Pressure-Corrected Carotid Stiffness and Young’s Modulus: Evaluation in an Outpatient Clinic Setting

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BACKGROUND
Conventional measures for assessing arterial stiffness are inherently pressure dependent. Whereas statistical pressure adjustment is feasible in (larger) populations, it is unsuited for the evaluation of an individual patient. Moreover, statistical “correction” for blood pressure may actually correct for: (i) the acute dependence of arterial stiffness on blood pressure at the time of measurement; and/or (ii) the remodeling effect that blood pressure (hypertension) may have on arterial stiffness, but it cannot distinguish between these processes.

METHODS
We derived—assuming a single-exponential pressure–diameter relationship—3 theoretically pressure-independent carotid stiffness measures suited for individual patient evaluation: (i) stiffness index \( \beta_0 \), (ii) pressure-corrected carotid pulse wave velocity \( \text{cPWV}_{\text{corr}} \), and (iii) pressure-corrected Young’s modulus \( E_{\text{corr}} \). Using linear regression analysis, we evaluated in a sample of the CATOD study cohort changes in mean arterial pressure \( \Delta \text{MAP} \) and comparatively the changes in the novel \( \Delta \beta_0 \), \( \Delta \text{cPWV}_{\text{corr}} \), and \( \Delta E_{\text{corr}} \) as well as conventional \( \Delta \text{cPWV} \) and \( \Delta E \) stiffness measures after a 2.9 ± 1.0-year follow-up.

RESULTS
We found no association between \( \Delta \text{MAP} \) and \( \Delta \beta_0 \), \( \Delta \text{cPWV}_{\text{corr}} \), or \( \Delta E_{\text{corr}} \). In contrast, we did find a significant association between \( \Delta \text{MAP} \) and conventional measures \( \Delta \text{cPWV} \) and \( \Delta E \). Additional adjustments for biomechanical confounders and traditional risk factors did neither materially change these associations nor the lack thereof.

CONCLUSIONS
Our newly proposed pressure-independent carotid stiffness measures avoid the need for statistical correction. Hence, these measures \( \beta_0 \), \( \text{cPWV}_{\text{corr}} \), and \( E_{\text{corr}} \) can be used in a clinical setting for (i) patient-specific risk assessment and (ii) investigation of potential remodeling effects of (changes in) blood pressure on intrinsic arterial stiffness.

Keywords: arterial remodeling; arterial stiffness; blood pressure; hypertension; pressure dependence

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Arterial stiffness measures are increasingly used in cardiovascular risk management.\textsuperscript{1–3} However, current measures are inherently pressure dependent, which confounds measured changes in arterial stiffness in a treatment setting.\textsuperscript{4,5} Usually, this pressure dependence is corrected for by adjusting for mean arterial pressure (MAP) in multivariable regression models. Whereas such statistical adjustment is feasible in (larger) populations, it is unsuited for the evaluation of an individual patient.\textsuperscript{4,6} Adjustment would be especially relevant in patients receiving antihypertensive drugs, where consequently measured changes in arterial stiffness may not necessarily reflect changes in intrinsic arterial wall properties. Moreover, statistical "correction" for blood pressure may actually correct for 2 processes\textsuperscript{6}: (i) the acute dependence of arterial stiffness on blood pressure at the time of measurement; and/or (ii) the remodeling effect that blood pressure (hypertension) may have on arterial stiffness in the long term, but it cannot distinguish between these processes. Therefore, pressure-independent arterial stiffness measures are much needed to accurately assess progression or regression of arterial stiffening in individual patients in a clinical setting.

Recently, we demonstrated a method that allows the calculation of a theoretically pressure-independent stiffness index $\beta_{0}$.\textsuperscript{7,8} The $\beta_{0}$ method uses an established single-exponential model (fitted to data from ultrasound and blood pressure measurements) to describe the pressure–diameter curve of an artery for an individual patient.\textsuperscript{9} For the carotid artery, local stiffness can be expressed as (carotid) pulse wave velocity (cPWV) using the Bramwell–Hill equation.\textsuperscript{5,10} In the present paper, we combine the Bramwell–Hill equation and single-exponential model to derive cPWV for a pre-defined pressure range (e.g., 80–120 mm Hg). The resultant pressure-corrected measure is (theoretically) fully pressure independent.

Stiffness index $\beta_{0}$ and cPWV are structural stiffness measures describing the dynamic elastic property of the artery as a whole. As such, they depend on material stiffness, as well as artery size and geometry. Provided that wall thickness measurements are also available, the above approach may also be used to derive a pressure-corrected incremental Young's modulus, which is a measure for wall material stiffness.\textsuperscript{1,11,12}

In the present paper, we derive pressure-corrected versions of cPWV (cPWV\textsubscript{corr}) and carotid artery Young's modulus $E$ (E\textsubscript{corr}) and comparatively evaluate them against their conventional counterparts (and $\beta_{0}$) in a clinical outpatient setting.\textsuperscript{13}

**METHODS**

**Study population**

The present study utilizes data of a cross-sectional study on carotid and aortic stiffness in essential hypertension in relation to classical cardiovascular risk factors and target organ damage (the CATOD study).\textsuperscript{13} Briefly, hypertensive patients were recruited from the hypertension outpatient clinic of the University Hospital of Pisa, Italy, between September 2007 and January 2011. Main exclusion criteria were known secondary forms of hypertension, end-stage renal disease, any other major comorbidities, and any other disease reducing life expectancy to less than 1 year.\textsuperscript{13} Patients were followed up after 2.9 ± 1.0 years (mean ± SD). Arterial stiffness assessment was part of their routine follow-up. The total CATOD population comprised 450 patients, of which 147 had follow-up measurements. For the present analysis, we included all consecutive outpatients that had complete vascular assessments at baseline and follow-up ($n=126$).

**Measurements**

The detailed measurement protocol is described elsewhere.\textsuperscript{13} In short, brachial blood pressures were measured under quiet conditions after the patient had rested in supine position for at least 10 minutes. Three consecutive measurements were taken at 2-minute intervals using an automatic oscillometric device (OMRON-705IT, Omron Corporation, Kyoto, Japan). Systolic ($P_{s}$) and diastolic ($P_{d}$) brachial blood pressures were taken as the averages of the respective second and third blood pressure readings. Common carotid artery B-mode scans (at a frame rate of 25 Hz) were obtained by a trained operator using a high-resolution ultrasound scanner with a 10 MHz linear array transducer (MyLab25; ESAOTE, Florence, Italy). Regular B-mode recordings provide reliable estimates of diameter and distension, if averaged over a sufficient number of beats.\textsuperscript{14,15} Specifically, the left common carotid artery was imaged at least 1 cm proximal to the carotid bulb in longitudinal orientation over a 1-cm-wide region (visually) free of plaques. The recordings were analyzed with commercial software (Carotid Studio, Cardiovascular Suite, Quipu srl, Pisa, Italy) validated for accuracy and precision against the gold-standard radiofrequency approach.\textsuperscript{14} Briefly, the software automatically detects arterial interfaces and estimates the instantaneous mean diameter as the distance between far and near media–adventitia interfaces. Intima–media thickness (IMT) was estimated at (end-)diastole as the spatial average of the far wall lumen–intima to media–adventitia interfaces. Intima–media thickness (IMT) was estimated at (end-)diastole as the spatial average of the far wall lumen–intima to media–adventitia interface distances, as previously described.\textsuperscript{14} The (left) common carotid artery systolic ($D_{s}$) and diastolic ($D_{d}$) diameters and IMT thus obtained were used to calculate carotid stiffness and Young's modulus. Figure 1 shows how the measurements are used to calculate outcome measures, as further detailed in the next section.

**Calculations**

The following calculations were performed using SPSS version 26 (IBM Corp, Armonk, NY).

**Conventional carotid stiffness measures** Local cPWV (in m/s) was estimated using the Bramwell–Hill equation\textsuperscript{16}:

\[
cPWV = \sqrt{\frac{P_{s} - P_{d}}{D_{s} - D_{d}} \cdot \frac{D_{d}}{2\rho}} \tag{1}
\]
Blood mass density, taken to be 1,050 kg/m³. The Bramwell–Hill equation was subsequently calculated using the rearranged Moens–Korteweg equation:

\[ E = \frac{P_{\text{ref}} \cdot D_s \cdot \rho}{\ln \left( \frac{D_s}{D_{\text{ref}}} \right) - 1} \]  

(4)

using a reference pressure \(P_{\text{ref}}\) of 100 mm Hg.7

Pressure-corrected cPWV and Young’s modulus Pressure-corrected versions of conventional cPWV \(c\text{PWV}_{\text{corr}}\) and \(E_{\text{corr}}\) were derived, based on the relationship given in equation (3). Full details on the derivation are given in Supplementary Digital Content 1 online.

Briefly, \(c\text{PWV}_{\text{corr}}\) and \(E_{\text{corr}}\) were obtained by the following consecutive steps: (i) parameterizing the exponential pressure–diameter \((P–D)\) relationship (finding \(\beta_0\) and \(D_{\text{ref}}\)) for each individual patient, (ii) calculating the diameters at predefined pressures of 120 and 80 mm Hg using the individualized \(P–D\) relationship, (iii) correcting IMT to 80 mm Hg to obtain \(IMT_{\text{corr}}\) (assuming incompressibility), and (iv) inputting the obtained values in equations (1) and (2) to calculate \(c\text{PWV}_{\text{corr}}\) and \(E_{\text{corr}}\).

Statistical analysis

Values are given as mean ± SD, unless noted otherwise. Because stiffening processes presumably have cumulative effects with progression of time17 and follow-up time varied between individuals, we normalized changes to the follow-up period, with Δs defined as: (follow-up value–baseline value)/(follow-up time in years) (Figure 1).

Changes between baseline and follow-up measurements were compared with a paired \(t\)-test for continuous variables, and McNemar’s test for categorical variables. We used multivariable linear regression analysis to assess to what extent the changes-over-time in the pressure-corrected \((\Delta c\text{PWV}_{\text{corr}}, \Delta E_{\text{corr}}\) and \(\Delta \beta_0\) and conventional \((\Delta \text{cPWV} \) and \(\Delta E\) \) measures were associated with the corresponding change in mean arterial pressure \((\Delta \text{MAP}; \) crude model) Model 2 was additionally adjusted for biomechanical factors \(\Delta \text{IMT}, \Delta \text{HR}, \) and drugs. Drugs were defined as a categorical variable for using antihypertensive drugs at follow-up (no drugs, 1 type of antihypertensive drugs, 2, or more types of antihypertensive drugs). Because IMT is mathematically related to \(E\) (see above), we did not include \(\Delta \text{IMT}_{\text{corr}}\) and \(\Delta \text{IMT}\) in the models 2 and 3 for \(\Delta E\) and \(\Delta E_{\text{corr}}\) to avoid collinearity. Model 3 was additionally adjusted for age, sex, smoking (yes/no), body mass index (BMI), diabetes (yes/no), and hypercholesterolemia (yes/no). For age, BMI, diabetes, and hypercholesterolemia, the value or status at baseline was taken (as applicable).

All statistical analyses were performed using SPSS (SPSS version 26, IBM Corp, Armonk, NY). A 2-sided \(P\) value ≤0.05 was considered statistically significant.

**RESULTS**

**Study population**

The total study population consisted of 126 patients, from which 2 were excluded because of missing covariates
(n = 1 for BMI, n = 1 for use of antihypertensive drugs) in 1 of the 2 visits. The main regression analysis was ultimately performed with 124 patients. Table 1 shows an overview of the general characteristics of the final study population. The mean follow-up time was 2.9 ± 1.0 years. Diastolic blood pressure and MAP were statistically significantly lower at follow-up compared with baseline. Heart rate and diastolic diameter were statistically significantly higher during follow-up. Although systolic blood pressure was lower during follow-up, this result was not statistically significant.

Group averages and SDs of the pressure-corrected and conventional carotid stiffness measures are shown in Table 2. By definition, the pressure-corrected measures were lower than their conventional counterparts, because the correction normalizes toward a normotensive pressure range of 120/80 mm Hg (systolic/diastolic). All carotid stiffness measures were statistically higher at follow-up compared with baseline.

**Carotid stiffness**

Table 3 shows the regression models for ΔcPWV and ΔcPWV corr. There was a significant positive relationship between ΔMAP and ΔcPWV (β = 0.023, confidence interval, CI: [0.000; 0.045] m/s/mm Hg, P = 0.047). For ΔcPWV corr, there was no significant relation with ΔMAP (β = −0.018, CI: [−0.040; 0.003] m/s/mm Hg, P = 0.091). Further adjustments in models 2 and 3 did not materially change these associations (Table 3).

### Table 1. Study population characteristics and carotid artery dimensions

| Parameter                              | Baseline | Follow-up |
|----------------------------------------|----------|-----------|
| Sex (# of m/f)                         | 83/41    | —         |
| Age (years)                            | 57.7 ± 8.6 | 61.8 ± 9.0** |
| Smoking (number, %)                    | 24 (19.4%) | 24 (19.4%) |
| Diabetes (number, %)                   | 35 (28.2%) | 35 (28.2%) |
| Hypercholesterolemia (number, %)       | 84 (67.7%) | 63 (67.7%)* |
| Antihypertensive drugs (number, %)     | 82 (66.1%) | 109 (87.9)** |
| Ps (mm Hg)                             | 142 ± 14 | 141 ± 17 |
| Pd (mm Hg)                             | 82 ± 9   | 79 ± 11** |
| MAP (mm Hg)                            | 102 ± 9  | 100 ± 11* |
| BMI (kg/m²)                            | 28.3 ± 4.0 | 28.1 ± 4.2 |
| Heart rate (bpm)                       | 68 ± 11  | 71 ± 12** |

Data are presented as mean ± SD, n = 124. Abbreviations: BMI, body mass index; Dd, diastolic common carotid diameter; IMT, common carotid intima media thickness (at diastolic pressure); MAP, mean arterial pressure; Pd, diastolic blood pressure; Ps, systolic blood pressure.

* = n = 93 due to missing information during follow-up.

Follow-up (2.9 ± 1.0 years) values were tested against baseline values using paired t-tests: *P < 0.05, **P < 0.001.

### Table 2. Conventional and corrected carotid dimensions and stiffness measures

| Parameter                              | Baseline | Follow-up | Δ (unit/year) |
|----------------------------------------|----------|-----------|---------------|
| IMT (mm)                               | 0.75 ± 0.15 | 0.78 ± 0.18 | 0.01 ± 0.08  |
| IMT corr (mm)                          | 0.76 ± 0.15 | 0.78 ± 0.18 | 0.01 ± 0.08  |
| Dd (mm)                                | 7.24 ± 0.85 | 7.55 ± 0.87 | 0.12 ± 0.30** |
| Dd corr (mm)                           | 7.20 ± 0.87 | 7.56 ± 0.88 | 0.13 ± 0.30** |
| cPWV (m/s)                             | 7.5 ± 1.3  | 7.7 ± 1.2  | 0.1 ± 0.6*   |
| cPWV corr (m/s)                        | 7.1 ± 1.2  | 7.5 ± 1.2  | 0.1 ± 0.6*   |
| E (MPa)                                | 0.59 ± 0.23 | 0.65 ± 0.23 | 0.02 ± 0.11* |
| E corr (MPa)                           | 0.53 ± 0.20 | 0.61 ± 0.22 | 0.03 ± 0.10** |
| \(\beta_0\)                            | 8.5 ± 2.9  | 9.3 ± 2.9  | 0.3 ± 1.3*   |

Data are presented as mean ± SD, n = 124. Δ = (follow-up value – baseline value)/(follow-up time in years). Abbreviations: \(\beta_0\), pressure-independent stiffness index; cPWV, carotid pulse wave velocity; cPWV corr, pressure-corrected cPWV; Dd, diastolic diameter; Dd corr, diameter corresponding to a pressure of 80 mm Hg; E, Young’s modulus; E corr, pressure-corrected Young’s modulus; IMT, intima media thickness; IMT corr, IMT corresponding to a pressure of 80 mm Hg.

Follow-up (2.9 ± 1.0 years) values were tested against baseline values using paired t-tests: *P < 0.05, **P < 0.001.
Notably, \( \Delta \text{IMT} \) was the only other significant determinant of \( \Delta \text{cPWV} \) in model 2 (\( \beta = 1.859, \text{CI}: [0.494; 3.224] \) m/s/mm, \( P = 0.008 \); data not shown in Table 3). In the final model (model 3), \( \Delta \text{IMT} \) remained a significant determinant of \( \Delta \text{cPWV} \) (\( \beta = 1.967, \text{CI}: [0.554; 3.380] \) m/s/mm, \( P = 0.007 \)). These findings were corroborated by the fact that in model 2, \( \Delta \text{IMT}_\text{corr} \) was the only significant determinant of \( \Delta \text{cPWV}_\text{corr} \) (\( \beta = 1.573, \text{CI}: [0.253; 2.894] \) m/s/mm, \( P = 0.020 \)) which persisted in model 3 (\( \beta = 1.694, \text{CI}: [0.328; 3.060] \) m/s/mm, \( P = 0.016 \)).

### Carotid Young's modulus

The change in MAP was a significant determinant of \( \Delta E \) (\( \beta = 0.007, \text{CI}: [0.003; 0.012] \) MPa/mm Hg, \( P = 0.001 \)) but not of \( \Delta E_{\text{corr}} \) (\( \beta = -0.001, \text{CI}: [-0.005; 0.002] \) MPa/mm Hg, \( P = 0.446 \)). Further adjustments in models 2 and 3 did not materially change these associations (Table 3).

### Stiffness index \( \beta_0 \)

Table 4 shows that, already in the crude model, \( \Delta \text{MAP} \) was not a significant determinant of \( \Delta \beta_0 \) (\( \beta = -0.042, \text{CI}: [-0.092; 0.009] \) mm Hg\(^{-1} \), \( P = 0.103 \)). Further adjustments in models 2 and 3 did not materially change the association (Table 4). \( \Delta \text{IMT} \) was a significant determinant of \( \Delta \beta_0 \) in models 2 and 3 (respectively: \( \beta = 3.422, \text{CI}: [0.321; 6.522] \) mm\(^{-1} \), \( P = 0.031 \); and \( \beta = 3.654, \text{CI}: [0.442; 6.866] \) mm\(^{-1} \), \( P = 0.026 \)).

### DISCUSSION

In the present study, we tested 3 novel pressure-corrected carotid artery stiffness measures (\( \beta_0, \text{cPWV}_\text{corr} \), and \( E_{\text{corr}} \)) in a hypertensive outpatient population followed up at 2.9 ± 1.0 years. We evaluated the association of changes in these novel measures and their conventional counterparts with changes in MAP as observed over the follow-up period. The changes in the conventional stiffness measures (cPWV and \( E \)) were significantly related to the changes in MAP, while the changes in the pressure-corrected measures were not. This finding is essential, as it illustrates the (known) pressure dependence of conventional stiffness measures. More importantly, the pressure-independent indices allow discrimination of potential remodeling effects due to blood pressure (hypertension), from acute confounding of blood pressure during vascular measurements.

An advantage of the presented pressure corrections is that they do not require any additional measurements. Therefore, reanalysis of existing datasets is possible. Both \( \Delta \beta_0 \) and \( \Delta \text{cPWV}_\text{corr} \) can be readily calculated when transverse carotid (or aortic) cyclic dimensions are available. In addition, regional (i.e., transit time) pulse wave velocity measurements can be similarly pressure corrected. When IMT data are also recorded during such measurements (as done in the present study), it is possible...
to gain additional information on material stiffness of the carotid wall, using the pressure-corrected Young's modulus, $E_{\text{corr}}$. This provides information on the material properties of the wall at a normalized pressure (of 80 mm Hg in this case). In our calculations, we assumed the artery wall to consist of a single, homogeneous material. Therefore, $E_{\text{corr}}$ represents the “average” material stiffness of the wall material.

In our statistical analyses, $\Delta$IMT was shown to be positively correlated to $\Delta$cPWV and, similarly, $\Delta$IMT$_{\text{corr}}$ was associated with $\Delta$cPWV$_{\text{corr}}$. Such associations are consistent with the Moens–Korteweg relationship (equation (2)), in which an isolated increase in vessel wall thickness will increase local pulse wave velocity.$^{1,11}$ Changes in carotid wall thickness have been described in relation to wall stress adaptation, with an increased IMT reflecting compensatory action to normalize wall stress.$^{1,21}$

In the present study, we did not find statistically significant associations between the change in stiffness measures and known risk factors (model 3). It is important to note that we assessed associations of “single-point accounts” of risk factors with changes in carotid stiffness over time and that this population showed a globally well controlled cardiovascular profile, achieved by an increase in use of cardiovascular medication over time. The present results indicate that there may not be a difference in the change of carotid stiffness or Young’s modulus related to age, sex, diabetes, smoking, or hypercholesterolemic status. Using actual blood glucose and total cholesterol levels (normalized to follow-up time) instead of the categorical variables diabetes and hypercholesterolemia did not lead to different results. Presumed there may be such differences, the follow-up time in the present study may have been insufficient to reveal them.

In our analysis, we chose to only use antihypertensive drug use as an explanatory variable, and not to stratify for different classes and dosages of drugs. This choice was made to avoid overfitting of our models. In the 10-year follow-up MESA study cohort, Gepner et al. found no consistent association of stiffness progression with specific antihypertensive drug classes, whereas plain blood pressure control as such was a clear determinant.$^{22}$ In future studies targeting arterial wall destiffening by specific drugs in outpatients, the pressure-corrected measures could be especially useful. Because the proposed measures are theoretically pressure-independent, statistical blood pressure correction can be avoided, potentially allowing smaller sample sizes in such studies.

The pressure correction as presented here is subject to an assumed single-exponential relationship between pressure and diameter (equation (3)).$^{9,23}$ Consequently, the correction will leave residual pressure dependence in case the pressure–diameter relation has a higher-order curvilinearity. This may potentially be the case in hypertensive and/or younger subjects, where elastin dominates arterial mechanics.$^{7,24}$

Finally, the total CATOD cohort comprised 450 patients.$^{19}$ Compared with patients that did not have a follow-up measurement, the patients included in this study had a less favorable cardiovascular risk profile and higher blood pressure (Supplementary Table S1 online). A possible explanation is that patients with better controlled hypertension and/or with a relatively favorable cardiovascular risk profile are often referred back to the GP. Therefore, our follow-up cohort might not be representative of the general hypertensive population.

In conclusion, our newly proposed pressure-independent carotid stiffness measures do not require statistical correction. Hence, these measures ($\beta_{\text{corr}}$, $\text{cPWV}_{\text{corr}}$ and $E_{\text{corr}}$) can be used in a clinical setting for (i) patient-specific risk assessment and (ii) investigation of potential remodeling effects of (changes in) blood pressure. Moreover, these measures may allow smaller sample sizes in intervention studies targeting arterial wall destiffening.

**SUPPLEMENTARY MATERIAL**

Supplementary data are available at American Journal of Hypertension online.

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**AUTHORS’ CONTRIBUTION**

S.T., L.G., and R.M.B. contributed to data acquisition; M.B., B.S., S.B., and K.D.R. contributed to data curation, formal analysis, and writing of the original manuscript; M.H.G.H., S.T., L.G., T.D., and R.M.B. critically edited and revised the manuscript.

**DISCLOSURE**

L.G. is a cofounder of QUIPU srl, a spin-off company of the National Research Council and the University of Pisa, Italy.

**DATA AVAILABILITY**

The data underlying this article will be shared on reasonable request to the corresponding author.

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