Comparison of two β_2 adrenoceptor agonists by different routes of administration to assess human endothelial function

Coronary and peripheral endothelial functions reflect represent a status of vascular health and impaired vasomotion is indicative of pathogenesis and prognosis of cardiovascular disease.[1] Testing endothelial function with noninvasive techniques provides an opportunity to evaluate large patient populations with cardiovascular risk factors. Photoplethysmography is one such potentially attractive technique that provides a simple and rapid means for deriving the digital volume pulse (DVP) by measuring the transmission of infrared (IR) light through the finger pulp.[1,2] Chowienczyk *et al*. demonstrated that albuterol (salbutamol), a β2-agonist, in part of reduces wave reflection by activation of the L-arginine-nitric oxide (NO) pathway and suggested that such a methodology might be applied for the assessment of endothelial function.[3] Wilkinson *et al*. described the effects of salbutamol inhalation on the aortic pressure waveform, which correlated with the effect of acetylcholine in the presence of endothelial dysfunction in hypercholesterolemic subjects.[4] Both these studies provide evidence that inhalation of salbutamol is a simple, reliable, noninvasive and reproducible method for assessing endothelial function. In another study, 2.5 mg of nebulized salbutamol was used in postmenopausal, obese women to assess endothelial function.[5] Lind *et al*. have used 0.25 mg of subcutaneous terbutaline for assessing endothelial function and have also investigated the mechanism of reduction of terbutaline-induced wave reflection (Reflection Index, RI) by systemic interventions with both L-N^G-monomethyl arginine (L-NMMA, a NOS inhibitor) and noradrenaline.[5,6] All these studies used two different β2 agonists for evaluation of endothelial function by three routes of administration. In the present study, we have compared the effects of two different β2 agonists used by different routes of administration for assessment of endothelial function.

Twenty healthy male subjects (mean age: 27 ± 7 years) were enrolled in the present study, which was approved by the IEC of Nizam's Institute of Medical Sciences (EC/NIMS/574/2005, Dt. 29/12/2005). Subjects gave their written informed consent and refrained from smoking or taking caffeine-containing beverages at least 12 hrs before recording the DVP. On the day of study, subjects were examined in supine position allowing 5 minutes rest before examination. DVP was obtained by using a photoplethysmograph (Micro Medical, Gillingham, Kent, U.K.), transmitting IR light at 940 nm, placed on the index finger of the right hand. The signal from the plethysmograph was digitized using a 12-bit analogue-to-digital converter with a sampling frequency of 100 Hz. DVP waveforms were recorded over a 10 sec period and the height of the late systolic / early diastolic portion of the DVP was expressed as a percentage of the amplitude of the DVP to give the RI as per the procedure described in detail by Millasseau *et al*.[2] From DVP recordings, three measurements of RI were calculated and the mean was determined. Subjects were randomized in a 3-way crossover design to receive either 400 μg of salbutamol by inhalation or 2.5 mg of salbutamol by nebulization or 0.25 mg of terbutaline subcutaneously, allowing four days wash-out between each period. Three readings of RI were recorded before and 20, 30 and 15 mins after the administration of β2 agonists respectively in all experiments. The difference in mean RI before and after the administration of β2 agonists was considered for studying the endothelial function as described.[4-6] One-way ANOVA followed by post hoc Bonferroni's multiple comparison test was used to find out the statistical difference between the three methods of β2-agonist administration.

Decrease in RI from the baseline by both the agonists-salbutamol and terbutaline, suggested normal endothelial function. These findings are in accordance with previous studies involving β2 agonists.[4-6] The mean and standard error (SE) values for the RI indices of the three groups are shown in Table 1. It can be seen that the maximum decrease in RI was obtained with terbutaline, followed by salbutamol inhalation and it was minimum in the salbutamol nebulization method. It has been suggested that a > 6% decrease in RI after administration of β2 agonists is reflects normal endothelial function.[3] In our study, except for salbutamol nebulization, both terbutaline and inhalation of salbutamol produced > 6% decrease in RI. The minimal effect on RI by salbutamol nebulization was associated with marked variability in response as compared to the other two methods. Although terbutaline had the greatest effect on RI, it needs subcutaneous administration by qualified personnel and will be more useful in subjects having respiratory pathology or those who cannot inhale salbutamol properly. On the other hand,

Table 1

Percentage change in reflection index before and after the administration of β2 adrenoceptor agonists

Drug treatment	*Reflection index (RI%)*		
	Before	*After*	*Percentage change*
A. Salbutamol inhalation	71.75 ± 2.46	62.35 ± 2.03	13.71 ± 2.38
B. Salbutamol nebuliser	70.8 ± 2.08	67.5 ± 3.31	4.49 ± 3.64
C. Terbutaline subcutaneous	67.3 ± 2.86	56.25 ± 2.69	17.69 ± 3.04

n = 20, Values are expressed as Mean ± SE., F = 4.883; df = (2, 57), P < 0.011 overall, A *vs* B: P > 0.05; A *vs* C: P > 0.05; B *vs* C: P < 0.05

salbutamol inhalation method is found to be reasonably good to study endothelial function. Its administration is simple but is limited in the presence of respiratory problems limiting the absorption from the lungs. In conclusion, inhalation of 400 µg of salbutamol inhalation is a good, simple and noninvasive method for studying endothelial function in a large population.

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