References

[1] Mewton N, Opdahl A, Choi EY, et al. Left ventricular global function index by magnetic resonance imaging—a novel marker for assessment of cardiac performance for the prediction of cardiovascular events: the multi-ethnic study of atherosclerosis. Hypertension 2013;61:770–8.
[2] McComb C, Berry C. Prognostic importance of a new measure of global systolic heart function in healthy adults. Hypertension 2013;61:762–4.
[3] Reinstadler SJ, Klug G, Feistritzer HJ, et al. Association of copeptin with myocardial infarct size and myocardial function after ST-segment elevation myocardial infarction. Heart 2013;99:1525–9.
[4] Reinstadler S, Klug G, Feistritzer H, et al. Relation of plasma adiponectin levels and aortic stiffness after acute ST-segment elevation myocardial infarction. Eur Heart J Acute Cardiovasc Care 2014;3(1):10–7.
[5] Klug G, Mayr A, Schenk S, et al. Prognostic value at 5 years of microvascular obstruction after acute myocardial infarction assessed by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2012;14:46.
[6] Mayr A, Klug G, Schocke M, et al. Late microvascular obstruction after acute myocardial infarction: relation with cardiac and inflammatory markers. Int J Cardiol 2012;157:391–6.
[7] Wu AH, Parsons L, Every NR, et al. Hospital outcomes in patients presenting with congestive heart failure complicating acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI-2). J Am Coll Cardiol 2002;40:1389–94.
[8] Wu E, Ortiz JT, Tejedor P, et al. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. Heart 2008;94:730–6.
[9] Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation 2005;112:3738–44.

0167-5273/$ – see front matter
http://dx.doi.org/10.1016/j.ijcard.2014.06.004

Pulse pressure affects the relationship between flow-mediated dilatation and cardiovascular risk

Andrea Cardona [a], Giuseppe Ambrosio [a,*], Anna Mengoni [a], Antonella D'Antonio [a], Maurizio Bentivoglio [a], Jose Milei [b], Fabio Angeli [a]

[a] Division of Cardiology, University Hospital of Perugia, Perugia, Italy
[b] Instituto de Investigaciones Cardiologicas "Alberto C. Taquini", University of Buenos Aires, Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 15 April 2014
Accepted 1 June 2014
Available online 10 June 2014

Keywords:
Endothelial function
Flow-mediated dilatation
Pulse pressure
Cardiovascular risk
Arterial stiffness

Endothelial dysfunction is recognized as a pivotal factor in the development of atherosclerosis [1]. Dilatation of the brachial artery in response to an increase in flow (flow-mediated dilatation, FMD) during post-ischemic reactive hyperemia currently represents the most suitable approach for non-invasive assessment of endothelial function [1].

Although numerous studies have shown a prognostic relationship between FMD and cardiovascular events [2], there are also data suggesting that the association between endothelial function of the brachial artery and cardiovascular risk may be influenced by the baseline risk profile of patients [3,4]. Indeed, a meta-analysis of 399 populations [3] demonstrated that endothelial function, as measured by FMD, was related to cardiovascular risk in subjects with a low baseline risk profile, whereas FMD was not significantly related to risk in medium- or high-risk subjects, independently of brachial artery diameter or technical aspects of FMD measurement.

A possible explanation for these observations might be that the brachial artery is stiffer in patients with frank atherosclerosis or greater cardiovascular risk factor burden, which would pose a physical constraint to its ability to dilate in response to the stimulus.

To get insights into this phenomenon, we analyzed the relationship between FMD and cardiovascular risk in subjects recruited in the setting of a primary prevention care unit, and stratified by different degrees of arterial stiffness.

The 10-year risk of cardiovascular events was estimated according to the Framingham risk score [5], while office pulse pressure was used as a surrogate marker of arterial stiffness [6]. FMD was measured in the morning after an overnight fast and under identical conditions [7]. A high resolution ultrasound system (General Electric, Vingmed System Five, Horten, Norway), with a 7.5 MHz linear array transducer positioned by a stereotactic manipulator was used to scan the brachial artery over a longitudinal section 5–10 cm above the elbow. After optimal positioning of the transducer, baseline lumen diameter was recorded using an automatic edge detection system (FMD Studiosystem, Institute of Clinical Physiology, National Research Council, Pisa) [8]. Flow-mediated vasodilatation was then assessed in response to increased blood flow [7,8]. A sphygmomanometer blood pressure cuff was positioned on the right forearm 2 cm below the elbow, inflated for 5 min at 250 mm Hg and then deflated to induce reactive hyperemia. FMD was expressed as the percentage increase in brachial artery diameter from baseline to maximal dilatation, which occurred 30–90 s after release of the cuff. Brachial artery flow velocity, expressed as velocity time integral (VTI), was also measured by pulsed wave Doppler at baseline, and throughout the post-ischemic phase. After allowing 30 min for vessel recovery, 25 μg of glyceryl-trinitrate (GTN) was administered sublingually; this dose has been shown to directly dilate brachial artery, without effects neither on distal microcirculation nor on blood pressure [9]; brachial artery diameter was measured again to estimate endothelium-independent vasodilatation. All exams were conducted by experienced investigators with homogeneous intra-

* Corresponding author at: Cardiologia e Fisiopatologia Cardiovascolare, Ospedale S. Maria della Misericordia, S. Andrea delle Fratte, 06156 Perugia, Italy. Fax: +39 075 5271244.
E-mail address: giuseppe.ambrosio@ospedale.perugia.it (G. Ambrosio).

Table 1
Main characteristics of the total population and of subgroups identified by tertiles of office pulse pressure.

Variable	Overall	Pulse pressure tertiles			
	(n = 141)	<45 mm Hg	45–53 mm Hg	>53 mm Hg	p
Age (years)	44.8 ± 14.8	43.1 ± 13.7	41.0 ± 14.0	50.2 ± 15.3*†	0.006
Sex (% men)	61.0	51.1	59.6	72.3	0.104
Current smokers (%)	14.9	12.8	8.5	23.4	0.113
Hypertension (%)	22.0	10.6	17.0	38.3	0.003
Diabetes (%)	2.8	4.3	2.1	2.1	0.773
Body mass index (kg/m^2)	25.0 ± 4.8	24.1 ± 3.9	25.8 ± 4.7	25.2 ± 5.7	0.236
Office systolic BP (mm Hg)	127.9 ± 12.3	118.8 ± 9.2	127.0 ± 9.8*	137.8 ± 9.6*†	<0.0001
Office diastolic BP (mm Hg)	78.0 ± 8.9	79.9 ± 7.9	77.8 ± 9.6	76.5 ± 8.9	0.185
Serum glucose (mg/dl)	89.3 ± 24.7	85.8 ± 23.9	90.5 ± 19.9	91.4 ± 29.5	0.658
Total cholesterol (mg/dl)	204.0 ± 38.2	205.3 ± 37.8	193.8 ± 36.3	212.2 ± 30.1	0.148
HDL cholesterol (mg/dl)	53.2 ± 14.6	56.9 ± 15.5	49.4 ± 13.0	53.4 ± 14.7	0.174
Framingham risk score (%)	9.3 ± 10.0	6.7 ± 8.1	7.9 ± 10.5	13.4 ± 10.1*†	0.002
FMD (%)	5.9 ± 2.2	6.1 ± 2.0	6.2 ± 2.7	5.5 ± 1.8	0.243
Basal diameter of the brachial artery (mm)	4.1 ± 0.8	4.0 ± 0.9	4.0 ± 0.8	4.2 ± 0.8	0.464
Post-ischemic maximal diameter (mm)	4.3 ± 0.9	4.2 ± 0.9	4.3 ± 0.8	4.4 ± 0.8	0.551
Absolute change in diameter (mm)	0.23 ± 0.07	0.24 ± 0.06	0.24 ± 0.08	0.21 ± 0.07	0.215
Maximal diameter after GTN (mm)	4.4 ± 0.87	4.2 ± 0.86	4.3 ± 0.90	4.5 ± 0.86	0.306
Baseline VTI (cm)	21.6 ± 8.5	21.2 ± 8.6	21.8 ± 9.2	21.9 ± 8.1	0.935
Post-ischemic VTI (cm)	80.1 ± 28.1	80.6 ± 24.6	77.6 ± 29.9	81.7 ± 30.3	0.837
Absolute change in VTI (cm)	58.2 ± 25.5	59.0 ± 22.6	55.3 ± 27.6	59.8 ± 26.7	0.754

* $p < 0.05$ vs. first tertile.
† $p < 0.05$ vs. second tertile.

and inter-coefficient of variation for FMD evaluation, as previously reported [8].

Data are presented as mean ± standard deviation (SD) for continuous variables, and as proportions for categorical variables. Differences in proportions between groups were analyzed using the χ^2 test. Mean values of variables were compared by analysis of variance (ANOVA). The strength of the relations between variables was assessed by regression analyses. Statistical analysis was performed using STATA 12 (StataCorp, USA) and R software version 3 (R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org).

Overall, 160 consecutive patients were evaluated; 19 had poor quality exam; the remaining 141 (mean age 45 years, 61% men) were included in the present analysis. The main characteristics of this entire cohort, and of subgroups identified by tertiles of pulse pressure distribution, are shown in the table.

As expected, Framingham risk score was higher for patients in the upper than in the middle and lowest tertiles of pulse pressure (all $p < 0.05$; Table 1). In the whole cohort, the association of FMD with Framingham risk score was significant ($r = -0.33$, $p < 0.0001$). However, when this association was examined across tertiles of pulse pressure, no significant differences were seen in patients stratified by degree of arterial stiffness (Table 1). Furthermore, all components of FMD (i.e., basal and maximal diameter, and absolute change in diameter of brachial artery) did not show on the average significant differences across tertiles of pulse pressure (Table 1). Interestingly, when the relationship between arterial stiffness and cardiovascular risk was examined in further details, as depicted in Fig. 1, a significant correlation could be appreciated between all FMD parameters and Framingham risk score for patients in either the lowest or the middle tertile of pulse pressure; in contrast, no correlation could be found when examining patients in the highest tertile with respect to both FMD and maximal diameter (Fig. 1; Panels A, C), and only a borderline significance was present with respect to basal diameter of brachial artery (Fig. 1; Panel B).

Importantly, this loss of correlation for patients in the highest tertile of pulse pressure also extended to non-endothelium dependent vasodilatation, as indicated by the findings with GTN-induced maximal brachial artery diameter (Fig. 1; Panel D). Of note, also the maximal diameter of the brachial artery measured after administration of GTN showed similar mean values in the three tertiles of pulse pressure (Table 1).

Our analysis shows that endothelial function, as assessed by FMD, is related to the estimated 10-year risk of cardiovascular events predominantly in subjects with lower values of pulse pressure (<53 mm Hg), and hence of arterial stiffness. The absence of a clear relationship between FMD and cardiovascular risk in subjects with increased arterial stiffness could recognize different mechanisms. One possibility could be that in subjects with increased arterial stiffness, reactive hyperemia following ischemia is reduced at the distal microcirculation level, which in turn would reduce shear stress at the brachial artery level, and hence induce less flow-mediated endothelial production of NO. However, our data do not support this hypothesis, since direct measurement of post-ischemic VTI (i.e., flow across the brachial artery) showed very similar values over the three tertiles of pulse pressure (Table 1), and therefore shear stress should have been comparable. An alternative explanation to invoke a role for NO in our observations is that as endothelial damage is the initial step in atherosclerosis, in subjects with stiffer arteries the intrinsic ability of endothelium to produce/release nitric oxide (NO) in response to stimuli is impaired; thus, magnitude of shear stress associated with reactive hyperemia may be similar, yet endothelial response is hampered. We cannot entirely rule out this possibility, as it would entail direct measurement of in vivo production of NO at the brachial artery site, which would not be feasible. However, in subjects with increased pulse pressure we demonstrated lack of significant arterial dilatation also following the administration of a direct, endothelium-independent vasodilator (i.e., nitroglycerine), which would instead indicate that it is the smooth muscle cells of the brachial artery that do not just relax as well in such subjects, consistent with increased arterial stiffness.

In conclusion, our data suggest that arterial stiffness may limit the ability of the brachial artery to dilate; as a consequence, accuracy of FMD as a measure of arterial properties may be hampered in subjects with stiffer arteries [10]. Further studies are needed to add new insights on this scenario, and to ascertain if the association between