Arterial compliance influences the measurement of flow-mediated vasodilation, but not acetylcholine-mediated forearm blood flow

The prospective investigation of the vasculature in uppsala seniors (PIVUS) study

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Abstract

Objectives: Flow-mediated vasodilation (FMD) is low even in healthy elderly and therefore relations between FMD and cardiovascular risk factors might be hard to evaluate in the elderly. Using data from the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS) study, we investigated if a reduced arterial distensibility could influence FMD measurements.

Methods: In the population-based PIVUS study (1016 subjects aged 70), assessments of arterial distensibility by ultrasound in the carotid artery (CCA) and FMD were performed. Endothelium-dependent vasodilation was also evaluated with the invasive forearm technique with acetylcholine (EDV) and by pulse wave analysis following terbutaline injection. A poor CCA distensibility was defined as <25th percentile in the healthy part of the population (n = 131).

Results: FMD was significantly related to the Framingham risk score only in those with a good CCA distensibility (r = −0.16, p = 0.0081 versus r = −0.06, p = 0.17 in those with a poor CCA distensibility, p = 0.0001 for difference). In contrast, the relationship between EDV and coronary risk was not affected by CCA distensibility (r = −0.11; p = 0.018 versus r = −0.13, p = 0.027).

Conclusions: A reduced CCA distensibility could in part explain the low FMD values in the elderly. FMD correlated to the Framingham risk score only in those with a good CCA distensibility, exemplifying a limitation of the use of FMD in elderly populations. On the contrary, EDV was not affected by arterial stiffness.

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1. Introduction

When the method of flow-mediated vasodilation (FMD) was introduced in 1992 [1], it was a non-invasive alternative to the existing methods to evaluate peripheral endothelium-dependent vasodilation in humans that required intra-brachial administration of acetylcholine [2]. In the original publication, FMD was measured in young healthy subjects and was found to be reduced in those with risk factors for cardiovascular disorders [3]. Due to its non-invasive character and rapid performance, FMD has now fruitfully been applied in large scale epidemiological research [4–9].

However, when FMD was applied in a sample of males aged 61, Wendelhag et al. did not find any relation to the major risk factors [10]. They suggested that this might be due to the fact that even in healthy elderly subjects FMD is reduced to a mean of 3–4% and that it is hard to detect relationships when the range of the measurements is so narrow.

Witte et al. recently published a meta-analysis of studies investigating the relationship between FMD and cardiovascular risk factors [11]. They came to the conclusion that the association between FMD and cardiovascular risk was limited to low-risk populations. These authors could in another...
publication show that this might be due to an increased arterial stiffness in the high-risk subjects, since they found FMD to correlate with smoking and age in the expected way in subjects with a normal arterial compliance, but not in those with a poor compliance [12].

We conducted the Prospective Investigation of the Vasculature in Uppsala Seniors (the PIVUS study) with the primary aim to validate endothelium-dependent vasodilation measurements in more than 1000 subjects aged 70 living in the community of Uppsala, Sweden [13]. In the present report, we evaluated if a reduced arterial compliance would influence the relationships between coronary risk, as evaluated by the Framingham risk score, and endothelium-dependent vasodilation in a conduit artery (FMD) compared to resistance arteries (the invasive forearm technique using local acetylcholine infusion).

2. Material and methods

This section has previously been given in detail together with basic characteristics and vasodilatory tests of the study sample [13].

2.1. Subjects

Eligible were all subjects aged 70 living in the community of Uppsala, Sweden. The subjects were randomly chosen from the register of community living. About 1016 subjects participated giving a participation rate of 50.1%.

The study was approved by the Ethics Committee of the University of Uppsala.

All subjects were investigated in the morning after an over-night fast. No medication or smoking was allowed after midnight. An arterial cannula was inserted in the brachial artery for blood sampling and later regional infusions of vasodilators. Blood pressure was measured by a calibrated mercury sphygmomanometer. From these data, the Framingham risk score was calculated [14].

A PIVUS cardiovascular healthy subsample was defined as being without any history of cardiovascular disorders or drugs, and showing no hypertension, diabetes, obesity, hyperlipidemia or current smoking at the examination.

2.2. The invasive forearm technique

Forearm blood flow (FBF) was measured by venous occlusion plethysmography (Elektromedicin, Kullavik, Sweden). After evaluation of resting FBF, local intra-arterial drug-infusions were given during 5 min for each dose.

The infused dosages were 25 and 50 μg/min for Acetylcholine (Clin-Alpha, Switzerland) to evaluate endothelium-dependent vasodilation (EDV) and 5 and 10 μg/min for SNP (Nitropress, Abbot, UK) to evaluate endothelium-dependent vasodilation (EIDV).

EDV was defined as FBF during infusion of 50 μg/min of Acetylcholine minus resting FBF divided by resting FBF. EIDV was defined as FBF during infusion of 10 μg/min of SNP minus resting FBF divided by resting FBF.

2.3. The brachial artery ultrasound technique

The brachial artery was assessed by external B-mode ultrasound imaging 2–3 cm above the elbow (Acuson XP128 with a 10 MHz linear transducer, Acuson Mountain View, California, USA) according to the recommendations of the International Brachial Artery Task Force [15]. Blood flow increase was induced by inflation of a pneumatic cuff placed around the forearm to a pressure at least 50 mm Hg above systolic blood pressure for 5 min. FMD was defined as the maximal brachial artery diameter recorded between 30 and 90 s following cuff release minus diameter at rest divided by the diameter at rest.

2.4. Carotid artery compliance

The diameter of the common carotid artery (CCA) of the right side 1–2 cm proximal of the bifurcation was measured at its maximal diameter in systole and the minimal diameter in diastole. The distensibility of the CCA was calculated as the change in diameter maximum to minimum in relation to the minimal diameter in diastole divided by the central pulse pressure obtained by pulse wave analysis (Sphygmocor, Pulse Wave Medical Ltd., Australia).

2.5. Statistics

Non-normally distributed variables were ln-transformed to achieve a normal distribution. Relationships between pairs of variables were evaluated by Pearson’s correlation coefficient. ANCOVA was performed to evaluate if correlation coefficients differed. Two-tailed significance values were given with p < 0.05 regarded as significant. The statistical programme package StatView (SAS Inc., NC, USA) was used.

3. Results

The CCA distensibility showed a skewed distribution in the total sample with a median of 0.12 (0.11 in women and 0.13 in men) and a range from 0 to 0.33%/mm Hg.

In the PIVUS cardiovascular healthy sample (n = 131), the median was 0.13 and the 25th percentile was close to 0.10%/mm Hg, which then was chosen as the cut-off point for poor arterial compliance in the present study. Only 37% of the total sample showed values for CCA above this cut-off limit.

When the relationship between FMD (median 4.4%) and the Framingham risk score (median 12 points) was calculated in the groups with good and poor arterial compliance,
Fig. 1. Relationship between Framingham risk score and flow-mediated vasodilation (FMD, ln-transformed) in subjects with a poor (<0.1%/mm Hg, top panel) and good distensibility in the carotid artery (>0.1%/mm Hg, lower panel) ($r = -0.16, p = 0.0081$ in those with good vs. $r = -0.06, p = 0.17$ in those with a poor carotid artery distensibility; $p = 0.0001$ for difference).

In contrast, the correlation was highly significant in the group with good compliance, but not in the group with poor compliance ($r = -0.16, p = 0.0081$ versus $r = -0.06, p = 0.17$ in those with a poor CCA distensibility, $p = 0.0001$ for difference, see Fig. 1).

4. Discussion

The present study showed that arterial compliance affects measurements of endothelium-dependent vasodilation in a conduit artery, but not when measured in resistance arteries in the elderly.

4.1. Flow-mediated vasodilation

In accordance with a previous study [13], the relationships between FMD and coronary risk factors were only present in subjects with a good arterial compliance, while this relationship was no longer significant in those with a poor compliance. This finding is possible due to an inability of a non-compliant conduit artery to dilate even if the endothelial production of nitric oxide is normal.

The cut-off limit for a good arterial compliance was in the present study defined as above the 25th percentile in the healthy part of the PIVUS sample. This limit is of course only arbitrary and has only been applied to the present sample. In a pilot study performed in young healthy subjects the median for CCA compliance was 0.55%/mm Hg, a value not seen in any of subjects in the present sample. Thus, it must be kept in mind that compared to young subjects, all individuals in the present study, cardiovascular healthy or not, have a reduced arterial compliance. This is probably one explanation why FMD is low in this age group and the relationship between...
coronary risk is lower than relationships reported in younger populations.

4.2. The invasive forearm technique

Contrary to the findings with FMD, no impact of arterial compliance on the relationships between coronary risk and EDV or EIDV was seen. EDV evaluates endothelium-dependent vasodilation mainly in resistance arteries. The increase in arterial stiffness seen with age is most pronounced in the aorta, which is most sensitive to the loss of elastin fibres that occurs by age, and then a gradual reduction in the impact of ageing on stiffness is seen at more proximal sites of the arterial system.

4.3. Limitation of the study

The present sample is limited to caucasians aged 70. So, caution should be made to draw conclusions to other ethnic and age-groups. In the present study, arterial compliance and FMD were not measured in the same artery. However, compliance measurement in the CCA is a widely accepted way to evaluate arterial stiffness in a medium-size artery. As the brachial pressure in the CCA is a widely accepted way to evaluate arterial stiffness in a medium-size artery. As the brachial arterial compliance affects the ultrasound assessment of endothelial-dependent flow-mediated vasodilation in the elderly. The prospective investigation of the vasculature in uppsala seniors (PIVUS) study. Atherosclerosis 2004;169:354–60.

5. Conclusion

The present study showed that arterial compliance affects measurements of endothelium-dependent vasodilation in a conduit artery (FMD), but not when measured in resistance arteries (the invasive forearm technique) in the elderly.

This limits the use of FMD determinations in elderly subjects.

References


