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Comparison of beta$_2$-adrenergic and hyperemia-induced arterial vasodilation assessed by digital pulse contour analysis

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ABSTRACT

Introduction. The Reflection Index (RIDVP) derived from digital volume pulse (DVP) analysis has proved to be useful in the assessment of endothelium-dependent vasodilation induced by albuterol. Little is known of the effect of shear-stress-induced vasorelaxation on RIDVP.

Material and Methods. Thirty three healthy volunteers (22 females, 11 males, mean age 57 yrs) were recruited. Assessment of endothelium-dependent vasorelaxation was performed by the analysis of digital volume pulse after albuterol challenge or locally-induced hyperemia.

Results. he hyperemia-induced vasodilation led to a significant decrease of RI_{DVP} in comparison with the values obtained at rest (ΔRI_{Hyper} 69 ± 2 % vs 64 ± 2, $p < 0.0001$). Similarly albuterol administration resulted in a significant drop in RI_{DVP} (ΔRI_{Alb} 71 ± 2 % vs 67 ± 2 %, $p < 0.0001$). There was no significant difference between ΔRI_{Hyper} and ΔRI_{Alb} (5.2 ± 0.8 % vs 4.6 ± 1.0 %, $p = 0.61$). We observed a significant correlation between the small vessel reaction in response to albuterol or hyperemia ($r = 0.52$, $p = 0.01$).

Conclusions. Our study demonstrated that hyperemia-induced changes in the Reflexion Index derived from the digital volume pulse are similar to those observed after albuterol-challenge and both are correlated.

Keywords: endothelial-dependent vasodilation, digital volume pulse, albuterol.

Introduction

Endothelial dysfunction is an early hallmark of a variety of arterial injuries including those from hypercholesterolemia, smoking, hypertension, diabetes and atherosclerosis [1, 2, 3]. A host of substances, including nitric oxide released by endothelium, are responsible for arterial vasodilation. Therefore assessment of endothelial vasomotor function is one of the most popular ways of obtaining an insight into the "global endothelial health". Endothelial dysfunction is a systemic disorder and can be measured in various vascular beds [4, 5]. Currently, endothelial testing is based on either the administration of vasoactive substances or an increasing shear-stress in the artery, followed by assessment of the subsequent vasodilation [6, 7].

The digital volume pulse (DVP) is obtained by measuring the transmission of infrared light through the finger. Pulse contour analysis of the waveform obtained lead to the establishment of two indices, one corresponding to the large artery stiffness (the SI_{DVP} — stiffness index) and another (the RI_{DVP} — reflexion index) which is related to

the tone of small arteries [8, 9]. Recently, Chowienczyk et al. [10] demonstrated that albuterol (a beta$_2$-adrenergic agonist) affects the RI_{DVP} which is in part, mediated through the nitric oxide pathway. This suggests that measurement of albuterol-induced changes in DVP may be useful in the evaluation of endothelium-dependent arterial vasodilation.

The brief period of arterial ischemia evoked by inflation of the sphygmomanometric cuff and subsequent cuff deflation is followed by shear-stress- induced NO generation and hence endothelium-dependent vasodilation. This flow-mediated vasodilation is frequently used for the assessment of endothelium vasomotor function [11]. We therefore, set out to compare albuterol-induced changes in Reflexion Index of DVP with those induced by local reactive hyperemia.

Material and Methods

Thirty three healthy people were recruited by means of advertising localy. The participants were normotensive and none were taking any medication at the time of the study. The clinical characteristics of the study group are given in **Table 1**. All the volunteers had a normal resting ECG and no cardiovascular and respiratory abnormalities were detected on physical examination. All patients gave their written informed consent before entering the study and the institutional ethics committee approved the study protocol.

Table 1. Clinical characteristics of the study participants

Characteristic	Mean ± SEM
Age (years)	57 ± 2
Female/male	22/11
Smoker/non-smoker	7/26
Body mass index (kg/m^2)	25.6 ± 0.7
Systolic blood pressure (mm Hg)	123 ± 3
Diastolic blood pressure (mm Hg)	76 ± 2
Heart rate (beats/min)	69 ± 2
Total cholesterol (mg/dl)	196 ± 7
Stiffness index (SI_{DVP}) (m/s)	9.3 ± 0.4

Beta$_2$-adrenergic arterial vasodilation and hyperemia-induced arterial vasodilation

Measurement was performed in the supine position, after 10-minutes rest with the use of a photoplethysmograph (Pulse Trace 2000, MicroMedical, UK). The digital volume pulse (DVP) waveforms were recorded over consecutive 10 cardiac cycles and then automatically averaged. The Reflection Index of DVP (RI_{DVP}) was determined as the height of the diastolic component of the DVP, expressed as a percentage of the systolic peak [8, 9]. The RI_{DVP} was considered as a measure of the amount of pulse wave reflection and of the tone of small arteries (**Figure 1**). Arm blood pressure was taken as a mean of three measurements obtained by an oscillometric method (Omron M-5).

In order to demonstrate flow-mediated vasodilation, hyperemia was induced on the arm where the digital volume pulse analysis was performed. After obtaining the baseline resting DVP waveform from a fingertip photoplethysmogram, the sphygmomanometric cuff was placed on the ipsilateral arm and was inflated to 230 mm Hg for

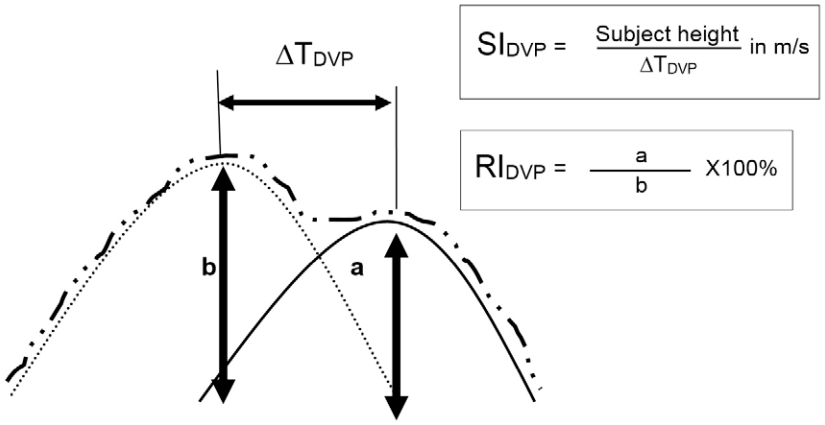

Figure 1. The Stiffness Index (SI_{DVP}) is obtained from subject height divided by the time between the systolic and diastolic peaks of the digital volume pulse (DVP). The Reflection Index (RI_{DVP}) is determined as the height of the peak (a) component of the DVP expressed as a percentage of the systolic peak (b)

5 minutes to induce transient ischemia. Subsequent deflation of the cuff induced a brief state of increased shear stress. The pulse wave was recorded 1, 2 and 3 mins after cuff deflation. Average waveforms were generated after acquisition of 10 sequential pulse wave forms. The response to hyperemia (ΔRI_{Hyper}) was defined as the maximum difference in RI_{DVP} between rest and the post-hyperemia period.

After 20 minutes rest, new baseline resting DVP waveforms were obtained and nitroglycerine (NTG) was then administred sublingually (50 μg) to estimate endothelium-independent arterial vasodilation [10]. Finger pulse waves were obtained after 1, 3 and 5 minutes. The response to NTG-induced vasodilation (ΔRI_{NTG}) was defined as the maximum difference in RI_{DVP} between baseline and the NTG-induced changes. After 20 minutes rest and obtaining a 3-rd baseline resting DVP waveform, albuterol (2 x 200 μg) was given by inhalation, with the use of a spacer, in order to estimate β2-adrenergic-induced vasodilation [10]. Recordings of pulse wave forms were made 5, 10 and 15 minutes after the albuterol inhalation. The response to albuterol (ΔRI_{Alb}) was defined as the maximum difference in ΔRI_{DVP} between rest and the post-albuterol period and was regarded as endothelium-dependent vasodilation [10].

Statistical analysis

The results of continuous variables are expressed as mean values ± SEM. Normal distribution of data was tested by Kolmogorov-Smirnov test. Comparisons between groups were made using the Student t-test and one-way ANOVA. Correlation was evaluated by the Pearson's coefficient test. All tests were two-sided. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using the GraphPad Instat version 3.06 for Windows (GraphPad Software, San Diego, CA, USA)

Results

The effects of hyperemia, albuterol and NTG on the heart rate and blood pressure were similar and did not differ significantly from the values observed at rest (**Table 2**). The hyperemia-induced vasodilation led to a significant reduction in RI_{DVP} in comparison to the background values (69 ± 2 % vs 64 ± 2, $p < 0.0001$, **Table 3**). Similarly, the administration of albuterol or NTG resulted in a significant drop in the RI_{DVP} (71 ± 2 % vs 67 ± 2 %, $p < 0.0001$ and 71 ± 2 % vs 58 ± 2 %, $p < 0.0001$ respectively, **Table 3**). There were no significant differences between ΔRI_{Hyper} and ΔRI_{Alb} (5.2 ± 0.8 % vs 4.6 ± 1.0 %, $p = 0.61$, **Figure 2**). We observed a significant correlation between small vessel reactivity in response to albuterol and hyperemia ($r = 0.52$, $p = 0.01$, **Figure 3**). Neither hyperemia nor albuterol-induced changes in RI_{DVP} correlated with ΔRI_{NTG} ($r = 0.14$, $p = 0.42$ and $r = 0.19$, $p = 0.27$, respectively). RI_{DVP} did not correlate significantly with age or systolic arterial pressure (data not shown).

Table 2. Changes in heart rate and blood pressure after hyperemia, albuterol or nitroglycerine in healthy subjects

Variable	Rest*	Hyperemia	Albuterol	Ntg	P**
Heart rate (beats/min)	67 ± 2	68 ± 2	67 ± 2	67 ± 2	0.7
Systolic blood pressure (mm Hg)	124 ± 2	123 ± 3	124 ± 2	123 ± 2	0.9
Diastolic blood pressure (mm Hg)	77 ± 1	77 ± 2	77 ± 2	76 ± 2	0.9

* The values represent mean of background taken before hyperemia, albuterol and nitroglycerine challenge
** The variation among means was estimated by the one-way ANOVA

Table 3. Changes in RI_{DVP} measurement after hyperemia, albuterol or nitroglycerine

Variable	Background	Hyperemia	Albuterol	NTG	P*
RI_{DVP} (%)	69 ± 2	64 ± 2	–	–	0.0001
	71 ± 2	–	67 ± 2	–	0.0001
	71 ± 2	–	–	58 ± 2	0.0001

* The mean of the differences was assessed by the paired t test

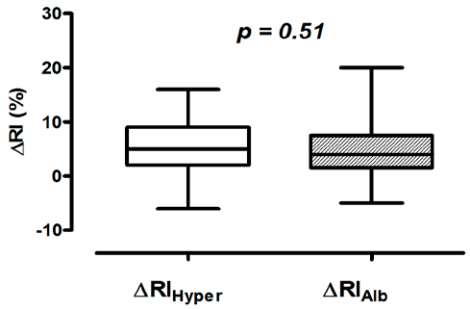

Figure 2. The difference in reflection indices after hyperemia(ΔRI_{Hyper}) or albuterol induced vasodilation (ΔRI_{Alb}). The difference in means was estimated by a paired t-test

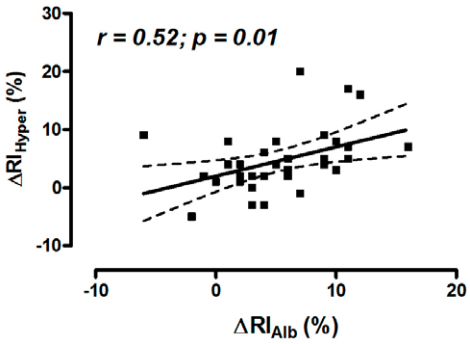

Figure 3. Correlation between hyperemia (ΔRI_{Hyper}) and albuterol induced vasodilation (ΔRI_{Alb})

Discussion

Endothelium plays a pivotal role in regulating vascular function. Endothelial cells lining blood vessels maintain a balance between vasoconstriction and vasodilation, pro and anti-thrombotic factors and pro and anti-inflammatory stimuli [12]. Nitric oxide is an endothelium-derived vasorelaxing substance that plays a central role in maintaining vascular tone and homeostasis [13]. Reduced bio-avaibility of nitric oxide is associated with impaired endothelium-dependent vasodilation [14, 15]. Moreover this diminished vasodilatory response is predictive of cardiovascular complications or of cerebrovascular events in patients with coronary artery disease [16, 17, 18]. The methods currently used for testing endothelium-dependent vasodilation are not easily applied, are time consuming and require considerable skill in order to be adequately performed.

It has been shown recently that β_2-adrenergic receptor stimulation results in the release of nitric oxide from endothelial cells. These receptors are also present in the walls of coronary arteries and are important in maintaining their vascular tone. As demonstrated by Chowienczyk et al. [10] the administration of a β_2-adrenergic agonist (albuterol), both systematically and by inhalation, led to significant changes in the RI_{DVP}. The action of albuterol on RI_{DVP} but not of NTG was attenuated by N^G-monomethyl-L-arginine (NO synthase inhibitor). This led to the conclusion that the effects of albuterol are mediated, in part, through the nitric oxide pathway. Several studies have shown that transient hyperemia, induced by postischemic dilation of vascular beds distal to temporary occlusion, is believed to be mediated by nitric oxide generated from endothelium. In our study the administration of albuterol led to a significant drop in RI_{DVP}. This observation is in accordance with that of others [10, 19]. A similar change in the reflection index was observed in our present study during the postischemic period following the release of temporary occlusion of the brachial artery. Moreover, the RI_{DVP} changes observed after albuterol-induced challenge correlated with the changes in the reflexion index induced by hyperemia. This may suggest that both are mediated, at least partly, by nitric oxide dependent mechanisms. The NTG-induced drop in RI_{DVP} is mediated by an endothelium-independent mechanism and did not correlate with the effects of albuterol (RI_{Alb}) or hyperemia (RI_{Hyper}). RI_{DVP} is affected by several factors such as age, heart rate or blood pressure. Here neither blood pressure nor heart rate were significantly affected by albuterol, hyperemia or NTG and we therefore conclude that the changes in the DVP index was not caused by these hemodynamic factors.

It is also noteworthy that there are some important differences between albuterol-induced vasodilation and the response to locally-produced hyperemia. Albuterol-induced vasorelaxation is caused by reaction evoked in the systemic circulation. Therefore it may be regarded as a measure of "general endothelial health". Reactive hyperemia generated in one arm is also at least partly endothelium — hence NO-dependent, but this reaction has local character, therefore it is more likely to be influenced by the metabolites generated locally in the response to ischemia. These discrepancies may account for the lack of higher than ~50% correlation between both studied methods. However, it is possible that the information gained from the assessment of locally induced hyperemia is to some extent as useful as derived from systemic circulation. For example flow-mediated dilation induced locally in

brachial artery appears to be suitable marker for cardiovascular complication [6, 7].

Limitation of the study

In order to answer the question of to what extent are the effects of hyperemia on RI_{DVP} mediated through L-arginine-NO, it will be necessary to examine this response in the presence and absence of N^G-monomethyl-L-arginine — a nitric oxide synthase inhibitor.

In summary, our study showed that changes in the Reflexion Index caused by locally-induced hyperemia are similar to those observed after albuterol-challenge in the systemic circulation and both are correlated.

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Conflict of interest statement
The authors declare no conflict of interest.

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