

RESEARCH

Open Access



The characteristics of elevated blood pressure in abdominal obesity correspond to primary hypertension: a cross-sectional study

Jyrki Taurio¹, Elina J. Hautaniemi², Jenni K. Koskela^{1,2}, Arttu Eräranta², Mari Hämäläinen³, Antti Tikkakoski^{2,4}, Jarkko A. Kettunen², Mika Kähönen^{2,4}, Onni Niemelä^{2,5}, Eeva Moilanen³, Jukka Mustonen^{1,2} and Ilkka Pörsti^{1,2*}

Abstract

Background Obesity-related hypertension and the associated metabolic abnormalities are considered as a distinct hypertensive phenotype. Here we examined how abdominal fat content, as judged by waist:height ratio, influenced blood pressure and hemodynamic profile in normotensive subjects and never-treated hypertensive patients.

Methods The 541 participants (20–72 years) underwent physical examination and laboratory analyses and were divided into age and sex-adjusted quartiles of waist:height ratio. Supine hemodynamics were recorded using whole-body impedance cardiography, combined with analyses of radial tonometric pulse wave form and heart rate variability.

Results Mean waist:height ratios in the quartiles were 0.46, 0.51, 0.55 and 0.62. Radial and aortic blood pressure, systemic vascular resistance, pulse wave velocity, markers of glucose and lipid metabolism, leptin levels and C-reactive protein were higher in quartile 4 when compared with quartiles 1 and 2 ($p < 0.05$ for all). Cardiac index was lower in quartile 4 versus quartile 1, while no differences were seen in heart rate variability, augmentation index, plasma renin activity, and aldosterone concentration between the quartiles. Linear regression analyses showed independent associations of abdominal obesity with higher aortic systolic and diastolic blood pressure, systemic vascular resistance, and pulse wave velocity ($p < 0.05$ for waist:height ratio in all regression models).

Conclusion Higher waist:height ratio was associated with elevated blood pressure, systemic vascular resistance, and arterial stiffness, but not with alterations in cardiac sympathovagal modulation or activation of the circulating renin-angiotensin-aldosterone system. Although obesity-related elevation of blood pressure has distinct phenotypic features, these results suggest that its main characteristics correspond those of primary hypertension.

Trial registration ClinicalTrials.gov NCT01742702 (date of registration 5th December 2012).

Keywords Abdominal obesity, Hypertension, Hemodynamics, Impedance cardiography, Pulse wave analysis

*Correspondence:

Ilkka Pörsti
ilkka.porsti@tuni.fi

¹Department of Internal Medicine, Tampere University Hospital, Tampere, Finland

²Faculty of Medicine and Health Technology, Tampere University, FI-33014 Tampere, Finland

³The Immunopharmacology Research group, Faculty of Medicine and Health Technology, Tampere University and Tampere University Hospital, Tampere, Finland

⁴Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland

⁵Laboratory and Medical Research Unit, Seinäjoki Central Hospital, Seinäjoki, Finland



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Background

Obesity is a major global health risk, and the prevalence of obesity has doubled since 1980 [1]. In 2015, high body mass index (BMI) was estimated to account for 4 million deaths predominantly from cardiovascular diseases [1]. BMI has been the gold standard in the estimation of excess body fat, but it does not discriminate between fat and fat-free mass, which may lead to flawed results on body composition [2]. In 1996, Ashwell et al. reported that the correlation between tomography-measured intra-abdominal fat with BMI was 0.69, but for waist:height ratio (WHtR) the correlation was 0.83 ($p < 0.001$ for the difference). WHtR was concluded to be the better anthropometric predictor of intra-abdominal fat in both sexes [2]. High waist circumference that indicates excess abdominal fat content is also a predictor of future hypertension [3].

Excess visceral fat is associated with changes in glucose and lipid homeostasis that predispose to the development of hypertension [4]. Increased perivascular fat content and the associated changes in synthesis and release of adipokines may influence the recruitment of inflammatory cells in the vasculature, vascular smooth muscle proliferation, and the control of arterial tone [5]. Obesity related adipokines like leptin have been linked with several cardiovascular risk factors, but previous results about the association of leptin with arterial stiffness are inconsistent [6, 7]. Impaired endothelial function and increased arterial stiffness have been associated with obesity [8]. Elevated sympathovagal balance [9] and upregulation of the renin-angiotensin-aldosterone system (RAAS) [10] may also contribute to the cardiovascular changes in obesity. Obese subjects may have increased cardiac output, while systemic vascular resistance may be low in obese normotensives and normal or elevated in obese hypertensives [11].

Although the underlying mechanisms are not completely understood, elevated blood pressure (BP) in obese subjects is considered to have distinct phenotypic features [9, 12]. Obesity predisposes to impaired nocturnal BP dipping, increased prevalence of masked hypertension, higher exercise related increase in systolic BP, and treatment resistant hypertension [13]. However, when compared with essential hypertension, no definite instructions for the treatment of obesity-related hypertension in addition to weight reduction are included in the guidelines regarding e.g. the choices of antihypertensive medications [13].

To evaluate the hemodynamic features associated with abdominal obesity, we examined the influence of visceral fat content, defined as WHtR, on BP and hemodynamic profiles in normotensive and previously undiagnosed hypertensive subjects without

antihypertensive medications. Cardiac autonomic modulation was evaluated utilizing analyses of heart rate variability (HRV).

Methods

Study subjects

The participants were recruited as previously described [14, 15]. All underwent physical examination and laboratory analyses for elevated BP [16]. Medical history and lifestyle habits including alcohol consumption and smoking were documented. Subjects with a history of coronary artery disease, stroke, cardiac failure or valve disease, heart rhythm other than sinus, chronic kidney disease, diabetes, secondary hypertension, alcohol or substance abuse, and psychiatric illnesses other than mild depression or anxiety were excluded.

Altogether 541 participants, aged 20–72 years, without antihypertensive medications were included. They were divided into age-adjusted quartiles of WHtR separately for sexes. The following medications were regularly used by the participants with no significant differences between the quartiles of WHtR: female hormones (contraception, hormone replacement therapy, $n=67$), intra-uterine hormonal device for contraception ($n=29$), antidepressants ($n=25$), vitamin-D supplements ($n=31$), thyroxin ($n=16$), inhaled glucocorticoids ($n=14$), antihistamines ($n=12$), statins ($n=11$), proton pump inhibitors ($n=9$), nonsteroidal anti-inflammatory agents ($n=4$), anxiolytic agents ($n=4$), allopurinol ($n=2$), antiepileptics ($n=2$), coxibs ($n=2$), varenicline ($n=2$), gabapentin or pregabalin ($n=2$), warfarin ($n=1$).

Signed informed consent was obtained from all participants. The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Tampere University Hospital (study code R06086M) and the Finnish Medicines Agency (Eudra-CT registration number 2006-002065-39) and was registered in a database (ClinicalTrials.gov NCT01742702).

Laboratory analyses

Blood and urine samples were drawn after ~12 h of fasting. Concentrations of leptin and adiponectin in plasma samples were determined using enzyme-linked immunosorbent assay (DuoSet ELISA; R&D Systems Europe Ltd, Abingdon, United Kingdom). Interassay coefficient of variation was 4.0% for leptin and 3.9% for adiponectin. The other laboratory analyses were performed as described previously in detail [15, 17].

Experimental protocol

Hemodynamics were recorded as described previously [14, 15]. Electrodes for impedance cardiography placed on body surface, tonometric sensor on left radial pulsation, and oscillometric cuff to the right upper arm. The

left arm was fixed to 90 degrees in a support. Hemodynamic data was captured continuously for 5 min, and mean values of each 1-minute period were calculated. The good repeatability and reproducibility of the measurements has been demonstrated [14, 15].

Pulse wave analysis

As in our previous reports, radial pulse wave form was continuously captured using a tonometric sensor (Colin BP-508T, Colin Medical Instruments Corp., USA) [14, 16]. Aortic BP was derived with the SphygmoCor system (SphygmoCor PWMx, Atcor Medical, Australia) [18]. Aortic pulse pressure, augmentation index (AIx, augmented pressure/pulse pressure*100), AIx adjusted to heart rate 75/min (AIx@75), and central forward wave amplitude were determined [19]. Large arterial compliance was evaluated as the ratio of stroke volume to aortic pulse pressure [20].

Whole-body impedance cardiography

Whole-body impedance cardiography (CircMon^R, JR Medical Ltd., Tallinn, Estonia) was used to determine heart rate, stroke volume, cardiac output, pulse wave velocity (PWV), and extracellular water balance, as previously described [21–23]. Systemic vascular resistance was calculated from the tonometric BP and cardiac output by CircMon^R. Stroke volume, cardiac output and systemic vascular resistance were related to body surface area and presented as indexes – SI, CI, and SVRI, respectively. The measured stroke volume and cardiac output values are in good agreement with 3-dimensional echocardiography [15] and the thermodilution and direct oxygen Fick methods [21], and the recorded PWV values show good correlation with ultrasound and tonometric values [22, 24].

Frequency domain analysis of heart rate variability

Recorded electrocardiograms (sampling rate 200 Hz) were analyzed using Matlab (MathWorks Inc., Natick, Massachusetts, USA). Normal R-R intervals were recognized, and a beat was considered ectopic if the interval differed >20% from previous values. Artefacts were processed using cubic spline interpolation method, and the frequency domain variables were calculated using Fast Fourier Transformation: (i) power in low frequency (LF) range (0.04–0.15 Hz), (ii) power in high frequency (HF) range (0.15–0.40 Hz), and (iii) LF/HF ratio [25].

Statistics

Analysis of variance was applied for normally distributed variables and the Kruskal-Wallis and Mann-Whitney U-tests for non-normally distributed variables. The Bonferroni correction was applied in all post-hoc analyses. IBM SPSS Statistics Version 26 (IBM Corporation,

Armonk, NY, USA) was used. The mean hemodynamic values from the minutes 3–5 were used when the signal was most stable. The LF power, HF power, and LF/HF ratio were transformed to natural logarithm for statistics due to skewed distributions, and the analyses were adjusted for heart rate [26]. The participants were divided to age-adjusted quartiles (Q) of WHtR separately for sexes.

Stepwise linear regression analyses were used to investigate factors associated with aortic systolic and diastolic BP, SVRI, and PWV. Smoking was categorized (current smokers, previous smokers, never smokers) using two discrete variables, alcohol consumption using three discrete variables (category either 0 or 1); cut-points for women 0, 1–7 (low), 8–14 (moderate), and ≥ 15 doses per week (high); for men 0, 1–14, 15–24, and ≥ 25 doses per week, respectively, according to the Finnish Guidelines [27]. The regression analyses included age, sex, WHtR, smoking status, categorized alcohol intake; plasma leptin, adiponectin, C-reactive protein (CRP), triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, sodium, calcium, parathyroid hormone (PTH), uric acid, renin activity, aldosterone; quantitative insulin sensitivity check index (QUICKI) [28] and estimated glomerular filtration rate (eGFR) as independent factors. In the analyses of aortic systolic and diastolic BP the model also included PWV, and in analyses of PWV the model also included mean aortic blood pressure. $P < 0.05$ was considered significant.

Results

Study population and laboratory values

Mean weight, waist circumference, and BMI were different in all quartiles of WHtR (Table 1). The difference in adiposity was substantial, as BMI was 9.0 (0.3) kg/m² [mean (standard error)] higher in Q4 than in Q1. Mean BMI in the study participants was 26.8 (0.2) kg/m². The Spearman correlation between WHtR and BMI was 0.895. Average height was slightly lower in Q4 of WHtR than in Q1 (Table 1).

No differences were observed in the prevalence of smoking and average alcohol intake between the quartiles of WHtR. Office systolic BP was higher in Q3 than in Q1, and in Q4 than in Q2 and Q1 (Table 2). The difference in office systolic BP between Q4 vs. Q1 was 15 (3) mmHg. Office diastolic BP was highest in Q4, and higher in Q3 than in Q2 and Q1. The difference in office diastolic BP between Q4 vs. Q1 was 10 (1) mmHg. Extracellular water balance was lower in Q3 and Q4 than in Q1 (Table 1).

Average blood hemoglobin and plasma concentrations of sodium, potassium, and calcium were within the normal range in all quartiles (Table 2). Plasma PTH and CRP were highest in Q4, while uric acid was higher in Q3 and Q4 than in Q1 and Q2. Creatinine and cystatin

Table 1 Study participants shown in age adjusted quartiles (Q) of waist:height ratio

Variable	Q1 (n = 132)	Q2 (n = 137)	Q3 (n = 138)	Q4 (n = 134)	Range (all quartiles)
Male / Female	68 / 64	71 / 66	71 / 67	68 / 66	
Age (years)	44.7 (12.4)	45.4 (11.6)	45.8 (11.0)	45.4 (11.4)	20–72
Waist:height ratio	0.46 (0.04)	0.51 (0.04)*	0.55 (0.04)*†	0.62 (0.05)*††	0.38–0.76
Weight (kg)	70.6 (12.7)	76.5 (13.6)*	82.1 (12.2)*†	94.1 (15.0)*††	45–135
Waist circumference (cm)	80.2 (9.6)	88.4 (10.1)*	95.6 (8.4)*†	106.5 (10.1)*††	63.0–132.0
Body mass index (kg/m ²)	22.8 (2.5)	25.1 (2.5)*	27.4 (2.6)*†	31.9 (3.7)*††	17.9–42.1
Height (cm)	175.0 (10.0)	173.8 (9.6)	172.8 (8.2)	171.5 (9.0)*	150–203
Current smokers (%)	12	10	15	13	10–15
Alcohol (standard drinks/week)	2 [1–4]	2 [1–5]	2 [1–7]	3 [1–7]	0–42
Office systolic BP (mmHg)	134 (20)	137 (20)	142 (22)*	149 (20)*†	100–216
Office diastolic BP (mmHg)	85 (11)	86 (11)	90 (13)*†	95 (13)*††	54–135
Extracellular water balance	1.00 (0.09)	0.98 (0.10)	0.96 (0.09)*	0.97 (0.09)*	0.63–1.55

Results shown as mean (standard deviation) or median [25th–75th percentile]; * $P < 0.05$ vs. Q1; † $P < 0.05$ vs. Q2; †† $P < 0.05$ vs. Q3

Table 2 Clinical characteristics and laboratory results in age adjusted quartiles (Q) of waist:height ratio

Variable	Q1	Q2	Q3	Q4	Range (all quartiles)
Hemoglobin (g/l)	142 (12)	144 (12)	146 (11)	145 (12)	113–177
Sodium (mmol/l)	140.7 (2.0)	140.2 (2.1)	140.3 (1.9)	140.3 (1.9)	134–146
Potassium (mmol/l)	3.82 (0.27)	3.75 (0.26)	3.83 (0.26)	3.85 (0.30)†	3.2–4.9
Calcium (mmol/l)	2.30 (0.11)	2.29 (0.10)	2.32 (0.12)	2.30 (0.10)	2.07–2.74
Parathyroid hormone (pmol/l)	4.4 (1.7)	4.3 (1.4)	4.5 (1.6)	5.0 (2.1)*††	1.4–9.9
C-reactive protein (mg/l)	0.6 [0.5–1.0]	0.6 [0.5–1.3]	1.0 [0.5–1.7]*	1.9 [0.8–3.1]*††	0.1–17.9
Uric acid (μmol/l)	277 (73)	287 (72)	313 (76)*†	328 (77)*†	103–600
Creatinine (μmol/l)	76 (14)	75 (14)	74 (13)	71 (14)*	42–116
Cystatin C (mg/l)	0.82 (0.14)	0.82 (0.16)	0.86 (0.14)*	0.87 (0.13)*†	0.47–1.31
Estimated GFR (ml/min/1.73m ²)	102 (17)	102 (19)	97 (18)	96 (17)*	53–152
Leptin (ng/ml)	8.6 (8.5)	12.1 (9.2)	15.9 (12.8)*	28.0 (20.1)*††	0.2–92.3
Adiponectin (μg/ml)	4.3 (2.4)	3.9 (1.6)	3.4 (1.7)*	3.5 (1.7)*	0.5–18.2
Renin activity (ng Ang I/ml/h)	0.8 [0.5–1.3]	0.8 [0.4–1.3]	0.7 [0.4–1.3]	0.6 [0.4–1.1]	0.1–10.0
Aldosterone (pmol/l)	436 [306–636]	434 [329–581]	459 [338–595]	416 [304–539]	68–1704
Aldosterone:renin ratio	597 [398–791]	634 [383–884]	640 [430–948]	632 [389–979]	45–2701
Fasting plasma					
Total cholesterol (mmol/l)	4.9 (1.0)	4.9 (1.0)	5.3 (1.1)*†	5.4 (1.0)*†	2.5–9.0
Triglycerides (mmol/l)	0.9 [0.6–1.2]	1.0 [0.7–1.3]	1.1 [0.8–1.5]*	1.2 [1.0–2.0]*†	0.3–5.5
HDL cholesterol (mmol/l)	1.8 (0.5)	1.6 (0.4)*	1.5 (0.4)*	1.4 (0.4)*†	0.7–3.1
LDL cholesterol (mmol/l)	2.8 (0.9)	2.8 (0.9)	3.2 (0.9)*†	3.3 (0.9)*†	0.8–5.8
Insulin (mU/l)	6.0 (3.6)	6.9 (4.7)	8.2 (5.3)*	11.5 (7.9)*††	1.0–51.8
Glucose (mmol/l)	5.3 (0.5)	5.4 (0.5)	5.5 (0.5)*	5.7 (0.8)*††	4.1–7.5
QUICKI	0.380 (0.056)	0.366 (0.036)*	0.354 (0.032)*	0.338 (0.033)*††	0.268–0.740

Results shown as mean (standard deviation) or median [25th–75th percentile]; BP, blood pressure; estimated GFR, estimated glomerular filtration rate based on cystatin C (CKD-EPI) [45]; QUICKI, quantitative insulin sensitivity check index [28]; * $P < 0.05$ vs. Q1; † $P < 0.05$ vs. Q2; †† $P < 0.05$ vs. Q3

C concentrations presented with minor differences between the quartiles, while eGFR derived from cystatin C was slightly lower in Q4 than in Q1. Less than 4% of the subjects presented with values of the above variables that were outside the normal range (Table 2).

Plasma leptin concentration was clearly highest in Q4, and higher in Q3 than in Q1, while adiponectin was lower in Q3 and Q4 than in Q1. Plasma renin activity, aldosterone concentration, and aldosterone:renin ratio did not differ between the quartiles (Table 2).

Q3 and Q4 of WHtR had less favorable lipid profiles than Q1 and Q2. Plasma total cholesterol, LDL cholesterol, and triglycerides were above the normal range in 53%, 47%, and 15% of the subjects, respectively. Plasma HDL cholesterol was below the normal range in 9% of the subjects. Fasting plasma insulin and glucose were higher in Q3 than in Q1, while both insulin and glucose were highest in Q4. Insulin was above the normal range in 2% and glucose in 13% of the participants. Based on

QUICKI, insulin sensitivity was highest in Q1 and lowest in Q4 (Table 2).

Blood pressure, arterial stiffness, cardiac variables, and heart rate variability

Radial systolic and diastolic BP were elevated in Q4 when compared with Q1 and Q2 (Fig. 1A and B). Aortic systolic BP was higher in Q3 when compared with Q1, and aortic systolic and diastolic BP were higher in Q4 than in Q1 and Q2 (Fig. 1C and 1D). The difference in aortic systolic / diastolic BP between Q4 vs. Q1 was 11 (2) / 7 (2) mmHg.

Aortic pulse pressure and forward wave amplitude were higher in Q4 than in Q1 and Q2 (Fig. 2A and B). Evaluated aortic compliance (stroke volume to central pulse pressure ratio) was lower in Q4 than in Q1 and Q2

(Fig. 2C), while aortic to popliteal PWV was higher in Q4 than in Q1 and Q2, and in Q3 than in Q1 (Fig. 2D). The difference in PWV between Q4 vs. Q1 was 1.0 (0.2) m/s. No differences were observed in AIx or AIx@75 (Fig. 2E F).

Heart rate was higher in Q4 than in Q1 and Q2 (Fig. 3A), while SI was different in all other quartiles but not between Q2 and Q3 (Fig. 3B). CI was lower in Q4 than Q1 (Fig. 3C), while SVRI was higher in Q4 than in Q1 and Q2, and in Q3 than in Q1. The difference in SVRI between Q4 vs. Q1 was 391 (71) dyn*s/cm⁵*m² (Fig. 3D).

The HRV measurements consisted of LF and HF power and LF/HF ratio determinations (Fig. 4). No differences were observed between the quartiles in these analyses.

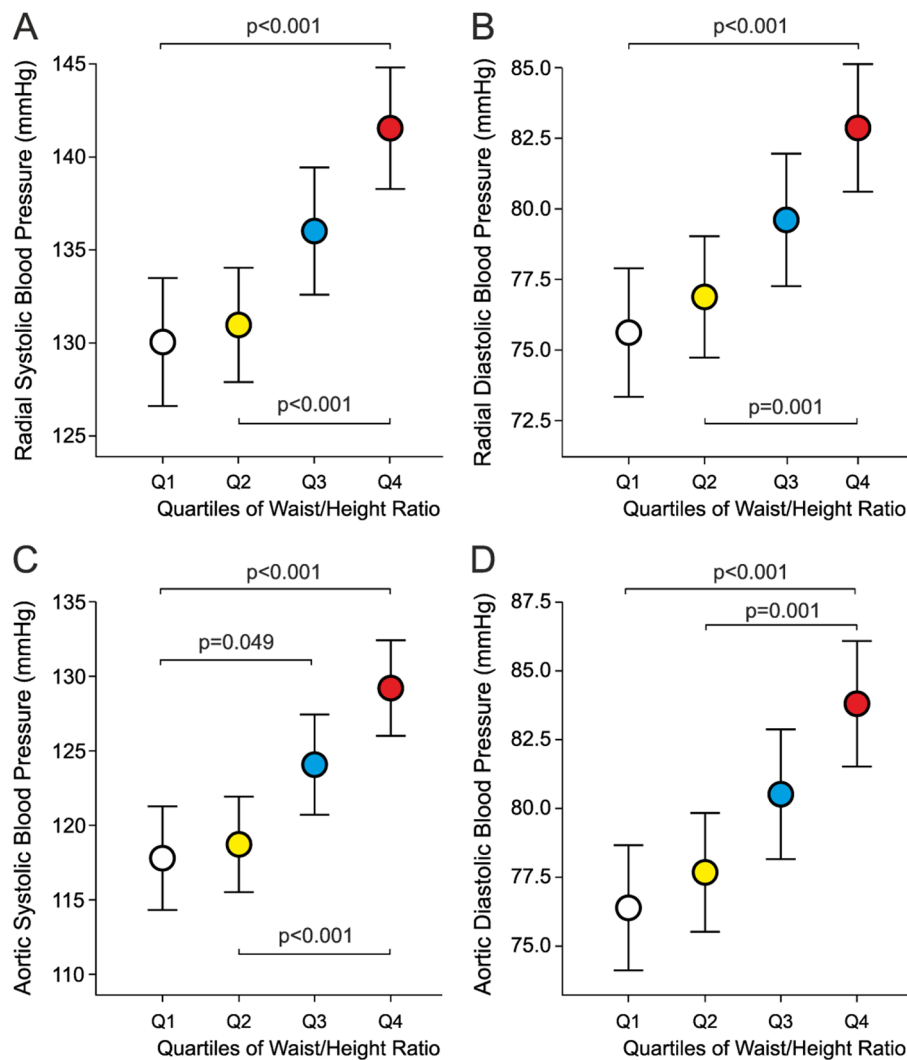


Fig. 1 Radial systolic (A) and diastolic (B) blood pressure, and aortic systolic (C) and diastolic (D) blood pressure during laboratory measurements in 541 subjects divided separately for sexes into age-adjusted quartiles of waist/height ratio; mean \pm confidence interval of the mean; significant differences shown between groups ($P < 0.05$)

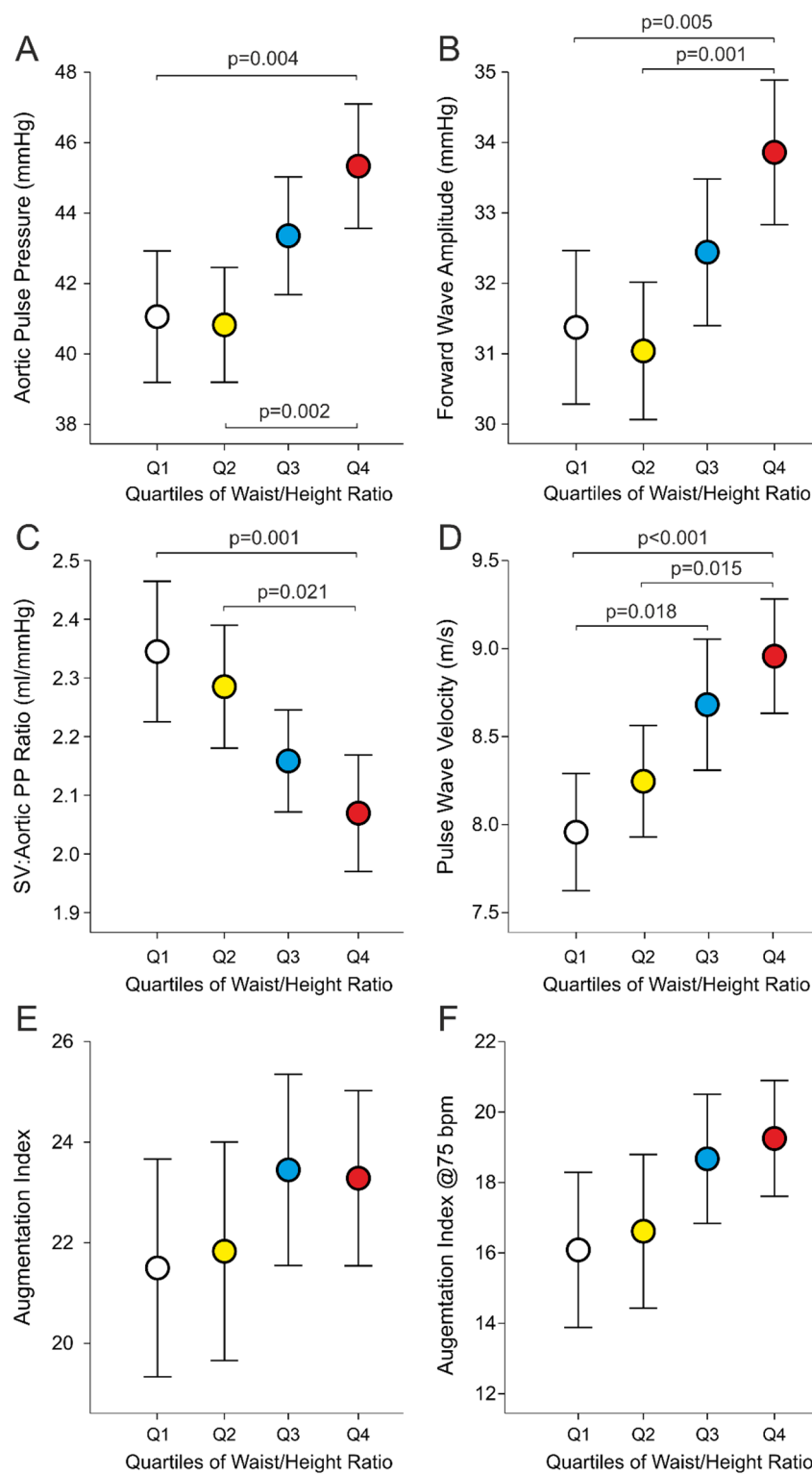


Fig. 2 Aortic pulse pressure (A), forward wave amplitude (B), stroke volume to aortic pulse pressure ratio (C), pulse wave velocity (D), augmentation index (E), and augmentation index adjusted to heart rate of 75 beats per minute (bpm) (F); statistics as in Fig. 1

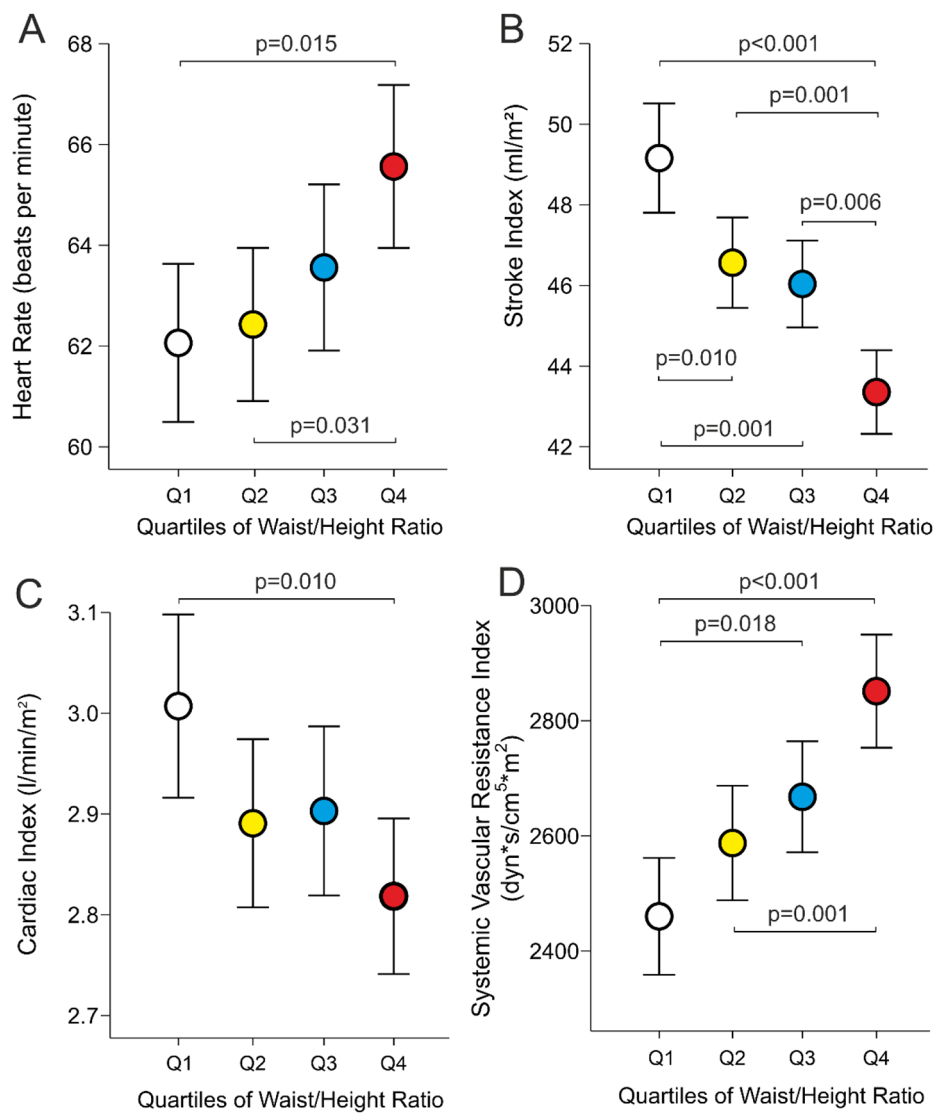


Fig. 3 Heart rate (A), stroke index (B), cardiac index (C), systemic vascular resistance index (D) in 541 subjects; statistics as in Fig. 1

Regression analyses of hemodynamic variables

The linear regression analyses showed statistically significant independent associations of (1) WHtR, PWV, eGFR, QUICKI, LDL cholesterol and triglycerides with aortic systolic and diastolic BP; (2) plasma sodium concentration and age with aortic systolic BP; and (3) male sex and high alcohol consumption category with aortic diastolic BP (Table 3).

WHtR, eGFR, LDL cholesterol, present smoking, and age were independently associated with SVRI. Age, uric acid, mean aortic pressure, WHtR, leptin, aldosterone, present smoking, and triglycerides were independently related with PWV (Table 3).

Discussion

Obesity-related hypertension is considered as a distinct phenotype [9, 12], but the underlying mechanisms remain elusive. The pathophysiology of obesity-induced hypertension involves various potential pathways [4, 5, 8–12]. Excess visceral adiposity is associated with altered secretion of bioactive peptides like adiponectin, leptin, interleukin-6, and tumor necrosis factor- α , predisposing to inappropriate inflammatory responses, insulin resistance, increased sympathetic activity and RAAS activation. These changes impair endothelial function and increase tubular reabsorption of sodium and water, leading to elevated BP [4, 9]. In the present study, aortic systolic BP, systemic vascular resistance, and large arterial stiffness were elevated with higher intra-abdominal fat content in the absence of changes in volume balance,

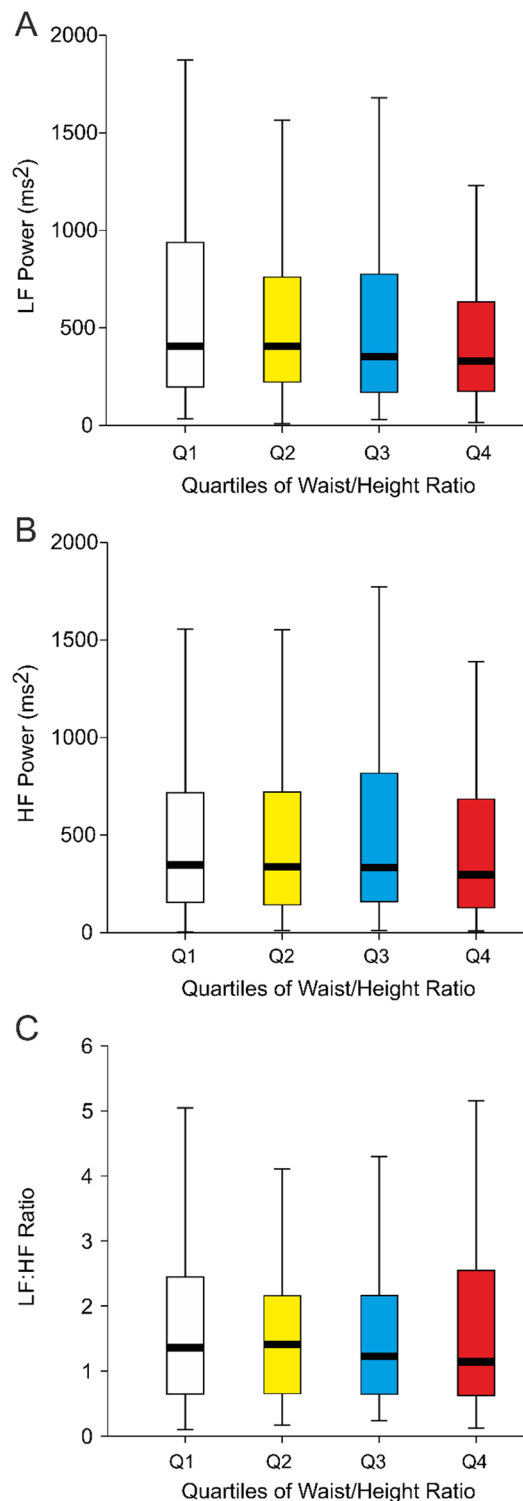


Fig. 4 Box plots show heart rate variability in age-adjusted quartiles of waist/height ratio divided separately for sexes. Low frequency (LF) power (A), high frequency (HF) power (B), and LF/HF ratio (C); median (thick line inside box), 25th -75th percentile (box), range (whiskers); outliers were omitted from the figures but were included in the statistics with logarithmically transformed values

modulation of cardiac sympathovagal balance, or circulating RAAS. The differences between the study quartiles emphasized the influences of SVRI and arterial stiffness as BP-elevating factors related with higher WHtR, and the regression analyses confirmed that WHtR was independently associated with aortic BP, SVRI, and large arterial stiffness.

WHtR better correlates with intra-abdominal fat content than waist circumference, BMI, or waist to hip ratio [2]. WHtR also presents with stronger inverse correlation with cardiovascular health than waist circumference [29]. A cutoff value of 0.5 for WHtR has been suggested for the risk assessment of cardiovascular disease [30], and this value was exceeded in three of the present quartiles that exhibited mean BMI values ranging from 25.1 to 31.9 kg/m². According to a recent survey, mean BMI in Finland is 27.7 kg/m² in men and 27.5 kg/m² in women, while 27% of men and 26% of women aged 30–64 years are obese [31]. The present study cohort with a mean BMI of 26.8 kg/m² well corresponds to the concurrent Finnish population.

Previously, a direct correlation between BMI and plasma aldosterone concentration was reported in overweight patients independent of age, sex and sodium intake [32]. In addition, weight loss was found to reduce plasma renin activity and aldosterone concentration in overweight subjects [33]. In the present study, no differences were detected in plasma renin activity, aldosterone concentration, or aldosterone:renin ratio between the quartiles, and measurements of extracellular volume balance did not indicate volume retention with higher WHtR. Thus, there were no findings indicating changes in circulating RAAS activity between the WHtR quartiles. However, increased WHtR was associated with an unfavorable lipid profile, and in linear regression analyses LDL cholesterol was associated with systolic and diastolic BP and SVRI, as previously reported [34].

As expected, systolic and diastolic BP were increased with higher WHtR. Heart rate was also increased, but stroke volume and cardiac output adjusted to body surface area were decreased with higher WHtR, suggesting that hyperdynamic circulation was not the cause for elevated BP. In contrast, SVRI was clearly increased with higher WHtR. Like in essential hypertension [35], the mechanisms leading to elevated SVRI are probably multifactorial. The hemodynamic pattern of reduced CI and increased SVRI has been shown in subjects with essential hypertension [36]. Also, Krzeński et al. reported that hypertensive patients with or without abdominal obesity presented with similar SVRI, whereas left ventricular contractility and thoracic fluid content were lower in hypertensive subjects with abdominal obesity [37].

PWV is an acknowledged measure of large arterial stiffness [38]. We found that PWV, and also forward wave

Table 3 Linear regression analyses with stepwise elimination of explanatory factors for aortic blood pressure, systemic vascular resistance index, and pulse wave velocity

	Unstandardized coefficient B	Standardized coefficient Beta	P value
Aortic systolic BP (mmHg)			
$R^2 = 0.398$			
(constant)	-4.147		0.935
Pulse wave velocity	2.218	0.225	<0.001
eGFR	-0.219	-0.198	<0.001
LDL cholesterol	3.469	0.165	<0.001
Waist:height ratio	32.486	0.119	0.006
Age	0.201	0.117	0.016
Plasma sodium	0.785	0.078	0.024
QUICKI	-42.355	-0.092	0.016
Triglycerides	-1.934	-0.092	0.019
Aortic diastolic BP (mmHg)			
$R^2 = 0.346$			
(constant)	92.850		<0.001
eGFR	-0.200	-0.266	<0.001
Pulse wave velocity	1.276	0.190	<0.001
LDL cholesterol	2.334	0.163	<0.001
QUICKI	-36.109	-0.115	0.003
Male sex	3.071	0.113	0.002
Triglycerides	-1.828	-0.127	0.003
High alcohol consumption category	8.757	0.091	0.014
Waist:height ratio	17.861	0.096	0.031
SVRI ($\text{dyn} \cdot \text{s} / \text{cm}^5 \cdot \text{m}^2$)			
$R^2 = 0.219$			
(constant)	1659		<0.001
Waist:height ratio	1911	0.235	<0.001
eGFR	-4.981	-0.151	0.002
LDL cholesterol	77.992	0.125	0.006
Present smoking	-178.938	-0.099	0.011
Age	5.297	0.103	0.037
Pulse wave velocity (m/s)			
$R^2 = 0.553$			
(constant)	-0.736		0.127
Age	0.074	0.475	<0.001
Uric acid	0.005	0.196	<0.001
Mean aortic pressure	0.018	0.152	<0.001
Waist:height ratio	4.895	0.199	<0.001
Leptin	-0.013	-0.113	0.001
Aldosterone	3.86×10^{-4}	0.081	0.008
Present smoking	-0.479	-0.087	0.003
Triglycerides	0.135	0.071	0.031

See Methods for included variables; BP, blood pressure; eGFR, estimated glomerular filtration rate using the CKD-EPI creatinine-cystatin C equation; HDL, high density lipoprotein; LDL, low density lipoprotein; QUICKI, quantitative insulin sensitivity check index; SVRI, systemic vascular resistance index; CRP, C-reactive protein

amplitude that has been associated with aortic stiffness [19], were increased with higher fat content in the central body. However, the indices of wave reflection A_{Ix} and $A_{Ix@75}$ [24, 38], did not differ between the quartiles. A_{Ix} is influenced by arterial stiffness, but also by height, sex, ventricular ejection duration, heart rate, and systemic vascular resistance [24, 38]. We also evaluated arterial compliance by calculating the ratio of stroke volume to aortic pulse pressure [20], and found that this variable was lower with higher WHtR. Our findings strongly

support the view that obesity is associated with increased arterial stiffness [39].

Obesity related increase in plasma leptin concentration is assumed to induce unfavorable cardiovascular changes via the activation of the sympathetic nervous system [40] and RAAS [41], leading to hypertension and increased large arterial stiffness. Studies investigating the association of leptin and arterial stiffness have provided variable results [6, 7]. In the present study, subjects with high WHtR presented with elevated plasma leptin levels, and

a 3.3-fold difference in leptin was detected between the highest and lowest quartiles of WHtR. Leptin was moderately related with PWV in the regression analysis, but RAAS activity or sympathetic modulation of HRV were not increased. Thus, the association of WHtR with BP and arterial stiffness may be more related to abdominal obesity itself than high level of circulating leptin.

Excess body fat has been associated with increased sympathetic activity, but the matter remains controversial [42–44]. We evaluated modulation of cardiac autonomic tone using HRV analyses, and found no differences in LF power or HF power, reflecting predominantly sympathetic and parasympathetic influences, respectively [25], or LF/HF ratio between the quartiles of WHtR. Previously, Skrapari et al. reported lower LF and HF power in obese (BMI~40 kg/m²) versus lean (BMI~22 kg/m²) subjects [43], while Hillebrand et al. found that BMI was associated with LF power but not with HF power [44]. Emdin et al. reported decreased LF power throughout the 24-hour recording period in obese (BMI~35 kg/m²) versus lean (BMI~24 kg/m²) subjects, while HF power was lower, and the LF/HF ratio was higher, during the post-prandial phases [42]. Higher daytime LF/HF ratios have been related with higher plasma insulin concentrations independent of BMI, sex, age, and heart rate [42]. In the present study, subjects in the upper quartiles of WHtR were more insulin resistant based on their QUICKI values, but no parallel changes in cardiac sympathovagal modulation were observed.

Study Limitations

Non-invasive recordings of hemodynamics were utilized in this study, which can be considered a limitation. Stroke volume and cardiac output were evaluated from the bio-impedance signal based on a mathematical algorithm and simplification of physiology [21]. However, these methods have been validated against invasive measurements, 3-dimensional echocardiography recordings, and carotid-femoral measurements of PWV [15, 18, 21, 24]. Although this study presented associations between BP, systemic vascular resistance, HRV, and arterial stiffness, the cross-sectional design does not allow conclusions about causality. Importantly, the participants included in this study were without antihypertensive medications that can cause significant confounding during hemodynamic measurements.

Conclusion

The present results showed that elevated BP related to abdominal obesity was characterized by increased systemic vascular resistance and arterial stiffness, but not by increased cardiac sympathovagal modulation, volume retention, or activation of the circulating RAAS. Although high BP in obese subjects has been

characterized by distinct phenotypic features including increased sympathetic tone, impaired endothelium-mediated vasodilatation and RAAS upregulation [9, 12], the present results suggest that the most characteristic features related with elevated BP during higher WHtR are corresponding to those in primary hypertension. Prospective future studies are required to evaluate the clinical significance of the principal phenotypic features related with abdominal obesity.

Abbreviations

AIx	augmentation index
AIx@75	augmentation index adjusted to heart rate 75/min
BMI	body mass index
BP	blood pressure
CI	cardiac index
CRP	C-reactive protein
eGFR	estimated glomerular filtration rate
HDL	high-density lipoprotein
HF	power in high frequency range
HRV	heart rate variability
LDL	low-density lipoprotein
LF	power in low frequency range
PTH	parathyroid hormone
PWV	pulse wave velocity
QUICKI	quantitative insulin sensitivity check index
RAAS	renin-angiotensin-aldosterone system
SI	stroke index
SVRI	systemic vascular resistance index
WHtR	waist:height ratio

Acknowledgements

The authors sincerely acknowledge research nurses Paula Liikanen, Emmi Hirvelä, Virpi Ryhänen and Reeta Kulmala, and laboratory assistant Niina Ikonen, for skillful technical assistance, and CSC – IT Center for Science, Finland, for computational resources.

Author contributions

Research idea and study design: JT, EH, JM, IP; First draft of the manuscript: JT, EH, IP; Data acquisition: JKK, AT, MH, JAK, MH, ON, EM; Data analysis/interpretation: JT, EH, JM, MK, IP; Statistical analysis: AE, IP; Supervision and mentorship: JM, EM, IP. Each author contributed to the intellectual content during manuscript drafting and accepts accountability for the work by ensuring that questions regarding the accuracy or integrity of the work have been appropriately investigated and resolved. All authors approved the submitted version of the manuscript.

Funding

Supported by the Finnish Foundation of Cardiovascular Research, Sigrd Jusélius Foundation, Pirkanmaa Regional Fund of the Finnish Cultural Foundation, Päivikki and Sakari Sohlberg Foundation, Finnish Medical Foundation, and Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (grants 9AA062 and 9AB057). The funding sources were not involved in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Open access funding provided by Tampere University including Tampere University Hospital, Tampere University of Applied Sciences (TUNI).

Data availability

The datasets of the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Signed informed consent was obtained from all participants. The study complies with the Declaration of Helsinki and was approved by the Ethics

Committee of the Tampere University Hospital (study code R06086M) and the Finnish Medicines Agency (Eudra-CT registration number 2006-002065-39) and was registered in a database (ClinicalTrials.gov NCT01742702).

Consent for publication

Not applicable.

Competing interests

The authors report no relevant conflicts of interest.

Received: 17 August 2022 / Accepted: 27 February 2023

Published online: 27 March 2023

References

- 2015 GBD, Collaborators O, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377:13–27.
- Ashwell M, Cole TJ, Dixon AK. Ratio of waist circumference to height is strong predictor of intra-abdominal fat. *BMJ*. 1996;313:559–60.
- Chen Y, Liang X, Zheng S, Wang Y, Lu W. Association of body fat mass and fat distribution with the incidence of hypertension in a population-based Chinese cohort: a 22 - year follow - up. *J Am Heart Assoc*. 2018;7:e007153.
- Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. *N Engl J Med*. 2017;376:254–66.
- Cao ZFH, Stoffel E, Cohen P. Role of perivascular adipose tissue in vascular physiology and pathology. *Hypertension*. 2017;69:770–7.
- Khiyami AM, Dore FJ, Mammadova A, Amdur RL, Sen S. The correlation of arterial stiffness with biophysical parameters and blood biochemistry. *Metab Syndr Relat Disord*. 2017;15:178–82.
- Tsai J-P, Hsu B-G, Lee C-J, Hsieh Y-H, Chen Y-C, Wang J-H. Serum leptin is a predictor for central arterial stiffness in hypertensive patients. *Nephrology*. 2017;22:783–9.
- Jordan J, Nilsson PM, Kotsis V, Olsen MH, Grassi G, Yumuk V, et al. Joint scientific statement of the European Association for the study of obesity and the European Society of Hypertension: obesity and early vascular ageing. *J Hypertens*. 2015;33:425–34.
- Leggio M, Lombardi M, Caldarone E, Severi P, D'Emidio S, Armeni M, et al. The relationship between obesity and hypertension: an updated comprehensive overview on vicious twins. *Hypertens Res*. 2017;40:947–63.
- Putnam K, Shoemaker R, Yiannikouris F, Cassis LA. The renin-angiotensin system: a target of and contributor to dyslipidemias, altered glucose homeostasis, and hypertension of the metabolic syndrome. *Am J Physiol Heart Circ Physiol*. 2012;302:H1219–1230.
- Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail*. 2013;1:93–102.
- Landsberg L, Aronne LJ, Beilin LJ, Burke V, Igel LI, Lloyd-Jones D, et al. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment: a position paper of the obesity society and the American Society of Hypertension. *J Clin Hypertens*. 2013;15:14–33.
- Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021–104.
- Tahvanainen A, Koskela J, Tikkakoski A, Lahtela J, Leskinen M, Kähönen M, et al. Analysis of cardiovascular responses to passive head-up tilt using continuous pulse wave analysis and impedance cardiography. *Scand J Clin Lab Invest*. 2009;69:128–37.
- Koskela JK, Tahvanainen A, Haring A, Tikkakoski AJ, Ilveskoski E, Viitala J, et al. Association of resting heart rate with cardiovascular function: a cross-sectional study in 522 Finnish subjects. *BMC Cardiovasc Disord*. 2013;13:102.
- Tikkakoski AJ, Tahvanainen AM, Leskinen MH, Koskela JK, Haring A, Viitala J, et al. Hemodynamic alterations in hypertensive patients at rest and during passive head-up tilt. *J Hypertens*. 2013;31:906–15.
- Wilenius M, Tikkakoski A, Tahvanainen A, Haring A, Koskela J, Huhtala H, et al. Central wave reflection is strongly associated with peripheral arterial resistance in addition to arterial stiffness in subjects without antihypertensive medication. *BMC Cardiovasc Disord*. 2016;15:131.
- Chen CH, Nevo E, Fetis B, Pak PH, Yin FC, Maughan WL, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation*. 1997;95:1827–36.
- Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension*. 2004;43:1239–45.
- Chemla D, Hébert JL, Coirault C, Zamani K, Suard I, Colin P, et al. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. *Am J Physiol*. 1998;274:H500–505.
- Kööbi T, Kaukinen S, Ahola T, Turjanmaa VM. Non-invasive measurement of cardiac output: whole-body impedance cardiography in simultaneous comparison with thermodilution and direct oxygen fick methods. *Intensive Care Med*. 1997;23:1132–7.
- Kööbi T, Kähönen M, Iivainen T, Turjanmaa V. Simultaneous non-invasive assessment of arterial stiffness and haemodynamics – a validation study. *Clin Physiol Funct Imaging*. 2003;23:31–6.
- Kööbi K, Koskinen, Kaukinen T. Comparison of bioimpedance and radioisotope methods in the estimation of extracellular water volume before and after coronary artery bypass grafting operation. *Clin Physiol*. 2000;20:283–91.
- Wilenius M, Tikkakoski AJ, Tahvanainen AM, Haring A, Koskela J, Huhtala H, et al. Central wave reflection is associated with peripheral arterial resistance in addition to arterial stiffness in subjects without antihypertensive medication. *BMC Cardiovasc Disord*. 2016;16:131.
- Malik M, Bigger J, Camm A, Kleiger R, Malliani A, Moss A, et al. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J*. 1996;17:354–81.
- Monfredi O, Lyashkov AE, Johnsen A-B, Inada S, Schneider H, Wang R, et al. Biophysical characterization of the underappreciated and important relationship between heart rate variability and heart rate. *Hypertension*. 2014;64:1334–43.
- Working group appointed by the Finnish Medical Society Duodecim and the Finnish Society of Addiction Medicine. Treatment of alcohol abuse. *Current Care Guideline*. 2015.
- Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab*. 2000;85:2402–10.
- Shen S, Lu Y, Qi H, Li F, Shen Z, Wu L, et al. Waist-to-height ratio is an effective indicator for comprehensive cardiovascular health. *Sci Rep*. 2017;7:43046.
- Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0.5 could be a suitable global boundary value. *Nutr Res Rev*. 2010;23:247–69.
- Koponen P, Borodulin K, Lundqvist A, Sääksjärvi K, Koskinen S. Health, functional capacity and welfare in Finland – FinHealth 2017 study. National Institute for Health and Welfare (THL). Report 4/2018, 236 pages. Helsinki, Finland 2018. Available online at: <http://www.julkari.fi/handle/10024/136223> (accessed 30.9.2019).
- Rossi GP, Belfiore A, Bernini G, Fabris B, Caridi G, Ferri C, et al. Body mass index predicts plasma aldosterone concentrations in overweight-obese primary hypertensive patients. *J Clin Endocrinol Metab*. 2008;93:2566–71.
- Engeli S, Böhnke J, Gorzelniak K, Janke J, Schling P, Bader M, et al. Weight loss and the renin-angiotensin-aldosterone system. *Hypertension*. 2005;45:356–62.
- Choudhary MK, Eräranta A, Tikkakoski AJ, Koskela J, Hautaniemi EJ, Kähönen M, et al. LDL cholesterol is associated with systemic vascular resistance and wave reflection in subjects naive to cardiovascular drugs. *Blood Press*. 2019;28:4–14.
- Harrison DG, Coffman TM, Wilcox CS. Pathophysiology of hypertension. *Circ Res*. 2021;128:847–63.
- Lund-Johansen P. Central haemodynamics in essential hypertension at rest and during exercise: a 20-year follow-up study. *J Hypertens Suppl*. 1989;7:52–5.
- Krzeńskiński P, Stańczyk A, Piotrowicz K, Gielerak G, Uziębło-Zyczkowska B, Skrobowski A. Abdominal obesity and hypertension: a double burden to the heart. *Hypertens Res*. 2016;39:349–55.
- Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588–605.

39. Wildman RP, Mackey RH, Bostom A, Thompson T, Sutton-Tyrrell K. Measures of obesity are associated with vascular stiffness in young and older adults. *Hypertension*. 2003;42:468–73.
40. Rahmouni K, Morgan DA. Hypothalamic arcuate nucleus mediates the sympathetic and arterial pressure responses to leptin. *Hypertension*. 2007;49:647–52.
41. Faulkner JL, Bruder-Nascimento T, Belin de Chantemèle EJ. The regulation of aldosterone secretion by leptin: implications in obesity-related cardiovascular disease. *Curr Opin Nephrol Hypertens*. 2018;27:63–9.
42. Emdin M, Gastaldelli A, Muscelli E, Macerata A, Natali A, Camastra S, et al. Hyperinsulinemia and autonomic nervous system dysfunction in obesity: effects of weight loss. *Circulation*. 2001;103:513–9.
43. Skrapari I, Tentolouris N, Perrea D, Bakoyiannis C, Papazafropoulou A, Katsilambros N. Baroreflex sensitivity in obesity: relationship with cardiac autonomic nervous system activity. *Obesity*. 2007;15:1685–93.
44. Hillebrand S, Swenne CA, Gast KB, Maan AC, le Cessie S, Jukema JW, et al. The role of insulin resistance in the association between body fat and autonomic function. *Nutr Metab Cardiovasc Dis*. 2015;25:93–9.
45. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367:20–9.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.