

Prognostic Value of Endothelial Function in Patients with Atherosclerosis: Systematic Review

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Abstract

Analysis of flow-mediated vasodilation (FMV) of the brachial artery by use of ultrasound allows assessing endothelial function, and provides pathophysiological, diagnostic and prognostic information.

This systematic review was aimed at assessing the literature level of evidence of the predictive capacity of endothelial function, measured through brachial artery FMV by use of ultrasound, regarding cardiovascular events in individuals with atherosclerosis.

The MEDLINE, SCIELO and LILACS databases were searched, and prospective cohort studies on human beings about the prognostic value of endothelial function, measured by use of brachial artery FMV in individuals with peripheral or coronary atherosclerosis, were selected. Studies with clear methodological biases were excluded.

The final selection consisted of 15 studies. Of the 13 studies that on univariate analysis showed statistical significance of the FMV method to predict cardiovascular events, 12 showed independent predictive capacity on multivariate analysis. None of the studies reviewed described the incremental predictive value of FMV to the traditional predictive models, such as the Framingham score. Results of three studies have suggested that the method adds prognostic value to isolated markers such as ankle-brachial index (ABI), diabetes, and high-sensitivity C-reactive protein (hsCRP).

In conclusion, brachial artery FMV predicts cardiovascular risk, but its incremental predictive value to clinical prognostic models has not been established. In addition, solid evidence supporting its use in routine clinical practice to predict cardiovascular risk still lacks.

Introduction

In Brazil, cardiovascular diseases account for the greatest

Keywords

Endothelial function; flow-mediated vasodilation; brachial artery; prognosis; atherosclerosis.

mortality by cause group (32%), ischemic heart diseases having the second highest mortality rate, of 48.5 per 100,000 inhabitants-year¹. Thus, stratifying the risk of cardiovascular events in individuals with some degree of atherosclerosis is an important research field, in the search for refined markers of prognostic assessment, in an attempt to change the clinical course of the disease.

Endothelial dysfunction plays a key role in atherogenesis, being associated with all major risk factors for cardiovascular disease. In addition, its involvement in acute ischemic processes has been confirmed, and it has been directly related to the instability of the atherosclerotic plaque.

The pioneer studies by Furchgott and Zawadzki² have confirmed that the endothelium plays a role in vascular tonus regulation, and that the method of flow-mediated vasodilation (FMV) of the brachial artery allows assessing endothelial function, being able to provide pathophysiological and diagnostic information. The FMV measures changes in the brachial artery diameter in response to flow increase due to reactive hyperemia (endothelium-dependent response) and sublingual nitrate (non-endothelium-dependent response), as standardized by the International Brachial Artery Reactivity Task Force³. Regarding the technique used, the automatic is more robust and accurate⁴; however, the manual technique is also reliable, enabling its use for diagnosing and monitoring the endothelial function⁵. This review was aimed at assessing the method regarding its prognostic data.

Despite the relevant information provided by the brachial artery FMV and the important role played by the endothelium in atherosclerosis, studies about the function of prognostic markers are very recent and are emerging as a perspective for the assessing armamentarium of individual risk and even of potential therapeutic targets. However, like any knowledge evolution, publications in this area have revealed heterogeneous methodologies, hindering a safe conclusion regarding the theme. Thus, this review was especially aimed at organizing the literature data to know whether the scientific knowledge currently available allows concluding about the predictive capacity of the endothelial function regarding cardiovascular events in individuals with atherosclerosis.

Methods

Literature search

The MEDLINE (Medical Literature Analysis and Retrieval System) database was the major source for the systematic review of articles on the theme. Articles not indexed in

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MEDLINE and carried out in Latin America were searched in the SCIELO (Scientific Electronic Library Online) and LILACS (*Literatura Latino-Americana e do Caribe em Ciências da Saúde*) databases, by using the same keywords used in MEDLINE. The bibliographic references of each original article and review article were checked to select studies that had not been identified in the database search.

Initially, the MeSH (Medical Subject Heading Terms) dictionary was used for defining the terms to be searched in the titles of the studies. The expressions *endothelial function* or *endothelial dysfunction* or *flow mediated vasodilation* or *reactive hyperemia* were chosen to be combined with the terms *prognosis* or *prognostic value* or *cardiovascular events* and with the term *atherosclerosis*, adding up to 12 combinations of three terms, by using the conjunction AND. After reading the titles and the abstracts found, studies with the following characteristics were selected: prospective cohort studies on human beings, with samples larger than 60 individuals, specifically assessing endothelial function with the non-invasive method of the brachial artery FMV, and with populations with some degree of atherosclerosis, either peripheral or coronary. Studies with evident methodological biases were excluded.

For each article, the following data were collected: author; population profile; sample size; mean age of the participants; outcomes considered; follow-up period; predictive capacity and independent prediction. The relative risk, incremental value, and adequate use of co-variables were also assessed.

Outcomes assessed

The screening of the articles took into consideration the presence of harder events, such as cardiovascular death, myocardial infarction, unstable angina, and ischemic stroke. Events not so hard, such as stent restenosis, need for revascularization, angioplasty and cardiac arrhythmias, were not part of the major analysis

Criteria for assessing the quality of the articles

The following criteria were used to assess the quality of the studies: whether multivariate analysis was performed; if affirmative, whether the methodology of including co-variables met the requirement of significance; and whether all those variables considered important due to biological plausibility were included in the model. The following items considered relevant were assessed: analysis of incremental value; randomization of the population; sample size; blinding; use of the standardized method of FMV; follow-up time; and technique of event collection.

Results

Selection of the studies

The studies were found as follows: 217 in the MEDLINE database; ten in the LILACS database; and one in the SCIELO database. Studies with the following characteristics were not included: methodological analysis of endothelial function other than brachial artery FMV; population of healthy

individuals or with pathologies other than atherosclerosis; not prospective cohorts or experimentation in animal models. The selection of the records identified is shown in a flow diagram according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement⁶ (Figure 1).

After the selection, the final set consisted of 15 articles (Table 1), all in English and originating from the MEDLINE database. All articles selected were on individuals with atherosclerosis, having either peripheral artery disease (PAD) or coronary artery disease (CAD), at a stable situation and during the acute phase of the syndrome. Their publication periods ranged from 2000 to 2009.

Characteristics of the studies

The search for assessing the predictive capacity of the FMV method in individuals with atherosclerosis began recently, in 2000⁷. The population samples have ranged from 73 to 444 participants^{7,8}.

Journals specialized in imaging and those of clinical research have published articles about the theme, the former providing more articles for this review. Prestigious international journals, such as the *Journal of The American College of Cardiology*, accounted for 4 of the 15 articles selected⁸⁻¹¹. Brazilian publications of randomized clinical trials about the specific theme of this review have not been found. A national record of a review with patients with type 1 diabetes has concluded that the early detection of endothelial dysfunction has a prognostic value for the development of vascular complications and has suggested that it might be important for primary prevention strategies against cardiovascular events¹².

The use of the correct methodology to assess endothelium-dependent vasodilation has not varied significantly among the studies, although half of the publications do not cite the most recent guideline³ published in 2002. The assessment of non-endothelium-dependent vasodilation using nitrate has varied significantly, and, in an expressive number of participants, that has not been performed^{11,13}.

In general, the quality of the studies was considered satisfactory, and the parameters used for that assessment were the inclusion of important co-variables and the routine use of multivariate analysis. However, the assessment of the incremental value of the established markers or scores was hindered.

The investigation of individuals with PAD has been published in four studies and has proved that endothelial dysfunction is an independent predictor of cardiovascular events in clinical and surgical patients. The cardiovascular outcomes considered in those studies were as follows: cardiac death; myocardial infarction; unstable angina; heart failure; myocardial revascularization; and stroke.

Eleven articles have been published about the predictive value of endothelial function, assessed by use of ultrasound of the brachial artery FMV, regarding the cardiovascular risk of events in individuals with CAD. Of those, three articles with populations with classic coronary syndrome [two studies on non-ST-segment elevation acute myocardial infarction (AMI) and one on ST-segment elevation AMI] have positively confirmed its predictive capacity.

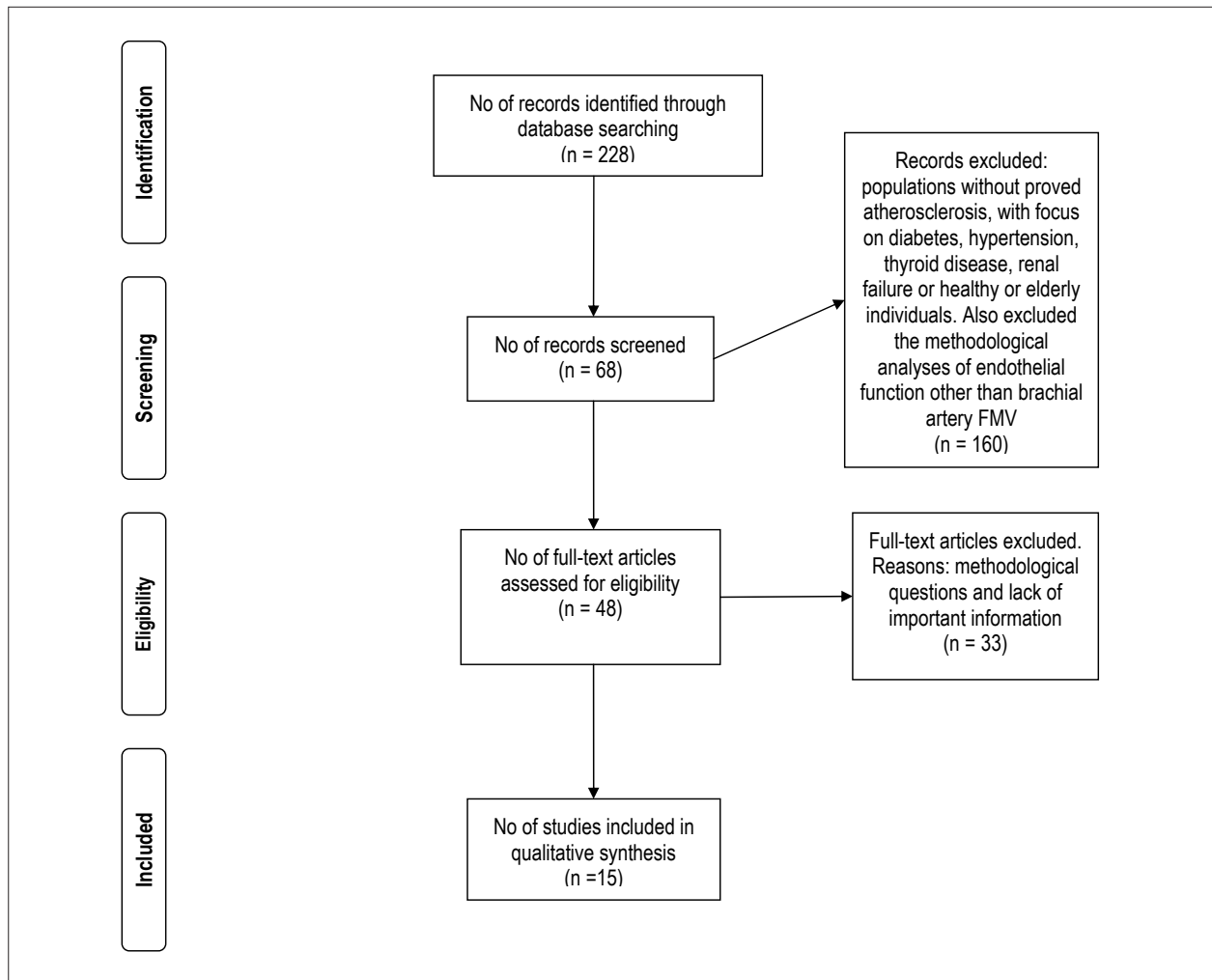


Figure 1 – Flow diagram of the different phases of a systematic review

Eight studies contemplating several spectra of CAD, such as stable disease, patients selected for stent implantation, patients with chest pain or with altered ischemic test referred for catheterization, have shown discordant information about the prognostic value of the method: five were favorable and three denied any potential for prediction.

Analysis of the prognostic value

Despite increasing evidence, publications about the prognostic value of reactive hyperemia are scarce. All studies have recognized the importance of endothelial function; however, the value of its prognostic capacity is controversial.

The prognostic value of FMV in patients with atherosclerosis will be assessed regarding three aspects: the general prognostic value (univariate analysis); the independent prognostic value (multivariate analysis); and the incremental prognostic value (C statistics). In those aspects, evidence of the prognostic importance of FMV in different populations

with atherosclerosis will be shown, allowing the observation of differences between the studies and the influence of the disease on the results.

General analysis of the prognostic value of FMV

Prognostic value of FMV

In most of the studies (13 of 15), univariate analysis to assess the predictive capacity of FMV regarding cardiovascular events has revealed statistical significance favorable to the method. Results repeat at different cutoff points for FMV and also for distinct clinical profiles. Only two studies, assessing populations of individuals with CAD, have found different results contrary to the prognostic value of the method.

Frick et al.¹⁰, studying a population of 398 individuals referred for catheterization because of chest pain or positive exercise test, have reported no difference in the number of events between the groups below and above the median of

Table 1 – Characteristics of the clinical trials that have assessed the predictive capacity for cardiovascular events of flow-mediated vasodilation in individuals with atherosclerosis

Author Journal Year (ref)	Population	N	Age (years)	Outcomes	Follow-up (months)	Prediction (univariate)	Independent prediction (multivariate)	Quality of adjustment (co-variables)	Incremental value *
Akcakoyun, Coron Artery Dis, 2008	CAD-PTCA	135	58 ± 10	CV events (cardiac death, MI, UA, NSTEMI, stroke, in-stent restenosis)	12	Yes	Yes	Good	Not tested
Brevetti, Circulation, 2003	PAD	131	63 ± 10	Fatal and non-fatal MI, UA, MR, ischemia of the lower limbs	23 ± 10	No	Yes	Regular	Not tested (related to ABI)
Chan, J Am Coll Cardiol, 2003	CAD	152	56 ± 6	Death of vascular cause, stroke, MI, UA, peripheral events, revascularization (carotid endarterectomy, PTCA, MR)	34 ± 10	Yes	Yes FMV/NMD	Regular	Not tested
Fathi, J Am Coll Cardiol, 2004	Risk of coronary events	444	58 ± 14	CV events and all-cause death	24(10-24)	Yes	No	Good	Not tested
Frick, J Am Coll Cardiol, 2005	Referred for CAT	398	54 ± 9	CV events: cardiac death, MI, PTCA, MR, angina worsens	39 ± 12	No	No	Regular	Not tested
Gokce, Circulation, 2002	PAD (pre-op)	187	67 ± 11	Post-op events: cardiac death, MI, UA, ischemic VF, stroke	01	Yes	Yes	Good	Not tested
Gocke, J Am Coll Cardiol, 2003	PAD (pre-op)	199	67 ± 10	Cardiac death, MI, UA, stroke	14	Yes	Yes	Good	Not tested
Guazzi M, Int J Cardiol, 2009	NSTEMI	179	65 ± 10	AMI, HF, MR, PTCA	14 ± 9.5	Yes	Yes	Good	Not tested (related to diabetes)
Huang AL, Arterioscler Thromb Vasc Biol, 2007	PAD (pre-op)	267	66 ± 11	Cardiac death, MI, UA, stroke	10	Yes	Yes	Good	Not tested
Huang PH, Clin Cardiol, 2007	Typical chest pain	205	63 ± 14	MI, hospitalization due to HF, PTCA, MR, stroke	24(8-37)	Yes	Yes	Regular	Not tested (related to hsCRP)
Karatzis, Am J Cardiol, 2006	NSTEACS	98	63 ± 11	CV death, MI, UA, stroke	25 ± 6	Yes	Yes	Good	Not tested
Neunteufl, Am J Cardiol, 2000	Referred for CAT (mixed)	73	49 ± 11	Death, MI, PTCA, MR	60(53-66)	Yes	Yes	Good	Not tested
Takase, Cardiovascular Ultrasound, 2008	CAD	103	62 ± 9	Cardiac death, MI, UA, acute HF due to ischemia	50 ± 15	Yes	Yes	Good	Not tested
Veneri, Int J Cardiol, 2007	Chest pain	195	60 ± 10	Death, AMI, MR	27	No	No	Good	Not tested
Wang, Coron Artery Dis, 2009	NSTEMI/ successful primary rescue PTCA	101	62 ± 9	CV events	12 ± 3	Yes	Yes	Good	Not tested

*The incremental value is tested by using C statistics (area under the ROC curve) of the usual predictive model (ex: Framingham score) with the C statistics of a new predictive model formed by the association of the usual model with the new marker in question. The new marker is considered to add prognostic value in the presence of an increment of at least 0.05 in C statistics.

PAD - peripheral arterial disease; CAD - coronary arterial disease; CAT - cardiac catheterization; NSTEMI – non-ST-segment elevation myocardial infarction; NSTEACS - non-ST-segment elevation acute coronary syndrome; PTCA – percutaneous transluminal coronary angioplasty; UA – unstable angina; MR - myocardial revascularization; VF - ventricular fibrillation; HF – heart failure; ABI – ankle-brachial index; hsCRP – high-sensitivity C-reactive protein; MI – myocardial infarction; NMV – nitrate-mediated vasodilation; FMV – flow-mediated vasodilation.

the brachial artery FMV in a follow-up of 39 ± 12 months (HR 1.52; 95% CI: 0.75 – 3.08; $p = 0.24$). The intima-media thickness of the brachial artery and the presence of CAD on angiography have shown predictive capacity, evidencing, thus, a greater prognostic value for morphology than for endothelial function. However, it is worth noting that that study has not informed whether statin was suspended before measuring FMV, and that the FMV of 7.6% exceeded the expected value for a supposedly ischemic population.

Similarly, in a population of 195 patients hospitalized due to chest pain syndrome, Venneri et al.¹⁴ have not obtained predictive significance in the univariate analysis for FMV, but the following variables proved to be predictors: left ventricular mass index; ejection fraction; and CAD.

Independent prognostic value of FMV

Of the 13 studies showing, on univariate analysis, statistical significance of the FMV method for predicting cardiovascular events, 12 also showed independent predictive capacity on multivariate analysis.

Analyzing the quality of the co-variables used on multivariate analysis, several authors have chosen to perform adjustments based exclusively on the significances previously shown on univariate analysis. In some situations, variables, such as diabetes and other classical risk factors, should be included due to biological plausibility and previous evidence. It is worth citing the study by Huang et al.¹⁵ about CAD, which, on multivariate analysis, has adjusted only for the co-variables significantly related to the cardiovascular events of univariate analysis [age, hypertension, FMV and high-sensitivity C-reactive protein (hsCRP)], and the study by Brevetti et al.¹⁶ about PAD [dyslipidemia, hypertension, previous stroke, ankle-brachial index (ABI) and FMV]. So far, no adjustment for a complete model, such as the Framingham and GRACE scores, has been detected in a more representative form in any of the analyses performed.

Assessment of the short postoperative prognosis (30 days) in a critically ill population of 187 individuals with PAD, such as surgical patients of carotid endarterectomy, peripheral arterial bypass, aortic aneurysm and amputation, has shown the independent predictive capacity of endothelial dysfunction, measured by reduced brachial artery FMV, for cardiovascular events [odds ratio (OR) 9.0; 95% CI: 1.2 – 68; $p = 0.03$], along with the variable age, which was also a predictor (OR 2.0; 95% CI: 1.2 – 3.3; $p = 0.006$). It has also been shown, by use of the Kaplan-Meier curve, that, in the greatest tertile of FMV (greater than 8.1%) and with relatively normal endothelial function, the risk of events was very low¹³. In the following year, those same authors have published the predictive value for a longer follow-up period, 1.2 year, confirming, by use of Cox regression model, that FMV is an independent predictor of cardiovascular risk, as age and more invasive surgery, such as carotid endarterectomy, also are. After controlling those two co-variables, the endothelial function remained an independent predictor (OR 9.6; 95% CI: 1.2 – 74; $p = 0.03$)¹¹.

Huang et al.¹⁷, studying 267 patients with PAD referred for surgery, have confirmed that both the reduced arterial dilation and the low flow velocity have predictive capacity for

cardiovascular risk (OR 4.2; 95% CI: 1.8 – 9.8; $p = 0.001$; and OR 2.7; 95% CI: 1.2 – 5.9; $p = 0.0018$, respectively), even when adjusted for other risk variables.

It is worth noting that, in those studies, nitrate-mediated vasodilation (NMV), which is the non-endothelium-dependent vasodilation, has shown no significant prognostic value for predicting cardiovascular risk.

The initial study on CAD has reported the results of the mean 5-year follow-up of a small cohort of 73 individuals, regarding the occurrence of death, infarction, coronary angioplasty and surgical revascularization, dividing the population into below and above 10% of brachial artery FMV. A greater number of events was found in the group with FMV lower than 10% (50% versus 15%, $P = 0.002$). On multivariate analysis, both FMV and NMV correlated with events, as did sex (OR 0.75, 1.25 and 3.9, respectively). In this study, however, although the patients were referred for catheterization, there was no clear clinical, electrocardiographic or enzymatic description characterizing acute coronary syndrome (ACS), the population being heterogeneous regarding CAD. The cutoff point of 10% is considered high (normal value) for a population with CAD, and might justify the lack of deaths in the five years of disease progression, and also the lack of significant correlation between those factors, when adjusted for CAD (stenosis $\geq 30\%$ in more than one vessel)⁷.

The capacity to predict the structural and functional status of the arterial system regarding coronary events in individuals with CAD, has been assessed by use of multivariate analysis, demonstrating that FMV/NMV and the atherosclerotic plaque area have independent predictive capacity for events. That study has shown that FMV alone was a predictor only on univariate analysis ($p = 0.03$)⁹.

Akcakoyun et al.¹⁸, in a prospective study with 135 patients referred for elective stent implantation, have reported that the only independent predictor of cardiovascular events and in-stent restenosis was FMV, with adjustment on multivariate analysis for the classical risk factors, such as stent length and diameter, sex, body mass index (BMI) and medicamentous treatment. However, the population studied originates from patients excluded from another study¹⁹ because of ACS and stroke, constituting a selection bias. In that study, the cutoff point of FMV for prediction was 7.5%.

The first study on ACS without ST-segment elevation has comprised a population sample of 98 participants of the male sex, and has recorded 20 cardiovascular events in the long-term follow-up. Those with FMV in the first tertile (<1.9%) have had a significantly higher number of events than those with FMV over that value. Cox multivariate regression, adjusting to adequate co-variables, has shown that FMV <1.9% had an independent predictive capacity for cardiovascular events (HR 3.035; 95% CI: 1.148 – 8.023, $p = 0.025$)²⁰.

In 101 patients with myocardial infarction with ST-segment elevation, after coronary angioplasty, 29 events were recorded in 12 months of follow-up, evidencing the independent predictive capacity of FMV (HR 0.705; 95% CI: 0.573 – 0.868; $p = 0.0010$), diabetes (HR 2.934; 95% CI: 1.314 – 6.548; $p = 0.0086$) and ejection fraction (HR 0.900; 95% CI:

0.832 – 0.973; $p = 0.0082$) when adjusted for baseline risk co-variables. The cutoff point suggested in that study was 5.5% for a significantly worse prognosis in that population²¹.

Contrarily, Fathi et al.⁸, studying for two years an Australian cohort comprising 444 patients, have reported that FMV, although lower in patients with events, was not an independent predictor of cardiovascular events. That population, with mixed risk for cardiovascular events, originated from a tertiary hospital and had a high prevalence of renal and transplanted patients, who, however, had been declared neither ischemic nor having atherosclerosis. The mean FMV values were considered low ($5.2 \pm 6.1\%$) and compatible with those found in studies with patients with CAD. Carotid intima-media thickness (IMT) was the vascular factor independently associated with mortality. When analyzing the low-risk subgroup, FMV has shown no independent predictive capacity, and in individuals referred for the ischemic test, the independent prognostic value was evidenced, similarly to the IMT.

Incremental prognostic value of FMV

None of the studies reviewed analyzed the incremental value of FMV, assessed by use of C statistics in a multivariate model, after incorporating the new marker, FMV, to a risk score (Framingham, TIMI, GRACE). In addition, there was no analysis of how much that incorporation would add to the performance of the score.

Of the 15 studies selected, only three have assessed whether the FMV method adds any predictive capacity to the other prognostic marker known; however, the models used to test that hypothesis allow no definitive conclusions.

Brevetti et al.¹⁶ have assessed 131 patients with claudication for a mean of 23 months, and have concluded that a low brachial artery FMV has independent risk predictive capacity. The authors have tested whether FMV adds prognostic value to the ABI, which is an index already established as a powerful marker of risk. In that study, the risk predictive accuracy was greater for the combination of the two indices FMV and ABI below the median [relative risk (RR) 13.0; 95% CI: 3.0 – 56.2; $P < 0.01$] than for the ABI (RR, 6.4; 95% CI: 1.4 – 29.1; $P < 0.02$) and FMV (RR, 4.8; 95% CI: 1.1 – 23.3; $P < 0.05$) alone. By use of the incremental assessment method, we can only infer the existence of the additional value, considering that $OR > 3$ can cause a clinically relevant increase in C statistics (> 0.05). As the analysis was univariate, those data can be overestimated.

In individuals with myocardial infarction without ST-segment elevation, a study has assessed whether FMV adds prognostic value to the predictive capacity for diabetes. Both FMV and diabetes have shown independent predictive capacity, with good accuracy demonstrated in the ROC curve of 63% and 67%, respectively. Its better cutoff point was 4.5%. In the Kaplan-Meier analysis, event-free survival in a mean 14-month follow-up was significantly lower in the group with diabetes and $FMV \leq 4.5\%$ (38.5%) than in the other following groups: no diabetes and $FMV > 4.5\%$ (88.7%); no diabetes and $FMV \leq 4.5\%$ (78.4%); and with diabetes and $FMV > 4.5\%$ (67.7%)²². In addition to the fact that the analysis performed

has not allowed conclusions on the incremental capacity of FMV, data collection by use of medical record review can be considered a limitation to the internal validity of that study.

The FMV has also been studied regarding the marker hsCRP in individuals with typical chest pain. A significant worsening in event-free survival in 36 months has been observed in the group of $FMV < 6\%$ combined with $hsCRP \geq 1$ mg/dL, as compared with each one alone and with the combination of $FMV \geq 6\%$ and $hsCRP < 1$ mg/dL. While the RR for the group of $FMV \geq 6\%$ and $hsCRP \geq 1$ mg/dL was 3.36, for the group of $FMV < 6\%$ and $hsCRP \geq 1$ mg/dL, RR increased to 12.5 ($p = 0.014$)¹⁵.

In the population studied by Takase et al., the ROC curve has shown equivalent accuracies for the FMV and exercise test (0.67×0.64) and lower accuracy as compared with that of the atherosclerotic load provided by IMT (0.68). The authors have not tested the incremental capacity of the method to any marker. It is worth noting that most individuals have not shown significant coronary stenosis (at least 25% - mild CAD)²³.

Discussion

In individuals known to have peripheral atherosclerosis, the FMV technique reinforces the role of endothelial dysfunction in the pathogenesis of cardiovascular disease and is likely to become a surrogate marker of cardiovascular risk. In the individual assessment of surgical risk, which depends on the history of comorbidities, type of surgery, and emergency degree of the procedure, FMV can become a new parameter of risk assessment, helping to identify subgroups at higher risk for acute cardiovascular events, and can lead to diagnostic and therapeutic strategies specific for each patient. However, there is no report in the literature about the prognostic value of brachial artery FMV in asymptomatic individuals with PAD, when the clinical importance of earlier diagnosed endothelial dysfunction would certainly enable interventions and change in disease course, with a reduction in the risk of future cardiovascular events.

The discrepancies in the results of the studies can be justified by the different characteristics of the populations, distinct clinical situations, and diversity of coronary anatomy, in addition to the variability or lack of uniformity in the application of the FMV method, which is still evolving, before becoming a recommended tool for clinical practice.

The lowest FMV values have been observed in the studies about ACS. Even among them, different FMV cutoff points have been detected, with higher values in the population with AMI with ST-segment elevation, as compared with those with AMI and no ST-segment elevation, in which poorer dilating responses have been detected, and where the endothelial role seems to be even more important. The pathophysiological mechanism of greater instability and great endothelial dependence involved in the ACS without ST-segment elevation is likely to explain that finding, because of the vasoconstricting and pro-thrombotic status of the coronary circulation in that specific situation.

Most studies are conducted on selected populations with atherosclerotic disease, which might lead to workup bias, which, in prognostic follow-up studies, might result in a false increase in the sensitivity of the method.

The different RR found for events cannot be compared in the studies because of the large heterogeneity between them, especially regarding the population selected. Relative risk values ranging from 0.7²¹ to 12.5¹⁵ have been observed.

The aggregation analysis of the predictive capacity of the method, which depends on the incremental capacity and the capacity for changing the outcome of patients, has not been properly tested in the studies with a clinical multivariate model considering all important variables.

It is worth considering the cost of that new method, which, by involving ultrasound and demanding considerable time for the exam, should be greater than that of the already established laboratory tests and scores. Similarly, the method is likely to face resistance regarding its acceptance because of practical questions and the reproducibility of its measures; thus, it is unlikely to replace an already standardized marker in clinical practice.

One can state that FMV meets the primary concept that its values differ between individuals with and without outcome; however, it has not been prospectively validated, that is, FMV only foresees the future development of outcomes in specific situations, such as shown in the prospective cohort studies assessed. In addition, the incremental value of the marker to add predictive capacity to an established standard marker has not been actually documented. The studies on ACS have not assessed its incremental capacity to the already validated scores, such as the TIMI and GRACE scores. In fact, most studies have not shown that the use of the method improves the estimate of outcomes in randomized clinical trials.

In addition, the use of FMV has not been shown to change any already standardized therapy, and, thus, its clinical usefulness has not been confirmed to risk assessment. Regarding cost-effectiveness, considering the previous findings, additional costs with that test are not justified in clinical practice.

Studies assessing the new marker regarding its incremental predictive capacity to already established risk markers are required; such studies should use statistical tests to show how

much significantly incremental prognostic information FMV adds to a risk model that includes already established markers. Only after confirming that, the importance of FMV to clinical practice will be able to be assessed through the following characteristics: discriminating capacity (to differentiate patients who will have the outcome from those who will not); calibration capacity (accuracy to predict the likelihood of an individual having the outcome); and reclassification capacity (to refine the risk stratification). Such characteristics, if demonstrated, could influence therapy and the course of disease.

Conclusion

Brachial artery FMV is a validated method to measure endothelial function and is associated with cardiovascular risk factors. However, despite its strong pathophysiological bases and the initial results about cardiovascular risk prediction, its incremental predictive value to clinical prognostic models has not been established. In addition, solid evidence supporting its use in routine clinical practice to predict cardiovascular risk still lacks.

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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