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LETTER

Relationship of carotid wall layers with noninvasively-measured central hemodynamic parameters and local circumferential wall tension

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Increased carotid intima-media thickness (cIMT) is a marker of cardiovascular risk [1], but it may represent distinct vascular processes: greater media thickness (cMT), typically associated with arteriosclerosis, and increased intima thickness (cIT), more closely linked to atherosclerosis [2–4]. Increased central blood pressure (cBP) and local hemodynamic forces, particularly carotid circumferential wall tension (CWT), are linked to cardiovascular events and augmented cIMT [5–8]; however, it remains unclear whether these associations are driven by cIT or cMT. A recent study showed that invasively-measured cBP was associated with cMT, but not with cIT [9]. Conversely, whether carotid CWT derived from cBP or peripheral blood pressure (pBP) measurements has distinct associations with carotid wall layers remains unknown. This study examined the relationship of noninvasively-measured cBP, additional central hemodynamics parameters [augmentation index (AIx) and pulse wave velocity (PWV)], pBP, and carotid CWT with carotid wall layers thickness.

We assessed clinical, carotid, and central hemodynamic parameters on the same day and extracted laboratory data from medical records dated within the prior six months for a convenience sample of 200 consecutive adults (>18 years) enrolled at an outpatient clinic in Paulo Afonso, Brazil, between 2021 and 2024. The study protocol was approved by the UNIRIOS Ethics Committee (45960621.9.0000.8166), and all participants provided written informed consent.

Carotid ultrasound was performed using a MyLabGamma ultrasound device (Esaote, Italy) equipped with a linear transducer (L3-11) set at 10 MHz by a skilled physician (Dr. Romero Barbosa). High-resolution images of both common carotid arteries were captured 2 centimeters proximal to carotid bifurcation. For each image, five measurements of cIT, cMT, and cIMT were manually obtained in plaque-free areas using ImageJ software (NIH, USA), as described previously [2, 3, 9]. Mean carotid wall layer values and internal diameters were obtained by averaging left and right carotid measurements. Prior studies reported intraobserver and interobserver variabilities <3 and <5%, respectively, for carotid wall sublayer measurements [2].

Systolic cBP (cSBP), diastolic cBP (cDBP), central pulse pressure (cPP), AIx, PWV, systolic pBP (pSBP), diastolic pBP (pDBP) and peripheral pulse pressure (pPP) were measured using the Arteris device (Cardios, Brazil), as previously described [10]. Each participant underwent three measurements taken in the sitting position at three-minute intervals, following a five-minute rest. The three readings were averaged for analysis. Peak carotid central CWT (cCWT) and peripheral CWT (pCWT) were estimated as (systolic cBP or pBP)*peak systolic internal diameter/2 [8].

Normally and non-normally distributed continuous variables are expressed as mean ± standard deviation and median [25th, 75th percentiles], while categorical variables are shown as proportions. Multivariable linear regression analyses assessed the associations between each hemodynamic parameter and carotid wall layers, entering only one hemodynamic variable per model and adjusting for age, sex, and other predictors independently linked to each layer, identified through forward stepwise regression. P-values < 0.05 were considered significant. Statistical analysis was performed using Stata 14.2.

The sample had age = 55 ± 14 years, 46% males, body mass index = 28.0 ± 4.8 kg/m^2, 5% smokers, 21% with diabetes, and 51% with hypertension. The values of pSBP, pDBP, pPP, cSBP, cDBP, cPP were 116.9 ± 15.3, 76.0 ± 10.8, 40.9 ± 10.7, 109.8 ± 14.3, 77.1 ± 10.9 and 32.7 ± 9.7 mmHg, respectively, while the values of PWV, AIx, peak pCWT and peak cCWT were 7.8 ± 2.0 m/s, 17.9 ± 10.9, 4.4 ± 0.9*10^{4}dyn/cm and 4.2 ± 0.8*10^{4}dyn/cm, respectively. Mean values of cIT, cMT, cIMT and carotid internal systolic diameter were 0.227 ± 0.042 mm, 0.423 ± 0.133 mm, 0.649 ± 0.148 mm and 5.7 ± 0.7 cm. The values of fasting glucose, LDL-cholesterol, HDL-cholesterol, triglycerides and creatinine were 95 [88, 107], 113 ± 38, 51 ± 13, 124 [97, 173] and 0.90 ± 0.22 mg/dL. There were 28, 32, 9, 9, 18 and 12% using statins, angiotensin-receptor blockers, angiotensin-converting-enzyme inhibitors, calcium-channel blockers, diuretics and beta-blockers, respectively

Supplemental Table 1 presents the unadjusted associations between clinical and laboratory variables and carotid parameters. Stepwise regression including studied clinical and laboratory

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Table 1. Multivariable linear regression analysis between hemodynamic parameters and carotid wall layers.

Variable	cIT*		cMT**		cIMT**	
	beta±SE	p-value	beta±SE	p-value	beta±SE	p-value
pSBP	0.01±0.19	0.98	0.98±0.53	0.06	1.02±0.58	0.08
pDBP	−0.02±0.28	0.95	0.46±0.77	0.55	0.50±0.84	0.55
pPP	0.03±0.28	0.91	1.58±0.76	0.039	1.63±0.83	0.053
cSBP	0.07±0.21	0.73	1.12±0.56	0.047	1.23±0.61	0.045
cDBP	−0.03±0.28	0.92	0.55±0.76	0.72	0.59±0.84	0.48
cPP	0.19±0.31	0.54	1.84±0.83	0.029	2.05±0.91	0.026
AIx	−0.14±0.28	0.61	0.32±0.77	0.68	0.17±0.84	0.84
PWV	−2.06±4.24	0.63	12.46±11.60	0.28	10.32±12.70	0.42
Peak pCWT	−0.76±3.72	0.84	19.37±10.08	0.06	19.31±11.04	0.08
Peak cCWT	0.07±4.04	0.99	22.13±10.91	0.044	23.07±11.95	0.06

cIT, cMT and cIMT values (in mm) were multiplied by 1000 before entering the multivariable models.
Only one hemodynamic parameter was included at a time in each model.
pSBP peripheral systolic blood pressure, *pDBP* peripheral diastolic blood pressure, *pPP* peripheral pulse pressure, *cSBP* central systolic blood pressure, *cDBP* central diastolic blood pressure, *cPP* central pulse pressure, *PWV* pulse wave velocity, *AIx* augmentation index, *cCWT* circumferential wall tension estimated by central blood pressure, *pCWT* circumferential wall tension estimated by peripheral blood pressure, *cIT* carotid intima thickness, *cMT* carotid media thickness, *cIMT* carotid intima-media thickness.
*Analyses were adjusted for age, sex and diuretics use.
**Analyses were adjusted for age and sex. Hypertension was not included in the model due to the risk of collinearity with hemodynamic parameters.

variables showed that cIT was associated with age and diuretics use, while cMT and cIMT were associated with age and hypertension (Supplemental Table 2).

Table 1 presents the results of adjusted linear regression analyses examining the relationship between hemodynamic parameters and carotid wall layers. cSBP and cPP were independently associated with cMT and cIMT, but not with cIT. Peak cCWT and pPP were independently associated solely with cMT. Among all measurements, cPP showed the strongest association with cMT and cIMT. Lastly, pSBP, pDBP, cDBP, PWV, AIx and peak pCWT did not independently associate with any carotid layer. As an exploratory analysis, cSBP and cPP thresholds of 121 and 33 mmHg showed the best ROC-based performance for identifying cMT values above the 95th percentile (0.659 mm), considered abnormal in this study.

Previous reports demonstrated associations of cBP and CWT with cIMT [6, 8]. Our findings extend this evidence by demonstrating that the associations of cSBP and cPP with cIMT are driven predominantly by increases in cMT rather than cIT. Moreover, cBP was more strongly associated with carotid wall thickness than pBP, and only CWT estimated using cBP, but not from pBP, was independently associated with cMT. Together, these findings suggest that noninvasive cBP measurements may be more reliable markers of adverse carotid remodeling and may better estimate local carotid hemodynamic forces than conventional pBP measurements.

A key finding of this study was that cPP, cSBP and cCWT were significantly associated with cMT, but not with cIT. Notably, cPP exhibited the most significant association with cMT among all studied hemodynamic parameters. These findings suggest that cBP and cBP-derived local hemodynamic measurements may be better markers of carotid arteriosclerosis rather than of atherosclerosis. Additionally, they indicate that arteriosclerotic changes in elastic arteries are more strongly reflected in cPP than in pBP, reinforcing the concept that pulsatile hemodynamics in central arteries substantially differs from those in peripheral muscular arteries [5]. Conversely, the direct associations of cPP, cSBP, and cCWT with cMT may reflect vascular smooth muscle cell responses to elevated local mechanical stress [11], promoting hypertrophy and extracellular matrix deposition that ultimately increase cMT [11].

Some aspects of our report warrant further discussion. First, consistent with our findings, Mello et al. [9] reported a direct association between cSBP and cMT using invasively-measured cSBP. Notably, they observed that this association reversed when cSBP exceeded approximately 150 mmHg, yielding an inverted U-shaped relationship. In our study, however, only one participant had cSBP >150 mmHg, which may have limited our ability to detect a similar non-linear pattern. Second, the observed association between CWT and cMT suggests that arteriosclerotic changes may contribute to the elevated cardiovascular risk associated with increased carotid CWT [7].

This study has limitations. Its cross-sectional design limits causal inferences and the single-center sample may reduce generalizability. Unmeasured inflammatory and metabolic factors may also influence artery wall alterations and could have affected the magnitude of the present findings. No direct comparison between ultrasound and histopathologic characteristics of the carotid wall was performed; however, prior studies demonstrated good correlations of carotid wall layers when measured by both methods [12]. Lastly, the use of a relatively small convenience sample may have limited our ability to detect additional significant associations, particularly between carotid parameters and pBP.

In conclusion, this study provides novel evidence that the associations of cSBP and cPP with cIMT are mediated by increases in cMT, and that cBP and cCWT show stronger associations with carotid wall thickness, particularly cMT, than pBP and pCWT. These findings support cBP as a potential marker of specific components of adverse carotid remodeling.

SUMMARY

What is known about topic

- Increased carotid intima-media thickness (cIMT) may result from thickening of either the intimal (cIT), more closely linked to atherosclerosis, or medial (cMT) layers, typically associated with arteriosclerosis.
- Increased central blood pressure (cBP) and local hemodynamic forces, particularly carotid circumferential wall tension (CWT), are linked to augmented cIMT, but it is less known whether these associations are driven by cIT or cMT.

What this study adds

- Associations of noninvasively-measured cBP with cIMT are mediated by increases in cMT and not in cIT.
- cBP and CWT derived from cBP show stronger associations with carotid wall thickness, particularly cMT, than peripheral blood pressure and CWT derived from peripheral blood pressure.
- Noninvasively-measured cBP may serve as a potential marker of specific components of adverse carotid remodeling.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are not publicity available but are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

RomB, and WNJ contributed to the conception and design of the work. RodB, DM, EBSN, ADMF, MAM-G, AMGP, WSB, ECDB, RTPO, LBCJ, JLL-F, JRM-S and ACS contributed to the acquisition, analysis, or interpretation of data for the work. RomB, RodB and WNJ drafted the manuscript. DM, EBSN, ADMF, MAM-G, AMGP, WSB, ECDB, RTPO, LBCJ, JLL-F, JRM-S and ACS critically revised the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

The study protocol was approved by the UNIRIOS Ethics Committee (number 45960621.9.0000.8166), and all participants provided written informed consent.

ADDITIONAL INFORMATION

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