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Increased Arterial Augmentation and Augmentation Index as Surrogate Parameters for Arteriosclerosis in Subjects with Diabetes Mellitus and Nondiabetic Subjects with Cardiovascular Disease

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Abstract

Background:
Arterial augmentation (AP) and the augmentation index (Aix) are surrogate parameters of arterial stiffness and are commonly used as predictors for cardiovascular risk. The aim of this study is to compare these parameters in diabetic subjects and nondiabetic cardiovascular risk subjects with healthy control subjects.

Methods:
One hundred sixty-six nonsmoking subjects aged between 35 and 70 years were included in the study, which included 100 subjects with cardiovascular disease but not diabetes (mean age 62.73±8.75 years), 33 subjects with type 2 diabetes (66.58±2.69 years), and 33 healthy controls (51.89±8.91 years). In these subjects, arterial stiffness was measured by the difference between the second and the first systolic peak of the central pressure waveform, and the Aix was calculated as the percentage of Aix from pulse pressure.

Results:
Arterial augmentation was increased in subjects with diabetes (DM) with 10.21±6.97 mm Hg and in subjects with cardiovascular disease but not diabetes (CV) with 10.74±5.29 mm Hg in comparison to healthy controls (C) with 6.59±3.97 mm Hg ($p < 0.0005$ DM vs C; $p < 0.00005$ CV vs C). Moreover, Aix was increased with 26.00±9.91% in CV subjects compared to healthy controls with 19.84±9.37% ($p < 0.02$ CV vs C). The augmentation index was increased with 21.12±11.21% in subjects with type 2 diabetes mellitus compared to controls, but failed to be statistically significant. There was no statistical significance in arterial augmentation or the augmentation index between CV and diabetic subjects.

Conclusion:
The results of our study revealed a comparable increased augmentation index as a surrogate measure of arterial stiffness and arteriosclerosis in subjects with diabetes mellitus and in nondiabetic subjects with cardiovascular disease.

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Abbreviations: (AP) augmentation, (Aix) augmentation index, (PWA) pulse wave analysis

Keywords: augmentation, augmentation index, cardiovascular risk, diabetes mellitus type 2, pulse wave analysis

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Introduction

Diabetes mellitus type 2 is associated with a higher risk of cardiovascular disease.[1,2] Morbidity and mortality in hypertension and cardiovascular disease are related to structural and functional alterations of the arterial wall.[3–5] Changes in the arterial wall can lead to increased arterial stiffness, which influences cardiovascular prognosis negatively.[6] Pulse wave analysis (PWA) is a noninvasive and reproducible technique[7–9] used to examine arterial elastic properties and has therefore been utilized in many clinical studies.[10–12] An increased augmentation index (Aix) is associated with increased cardiovascular risk,[13,14] and an increased augmentation index was reported in patients with either type 2 diabetes (DM) or impaired glucose tolerance.[15] The aim of this study is to compare changes in the augmentation index in patients with DM and in nondiabetic cardiovascular risk patients with healthy controls.

Patients and Methods

One hundred sixty-six subjects (89 male and 77 female) aged between 35 and 70 years were included in the study: 100 subjects with increased cardiovascular risk but not diabetes, 33 subjects with type 2 diabetes, and 33 healthy controls. The clinical characteristics and demographical data of the different subject groups are given in **Table 1**. All subjects were nonsmokers. Type 2 diabetes mellitus was defined by American Diabetes Association criteria; increased cardiovascular risk was defined as having a current or past history of hypertension, coronary heart disease, myocardial infarction, or stroke, but not diabetes. Patients with heart failure were excluded from the study.

Table 1. Characteristics of Patients with Diabetes Mellitus Type 2, Cardiovascular Risk Patients, and Healthy Controls

	Diabetes mellitus type 2	Nondiabetic cardiovascular risk	Healthy subjects
n	33	100	33
Age (years)	66.58±2.69	62.73± 8.75	51.89± 8.91
Gender (male/female)	19/14	52/48	18/15
Body mass index (kg/m^2)	33.12	29.86	26.24

Pulse Waveform Analysis

Arterial stiffness, which is predictive of vascular disease outcomes, can be measured by analysis of the arterial waveform to determine pulse waveform and augmentation index.[16] In our study, arterial stiffness was assessed noninvasively with a commercially available SphygmoCor system (AtCorMedical, Australia) from the radial artery at the left wrist using applanation tonometry.

After 20 sequential waveforms were recorded, a validated generalized transfer function was used to generate the corresponding central aortic pressure waveform.[17–19] On the generated central aortic pressure waveform, the merging curve of the incident and the reflected wave (the inflection point) was identified (**Figure 1**). The augmentation (AP) of the central aortic pressure is a manifestation of early wave reflection and is the boost of pressure from the first systolic shoulder to the systolic pressure peak.[6] Augmentation is calculated as the difference between the second and the first systolic shoulder of the central pressure wave curve, and the augmentation index is expressed as the percentage of AP from total pulse pressure (**Figure 1**). Because Aix is influenced in an inverse and linear manner by heart rate, according to Wilkinson *et al.*,[20] the Aix was normalized for a heart rate of 75 bpm (Aix@75). Higher values of Aix indicate increased wave reflection from periphery or earlier return of the reflected wave as a result of increased pulse wave velocity, which can be contributed to an increased arterial stiffness. Lower values for Aix indicate a good elasticity of the arterial wall.

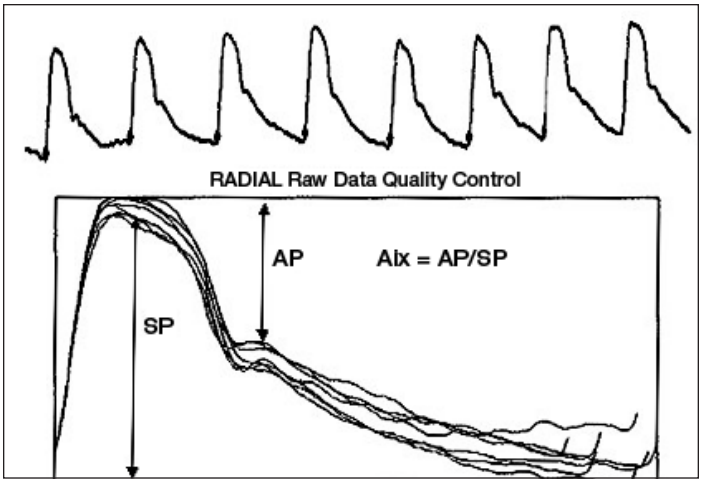

Figure 1. Pulse wave analysis: Calculation of augmentation (AP) and augmentation index (Aix) from superimposed sequential pulse (SP) waves.

All PWA recordings were performed on a subject lying in a quiet room after a rest of at least 5 minutes. Recordings were performed by one of two trained investigators.

Only high-quality recordings, controlled by internal quality definitions (in-device quality index >80%) and an acceptable curve by visual inspection, were included in the analysis.

Statistics

All results are presented as mean±1 SD and as the number/proportion of patients with a characteristic for categorical variables. Differences in mean values among the three groups were compared by using unpaired *t* tests. The Shapiro–Wilk test was used for the characterization of data distribution. All analyses were performed in exploratory and nonconfirmatory settings and all *p* values <0.05 are interpreted as significant.

Results

As shown in **Figure 2**, AP was increased both in patients with DM with 10.21±6.97 mm Hg and in cardiovascular risk patients without diabetes (CV) with 10.74±5.29 mm Hg compared to healthy controls (C) with 6.59±3.97 mm Hg ($p < 0.0005$ DM vs C; $p < 0.00005$ CV vs C).

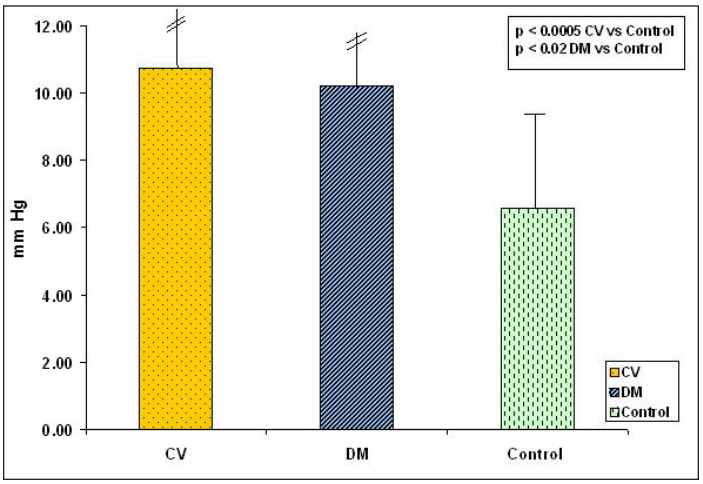

Figure 2. Augmentation in cardiovascular risk patients (CV), patients with diabetes mellitus type 2 (DM), and healthy controls.

The augmentation index in CV subjects (26.00±9.91%) compared to healthy controls (19.84±9.37%) was increased significantly ($p < 0.02$ CV vs C). The augmentation index was also increased in patients with DM (21.12±11.21%), but failed statistical significance ($p = 0.5$) (**Figure 3**).

No difference was found between cardiovascular risk patients and diabetic patients, neither in AP ($p = 0.56$) nor in Aix ($p = 0.2$).

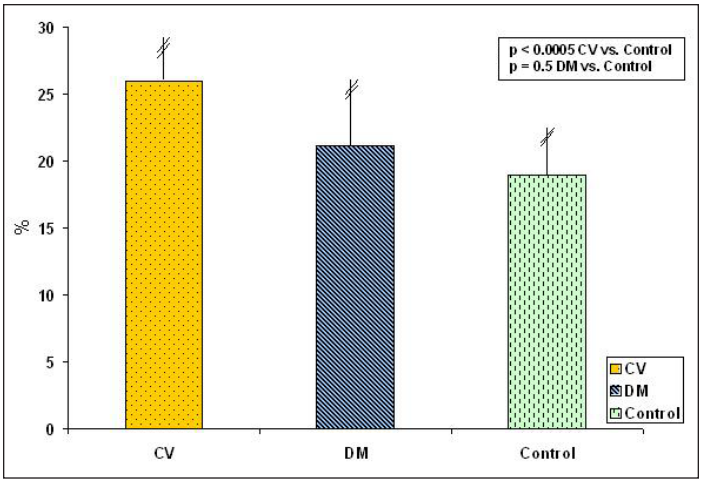

Figure 3. Augmentation index (Aix@75) in cardiovascular risk patients (CV), patients with diabetes mellitus type 2 (DM), and healthy controls.

Discussion

The main finding of our study is that subjects with type 2 diabetes have a comparable increased arterial stiffness (compared to healthy controls) as subjects with increased cardiovascular risk and no diabetes. In the Hoorn study, an increased augmentation index in patients with type 2 diabetes mellitus was found to be independent of other potential confounders, such as age, sex, or mean arterial blood pressure.[15] Moreover, an increased pulse pressure, measured noninvasively by PWA, was associated with increased cardiovascular mortality in these patients.[21] Even in patients with an impaired glucose tolerance, the augmentation index was higher compared to healthy controls.[15] These findings demonstrate the destructive effect of metabolic disturbances on the vascular wall even in subjects not already defined as having diabetes. The relationship between measured arterial stiffness and type 2 diabetes and cardiovascular disease suggests that impairment in glucose metabolism or reduced vascular insulin sensitivity might cause functional and/or anatomical changes in the arterial wall. These changes might be due to alterations in elastin and collagen fibers caused by glycation of proteins and formation of advanced glycation end products.[22] Other studies have revealed an independent association between an increased augmentation index as a marker for arterial stiffness and the presence and severity of coronary heart disease.[13,14] Findings of the aforementioned studies confounded our results of increased arterial stiffness measured by PWA in patients with diabetes mellitus type 2 and in subjects with increased cardiovascular risk but without diabetes. There was no significant difference between patients with diabetes and cardiovascular diseases, suggesting that diabetes mellitus type 2 causes similar changes in arterial elasticity as cardiovascular diseases. This finding is in accordance

with epidemiological studies showing a comparable risk for cardiovascular end points such as myocardial infarction and stroke in patients with type 2 diabetes compared with patients suffering from coronary artery disease.[23] The same method has been used previously in type 2 diabetic patients[15] and in type 1 diabetes.[24] The main topic of our study was to compare this method in diabetic and nondiabetic patients at cardiovascular risk, whereas in the cited paper of Schram *et al.*,[15] patients with diabetes type 2 or impaired glucose tolerance were investigated.

There are some limitations of our study. The healthy controls were slightly younger than the cardiovascular and diabetic patients. Although it is generally supposed that arterial stiffness increases with increasing age, a previous study did not detect age as a confounder for the augmentation index in patients with diabetes or cardiovascular risk.[13] Moreover, the CV subjects received vasodilating drugs such as nitrates, angiotensin-converting enzyme inhibitors, and calcium channel blockers to a greater extent than the other groups did; these drugs all decreased the augmentation index.[24] If these drugs had been withdrawn, then the difference in AP or Aix between CV patients and controls might have been even more pronounced.

In conclusion, arterial stiffness in type 2 diabetic patients is increased comparable to that in patients with cardiovascular disease who do not have diabetes. Our findings of a comparable restriction in arterial elasticity in type 2 diabetic subjects and nondiabetic cardiovascular risk subjects highlight the significance of early metabolic alterations in the pathophysiology of arteriosclerosis. This noninvasive measurement of augmentation or the augmentation index would be a valuable tool for risk characterization in these patient populations because these measures appear to be surrogate measures of atherosclerosis.

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