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Chapter 4

Arterial stiffness is increased in families with premature coronary artery disease

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ABSTRACT

Objective A positive family history for premature coronary artery disease (CAD) is a risk factor for cardiovascular disease (CVD), independent from traditional risk factors. Therefore, currently used risk algorithms poorly predict risk in these individuals. Hence, novel methods are needed to assess cardiovascular risk. Pulse wave velocity (PWV) might be such a method, but it is unknown whether PWV is increased in first degree relatives (FDRs) of patients with premature CAD.

Design Observational case control study.

Setting Academic hospital.

Patients Patients with premature CAD and a positive family history for premature CAD (n=50), their FDRs without CVD (n=50) and unrelated controls (n=50).

Interventions None

Main outcome measures We assessed differences in PWV, using an Arteriograph system, between these groups by a generalized linear model and multinomial logistic regression.

Results Patients with premature CAD had higher PWV compared to FDRs and controls (9.7±2.9m/s vs. 8.2±2.0m/s and 7.4±1.1m/s; p<0.05 patients versus all groups). Linear regression showed all groups related to PWV, with patients having the highest PWV and controls the lowest (p<0.0001). Furthermore, PWV was associated with FDRs (Odds Ratio (OR) 1.32 (95% Confidence interval (CI) 1.02-1.72); p<0.05) and premature CAD (OR 1.72 (95% CI 1.32-2.24); p<0.05) compared to controls. These findings were independent of blood pressure and other traditional risk factors.

Conclusions Patients with premature CAD and their FDRs had higher PWV compared to controls, independent of other risk factors. This holds promise for the future, in which arterial stiffness might play a role in risk prediction within families with premature CAD.
INTRODUCTION

A positive family history for premature coronary artery disease (CAD) is an important risk factor for cardiovascular disease (CVD) and is, in fact, independent from other risk factors.\(^1\)\(^-\)\(^3\) The associated risk increases further when relatives are affected at a younger age, with an odds ratio (OR) of 1.3 in individuals with relatives affected below 55 years, to OR’s of 10 and higher in individuals with relatives affected below 45 years of age.\(^4\)\(^,\)\(^5\)

Whereas a positive family history for CVD identifies whole families at risk, it fails to identify which specific kindred are at risk within the family. This emphasizes the need to further refine risk among siblings in these families. Traditional risk score algorithms poorly predict cardiovascular risk in general, but even more in relatives of patients with premature CAD.\(^6\) The latter reflects the fact that these subjects are referred for cardiovascular risk evaluation at a relatively younger age, whereas in the traditional risk score algorithms age is the most potent factor determining CVD. In addition, risk score algorithms use markers of risk in stead of identifying disease itself. Therefore, investigators keep on searching for practical tools for assessing subclinical disease, to identify subjects with early onset CVD.

Pulse wave velocity (PWV), the gold standard of arterial stiffness,\(^7\) has emerged as a novel biomarker for predicting cardiovascular mortality and morbidity, independent from traditional cardiovascular risk factors.\(^8\) Overall, arterial stiffness only poorly predicts cardiovascular risk, which may relate to the heterogeneity of the studied populations. Interestingly, a recent prospective trial concluded that PWV measurement could be particularly useful in younger individuals with a genetic predisposition for CVD.\(^9\) To date, this hypothesis has not been tested. In the present study, we therefore evaluated whether “healthy” first degree relatives (FDRs) without overt CVD of patients with premature CAD are characterized by an increased PWV compared to controls with a negative family history for CVD. To test this, we assessed PWV in patients with premature CAD, their FDRs and unrelated controls.

METHODS

Study design

We recruited 50 patients with premature CAD with a positive family history of premature CVD. Hereby, we were able to select a population of individuals with a genetic predisposition for CVD. In the families of these participants, we also recruited 50 FDRs without overt CVD. In addition, we recruited 50 unrelated controls without overt CVD. We matched for gender and age.

The primary objective of the study was to evaluate whether there are differences in PWV between patients with premature CAD, their FDRs and controls. The secondary objectives were to explore the association between PWV and patients with premature CAD and their FDRs with and without adjustment of possible confounders.
In all groups we assessed traditional risk factors for CVD according to the standard procedures in our hospital. For the FDRs and controls, we assessed Framingham Risk Score. The FDRs and controls were not allowed to have a past history of CVD and were excluded if they had any symptoms of CVD, which was both assessed by a standardized questionnaire. Furthermore, controls were not allowed to use any medication and they were not allowed to have a positive family history for CVD. Furthermore, we assessed coronary calcium (CAC) scores in the FDRs, to evaluate subclinical atherosclerosis. To further minimize the influence of other cardiovascular risk factors, individuals in all groups were excluded if they had severe hypertension (>180/110 mmHg), diabetes mellitus or known familial hypercholesterolemia. Individuals were excluded if they were under the age of 18 years, if they were unable to give informed consent or in case of pregnancy or lactation. This work was conducted in accordance to the Declaration of Helsinki. All participants gave written informed consent and the study was approved by the local Institutional Review Board.

Definitions

CAD was defined as an acute myocardial infarction or coronary artery disease, needing revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Premature CAD is usually defined as an event occurring before the age of 55 years in men and 60 years in women. To increase the likelihood of including families with a genetic predisposition for CVD, the age limits were lowered to 41 years in men and 46 years in women. For the same reasons, the age limits for family history were also lowered. A positive family history was defined as ≥ 1 first degree and/ or ≥ 2 second degree family members with CVD before the age of 51 years in men and 56 years in women, in line with the GENECARD definition, found in the literature. CVD was defined in the same matter as CAD, with the extension of strokes and peripheral artery disease necessitating percutaneous transluminal angioplasty or bypass surgery.

Hypertension and hypercholesterolemia were defined in patients as the use of blood pressure or cholesterol lowering medication before the first event or, in case of a FDR, as medication use at the time of the study visit. Blood pressure lowering medication use was defined as the use of beta-blockers, calcium antagonists, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists or diuretics. In individuals who did not use medication, hypertension was defined as a blood pressure above 140/90 mmHg in rest and hypercholesterolemia as a fasting total cholesterol above 6.2 mmol/L, as defined by the Third Report of the National Cholesterol Education Program. Smoking was defined as current smoking or past smoking ≤ 5 years ago.

Pulse wave velocity

Participants visited the hospital after an overnight fast and were asked to refrain from smoking at least 8 hours before the visit. All measurements were performed in supine position after 15 minutes rest in a quiet, temperature controlled room. Arterial stiffness was assessed using...
the Arteriograph system (Tensiomed Kft. Budapest, Hungary), which shows close correlation with the widely used Sphymocor system.\textsuperscript{12} The Arteriograph is an operator independent non-invasive device, which uses oscillometric pressure curves registered by an upper arm blood pressure cuff to determine blood pressure and PWV as described and validated previously.\textsuperscript{13, 14} In short, PWV measurements are performed when cuff pressure exceeds systolic blood pressure by 35–40 mmHg, with a completely occluded brachial artery. The measurement is based on the fact that during systole, blood volume ejected into the aorta generates a pulse wave, the so-called ‘early systolic peak’. As this pulse wave runs down the periphery, it reflects from the bifurcation of the aorta, creating a second wave the ‘late systolic peak’. Return time of the pulse waves was calculated as the time difference between the first and the reflected systolic wave. PWV is calculated from this transit time and the distance travelled by the pulse wave. Estimation of the distance travelled by the pulse wave (from the heart to the bifurcation and back), is based on measuring the distance between the sternal notch and the pubic symphysis using a tape measure. PWVs were recorded as continuous data. Also, the percentage of individuals with a PWV above 12 m/s was assessed among the groups, which is comparable with subclinical organ damage according to the 2007 European Society of Hypertension Guidelines.\textsuperscript{15}

**Coronary artery calcification**

In all FDRs we performed a coronary computed tomography (CT) to assess the presence of coronary lesions through CAC. All CT’s were performed using a 64-slice multidetector CT scanner (Philips Medical Systems, Best, the Netherlands). The scanning protocol was as follows: tube voltage, 120 kV; tube current, 55 mAs; detector collimation, 40 × 2.5 mm; gantry rotation, 420 ms. Data was transferred to a post processing workstation (Extended Brilliance Workplace, Philips Medical Systems). We recorded CAC for the main arteries, the total score was calculated by summing lesion scores of all sections. We evaluated CAC according to Agatston\textsuperscript{16} and expressed further as age/sex percentiles. FDRs were divided in two groups, according to the results of the CAC. A score above the 80\textsuperscript{th} percentile was considered as abnormal, consistent with literature,\textsuperscript{17} lower scores as normal.

**Statistical analyses**

Sample size was calculated via a pilot study, where we found a difference in PWV between patients and controls of 1.3 ± 2.1 m/s. Using a power of 0.80 and a \( p \)-value of 0.05, a calculated sample size of 48 individuals was needed in each group.

Differences in baseline characteristics were assessed between the three groups by using chi-square tests (in case of proportions), or ANOVA (in case of continuous data) and individual group comparison was done by Fisher’s Least Significant Difference (LSD) correction. Association of PWV as a continuous variable with the different groups was assessed in two different manners. First, we computed OR’s using multinomial logistic regression, considering the PWV, as a continuous variable and the different groups as outcome. In this analysis, all FDRs were
used as one group. We adjusted the crude model (model 1) for age and sex (model 2) and finally, for other confounders such as hypercholesterolemia, smoking and systolic blood pressure (model 3). We corrected for systolic blood pressure, since PWV is directly dependent on the blood pressure during the measurement.\textsuperscript{18} Furthermore, we corrected for factors, which differed significantly among the groups. In this model, we used the controls as reference category. Secondly, we performed a generalized linear model, which considers the different groups as variable and the PWV as outcome measure. To test whether there were differences in PWV in FDRs according to the CAC score, we performed a multinomial logistic regression in the same manner as stated above, but now dividing the FDRs in two groups: one with CAC scores above the 80\textsuperscript{th} percentile and one with CAC scores below this point. Finally, to assess influences of family relations, we analyzed our data in a mixed model, where family relation was included as a paired variable. This had no influence on the outcome and the results remained similar (data not shown). A \textit{p}-value <0.05 was considered statistically significant. Data were analysed using SPSS software version 16.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Baseline characteristics

Characteristics of the participants are listed in table 1. The groups were well matched for both age and sex. We found that FDRs were more often smokers (38\% vs 20\%; \textit{p}<0.05), had higher total cholesterol (TC) levels (5.4±0.9 mmol/L vs 5.0±0.8 mmol/L; \textit{p}<0.05), and higher low density lipoprotein cholesterol (LDL-c) levels (3.5±0.9 mmol/L vs 3.1±0.7 mmol/L; \textit{p}<0.05) compared to controls. The Framingham Risk Score was somewhat higher in FDRs compared to controls, but did not reach statistical significance. Patients with premature CAD had higher glucose levels (5.5±0.8 mmol/L vs 5.2±0.7 mmol/L and 5.1±0.4 mmol/L; \textit{p}<0.05), lower TC levels (4.2±1.0 mmol/L vs 5.4±0.9 mmol/L and 5.0±0.8 mmol/L; \textit{p}<0.05), lower LDL-c levels (2.2±0.7 mmol/L vs 3.5±0.9 mmol/L and 3.1±0.7 mmol/L; \textit{p}<0.05) and higher triglycerides (2.1±3.8 mmol/L vs 1.1±0.6 mmol/L and 1.0±0.5 mmol/L; \textit{p}<0.05) compared to FDRs and controls. The patients also used more often antihypertensive and cholesterol lowering medication, mostly for secondary prevention reasons.

With regard to blood pressure, the systolic blood pressure was comparable between the groups (patients 131±19 mm±11 mmHg; controls 125±16 mmHg). The diastolic blood pressure was higher in patients compared to controls (85±10 vs 80±10 mmHg; \textit{p}<0.05). Unadjusted PWVs of FDRs did not significantly differ from controls (8.2±1.9 m/s vs. 7.5±1.2 m/s), whereas patients had higher PWVs compared to FDRs and controls (9.6±2.9 m/s vs. 8.2±1.9 m/s and 7.5±1.2 m/s; \textit{p}<0.05).
Vascular aspects of Fabry disease

Association between PWV and the different groups

In the multinomial logistic regression, PWV was positively associated with both patients (OR 1.72 (95% confidence interval (CI) 1.32-2.24); p<0.05) and FDRs (OR 1.32 (95% CI 1.02-1.72); p<0.05) compared to controls (figure 1 and table 2). This association retained statistical significance after adjustment for confounders (model 2 and 3). PWV was also positively associated with patients compared to all FDRs (OR 1.30 (95% CI 1.08-1.57); p<0.05). Again, this association remained after adjustment for confounders. These findings were confirmed in the linear regression analysis, which showed all three groups to be linearly related to PWV (p<0.0001, data not shown).

Table 1 Baseline characteristics of the participants

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=50)</th>
<th>FDRs (n=50)</th>
<th>Patients with CAD (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>45.6 ± 6.6</td>
<td>45.6 ± 7.9</td>
<td>46.0 ± 3.6</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>27 (54)</td>
<td>27 (54)</td>
<td>27 (54)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>10 (20)</td>
<td>19 (38) *</td>
<td>28 (56) *</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>125.2 ± 15.6</td>
<td>129.7 ± 11.3</td>
<td>130.7 ± 18.5</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>79.4 ± 9.9</td>
<td>82.6 ± 8.8</td>
<td>84.8 ± 10.4 *</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.0 ± 4.4</td>
<td>23.7 ± 3.9</td>
<td>24.4 ± 5.0</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.1 ± 0.4</td>
<td>5.2 ± 0.7</td>
<td>5.5 ± 0.8 *†</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.0 ± 0.8</td>
<td>5.4 ± 0.9 *</td>
<td>4.2 ± 1.0 *†</td>
</tr>
<tr>
<td>HDL-c, mmol/L</td>
<td>1.5 ± 0.4</td>
<td>1.4 ± 0.4</td>
<td>1.2 ± 0.3 *†</td>
</tr>
<tr>
<td>LDL-c, mmol/L</td>
<td>3.1 ± 0.7</td>
<td>3.5 ± 0.9 *</td>
<td>2.2 ± 0.7 *†</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.0 ± 0.5</td>
<td>1.1 ± 0.6</td>
<td>2.1 ± 3.8 *†</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>72.9 ± 11.2</td>
<td>72.5 ± 11.9</td>
<td>70.7 ± 13.6</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>0 (0)</td>
<td>6 (12)</td>
<td>10 (20) *</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>0 (0)</td>
<td>7 (14) *</td>
<td>11 (22) *†</td>
</tr>
<tr>
<td>Framingham Risk Score</td>
<td>2.3 (1.2; 3.3)</td>
<td>3.2 (1.2; 4.8)</td>
<td>-</td>
</tr>
</tbody>
</table>

Medication use

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=50)</th>
<th>FDRs (n=50)</th>
<th>Patients with CAD (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive, n (%)</td>
<td>0 (0)</td>
<td>5 (10)</td>
<td>46 (92) *†</td>
</tr>
<tr>
<td>Cholesterol lowering, n (%)</td>
<td>0 (0)</td>
<td>6 (12)</td>
<td>46 (92) *†</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>7.5 ± 1.2</td>
<td>8.2 ± 1.9</td>
<td>9.6 ± 2.9 *†</td>
</tr>
<tr>
<td>PWV &gt;12 m/s, n (%)</td>
<td>0 (0)</td>
<td>3 (6)</td>
<td>10 (20) *†</td>
</tr>
</tbody>
</table>

* p<0.05 compared to controls; † p<0.05 compared to FDRs;
FDRs=first degree relatives, BMI=Body mass index, LDL-c=Low density lipoprotein cholesterol, HDL-c=High density lipoprotein cholesterol, SBP=systolic blood pressure, DBP=diastolic blood pressure, PWV=pulse wave velocity.
Continuous data are expressed as mean ± standard deviation except for Framingham which is expressed as median (25th; 75th percentiles), categorical data as absolute numbers with (percentages).
Association between PWV and different groups according to CAC results

Assuming a hereditary component in the families, the FDRs might consist of individuals which have and which have not inherited the genetic defect. Since we do not know the specific defect in the families, we chose to evaluate subclinical atherosclerosis via CAC. After dividing the FDRs in a group with high and group with normal CAC score, we found that 34% (n=17) of all FDRs had a high CAC score (above the 80th percentile). In the multinomial logistic regression, we found that PWV was positively associated with both patients (OR 1.72 (95% CI 1.32-2.24); \( p<0.05 \)) and FDRs with high CAC (OR 1.49 (95% CI 1.09-2.04); \( p<0.05 \)), compared to controls (table 3). Furthermore, we found that PWV was positively associated with patients (OR 1.41 (95% CI 1.11-1.79); \( p<0.05 \)) compared to FDRs with normal CAC). This association remained after adjustment for confounders.

Table 2 Multinomial logistic regression to assess the relation between PWV and patients, FDRs and controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Controls</th>
<th>FDRs</th>
<th>Patients with CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWV Model 1</td>
<td>1.00</td>
<td>1.32 (1.02-1.72) *</td>
<td>1.72 (1.32-2.24) *†</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.00</td>
<td>1.38 (1.04-1.83) *</td>
<td>1.91 (1.43-2.57) *†</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.00</td>
<td>1.51 (1.05-2.17) *</td>
<td>2.18 (1.49-3.19) *†</td>
</tr>
</tbody>
</table>

* \( p<0.05 \) compared to controls; † \( p<0.05 \) compared to FDRs

Controls are used as reference

Model 1: Crude; Model 2: adjusted for age and sex; Model 3: additionally adjusted for hypercholesterolemia, smoking, hypertension and systolic blood pressure. FDRs=first degree relatives, PWV=pulse wave velocity.

Association between PWV and different groups according to CAC results

Assuming a hereditary component in the families, the FDRs might consist of individuals which have and which have not inherited the genetic defect. Since we do not know the specific defect in the families, we chose to evaluate subclinical atherosclerosis via CAC. After dividing the FDRs in a group with high and group with normal CAC score, we found that 34% (n=17) of all FDRs had a high CAC score (above the 80th percentile). In the multinomial logistic regression, we found that PWV was positively associated with both patients (OR 1.72 (95% CI 1.32-2.24); \( p<0.05 \)) and FDRs with high CAC (OR 1.49 (95% CI 1.09-2.04); \( p<0.05 \)), compared to controls (table 3). Furthermore, we found that PWV was positively associated with patients (OR 1.41 (95% CI 1.11-1.79); \( p<0.05 \)) compared to FDRs with normal CAC). This association remained after adjustment for confounders.
In this prospective case control study, we show that PWV is increased in both patients with premature CAD as well as in FDRs without overt cardiovascular disease. These data imply that apparently healthy asymptomatic FDRs of patients with premature CAD display features of stiffened arteries at a relatively young age, suggesting established vascular damage.

The increased PWV in FDRs of patients with premature CAD is in agreement with previous studies showing signs of subclinical atherosclerosis in individuals with a positive family history for CAD. In 1,662 subjects a family history for early-onset premature CAD was shown to be independently correlated with carotid intima media thickness, whereas family history of late-onset CAD was not. Others studies confirm these findings with regard to intima media thickness, not only in adults but even in children with a positive family history. Previous studies have also shown that coronary artery calcium scores were associated with a positive family history for CAD.

With respect to the patients with premature CAD, it is known that various conditions such as hypertension, end-stage renal disease and diabetes are associated with the development of arterial stiffness. The FDRs had a higher prevalence of classic risk factors compared to controls, which are also associated with an increased PWV. However, the Framingham Risk Score was comparable and after correction for classic risk factors in relatives and patients, PWV remains higher, which could indicate a specific hereditary component.

In recent years, the genetic component of CAD had much attention. Via genome wide association studies, several candidate genes were pointed out associated with CAD. The responsible pathway for these genes is mostly unknown, but accelerated arterial stiffening could be a possible mechanism. In line, the impact of heritable factors on PWV has recently been confirmed, but it is unknown whether PWV plays a role in familiar CVD. More research is needed in this field.

The striking elevation of PWVs - up to 15 m/s – in these apparently “healthy” individuals with a genetic predisposition for premature CAD, could imply a causal role in the development of

**Table 3 Multinomial logistic regression to assess the relation between PWV and patients, FDRs with and without high CAC score and controls.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Controls</th>
<th>FDRs</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal CAC</td>
<td>Abnormal CAC</td>
<td>Normal CAC</td>
</tr>
<tr>
<td>PWV</td>
<td>1.00</td>
<td>1.23 (0.91-1.65) *</td>
<td>1.49 (1.09-2.04) *</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.00</td>
<td>1.31 (0.96-1.79) *</td>
<td>1.53 (1.08-2.17) *</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.00</td>
<td>1.46 (0.99-2.14) *</td>
<td>1.61 (1.02-2.54) *</td>
</tr>
</tbody>
</table>

* p<0.05 compared to controls; † p<0.05 compared to FDRs with normal CAC

Controls are used as reference

Model 1: Crude Model; Model 2: adjusted for age and sex; Model 3: additionally adjusted for hypercholesterolemia, smoking and systolic blood pressure

Abbreviations as in table 2; CAC=Coronary artery calcification.
premature CAD. Therefore, PWV measurements might be a practical tool for risk assessment, since the classic risk factors fail to do so in this particular high risk subset of individuals. Indeed, a previous study found that a high PWV, in subjects with a low SCORE risk (<5%), was a strong predictor for cardiovascular events, suggesting a better risk prediction by PWV in these individuals. Furthermore, another study showed the same disagreement between Framingham risk score and PWV, in which the highest predictive value of PWV for CAD was found in subjects with a low Framingham risk. This implies that PWV is particularly useful in younger subjects, since age is the major contributor in these models. Whether PWV is indeed a good predictor of premature CAD in these relatives needs to be confirmed in prospective trials.

The limitations of our study merit some consideration. A major limitation of this study is that we do not have follow-up data to establish the true predictive value of PWV in FDRs of patients with premature CAD. A second limitation was that, assuming a hereditary component in the families, the FDRs probably consisted of individuals which have and which have not inherited the genetic defect. This could be the reason of the large distribution in this group. Ideally, there would be a method to test for the unknown genetic defect. Separating the FDRs in a group with and a group without the genetic defect could increase the association with PWV in FDRs with a genetic defect.

We have tried this substitute this by performing a CAC score. Prospective follow-up studies show that CAC predicts cardiovascular events, independent of other risk factors, also the elevated CAC score is highly abnormal in these young individuals. Taking into account the logistic regression, the association with PWV increases in the FDRs with abnormal CAC, while it decreases in the group with normal CAC, compared to analyzing the FDRs as one group. However, we do not know whether the increased familial risk in FDRs co-segregates with an elevated CAC score.

In conclusion, we found that FDRs without overt CVD of patients with premature CAD had higher PWV compared to unrelated controls, independent of other risk factors. Interestingly, a high PWV was related to FDRs with high CAC scores, while it was not in FDRs with a normal CAC score. This holds promise for the future, in which arterial stiffness could play an important role as risk prediction within families with premature CAD. However, to be able to evaluate the prognostic value of PWV, prospective studies in families with premature CAD are needed.
REFERENCES


