWV and △C (r=0.18, 0.13 respectively, p>0.05 for each). △Ci had a poor correlation with △HR (r=0.22, p<0.05). However, only 4.6% of △Ci could be referred to △HR (r^2=0.046).

Conclusion : Aortic stiffness was not affected by acute changes in HR produced by isoproterenol which suggests that it is not necessary to consider acute changes in HR when measuring aortic PWV.

Key Words : Aorta, Stiffness, Heart rate, Hypertension

INTRODUCTION

An increased aortic stiffness is a reliable factor of prognosis for all-cause and cardiovascular mortality in patients with hypertension[1-3]. The measurement of the aortic stiffness can serve as an important method of identification of hypertensive patients at an increased risk of the cardiovascular disease[1, 2]. The aortic stiffness can be assessed non invasively by measurement of the pulse wave velocity (PWV) a simple, reproducible, and widely used method[3, 4]. Measurement of PWV is also routinely/ or often used to evaluate the effect of antihypertensive drugs on the aortic stiffness.

Acute changes of blood pressure (BP) affect the measurement of PWV. The level of BP positively correlates with PWV. Therefore, the compliance index (Ci), which is BP independent index of arterial distensibility, was proposed, to evaluate the aortic stiffness[5]. However, the data on the influence of acute changes in the heart rate (HR) on the aortic PWV is limited. Recent studies[6, 7] show that an increase of HR in the atrial pacing does not alter the aortic PWV. These studies included patients without hypertension[6, 7] and were conducted without discontinuation of vasoactive drugs[7]. It has not yet been clearly elucidated whether PWVs measured at different HRs can be used in the follow-up of the aortic stiffness in hypertensive patients.

Therefore, we evaluated the influence of acute changes in

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HR effected by isoproterenol on the aortic stiffness, as assessed by PWV measurements, in hypertensive patients.

MATERIALS AND METHODS

1. Subjects

This study included patients with essential hypertension, in whom the diagnostic coronary angiography was planned for evaluation of the chest pain. The exclusion criteria were: cardiac arrhythmia, unstable angina, myocardial infarction, valvular heart disease, cerebrovascular disease, congestive heart failure, and carotid arterial disease. Subjects with HR above 80 bpm at rest or increased by 15% or more at the baseline, i.e., just before the measurement of PWV, compared with that at rest, were also excluded from the study.

2. Study design

Vasoactive drugs, except aspirin, were discontinued at least 3 days before the coronary angiography. All patients were given 5 mg of oral diazepam before the coronary angiography. Informed consent was obtained from all the patients before the procedure.

PWV was measured after the coronary angiography. After recording of the pulse waves, HR and BP at the baseline, isoproterenol was infused intravenously at the starting dose of 2 mg/min. The dose of isoproterenol was increased by 2 mg/min at every 5 minutes intervals. During the whole procedure, HR and BP were continuously monitored. The pulse waves were recorded at every 5 to 10 bpm increase in HR. Recording of the pulse waves was stopped when HR increased by more than 60% in respect of the baseline HR. HR and BP were measured simultaneously with the pulse wave recording. HR was determined from the 3-lead orthogonal ECG. BP was measured by the fluid-filled manometer system through the sidearm of the 6F arterial sheath of the right femoral artery.

3. *Measurement of aortic PWV*

The aortic pulse waves were recorded simultaneously with TY-307 Fukuda pressure sensitive transducers (Fukuda, Tokyo, Japan) at two sites: the left common carotid artery at the base of the neck and the left femoral artery at the groin level. The pulse waves were recorded at a high speed (200 mm/sec) in the paper chart recorder (MCS 5500, Fukuda, Tokyo, Japan).

PWV was determined by the foot-to-foot method[8, 9]. The foot of the pulse wave was defined as the point of intersection of the horizontal line that passed through the point of the minimum pressure at the foot and the line that was drawn from the center of the sharp systolic upstroke of the next pulse wave. The foot-to-foot time delay (TD) was measured between the feet of the simultaneously recorded waves of the left carotid artery and the left femoral artery, and calculated as the mean of at least 10 consecutive waves. The distance covered by the pulse waves was measured over the surface of the body with a tape measure. The distance from the suprasternal notch to the left carotid site (D2) was subtracted from the total distance between the left carotid site and the femoral site (D1). PWV was calculated as the ratio between the distance covered by the pulse and the foot-to-foot TD and expressed in meters per second.

PWV (m/sec) = (D1-D2)/TD

The aortic compliance (C) was calculated per 10 mmHg of the pulse pressure, as previously reported[10] : $C = 66.7/PWV^2$.

The compliance index (Ci), the expression of the aortic compliance, which is independent from BP changes, was also calculated as previously reported[5, 10] : $Ci = C\ (DP\ 10^{-3})/LN(Ps/Pd)$, where Ps and Pd are systolic and diastolic BP, and DP is the pulse pressure.

4. *Analysis*

HR, PWV, C and Ci were expressed as percent changes (△) from the baseline values. HRb, PWVb, Cb and Cib indicate the baseline HR, PWV, C and Ci.

Percent changes of the heart rate (△HR) =
100 x (HR-HRb)/HRb
Percent changes of PWV (△PWV) =
100 x (PWV-PWVb)/PWVb
Percent changes of compliance (△C) = 100 x (C-Cb)/Cb
Percent changes of compliance index (△Ci) =
100 x (Ci-Cib)/Cib

△HR were grouped by every 10% increase (group 1 : 0% △HR < 10%; group 2 : 10% △HR < 20%; group 3 : 20% △HR < 30%; group 4 : 30% △HR < 40%; group 5 : 40% △HR < 50%; group 6 : 50% △HR < 60%). Comparisons among groups were made using one-way ANOVA and independent-samples *t*-test. To evaluate the correlations of △HR with △PWV, △C, and △Ci, a linear regression analysis was performed. Statistical analysis was performed using SPSS for Windows Version 10.0.7. (SPSS inc). Unless it is stated otherwise, the results are presented as mean±SEM, and a $p<0.05$ was considered as statistically significant.

RESULTS

We studied 17 patients, 3 men and 14 women (age 59±9 years [mean SD]). At the baseline, systolic and diastolic BP were 172±2 mmHg and 92±1 mmHg, HR was 76±9 bpm.

(mean±SD). Figure 1 shows the influence of acute changes in HR on the aortic stiffness when △PWV, △C, and △Ci were analyzed between grouped DHR. Although DPWV showed a tendency to increasewith an increase in DHR, there was no significant difference among the groups (p>0.05 by ANOVA and independent-samples t-test). △C and △Ci also showed a tendency to decrease without significant difference among the groups (p>0.05 by ANOVA and t-test).

Figure 2 shows the results of the linear regression analysis, which evaluated the correlation between △HR and △PWV, △C, and △Ci. There was also an increasing tendency of △PWV (r=0.18, r^2=0.033), and a decreasing tendency of △C (r=0.13, r^2=0.017) with an increase

in △HR. However, △PWV and △C showed no significant correlation with △HR (p>0.05). Although △Ci showed a very weak negative correlation with △HR, r^2 was 0.0046, indicating that only 4.6% of the changes in the compliance index could be referred to changes in the heart rate.

DISCUSSION

The arterial compliance plays an important role in cardiovascular diseases. An increased aortic stiffness has a positive correlation with the presumed atherosclerotic load[11] and high HR[12]. The aortic stiffness is a strong independent predictor of all-cause and cardiovascular mortality in patients with essential hypertension[1-3] as well as hemodialysed patients with the end-stage renal disease[13]. Thus, the measurement of the aortic stiffness could serve as an important tool in identifying patients at an increased risk of the cardiovascular disease.

The aortic stiffness can be assessed by non-invasive methods[14]. Pulse pressure measurement, applanation tonometry, measurement of intimal medial thickness or arterial distension by the echo-tracking signal, and PWV measurement are routinely used methods. The aortic PWV measurement can be done easily, without expensive equipment and is now widely used to evaluate the aortic stiffness in hypertensive patients[15]. Recently, a large-scale intervention trial demonstrated feasibility of the aortic PWV measurement as the endpoint in hypertensive patients[16].

Two non-invasive methods are generally used to measure PWV-the Doppler method and the pressure transducer method. The latter method is the most commonly used. PWV is derived from the measurement of the pulse transit time and the distance covered by the pulses between the two recording sites. The pulse transit time is determined from the time delay between the feet of the two corresponding waves, which are usually recorded from the carotid artery and the femoral artery simultaneously. The distance covered by the pulses is obtained from the superficial measurement of the distance between the two transducers. PWV is calculated by dividing the distance by the pulse transit time.

The measurement of PWV is influenced by BP level[5]. An elevation of BP can increase the aortic PWV. Therefore, Ci which is independent from the blood pressure is proposed and routinely used what?[5]. However, only few studies have evaluated the influence of acute changes in HR on the measurement of the aortic PWV.

High HR and sympathetic tone have an arterial stiffening effect[12, 17, 18]. Mangoni et al.[18] report that in rats, an acute increase in HR due to pacing was accompanied by a marked reduction in the distensibility of the common carotid artery, whereas the distensibility of the femoral artery was much less consistently affected. In the carotid artery, the stiffening effects of tachycardia were exerted independently /or irrespective of/

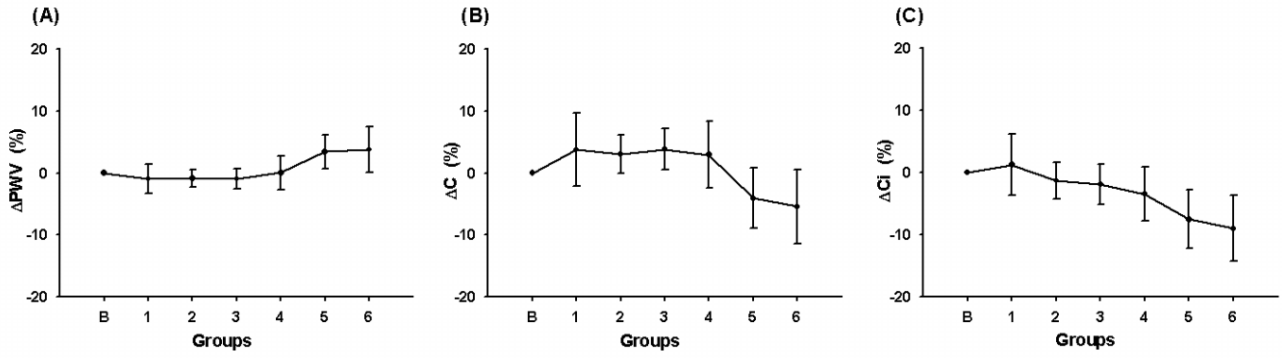

Figure 1. Effects of acute changes of heart rate on aortic pulse wave velocity. Changes of heart rate (△HR) are grouped by every 10% increase of heart rate. Relationship between (A) △HR and % changes of aortic pulse wave velocity (△PWV), (B) △HR and % changes of aortic compliance (△C), (C) HR and % changes of aortic compliance index (△Ci). Values represent means±SEM. By ANOVA and t-test, △PWV, △C and △Ci showed no difference between groups (p>0.05 by ANOVA and unpaired t-test). B represents basal value.

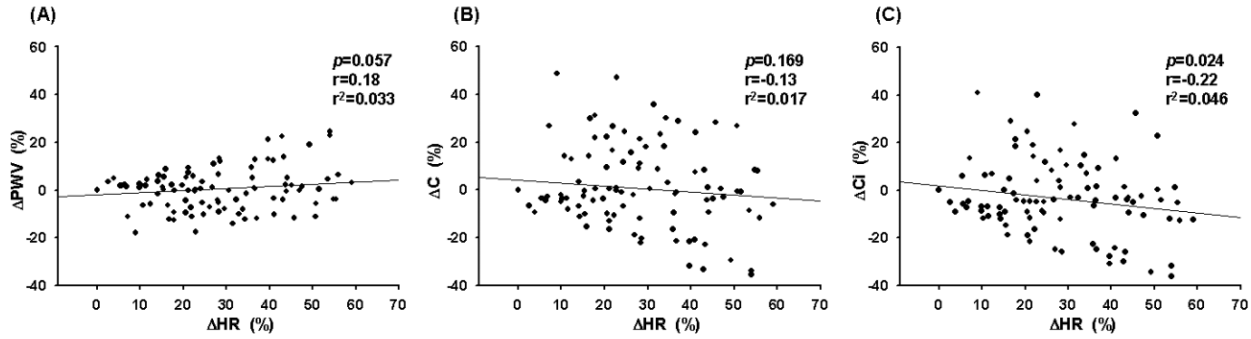

Figure 2. Correlations between, (A) % changes of heart rate(△HR) and % changes of aortic pulse wave velocity (△PWV), (B) HR and % changes of aortic compliance (△C), and (C) HR and % changes of aortic compliance index (△Ci). By linear regression analysis, PWV and △C do not significantly correlate with △HR. △Ci very weakly correlates with HR. However, only 4.6% of △Ci can be referred to △HR. Linear regression line is shown.

from the sympathetic modulation, and in the femoral artery, removal of sympathetic influence unmasked the stiffening effects of tachycardia. Albaladejo et al.[7] evaluated, in patients with the pacemaker monitoring, the influence of acute changes in HR on PWV. HR was increased by pacing, and was grouped into low, middle, and high HR. Although a higher aortic pulse wave velocity was noted in the high HR group, it was not statistically significant. Wilkinson et al.[6] also reported that in patients undergoing electrophysiologic testing or cardiac catheterization, the incremental atrial pacing over the physiologic range of HR did not influence the aortic stiffness. However, these studies included patients without hypertension[6, 7] and the evaluation was made without discontinuation of vasoactive drugs[7]. It is not simple to apply the previous results[6, 7] directly to the aortic PWV measurement in hypertensive patients. Hypertensive patients have arterial properties different from those of normotensive subjects. Antihypertensive medication, such as calcium antagnoists and angiotensin, converting enzyme inhibitors can also affect the aortic stiffness. Therefore, the influence of acute changes in HR on PWV measurement in hypertensive patients might be different from that in normotensive patients.

The present study has some different aspects in the study design compared with the previous studies[6, 7]. Only subjects with hypertension were included into the study. To minimize the influence of vasoactive drugs on the PWV measurement, all vasoactive drugs were discontinued at least 3 day before the evaluation. PWV was also measured continuously at every 5 to 10 bpm increase in HR.

In the present study, although the aortic stiffness showed a tendency to with an increase in HR, it was not statistically significant. There was no significant correlation of acute changes in HR with changes in PWV and the compliance. Changes of Ci showed a very weak negative relationship with acute changes of HR. However, r^2 of DCi to changes of HR was 0.0046, which indicates that only 4.6% of changes of Ci could be referred to the changes in HR. The predictive power was very low.

The findings of the present study indicate that the influence of acute changes in HR on the aortic stiffness is negligible, which is consistent with the previous studies[6, 7]. Thus, when we evaluate the aortic stiffness with PWV, to identify hypertensive patients at an increased risk of the cardiovascular disease or to assess the effect of antihypertensive drugs on the aortic stiffness, it seems not to be necessary to consider acute changes of HR.

The present study has limitations. First, the number of the study subjects was small. To apply these results to all hypertensive patients, further studies with a large number of patients are needed. Second, we used isoproterenol to increase HR. Isoproterenol dilates peripheral vessels. There may be a potential influence of dilatation of peripheral arteries at the PWV measurements. There are no data of the influence of dilatation of peripheral arteries on aortic PWV. However, the findings of the present study are consistent with the previous studies[6, 7], which showed no association between acute changes of HR caused by atrial pacing and aortic PWV in normotensive subjects. In addition, the present study is the first attempt to evaluate the effect of isoproterenol on aortic PWV. Third, we measured only PWV and calculated C and Ci from PWV, to evaluate the aortic stiffness. It is unknown whether other methods of evaluation of the aortic stiffness will give the same results.

In summary, acute changes in HR do not significantly affect the aortic stiffness in hypertensive patients, measured by PWV. These results suggest that it is not necessary to consider the influence of acute changes in HR, when we evaluate the aortic stiffness.

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