Evaluation of Endothelial Function on Atherosclerosis using Perfusion Index from Pulse Oximeter

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Abstract

Background: Endothelial dysfunction is vascular phenomenon that plays an important role in atherosclerosis development. With the purpose of improving the prevention and treatment of atherosclerotic diseases, the searching for accurate, practical and cheaper methods for evaluating endothelial function have become of interest.

Objectives: Verify the potential of Peripheral Perfusion Index from pulse oximetry (IPP) as a method of endothelial dysfunction evaluation in patients with atherosclerotic diseases.

Methods: There were recruited 18 control patients and 24 patients with atherosclerotic diseases under optimized treatment, in basic health units. The values of IPP were evaluated before and after an endothelial-dependent stimulus, the reactive hyperemia. The values of IPP were also evaluated in period which the major contribution of Nitric Oxide (NO) for the vasodilation occurs (IPP_{90-120}). The results of IPP were discussed using the literature and estimating their diagnostic and prognostic potential

Results: The endothelium-dependent vasodilatory response measured by IPP was significantly lower in patients with atherosclerosis compared to control group, since 45 seconds after reactive hyperemia. Also, the values of IPP_{90-120} were significantly lower in patients with atherosclerosis [35% (4 - 53%) vs 73% (55 – 169%); p<0,001]. Similarly, the IPP values were lower in atherosclerosis group when it was separated by gender.

Conclusion: The results of this study, in association with the low cost of pulse oximeter, suggest a good potential for IPP as an endothelial dysfunction evaluation method. New studies must be done in order to clarify this potential and possibly contribute with the prevention and treatment of atherosclerotic diseases. (Arq Bras Cardiol. 2014; 102(3):237-244)

Keywords: Pulsatile Flow; Atherosclerosis; Endothelium / physiopathology.

Introduction

The impact of circulatory diseases on morbidity/mortality in Western countries is undeniable. In Brazil, atherosclerotic diseases have a significant impact. In 2007 only, they caused 1,157,509 hospitalizations and 308,466 deaths[1].

Therefore, methods to evaluate cardiovascular risk and therapeutic interventions for atherosclerotic diseases are urgently required. A recently proposed viable method is the study of endothelial function[2-4].

There is strong evidence suggesting that endothelial dysfunction occurs early during the atherogenic process, thus contributing to the formation, progression, and complications of atherosclerotic plaque[5]. Other studies have demonstrated that patients with cardiovascular risk factors and without diagnosed atherosclerosis exhibit endothelial dysfunction that is evident in the decreased vascular endothelial responsiveness to acetylcholine and bradykinin[6]. Taken together, these findings suggest that the dysfunction may be a mechanism that links cardiovascular risk factors with the development of atherosclerosis[3].

Considering that vascular–endothelial dysfunction is a systemic pathology, it is possible to estimate large and medium arteries through the evaluation of peripheral arteries[2]. Among the techniques used for this evaluation, we highlight the ones using reactive hyperemia as a vasodilator stimulus, such as the dilation of the flow-mediated brachial artery[7] and, more recently, digital pulse amplitude tonometry[8]. Both methods have shown significant diagnostic, therapeutic, and prognostic results in patients with risk factors or established atherosclerosis[2,8]. However, their application in clinical practice is still difficult because they require expensive equipment. The former method requires ultrasound experience that can be acquired through long and little available training.

Newer generation pulse oximeters calculate the peripheral perfusion index (PPI), thus measuring microvascular peripheral perfusion indirectly. The PPI was used to study the vascular arterial reactivity following reactive hyperemia

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in critically ill patients[9]. However, till date, no studies have used this method to evaluate endothelial function in patients with atherosclerosis.

This study aimed to assess endothelial function in individuals with and without atherosclerosis using the PPI and discuss its potential to estimate endothelial dysfunction according to a literature review.

Methods

All participants in this study provided written informed consent, and the research was approved by the Research Ethics Committee of the Universidade Federal do Paraná (protocol: 362ext039/2010-11). Therefore, the study protocol was in accordance with the national and international ethical norms on research with human beings.

The patients were selected from Basic Health Units of the municipalities of Pinhais, Colombo, and Quatro Barras in the Metropolitan Region of Curitiba, State of Paraná. The selection estimate for this type of study was 14 to 30 patients per group according to the literature[9-12].

Eighteen control patients without known cardiovascular risk factors and 24 patients with cardiovascular risk factors and diagnosed atherosclerotic diseases were enrolled.

In this study, the belowmentioned cardiovascular risk factors were considered.

1) History of smoking at least 1 cigarette/day for a minimum of 1 year

2) Systemic arterial hypertension (AP) of > 140 × 90 mmHg or use of antihypertensive medication

3) History of diabetes mellitus, indicated by two fasting glucose test results of ≥126 mg/dL or a random glucose test result of ≥ 200 mg/dL with disease symptoms or an oral glucose tolerance test (OGTT) result of ≥ 200 mg/dL. Patients with normal glucose levels who were on medication for diabetes mellitus were also considered.

4) Dyslipidemia, indicated by a triglyceride level of >150 mg/dL and/or a total cholesterol level of >200 mg/dL and/or a low-density lipoprotein (LDL) cholesterol level of >160 mg/dL and/or a high-density lipoprotein (HDL) cholesterol level of < 40 mg/dL and/or the use of lipid-lowering medication.

5) Obesity, indicated by a body mass index (BMI) of > 30 kg/m^2.

In this study, a diagnosis of established atherosclerotic disease was established on the basis of the presence of stable angina; history of acute myocardial infarction; presence of carotid, aortic, or peripheral atherosclerotic disease; and history of previous ischemic cerebrovascular disease.

Patients with renal disease who were undergoing dialysis, those with cancer, those with acute or chronic inflammatory diseases, and those with diseases other than atherosclerosis were excluded from the study.

Clinical and Laboratory Evaluation

All patients were subjected to a comprehensive clinical evaluation, with an emphasis on the cardiovascular system. The body weight and height were determined to calculate the BMI. Abdominal circumference and systemic AP were also measured.

During the study week, blood samples were collected for laboratory tests, which included the measurement of fasting glucose, total cholesterol, HDL and LDL cholesterol, and triglyceride levels. For smokers, the number of cigarettes smoked per year was also determined.

PPI and Assessment of Endothelial Function

To determine the PPI, a portable pulse oximeter (Finger Oximeter PM100C, New Tech, U.S.A) was used. The same researcher performed all tests.

Because numerous factors can affect vascular reactivity, the participants of the study were made to fast for 8 to 12 hours before the tests and were assessed in a quiet room with a controlled temperature. They were instructed not to exercise, consume caffeine or foods rich in fat and vitamin C, or smoke for at least 4 to 6 hours before the study. In addition, women were asked about the status of their menstrual cycle because hormonal changes can alter vascular reactivity[7]. Any medication having vasoactive effects (antihypertensive) was stopped, whenever possible, 12 to 24 hours before the study, which is in accordance with the literature[10].

The patients were made to sit for approximately 30 minutes before evaluation. The pulse oximeter was placed on the index finger of the right hand, which was positioned at the height of the heart. the PPI was measured for a period of 3 minutes (basal value) after signal stabilization. Subsequently, a sphygmomanometer cuff was inflated around the homolateral arm, 30 to 50 mmHg above the systolic pressure to occlude the arterial flow, for a period of 5 minutes[7, 9-12].

Reactive hyperemia occurred on deflation of the cuff; this was the hemodynamic stimulus for endothelial evaluation. The PPI was determined every 15 seconds for a period of 5 minutes to create a curve of PPI variation (Δ PPI) as a function of time. The variation in the PPI was calculated at each assessed time point using the following formula:

$$\Delta PPI: PPI\ time - PPI\ basal / PPI\ basal\ (\times 100)$$

Subsequently, the time–response curves for the PPI in the groups under study were compared.

Next, the mean variation in the PPI was determined 90 to 120 seconds after cuff deflation (ΔPPI_{90-120}). This time interval was chosen because recent findings showed that the strongest correlation between cardiovascular risk factors and endothelial dysfunction was observed during this time period[13]. Moreover, it is included in the time period during which nitric oxide mostly contributes to the vasodilator effects of reactive hyperemia[12]. The ΔPPI_{90-120} was compared between groups.

Furthermore, the heart rate was measured before and after reactive hyperemia to investigate a possible contribution of this parameter to peripheral perfusion.

Statistical Analysis

The Shapiro–Wilk test was used to test the normalcy of the sample. Values for parametric samples are expressed as means ± standard deviations, whereas those for nonparametric samples are expressed as medians and interquartile ranges. The categorical variable (gender) is expressed as a percentage.

Student's t-test, the Mann–Whitney U test, and the chi-square test were used to determine the significance of differences in parametric, nonparametric, and categorical variables, respectively, between groups. The level of significance in all analyses was $p < 0.05$. The statistical program GraphPad Prism version 3.02 was used for all statistical analyses.

Results

Table 1 shows the main demographic, laboratory, and clinical characteristics of the patients under study. There were no statistically significant differences in age and diastolic AP. However, the systolic AP was higher, heart rate was lower, and obesity parameters were higher in the atherosclerosis group than in the control group.

The number of women was higher in the control group than in the atherosclerosis group; however, this difference was not statistically significant. All women who participated in the study were menopausal.

With regard to metabolic parameters, triglyceride levels were higher in the atherosclerosis group than in the control group, and there were no differences in total cholesterol levels. Although we observed trends of differences in HDL and LDL cholesterol and fasting glucose levels, the differences were not statistically significant. All patients were on lipid-lowering medications, and patients with diabetes were receiving oral hypoglycemic drugs.

Although the basal PPI values tended to be elevated in the atherosclerosis group, the difference was not statistically significant. It is worth noting that there was no statistically significant difference in heart rate before and after the PPI test in both groups.

In the atherosclerosis group, 13 patients had ischemic coronary disease (54%), 7 had cerebrovascular disease (29%), 5 had aortic atheroma (21%), 4 had carotid atheroma (16%), and 1 (4%) had peripheral arterial disease of the lower limbs.

With regard to the primary medications, all patients with atherosclerosis were consuming anti-platelet aggregation drugs (AAS, clopidogrel) and statins, 11 were consuming angiotensin-converting enzyme inhibitors, 7 were consuming

Table 1 – Demographic, metabolic, and hemodynamic characteristics as well as peripheral perfusion index (PPI) values for the controls and patients with atherosclerosis. The parametric data are expressed as means ± standard deviations, while the nonparametric (basal IPP) data are expressed as medians and interquartile ranges (parentheses)

	Control	Atherosclerosis	p
n	18	24	----
Age (years)	59 ± 10	61 ± 8	0,.48
Gender (M/F)	8/10	14/10	0.37
BMI	24 ± 3	28 ± 4	0.007
Abdominal circumference (cm)	87 ± 7	97 ± 12	< 0.001
Dyslipidemia (%)	0	20/24*	----
Total cholesterol (mg/dL)	171 ± 27	163 ± 41	0.47
LDL cholesterol (mg/dL)	103 ± 28	84 ± 35	0.07
HDL cholesterol (mg/dL)	49 ± 8	44 ± 11	0.10
Triglycerides (mg/dL)	99 ± 39	161 ± 87	0.006
Diabetes mellitus	0	6/24 *	----
Fasting glucose (mg/dL)	86 ± 7	101 ± 34	0.08
Arterial hypertension	0	20/24 *	----
SAP (mmHg)	112 ± 11	125 ± 18	0.012
DAP (mmHg)	72 ± 09	75 ± 13	0.42
HR before inflation (bpm)	71 ± 8	63 ± 2	< 0.001
HR after deflation (bpm)	70 ± 8	62 ± 2	< 0.001
Smoking	0	9/24	----
Qt. of cigarettes smoked (packets-year)	0	28	----
Basal PPI (%)	2.6 (2.4–8.6)	7.2 (3.6–9.8)	0.11

*BMI: body mass index; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; HR: heart rate. *treated patients*

angiotensin II receptor blockers, 13 were consuming beta blockers, 10 were consuming calcium channel blockers, 12 were consuming diuretic drugs, and 6 were consuming nitrates.

PPI Studies

Table 2 shows the variations in the PPI (ΔPPI) after deflation of the sphygmomanometer cuff. There was an evident difference in the increase in the PPI between the atherosclerosis group and the control group. These differences become statistically significant 45 seconds after deflation of the cuff.

In addition, Figures 1 and 2 show that the mean values measured in the 90–120-second (ΔPPI_{90-120}) interval were lower in the atherosclerosis group than in the control group. These statistically significant differences were observed in both men and women.

Discussion

Pulse oximetry, in particular its derived data (oxygen saturation and plethysmographic curve), has become a leading method for clinical monitoring in intensive care environments and emergency, surgical, and anesthetic rooms. The main finding of this preliminary study concerns the possibility of a novel clinical application for pulse oximetry, i.e., evaluation of endothelial function using the PPI.

Peripheral perfusion is a physiological parameter that is directly associated with local blood flow, the regulation of which involves resistance arteries. Resistance arteries are the primary blood vessels responsible for the maintenance of systemic AP[14]. One noninvasive form to evaluate peripheral perfusion and, indirectly, the vascular activity of resistance arteries is the use of the PPI.

The PPI is derived from the oximetry photoelectric plethysmographic signal and is obtained from the difference in light absorbance between the pulsatile component (pulsatile arterial blood) and the nonpulsatile component (venous and capillary blood, other tissues, and bones). Changes in peripheral perfusion are accompanied by variations in the pulsatile component and not the nonpulsatile component; the PPI variation is thus obtained[15].

Shear stress acting on the endothelium probably represents the major physiological stimulus for the release of vasoactive factors and regulation of vascular tonus. An increase in shear stress can be induced by reactive hyperemia, which is an increase in blood flow followed by a short period of ischemia of the distal tissues. The endothelium dynamically responds to this stimulus by releasing vasoactive factors, particularly NO, thus leading to arterial vasodilation[3]. On the basis of this principle, it is possible to evaluate the endothelial function of human beings by determining the degree of endothelium-dependent arterial vasodilation. The variation in IPP was determined following the onset of reactive hyperemia.

Endothelial dysfunction plays an important role in all phases of atherogenesis and has a clear prognostic value in studies with a significant number of heterogeneous groups of patients with well-established disease[16]. Therefore, patients with atherosclerosis at various vascular sites were evaluated on the basis of the common concomitance of involved sites and the systemic characteristics of the disease[2] and because they had potential endothelial dysfunction. In this study, the PPI after reactive hyperemia enabled us to clearly distinguish normal patients from those with atherosclerosis, which is unprecedented in the literature.

Table 2 – Variations in the peripheral perfusion index (ΔPPI) after cuff deflation in the controls and patients with atherosclerosis. Values are expressed as medians and interquartile ranges (parentheses) * p < 0.05 *vs.* control; ** p < 0.01 *vs.* control; *** p < 0.001 *vs.* control

Time after deflation (seconds)	ΔPPI (%)	
	Control (n = 18)	Atherosclerosis (n = 24)
0	0	0
15	04 (−35–56)	−12 (−42–25)
30	37 (5–93)	05 (−19–42)
45	51 (21–120)	14 (−6–54) *
60	73 (29–158)	25 (6–45) *
75	84 (36–156)	26 (−8–50) **
90	74 (47–163)	33 (9–59) **
105	105 (47–199)	36 (−3–54) ***
120	70 (46–157)	36 (14–49) ***
150	87 (36–205)	23 (13–54) **
180	67 (29–178)	30 (−8–61) **
210	81 (51–210)	21 (−07–43) ***
240	56 (37–200)	11 (01–51) ***
270	55 (43–172)	12 (−13–45) ***
300	52 (34–140)	11 (−13–56) **

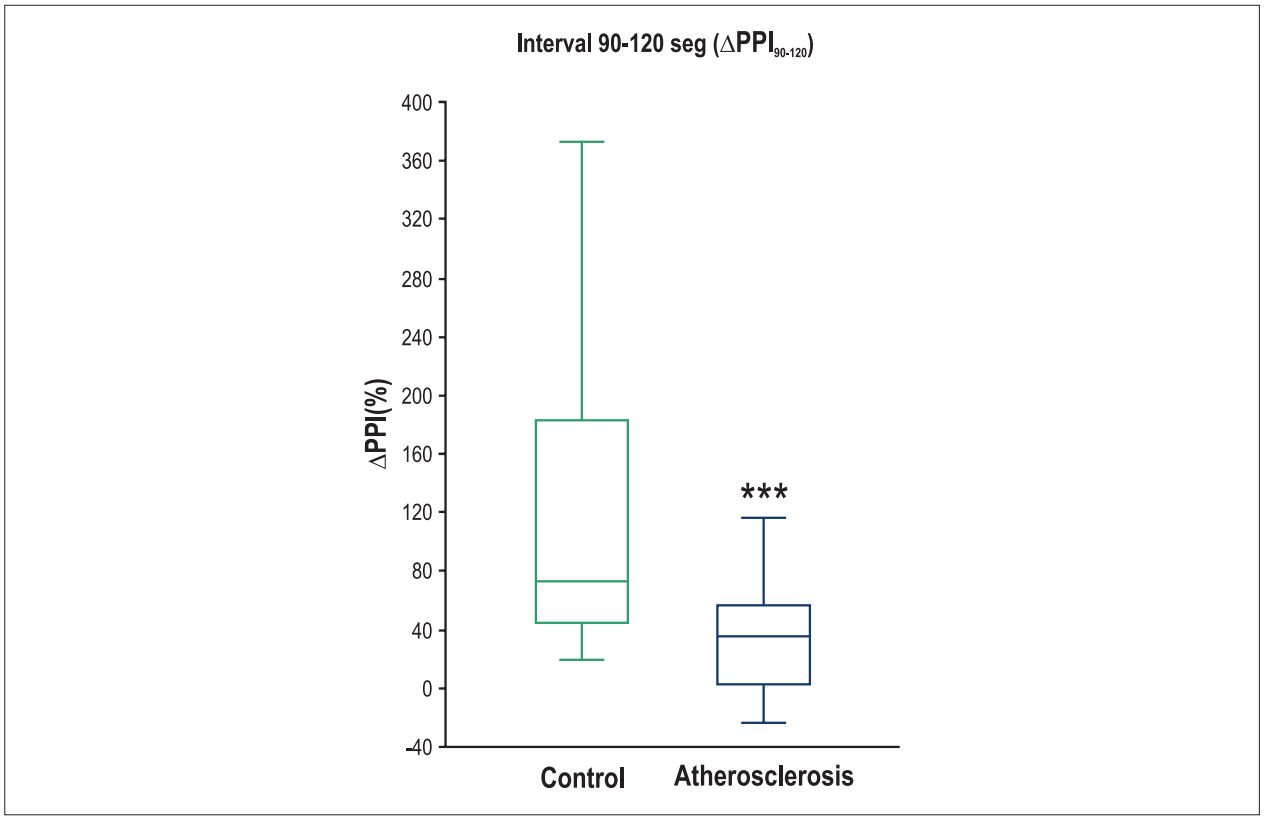

Figure 1 – *Box and whiskers graph showing variations in the peripheral perfusion index in the 90–120-second interval (ΔPPI_{90-120}) after cuff deflation in the controls and patients with atherosclerosis. The graph expresses medians, interquartile ranges, and maximum and minimum values. *** p < 0.001 vs. control*

Considering that endothelial dysfunction is, at least in part, a disorder that is reversible when cardiovascular risk factors are appropriately treated[17], and considering that the patients under study were receiving appropriate therapy, we hypothesized that the results of this study may be even more promising in terms of diagnostic tests for untreated patients.

NO is a free radical that is considered to be one of the main endothelial vasoactive mediators responsible for the maintenance of the vasorelaxant, anti-inflammatory, antioxidant, antithrombotic, and profibrinolytic properties of this tissue. There is agreement in the current literature that the decreased bioavailability of NO, which is a result of decreased synthesis and increased oxidative degradation, is the most relevant mechanism underlying the multifactorial process of endothelial dysfunction and primary cardiovascular dysfunction[18]. In this study, the PPI also allowed us to distinguish between patients during the period when NO contributes the most to the effects of reactive hyperemia. It should be added that, for practical clinical use, the use of absolute data is preferred over the study of curves. Moreover, a strong correlation with cardiovascular risk factors was observed during this period[13]. Therefore, this study suggests the use of the ΔPPI_{90-120} value for future clinical studies.

With regard to basal values, results previously described in the literature showed that there were no significant differences between patients with or without cardiovascular risk factors[19]. The results of the present study showed that the PPI tended to be increased in patients with established atherosclerosis, which may be explained by mechanisms that compensate chronic ischemia[14]. However, there was no statistically significant difference in this sample, and these findings should be confirmed in future studies.

In this study, the number of women was higher in the control group than in the atherosclerosis group, although the difference was not statistically significant. This can be explained by the well-known fact that the number of healthy men is overall lower than that of healthy women in basic health units (primary care)[20], which hinders sample homogenization in terms of gender. Despite this fact, even when the PPI values were separately analyzed, they were significantly different between the control group and the atherosclerosis group for both men and women.

This study had some limitations. First, the study was a cross-sectional study, which limited the research in terms of the development of a hypothesis. Moreover, a single measure was obtained per patient, and this limits conclusions about the intraindividual reproducibility of the method.

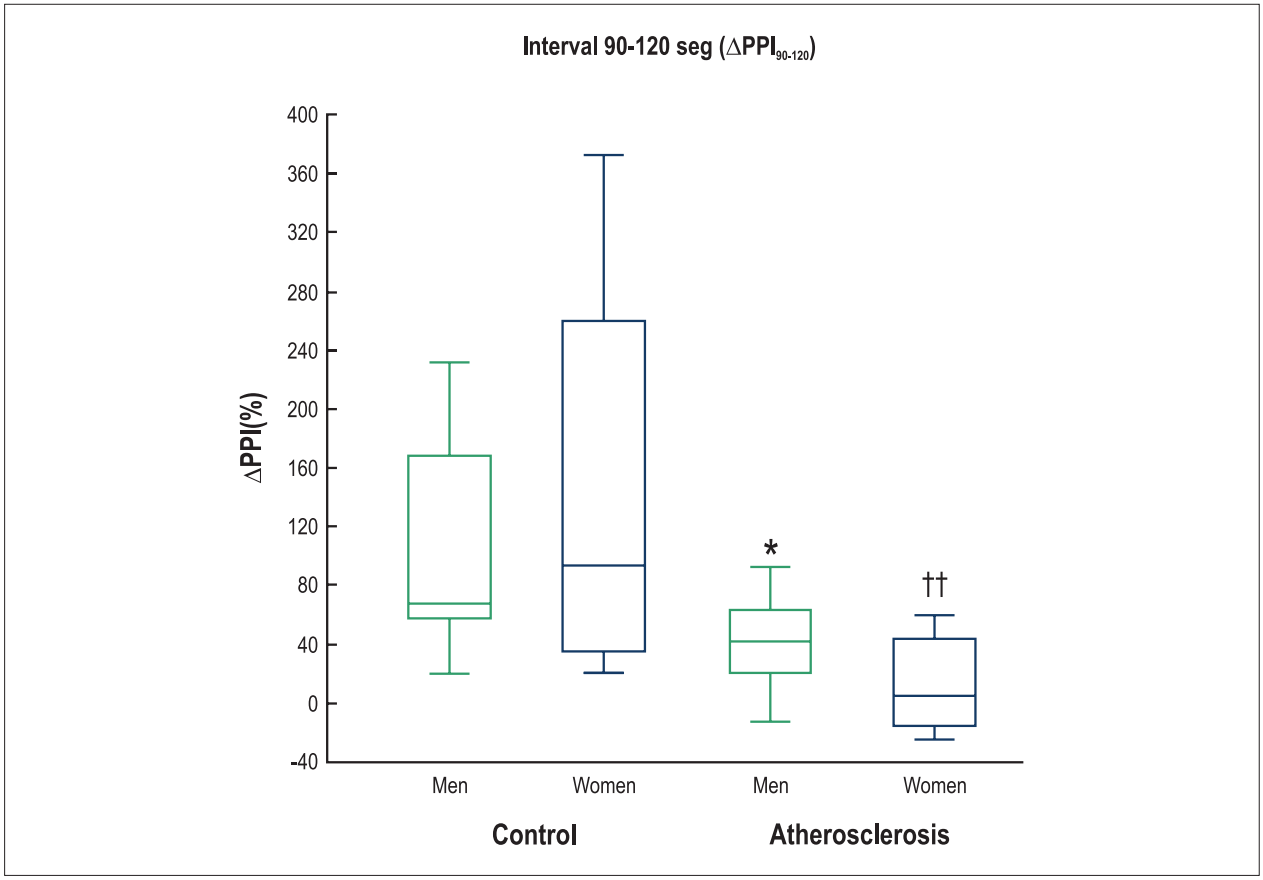

Figure 2 – *Box and whiskers graph showing variations in the peripheral perfusion index in the 90–120-second interval (ΔPPI_{90-120}) after cuff deflation in men and women in the control and atherosclerosis groups. The graph expresses medians, interquartile ranges, and maximum and minimum values. * p < 0.05 vs. men (controls), ††p < 0.01 vs. women (controls).*

The main limitation was the absence of a correlation with a validated method for evaluating endothelial function. The most precise methods that are currently available are invasive methods such as those that measure the coronary vasodilator response to acetylcholine and nitroprussiate[3,10]. Because of the limitations resulting from the nature of the test (risk of complications caused by invasiveness, impossibility of frequent repetition, and limitations to certain clinical contexts), noninvasive techniques such as flow-mediated brachial artery dilation have been developed. Recent results suggest a significant correlation if this method is used[21].

In an evaluation of 83 normal patients and patients with various cardiovascular risk factors, it was observed that after reactive hyperemia, data from the oximetry plethysmographic curve exhibited a behavior similar to that observed in studies using brachial artery Doppler[21]. It is conceptual that the same pulsatile signal used for the calculation of the PPI also originates from the pulse oximetry plethysmographic curve[22]. The advantage of the PPI over the plethysmographic curve is the practicality and speed of determination in an outpatient environment. In addition, not all equipment with plethysmographic curves have the appropriate software and devices that allow for accurate and reproducible calculations according to scientific requirements[23]. However, further studies are required to confirm these affirmations.

In conclusion, given the importance of endothelial dysfunction in the development and progression of atherosclerotic diseases, the search for clinically useful evaluation methods that are accurate, noninvasive, and easy to use has been encouraged for years[2]. Our results obtained with the PPI used for the evaluation of atherosclerotic patients, in addition to the low cost of the equipment, make this method attractive for future trials and for improvement in the prevention and treatment of these diseases.

Author contributions

Conception and design of the research: Menezes IAC, Cunha CLP; Acquisition of data and Statistical analysis: Menezes IAC; Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Menezes IAC, Santos MRV, Cunha CLP.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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