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COMPARISON OF MERCURY BLOOD PRESSURE READINGS TO OSCILLOMETRIC AND CENTRAL BLOOD PRESSURE IN PREDICTING TARGET ORGAN DAMAGE IN YOUTH

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Abstract

Objective—Hypertension (HT) is an important risk factor for target organ damage (TOD). New methods for measuring BP are replacing mercury sphygmomanometry in many clinics. We examined the utility of different BP measurement techniques in predicting subclinical TOD in adolescents and young adults.

Methods—Subjects in a study of the CV effects of obesity and type 2 diabetes (T2DM) were evaluated (N=677, 18 ± 3.3 years, 35% male, 60% non-Caucasian, 30% T2DM). We measured adiposity, lab, left ventricular mass, carotid intima-media thickness & pulse wave. BP was measured 3 times with mercury sphygmomanometry (BPm) an oscillometric device (BPo) and central aortic BP (BPc) was derived with arterial tonometry. Subjects were stratified as normotensive (N), pre-hypertensive (P) or hypertensive (H).

Results—The prevalence of HT this cohort with mean BMI of 31 was highest with BPo (16%), followed by BPm (11%) and BPc (9%), p = 0.001. BPm was most consistent in differentiating left ventricular mass and pulse wave velocity among subjects in the P group as compared to the N & H groups. Mercury BP was also more sensitive and specific in predicting greater left ventricular mass, pulse wave velocity and carotid thickness than the other BP measurement techniques in logistic regression.

Conclusions—We conclude that mercury sphygmomanometry should remain the gold standard for evaluation of HT and the risk for TOD in adolescents and young adults.

Keywords

Hypertension; Blood Pressure Measurement; Pediatrics; Carotid Artery; Arterial Stiffness; Elasticity; Left Ventricular Hypertrophy

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Introduction

Hypertension (HT) is an important risk factor for target organ damage (TOD) in children and adults. Autopsy studies such as the Bogalusa Heart Study and the PDAY study (Pathobiologic Determinates of Atherosclerosis in Youth) have demonstrated increased atherosclerosis at higher blood pressure (BP) levels in youth.^{1, 2} Other large and well-designed studies have shown higher left ventricular mass (LVM),³ greater carotid intima-media thickness (IMT),³ stiffer arteries,³ reduced endothelial function,⁴ renal,⁵ and neurologic⁶ compromise in youth with high BP. Therefore, accurate evaluation of BP levels for identification of youth at highest risk for developing TOD is critical as outlined in current pediatric guidelines for cardiovascular (CV) risk reduction.⁷

New methods for measuring BP including automatic oscillometric BP (BPo) instruments are replacing the gold-standard of mercury sphygmomanometry (BPM) in many clinics. There are also devices that obtain radial artery pressure curves from which central aortic BP (BPc) is estimated. However, it is not known whether these new techniques are equivalent to mercury sphygmomanometry in ability to predict target organ damage in young subjects. Therefore, we sought to determine which method of measuring BP was most sensitive and specific in identifying sub-clinical TOD in adolescents and young adults.

Methods

Subjects participating in a study of the CV effects of obesity and type 2 diabetes (T2DM) were evaluated (N=677). Pregnant females were excluded from the study. Investigational review board approval was obtained, and written informed consent was obtained from subjects ≥18 years or the guardian for subjects <18 years. Written assent was obtained for subjects <18 years. After an overnight fast, questionnaire, anthropometric, BP, laboratory, arterial stiffness, echocardiographic and carotid ultrasound data were collected. The mean of 2 measures of height was obtained with a calibrated stadiometer (Veeder-Rood, Elizabethtown, North Carolina) and mean of 2 measures of weight with a Health-O-Meter electronic scale (Jarden Consumer Solutions, Rye, New York). Laboratory methods for analysis of fasting plasma glucose, insulin, lipids, high sensitivity C-reactive protein (CRP) and glycated hemoglobin A1c (HbA1c) have been published previously.⁸ Subjects were classified as diabetic according to ADA standards.⁹ The mean of 3 resting measures of BP was obtained by trained observers using the same rigorous protocol with mercury sphygmomanometry (BPM, W.A. Baum Co., Copiague, N.Y.), an oscillometric device, (DynaPulse, PulseMetric, San Diego, CA) with BP adjusted for differences in oscillometric versus auscultatory technique according to previously published comparison data.¹⁰ Central aortic BP was derived with arterial tonometry (SphygmoCor, Atcor Medical, Sydney, Australia). Careful attention to cuff size and measurement technique was taken as per the Fourth Report on BP in Children¹¹ or JNC7.¹² These guidelines specify that the inflatable bladder width is at least 40 percent of the arm circumference at a point midway between the olecranon and the acromion.¹³ All devices were calibrated according the manufacturers recommended schedule. Both the oscillometric¹⁴ and arterial tonometry device¹⁵ BPs were validated against catheterization data. Inter-observer reproducibility of BP measurement was assessed by calculation of coefficients of variation for SBP and DBP for the 3 readings

obtained on each subject. All methods had excellent reproducibility (CV in % for SBP: mercury = 1.9, oscillometric = 2.1, central = 1.8; for DBP: mercury = 4.1, oscillometric = 3.4, central = 0.6).

Arterial Stiffness Measurements

The mean of 3 resting measures of carotid-femoral pulse wave velocity (PWV) was obtained with a SphygmoCor SCOR-PVx System (Atcor Medical, Sydney, Australia) using directly measured carotid to femoral path length and a pressure tonometer to determine ECG-gated timing of the pressure wave propagation as previously described.⁸ Repeat measures in our laboratory show excellent reproducibility with coefficients of variability less than 7%.⁸

Carotid Ultrasonography

Carotid ultrasound studies were performed by a single registered vascular technologist using high-resolution B-mode ultrasonography (GE Vivid7; GE Healthcare, Milwaukee, Wisconsin) with a linear array broadband transducer (3.7–8 or 5.6–14 MHz). For each segment (common, bulb, internal), the thickest intima-media thickness was recorded as multiple digital loops. The average of 3 images was obtained with off-line readings using a manual trace technique on the Camtronic Medical systems (Camtronic Medical Systems, Hartland, Wisconsin) software from leading edge to leading edge. Composite carotid artery intima-media thickness (IMT) was calculated as mean right and left, common, bulb and internal carotid artery thickness. Our laboratory has measured coefficients of variation of 5.3 to 8.0% with this technique.¹⁶

Echocardiography Technique

Echocardiography was performed with a GE system (Andover, Massachusetts). Absence of structural heart disease was confirmed and then parasternal long and short-axis views were recorded. The mean of 3 readings of left ventricular end-diastolic, end-diastolic septal thickness and end-diastolic posterior wall thicknesses were measured off-line by either of two sonographers using a Digiview Image Management and Reporting System (Digisonics, Houston, Texas). LVM was calculated by the Devereaux formula¹⁷ and normalized to $ht^{2.7}$ as recommended by De Simone.¹⁸

Statistical Analysis

Analyses were performed with Statistical Analyses Software (SAS, version 9.3, Cary, North Carolina). Subjects were stratified as normotensive (N), pre-hypertensive (P) or hypertensive (H) based on BPm using pediatric guidelines⁷ if < 18 and JNC7¹² if ≥ 18 years. Subjects on anti-hypertensive medication were considered HT regardless of resting BP. BP z-scores were calculated for all 3 BP measurement techniques using the pediatric guidelines age-, sex- and height-specific means. Mean and standard deviations for variables were calculated for the entire group and stratified by HT classification 3 times (once each by BPm, BPo and BPc). Chi square analyses were done to examine differences in prevalence of HT by BP technique. ANOVA was used to determine differences in CV risk factors and sub-clinical target organ damage (TOD: IMT, LVM, PWV) when subjects were classified into a BP group by mercury, and then by the other 2 BP techniques. Variance stabilizing

measures were used to transform non-normal values. Bivariate Pearson correlations were calculated between measures of TOD and the SBP and DBP measured by the 3 techniques. Subjects were categorized as having TOD if their IMT or PWV was $\geq 95^{\text{th}}$ for our healthy lean subjects (N=250). Cut-points were derived from our population since there are no larger published pediatric studies of healthy youth from which to define normal values. Left ventricular hypertrophy (LVH) was defined by an LVM $\geq 51 \text{ g/m}^2$ ¹⁹ according to adult guidelines since this was similar to the 95^{th} for healthy subjects in our study. Logistic regression was performed to determine which BP z-score provided the highest C-statistic (area under the curve) for explaining the presence of measures of TOD. Covariates significant in correlation analyses were added. Non-significant variables were removed until all variables remained at $p \leq 0.05$. To determine if differences in AUC were statistically significant, we employed the non-parametric approach of DeLong et al.²⁰

Results

Mean age of participants was 18 ± 3 years, with 35% male and 60% non-Caucasian, predominantly African-American (1.6% mixed race). Due to the study design where youth with T2DM (diagnosed by primary provider) were recruited (30% of the cohort), and then were matched to both a lean and obese control, this was a relatively obese group with a BMI 31.0 g/m^2 . Since the prevalence of T2DM in adolescents and young adults in Cincinnati is highest in African-American females, this study design also led to a predominance of this demographic pattern in our cohort. Despite the relative adiposity of the population, the mean BP by mercury ($115/64 \pm 12/13 \text{ mmHg}$), LDL ($100 \pm 29 \text{ mg/dl}$), HDL ($50 \pm 13 \text{ mg/dl}$) and TG ($102 \pm 70 \text{ mg/dl}$) for the group overall were within normal limits. Oscillometry provided the highest prevalence of hypertension (16%) followed by mercury (11%) and central BP (9%). In contrast, measurement with mercury sphygmomanometry identified the highest prevalence of pre-hypertension (20%), followed by central (10%) and oscillometric technique (6%). Chi square for Oscillometric BP category by Central BP category for each level of mercury BP category had $p \leq 0.0001$ indicating that measurement technique affected the diagnosis of hypertension in our cohort.

Average values stratified by mercury BP category are found in table 1. Regardless of BP measurement technique, hypertensive subjects had the most adverse CV risk profile with a higher BMI, lipids, CRP, and poorer metabolic control (all $p \leq 0.05$). Pre-hypertensive subjects had CV risk factor levels that were generally intermediate to subjects who were in the normotensive or hypertensive groups. These patterns were consistent for all BP measurement techniques (data not shown). Furthermore, regardless of BP measurement techniques, hypertensives had the most adverse levels of TOD (thicker IMT, higher LVM and PWV). Carotid IMT was equal in the pre-hypertensive and hypertensive groups (both higher than normotensives) for all BP techniques (pre-hypertensive and hypertensive $>$ normotensive). LVM was also equal in pre-hypertensive and hypertensives (both higher than normotensives) when BP was measured by oscillometry (BPo) or centrally (BPc). However, BP measured with mercury (BPm) was able to distinguish all 3 categories (LVM for hypertensive $>$ pre-hypertensive $>$ normotensive). Similarly, both BPm and BPo found differences in PWV among all groups (hypertensive $>$ pre-hypertensive $>$ normotensive) but BPc did not (all $p \leq 0.05$). This is graphically displayed for LVM in Figure 1.

When TOD was defined by cutpoints, 11% had thick IMT, 6.2% had LVH, and 24% had elevated PWV. Correlations between BP z-scores and TOD were similar in magnitude and significance for all BP measurement techniques (data not shown, all $p < 0.05$). In fully adjusted logistic regression models (table 2), mercury SBP z-score (for LVH) and mercury DBP z-score (for higher IMT and PWV) provided the greatest sensitivity and specificity (highest C-statistic) in predicting the TOD of interest. Additional covariates that entered the models included: presence of T2DM for IMT; T2DM, BMI z-score and HR for LVM and race; BMI z-score, triglycerides, glucose, CRP and race by CRP interaction for PWV. The C-statistic for mercury SBP predicting LVM was significantly higher than for oscillometric or central BP (figure 2). There was no difference in C-Statistic for PWV or IMT.

Discussion

Our data demonstrate that when evaluated statistically, mercury BP measurements may be more sensitive and specific in predicting which subjects may have TOD compared to oscillometric and central BP in young patients. However, the magnitude of the benefit in using mercury to predict TOD may not be clinically relevant. That said, there are other important reasons for recommending use of mercury sphygmomanometers to measure BP levels in children. First, normal values for BP in youth are based on mercury BP values.⁷ Second, there are insufficient normative data in youth to establish cut-points for oscillometric and central BP levels.

Many adult experts continue to recommend mercury sphygmomanometer usage because oscillometric devices need periodic calibration (every 6 months),²¹ which often can only be performed by the manufacturer.²² Our devices were maintained according to manufacturer recommendations. Failure to perform periodic calibration may result in misclassification rates varying from 15 to 31%.²³ Additionally, few devices have been validated in children (<http://www.dableducational.org/>) and one study suggested agreement depended upon the subjects' mean BP level with more underestimation of SBP in hypertensive and overestimation in normotensive youth.²⁴ Agreement between mercury and automatic devices also varies by device from nearly identical,²⁵ to as much as 10 mmHg difference.²⁶ The direction of the difference also varies with some devices consistently overestimating SBP^{27, 28} or DBP²⁹ compared to mercury and others underestimating SBP^{30, 31} or DBP.^{32, 33} There also appears to be a 'first reading effect' with the difference between the device and mercury diminishing on subsequent automatic recordings of BP.³² Although the Dynapulse device has not undergone strict validation testing according to either protocol, it has been applied simultaneously with mercury sphygmomanometry in large epidemiologic studies and a high reliability coefficient (0.85) and excellent precision (systolic and diastolic BP within 5 mmHg of mercury) was found.¹⁰ Furthermore, we used the 'auscultatory equivalent' BP levels supplied by the device that were 'calibrated' using Bogalusa Heart Study data in over 1000 subjects to be closer to mercury BP levels.

The consequence of error in BP measurement is that patients may be misclassified as being normotensive or having hypertension.^{34, 35} Current validation protocols give devices a passing grade even though the difference between the device and mercury is >5 mmHg up to 30% of the time.^{36, 37} Although small systematic differences may not seem clinically

relevant, in children, they can result in substantial errors in diagnosis as there is a narrow range between the percentiles defining pre- and true-hypertension.^{7, 38} Therefore it is not surprising that a study of high risk children with chronic kidney disease found oscillometric and mercury devices agreed on BP classification only 60% of the time.³⁹ Furthermore oscillometric machines have been proven less accurate in settings of increased vascular stiffness.⁴⁰ This would suggest that these types of devices may be less useful in identifying patients with hypertension-related arterial stiffening.

Use of estimated central aortic BP values in risk stratification is seeing increasing usage in adults with hypertension⁴¹ as central BP may be superior in predicting CV events.⁴² This is because intervening on a BP measured closer (central) to a target organ (i.e. the heart) may show a greater effect of a BP lowering treatment.⁴³ However, central to peripheral BP difference may be greater in hypertensive as compared to normotensive adults.⁴⁴ We also found a greater central-peripheral difference at higher BP levels (peripheral – central SBP for N = 9.4; P = 15.6; H = 17.7 mmHg). However, despite the apparent superiority of central BP in predicting events in adults, in our data, subjects classified by mercury BP were more likely to have TOD. Therefore, until more data on young subjects is available, we question the appropriateness of classifying young patients based on central BP measures.

Limitations

Lack of large scale multi-racial studies defining normal values for oscillometric and central BP levels in adolescents and young adults are lacking. Therefore, we used the most up-to-date pediatric guidelines⁷ to develop our BP z-scores. Although oscillometric BPs may be higher and central BPs may be lower due to pulse wave amplification along the arterial tree,⁴¹ calculating z-scores using data from the pediatric guidelines (N=63,227) would not change the rank order of subjects thus this approach still statistically robust. Using our lean subjects to derive z-scores would be problematic since stratifying this small number of individuals (N=275), by sex and height would lead to z-scores with wide confidence intervals possibly leading to inaccuracies in BP and height classification by the BPo and BPc techniques.

Another limitation is the lack of clear cut-points to define TOD in youth. We used the adult cut-point for LVH of 51 g/m^{2.7} which is heavier than the 95th% for LVM in a healthy children (39.4 g/m^{2.7} for males and 40.0 g/m^{2.7} for females 16 years old)⁴⁵ this is a more conservative approach. There are no published guidelines defining increased IMT in youth. However, in 635 adolescents and young adults in the Muscatine Offspring Study,⁴⁶ the mean (0.49 mm) and standard deviation (0.04) for composite IMT yielded a 95th% of 0.556 mm similar to the 95th% used in our study of 0.565 mm. Few studies of PWV in youth have been published. Regression equations from two large adult studies that included subjects 18 to 21 years of age, would result in an estimated 95th% for PWV for 18 year olds between 5.66 and 5.99 m/sec.^{47, 48} We used 6.57 m/sec based on the healthy lean subjects in our cohort, a more conservative estimate.

Our cohort of 1/3 diabetic subjects represents a higher risk group than seen in the average pediatrician's office. This may limit generalizability although there is no reason to suspect that BP levels relate to TOD in a different fashion in diabetics as compared to non-diabetic

individuals. Additionally, measurements were taken by trained research assistants, which may not reflect conditions in the average practitioner's office. However, all three BP measurement types were obtained by the same research assistant on the same day thus reducing this potential bias. Some researchers suggest that many young patients with 'high BP,' especially tall, thin, males, may actually have a benign condition called 'spurious hypertension' (hypertensive brachial BP value with normal central BP) that is associated with normal arterial stiffness.⁴⁹ We found only 3 subjects who were classified as hypertensive by mercury SBP and normotensive by central BP (data not shown), none of whom were tall or thin, therefore we do not believe this is a major factor confounding our results.

Conclusions

Further large scale studies are needed to develop normative data for oscillometric and central BP levels in adolescents and young adults as many institutions are removing mercury devices from use due to safety concerns and their operator dependence. This is one reason to continue to use mercury sphygmomanometers for evaluation of risk for hypertensive target organ damage. However, oscillometric and central BP measures relate to target organ damage in a similar fashion to mercury measures and may be suitable substitute in situations where mercury devices are prohibited.

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Figure 1.

LVM for normotensive, pre-hypertensive and hypertensive subjects classified by three methods of measuring BP.

****All model $P \leq 0.0001$. Models are unadjusted.***

Figure 2.

ROC curves for LVM by SBP z-score using three methods of measuring BP. Unadjusted models.

Table 1

Average values (mean and standard deviation) by BP category classified with mercury sphygmomanometry

Variable	N (N=469)		P (N=136)		H (N=72)		Significant Difference*
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	17.5	3.4	19.8	2.6	17.8	2.9	P>N&H
Sex (%Male)	30.3		48.5		40.3		H>P>N
Race (% Caucasian)	39.9		41.9		40.3		NS
% with T2DM	19.4		41.9		79.2		H>P>N
Height (cm)	165.6	9.9	170.8	10.0	170.4	11.6	P&H>N
Weight (kg)	78.8	25.8	103.2	29.1	114.2	28.6	H>P>N
BMI (kg/m ²)	28.5	8.6	35.4	9.9	39.1	8.4	H>P>N
Total Cholesterol (mg/dl)	168.4	33.1	180.3	38.7	169.2	36.4	P>N&H
LDL-C (mg/dl)	98.5	27.9	108.2	33.7	96.8	26.5	P>N&H
HDL-C (mg/dl)	51.6	12.6	46.6	12.5	42.8	11.6	N>P>H
Triglycerides (mg/dl)	90.4	54.2	123.9	79.9	140.6	109.3	P&H>N
Glucose (mg/dl)	101.2	42.0	123.1	68.7	132.1	66.9	P&H>N
Insulin (microU/ml)	16.8	10.5	20.5	13.0	34.1	20.6	H>P>N
HbA1c (%)	5.9	1.8	6.7	2.5	7.2	2.5	H>P>N
CRP (mg/L)	1.9	2.2	3.2	2.7	3.9	3.2	P&H>N
SBP mercury (mmHg)	109.4	8.4	125.1	6.1	133.3	12.9	H>P>N
DBP mercury (mmHg)	60.6	11.4	72.5	10.4	72.9	17.7	P&H>N
SBP oscillometric (mmHg)	113.8	9.8	124.7	10.0	132.5	13.0	H>P>N
DBP oscillometric (mmHg)	67.2	6.7	73.9	7.3	76.5	10.4	H>P>N
SBP central (mmHg)	100.0	8.9	109.4	8.6	115.7	12.3	H>P>N
DBP central (mmHg)	68.1	6.8	74.7	7.2	77.6	11.1	H>P>N
HR (beats/min)	65.4	10.6	66.3	10.8	72.4	11.4	H>N&P
Composite IMT (mm)	0.46	0.07	0.50	0.09	0.51	0.08	H>N&P
LVM (kg/m ^{2.7})	31.8	8.5	37.4	9.1	42.4	11.7	H>P>N
PWV (m/sec)	5.7	0.9	6.6	1.2	7.1	1.3	H>P>N

* ANOVA model P 0.0001 and parameter P 0.05.

Table 2

Comparison of C-statistic from logistic regression (fully adjusted models)

Measure of TOD	Mercury			Oscillometric			Central	
	SBP z-score	DBP z-score	SBP z-score	DBP z-score	SBP z-score	DBP z-score	SBP z-score	DBP z-score
IMT	0.707	0.733	0.72	0.712	0.719	0.711		
LVM	0.908	0.879	0.887	NS	0.883	NS		
PWV	0.799	0.821	0.796	0.806	0.792	0.807		

All model P 0.0001 and parameter P 0.05.