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Postocclusive Reactivity of Radial Artery in Patients with Essential Hypertension, Hypercholesterolemia or Diabetes Mellitus

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Abstract To investigate the peripheral vascular reactivity in patients with hypertension (HT), hypercholesterolemia (HC) or diabetes mellitus (DM), one minute postocclusive reactive hyperemia (PORH) response of the radial artery by pulsed Doppler echography was assessed. Subjects were 10 patients with HT, 8 patients with HC, 8 patients with DM, and 19 control subjects [11 older controls (Group O) and 8 younger controls (Group Y)] without HT, HC nor DM. Ages were matched between Groups O, HT, HC and DM. The pulsed Doppler indices were time to peak response (Tp) and recovery half-time (T1/2) of time-velocity integral of the radial arterial flow velocity signals. Also, the percent increase of the radial arterial luminal diameter from rest (%ΔD) was determined on a color flow imaging. Tp was significantly longer in Group O (2.3±0.3 sec) than in Group Y (1.4±0.1 sec) ($p<0.05$). Also, T1/2 was significantly longer in Group O (7.4±0.9 sec) than group Y (4.3±0.5 sec) ($p<0.05$). These data suggested that the early PORH response was prolonged and the reactivity of the resistance vessels was impaired with aging. Then, %ΔDs of HT, HC and DM groups were compared with that of Group O. %ΔD was significantly smaller in HT group than group O within the initial 30 seconds after reperfusion, and significantly smaller in HC group until 3 minutes after reperfusion ($p<0.05$). DM group was not different from group O in %ΔD. These results suggested that flow-mediated dilatation of the radial artery during PORH response was impaired in the HT and HC groups. Thus, the analyses of the PORH response using Doppler echogram and color flow imaging were useful for evaluation of peripheral vascular reactivity in the radial artery.

Key words: Postocclusive reactive hyperemia, Pulsed Doppler echography, Color flow imaging, Radial artery, Flow-mediated dilatation

Introduction

Postocclusive reactive hyperemia (PORH) response is a local phenomenon that occurs after temporary occlusion of the blood supply[1], and the PORH response is an alternative functional test[2-5] used to assess the circulation of the upper extremities. Development of a color duplex and Doppler instrument with high frequency probe made it possible to analyze the blood flow and view of peripheral vessels. In this study, by using the pulsed Doppler and color flow ultrasonographic indices of the PORH response the

peripheral vessel reactivity was noninvasively investigated in younger and older controls, and patients with hypertension (HT), hypercholesterolemia (HC) or diabetes mellitus (DM).

Materials and Methods

Materials

Twenty-six patients with one of the three major risk factors for arteriosclerosis, HT, HC or DM (16 men and 10 women, aged 41 to 81 years, mean age: 64±2 years old) and 19 control subjects without these three diseases (12 men and 7 women, aged 26 to 83 years, mean age: 50±5 years old) were investigated. The patient group consisted of 10 patients with HT (7 men and 3 women, mean age: 65±3 years old), 8 patients with HC (3 men and 5 women, mean: age 64±3 years old), and 8 patients with DM (6 men and 2 women, mean age: 61±4 years old). To examine the influence of aging on the PORH response, data for 8 control subjects younger than 39 years old (Group Y: 7 men and 1 woman, mean age 30±2 years old) and 11 control subjects older than 40 years old (Group O: 5 men and 6 women, mean age 65±4 years old) were analyzed. HT, HC and DM groups were consisted of the patients who were diagnosed and treated as essential hypertension, hypercholesterolemia or diabetes mellitus, respectively. All hypertensive and cardiovascular medications were discontinued at least 24 hours prior to the study. Informed consent was obtained from all subjects.

Methods

The patients were at rest at least 10 minutes before initiation of the study. The resting left brachial blood pressure was measured by sphygmomanometry. The

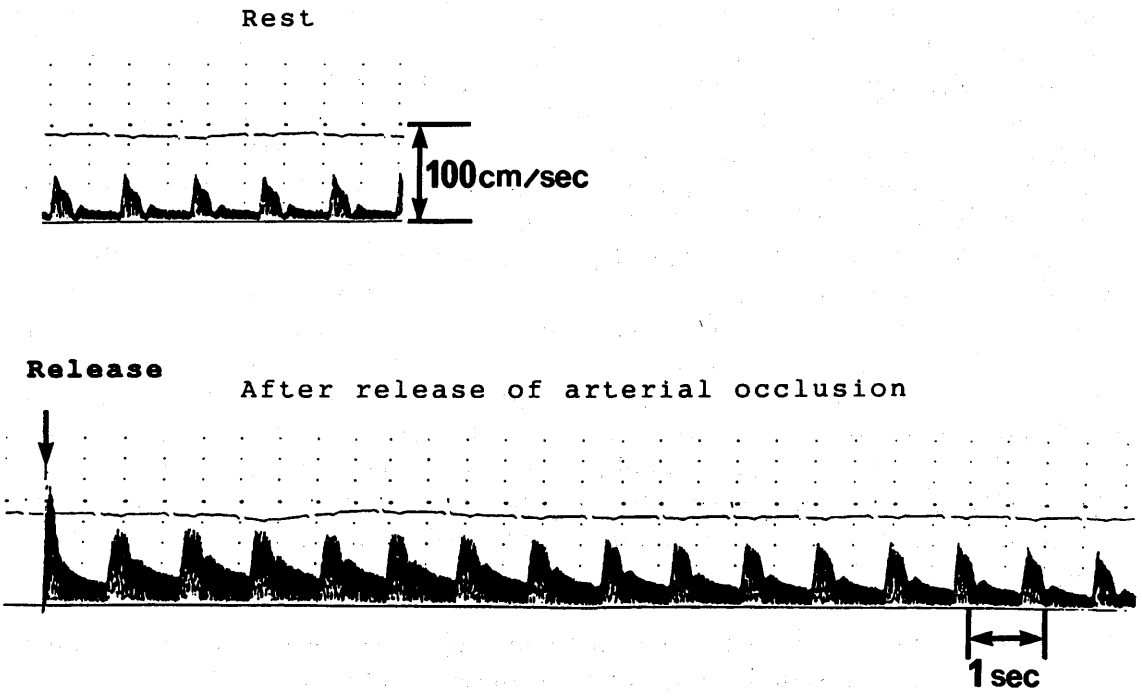

Figure 1. Representative recordings of radial arterial flow velocity (RAFV) at rest and postocclusive reactive hyperemic response.
After the recording of the resting RAFV (upper tracing), an arm-cuff was inflated with a pressure at least 30 mmHg above the systolic blood pressure for one minute. The cuff was then completely deflated ("Release" in the lower tracing). The RAFV was recorded through the first one minute and for several seconds at 3 and 5 minutes after reperfusion.

PORH response was measured using a duplex ultrasound instrument (HITACHI EUB 565A) with a 7.5-MHz linear probe (HITACHI EUP L33S). The right radial arterial Doppler flow signal was recorded for several seconds at the radial artery located on the distal portion of the forearm, and the luminal diameter of the radial artery was recorded on a video-tape. After the recording of the resting radial arterial Doppler signal (upper tracing of Fig.1), the PORH response was induced as below. Namely, an arm-cuff was inflated with a pressure at least 30 mmHg above the systolic blood pressure for one minute. The cuff was then completely deflated ("Release" in the lower tracings of Fig.1). The radial arterial Doppler flow signal was recorded through the first one minute and for several seconds at 3 and 5 minutes after reperfusion. Time integrals of the radial arterial flow velocity (IntRAFV) at rest and 3 and 5 minutes after PORH response were measured for 4 seconds from the beginning of the percussion wave and the IntRAFV per minute was obtained by multiplying 4-second IntRAFV by 15. Ten minutes after the reperfusion, the luminal diameter of the radial artery was determined by color flow imaging and the value was assumed as the diameter at the rest. Then, radial arterial PORH was induced again by one-minute arm cuff compression as before. The luminal diameter of the radial artery was recorded at 5 and 30 seconds, and 1, 3, and 5 minutes after PORH response. The luminal diameter was measured at the R wave on ECG.

Definition and calculation of indices

The time to peak response (Tp) was defined as an interval from the time of the reperfusion to the midpoint of the peak IntRAFV beat. The interval from the beginning of the reperfusion to the midpoint of the beat of which IntRAFV was 50% decrease from the peak IntRAFV per beat during the PORH response (recovery half-time: T1/2) was determined (Fig.2). The percent increase in the luminal diameter of the radial artery during the PORH response (%ΔD) was determined by the following equation:

$$\%\Delta D\ [\%] = (D'-D/D) \times 100$$

where D' is the radial luminal diameter during the PORH response and D is the luminal diameter at rest. The %ΔD was calculated at 5 and 30 sec, and at 1, 3, and 5 min after the

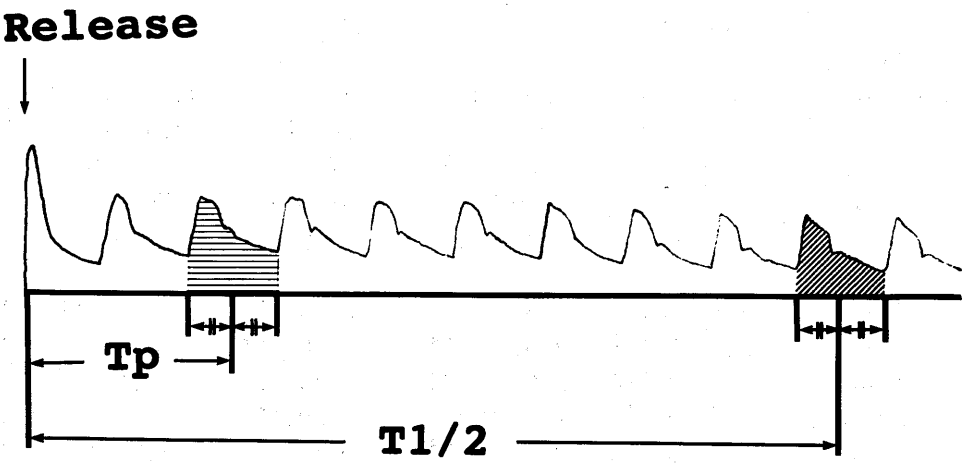

Figure 2. Diagram of the radial arterial flow trace after reperfusion.
This trace annotates on the indices of Tp and T1/2. The transverse lined area is the beat of peak time-velocity integral of radial artery flow velocity (IntRAFV). The oblique lined area is the beat of 50% decrease from the peak value in the time velocity integral after reperfusion. Tp is the time from the reperfusion (Release) to the midpoint of the beat of peak IntRAFV. T1/2 is the time from the reperfusion to the midpoint of the beat of 50% decrease from the peak IntRAFV.

reperfusion. Values were expressed as the mean ± standard error (S.E.). Data were analyzed by ANOVA and when differences between groups were indicated, the Sheffe's F-test was used. A p value of <0.05 was considered statistically significant.

Results

PORH response in control subjects

The IntRAFV per minute during the first 30 seconds of PORH response in Group Y did not increase significantly compared to that of at rest, although there was significant increase in Group O during the first 30 seconds after reperfusion (Table I). The IntRAFV per minute during the next 30 seconds of PORH response in Group Y did not change significantly compared to that of at rest, although there was significant decrease in Group O during the next 30 seconds after reperfusion (Table I). The luminal diameter of the radial artery was significantly increased at 5 and 30 sec and at 1, 3, and 5 minutes after reperfusion compared with the resting values in Groups Y and O (Table I). There was no significant difference in the % ΔD between Group Y and Group O throughout the PORH response (Table II). Tp was significantly longer in Group O (2.3±0.3 sec) than Group Y (1.4±0.1 sec, $p<0.05$) (Fig 3). Also, T1/2 was longer in group O (7.4±0.9 sec) than Group Y (4.3±0.5 sec, $p<0.01$) (Fig. 4). Heart rate was significantly decreased during PORH response in Group Y, and not changed in Group O (Table I).

PORH response in HT, HC or DM Groups

The IntRAFV per minute significantly increased during the first 30 seconds after reperfusion in HT, HC and DM groups($p<0.01$, $p<0.01$ and $p<0.05$, respectively), and significantly decreased during the next 30 seconds after reperfusion in the HT group compared to resting value ($p<0.05$) (Table I). The luminal diameter of the radial artery

Table I Doppler echographic variables at rest and during the PORH response in control subjects, and patients with HT, HC, or DM

		Group Y	Group O	HT	HC	DM
IntRAFV	rest	1362±98	1365±155	1282±144	1222±128	1319±182
	PORH					
[cm/min]	0-30sec	1452±98	1566±144*	1786±170**	1758±162**	1640±168*
	30-60sec	1376±142	1104±134*	1098±152*	1124±172	1224±218
	3 min	1269±96	1270±177	1224±147	1143±182	1329±191
	5 min	1272±116	1220±172	1302±131	1298±174	1176±183
D	rest	2.6±0.1	2.4±0.1	2.4±0.1	2.4±0.1	2.5±0.1
[mm]	PORH					
	5sec	2.8±0.1††	2.6±0.1††	2.5±0.1††	2.5±0.1††	2.7±0.1††
	30sec	2.7±0.1††	2.6±0.1††	2.5±0.1††	2.5±0.1††	2.6±0.1††
	1min	2.7±0.1††	2.6±0.1††	2.5±0.1††	2.5±0.1**	2.6±0.1†
	3min	2.7±0.1††	2.5±0.1††	2.5±0.1††	2.5±0.1	2.6±0.1†
	5min	2.6±0.1**	2.5±0.1††	2.5±0.1**	2.4±0.1	2.6±0.1†
H R	rest	73±3	74±2	70±4	68±2	71±6
[b p m]	PORH	69±2*	72±2	69±4	68±3	70±6

*p<0.05, **p<0.01 †p<0.0005 ††p<0.0001 vs rest

Values are mean ± S.E. *p<0.05, **p<0.01 vs rest

IntRAFV: time velocity integral of the radial arterial flow velocity, D: luminal diameter of the radial artery, H R: heart rate, PORH: postocclusive reactive hyperemia, Group Y: younger control subjects, Group O: older control subjects, HT: hypertension, HC: hypercholesterolemia, DM: diabetes mellitus.

Table II Percent increase in luminal diameter of the radial artery during PORH response.

[%]	Group Y	Group O	HT	HC	DM
5 sec	8.2±0.4	8.7±0.4	5.0±0.5*	4.7±0.6*	6.6±0.8
30sec	6.9±0.7	8.7±0.4	4.6±0.3*	4.7±0.6*	6.0±0.7
1 min	6.9±0.7	8.0±0.5	4.6±0.3	4.2±0.8*	5.6±0.7
3 min	4.4±0.4	5.5±0.9	4.2±0.1	2.1±1.1*	4.0±0.7
5 min	3.4±0.8	3.5±0.6	2.2±0.7	1.0±0.7	3.0±1.0

Values are mean ± S.E. * $p<0.05$ vs Group O
Abbreviations are the same as in Table I.

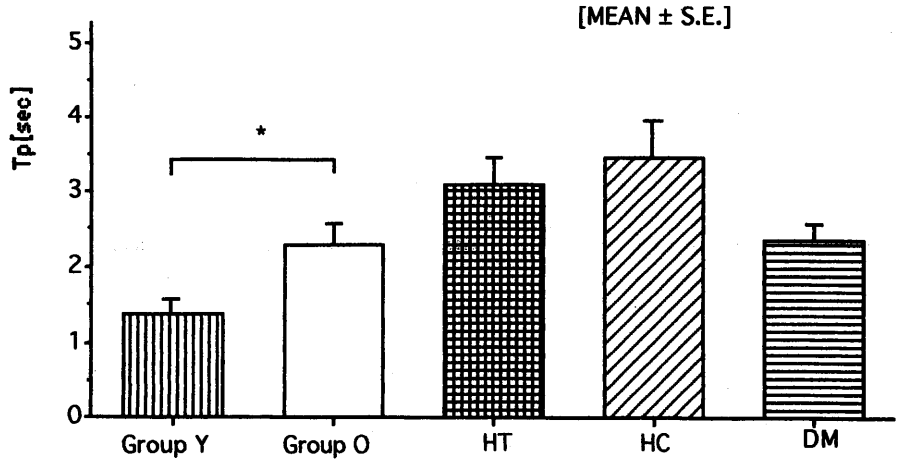

Figure 3. Time to peak of IntRAFV (Tp).
Group Y: younger control subjects, Group O: older control subjects, HT: hypertension, HC: hypercholesterolemia, DM: diabetes mellitus.
* $p<0.05$ vs Group O

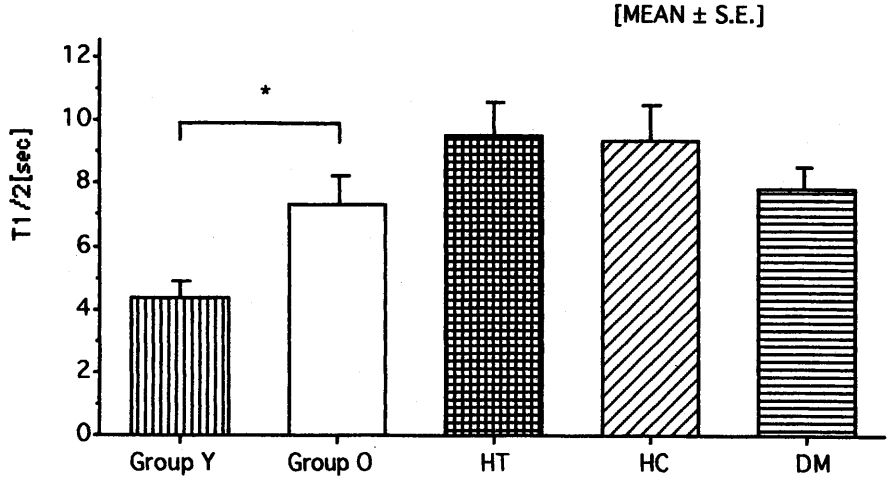

Figure 4. Recovery half time of IntRAFV (T1/2).
Abbreviations are the same as in Figure 3.
* $p<0.05$ vs Group O

increased significantly throughout the PORH response in the HT and DM groups, and until 1 min after reperfusion in the HC group compared to their resting values (Table I). There were significant decreases in %ΔD until 30 sec after reperfusion in the HT group, and until 3 min after reperfusion in the HC group compared to Group O, whereas %ΔD during PORH response in the DM group was not different from Group O (Table II). Tps in HT, HC and DM groups (3.1±0.4 sec, 3.5±0.6 sec, and 2.4±0.2 sec, respectively) were not significantly different from Group O (2.3±0.3 sec) (Fig.3). Also, T1/2s in HT, HC and DM groups (9.6±1.0 sec, 9.4±1.1 sec, and 7.9±0.6 sec, respectively) were not significantly different from Group O (7.4±0.9 sec) (Fig.4). Heart rate was not changed significantly in HT, HC and DM groups (Table I).

Discussion

To assess the characteristics of the forearm blood flow and the vascular reactivity of the resistance vessels, the PORH response was induced in the radial artery. The flow velocity and its integral, and the changes in the luminal diameter of the radial artery were investigated.

Two major theories have been proposed for the PORH response. One is the myogenic hypothesis[6,7]. This hypothesis proposed that the artery reacted to stretching force by contraction and to diminution of tension by relaxation. Another theory is the metabolic hypothesis proposed by Lewis et al[1]. This theory suggested that the arterial dilatation during PORH response resulted from the accumulation of metabolic products during circulatory disturbance. Arterial reactivity for the control of vascular resistance has been found to be localized primarily in the smallest arteries and arterioles.

In this study, occlusive time was one minute. Lewis et al. found that the PORH response was maintained approximately a half to three fourths of the ischemic period[1]. Increased flow velocity during PORH response was observed for a relatively similar period in this study. However, the dilatation of the radial artery was observed at least for 5 minutes after reperfusion in most of the individuals.

Age and Tp, T1/2, and %ΔD

In the present study, significant prolongation of Tp and T1/2 was observed in old control subjects. This observation indicated the prolongation of early PORH response, which means the impairment of the resistance vessel reactivity in the forearm, with age. Auerbach et al. reported that the fibrous thickening and an increasing in wall/lumen ratio in small arteries and arterioles was associated with age[8]. The impairment of reactivity in resistance vessels may relate to the arteriolosclerosis with aging.

On the other hand, there were no significant changes in the %ΔD during the PORH response associated with age in the present study. Flow-mediated dilatation may not be impaired with age. Flow-mediated dilatation was considered to relate to the endothelial function of producing endothelium-derived relaxing factor (EDRF)[9,10,11] and arterial distensibility. Buntin and Silver have reported that pressure-strain, and circumferential elastic modulus remain stable with age in the brachial artery[12]. The %ΔD of the radial artery during the PORH response in the present study suggested that there would be no or little endothelial dysfunction[11] nor impairment of arterial distensibility by age.

Tp, T1/2, and %ΔD in essential hypertension, hypercholesterolemia, or diabetes mellitus

There were no significant differences in Tp and T1/2 in the hypertension, hypercholesterolemia or diabetes mellitus groups compared with age-matched control subjects (Figs. 3 and 4). Since the resistance of peripheral vessels in the forearm was maintained by the dilatation of resistance vessels in hypertension[13], the reactivity of the resistance vessels in the forearm might not be impaired in hypertension, hypercholesterolemia and diabetes mellitus.

The %ΔD decreased significantly from 5 sec to 30 sec in the hypertension group, from 5 sec to 3 min in the hypercholesterolemia group during PORH response (Table II). The media-intimal wall was thickened in the radial artery in patients with

hypertension[13,14], and in the carotid and femoral arteries in patients with hypercholesterolemia[15]. Additionally, in patients with hypertension, endothelium-mediated vasodilatation was impaired[16]. Therefore, impairment of flow-mediated dilatation of the radial artery in this study might correspond with these reports. Namely, impairment of the flow-mediated dilatation or reduction of %ΔD in hypertension and hypercholesterolemia might be caused by the endothelial dysfunction or the decreased arterial distensibility or both of them.

Limitations

Although the results obtained in this study were useful, there were some limitations. Firstly, precise measurement of the luminal diameter was difficult, because of the resolution of the echo image. If the higher frequency probe was used, the measurement would be more accurate. Secondly, by this method of this study, it was impossible to record the flow velocity signal and the luminal diameter of the radial artery simultaneously. Also, the determination of the time-velocity integral of the radial arterial flow was rather complicated for daily use.

Clinical Implications

Because PORH response is dependent on the endothelial function of the peripheral vessels, it may be possible to evaluate the dysfunction of the peripheral vessels in several diseases causing arteriosclerosis by analyzing PORH response with Doppler echography.

Conclusions

In summary, Tp and T1/2, indices of radial artery flow velocity, may reflect the reactivity of resistance vessels in the forearm, and decreased with age. %ΔD, an index of the radial arterial reactivity, decreased in patients with essential hypertension and hypercholesterolemia and not decreased in patients with diabetes mellitus. Thus, it would be possible to analyze the reactivity of the peripheral artery in the forearm by providing these indices of Tp, T1/2 and %ΔD using echography.

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