Assessment of Aortic Pulse Wave Velocity and Cardiac Diastolic Function in Subjects With and Without the Metabolic Syndrome

HDL-cholesterol is independently associated with cardiovascular function

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Objective - The influence of lipid and glucose metabolism in the metabolic syndrome (MS) on aortic pulse wave velocity (PWV) and left ventricular (LV) diastolic function was evaluated using magnetic resonance imaging (MRI).

Research Design and Methods - Aortic PWV and LV diastolic function were assessed using MRI in 32 subjects with (n=16) and without the MS (n=16), matched for age, waist circumference and blood pressure. The groups were compared with the unpaired t-test or Mann-Whitney U-test and linear regression analysis was applied.

Results - Aortic PWV was increased and LV diastolic function was decreased in subjects with compared to subjects without the MS. HDL-cholesterol was independently associated with aortic PWV \( (R=-0.470, p<0.01) \) and LV diastolic function \( (R=-0.421, p=0.02) \).

Conclusions - Increased aortic PWV and decreased LV diastolic function is observed in subjects with the MS, regardless of blood pressure. Moreover, HDL-cholesterol is independently associated with aortic PWV and LV diastolic function.
Previous studies demonstrated that the metabolic syndrome (MS) is associated with increased arterial stiffness and left ventricular (LV) dysfunction. However, the exact mechanism responsible for these alterations is unclear and has not yet been studied with magnetic resonance imaging (MRI). We hypothesized that abnormalities in lipid or glucose metabolism contribute to the adverse cardiovascular changes in the MS. Accordingly, the study purpose was to compare aortic pulse wave velocity (PWV) and LV function using MRI in subjects with and without the MS and to evaluate the relation between lipid and glucose metabolism and cardiovascular function.

**RESEARCH DESIGN AND METHODS**

MRI examination was performed in 16 Caucasian males with recently diagnosed, untreated MS (IDF-criteria) and 16 Caucasian males without the MS (sample size calculation, 80% power, \( \alpha = 0.05 \) (3)), matched for age, waist circumference and blood pressure. Only males were included to avoid potential confounding effects of gender on MRI results and blood values. No participants showed evidence of cardiovascular disease, diabetes mellitus or were smokers. Laboratory measurements (triglycerides, high-density lipoprotein cholesterol (HDLc), total cholesterol, fasting blood glucose, glycated hemoglobin, insulin, high-sensitivity CRP (hs-CRP)) were performed just prior to the MRI. Approval by the local ethics committee and informed consent were obtained.

MRI was performed on a 1.5-T scanner (Philips) using a 5-element cardiac coil and heart-rate was registered.

Aortic PWV was assessed with a technique with good reproducibility, using a retrospectively ECG-gated fast-field-echo sequence with velocity encoding (temporal resolution 6-10 ms), acquired at two predefined levels (thoracic ascending and abdominal aorta).(4,5)

For evaluation of LV systolic function, the heart was imaged in short-axis view using a ECG-triggered balanced turbo-field-echo sequence.(4)

A 3-dimensional 3-directional velocity-encoded MRI (3D-VE-MRI) technique was used for assessment of transmitral flow for evaluation of LV diastolic function.(6)

Data were analyzed with MASS/FLOW (Medis). PWV was calculated as: aortic path length between 2 imaging sites divided by transit time between arrival of the pulse wave at these sites.(4)

LV end-systolic volume, end-diastolic volume, ejection-fraction and end-diastolic mass were assessed.

The transmitral flow was reconstructed from the 3D-VE-MRI acquisitions.(6) The following variables of diastolic function were derived: peak filling rate (PFR) of the early filling wave (E), E deceleration peak and mean, E deceleration time, PFR of the atrial filling wave (A) and E/A peak flow ratio.

Data were expressed as mean ± SD or median (interquartile range). Differences between groups were analyzed using the unpaired \( t \)-test or Mann-Whitney \( U \) test. After log-transformation of non-normally distributed variables, univariate linear regression analysis was performed in the pooled dataset to analyze the association between clinical and MRI variables (Pearson correlation coefficients (R), \( p \)-values reported). Variables with a univariate linear regression with \( p<0.10 \) were included in a stepwise multiple linear regression analysis. \( p<0.05 \) was considered statistically significant.

**RESULTS**

Table 1 shows clinical characteristics and MRI results. Heart-rate was similar in the two groups during MRI-examination.
PWV was significantly higher in subjects with compared to subjects without the MS. Univariate linear regression analysis showed that HDLc was significantly associated with PWV ($R=-0.470$, $p<0.01$). This association was more pronounced in the aortic arch than in the more distal aorta (data not shown). A trend towards a correlation between hs-CRP and PWV ($R=0.326$, $p<0.1$) was also observed. No significant association was observed between age, waist circumference, blood pressure, remaining laboratory measurements and PWV. Multiple regression analysis including HDLc and hs-CRP, showed that only HDLc was significantly associated with PWV.

Significant differences in E deceleration peak and mean between the two groups were observed, indicating decreased diastolic function (impaired relaxation) in subjects with the MS. Univariate linear regression showed that HDLc was significantly associated with E deceleration mean and E deceleration time (resp.$R=-0.421$, $p=0.021$, $R=-0.380$, $p=0.038$). No significant association was observed between age, waist circumference, blood pressure, other laboratory measurements and diastolic function. Similar correlations were detected between total cholesterol/HDLc-ratio and cardiovascular function (data not shown).

**CONCLUSIONS**

To our knowledge, this is the first study that evaluated aortic stiffness and LV diastolic function in one examination using MRI in the MS. The results demonstrate increased PWV and impaired LV diastolic function in subjects with the MS, regardless of blood pressure. Moreover, HDLc was independently associated with PWV and LV diastolic function, suggesting adverse cardiovascular changes in the presence of low HDLc levels.

The present findings of increased arterial stiffness and decreased LV diastolic function in the MS are in line with previous studies, using other techniques than MRI.(1,2) Importantly, in our study, these unfavourable changes could not be ascribed to age, waist circumference or blood pressure. This observational study does not allow to unravel the exact underlying mechanism of the observed alterations, however, the significant association between HDLc and PWV and diastolic function suggests that lipid metabolism might play a role. The anti-atherogenic properties of HDLc (including maintenance of endothelial function (nitric-oxide), reverse cholesterol-transport, anti-inflammatory properties) might protect against arterial stiffening. Furthermore, insulin resistance and low-grade inflammation may contribute to arterial stiffening.(7) In contrast to patients with diabetes mellitus, formation of advanced glycation end products (AGEs) is not likely to play a major role in arterial stiffening in our normoglycaemic subjects. Increased arterial stiffness itself can hamper diastolic function through early reflection of the pulse wave leading to increased LV afterload and decreased myocardial perfusion. Other possible factors contributing to diastolic dysfunction include macrovascular (coronary) and microvascular endothelial dysfunction and insulin resistance.(8)

Limitations are the small sample size and inclusion of only males, therefore, our results require confirmation in larger study groups including males and females.
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REFERENCES
1. de las FL, Brown AL, Mathews SJ, Waggoner AD, Soto PF, Gropler RJ, Davila-Roman VG: Metabolic syndrome is associated with abnormal left ventricular diastolic function independent of left ventricular mass. *Eur.Heart J.* 28:553-559, 2007
2. Safar ME, Thomas F, Blacher J, Nzietchueng R, Bureau JM, Pannier B, Benetos A: Metabolic syndrome and age-related progression of aortic stiffness. *J.Am.Coll.Cardiol.* 47:72-75, 2006
3. van der Meer RW, Diamant M, Westenberg JJ, Doornbos J, Bax JJ, de Roos A, Lamb HJ: Magnetic resonance assessment of aortic pulse wave velocity, aortic distensibility, and cardiac function in uncomplicated type 2 diabetes mellitus. *J.Cardiovasc.Magn Reson.* 9:645-651, 2007
4. Grotenhuis HB, Ottenkamp J, Westenberg JJ, Bax JJ, Kroft LJ, de Roos A: Reduced aortic elasticity and dilatation are associated with aortic regurgitation and left ventricular hypertrophy in nonstenotic bicuspid aortic valve patients. *J.Am.Coll.Cardiol.* 49:1660-1665, 2007
5. Leeson CP, Robinson M, Francis JM, Robson MD, Channon KM, Neubauer S, Wiesmann F: Cardiovascular magnetic resonance imaging for non-invasive assessment of vascular function: validation against ultrasound. *J.Cardiovasc.Magn Reson.* 8:381-387, 2006
6. Westenberg JJ, Roes SD, Binnendijk NMJ, de Roos A, Reiber JH, van der Geest RJ: Accurate Quantification of True Transvalvular Flow Simultaneously over Mitral and Tricuspid Valve Using 3D Velocity-encoded MRI with Retrospective Valve Tracking (Abstract). *RSNA 2007-514-515, 2007*
7. Vlachopoulos C, Aznaouridis K, Stefanadis C: Clinical appraisal of arterial stiffness: the Argonauts in front of the Golden Fleece. *Heart* 92:1544-1550, 2006
8. Wisniacki N, Taylor W, Lye M, Wilding JP: Insulin resistance and inflammatory activation in older patients with systolic and diastolic heart failure. *Heart* 91:32-37, 2005
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Table 1. Clinical characteristics and MRI results of the study population.

| Clinical characteristics                        | Subjects without MS | Subjects with MS | P-value |
|------------------------------------------------|---------------------|------------------|---------|
| Age (years)                                     | 60 ± 5              | 60 ± 5           | 0.8     |
| Waist circumference (cm)                        | 106 ± 9             | 111 ± 11         | 0.2     |
| Systolic blood pressure (mmHg)                  | 142 ± 17            | 145 ± 17         | 0.6     |
| Diastolic blood pressure (mmHg)                 | 89 ± 9              | 88 ± 8           | 0.9     |
| Triglycerides (mmol/l)                          | 1.3 ± 0.7           | 1.9 ± 0.6        | < 0.01  |
| HDLc (mmol/l)                                   | 1.8 ± 0.3           | 1.2 ± 0.2        | < 0.001 |
| Total cholesterol (mmol/l)                      | 5.7 ± 0.9           | 5.9 ± 1.0        | 0.6     |
| Total cholesterol / HDL ratio                   | 3.3 ± 0.7           | 5.1 ± 0.7        | < 0.001 |
| Fasting plasma glucose (mmol/l)*                | 4.7 (1.0)           | 5.0 (1.3)        | 0.029   |
| HbA1c (%)                                       | 5.0 ± 0.4           | 5.2 ± 0.5        | 0.1     |
| Insulin (mU/l)*                                 | 6.5 (4.5)           | 12.0 (11.5)      | 0.014   |
| HOMA-IR (mmol/L x mU/L) *                       | 1.2 (0.83)          | 2.9 (3.0)        | 0.010   |
| hs-CRP (mmol/l)*                                | 1.1 (0.98)          | 2.7 (2.5)        | < 0.001 |
| Aortic stiffness                                |                     |                  |         |
| Aortic PWV (m/s)                                | 6.0 ± 1.0           | 7.4 ± 2.0        | 0.018   |
| Cardiac volumes and function                    |                     |                  |         |
| LVEDV-I (ml/m²)                                 | 82 ± 27             | 84 ± 12          | 0.7     |
| LVESV-I (ml/m²)                                 | 33 ± 12             | 35 ± 6           | 0.7     |
| LVEDM-I (g/m²)                                  | 56 ± 17             | 58 ± 9           | 0.7     |
| LV ejection fraction (%)                        | 59 ± 5              | 59 ± 4           | 0.7     |
| E peak filling rate (ml/s)                      | 503 ± 100           | 456 ± 98         | 0.2     |
| E deceleration peak (ml/s²) x 10⁻³              | -4.6 ± 1.3          | -3.7 ± 1.0       | 0.044   |
| E deceleration mean (ml/s²) x 10⁻³              | -3.0 ± 0.9          | -2.4 ± 0.7       | 0.032   |
| E deceleration time (ms)                        | 155 ± 27            | 180 ± 36         | 0.043   |
| A peak filling rate (ml/s)                      | 448 ± 76            | 463 ± 61         | 0.5     |
| E/A peak ratio                                  | 1.1 ± 0.2           | 1.0 ± 0.2        | 0.1     |

A: atrial filling wave, E: early filling wave, HbA1c: glycated hemoglobin, HDLc: high-density lipoprotein cholesterol, hs-CRP: high sensitivity C-reactive protein, LV: left ventricular, LVEDM: left ventricular end-diastolic mass, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, MS: metabolic syndrome, PWV: pulse wave velocity. Insulin resistance was calculated according to the homeostatic model assessment method defined as: HOMA-IR(mmol/L x mU/L): = fasting glucose (mmol/L) x fasting insulin (mU/L)/22.5.

* These variables were non-normally distributed and therefore expressed as median (interquartile range) and the Mann-Whitney $U$ test was used to compare the two groups. The remaining variables were normally distributed and expressed as mean ± SD and the unpaired $t$-test was used to compare the two groups.

Diastolic function could not be calculated in two subjects with the MS due to technical problems.