

# Brachial artery flow-mediated dilatation and intima-media thickness of carotid and brachial arteries: evaluation of individuals with and without risk factors for atherosclerosis\*

*Dilatação fluxo-mediada da artéria braquial e complexo médio-intimal das artérias carótida e braquial: avaliação de indivíduos com e sem fatores de risco para aterosclerose*

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**Abstract** **OBJECTIVE:** To evaluate endothelial function in patients with risk factors for atherosclerosis by measuring brachial artery flow-mediated dilatation (BAFMD) and intima-media thickness (IMT) of carotid and brachial arteries. **MATERIALS AND METHODS:** A cross-sectional, case-control study in which endothelial function was evaluated by measurement of BAFMD and IMT of carotid and brachial arteries and presence or absence of risk factors in 112 patients distributed as follows: women with risk factors ( $n = 49$ ), women control group ( $n = 24$ ), men with risk factors ( $n = 21$ ), men control group ( $n = 18$ ). **RESULTS:** BAFMD was significantly compromised in the group with risk factors as compared with the control group, regardless of sex: in women,  $15.2 \times 25.3$  ( $p < 0.01$ ); in men,  $11.8 \times 16.8$  ( $p < 0.02$ ). On the other hand, IMT was not significant both for the carotid and brachial arteries, regardless of sex: brachial artery in women,  $0.3 \times 0.3$  ( $p < 0.06$ ); brachial artery in men,  $0.36 \times 0.23$  ( $p < 0.07$ ); carotid artery in women,  $0.6 \times 0.4$  ( $p < 0.07$ ); carotid artery in men,  $0.85 \times 0.38$  ( $p < 0.08$ ). The significance level was set at 5% ( $p < 0.05$ ). **CONCLUSION:** Measurement of BAFMD was effective for detecting endothelial impairment in a population with risk factors for atherosclerosis. **Keywords:** Atherosclerosis; Endothelial dysfunction; Brachial artery flow-mediated dilatation; Intima-media complex of the carotid and brachial arteries.

**Resumo** **OBJETIVO:** Avaliar a função endotelial em pacientes com fatores de risco para aterosclerose pela dilatação fluxo-mediada da artéria braquial (DILA) e complexo médio-intimal (CMI) das artérias carótida e braquial. **MATERIAIS E MÉTODOS:** Estudo transversal, caso controle, no qual foi avaliada a função endotelial pelo DILA e CMI das artérias carótida e braquial e presença ou não de fatores de risco para aterosclerose, em 112 pacientes assim distribuídos: mulheres com fatores de risco ( $n = 49$ ), mulheres grupo controle ( $n = 24$ ), homens com fatores de risco ( $n = 21$ ) e homens grupo controle ( $n = 18$ ). **RESULTADOS:** O DILA esteve comprometido significativamente no grupo fator de risco, quando comparado ao controle, independente do sexo: em mulheres,  $15,2 \times 25,3$  ( $p < 0,01$ ); em homens,  $11,8 \times 16,8$  ( $p < 0,02$ ). Já o CMI, tanto na braquial quanto na carótida, não foi significativo, independente do sexo: braquial em mulheres,  $0,3 \times 0,3$  ( $p < 0,06$ ); braquial em homens,  $0,36 \times 0,23$  ( $p < 0,07$ ); carótida em mulheres,  $0,6 \times 0,4$  ( $p < 0,07$ ); carótida em homens,  $0,85 \times 0,38$  ( $p < 0,08$ ). Utilizou-se como índice de significância  $p < 0,05$ . **CONCLUSÃO:** O DILA foi eficiente para atestar comprometimento endotelial em população de risco para aterosclerose. **Unitermos:** Aterosclerose; Disfunção endotelial; Dilatação fluxo-mediada da artéria braquial; Complexo médio-intimal das artérias braquial e carótida.

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## INTRODUCTION

Atherosclerosis is a degenerative disease of multicausal etiology. Different (genetic and acquired) risk factors together may determine the occurrence of such disease in more than 50% of the adult population worldwide. Several conditions may affect carotid arteries of both men and women from their birth to the oldness.

Among the main arteries affected by this condition, carotid arteries are the most studied ones, and among all the lesions of carotid arteries responsible for cerebrovascular disease of extracranial origin, 90% occur as a result of atherosclerosis. Other conditions are represented by non-atherosclerotic diseases such as kinking, Takayasu's arteritis, fibromuscular dysplasia, extrinsic compressions, intimal dissection, aneurysm and trauma<sup>(1)</sup>.

Cerebrovascular accident (CVA) is one of the major causes of death worldwide, and the leading cause of disability in the population with > 50 years of age, being responsible for 10% of total deaths, 32.6% of deaths due to vascular causes, and 40% of early retirements in Brazil that is among the top ten countries with highest mortality rates for CVA<sup>(2)</sup>.

Cardiovascular disease is the first cause of death in developed countries, with high socioeconomic costs<sup>(3)</sup>. In 2003, 69% of deaths with defined causes in Brazil were caused by non-transmissible chronic diseases, 32% of them of cardiovascular nature. In 2005, of five billion reais spent with the payment of authorizations for hospital admissions (except for labors), chronic diseases represented 58% of total expenditures, with 22% corresponding to the leading expenditures for cardiovascular diseases. Additionally, such chronic diseases may worsen the patients' quality of life, affecting familial budgets in the poorest populations most frequently affected by these diseases and respective complications<sup>(4)</sup>.

The silent onset of vascular disease in the arterial wall progresses through the already known mechanisms including endothelial dysfunction, inflammation, plaque formation and vascular remodeling, later atherosclerotic plaque rupture and thrombosis<sup>(5)</sup>.

Endothelial dysfunction is a relevant step in the development of cardiovascular diseases<sup>(6)</sup> participating in the atheroma rupture responsible for 70% of acute myocardial infarctions in asymptomatic patients<sup>(7)</sup>.

The endothelial profile can be evaluated by the measurement of brachial artery flow-mediated dilatation (BAFMD), that is based on the capacity of production of nitric oxide released by the endothelium<sup>(8)</sup>, which will promote arterial dilatation. Such measurement is achieved by means of ultrasonography, a noninvasive, low-cost method that allows the detection of preplaque endothelial dysfunction and provision of prophylactic treatment to avoid the worsening of the condition resulting from such alterations.

Another aspect of carotid disease to be observed is its relationship with intima-media thickening (IMT), that is considered as a cardiovascular risk factor and can be a good marker for the development and prediction of future systemic vascular accidents<sup>(9)</sup>. In healthy individuals, the maximum intima-media thickness of the common carotid artery at the prebifurcation site is 0.8 mm. Values between 0.9 and 1.4 mm are considered as thickening. In cases where the thickness is > 1.4 mm, atheromatous plaque is characterized<sup>(10)</sup>.

The present study was aimed at observing the vascular profile of both men and women with risk factors for atherosclerosis, utilizing BAFMD and IMT of carotid and brachial arteries.

## MATERIALS AND METHODS

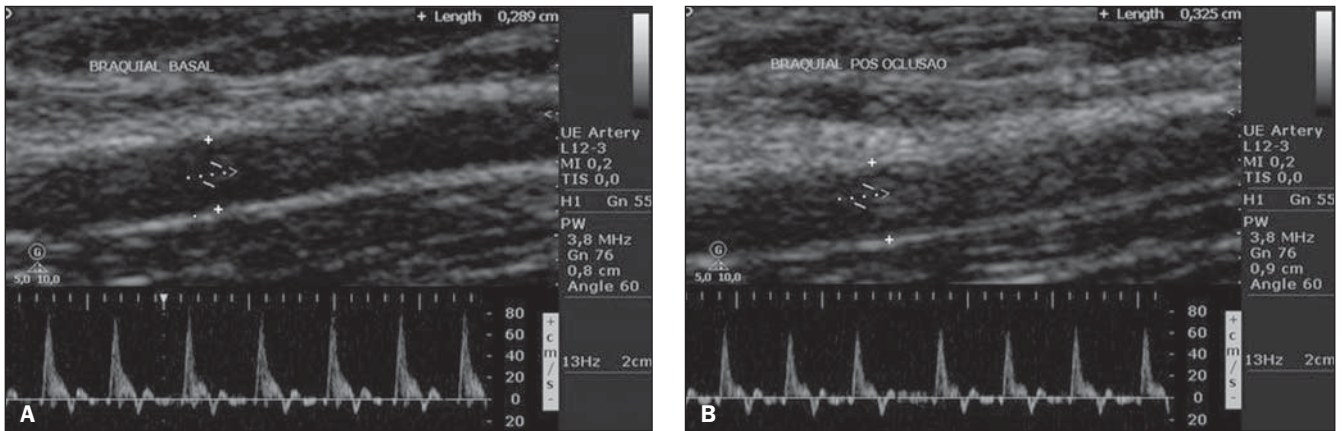
In the period from March to August 2004, 112 patients of the general and specialty infirmaries of Santa Casa da Misericórdia do Rio de Janeiro, RJ, Brazil, were invited to participate in the study. Such patients were divided into groups as follows: women with risk factors ( $n = 49$ ), female control group ( $n = 24$ ), men with risk factors ( $n = 21$ ) and male control group ( $n = 18$ ). All the patients included in the control groups were normotensive, non-smokers, non-diabetic, with no familial history of vascular diseases, cholesterol levels  $\leq 200$  mg/dl and age range between 19 and 50 years. All the women were in the

menopausal phase. The following risk factors for atherosclerosis were considered: obesity, diabetes mellitus, dyslipidemia, atherosclerosis, systemic arterial hypertension, metabolic syndrome, smoking, osteoporosis and thyroid hormone disorders.

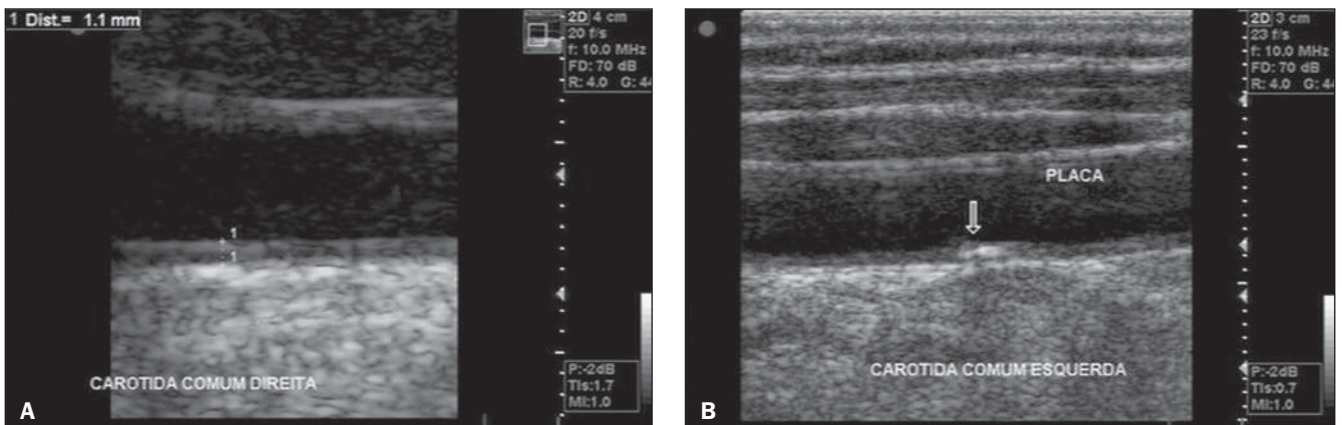
After approval of the study by the Committee for Ethics in Research of the institution, and signature of a term of free and informed consent, all the patients were submitted to ultrasonography for evaluation of BAFMD and IMT of carotid and brachial arteries.

BAFMD was applied according to the technique described by Celemajer et al. in 1992<sup>(11)</sup> and modified by Montenegro in 2004<sup>(12)</sup>, by a single observer in all the situations, with the patients in dorsal decubitus, at rest, in a calm environment and under controlled room temperature. There was no food/drug restriction, since the objective of the study was to evaluate the patients' conditions in their daily habits. The right brachial artery was identified with the aid of a Toshiba Nemio 2D color and spectral Doppler US unit (Toshiba Medical Systems, Tokyo, Japan), equipped with a linear, 14 MHz, high-resolution, B-mode transducer, placed between 2 and 5 cm above the cubital fold. The measurement limited by the intima-lumen interface (D1) at diastole was standardized for measuring the brachial artery diameter. Ischemia was provoked with the sphygmomanometer cuff previously positioned on the patient's right arm, with 200 mmHg pressure for all the patients during five minutes. A new measurement was performed between 60 and 90 seconds following the compression interruption (D2), at diastole, with the aid of pulsatile Doppler US. The brachial artery flow-mediated dilatation was calculated with the formula  $(D2 - D1)/D1 \times 100$ , and the results were expressed in percentages (Figure 1). The value established by Regattieri et al. (10%) was utilized as a normality parameter<sup>(13)</sup>.

IMT is defined as the distance between the leading edge of the first echogenic line and the leading edge of the second echogenic line<sup>(14)</sup>. The carotid IMT measurement was performed according to the description proposed by Salonen<sup>(15)</sup>, where the first line represents the intima lumen interface, and the second line represents the



**Figure 1.** Longitudinal echographic image of brachial artery of a patient with no risk for atherosclerosis, with measurement of the initial diameter of the brachial artery (pre-occlusion) corresponding to 0.8 cm and final to 0.9 mm, with BAFMD value calculated in 12.5%.



**Figure 2.** Longitudinal echographic image of right and left common carotid arteries of patients presenting risk for development of atherosclerosis, where thickening (A) and atheromatous plaque (B) could be visualized.

carotid media-adventitia interface. In the present study, the evaluation was performed with the transducer placed on the most distal wall of the distal common carotid artery, at 1-2 cm proximal to the carotid bifurcation (Figure 2). The same technique was utilized in the approach of brachial arteries.

The statistical significance threshold was set at  $p < 0.05$ , and the Mann-Whitney test of the SPSS package 16.02 for Windows (SPSS Inc.; Chicago, IL, USA) was utilized for statistical processing and analysis of results. Such test is proposed for independent samples, in cases where there is a rupture of parametric assumptions, particularly those regarding normality and homoscedasticity (assumption of constant variance across subsets of data). The results were expressed in mean  $\pm$  standard deviation.

## RESULTS

The BAFMD was significantly compromised in the group with risk factors as compared with the control group, regardless of sex. In the women with risk factors, BAFMD was 15.2% ( $\pm 8.1\%$ ) and in the female control group, 25.3% ( $\pm 5.4\%$ );  $p < 0.01$ . In the men with risk factors BAFMD was 11.8% ( $\pm 7.2\%$ ), and in the male control group, 16.8% ( $\pm 4.2\%$ );  $p < 0.02$ .

The values observed in the statistical analysis of IMT in both risk and control groups, respectively were the following: for the brachial artery – women, 0.3% ( $\pm 0.1\%$ )  $\times$  0.3% ( $\pm 0.1\%$ ),  $p < 0.06$ ; men, 0.36% ( $\pm 0.1\%$ )  $\times$  0.23% ( $\pm 0.05\%$ ),  $p < 0.07$ ; for the carotid artery – women, 0.6% ( $\pm 0.2\%$ )  $\times$  0.4% ( $\pm 0.1\%$ ),  $p < 0.07$ ; men, 0.85% ( $\pm 0.3\%$ )  $\times$  0.38% ( $\pm 0.1\%$ ),  $p < 0.08\%$ , demonstrating that both for the brachial and

carotid arteries, the IMTs were not significant. No significant correlation was observed between BAFMD, carotid IMT and brachial IMT among the groups of the present study.

## DISCUSSION

Cerebrovascular and cardiovascular diseases constitute one of the facets of generalized disorder of vascular function, a true “pan-arterial” process. The first phase corresponds to endothelial dysfunction leading to intima-media thickening, with eventual development of atheromatous plaque. A persistent endothelial dysfunction may determine surface instability, erosion of the fibrotic capsule of the plaque, rupture and vascular thrombosis.

The identification of changes in the arterial walls of asymptomatic individuals al-



lows a more rigorous management of cardiovascular risk factors in order to prevent a future coronary event.

Population and hospital studies utilize noninvasive techniques such as IMT measurement, endothelial dysfunction test and coronary artery calcification study to evaluate premature alterations in the arterial wall structure and function<sup>(16)</sup>.

Chequer et al.<sup>(17)</sup> have reported a significant correlation between BAFMD and intimal-media thickening, that is also an early indicator of atherosclerosis.

The present study indicates that patients with risk factors for atherosclerosis present endothelial dysfunction, which has been confirmed by altered BAFMD, and that IMT, both for carotid and brachial arteries were not significantly altered.

The endothelial function is affected by chronic conditions such as obesity, diabetes, hypercholesterolemia, smoking and arterial hypertension, and so does, acutely, by sleep deprivation, mental stress, hormonal changes, physical exercises, menstrual cycle and feeding habits. Changes in the vascular reactivity triggered by such conditions can be observed by BAFMD, and also can affect the method reliability.

Originally, the measurement of BAFMD was noninvasively performed by ultrasonography, with a cuff positioned on the patient's arm and later blood flow occlusion that deflagrated reactive hyperemia. Currently, blood flow occlusion in the forearm or wrist has been most frequently utilized, as it seems to express a dilatation promoted exclusively by nitric oxide. With distal occlusion, BAFMD values are lower than those observed with proximal occlusion in the arm ( $6.8 \pm 3.8\% \times 9.8 \pm 5.7\%$ , respectively). However, BAFMD reliability seems not to be affected by the site where the cuff is positioned<sup>(18)</sup>.

According to Doshi et al.<sup>(19)</sup>, the finding that forearm occlusion results in hyperemia purely mediated by nitric oxide may not by itself justify the abandonment of the technique based on the arm occlusion, because the dilatation promoted by the cuff positioned on the forearm is poor, so the identification of endothelial dysfunction and alterations resulting from changes in feeding habits/physical exercises becomes difficult.

A variable that may affect the measurement reliability is the transducer frequency. Herrington et al.<sup>(20)</sup> have compared the BAFMD stability measured at the line M (media-adventitia interface) and have observed significantly better results in measurements performed with 13 MHz transducers (mean coefficient of variation = 26.3%) than with 7.5 MHz transducers (mean coefficient of variation = 45.3%).

Another aspect to be considered is the occlusion time. Leeson et al.<sup>(21)</sup> have demonstrated that maximal arterial responses can be achieved after 4- to 5-minute occlusion with no additional effect resulting from longer occlusion times. Bots et al.<sup>(22)</sup> have demonstrated that most studies (~ 51%) have utilized occlusion times > 4.5 minutes. Taking all the variables into consideration, in the present study the authors have opted to evaluate the BAFMD with occlusion of the right arm, utilizing a pressure of 200 mmHg during five minutes and with an US unit equipped with a 14 MHz transducer.

The measurement of carotid artery IMT with high-resolution B-mode ultrasonography is a noninvasive method to evaluate the presence of atherosclerosis and disease progression over the years. A good correlation is observed between this measurement and the risk for cardiovascular events. Studies have shown that with an increase of 0.1 mm in carotid IMT, the risk for future myocardial infarction increases in about 10% to 15%, and for stroke in 13% to 18%<sup>(23)</sup>.

Isolatedly, the IMT measurement has the same relevance as other most common risk factors, and does not increase the predictive value for cardiovascular events if utilized exclusively for screening purposes<sup>(24)</sup>.

Maybe, the absence of significance of the results observed in IMT measurements has occurred because the intima-media thickening is more precociously detected in the subclavian artery than in the carotid arteries, the first one being a more precocious marker for detecting cardiovascular risk than the second one<sup>(25)</sup>.

Although the ideal method for diagnosing endothelial dysfunction is still to be established, there are evidences that BAFMD allows an appropriate evaluation of the

endothelial behavior and reflects the coronary endothelial function and behavior<sup>(26)</sup>.

Training and accurate technique are required for the performance of this methods. The observer must be fully skilled and appropriate equipment is required. Brachial artery flow-mediated dilatation is another useful tool for identifying individuals with cardiovascular diseases and, with the technique standardization, BAFMD tends to become a worldwide accepted method for evaluating endothelial function. The study developed by Meirelles et al.<sup>(27)</sup> confirms that baseline and post-occlusion diameters and BAFMD measurement by means of manual US technique is highly reliable, allowing its use for endothelial function diagnosis and monitoring.

According to Quyyumi<sup>(28)</sup>, markers for systemic inflammation such as BAFMD, carotid IMT and pulsewave analysis have gained popularity as methods for evaluating the risk for atherosclerosis. This author recommends the inclusion of such methods, the biochemical ones included, in randomized studies for screening and diagnosis of cardiovascular risk.

## CONCLUSIONS

BAFMD was an effective criterion to demonstrate endothelial involvement in a population at risk for atherosclerosis. However, this is not valid for IMT of carotid and brachial arteries.

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