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ORIGINAL ARTICLE

Contribution of systemic vascular reactivity to variability in pulse volume amplitude response during reactive hyperemia

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Abstract

Purpose The aim of the present study was to investigate why the magnitude of reactive hyperemia (RH) observed by pulse volume amplitude (PVA) after arm occlusion differs greatly among study subjects.

Methods Healthy subjects ($n = 12$) in the age range of 22–30 years participated in this study. Vascular reactivity was assessed by measuring the changes in finger PVA simultaneously in the test (occluded arm) and control arm (contralateral non-occluded arm) using two separate Photoplethysmographic sensors. Short-term HRV was computed from simultaneously acquired lead II ECG signal to monitor the changes in cardiac sympathetic nervous activity.

Results The observed coefficient of variation for inter-subject variability in PVA response in test arm during second minute of RH was 115.3%. In the control arm, significantly reduced PVA was observed during the period of occlusion as well as RH. This observation was corroborated by simultaneously acquired short-term HRV which showed a significant rise in total power (p value < 0.005) and low-frequency (LF) power (p value < 0.05) during release of occlusion when compared to the baseline. A significant positive correlation (Spearman $r = 0.33$; $p = 0.02$) was observed between % change in PVA in the control arm and in the test arm for first 3 min of RH.

Conclusions Sympathetic activation possibly plays an important role in mediating the inter-subject variability of vascular responses during reactive hyperemia which warrants simultaneous recording of both the test and the control arm responses during RH to accurately assess endothelial function.

Keywords Photoplethysmography · Reactive hyperemia · Sympathetic activity · Inter-subject variability

Abbreviations

ECG	Electrocardiogram
FMD	Flow-mediated dilatation
HRV	Heart rate variability
PPG	Photoplethysmography
PVA	Pulse volume amplitude
RH	Reactive hyperemia

Introduction

Reactive hyperemia (RH) is the transient augmentation of blood flow to an organ or tissue when circulation is restored after a period of complete circulatory arrest. There has been an increase in evidence supporting the role of an altered endothelial function in the initiation and progression of atherosclerosis (Lockhart et al. 2011). This has resulted in a growing impetus over the development and usage of non-invasive tests such as measurement of vascular responses during RH for assessment of endothelial function (Zahedi et al. 2008; Selvaraj et al. 2009).

While measurement of flow-mediated dilatation (FMD) of brachial artery by ultrasonography has been considered as the gold standard for assessment of conduit artery endothelial function, finger photoplethysmography (PPG)-based measurement of digital pulse volume amplitude (PVA) during RH can be used as a simple, valid, objective, operator independent, and cheaper alternative to ultrasonography (Kuvin et al. 2003; Zahedi et al. 2008; Chandran et al. 2011).

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FMD shows marked variability which may limit its clinical use in risk stratification of patients (Järvisalo et al. 2006; Widlansky 2009). FMD is characterized by the vasodilation observed in the conduit artery in response to an increase in shear stress mediated by a transient increase in blood flow occurring after release of forearm arterial occlusion. A variability in the amplitude of the hyperemic shear stress amongst individuals can, therefore, contribute to the variability in the measured FMD (Mitchell et al. 2004; Thijssen et al. 2009; Widlansky 2009). Besides shear stress, the other contributing factors could be variations in the gross and microanatomy of the vasculature (Widlansky 2009), presence of cardiovascular risk factors influencing endothelial NO bioavailability (Widlansky et al. 2003), gene polymorphisms which may influence the endothelial response to a given shear stimulus (Paradossi et al. 2004), differences in sympathetic reactivity (Palatini 2001; Widlansky 2009), and possibly other yet unrecognized factors.

Interestingly, physiological maneuvers which increase sympathetic activity, including cold pressor test (Awad et al. 2001; Lind et al. 2002; Dyson et al. 2006) and lower body negative pressure (Hijmering et al. 2002), have shown to impair both, brachial artery FMD as well as RH-induced increase in PVA. This indicates that sympathetic activation may alter the vascular response during RH. While these studies supplemented RH with an external sympatho-excitatory stimulus, it is also possible that circulatory arrest during the phase of occlusion may by itself, inherently lead to sympathetic activation. It is known that exercise results in release of metabolic byproducts which increase the sympathetic neural activity to the systemic vasculature through muscle metaboreflex (Hansen et al. 1994; Kagaya et al. 1996; Tschakovsky and Hughson 1999; Koba et al. 2006). A similar response through chemosensitive afferents activated by ischemic metabolites which tend to accumulate in response to circulatory arrest in forearm may be associated with RH and can lead to sympathetic activation.

It was, therefore, postulated that sympathetic activation during RH may contribute to the variability in response amongst study subjects. Finger photoplethysmography was preferred as the method for the assessment of response to RH because of its ability to reliably estimate sympathetic vasomotor responses (Barron et al. 1993). The study aims to characterize the influence of sympathetic activation on the observed variability in PVA response to RH. PVA response to RH was assessed bilaterally in the occluded and non-occluded arm. This experimental design was adopted with the basic premise that systemic sympathetic activation induced by RH would mediate the changes, if any, in the non-occluded arm. Autonomic modulation of heart rate was also studied simultaneously using short-term heart rate variability (HRV) analysis as an additional parameter to monitor the changes in sympathetic nervous activity.

Methods

Selection of subjects

Twelve healthy volunteers in the age range of 22–30 years participated in the present study. None of the subjects had any history of cardiovascular, respiratory, endocrine, or neural diseases, and were normotensive (resting blood pressure < 140/90 mm Hg), non-obese (body mass index < 30 kg/m^2), non-smokers, and free from intake of any medications. Subjects were asked to avoid intake of food for 2 h and abstain from intake of tea, coffee, and strenuous physical activity for 12 h before the tests. Out of the 12 subjects, 4 subjects underwent occlusion of right brachial artery on day 1 (right arm-test arm; left arm-control arm) and left brachial artery on day 2 (left arm-test arm; right arm-control arm). In the remaining eight subjects, brachial artery was occluded only on one side. The 16 pulse waveform recordings thus obtained were analyzed further.

Ethics statement

The study protocol was approved by the ethics committee for research in human subjects, All India Institute of Medical Sciences, New Delhi with reference number IEC/NP-345/2012. Written informed consent was obtained from all the subjects before enrollment in the study.

Assessment of vascular reactivity and autonomic modulation of heart rate (heart rate variability)

Vascular reactivity was assessed by measuring the changes in finger pulse volume amplitude (PVA) simultaneously in the test arm and control arm using two separate photoplethysmograph (PPG) probes. Short-term HRV was computed from simultaneously acquired lead II ECG signal. PowerLab 8/30 (AD Instruments, Australia), a computer-based digital data acquisition system, and software LabChart Pro 7 (Version 7.0) were employed to record ECG and PPG signals at a sampling rate of 1 kHz. PPG acquisition unit comprised of an infrared (IR) (860 ± 6 nm), reflection-type photoelectric sensor (MLT1020EC IR; AD Instruments) connected to the main PowerLab unit digitally equipped with a band pass filter of 0.05–15 Hz. Another differential, bio potential amplifier (FE132 Bio Amp: AD Instruments) with gain 1000 and cut-off frequencies 0.05–35 Hz was used to record ECG signal in the bipolar limb lead II mode using disposable Ag–AgCl electrodes.

All recordings were done in controlled ambient temperature and luminance. Subjects were given 15 min of supine rest after which baseline blood pressure was taken.

Sphygmomanometer cuff was kept fastened to the arm for subsequent use when arterial occlusion had to be produced. Disposable Ag–AgCl electrodes were applied for recording the standard bipolar limb lead II ECG. PPG probes were fixed to the middle fingers of both the hands with the help of an attached Velcro strap. The entire recording period comprised of 5 min of baseline, 5 min of arterial occlusion, and 5 min post-release of occlusion during the phase of reactive hyperemia. After 5 min of baseline recording of ECG and PPG signals, arterial occlusion was produced in the test arm by a supra-systolic cuff pressure (50 mm Hg above the subject's baseline systolic BP) and signal acquisition was continued during the period of occlusion. Completeness of occlusion was ensured by constantly verifying the absence of pulse waveform signal from the computer display. Cuff pressure was released completely after 5 min of arterial occlusion and all recordings were continued during the phase of reactive hyperemia.

Analysis of pulse volume amplitude

PPG signals were analyzed offline using LabChart Pro 7® software for the detection of pulse waveform peaks using appropriate peak detection algorithm and beat-to-beat PVA data were extracted. Mean values of PVA were computed for the entire baseline recordings [for both the non-occluded (control) and the occluded (test) arms], for every 1-min period of occlusion (of control arm) and reactive hyperemia (of both control and test arm). To normalize the pulse waveform responses, percentage changes in PVA during each 1-min segment of arterial occlusion and/or release were calculated with reference to the respective baseline means for the control and test arms of each subject.

Analysis of heart rate variability

Short-term heart rate variability (HRV) analysis was done using HRV module in the signal analysis software LabChart Pro 7 (AD Instruments, Australia). Lead II ECG signal was band pass filtered (0.05–35 Hz) and the identification of individual heart periods was done considering the peak of R wave as the fiducial point. R wave peaks were detected using appropriate peak detection algorithm and a manual inspection of the tachogram was done before proceeding for frequency-domain analysis to ensure the detection of any missed peaks. Ectopic beats if detected were excluded from analysis. A frequency-domain analysis was done in 2 min bins using Fast Fourier Transform (FFT) algorithm corresponding to the fourth and fifth minute of baseline and occlusion phase and first and second minute of reactive hyperemia phase.

Statistical analysis

Each parameter was tested for normality in the distribution of data using standard normality tests. Data were expressed as mean ± SD or median with inter-quartile range (first quartile–third quartile) depending upon the nature of data distribution. The data showing non-parametric distribution were log transformed before statistical analysis. For intra-group comparison, repeated-measures ANOVA with post hoc Dunnett's test or its non-parametric variant was used as appropriate. To study the correlation between test arm and control arm responses, Spearman correlation coefficient was determined. The level of statistical significance was set at $p < 0.05$. All statistical analyses were done using GraphPad prism version 5.00 for Windows (GraphPad Software, Inc., USA).

Results

PPG recordings were obtained simultaneously from the test and control arms during baseline, phase of arterial occlusion, and the phase of RH, post-release of forearm arterial occlusion. As shown in Figs. 1, 2, and Table 1, marked variability amongst study subjects was observed in the response during RH in the test arm. PVA response in the test arm during the second minute of RH greatly differed among the study subjects and coefficient of variation of this difference observed across study subjects was as high as 115%. There was a significant reduction in the PVA in the control arm during the period of occlusion and during the period of RH (Fig. 3).

The present study also investigated the relationship between sympathetically induced changes in PVA in the control arm during RH and simultaneously observed PVA response in the test arm. To study the relationship between the two, correlation between the percentage changes in PVA during the first 3 min of RH for both control and test arms was assessed. A significant positive correlation was observed (Spearman $r = 0.33$; $p = 0.02$) between the two variables indicating that, greater the percentage reduction in PVA of control arm, lesser the increase in PVA in test arm during RH (Fig. 4). Furthermore, the subjects were divided into two groups (A and B) based on the extent of reduction in PVA during occlusion in the control arm. Group A ($n = 8$) consisted of records which showed a greater reduction (more reactive) in the PVA during occlusion in the control arm, while Group B ($n = 8$) showed a lesser reduction (less reactive) in PVA during occlusion in the control arm (Fig. 1). When the PVA response during the second minute of RH in the test arm was compared between these two groups, it was found to be significantly lower in Group A as compared to Group B ($p = 0.037$) (Fig. 5).

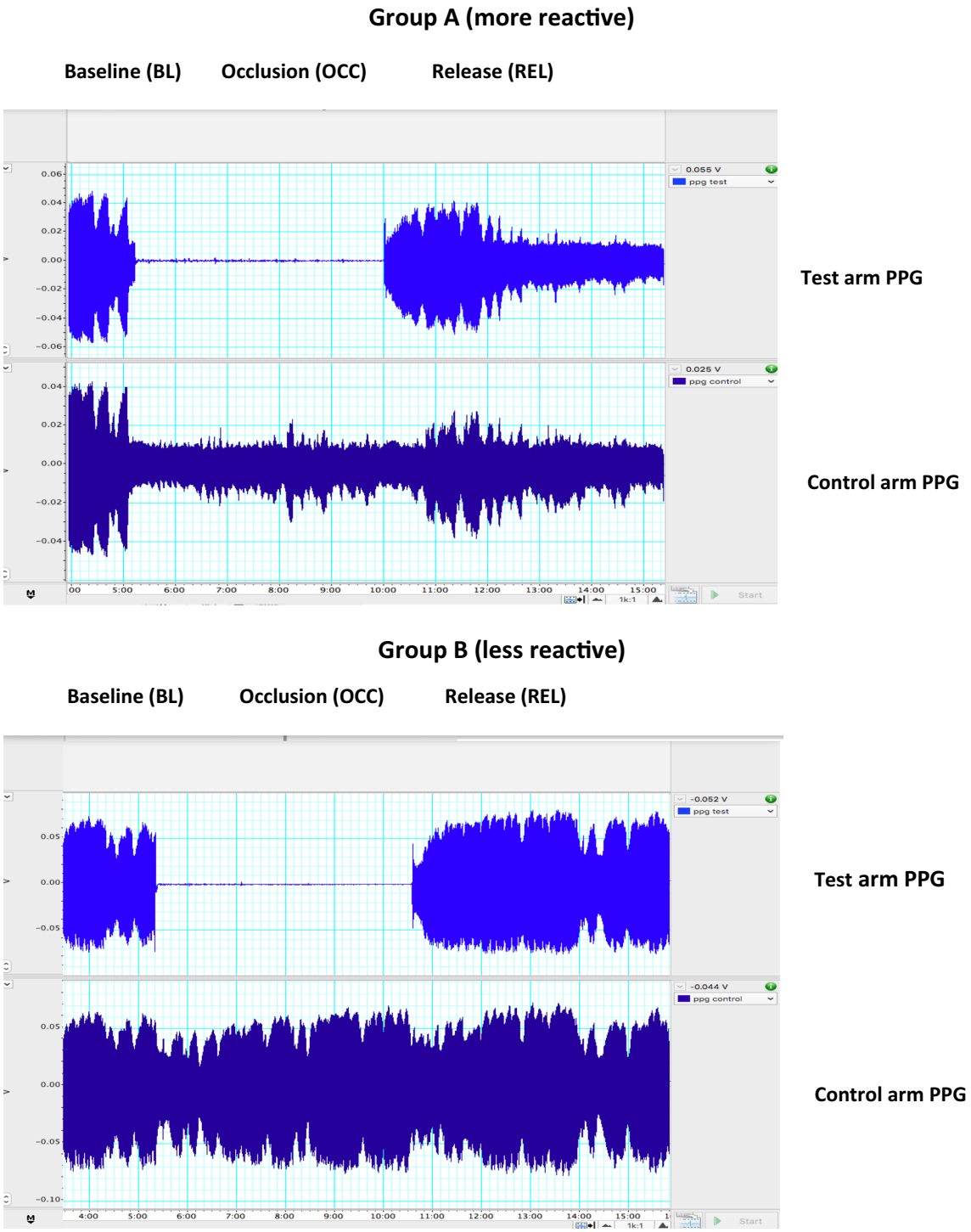

Fig. 1 Representative records of test arm and control arm responses in Group A (showing more reduction in the control arm Pulse Volume Amplitude (PVA) during occlusion) and Group B (showing less reduction in the control arm PVA during occlusion). Figure shows changes in PVA (*Y*-axis) in test and control arms during baseline, phase of forearm arterial occlusion and release of occlusion of test arm

The autonomic modulation of heart rate was also studied as an indirect measure of the changes in sympathetic neural outflow. 2-min bins of lead II ECG, obtained during the third and fourth minute of baseline, first and second minute of occlusion, and first and second minute of RH, were analyzed to monitor the state of cardiac

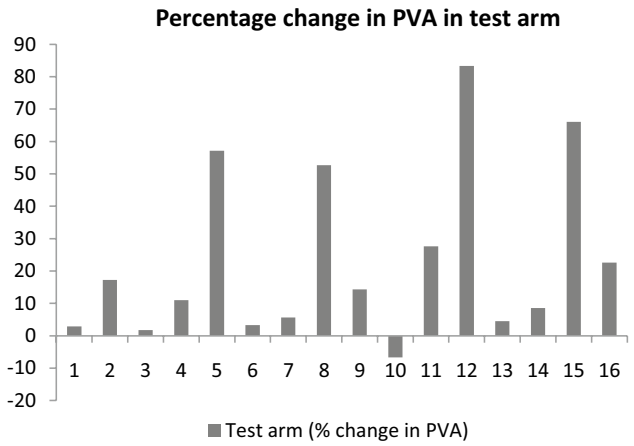

Fig. 2 Bar diagram showing % change in pulse volume amplitude (PVA) in test arm during second minute of reactive hyperemia (RH) in each of the 16 records (numbered along the *X*-axis) indicating the marked variability in responses

sympathetic activation. Frequency-domain indices of R–R interval variability were calculated, and values obtained during occlusion and release were compared with baseline. The total power (p value < 0.005) and low-frequency (LF) power (p value < 0.05) increased significantly during RH when compared to baseline (Fig. 6). However, the changes in LF power, which is an indirect estimate of sympathetic activation, during first and second minute of RH did not correlate with simultaneously observed PVA responses in the control arm.

Discussion

The present study aimed to evaluate the contribution of sympathetically mediated systemic vascular reactivity to the observed variability in finger PVA response to RH. A significant reduction in the PVA in control arm during occlusion and RH was observed which is suggestive of sympathetically mediated vasoconstriction. Similar reduction in PVA or FMD response has been observed on activation of vascular sympathetic outflow either by applying lower body negative pressure (Hijmering et al. 2002) or using cold pressor test (Awad et al. 2001). In addition, there was an increase in the total and LF power of HRV during RH when compared to baseline, which corroborates sympathetic activation. Furthermore, the subjects who showed a greater reduction in PVA during occlusion in the control arm (Group A), indicating greater sympathetic activation, showed lesser vasodilation during RH in the test arm as compared to those who showed little or no reduction in PVA during occlusion in the control arm (Group B). From a methodological perspective, results of the present investigation indicate that opposing influences of endothelium-dependent vasodilatation and sympathetically mediated vasoconstriction possibly determines the resultant PVA response in the test arm during RH. These findings signify the need for simultaneous recording of pulse waveform signal from both control and test arms for accurate assessment of endothelial function using RH.

It is known that chemosensitive-type IV afferent nerve fibers originating from skeletal muscles are stimulated by chemical byproducts of muscle metabolism which produces a reflex increase in efferent muscle sympathetic nerve activity to blood vessels (Joyner 1992; Tschakovsky and Hughson 1999). This reflex, which is of metabolic origin (muscle

Table 1 Inter-subject variability in test arm responses during reactive hyperemia

Event	Percent change in pulse volume amplitude in comparison to baseline		Coefficient of variation for test arm response (%)
	Control arm ($n = 16$) (mean ± SD)	Test arm ($n = 16$) (median with inter-quartile range)	
During occlusion			
First min	− 19.62 ± 29.18	–	–
Second min	− 13.90 ± 30.10	–	–
Third min	− 17.53 ± 25.15	–	–
Fourth min	− 16.89 ± 27.57	–	–
Fifth min	− 21.77 ± 27.94	–	–
Post-release of occlusion			
First min	− 27.57 ± 25.13	12.99 (− 1.48–44.50)	149.84
Second min	− 22.77 ± 22.97	12.69 (3.63–46.38)	115.31
Third min	− 23.99 ± 24.29	0.61 (− 15.32–23.07)	− 227355.62
Fourth min	− 27.38 ± 21.17	− 14.23 (− 33.61–6.59)	− 220.74
Fifth min	− 33.02 ± 23.94	− 19.60 (− 40.49–0.81)	− 119.64

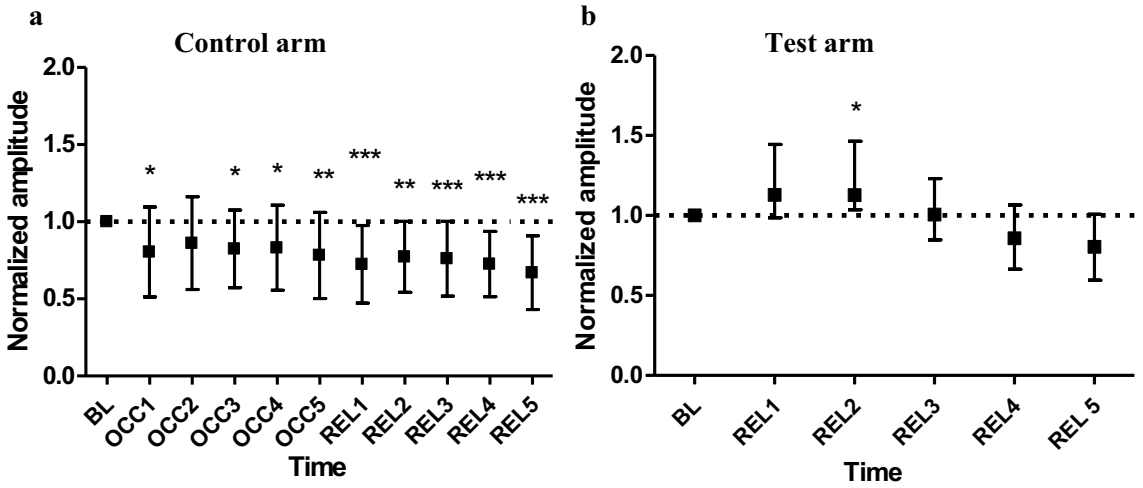

Fig. 3 **a** Normalized pulse volume amplitude of control (**a**) and test arm (**b**). Figure shows the normalized pulse volume amplitude (*Y*-axis) recorded from control and test arm during baseline (BL), occlusion (OCC), and after release (REL) of occlusion (*X*-axis). Numbers indicate minutes after onset of occlusion (OCC) and release of occlusion (REL). Values are plotted as mean ± SD for control arm and median with inter-quartile range for test arm. **p* value < 0.05, ***p* value < 0.01, and ****p* value < 0.001 for intra-group comparison with respect to mean baseline values (Dunnett's multiple comparison test and Friedman test)

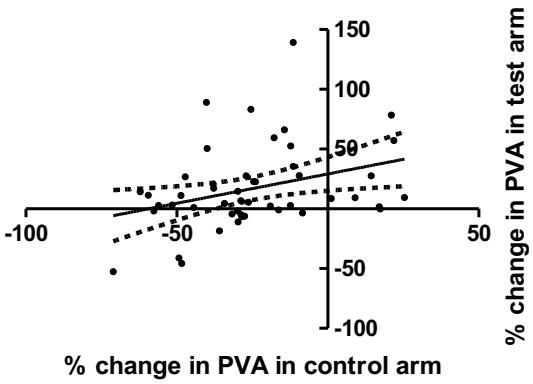

Fig. 4 Correlation between control arm and test arm pulse volume amplitude (PVA) response during first 3 min of reactive hyperemia (Spearman $r = 0.33$; $p = 0.02$)

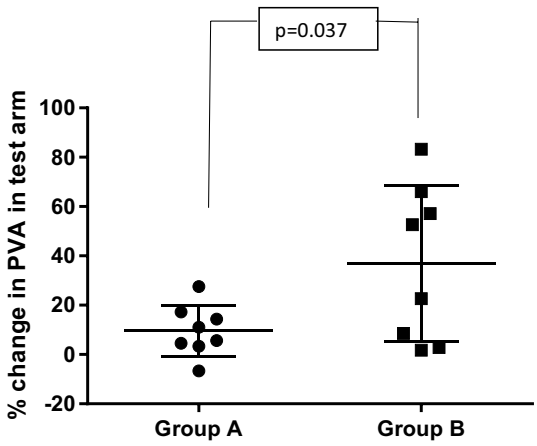

Fig. 5 Percentage change in pulse volume amplitude (PVA) of test arm in Group A (showing more reduction in the control arm PVA during occlusion) and Group B (showing less reduction in the control arm PVA during occlusion). Figure shows percentage change in pulse volume amplitude (*Y*-axis) recorded from test arm during second minute of reactive hyperemia in Groups A and B (*X*-axis) as scattered dot plot denoting individual values along with the error bars (mean ± SD)

metaboreflex), results in global enhancement of sympathetic nerve activity to non-exercising muscles and other tissues, and can be maintained by maneuvers that can sustain post exercise ischemia (Hansen et al. 1994). Circulatory arrest produced by forearm arterial occlusion in the present set of experiments could have possibly activated muscle metaboreflex to produce a state of sympathetically mediated systemic vasoconstriction (Tschakovsky and Hughson 1999), that resulted in the decrease in PVA in control arm during the phase of occlusion and had a lasting influence on the test arm even during the phase of RH. However, appearance of vasoconstriction in the control arm as early as in the first minute of occlusion contradicts this hypothesis grounded on muscle metaboreflex and leaves the questions on the exact cause and origin of sympathetically mediated vasoconstriction to be investigated by future studies using appropriate experimental models.

The previous studies have reported marked variability in FMD response measured across study participants (Järvisalo et al. 2006; Padilla et al. 2008; Widlansky 2009). Besides structural and genetic factors, differences in sympathetic activity may also contribute to variability of FMD response,

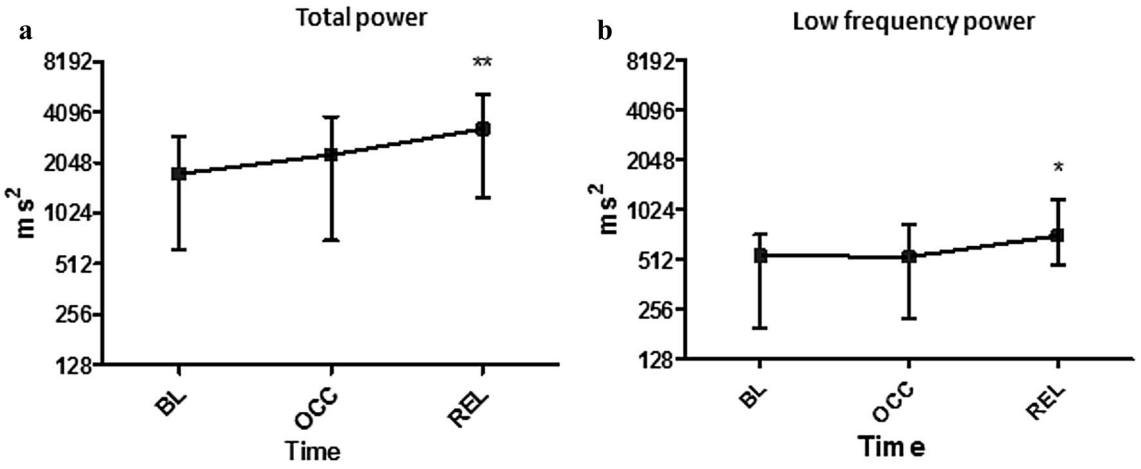

Fig. 6 **a** Total power and **b** low-frequency power of HRV. Figure shows total and low-frequency power of HRV (*Y*-axis) during baseline (BL), occlusion (OCC), and post-release of occlusion (REL). Values are plotted as median with inter-quartile range. **p* value < 0.05 and ***p* value < 0.01 for intra-group comparison with respect to median baseline values (Friedman test, Dunn's multiple comparison test)

even though its role is not yet fully characterized. As the cutaneous blood supply to finger is characterized by the presence of abundant arterioles and arteriovenous anastomoses which are under the direct influence of cutaneous sympathetic nerve activity, we used PVA changes measured by PPG from finger microvasculature as a sensitive surrogate measure of vascular sympathetic activity to interrogate why PVA response during RH greatly varied amongst study subjects.

In the present study, a marked variability has been observed in test arm response during RH. To the best of our knowledge, this is the first study demonstrating variability in RH response assessed by PPG, even though a marked variability has been reported in FMD response in the previous studies using ultrasound (Järvisalo et al. 2006; Padilla et al. 2008; Widlansky 2009).

The major limitation of the present study is that sympathetic activation has been studied indirectly using vascular (control arm PVA) and cardiac (LF power in HRV) surrogates. Future studies using direct muscle sympathetic nerve activity (MSNA) recording could generate conclusive evidence to establish the findings of this study.

Conclusion

Sympathetically mediated systemic vascular reactivity possibly plays an important role in mediating the inter-subject variability of vascular responses during reactive hyperemia. Interaction between endothelium-dependent vasodilatation and sympathetically mediated vasoconstriction determines the resultant PVA responses observed during reactive hyperemia. These findings signify the need to record pulse waveform signal simultaneously from both the occluded (test arm) and the non-occluded (control) arms to accurately estimate endothelial function using reactive hyperemia.

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Author contributions AKJ and DSC conceived and designed research. GB and DSC conducted experiments. AT and KKD provided new analytical tools. DSC and GB analyzed data. GB and DSC wrote the manuscript. All authors read and approved the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Written informed consent was obtained from all the subjects before enrollment in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research/ethics committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Research involving human participants This article does not contain any studies with animals performed by any of the authors.

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