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Inconsistent Correlation Between Carotid Artery Intima-Media Thickness and Peripheral Arterial Tonometry

Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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Abstract: To estimate the association between 2 markers for atherosclerosis, measurements of carotid artery intima-media thickness (IMT) and of peripheral arterial tonometry (PAT), and to evaluate the role of traditional cardiovascular risk factors in this association.

We applied the 2 diagnostic tests to 588 participants from the ELSA-Brazil longitudinal study cohort. The PAT measurements, obtained with the EndoPAT2000, were the reactive hyperemia index (RHI), the Framingham RHI (F-RHI), and the mean basal pulse amplitude (BPA). We used the mean of the mean scores of carotid IMT of the distal layers of the left and right common carotids obtained by ultrasonography after 3 cardiac cycles. We used linear regression and the Spearman correlation coefficient to test the relationship between the 2 markers, and multiple linear regressions to exam the relationship between the RHI/F-RHI scores and the mean BPA and IMT scores after adjusting for cardiovascular risk factors.

In the multivariate analysis, RHI (but not F-RHI) was positively correlated with the mean of the means of the IMT values after adjusting for sex and risk factors connected with both measures ($\beta = 0.05$, $P = 0.02$). Mean BPA did not remain significantly associated with IMT after adjusting for common risk factors.

We found that the higher the IMT (or the worse the IMT), the higher the RHI (or the better the endothelial function). F-RHI was not associated with IMT. These 2 results are against the direction that one would expect and may imply that digital endothelial function (RHI and F-RHI) and IMT correspond to distinct and independent stages of the complex atherosclerosis process and represent different pathways in the disease's progression. Therefore, IMT and PAT measures may be considered complementary and not interchangeable.

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Abbreviations: ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers, BAR = brachial artery reactivity with ultrasonography, BMI = body mass index, BPA = mean basal pulse amplitude, CRP = C-reactive protein, ELSA-Brasil = Estudo longitudinal de Saúde do Adulto (Longitudinal Study of Adult Health), FAPEMIG = Fundação de Amparo à Pesquisa do Estado de Minas Gerais (Research Support Foundation of the State of Minas Gerais), F-RHI = Framingham RHI, IMT = intima-media thickness, PAT = peripheral arterial tonometry, RHI = reactive hyperemia index.

INTRODUCTION

Atherosclerosis is a physiopathological sign present in both coronary disease and stroke, which are the first and second most frequent causes of death in the world.[1,2] Atherosclerosis is a chronic inflammatory disease that involves complex pathological processes that occur in the blood vessels and develop throughout the years, with a long preclinical phase.[2] There is strong evidence that the endothelium performs a fundamental role in the development and progression of atherosclerotic disease.[3,4]

Results from recent studies indicate the endothelium as the main regulator of tonus and of vascular remodeling. The endothelium also produces substances that affect arterial inflammation and the thrombogenic process, contributing to atherogenesis.[3–6] Endothelial dysfunction can be interpreted as a sign of structural changes in the vascular wall, and participates in both the development and the progression of atherosclerosis.[7] Because it is a potentially reversible alteration, endothelial dysfunction has been considered to be a cardiovascular risk-factor that can be used to monitor the patient's response to treatments for cardiovascular diseases, and thus has a potential preventive effect and therapeutic impact.[8–11]

Endothelial function has been evaluated through the endothelium-dependent vasodilator response. This response is also related to the bioavailability of nitric oxide,[8,11,12] which has been measured by using noninvasive techniques[13,14] such as the measure of brachial artery reactivity with ultrasonography[15] and, more recently, by peripheral arterial tonometry (PAT).[16] PAT is an easy technique with automatic interpretation that does not require an expert examiner. Microvascular peripheral function is a function of the variation between the secondary digital pulse and reactive hyperemia, which occurs after the occlusion of blood flow in the arm.[17,18] This method has been shown to have validity and reproducibility[19–21] as well as to be associated with cardiovascular risk factors[22–26] and the prediction of cardiovascular events.[27]

Carotid intima-media thickness (IMT) has been studied for more than 2 decades and represents a structural marker for cardiovascular risk, predicting cardiovascular events in

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population groups.[28–30] IMT can be measured using ultrasonography of the carotid artery, and may be correlated to structural alterations in the vascular wall even when it does not display clinical manifestations.

Very few studies have investigated the correlation between IMT and PAT measures, and to our knowledge, none of them have investigated the correlation between IMT and the PAT mean basal pulse amplitude (BPA). In 2011, Fitch et al[31] reported a significant correlation between the IMT scores and reactive hyperemia index (RHI) obtained by PAT in a small cohort of 54 adults (rho = 0.35, $P = 0.02$) without adjusting for any cardiovascular risk factor. Thus, the correlation between IMT and PAT measurements remains an unanswered question. The object of this study is to investigate the correlation between the PAT and IMT measures in a large sample of adult and elderly participants of a cohort study aimed at investigating determinants of cardiovascular disease in Brazil,[32] after adjusting for common cardiovascular risk factors.

MATERIALS AND METHODS

Design and Population of the Study

The study of the correlation between diagnostic tests is a secondary project to the Longitudinal Study of Adult Health (ELSA-Brasil),[31] which is a cohort of governmental employees (active and retired) from teaching and research institutions located in 6 different states in Brazil (Minas Gerais, São Paulo, Rio de Janeiro, Espírito Santo, Rio Grande do Sul and Bahia). For the present study, we included only 588 participants who underwent carotid ultrasonography examination and PAT measures during their baseline visit to the ELSA Research Centre of Minas Gerais. The study took place from 2008 to 2010.

Of the 3115 participants in the ELSA-MG, 1648 undertook the PAT measurements and 1535 of these were valid.[26] Among these, 589 also underwent the IMT examination and 1 was excluded because it was an outlier measure. The final number of participants who underwent both tests and thus participated in this study was 588 (Figure 1).

Clinical Characteristics and Risk Factors

The socio-demographic, anthropometric, clinical and laboratory data of all participants were collected from the ELSA-Brasil study.[31] The data collection included face-to-face interviews and anthropometric, clinical and laboratory measures, and was carried out according to pre-established protocols conducted by trained and certified examiners.[32,33]

Height, weight, and body mass index (BMI) were calculated, as well as the waist-hip and waist-height ratios. Arterial pressure was measured 3 times with the participant sitting down and after 5 min of rest between the 2 tests; the mean of the second and third measures was used in data analysis. The presence of arterial hypertension was defined[34–36] as systolic and/or diastolic arterial pressure $\geq$140/90 mm Hg and/or as the use of anti-hypertensive medication during the 2 weeks before the interview. The presence of diabetes was self-reported. Participants who reported previous myocardial infarctions, angina and myocardial revascularization surgeries were classified as having prior coronary heart disease. The blood samples for laboratory examinations were collected after 12 h of fasting and the urine sample was collected during the 12 h before the visit to the research center. All the analyses were conducted by a certified laboratory technician in the ELSA Research Center at the University of São Paulo. In this study, we used the values of fasting serum glucose levels after an overload of dextrosol. We also measured glycohemoglobin, total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein cholesterol, triglycerides, C-reactive protein, and urinary albumin and creatinine. The total-HDL cholesterol ratio and the urinary albumin to creatinine ratio were calculated and used in data analysis. We also made sure that participants were not taking any medicines that could interfere with endothelial function (eg, angiotensin-converting enzyme inhibitors [ACEI], angiotensin receptor blockers [ARB], and statins). More details about the methodology of ELSA-Brazil and the cohort profile are available in Aquino et al[32] Schmidt et al,[33] and Mill et al.[36]

Peripheral Arterial Tonometry

PAT measurements were obtained with the EndoPAT 2000 in a silent and quiet environment after 2 h of fasting and at a room temperature of 21 to 24°C. A previous study from our group showed that the method has an acceptable reproducibility (Coefficient of Variation = 18% and Intraclass Correlation Coefficient = 0.61).[21]

The device was connected to participants' right and left index fingers through specific sensors. A sphygmomanometer cuff was placed around the nondominant arm, 2 cm above the cubital fossa, while the other arm was used as a control. During the examination, the digital sensors remained inflated with pressure electronically set at 10 mm Hg below the participant's diastolic pressure (maximum of 70 mm Hg). After stabilizing the signal for 1 min, the test was begun. It comprised recording of the PAT signal during three 5-min intervals: a basal period; the interval after interruption of blood flow by inflating the cuff (60 mm Hg above the systolic pressure or maximum of 200 mm Hg); and the period after reestablishment of blood flow by deflating the cuff and inducing reactive hyperemia (Figure 2). The RHI, automatically calculated by the program, is the ratio between the mean signal amplitude minutes before the insulation (basal), normalized for the contralateral arm (control), and corrected for the basal tonus (Figure 2). In addition to the RHI

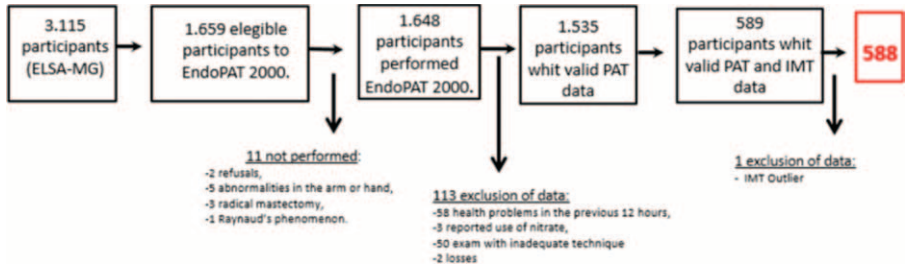

FIGURE 1. Study population obtained from participants in ELSA-Brazil (2008–2010).

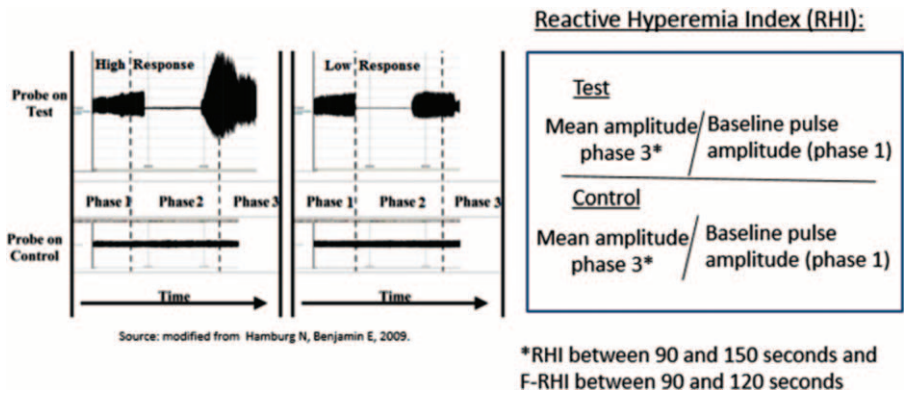

FIGURE 2. Example a register of the peripheral arterial tonometry test using the EndoPAT 2000, including the 3 phases of the test and the schematic formula for calculating the reactive hyperemia index.

obtained by the program, we used the RHI natural logarithm between 90 and 120 s (Framingham RHI, F-RHI) without adjustment for basal tonus, as proposed in the Framingham Heart Study.[22] We also recorded the value of the mean BPA, which corresponds to the mean of the natural logarithm of the BPA in the occluded and control arms.

Measurement of the Carotid IMT

Measurement of the common carotid IMT was standard and conducted on all study participants using the Aplio XG^{TM} device (Toshiba, Tokyo, Japan) with a 7.5 MHz transducer. The IMT evaluation was carried out on a 10-mm section, always on the most distant wall in relation to the observer in a region free from plaques starting 1 cm away from the carotid bifurcation. The digitalized images were forwarded to the ultrasonography-reading center. Interpretation of the test results was centralized and automated, using the software MIA^{TM} (Medical Imaging Applications, Coraville, IA), in 3 cardiac cycles.[37] The measures were summarized in 6 values: minimum, maximum, and mean for each artery (right and left). We created a variable that corresponds to the mean of the mean measures on each side, recommended in the literature because it is more reproducible and less susceptible to the influence of extreme values.[38,39]

Statistical Analysis

We carried out the descriptive analysis of the test values and participant co-variables using means and standard deviations for the continuous variables and frequencies and proportions for the categorical ones. Age, sex, smoking, use of statin, and use of ACEI and/or ARB were classified as categorical variables, while all others were classified as continuous. Simple linear regression was used to estimate the association between the IMT and PAT measures with the risk factors studied. Subsequently, we verified the correlation between the mean of the mean IMT and PAT measures using the Spearman coefficient and simple linear regression. The association was also assessed in subgroups defined by sex and age ($\geq$50 vs $<$50 years), excluding from the analysis those participants using ACEI and/or ARB or statin. Multiple linear regression, in which IMT was the dependent variable, was used in order to estimate the independent association between reactive hyperemia (RHI and F-RHI) and mean BPA, after adjusting for risk factors common to both measures. Due to its abnormal distribution, the IMT measure was transformed into a base-10 logarithm and the RHI provided by the device was transformed into a natural logarithm. F-RHI and mean BPA are already measures with logarithm conversion. We also performed the same analysis using the maximum of the maximum IMT scores and the results did not vary from those presented here. The significance level adopted as the cut-off point for entry into the multivariate analysis was 0.10 and, for remaining in the final models, 0.05. All the analyses were carried out using the STATA.12^{TM}—StataCorp LP software.

Ethical Considerations

The study was approved by the Ethics Research Committee of the UFMG-COEP (ETIC 186/06). All the participants signed a free and informed consent term. The study was funded by the Brazilian Ministry of Health and Ministry of Science and Technology, and the PAT evaluation was supported by FAPEMIG in the state of Minas Gerais (project 505-07).

RESULTS

Among the 588 participants, 55.9% were men, the average age was 52.1 ($\pm$8.9) years old and 88.7% were under 65 years old. More than 60% of participants presented altered values for abdominal obesity (waist-hip and waist-height ratios), 19.4% were obese (BMI $\geq$ 30 kg/m^2) and 36.4% were hypertensive. The prevalence of self-reported diabetes was 5.6% and of prior cardiovascular disease, 2.5%. A total of 12.7% of participants used some type of statin and 17.6% used ACEI and/or ARB. Table 1 shows the mean and median IMT and PAT measures.

Table 2 shows that, in general, the IMT measure and the mean of the BPA were associated with a greater number of risk factors than the 2 reactive hyperemia measures (RHI and F-RHI). It also shows that the F-RHI was associated with more risk factors than the RHI. The use of ACEI and/or ARB revealed a borderline inverse association with the F-RHI values, but not with the RHI. The waist/hip ratio, glucose 2 h after overload, total/HDL cholesterol ratio, and triglycerides were the only risk factors statistically associated with both IMT and PAT measures.

Correlations between IMT and RHI or F-RHI did not reach statistical significance, although the *P*-values were borderline for RHI (Table 3). Mean BPA had a statistically significant positive correlation with IMT. After excluding 104 participants who were using ACEI and/or ARB, a significant correlation emerged between IMT and RHI, but not between IMT and F-RHI, in the univariate analysis ($\beta = 0.075$; $P = 0.03$;

TABLE 1. IMT and PAT Measures in 588 ELSA-Brasil Participants (2008–2010)

	Mean ± SD	Median (Q1; Q3)
Carotid IMT		
Mean of the means, mm	0.6 ± 0.1	0.5 (0.5; 0.6)
PAT measures		
RHI	1.9 ± 0.5	1.8 (1.5; 2.2)
ln RHI	0.6 ± 0.2	0.6 (0.4; 0.7)
F-RHI	0.5 ± 0.3	0.5 (0.1; 0.8)
Mean BPA	5.8 ± 0.8	5.9 (5.2; 6.4)

BPA = basal pulse amplitude; F-RHI = Framingham's modified RHI, already calculated at the base logarithm (ln); IMT = intima-media thickness; ln RHI = natural logarithm of the RHI; PAT = peripheral arterial tonometry; Q1 = percentile 25; Q3 = percentile 75; RHI = reactive hyperemia index; SD = standard deviation.

rho = 0.099, $P = 0.029$). This correlation was not affected by the exclusion of participants using statin.

In the multivariate analysis, RHI was positively associated with the means of IMT values after adjusting for sex and risk factors connected with both measures (Table 4), indicating that the higher the IMT, the higher the RHI (ie, the better the endothelial function).

Mean BPA remained positively associated with IMT after adjusting for sex and age, but the association was no longer statistically significant after adjusting for risk factors associated to both measures (Table 4). As there was no statistical association between F-RHI and IMT in the univariate linear regression, we did not conduct the multivariate analysis.

DISCUSSION

Among the 588 participants from the ELSA-Brazil included in the present study, there was a direct correlation between the IMT and the RHI measures, after adjusting for common cardiovascular risk factors. This finding is different from those reported by Fitch et al[31] and Wilk et al[40] that also correlated these measures. Fitch et al showed an inverse correlation in the univariate analysis but no association between the 2 measures in the multivariate analysis ($\beta = -1.07$, $P = 0.14$) in a cohort of 54 participants with an average age of 49 years. Wilk et al[40] found no association between the RHI and the mean of the IMT values in 80 participants with an average age of 43 years with low or moderate cardiovascular risk. In spite of the fact that F-RHI is associated with a greater number of

TABLE 2. Association Between the Mean of the Mean IMT and Mean PAT Measures, With Selected Cardiovascular Risk Factors in 588 Adults From ELSA-Brasil (2008–2010) in the Linear Regression Analysis

	Beta Coefficient (Standard Error)			
Variable	**IMT**	**RHI (ln)**	**F-RHI**	**Mean BPA**
Age, yr	0.012 (±0.001)*	0.001 (±0.001)	−0.0002 (±0.002)	0.008 (±0.004)*
Sex				
Male	–	–	–	–
Female	−0.040 (±0.016)*	0.050 (±0.021)*	0.201 (±0.030)*	−0.632 (±0.063)*
Smoking (current)				
Yes	0.060 (±0.018)*	0.001 (±0.036)	−0.012 (±0.054)	0.036 (±0.123)
No	–	–	–	–
BMI, kg/m^2	0.010 (±0.001)*	0.001 (±0.002)	−0.008 (±0.004)*	0.045 (±0.008)*
Abdominal obesity				
Waist measure, cm	0.004 (±0.001)*	−0.0003 (0.001)	−0.006 (±0.001)*	0.026 (±0.003)*
Waist/hip ratio	0.720 (±0.098)*	−0.279 (±0.132)*	−1.419 (±0.187)*	4.789 (±0.400)*
Waist/height ratio	0.803 (±0.113)*	−0.049 (±0.152)	−0.771 (±0.222)*	3.219 (±0.495)*
Mean systolic pressure, mm Hg	0.004 (±0.0004)*	0.001 (±0.001)	−0.0005 (±0.001)	0.008 (±0.002)*
Mean diastolic pressure, mm Hg	0.003 (±0.001)*	0.001 (±0.001)	−0.002 (±0.001)	0.010 (±0.003)*
Fasting glucose, mg/dL	0.001 (±0.0003)*	−0.0003 (±0.0004)	−0.002 (±0.001)*	0.007 (±0.001)*
Glycohemoglobin, %	0.066 (±0.012)*	0.015 (±0.015)	0.007 (±0.023)	0.033 (±0.052)
Glucose 2 h after overload	0.001 (±0.0001)*	−0.0004 (±0.0002)*	−0.001 (±0.0003)*	0.004 (±0.001)*
Cholesterol, mg/dL				
Total	0.0003 (±0.0002)	0.00005 (±0.0002)	−0.0001 (±0.0003)	0.001 (±0.001)
LDL	0.0004 (±0.0002)	−0.00003 (±0.0003)	−0.0002 (±0.0004)	0.001 (±0.001)
HDL	−0.0002 (±0.0005)	0.002 (±0.001)	0.006 (±0.001)*	−0.014 (±0.002)*
Total/HDL cholesterol ratio	0.019 (±0.008)*	−0.028 (0.011)*	−0.085 (±0.015)*	0.216 (±0.035)*
Triglycerides, mg/dL	0.0001 (±0.0001)	−0.0004 (±0.0001)*	−0.001 (±0.0001)*	0.002 (±0.0004)*
C-reactive protein, mg/mL	0.006 (±0.002)*	−0.003 (±0.003)	0.001 (±0.001)	−0.005 (±0.009)
Microalbuminuria, mg/L	0.001 (±0.0004)	0.0004 (±0.0005)	0.0001 (±0.001)	−0.002 (±0.002)
Use of statin	0.112 (±0.024)*	0.026 (±0.032)	−0.022 (±0.047)	0.172 (±0.107)
Use of ACEI and/or ARB	0.151 (±0.021)*	−0.022 (±0.028)	−0.080 (±0.041)*	0.270 (±0.093)*

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BMI = body mass index; BPA = basal pulse amplitude; F-RHI = Framingham RHI; HDL = high-density lipoprotein cholesterol; IMT = intima-media thickness; LDL = low-density lipoprotein cholesterol; PAT = peripheral arterial tonometry; RHI (ln) = reactive hyperemia index (natural logarithm).
* $P \leq 0.05$.

TABLE 3. Correlation of the Mean of the Means of the IMT With the PAT Measures in 588 ELSA-Brasil Participants (2008–2010)

	Mean of the Mean IMT Scores			
	Spearman's		Simples Linear Regression	
PAT	**rho**	***P***	**B**	***P***
Total population				
RHI	0.078	0.059	0.058 (±0.031)	0.070
F-RHI	−0.033	0.429	−0.016 (±0.022)	0.453
Mean BPA	0.175	<0.001	0.039 (±0.009)	<0.001

BPA = basal pulse amplitude; F-RHI = Framingham RHI; IMT = intima-media thickness, transformed into base-10 logarithm; PAT = peripheral arterial tonometry; RHI = reactive hyperemia index, transformed into natural logarithm; rho = Spearman's rank correlation coefficient.

cardiovascular risk factors than the RHI, we did not observe an association between F-RHI and IMT. As this is the first study that evaluates the correlation between IMT and F-RHI, we have no other studies to which we can compare our results. Mean BPA, assessed by PAT, was positively associated with IMT in the univariate and sex-age adjusted analysis, but this association lost statistical significance after adjusting for other common risk factors.

In this study, the IMT measure was associated to most risk factors here evaluated, while the association with RHI was weakly associated and only to 4 of these risk factors (being female, RHI waist/hip ratio, HDL, and Triglycerides). This finding may explain why the association between RHI and IMT here found is contrary to that expected. In other words, we expected a higher IMT being correlated to a smaller RHI. On the other hand, we found no statistical significance between IMT and the corrected RHI (by Framingham). This latter finding seems also surprising, as the F-RHI is associated with more Cardiovascular Disease (CVD) risk factors and more strongly than the RHI, because it refers to the period of greatest nitric oxide release (90120 seg). Moreover, the F-RHI is not corrected by the BPA, as BPA correlates very strongly with most CVD risk factors in this study and might also result from vascular dysfunction.[23] Taken together, these 2 findings suggest that endothelial dysfunction in microvasculature and structural alterations of the vascular wall of large blood vessels, such as the carotid, are 2 phenomena that may occur at different moments and have no correlation to a single measure. As this is a cross-sectional analysis, this particularity may have been missed. Furthermore, the reversibility of endothelial function, already evaluated in some studies,[41–45] and the lower reversibility of arterial wall lesion, expressed in the IMT, may explain this lack of a correlation. Individuals who present abnormal IMT values may have improved endothelial function through behavioral and medical interventions, which does not reverse the already established structural anatomical alterations.

Other possible explanations for the lack of association between F-RHI and IMT and the weak positive association between RHI and IMT after adjustments may be related to the fact that PAT evaluates the dilation of the peripheral digital vasculature, where nitric oxide activity corresponds to only 60% of the reactive hyperemia phenomenon.[46] Hence, there may be other factors or mediators that are still unknown or were not addressed in this study that affect the PAT measures and do not correlate with structural alterations in the vascular wall.

Finally, Baldassarre et al[47] observed that in order to implement cardiovascular risk classification, more elaborated images of IMT and of other arterial alterations would be preferable to the common carotid IMT measure, in line with Polak et al.[48,49] It is thus possible that the common carotid IMT measure used in this study is not the best subclinical cardiovascular marker for comparison with the measures obtained from the endothelial function test. Other more specific measures, such as the presence of atherosclerotic plaques or even the IMT of the internal carotid, could be more precise and present a different association with endothelial function.

The merit of this study was the great number of participants and the use of protocols for standard operating procedures and supervision for quality control, minimizing the influence of measurement errors.[26,50]. PAT measurement means were similar to values found in the Framingham Heart Study[22] and in the Gutenberg study.[24]

TABLE 4. Association Between the Mean of the Mean of IMT and the Means of RHI and of Basal Pulse Amplitude Values in 588 ELSA-Brasil Participants (2008–2010) in the Multiple Linear Regression Model

Models	**Coefficient β**	**SE**	***P* Value**
PAT RHI			
No adjustment	0.058	0.031	0.070
Adjusted for sex	0.066	0.031	0.039
Adjusted for age and sex	0.050	0.026	0.058
Adjusted for age, sex, waist-hip ratio, total-HDL cholesterol ratio, glucose 2 h after overload	0.060	0.026	0.023
PAT basal pulse amplitude			
No adjustment	0.039	0.009	<0.001
Adjusted for sex	0.036	0.010	<0.001
Adjusted for age and sex	0.021	0.008	0.012
Adjusted for age, sex, waist/hip ratio, total/HDL cholesterol ratio, mean systolic pressure, fasting glucose, glucose 2 h after overload, BMI, use of ACEI and/or ARB	0.010	0.008	0.221

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BMI = body mass index; HDL = high-density lipoprotein cholesterol; IMT = intima-media thickness; PAT RHI = peripheral arterial tonometry, reactive hyperemia index; SE = standard error.

The limitations of the cross-sectional design may influence the analysis of endothelial function, since, unlike other measures of vascular wall morphology, it has an intrinsic biological variability. A single measure may provide instant and restricted information on the real digital endothelial activity of individuals.[11] A limitation that goes beyond our study is the precarious understanding in the literature of the appropriate physiological interpretation of the measures of digital reactive hyperemia and mean BPA provided by PAT, and how these measures are affected by and correlate to larger vasculatures.

The difference between the results obtained for the digital microvasculature versus the macrovascular conducting arteries indicates that arterial physiology and mechanisms of vasodilation differ according to the vascular bed studied.[11,22] Despite the fact that basal endothelial tonus is mainly regulated by the nitric oxide and that its reduction is an important cause of microvascular dysfunction, the role of the nitric oxide is complex and may also vary according to the vascular bed.[24] The lack of correlation between IMT and F-RHI suggests that these measures contribute in different ways to the understanding of the progression of cardiovascular disease and are, hence, complementary. Furthermore, our findings regarding the association between mean BPA with most of the cardiovascular risk factors and its direct correlation to IMT, in agreement with other studies,[22,24] indicates that both measures are related to permanent alterations of the vessel. Mean BPA reflects blood flow, tonus, and endothelial compliance and can be an important indicator of structural microvascular alterations.[23] The prospective analysis of these measures in ELSA-Brasil will help to clarify the clinical utility of PAT in the prediction of cardiovascular risk.

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