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Blood pressure load per body surface area is higher in women than in men

Running title: Blood pressure load and body surface area

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Abstract

Many unexplained sex differences have been observed in blood pressure (BP) related morbidity. However, there has been little research about the most obvious difference between men and women – body size. Given that blood vessels are organs of tubular shape, we hypothesized that correction of BP for body surface area (BSA), a two-dimensional measurement of body size, would allow comparison of BP load between men and women.

We assessed the relationship of 24-hour ambulatory BP measurements and BSA in 534 participants (mean age 61 ± 3 years, 51 % women) from the Helsinki Birth Cohort Study. The study subjects had no previous medication affecting vasculature or BP.

When BP values were adjusted for age, smoking, physical activity, and body fat percentage, males had higher ambulatory daytime mean systolic BP (131 mmHg vs. 127 mmHg, p <0.001), diastolic BP (83 mmHg vs. 78 mmHg, p <0.001), and mean arterial pressure (100 mmHg vs. 96 mmHg, p <0.001) than females. However, all BP components per unit of BSA were significantly lower in males: daytime mean systolic BP (65 mmHg vs. 71 mmHg, p <0.001), diastolic BP (41 mmHg vs. 44 mmHg, p <0.001), pulse pressure (24 mmHg vs. 28 mmHg, p=0.013), and mean arterial pressure (49 mmHg vs. 54 mmHg, p <0.001). The same phenomenon was observed in night-time BP values.

BP load per BSA is higher in women than in men, which may explain many reported sex differences in cardiovascular morbidity. Relatively small-sized individuals might benefit from a more aggressive therapeutic strategy.
Introduction

Hypertension is one of the most studied medical conditions due to its critical role in cardiovascular morbidity and mortality as well as high global prevalence. However, there are several unanswered questions in relation to sex differences in hypertension-related morbidity.

The prevalence of hypertension is higher among men until the age of 45 years, but hypertension becomes more prevalent in women in older age (>60 years) both in developed and developing countries [1-3]. Many hypotheses have been proposed for this age-dependent disparity between the sexes, effects of estrogen excess and deficiency being the prevailing for the time being. There are reports indicating that although female patients are more likely aware of having hypertension, they are less likely to have their blood pressure (BP) adequately controlled than men, especially at advanced age (>60 years) [4, 5]. Further, hypertensive women are more likely to develop concentric left ventricular hypertrophy (LVH) [6] and have more often heart failure with preserved ejection fraction than men [7]. Moreover, regression of LVH with antihypertensive medication is less pronounced in women than in men [8].

Sex differences in vascular tone and function have also been verified using novel medical technology. In older women, arterial stiffness is more pronounced [9, 10] and flow-mediated dilatation abnormalities more prevalent [11] than in men. Pulse pressure amplification, i.e. the consistently higher BP in peripheral than central arteries, is particularly increased in post-menopausal women [12].

While the mechanisms for the above mentioned BP-related sex differences are still unknown, there has been little research about the most obvious difference between men and women – body size. In medicine, a commonly used measure of body size is body mass index (BMI). As a ratio of weight and the square of height, BMI does not take height into account as an
absolute measure. However, increased adult height has been shown to be strongly associated with decreased mortality from coronary heart disease, stroke and heart failure [13]. We have previously shown using a sex-specific standardized z-score that adult height is inversely related to BP in a population of elderly men and postmenopausal women [14]. Yet, height is a one-dimensional measure of body size. Given that blood vessels are organs of tubular shape, we hypothesized that correction of BP for body surface area (BSA), a two-dimensional measurement, would better allow comparison of BP load between men and women.
Patients and Methods

The Helsinki Birth Cohort Study (HBCS) includes 8760 men and women who were born at Helsinki University Central Hospital between 1934 and 1944. The weight and length of the newborn were recorded at the maternity hospital. For the clinical study, we used random-number tables to select a subset of people from the initial epidemiological study cohort who were still alive and living in Finland in 1971. In order to achieve a sample size in excess of 2000 people, we selected 2691 subjects for the study, and 2003 of them visited the clinic in the years 2001-2004. The procedures used at the clinic visit have been described in greater detail previously [15]. Briefly, the subjects attended the clinic after an overnight fast. The clinical examination included measurements of height, weight, waist circumference, plasma lipids, plasma glucose, and blood pressure.

Height and weight were measured in light indoor clothing and without shoes. Height was measured with a Kawi stadiometer to the nearest 0.1 cm. Weight was measured on Seca Alpha 770 scales to the nearest 0.1 kg.

BMI was calculated as weight (kg) divided by the square of height (m$^2$). Categories of BMI were defined as BMI <25.0 kg/m$^2$ (normal weight), BMI 25.0–29.9 kg/m$^2$ (overweight), and BMI ≥30.0 kg/m$^2$ (obese).

Adult BSA was calculated according to the Mosteller formula [weight (kg) x height (cm)/3600]$^{1/4}$ [16]. Study subjects were divided to tertiles of BSA: I <1.81 m$^2$, II 1.81 – <2.00 m$^2$, III ≥2.00 m$^2$. BSA at birth was calculated according to the Meban-BSA formula, which has been proved to be the most accurate formula to calculate infant-BSA [17].

Office BP was measured from the right arm while the subject was in the sitting position, and it was recorded as the mean of two successive readings from a mercury sphygmomanometer. For 24-hour ambulatory BP measurement, oscillometric Spacelabs 90207 monitors (Spacelabs Healthcare, Issaquah, Washington) were used with cuffs of
appropriate size applied to the non-dominant arm. The measurement protocol for each subject included a reading once in every 30 minutes, except from 10 PM to 7 AM, when it included one reading in every hour. We aimed at a number of readings that meets recommendations [18] but allows maximal compliance. Pulse pressure (PP) was defined as the difference between systolic and diastolic BP. Mean arterial pressure (MAP) was calculated as diastolic BP + (systolic BP – diastolic BP)/3.

Body fat percentage was estimated by the relative fat mass (RFM) equation as follows: 76 – [20 x (height/waist)] for women, and 64 – [20 x (height/waist)] for men [19].

Leisure-time physical activity (LTPA) was assessed with the validated 12-month Kuopio Ischemic Heart Disease questionnaire [20]. Information on type, mean duration/month and mean frequency/month of LTPA was collected. We defined a specific metabolic equivalent of task (MET, 1 MET = 3.5 ml of O2/kg⁻¹/min⁻¹ or 1 kcal/kg⁻¹/h⁻¹) for each reported activity (n = 47) to determine the absolute intensity of the activities. LTPA was reported as a time-weighted average intensity (TWA-MET) as previously reported [21].

Years of education, smoking status, and current medication were assessed by questionnaires. For the present analysis, we selected only subjects who had no cardiovascular medication.
Ethical approval

Written informed consent was obtained from each subject before any procedures were carried out. The Ethics Committee for Epidemiology of Helsinki and Uusimaa Hospital District approved the study.

Statistical analysis

The characteristics of the study population are presented as means with standard deviations (SD) or as counts with percentages. Statistical significances for the hypothesis of linearity of daytime and night-time ambulatory BP components across categories of BSA (I=<1.81, II=1.81-2.00 and III=>2.00) tertiles were evaluated by using the analysis of variance with an appropriate contrast (orthogonal polynomial). Multivariate linear regression analysis was used to identify the relationship between BSA as a continuous variable and the ambulatory BP components with standardized regression coefficient Beta (β). The Beta value is a measure of how strongly the predictor (BSA) variable influences the criterion variable. The Beta is measured in units of SD. Cohen’s standard for Beta values above 0.10, 0.30 and 0.50 represents small, moderate and large relationships, respectively.

The difference between sexes in BSA, BMI and BP components were evaluated by using a t-test or ANCOVA. Adjusted models included age, smoking, LTPA, and body fat percentage as covariates. In the case of violation of the assumptions (e.g. non-normality), a bootstrap-type test was used (10 000 replications). BSA distributions were compared between sexes by an Epps-Singleton (ES) two-sample empirical characteristic function test. ES tests the hypothesis that the distribution functions underlying two independent samples are identical. The normality of variables was evaluated by the Shapiro-Wilk W test. All analyses were performed using STATA 15.0.
Results

We evaluated 534 individuals who had never had medication affecting cardiovascular system. Mean age of the study population was 61 (SD 3) years, and 51% were females.

Characteristics of the study subjects are displayed in Table 1. The average BSA, height and weight also at birth were higher in men than in women. Women had higher mean body fat percentage, total cholesterol and HDL cholesterol levels than men. Plasma glucose and triglyceride values, office DBP measurement and MAP were higher in men. They also had higher level of LTPA and were more often current smokers than women.

Distributions of BSA in men and women are shown in Figure 1 (p <0.001 for equality of BSA distributions). Although there was no statistical difference in the mean BMI values between the sexes (p=0.40), mean BSA was significantly higher in men than in women, p <0.001 (Figure 2). The mean ratio between men and women was 1.01 (95% CI: 0.98 to 1.04) for BMI and 1.13 (95% CI: 1.12 to 1.15) for BSA.

Ambulatory daytime and night-time systolic BP, diastolic BP, and MAP showed positive relationship with BSA, remaining statistically significant also after adjustment for age, smoking, LTPA, and body fat percentage. Adjusted night-time PP increased linearly with BSA. (Table 2)

When ambulatory BP values were stratified according to sex, males had higher systolic and diastolic BP, and MAP than females. However, all BP components per BSA were significantly higher in females (p <0.001 in all comparisons) as demonstrated in Table 3 and Figure 3.

In multiple regression analysis, a positive relationship was observed between BSA and the ambulatory measurements of SBP, DBP, and MAP (Figure 4).
Discussion

This study implies that BSA, even when the effect of adiposity is removed, shows a positive relationship with ambulatory daytime and night-time BP values. Importantly, BP load per BSA is significantly higher in women than in men, which may explain some of the reported sex differences in BP-related morbidity. To our knowledge, this is the first study to address the rationale for scaling BP level over the range of body sizes.

BP is the force exerted by the blood against any unit area of the vessel wall [22]. According to our results, this force is stronger in women than in men with mean age of 61 years and is related to women’s smaller body size. In shorter individuals it has indeed been shown that they have smaller arterial lumen diameter [23]. Further, women have smaller coronary arteries than men [24]. Moreover, the Poiseuille’s law states that the rate of blood flow is directly proportional to the fourth power of the radius of the vessel, i.e. radius to the power 4 (radius^4). Thus, the diameter of an artery plays by far the greatest role of all factors determining the rate of blood flow through a vessel [22].

Greater pressure overload against the arterial wall probably predispose smaller individuals to endothelial dysfunction, arterial and cardiac remodeling, formation of fibrosis and subsequent arterial stiffness. These pathophysiological phenomena among women usually become evident after menopause, probably because younger women are protected by estrogen-induced vasorelaxation and arterial elasticity [25]. In postmenopausal women, the mechanical stress that BP exerts over the unit of area to the arterial wall rises more sharply than in men and may explain why cardiovascular diseases (CVDs) are the leading cause of death also in women although they develop CVDs almost a decade later than men. The elevated BP load per unit of BSA may also be a contributing factor to the higher prevalence of stroke and
coronary microvascular dysfunction [27], and faster decline in renal function [28] seen in postmenopausal women compared with men.

Current guidelines for BP targets do not take into account sex or body size, and we use the same normal BP ranges for adult men and women. In nonhuman mammals, it is well known that BP varies by size [29]. Our findings confirm that in humans, BP load over the unit of BSA is larger in a smaller than in a larger person. Thus, correcting BP values for body size, e.g. BSA, might partly address the question why women have more uncontrolled hypertension [4, 5], LVH [6], heart failure with preserved ejection fraction [7], worse outcomes after stroke [26] and following percutaneous coronary intervention or coronary bypass surgery [30]. Indexing BP values by BSA might also improve prediction of cardiovascular events in persons at risk with different body sizes. BSA has already been shown to be inversely associated with total and cardiovascular mortality in patients with chronic heart failure [31, 32]. However, we cannot be certain that indexing BP values for BSA is the optimal method for scaling BP for body size.

BMI is the most commonly used anthropometric measure to assess obesity in BP-related studies. We have previously demonstrated in this study population that the relationship between BP and height is independent of BMI up to a BMI level of 27-28 kg/m² [14]. The present study shows that BSA recognizes the normal variation in body size better than BMI (Figure 2). The clinical fact that not all obese subjects develop hypertension while some lean subjects do, has gained support from a twin study demonstrating that acquired obesity is related to BP, but unrelated to measures of arterial stiffness [33]. Thus, we suggest that the size of arteries and the subsequent BP load per unit area of vessel wall is mainly determined by the BSA of a person. The logical role of indexing BP for BSA is to make comparison possible between subjects with different body size. However, this indexation cannot be used in follow-up of an adult person who gains weight during follow-up.
This study is cross-sectional and we cannot confirm our theory about the predictive accuracy of BP indexation for BSA in CVDs. A better measure to explain sex differences in BP would be artery size. By using ambulatory BP measurements we could measure circadian blood pressure levels and exclude white coat effect and masked hypertension. Moreover, by excluding patients with vasoactive medications we could observe exclusively the relation between BP, BSA and BMI. The Mosteller’s formula which was used to calculate BSA, is recommended as an accurate measure to estimate BSA also in overweight and obese individuals [34], and is commonly used in clinical and laboratory medicine. Another strength of our study is the phenotypic richness including data on anthropometric measures at birth.

In conclusion, indexing BP values for BSA highlights BP load and may explain many sex differences in cardiovascular morbidity. Relatively smaller-sized individuals might benefit from initiating antihypertensive medication earlier and targeting to a lower BP level than relatively larger-sized subjects. Further studies are warranted to define a threshold for body size gaining advantage from a more aggressive therapeutic strategy.

**Conflict of Interest**

The authors have nothing to disclose.

**Funding**

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References


19. Woolcott OO, Bergman RN. Relative fat mass (RFM) as a new estimator of whole-body fat percentage – A cross-sectional study in American adult individuals. Scientific reports. 2018; 8: 10980


Table 1. Characteristics of the study population according to sex

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women N=274</th>
<th>Men N=260</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body surface area, m², mean (SD) [range]</td>
<td>1.79 (0.15)</td>
<td>2.03 (0.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, cm, mean (SD)</td>
<td>163 (6)</td>
<td>177 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>71 (11)</td>
<td>84 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>26.8 (4.2)</td>
<td>26.9 (3.5)</td>
<td>0.84</td>
</tr>
<tr>
<td>Body fat percentage, mean (SD)</td>
<td>32.6 (6.4)</td>
<td>23.0 (5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>61 (3)</td>
<td>61 (3)</td>
<td>0.49</td>
</tr>
<tr>
<td>Education years, mean (SD)</td>
<td>11.8 (3.4)</td>
<td>12.4 (3.8)</td>
<td>0.034</td>
</tr>
<tr>
<td>Length at birth, cm, mean (SD)</td>
<td>50.0 (1.9)</td>
<td>50.8 (2.0)</td>
<td>&lt;&lt;0.001</td>
</tr>
<tr>
<td>Weight at birth, g, mean (SD)</td>
<td>3369 (483)</td>
<td>3517 (499)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body surface area at birth, cm², mean (SD)</td>
<td>2159 (190)</td>
<td>2224 (197)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose, mean (SD)</td>
<td>5.44 (0.80)</td>
<td>5.97 (1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l, mean (SD)</td>
<td>6.18 (1.02)</td>
<td>5.92 (1.05)</td>
<td>0.003</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l, mean (SD)</td>
<td>1.79 (0.45)</td>
<td>1.50 (0.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mmol/l, mean (SD)</td>
<td>1.34 (0.74)</td>
<td>1.50 (0.82)</td>
<td>0.015</td>
</tr>
<tr>
<td>Office blood pressure, mmHg, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>145 (21)</td>
<td>146 (19)</td>
<td>0.41</td>
</tr>
<tr>
<td>Diastolic</td>
<td>87 (10)</td>
<td>91 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>70 (10)</td>
<td>70 (13)</td>
<td>0.71</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>107 (12)</td>
<td>109 (12)</td>
<td>0.011</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>45 (16)</td>
<td>66 (25)</td>
<td>0.011</td>
</tr>
<tr>
<td>Leisure-time physical activity, TWA-MET, mean (SD)</td>
<td>4.4 (0.9)</td>
<td>4.8 (1.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: HDL, high-density lipoprotein; TWA-MET, time-weighted average intensity in metabolic equivalent of task
Table 2. Ambulatory blood pressure findings according to tertiles of body surface area

<table>
<thead>
<tr>
<th></th>
<th>I N=178</th>
<th>II N=178</th>
<th>III N=178</th>
<th>P for linearity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daytime BP, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>127 (14)</td>
<td>129 (13)</td>
<td>132 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77 (9)</td>
<td>81 (8)</td>
<td>83 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PP</td>
<td>49 (10)</td>
<td>48 (8)</td>
<td>49 (8)</td>
<td>0.71</td>
</tr>
<tr>
<td>MAP</td>
<td>95 (10)</td>
<td>98 (9)</td>
<td>100 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Daytime heart rate,</strong></td>
<td>75 (9)</td>
<td>75 (10)</td>
<td>75 (11)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>beats/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Night-time BP, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>114 (13)</td>
<td>116 (13)</td>
<td>119 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>66 (8)</td>
<td>69 (8)</td>
<td>71 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PP</td>
<td>47 (9)</td>
<td>47 (8)</td>
<td>48 (8)</td>
<td>0.49</td>
</tr>
<tr>
<td>MAP</td>
<td>83 (9)</td>
<td>86 (9)</td>
<td>88 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Night-time heart rate,</strong></td>
<td>65 (8)</td>
<td>65 (9)</td>
<td>66 (11)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>beats/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD).

*Adjusted for age, smoking, leisure-time physical activity, and body fat percentage.

Abbreviations: BP, blood pressure; PP, pulse pressure; MAP, mean arterial blood pressure.
Table 3. Ambulatory blood pressure mean values in mmHg and mmHg per body surface area according to sex

<table>
<thead>
<tr>
<th></th>
<th>mmHg</th>
<th>mmHg / BSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Daytime BP, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>127 (13)</td>
<td>131 (13)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78 (8)</td>
<td>83 (9)</td>
</tr>
<tr>
<td>PP</td>
<td>49 (10)</td>
<td>48 (8)</td>
</tr>
<tr>
<td>MAP</td>
<td>96 (9)</td>
<td>100 (10)</td>
</tr>
<tr>
<td>Night-time BP, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>115 (13)</td>
<td>117 (12)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>67 (8)</td>
<td>71 (8)</td>
</tr>
<tr>
<td>PP</td>
<td>48 (9)</td>
<td>46 (8)</td>
</tr>
<tr>
<td>MAP</td>
<td>84 (9)</td>
<td>87 (9)</td>
</tr>
</tbody>
</table>

Values are mean (SD).

*Adjusted for age, smoking, leisure-time physical activity, and body fat percentage.

Abbreviations: BP, blood pressure; PP, pulse pressure; MAP, mean arterial blood pressure
Figure 1. Distribution of body surface area according to sex
Figure 2. The means of body mass index and body surface area in men and women. Adjusted for age, smoking, and leisure-time physical activity. Whiskers show 95% CIs.
Figure 3. Mean ratio between men and women in different daytime and night-time ambulatory blood pressure components. Adjusted for age, smoking, leisure-time physical activity, and body fat percentage. Whiskers show 95% CIs.
Figure 4. Magnitude of the effect of body surface area as a continuous variable on the ambulatory blood pressure components. Beta (β) -values with 95% confidence intervals were adjusted using age, smoking, leisure-time physical activity, and body fat percentage.
Summary Table

**What is known about topic**

- There are many unexplained sex differences regarding hypertension-related morbidity.
- In nonhuman mammals, it is well known that blood pressure varies by size.

**What this study adds**

- Body surface area, even when the effect of adiposity is removed, has a positive relationship with ambulatory daytime and night-time blood pressure values.
- Blood pressure load per body surface area is significantly higher in women than in men, which may explain many reported sex differences in cardiovascular morbidity.