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Research Article

Changes in Carotid Radial Pulse Wave Velocity Induced by Hyperemia and Passive Leg Rising - @

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ABSTRACT

Carotid to Radial Pulse Wave Velocity (CR-PWV) normally decreases the following hyperemia and has been proposed to assess arterial vasodilator reserve. Passive Leg Raising (PLR) also elicits brachial artery dilation. Using applanation tonometry, we assessed changes (Δ) in CR-PWV induced by PLR in 54 subjects with/without cardiovascular disease/risk factors (age 44 ± 18 years). CR-PWV was assessed before and 1 minute after each hyperemia (release of brachial artery occlusion) and PLR to 60 degrees. Both provocations significantly decreased CR-PWV (8.9 ± 1.6 to 7.7 ± 1.5 m/s, $p < 0.001$) and (8.8 ± 1.5 to 8.0 ± 1.7 m/s, $p < 0.001$) with greater decline for hyperemia than PLR (-12.9% vs. -8.8% , $p = 0.037$). $\% \Delta$ PWV induced by both techniques were significantly correlated on univariate ($r = 0.42$, $p = 0.002$) and multivariate analyses. In conclusion, PLR decreases PWV. $\% \Delta$ PWV induced by PLR is correlated with but less in magnitude than $\% \Delta$ PWV induced by hyperemia. Clinical factors associated with PLR-CR-PWV responses and the prognostic value merit further study.

Keywords: Passive leg raising; Endothelial function; Ischemic conditioning

INTRODUCTION

Endothelial dysfunction is an early step in the development of atherosclerosis and an independent predictor of increased Cardiovascular (CV) events [1,2]. Endothelial dysfunction contributes to the formation, progression, and complications of the atherosclerotic plaque [2]. Increased arterial stiffness measured by Pulse Wave Velocity (PWV) is another measure of vascular dysfunction that is associated with higher CV risk, reduced exercise capacity, and isolated systolic hypertension [3,4]. PWV is acutely influenced by the vascular tone and constitutively released Nitric Oxide (NO) [5]. Prior studies have suggested hyperemia induced changes (Δ) in PWV as a technique to assess vasodilatory reserve and possibly endothelial function [6-11]. Carotid-Radial PWV (CR-PWV) decreases by 12 to 40% in healthy subjects with upper arm hyperemia and the response are attenuated in the presence of hypertension, congestive heart failure, diabetes, and hyperlipidemia [12]. Two prior studies have found Δ CR-PWV correlated with flow-mediated dilation induced by upper arm occlusion [8,13].

Passive Leg Raising (PLR) is a diagnostic maneuver that has been used to assess baroreceptor function, detect subclinical left ventricular dysfunction, and unmask pulmonary hypertension [14-17]. In healthy subjects and patients with cardiovascular disease, PLR induces systemic arterial vasodilation, with a decrease in Blood Pressure (BP) that is inversely related to baseline CR-PWV, and a decrease in reflected arterial pressure wave amplitude as assessed by applanation tonometry [10,16,18,19]. Accordingly, PLR has been proposed as a measure of arterial vasodilator reserve and endothelial function. The degree of Brachial Artery (BA) dilation induced by

PLR highly has been found highly correlated with that of hyperemia induced BA dilatation [11]. Several lines of evidence including a lack of change in Heart Rate (HR) and in HR variability suggest PLR induced BA dilatation to occur via an endothelial-dependent mechanism [12]. Therefore, the objective of this study is to assess changes in CR-PWV induced by PLR and compare them to upper arm hyperemia in subjects with and without CV disease/risk factors.

METHODS

We assessed CR-PWV induced by PLR and by upper arm hyperemia in 54 subjects, age 44 ± 18 years. The cohort included 32 healthy participants without known cardiovascular disease or risk factors, and 22 participants with known cardiovascular disease risk factors (age 33 ± 9 vs. 59 ± 17 years; $p < .001$). Characteristics of the entire cohort are given in (Table 1). The study was approved by the institutional review board and written consent was obtained from participating subjects. Procedures followed were in accordance with institutional guidelines. Cardiovascular risk factors including history of hypertension, diabetes, hypercholesterolemia and smoking were identified by history. Smoking history was defined as any previous tobacco use. Patients were excluded if they actively smoked, if pulses were not adequate to have arterial tonometry performed or if they were not in sinus rhythm. After 12 hour fasting (including caffeine, nicotine, and alcohol), studies were performed in a quiet, temperature-controlled room in the morning (8 am-10 am) so as to standardize conditions for the vascular studies to be performed among different subjects. Subjects were allowed to rest for 10 min in the supine position. Baseline Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were obtained by an automated

Table 1: Baseline characteristics of the normal, diseased and combined groups (mean \pm standard deviation).

Variable	Normal (n = 32)	Diseased (n = 22)	Combined (n = 54)	p value
Age (yr)	33 \pm 9	59 \pm 17	44 \pm 18	<.001
Weight (kg)	74.3 \pm 12.9	79.9 \pm 17.7	76.6 \pm 15.1	.175
Height (in)	68.6 \pm 3.1	65.6 \pm 3.6	67.4 \pm 3.6	.002
Body Mass Index (kg/m ²)	24.3 \pm 3.3	28.8 \pm 6.1	26.1 \pm 5.1	.001
Baseline SBP (mmHg)	119 \pm 12	141 \pm 16	127.8 \pm 17	<.001
Baseline DBP (mmHg)	71 \pm 7	85 \pm 12	77 \pm 12	<.001
Baseline MAP (mmHg)	86 \pm 8	104 \pm 13	94 \pm 14	<.001
Males (%)	72	50	63	.11
Hypertension (%)	0	96	39	<.001
Diabetes (%)	0	36	15	<.001
Smoking history (%)	0	27	11	.002
Hypercholesterolemia (%)	0	41	17	<.001

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure

Table 2: Univariate correlations between baseline characteristics and hyperemic and passive leg raising induced change in carotid-radial pulse wave velocity (n = 54)..

Variable	Hyperemia%Δ CR-PWV	PLR%Δ CR-PWV
Hyperemia%Δ CR-PWV Correlation Coefficient p value	1	.420* .002
Baseline SBP Correlation Coefficient p value	.003 .986	.220 .172
Age Correlation Coefficient p value	-.049 .725	.142 .307
Gender Correlation Coefficient p value	-.125 .366	.000 1.000
Weight (kg) Correlation Coefficient p value	.171 .216	.063 .650
Height (in) Correlation Coefficient p value	.024 .866	.027 .845
BMI Correlation Coefficient p value	.219 .112	.014 .922
Hypertension Correlation Coefficient p value	-.065 .643	-.055 .694
Elevated cholesterol Correlation Coefficient p value	-.187 .177	-.295* .030
Diabetes Correlation Coefficient p value	-.197 .153	-.074 .597
Smoking History Correlation Coefficient p value	.006 .966	.125 .367

Hyperemia %Δ CR-PWV: Hyperemia % change in Carotid-Radial Pulse Wave Velocity; PLR%Δ CR-PWV: Passive Leg Raising induced % change in Carotid-Radial Pulse Wave Velocity; BMI: Body Mass Index; SBP: Systolic Blood Pressure

device (Omron HEM-780). Pulse Pressure (PP) was calculated by subtracting DBP from SBP. Mean Arterial Pressure (MAP) was calculated using the equation: $DBP \pm 1/3PP$.

BP and HR were obtained immediately before each of the 2 provocations using an automated BP device (Omron HEM-780). CR-PWV was obtained immediately before and 1 minute after each of the 2 provocations by applanation tonometry (Sphygmocor, Software version 8.0, AtCor Medical, New South Wales, Australia), according to previously published methods [11]. Sequential recordings of the arterial pressure waveform at the carotid and radial arteries were used to measure CR-PWV. Distances from the suprasternal notch to the carotid sampling site (distance A) and from the supra-sternal notch to the radial artery (distance B) were measured. CR-PWV distance was calculated as distance B minus distance A. The CR-PWV was calculated as the ratio of the distance in meters to the transit time in seconds.

Hyperemia and PLR were performed in random order that was selected upon recruitment of the subject into the study with an intervening time interval of 30 minutes between the 2 provocations. After a 30 min interval, the same procedure was repeated using the other provocation type. Hyperemia was induced using a Hokanson® rapid inflation cuff (DE Hokanson Inc, Bellevue, WA, USA) that was applied to the right upper arm and inflated 50 mmHg above SBP for 5 min then deflated. For PLR, after baseline measurements, the legs

of each subject were passively elevated to a 60-degree angle above the bed by means of a foam wedge [11].

STATISTICS

All values are expressed as mean ± Standard Deviation (SD). Paired t-test was used to compare CR-PWV before and after hyperemia and PLR. Student’s t test was used to compares percent changes (%Δ) in CR-PWV elicited by the 2 techniques. Pearson correlation analysis was used to assess the relation between %ΔCR-PWV induced by hyperemia and by PLR. Multivariate linear regression was performed to determine whether PLR induced %ΔCR-PWV (dependent variable) is independently related to hyperemic %ΔCR-PWV (independent variable). All statistical analyses were achieved using the Statistical Package for Social Sciences (SPSS) 20.0 software (SPSS Inc, Chicago, IL). A p value <.05 was considered significant.

RESULTS

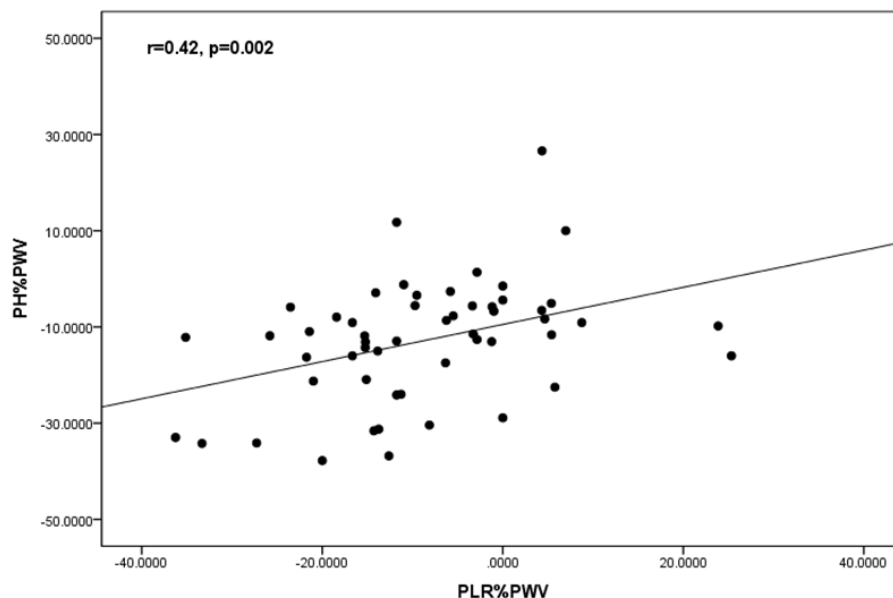
Hyperemia (8.9 ± 1.6 to 7.7 ± 1.5 m/s, $p < 0.001$) and PLR (8.8 ± 1.5 to 8.0 ± 1.7 m/s, $p < 0.001$) both significantly decreased CR-PWV. %ΔCR-PWV responses were normally distributed for both techniques. There was a greater %ΔCR-PWV with hyperemia than with PLR ($-12.9 \pm 12.5\%$ vs. $-8.8 \pm 12.6\%$, $p = 0.037$). On univariate analysis, %ΔCR-PWV induced by hyperemia and by PLR were significantly correlated ($r = 0.42$, $p = 0.002$) (Figure 1). On multivariate analysis, hyperemic %ΔCR-PWV was an independent predictor of PLR induced %ΔCR-PWV ($B = 0.40$, $p = 0.003$) after adjustment for differences in HR and MAP prior to the two studies ($R^2 = 0.22$, $p = 0.006$). There were no significant differences between normal and diseased subjects for hyperemic %ΔCR-PWV (-13.5 ± 11.2 vs. -12.0 ± 14.4 , $p = 0.66$) or PLR %ΔCR-PWV (-9.5 ± 10.6 vs. -7.8 ± 15.5 , $p = 0.64$). There were no significant correlations between the baseline characteristics of age, systolic BP, gender, body mass index, history of diabetes, hypertension or smoking with the hyperemic or PLR induced %ΔCR-PWV. There was an inverse relationship for hypercholesterolemia with PLR induced %ΔCR-PWV ($p = 0.03$) but not for the hyperemia induced change.

DISCUSSION

This study characterized changes in CR-PWV induced by PLR and compared the changes in CR-PWV responses to those induced by hyperemia. Hyperemia induced by release of upper arm occlusion resulted in a 12.9% mean decrease in PWV, whereas PLR resulted in an 8.8% decline. The hyperemic change in CR-PWV was an independent predictor of the PLR induced change in CR-PWV on multivariate analysis.

In recent years, there has been a growing interest in the use of arterial applanation tonometry, a technique that allows for the non-invasive high fidelity recording of arterial pressure waveforms [3]. The timing of the onset of pressure waveforms relative to the ECG-QRS complex at different locations along the arterial tree allows for the determination of PWV. While carotid to femoral PWV more closely approximates central aortic stiffness, CR-PWV has been used as a convenient surrogate in clinical studies [3]. The utility of CR-PWV measurement may be enhanced when combined with a provocation such as a hyperemia [8-10]. CR-PWV decreases following hyperemia, presumably due to vasodilation as vascular tone and constitutively released nitric oxide have been shown to acutely affect PWV [5].

As PLR has been shown to elicit BA dilation, we assessed PLR induced CR-PWV responses. We are unaware of a prior study that



PH%PWV: hyperemic %change in CR-PWV; PLR%PWV: PLR induced %change in CR-PWV

Figure 1: Relationship between hyperemic and passive leg raising induced changes in ca radial pulse wave velocity.

has evaluated PLR in this manner. As expected, PLR decreased CR-PWV less markedly than did hyperemia. This finding is consistent with prior studies showing less marked BA dilation following PLR than upper arm occlusion measured by ultrasound [11]. Of note, hyperemia was observed to decrease CR-PLR in healthy subjects to a similar extent as has been previously reported [8-10]. Since the decrease in CR-PWV by PLR was correlated with that induced by hyperemia, it is possible that similar mechanisms are responsible for changes induced by the 2 provocations. Hyperemia is well known to involve microvascular dilation, which increases flow and shear stress, which in turn elicits macrovascular dilation [3]. PLR has been shown to elicit BA dilatation, or macrovascular dilatation, without increasing microvascular flow [20]. Moreover, several prior findings have found PLR induced BA dilation to more likely reflect endothelial function than baroreceptor activation. Nevertheless, a CR-PWV decline by either method likely reflects vasodilatory reserve. Although many published studies have established the safety of 5 minute BA occlusion, PLR may serve as an attractive option in patients who may be at elevated risk for vascular thrombosis, such as patients with sickle cell disease and hypercoagulable states.

Reactive hyperemia normally results in BA dilation as a consequence of increased blood flow velocity measured by Doppler techniques. In contrast, the speed of pressure wave propagation, measured by PWV, would be expected to decrease during flow-mediated vasodilatation. PWV was positive in some participants. This may suggest that hyperemia decreases PWV in the presence of arterial dilation, however, may increase PWV in the absence of arterial dilation. Therefore, the PWV response may represent the net balance between increased driving force and pressure and flow-mediated relaxation. This merits further study.

This study has several limitations. The sample size was small and the study was a pilot in nature. We studied subjects with and without CV risk factors/disease to provide a wide range of vascular responses. The study was powered to evaluate the relationship between the 2

provocations but not to evaluate the effect of CV disease/risk factors on CR-PWV, likely accounting for the lack of statistical difference between normal subjects and those with CV risk factors/disease for hyperemic or PLR induced CR-PWV changes.

Nitroglycerin was not administered and therefore endothelial independent mechanisms accounting for Δ CR-PWV cannot be excluded. These issues merit further study. Despite these limitations, it is concluded that PLR decreases CR-PWV at 1 minute. Δ CR-PWV induced by PLR is correlated with but less in magnitude than Δ CR-PWV induced by hyperemia. Clinical factors related to the magnitude of PLR induced decline in CR-PWV as well as its prognostic value merit further study. Larger studies are required to assess the usefulness of this technique in clinical practice and its application in clinical disorders.

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