

Association of Local Arterial Stiffness and Windkessel Model Parameters with Ageing in Normotensives and Hypertensives

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Abstract— Computation of arterial stiffness is a well-established, widely accepted method for estimating vascular age. Although carotid-femoral pulse wave velocity is typically used for vascular age assessment, most recent studies have reported the need to consider a combination of local and regional stiffness indices possessing distinct association with the vascular structure and/or function for better prediction of early vascular ageing syndrome. In this work, we investigate the association of clinically validated local stiffness (obtained using biomechanical relations), global stiffness (obtained from 3-element Windkessel modelling), and pulse contour indices from the aorta with ageing and their distribution in normotensives and hypertensives. The analysis was performed on 420 (virtual) subjects (age: 65 ± 11 years) with an equal proportion of hypertensive (age: 65 ± 11 years) and normotensive (age: 65 ± 11 years) subjects. Multivariate linear regression analysis revealed an independent association of each of the indices with age (Adjusted $r = 0.75$, $p < 0.01$). Specific stiffness index ($r = 0.67$, $p < 0.001$), Augmentation index ($r = 0.55$, $p < 0.001$) and total arterial compliance ($r = -0.50$, $p < 0.001$) depicted highest correlation with age. There was a significant difference ($> 16\%$, $p < 0.001$) in mean values of the measured indices between hypertensive and normotensive subjects. The study findings further emphasize the need to combine multiple non-invasive vascular markers to capture the unique aspects of age-induced arterial wall remodelling for reliable monitoring and management of the early vascular ageing syndrome.

Clinical Relevance— This study demonstrates an independent and combined predictive role of local/global stiffness and pulse contour indices in ageing.

Keywords — Arterial stiffness, Hypertension, Vascular ageing, Vascular markers, Windkessel model

I. INTRODUCTION

Advancing vascular age is a highly potent risk factor for predicting future cardiovascular events, majorly manifested as impaired vascular structure and function [1]. The influence of cardio-metabolic risk factors, physical inactivity, genetic factors, as well as lifestyle patterns found to accelerate ageing of the blood vessels, resulting in a phenomenon widely known as Early Vascular Ageing (EVA) syndrome [2]. Vascular

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ageing progresses with acute change in the biomechanical, structural, and functional properties of vessel walls [1]. Major adaptations in the vasculature are seen in the central elastic arteries, such as the aorta and carotid artery, with endothelial dysfunction, fragmentation of elastin fibres, accumulation of collagen, and deposition of calcium salts. Their combinational effect indeed accelerates the thickening and stiffening of arterial walls and alters the characteristics and buffering capacity of blood vessels, resulting in EVA.

Traditionally, vascular ageing is assessed using the well-known prediction model called the Framingham heart age [3], where cardiovascular risk factors such as the High-Density Lipoprotein Cholesterol, systolic blood pressure, gender, chronological age, smoking, etc., are used to predict or estimate the age of one's blood vessel. Further, the addition of non-invasive vascular biomarkers (measured via imaging) to conventional cardiovascular risk factors exhibited a better predictive performance [4]. The vascular biomarker is typically studied as the age-induced changes in mechanical, structural, and functional properties of large elastic arteries [1] and is captured using regional/global vascular stiffness indices and pulse contour indices [3][4]. Studies conducted for the assessment of vascular ageing by integrated measurement of the carotid or aortic intima-media thickness and the traditional stiffness markers such as the carotid-femoral pulse wave velocity and augmentation index have shown the efficiency of a reliable combination of biomarkers for improved cardiovascular risk stratification [4].

In this work, we investigate the association of clinically validated [5] (i) local stiffness indices obtained using established biomechanical relations [6], (ii) global stiffness indices derived from the three-element Windkessel modelling [7], and (iii) pulse contour indices [8] from the aorta, with ageing and their distribution in normotensives and hypertensives. The aortic (systolic and diastolic) blood pressure, lumen diameter, and distension values are used to evaluate the local vascular stiffness indices (refer [6] for equations), namely, specific stiffness index (β), pressure-strain elastic modulus (E_p), arterial compliance (AC), and local pulse wave velocity (PWV). A three-element Windkessel equivalent model of the arterial system is used to find the global stiffness indices [7], namely, total peripheral resistance (TPR), total arterial compliance (TAC) and characteristic impedance (Z_c) (Three-element model was chosen for minimizing the computational complexity while ensuring acceptable model accuracy). The augmentation index (AIx) was used as the pulse contour index and evaluated from the pressure signal following established techniques [8].

These indices, henceforth, together referred to as ‘vascular health markers’.

The correlation between vascular health markers and age was investigated, and associated changes in their values for hypertensive and normotensive subjects were evaluated. A multivariate linear regression analysis was also performed to assess their combined effect on ageing. A brief of the study materials and methods is presented in Section II. A detailed discussion on the results and observations are discussed in Section III, followed by limitations and future scope. The study conclusions are outlined in Section IV.

II. MATERIALS AND METHODS

A. Study Population

The sample space for the study was taken from the virtual subject database developed by the Hemodynamic Modelling Research Group of Kings College, London, UK [9], created by varying the haemodynamic parameters of a healthy subject. The sample space used for the present analysis included 420 subjects aged between 35 – 75 years, consisting of an equal proportion of both hypertensive and normotensive subjects (210 subjects in each category). The age distribution for both groups was selected evenly to ensure data diversity.

B. Measurement of Vascular Health Markers.

For the calculation of aforesaid vascular health markers for the aorta, the blood pressure (in mmHg), flow velocity (in m/s), and luminal diameter (in mm) waveforms at the aortic root were taken from the selected subset and sampled at 500 Hz. A continuous waveform of signals described above was generated by concatenating the minimum points set using a custom pulse cycle-cutting algorithm. It was then smoothed using a moving average filter ($M = 5$ points). Further, baseline wandering was removed using a linear baseline estimator.

The higher derivative of the waveforms [10] was calculated and filtered using the Savitzky-Golay filter (polynomial order = 4, side points = 36) [11]. This waveform was then used to calculate AIx [8]. The local stiffness indices (β , Ep, AC) were calculated using the systolic and diastolic (aortic) blood pressure and the corresponding end-diastolic and peak-systolic diameter values, with the help of widely used biomechanical equations [6]. The blood volume and blood density values were used along with blood pressure to calculate the local PWV using the Bramwell-Hill equation [12].

Global estimates of vascular stiffness experienced by the aorta were calculated by the lumped parametric three-element Windkessel model [7]. Note that the Windkessel model with the pressure and flow in hydraulic form as input was fitted into an electrical equivalent model with the input voltage and current, respectively, as the corresponding parameters. The electric network components were derived using Kirchoff’s equation from the model, yielding the parallel capacitor and resistor analogous to TAC and TPR, respectively, and the series resistance corresponds to the characteristic input impedance of the vascular bed as seen by the aorta. A transfer function model was then derived to calculate the Windkessel parameters from the aortic pressure and flow data. The calculation method was implemented and automated in the

TABLE I. SUBJECT DEMOGRAPHY AND PARAMETER DESCRIPTION

Parameter	Hypertensive	Normotensive
Number of subjects	210	210
Age (years)	35 – 75	35 – 75
Systolic blood pressure (mmHg)	145.79 ± 6.191	115.36 ± 10.604
Diastolic blood pressure (mmHg)	62.605 ± 6.77	72.834 ± 6.968
Systolic-peak diameter (mm)	41.086 ± 3.23	42.96 ± 3.52
End-diastolic diameter (mm)	39.839 ± 3.308	41.816 ± 3.58
β	16.89 ± 3.57	11.208 ± 3.79
Ep (kPa)	333.26 ± 103.5	165.6 ± 77.3
AC (mm ² .kPa ⁻¹)	1.10 ± 0.304	2.613 ± 0.952
Local PWV (m.s ⁻¹)	10.03 ± 1.37	7.81 ± 1.43
AIx	43.79 ± 14.73	29.45 ± 13.15
Zc (mmHg.s.cm ⁻³)	0.0064 ± 0.0014	0.0043 ± 0.0005
TPR (mmHg.s.cm ⁻³)	0.119 ± 0.034	0.134 ± 0.021
TAC (mmHg ⁻¹ .s ²)	4.64 ± 0.79	4.95 ± 0.65

LabVIEW® platform (National Instruments, USA) with a set of model accuracy indices to ensure fitting efficiency for each subject’s data.

C. Statistical Analysis

Continuous variables are presented as a range and/or mean ± standard deviations. The relation between two continuous variables was analysed by linear regression analysis using the Pearson correlation coefficient (r) and statistical significance using the Students’ t-test in terms of the p-value. The independence of association between multiple variables was evaluated using the multivariate regression analysis and obtained the model coefficients with 95% confidence intervals (CI) and p-values. The percentage difference in group-average value was used to compare the measurements between any two groups, and the ANOVA test was performed to verify statistical significance. A p-value less than 0.05 is considered statistically significant.

III. RESULTS AND DISCUSSION

The subjects’ baseline demographics and vascular health markers are detailed in Table I. The normo- and hypertensive groups were matched concerning their age and sample size.

A. Association of Vascular Health Markers with Age

A statistically significant correlation was obtained for all the local stiffness indices (β , Ep, AC and local PWV) with the age in healthy (normotensive) subjects. Among them, values of β showed the highest correlation with age ($r = 0.67$, $p < 0.001$), followed by Ep ($r = 0.50$, $p < 0.001$), local PWV ($r = 0.44$, $p < 0.001$) and AC ($r = 0.27$, $p < 0.001$). It was found that local PWV in the older population (aged between 55 and 75) is higher (14.27%, $p < 0.001$) than the younger population having age < 55 years. There was a 22.4% ($p < 0.001$) and 31.96% ($p < 0.001$) increase in the group-average values of β and Ep, respectively for the older population compared to the younger group; whereas 16.55% ($p < 0.001$) decrease in group-average AC between these age groups. It may be noted that ageing in individuals modifies the arterial

wall structural architecture, besides an increase in the plasma lipids and fatty glucose levels, resulting in luminal enlargement and progressive reduction in the elastic properties of large arteries, thereby making the artery stiffer. Stiffer arteries experience a lower diameter distention and higher transmural pressure, resulting in higher stiffness with escalated β/Ep , and lower AC values [13]. The correlation of local PWV with age further confirms the direct influence of pulse wave transit dynamics on arterial stiffness [14] [15].

A statistically significant negative correlation ($r = -0.50$, $p < 0.001$) was observed between TAC and age. For the healthy population (aged 35 – 75 years), there was only a moderate correlation for Zc and TPR with age ($r < 0.24$, $p < 0.001$). A moderate correlation was also observed for the different age groups; with Zc depicting a negative correlation with age ($r = -0.16$, $p < 0.001$) for the older population (aged 55 – 75 years) and TPR depicting a positive correlation with age ($r = 0.39$, $p < 0.001$) for younger population (aged 35-55 years). Among these groups, TAC correlated negatively with age ($r = -0.37$ for age 35 – 55 years and $r = -0.33$ for age 55 – 75 years) which corroborates with earlier studies reporting variations of arterial compliance with ageing [16].

The observed significant correlation of AIx with age ($r = 0.55$, $p < 0.001$) describes the faster propagation of the reflected pressure waves into early systole ascribed to stiffer arteries (or vascular ageing). It was also found that the group-average AIx was significantly higher in an older population, with a mean increase of 42.35% compared to the younger group. Yet, the value of AIx tends to remain comparable after 65 years of age with only a mild increase (10.09%, $p < 0.001$) in its mean value at 75 years; which is similar to the results in a study describing a plateau trend for AIx at an age beyond 60 years [17].

B. Distribution of Vascular Health Markers in Normotensive and Hypertensive Subjects

The variations of local/global stiffness and pulse contour indices for the normotensive and hypertensive subjects are presented in Fig. 1. There was a significant increase ($p < 0.001$) in group-average values of β , Ep and local PWV by 33.63%, 50.30% and 22.16%, respectively, between the normotensives and hypertensives (and a decrease in group-average of AC by 57.83%). This observation was in agreement with the allied studies [16] [18] and further demonstrated the potential of local stiffness indices in reliably assessing load-dependent stiffening from higher (deranged) blood pressure. The mean variation (across all age groups) in

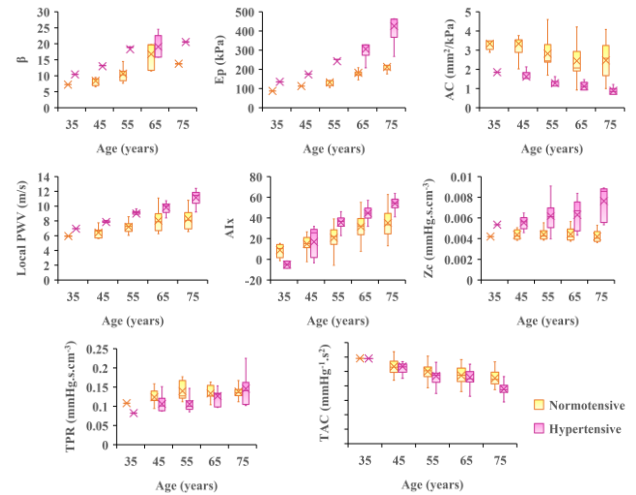


Figure 1. Distribution of aortic local/regional stiffness indices and pulse contour indices in hypertensive and normotensive subjects.

AIx for the hypertensive and normotensive subjects was 32.75% ($p < 0.001$), which shows an elevated AIx for hypertensives similar to that of the study conducted in a community pharmacy [19].

An evident increase (32.81%, $p < 0.001$) in the mean value of Zc was observed in hypertensive subjects compared to that of normotensives (Fig. 1). It may be attributed to an escalated pulse pressure and lower luminal diameter in hypertensives, causing higher Zc [16]. The group-average value of TPR was found to reduce in hypertensives with marginal significance within different age groups (Fig. 1). TPR having a low significance between normotensives and hypertensives could be attributed to its independence with the measurement site (large arteries), since the luminal diameter of the arterioles (small arteries) is the primary determinant of TPR [20]. Further, TAC showed a lower group-average value for hypertensives than that of the normotensive owing to its inherent inverse relation with pulse pressure [13] [21], though the reduction was not significant (~5.89%).

C. Independent Association of Vascular Health Markers with Age in Multivariate Linear Regression Analysis

Table II summarizes the multivariate regression analysis to assess the independent associations of age with vascular health markers. The study demonstrated a significant ($p < 0.01$) association between aortic local/global stiffness indices, and pulse contour indices with age, yielding an adjusted $r = 0.75$ ($p < 0.01$). Note that the multiple regression model

TABLE II. RESULTS OF MULTIVARIATE REGRESSION ANALYSIS

Model	Dependent Variables	Coefficients	p-value	CI: Lower 95%	CI: Upper 95%
Age Multiple $r = 0.72$ Adjusted $r = 0.75$ $p < 0.01$	β	2.459	0.001	1.355	3.564
	Ep	2.856	0.008	-0.361	-0.052
	AC	3.619	0.001	0.450	0.788
	Local PWV	4.578	0.001	6.309	15.535
	AIx	2.324	0.001	0.227	0.531
	Zc	-3.349	0.004	-5.630	-1.067
	TPR	-3.257	0.004	-5.475	-1.038
	TAC	-2.967	0.001	-4.744	-1.190

combining a set of aortic stiffness indices and pulse contour indices provided a correlation with age (multiple $r = 0.72$, adjusted $r = 0.75$, $p < 0.01$) better than their individual associations (refer Section III.A). This finding, indeed, emphasizes the need for combining multiple non-invasive biomarkers [22] (measured using continuous measurements of blood pressure [23], blood flow and lumen diameter [24]) that capture unique aspects of age-induced vascular remodelling for reliable monitoring, risk stratification, and management of EVA. Efforts for the same are currently in progress.

D. Limitations and Future Scope

Reported observations should be interpreted by underlining the study limitations, majorly the use of virtual subjects' data. However, the data set has been generated using measurements from reference in-vivo subjects by applying well-established biomechanical models of pressure, diameter, and flow. Thus, the reported associations are reliable and corroborate with allied in-vivo studies to a large extent. Further efforts are in progress to extend this study into a clinical setting by recruiting humans and to propose a set of reliable models combining multiple vascular health markers for predicting vascular ageing. Above all, there is a lack of an instrumentation setup that can perform a combined estimation of the transmural pressure, luminal diameter, and blood flow velocity from an arterial site for accurate and synchronized measurement of said vascular health markers. Such instrumentation setups and comprehensive models that can provide reliable estimates of vascular age are underway.

IV. CONCLUSION

This work investigates the association of a set of vascular health markers obtained from the aorta with age using the virtual subject database. A significant association was observed for the age versus local and global aortic stiffness as well as pulse contour indices. Each of the vascular health markers, except the TPR value, depicted reliable stratification of normotensives and hypertensives across multiple age groups (decade bins). Notably, the developed multivariate regression model of age with the combination vascular health markers revealed an association better than their individual (one-to-age) relation. It indicates the scope of models that can predict vascular age using the combination of critical vascular parameters that capture the unique aspects of age-induced vascular remodelling for reliable monitoring, risk stratification, and management of EVA. Efforts by our group are in progress to realize methods and systems employing such comprehensive vascular ageing models in affordable, non-invasive devices.

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