



Vascular characteristics in patients with resistant hypertension and type-II-diabetes mellitus

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Abstract *Background:* Resistant hypertension is presumed to be common in patients with type-II-diabetes mellitus (type-II-DM) and arterial stiffness has been proposed to play a major role in the development hereof. Our objective with this study was to examine differences in vascular characteristics in patients with controlled (CH), uncontrolled (UH) and resistant hypertension (RH) and type-II-DM and to assess whether increased arterial stiffness could explain the prevalence of resistant hypertension.

Methods and results: Vascular characteristics were examined using ambulatory blood pressure measurements, applanation tonometry and cardiac ultrasound. We estimated carotid-to-femoral pulse wave velocity using Sphygmocor. Characteristic impedance, arterial resistance, arterial compliance and augmentation index was estimated from analysis of pressure- and flow-curves. Finally ambulatory arterial stiffness index was estimated using ambulatory blood pressure measurements. We included 114 patients in the study of whom 39 had RH. When compared to patients with CH, patients with RH had increased pulse wave velocity (10.8 m/s [8.78; 12.23] versus 8.55 m/s [7.55; 10.6], $P = 0.002$) and reduced total arterial compliance (0.81 ml/mmHg [0.55; 0.95] versus 0.93 ml/mmHg [0.68; 1.36], $P = 0.03$) however differences were non-significant when adjusted for blood pressure ($P = 0.2$ and $P = 0.2$) Following statistical adjustment patients with UH had increased total arterial resistance though as compared to patients with CH (1.63 mmHg/ml*s⁻¹ [1.37; 1.92] versus 1.38 mmHg/ml*s⁻¹ [1.2; 1.71]) ($P = 0.03$).

Conclusion: In the present study patients with RH and type-II-DM do not have increased intrinsic arterial stiffness when compared to patients with CH, thus we conclude that increased

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intrinsic arterial stiffness is not the cause of resistant hypertension in the present study.
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Background

Prevalence of cardiovascular disease is markedly increased in patients with type-II-diabetes mellitus (type-II-DM) when compared to non-diabetics and more than 60% of all deaths in patients with type-II-DM are due to cardiovascular disease.¹

Prevalence of hypertension among patients with type-II-DM is almost three times higher than among non-diabetics.^{2,3} In addition the prevalence of resistant hypertension (RH) is also presumed to be high in patients with type-II-DM.^{1,4,5} Although the exact mechanism behind RH is unknown it has been proposed to be due to increased stiffness of the arterial system in patients with type-II-DM, as patients with type-II-DM have been found to have increased arterial stiffness, when compared to matched individuals without type-II-DM.^{6,7} With increasing age the arterial wall undergoes structural and functional changes, whereby stiffness of the arterial wall increases.⁸ In patients with type-II-DM biochemical changes, such as i.e. increased levels of advanced glycosylated end-products and increased blood levels of aldosterone, leads to an earlier vascular aging of the vessel wall, thereby increasing arterial stiffness.^{9,10}

Measurements of arterial stiffness have gained increased attention over the last decades and several methods for estimating arterial stiffness have been proposed. Increased carotid-to-femoral pulse wave velocity (c-f-PWV) has been shown to be an independent predictor of cardiovascular disease and was added to the 2007 guidelines from the European Society of Hypertension.¹¹

The present study set out to examine differences in estimates of arterial stiffness in patients with type-II-DM divided into groups with controlled (CH)-, uncontrolled (UH)- and RH, and to assess whether increased arterial stiffness could explain the prevalence of RH.

Methods

Study population

Patients were screened consecutively from the diabetes out-patient clinic at Odense University Hospital, Svendborg Hospital from the 1st of July 2009 until the 1st of July 2010.

Patients between 18 and 80 years of age with type-II-DM and hypertension were eligible for inclusion. All patients had to provide written informed consent. Lack of informed consent, atrial flutter or -fibrillation, plasma creatinine above 200 $\mu\text{mol/L}$, secondary hypertension and known non-compliance were exclusion criteria.

The study was approved by the ethics committee of the Region of Southern Denmark and conducted in agreement with the latest revision of the Helsinki declaration.¹² All patients provided written informed consent.

All examinations were performed by the same operator.

Blood pressure measurement

Clinic blood pressure (BP) measurements were performed using Omron model HEM-757 (Omron Healthcare, Netherlands) according to guidelines¹³ and ambulatory BP measurement (ABPM) was performed using Kivex TM 24302430 (Kivex, Hoersholm, Denmark) and Spacelab 90217 (Spacelabs Healthcare, Washington, US) devices.¹⁴ Devices were calibrated at the beginning of the study and thereafter every six months (Omron clinic device) or once a year (Kivex and Spacelab ABPM devices) according to manufacturer's instructions. Cuff size was chosen according to guidelines. For repeated measures patients always had their ABPM measured using the same device. Both devices were preprogrammed to measure with intervals of 15 min from 7AM to 11PM and 30 min from 11PM to 7PM. An ABPM was considered successful when there were at least 14 daytime readings and 7 nighttime readings according to guidelines from ESH and when number of successful readings was $\geq 70\%$.¹⁴

Patients were characterized as having CH, UH or RH based on their ABPM BP and number of antihypertensive agents. RH was defined as uncontrolled BP (ABPM BP $> 130/80$ mmHg) on three or more antihypertensive agents, or controlled BP (ABPM BP $\leq 130/80$ mmHg) on four or more antihypertensive agents, of which one should ideally be a diuretic.⁴ CH was defined as blood pressure of $\leq 130/80$ mmHg on ≤ 3 antihypertensive agents.^{4,11} Thus UH was defined as ABPM BP of $> 130/80$ mmHg on less than three antihypertensive agents. ABPMs were used for classification of RH in order to avoid overestimation of the prevalence of RH due to white-coat-hypertension. Adherence to therapy was examined via endorsed prescriptions. It was assumed that if the patient had bought the prescribed antihypertensive agent, then the patient also took the medicine. Patients that were found to be non-compliant were excluded from data analysis.

Ambulatory arterial stiffness index (AASI) was calculated as 1-regression slope of diastolic on systolic BP measurements.¹⁵ We did not differentiate between daytime and nighttime AASI.

Pulse wave analysis

C-f-PWV was measured using Sphygmocor (Atcor Medical, Sydney, Australia) under standardized examinations conditions as recommended.¹⁶ Furthermore patients did not take their morning medication on the day of examination. We used the subtracted distance measurement for estimation of aortic length (length from the suprasternal notch to the site of measurement over the femoral artery minus the length from the site of measurement over the carotid artery to the suprasternal notch). BP was measured prior to measurement of PWV after the patient had rested for

15 min. This BP value was used for statistical adjustment of PWV measurements. PWV measurement was performed twice. If the measurements differed more than 10% further measurements were performed. The mean value of the two most reproducible measurements was used. Patients in which it was not possible to perform measurement of PWV were excluded from analysis.

The central pressure wave was estimated using the generalized transfer function in the Sphygmocor device. Brachial BP was measured prior to performance of pulse wave analysis. Sphygmocor was calibrated using brachial diastolic and mean arterial pressure (MAP), as there might be an underestimation of central BP when calibrating with systolic and diastolic BPs. MAP was estimated using the 40% pulse pressure method.^{17,18} Radial tonometry was performed following measurement of PWV. Tonometry was performed twice. The pressure wave was accepted when the operator index was above 80 and the pressure wave with the highest operator index was chosen for further analysis. Analysis of the pressure wave was done offline in customized software written in Matlab (Mathworks, Massachusetts, USA).^{19,20}

Echocardiography

Echocardiography was performed to obtain flow profiles throughout the left ventricular outflow tract (LVOT). We used GE Vivid 7 (GE Healthcare, Europe) and a 3.5 MHz probe. LVOT flow measurements were performed from a five chamber view, placing a pulsed wave Doppler sample above the level of the aortic valve. An insonation angle of $<30^\circ$ was accepted. The flow-curves were processed offline in customized software written in Matlab.

Blood samples

Patient had blood samples drawn on the day of examination. These were analyzed for HbA1c, lipid profile and electrolytes.

Analysis of pressure and flow waves

Using dedicated software written in Matlab the pressure and flow waves were visually aligned using 1) the rapid systolic upstroke of pressure and flow and 2) the dicrotic notch in the pressure signal and cessation of flow as reference points. Characteristic impedance was assessed in the frequency domain by averaging the modulus of 3rd to 10th harmonic using Fourier transform. Total arterial resistance was estimated as the modulus of input impedance at 0 Hz, whereas total arterial compliance was estimated using the pulse pressure method based on a 2-element Windkessel model. The reflection coefficient was estimated from characteristic impedance and was reported as the real part of the amplitude of the fundamental frequency. Augmentation index (AIx) was estimated as the amplitude of second systolic peak divided by the amplitude of the first systolic peak using the 4th derivative of the pressure signal to identify the characteristic point on the pressure wave.²⁰

Statistical analysis

Statistical analysis was performed using Stata11 (Statacorp LP, USA). Data were expressed as medians and interquartile ranges because of asymmetrical distribution. Linear regression was used to assess differences in patient characteristics and estimates of arterial stiffness between groups. Data were transformed using the ladder function, which suggests the best transformation, and residual plots were employed to test for normal distribution of data after transformation. Adjustment for covariates with the dependent variable being hypertension groups (CH, UH and RH) was done using stepwise backwards multiple linear regression on transformed data. Covariates selected for inclusion in the model were those significant in univariate regression analysis. Covariates tested were sex, age, duration of diabetes, smoking habits, height, weight, plasma creatinine, urine albumin-creatinine ratio, antihypertensive agents, heart rate and mean arterial pressure. MAP used for statistical adjustment was calculated from measurement of BP performed immediately before measurement of PWV. Testing which model was the least complicated was carried out using likelihood-ratio test. Linear regression was used to examine correlation between estimates of arterial stiffness. A *P*-value of <0.05 was considered statistically significant.

Results

In total 310 patients were screened for eligibility and 180 patients provided informed consent and were included from the 1st of July 2009 until 1st of July 2010. Baseline measurements were not obtained in 16 patients due to exclusion criteria and withdrawal of consent, and in 50 patients quality of the pulse wave analysis was too poor (operator index below 80) leaving 114 patients for analysis. None of these patients were found to be non-compliant.

Patients who were excluded or withdrew consent did not differ from patients included in the study with regards to demographics.

Patients with CH, UH and RH were comparable with the exception of body-weight, P-Creatinine, BPs and antihypertensive treatment (Table 1). Patients with UH and RH had significantly higher clinic and ambulatory BP when compared to patients with CH, and patients with RH were treated with significantly more antihypertensive agents when compared to patients with CH and UH.

Vascular characteristics

As shown in Table 2 c-f-PWV was higher in patients with RH than in patients with UH and CH. We used a backwards stepwise regression model (Table 3) including in the full model age, duration of diabetes, height, weight, smoking habits, exercise, heart rate, creatinine, sex, MAP and antihypertensive medication (diuretics, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), aldosterone antagonists, renin inhibitors, beta-blockers, calcium channel blockers (CCBs), imidazole antagonists, alpha-blockers). This model did not show any statistically significant differences in c-f-PWV between

Table 1 Patient characteristics. Values are reported as medians and interquartile ranges. *P*-values describe differences between groups of CH and UH and between CH and RH.

Variable	Whole sample population (<i>N</i> = 114)	Controlled hypertension (<i>N</i> = 37)	Uncontrolled hypertension (<i>N</i> = 38)	Resistant hypertension (<i>N</i> = 39)
Age (years)	63 [56; 67]	64 [56; 68]	59 [55; 67]	63 [58; 67]
Males, <i>N</i> (%)	79 (69%)	22 (60%)	27 (71%)	30 (79%)
Height (cm)	175 [166; 180]	176 [165; 179]	175 [167; 181]	174 [166; 178]
Weight (kg)	95 [87; 110]	95 [86; 105]	94 [87; 104]	103 [89; 122] ^a
Hip-waist-ratio	1.04 [1; 1.09]	1.04 [1.; 1.1]	1.04 [1; 1.1]	1.03 [0.98; 1.08]
Duration of diabetes (years)	10 [6; 15]	8 [5; 15]	10 [7; 15]	10 [8; 15]
HbA1c (%)	7.3 [6.9; 8.4]	7.3 [6.8; 7.9]	7.3 [6.9; 8.5]	7.2 [6.9; 8.7]
Creatinine (μmol/L)	74 [62; 93]	72 [62; 82]	69 [60; 86]	84 [67; 106] ^a
Increased urinary albumin/creatinine ratio <i>N</i> (%)	36 (32%)	9 (24%)	11 (29%)	16 (41%)
Peripheral systolic blood pressure (clinic) (mmHg)	142 [132; 153]	137 [127; 142]	142 [133; 158] ^a	149 [141; 161] ^a
Peripheral diastolic blood pressure (clinic) (mmHg)	87 [79; 93]	84 [77; 91]	89 [78; 94] ^a	87 [79; 93] ^a
Peripheral systolic blood pressure (ABPM) (mmHg)	135 [126; 142]	123 [118; 128]	140 [135; 150] ^a	139 [132; 145] ^a
Peripheral diastolic blood pressure (ABPM) (mmHg)	75 [70; 81]	71 [66; 75]	81 [76; 84] ^a	75 [70; 79] ^a
Non-dippers <i>N</i> (%)	63 (60%)	22 (60%)	16 (42%) ^a	25 (64%)
Heart rate (ABPM) (bpm)	75 [66; 82]	73 [66; 80]	77 [74; 83] ^a	69 [64; 81]
Number of antihypertensive agents	2 [2; 3]	2 [1; 3]	2 [1; 2]	4 [3; 4] ^a
Diuretics <i>N</i> (%)	75 (70%)	24 (65%)	17 (45%)	34 (87%) ^a
ACE-inhibitors <i>N</i> (%)	61 (54%)	18 (49%)	18 (47%)	25 (64%)
Angiotensin-receptor blockers <i>N</i> (%)	43 (38%)	11 (30%)	14 (37%)	18 (46%)
Aldosterone antagonists <i>N</i> (%)	7 (6%)	2 (5%)	0 (0%)	5 (13%)
Calcium channel blockers <i>N</i> (%)	51 (45%)	10 (27%)	9 (24%)	32 (82%) ^a
Beta blockers <i>N</i> (%)	37 (33%)	7 (19%)	5 (13%)	25 (64%) ^a

^a Indicates *P* < 0.05.

patients with CH and RH (*P* = 0.36). Using likelihood-ratio test the least complicated and final statistical model was found to include age, weight, smoking habits, heart rate, creatinine and the use of ACE-Is and revealed a statistical significant difference between patients with CH and RH (*P* = 0.005). As c-f-PWV is recommended to always be adjusted for sex and MAP even if sex and MAP are not found to be of significance in the regression model^{16,21} we did so.

When adjusted for sex the difference between patients with CH and RH was still significant (*P* = 0.007), however when adjusted for MAP the difference lost significance (*P* = 0.2). We found a weak although statistically significant correlation between PWV and MAP (*R*² = 0.12, *P* < 0.0001).

To examine the influence of arterial stiffness on BP we tried adjusting pulse pressure (PP) for different arterial

Table 2 Vascular characteristics in patients with CH, UH and RH. Values are reported as medians and interquartile ranges. *P*-values describe differences between groups of CH and UH and between CH and RH. *P*-values are reported adjusted.

Variable	Controlled hypertension	Uncontrolled hypertension	Resistant hypertension
Pulse wave velocity (m/s)	8.55 [7.55; 10.6]	9.38 [8.15; 10.9]	10.8 [8.78; 12.23]
Characteristic impedance (frequency domain) (mmHg/(ml/s))	0.07 [0.05; 0.1]	0.08 [0.06; 0.11]	0.1 [0.07; 0.13]
Total vascular resistance (mmHg/(ml/s))	1.38 [1.2; 1.71]	1.63 [1.37; 1.92] ^a	1.53 [1.34; 1.87]
Total vascular compliance (ml/mmHg)	0.93 [0.68; 1.36]	0.8 [0.61; 95]	0.81 [0.55; 0.95]
Reflection coefficient	0.52 [0.45; 0.63]	0.54 [0.47; 0.62]	0.56 [0.47; 0.6]
Augmentation index (%)	140 [135; 151]	147 [134; 154]	142 [134; 161]
Ambulatory arterial stiffness index (AASI)	0.57 [0.45; 0.67]	0.61 [0.49; 0.7]	0.56 [0.48; 0.66]

^a Indicates *P* < 0.05.

Table 3 Variables entered and retained in regression of c-f-PWV in hypertension groups showing differences between patients with CH and RH.

Variable entered (Inverse square root transformation)	β	SE	<i>t</i>	<i>P</i>	R^2
Age	−0.03	0.01	−3.17	0.02	0.14
Weight	−0.02	0.01	−2.51	0.01	0.25
Smoking habits	−0.03	0.01	−3.07	0.003	0.09
Heart rate	−0.03	0.01	−2.97	0.004	0.11
Creatinin	−0.03	0.01	−2.82	0.01	0.16
ACE-I's	−0.04	0.01	−3.74	<0.001	0.2

stiffness parameters. Adjusting PP for sex, age, height and weight we found a R^2 of 0.16 for the model, and adding c-f-PWV to this statistical model R^2 increased to 0.24. Further adding of characteristic impedance, compliance and resistance to the model increased R^2 to 0.35.

In agreement with c-f-PWV total arterial compliance was reduced in patients with RH (Table 2) following statistical adjustment for sex, age, weight, smoking habits and heart rate ($P = 0.03$), however with inclusion of MAP in the statistical model this difference too lost significance ($P = 0.24$). Total arterial resistance however was significantly increased in patients with UH also following adjustment for sex, heart rate and PP ($P = 0.03$).

There were no significant differences in characteristic impedance, reflection coefficient, augmentation index or AASI between hypertension groups (Table 2).

Discussion

Several studies have shown that patients with type-II-DM and/or hypertension have increased arterial stiffness measured as c-f-PWV^{6,22,23} and it has been suggested that the prevalence of RH is related to increased arterial stiffness.²⁴

In the present study measures of arterial stiffness did not differ between patients with CH, UH and RH, when the effect of BP was taken into account. This is in contrast to previous suggestions and findings.²⁴ Three recent studies have reported an increased c-f-PWV in patients with UH or RH, when compared to patients with CH or normotension.^{25–27} In the study by Pabuccu et al. measures of c-f-PWV however has not been statistically adjusted for MAP. In the present study we too found that c-f-PWV was significantly higher in patients with RH and borderline significantly higher in patients with UH as compared to patients with CH when MAP was not included as a confounder in the statistical model. We also found, that patients with UH and RH had significantly reduced arterial compliance, however this difference also lost significance with inclusion of MAP in the statistical model.

Both c-f-PWV and compliance would expectedly be affected by increasing BP (c-f-PWV increased and compliance reduced) because of increased transmural pressure. As such it seems warranted to adjust c-f-PWV for MAP in

order to draw conclusions with regards to the intrinsic stiffness of the arterial wall.

In the study by Salles et al. statistical adjustment of c-f-PWV for MAP was done using MAP obtained from ABPM. Although we do acknowledge that measures of BP obtained from ABPMs better reflect the cardiovascular risk of the patient, it does however not reflect the transmural pressure at the time of c-f-PWV measurement. Thus it seems warranted that the BP used for statistical adjustment should be one obtained immediately before measurement of c-f-PWV.

In the study by Figueiredo et al. who also found that PWV was significantly higher in patients with RH as compared to patients with CH and normotension statistical adjustment for MAP had been done. The study however is not directly comparable to the present study as patients with i.e. diabetes mellitus were excluded from their population. Although our finding, that intrinsic stiffness was not higher in patients with RH, was supported by the fact that characteristic impedance (less dependable on transmural pressure) was not significantly higher in patients with RH as compared to those with CH, it might be that our results are not directly transferable to a general hypertension population. It could be that patients with type-II-DM develop RH due to other mechanisms than other specific populations. I.e. we found that only 19% of the differences in BP could be explained by differences in arterial stiffness in this population.

It has previously been shown that patients with RH and type-II-DM have increased levels of circulating catecholamines²⁸ as well as it has been suggested that there is an increased prevalence of primary hyperaldosteronism in these patients.^{9,28} As total arterial resistance is primarily determined by changes in diameter of vessels and blood viscosity, and increased blood levels of catecholamines and aldosterone would cause vasoconstriction, this could lead to increased arterial resistance. Total arterial resistance usually lies between 0.54 and 1.2 mmHg/ml*s^{−1} and total arterial resistance in all patients in the present study lie above this value.

Finally total arterial resistance was significantly increased in patients with UH, however significantly more patients with RH were treated with CCBs, which are known to decrease total arterial resistance. CCBs did not turn out to be associated with total arterial resistance in the statistical model, and adjusting for CCBs statistically did not change the statistical outcome. Although speculative it seems likely though, that patients with RH would have even higher total arterial resistance, if the effect of CCBs could be removed and this could support the theory that many patients with RH have increased blood levels of catecholamines and aldosterone, as well as it could support the finding, that aldosterone antagonists have a substantial treatment effect in patients with RH.²⁹

Limitations

There are several limitations to the present study with the most important being a small sample size of the different hypertension groups, a high median age of the sample population and the fact that we cannot precisely evaluate

the different effects of antihypertensive agents due to individual treatment regimens. Furthermore we cannot with certainty state that the assumption made, that patients who endorse their prescriptions are compliant, is valid.

Several types of antihypertensive agents have been found to influence both c-f-PWV and wave reflections. In the statistical analysis we chose only to test antihypertensive agents for statistical significance, as well as we chose only to adjust for those agents that turned out to be of statistical significance in the model. As such we did not adjust for different types of anti-diabetic medication or statins. The reason for this approach was that most antihypertensive medication have been shown to decrease c-f-PWV and other estimates of arterial stiffness, which in theory could mean, that if the effect of these drugs could be totally eliminated from the measurements, the difference between the hypertension groups could become more pronounced, as especially patients with RH were treated with significantly more antihypertensive agents than patients with CH. However it is not clear whether the reduction in c-f-PWV reported for antihypertensive agents is pressure independent.

Conclusion

In the present study patients with RH do not have an increased intrinsic arterial stiffness as compared to patients with CH. We found that the increased c-f-PWV and reduced compliance in patients with RH was due to higher BP, and when examining a less load dependent measure of arterial stiffness (characteristic impedance), we found no differences between patients with CH and RH. We did however find that total arterial resistance was significantly higher in patients with UH and we speculate whether RH in the present study might be due to higher total arterial resistance and not increased intrinsic arterial stiffness in these patients.

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