# Magnetic resonance imaging techniques for risk stratification in cardiovascular disease

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# Chapter 7

## 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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## Abstract

### Objective

To evaluate the influence of lipid and glucose metabolism in the metabolic syndrome on aortic pulse wave velocity (PWV) and left ventricular (LV) diastolic function using magnetic resonance imaging (MRI).

### Research design and methods

Aortic PWV and LV diastolic function were assessed using MRI in 16 subjects with the metabolic syndrome and 16 subjects without the metabolic syndrome matched for age, waist circumference, and blood pressure. The groups were compared using 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 those without the metabolic syndrome. 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 metabolic syndrome, regardless of blood pressure. Moreover, HDL cholesterol is independently associated with aortic PWV and LV diastolic function.

## Introduction

Previous studies have demonstrated that the metabolic syndrome is associated with increased arterial stiffness and left ventricular (LV) dysfunction (1,2). 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 metabolic syndrome. Accordingly, the study purpose was to compare aortic pulse wave velocity (PWV) and LV function using MRI in subjects with and without the metabolic syndrome and to evaluate the relation between lipid and glucose metabolism and cardiovascular function.

## Research design and methods

MRI examination was performed in 16 Caucasian male subjects with recently diagnosed, untreated metabolic syndrome (per International Diabetes Federation criteria) and 16 Caucasian male subjects without the metabolic syndrome (sample size calculation: 80% power, $\alpha$ 0.05) (3) matched for age, waist circumference, and blood pressure. Only male subjects were included to avoid potential confounding effects of gender on MRI results and blood values. No participants showed evidence of cardiovascular disease, diabetes, or being a smoker. Laboratory measurements (triglycerides, high-density lipoprotein [HDL] cholesterol, total cholesterol, fasting blood glucose, glycated hemoglobin, insulin, high-sensitivity C-reactive protein [hs-CRP]) were performed just before the MRI. Approval from the local ethics committee and informed consent were obtained.

MRI was performed on a 1.5T 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 electrocardiogram-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 an electrocardiogram-triggered balanced turbo field echo sequence (4). A three-dimensional three-directional velocity-encoded (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, Leiden, The Netherlands). PWV was calculated as the aortic path length between two 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 ± standard deviation (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 than in those without the metabolic syndrome. Univariate linear regression analysis showed that HDL cholesterol 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 HDL cholesterol and hs-CRP, showed that only HDL cholesterol 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 HDL cholesterol was significantly associated with E deceleration mean and E deceleration time ($r = -0.421$, $p = 0.021$, and $r = -0.380$, $p = 0.038$, respectively). No significant association was observed between age, waist circumference, blood pressure, other laboratory measurements, and diastolic function. Similar correlations were detected between total cholesterol-to-HDL cholesterol ratio and cardiovascular function (data not shown).

**Table 1.** Clinical characteristics and MRI results of the study population.

| | Subjects without the metabolic syndrome | Subjects with the metabolic syndrome | P-value |
|---|---|---|---|
| **Clinical characteristics** | | | |
| 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 |
| HDL cholesterol (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 cholesterol 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 × 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** | | | |
| LV EDV-I (ml/m$^2$) | 82 ± 27 | 84 ± 12 | 0.7 |
| LV ESV-I (ml/m$^2$) | 33 ± 12 | 35 ± 6 | 0.7 |
| LV EDM-I (g/m$^2$) | 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/s$^{2)}$ × $10^{-3}$ | -4.6 ± 1.3 | -3.7 ± 1.0 | 0.044 |
| E deceleration mean (ml/s$^{2)}$ × $10^{-3}$ | -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 |

Insulin resistance was calculated according to the homeostatic model assessment method defined as: HOMA-IR (mmol/L × mU/L): = fasting glucose (mmol/L) × fasting insulin (mU/L) / 22.5. * These variables were non-normally distributed and therefore expressed as median (interquartile range); Mann-Whitney *U*-test was used to compare the two groups. The remaining variables were normally distributed and expressed as mean ± SD; unpaired *t*-test was used to compare the two groups. Diastolic function could not be calculated in two subjects with the metabolic syndrome due to technical problems.
A: atrial filling wave, E: early filling wave, HbA1c: glycated hemoglobin, HDL cholesterol: high-density lipoprotein cholesterol, hs-CRP: high sensitivity C-reactive protein, LV: left ventricular, LV EDM: left ventricular end-diastolic mass, LV EDV: left ventricular end-diastolic volume, LV ESV: left ventricular end-systolic volume, PWV: pulse wave velocity.

## Conclusions

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

The present findings of increased arterial stiffness and decreased LV diastolic function in the metabolic syndrome are in line with previous studies using techniques other 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 for revelation of the exact underlying mechanism of the observed alterations; however, the significant association between HDL cholesterol and PWV and diastolic function suggests that lipid metabolism might play a role. The anti-atherogenic properties of HDL cholesterol (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, formation of advanced glycation end products is not likely to play a major role in arterial stiffening in these normoglycemic 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 of this study are the small sample size and inclusion of only male subjects; our results therefore require confirmation in larger study groups including male and female subjects.

## References

1. de las Fuentes L, Brown AL, Mathews SJ, et al. Metabolic syndrome is associated with abnormal left ventricular diastolic function independent of left ventricular mass. Eur Heart J 2007;28:553-559.
2. Safar ME, Thomas F, Blacher J, et al. Metabolic syndrome and age-related progression of aortic stiffness. J Am Coll Cardiol 2006;47:72-75.
3. van der Meer RW, Diamant M, Westenberg JJM, et al. Magnetic resonance assessment of aortic pulse wave velocity, aortic distensibility, and cardiac function in uncomplicated type 2 diabetes mellitus. J Cardiovasc Magn Reson 2007;9:645-651.
4. Grotenhuis HB, Ottenkamp J, Westenberg JJM, et al. Reduced aortic elasticity and dilatation are associated with aortic regurgitation and left ventricular hypertrophy in nonstenotic bicuspid aortic valve patients. J Am Coll Cardiol 2007;49:1660-1665.
5. Leeson CP, Robinson M, Francis JM, et al. Cardiovascular magnetic resonance imaging for non-invasive assessment of vascular function: validation against ultrasound. J Cardiovasc Magn Reson 2006;8:381-387.
6. Westenberg JJM, Roes SD, Binnendijk NMJ, et al. Mitral valve and tricuspid valve blood flow: accurate quantification with 3D velocity-encoded magnetic resonance imaging with retrospective valve tracking. Radiology 2008;249:792-800.
7. Vlachopoulos C, Aznaouridis K, Stefanadis C. Clinical appraisal of arterial stiffness: the Argonauts in front of the Golden Fleece. Heart 2006;92:1544-1550.
8. Wisniacki N, Taylor W, Lye M, et al. Insulin resistance and inflammatory activation in older patients with systolic and diastolic heart failure. Heart 2005;91:32-37.