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Effect of Large Arteries on Blood Pressure Variability*

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Abstract— **Blood pressure (BP) variability is generally considered to be due to neurogenic influences on arterioles modulating peripheral resistance, as well as variations in stroke volume (SV). However, for a given change in peripheral resistance or SV, the degree of BP variability is modulated by the stiffness of large conduit arteries. Recent epidemiological evidence shows that cardiovascular risk is not only related to the average arterial pressure, but also to the degree of diurnal variability. In addition, short-term variability has been shown to be related to aortic stiffness measured as pulse wave velocity, a strong independent predictor of cardiovascular risk. This study addresses the relation between large artery stiffness and BP variability using a lumped parameter model of the systemic circulation described by total arterial compliance, total peripheral resistance (TPR) and aortic characteristic impedance. The variability in TPR is simulated using a random function with a Gaussian distribution and changes in arterial stiffness are simulated by variation in compliance, where compliance is either linear (pressure independent) or non-linear (pressure dependent). Simulation results show that (i) BP variability is greater when due to changes in TPR compared to similar relative changes in SV, (ii) pressure dependency of arterial stiffness results in a curvilinear relation between systolic BP variability and mean arterial pressure (MAP), such that a critical mean pressure (MAP_c) exists for minimal BP variability, (iii) increase in arterial stiffness (as occurs with aging) result in a higher MAPc for minimal BP variability, or increased BP variability at older age for similar values of MAP. These findings suggest that interventions aimed at reducing BP variability will need to consider large artery stiffness for optimal efficacy.**

I. Introduction

Elevated arterial blood pressure (BP) is the major contributor to increased cardiovascular risk in the aging population, leading to increased mortality and morbidity [1]. However, the physiological level of BP, even when elevated, is not necessarily constant, with variations occurring due to a complex array of signals, some of which activate BP control systems (eg. baroreceptors) [2]. Because of the normal physiological variability of BP, 24-hour ambulatory BP measurement has been increasingly used to ascertain the extent of BP variation throughout the day and night [3]. These measurements have revealed wide patterns of BP variability leading to studies examining the association between cardiovascular risk and degree of BP variability, in addition to average levels of BP. Recent evidence indicates a significant increase in risk of stroke with increased visit-to-visit BP variability, independent of the average value of systolic BP [4].

The underlying mechanisms related to BP variability are complex and multifunctional, involving neurogenic influences on the peripheral vasculature and cardiorespiratory function, as well as compartmental fluid shifts [2], [5]. Factors affecting resistance vessels influence mean BP, but variability is usually assessed by changes in systolic and diastolic BP [4]. For a given stroke volume (SV), pulse pressure (PP) is determined by the windkessel properties of the aorta as well as peripheral wave reflection [6]. In addition, the stiffness of large arteries also increases with distending pressure, so changes in mean BP will also have an inherent effect on PP. Hence, these interacting mechanisms can also play a role in the dynamic changes in BP affected by the passive mechanical elastic properties of large conduit arteries, separate from the active mechanisms involved in closed loop control of BP [2]. Indeed, recent studies assessing BP variability with 24-hour measurements have shown that all indices of SBP variability are related to levels of aortic stiffness as measured by carotid-femoral pulse wave velocity [7].

This study simulates the effect of large artery stiffness on BP variability by the use of a lumped parameter model of the systemic arteries with variations in BP driven by randomly distributed changes in peripheral resistance or SV. Simulations also assess the role of the pressure dependency of arterial stiffness on BP variability.

II. Arterial model

A. Circuit components

The systemic arteries are represented by a 4-element windkessel model with the equivalent circuit elements of aortic characteristic impedance (Z_c), blood inertance (L), total peripheral resistance (TPR) and aortic compliance (C), which is also a function of pressure ($C(P)$) (Fig. 1). The nominal values for the circuit elements are shown in Table I. The input to the model is a physiological flow wave at a nominal heart rate of 60 beats/min. All simulations were performed in Simulink and Matlab.

B. Random function generation

The variation in blood pressure is brought about by variation in TPR or in SV. For variation in TPR, a random function is generated with a Gaussian distribution such that the value (TPR_v) varies randomly around a constant value (TPR_c) beat-to-beat. The function is described by (1), where a and c are real constants and x is the seed for the random function generator. An example of the resulting variation is

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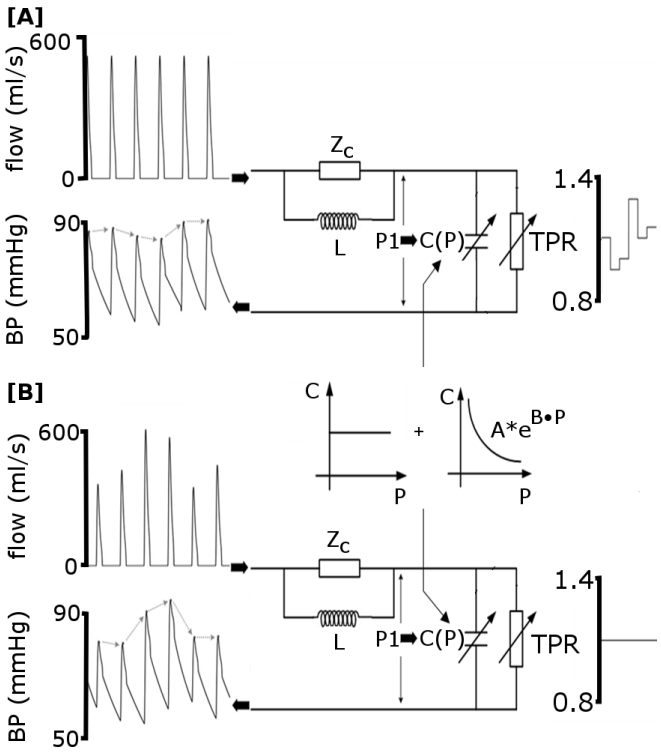

Fig. 1. Circuit representation of a 4-element windkessel model: aortic characteristic impedance (Z_c), blood inertance (L), TPR and aortic compliance (C), which is also a function of pressure ($C(P)$), the exponential relation shown center. [A] The flow input is constant (upper trace) and the blood pressure (lower trace) varies due to randomly varying value of TPR (right). [B] TPR is constant and blood pressure (lower trace) varies due to variation in SV (upper trace).

TABLE I

NOMINAL VALUES FOR MODEL COMPONENTS

parameter	symbol	value
characteristic impedance	Z_c	0.05 mmHg·ml^{-1}·s
blood inertance	L	0.008 mmHg·ml^{-1}·s^2
arterial compliance	C	2 ml·mmHg^{-1}
total peripheral resistance	TPR	1.2 mmHg·ml^{-1}·s

shown graphically in Fig. 2 for an interval of 5 minutes. A similar function as in (1) is used for the beat-to-beat variability in SV, which is used as the input signal into the lumped model.

$$TPR_v = a \cdot exp\left[\frac{-(x - TPRc)^2}{2c^2}\right] \quad (1)$$

III. SIMULATION OF BLOOD PRESSURE VARIABILITY

While there are many forms of defining BP variability, in this study, the index for BP variability, systolic blood pressure variability (SBP$_v$) (%), was determined from the standard deviation (SD) and mean of systolic pressure (SBP$_m$) over 5 minute epochs (2).

$$SPB_v(\%) = 100 \cdot \frac{SD}{SBP_m} \quad (2)$$

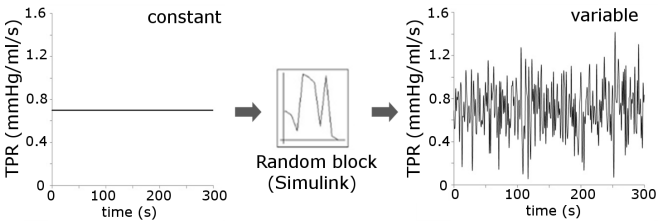

Fig. 2. The random variation in TPR as described by the Gaussian distribution function (1) shown for an interval of 300 seconds. Variation is beat-to-beat at a heart rate of 60 beats/min.

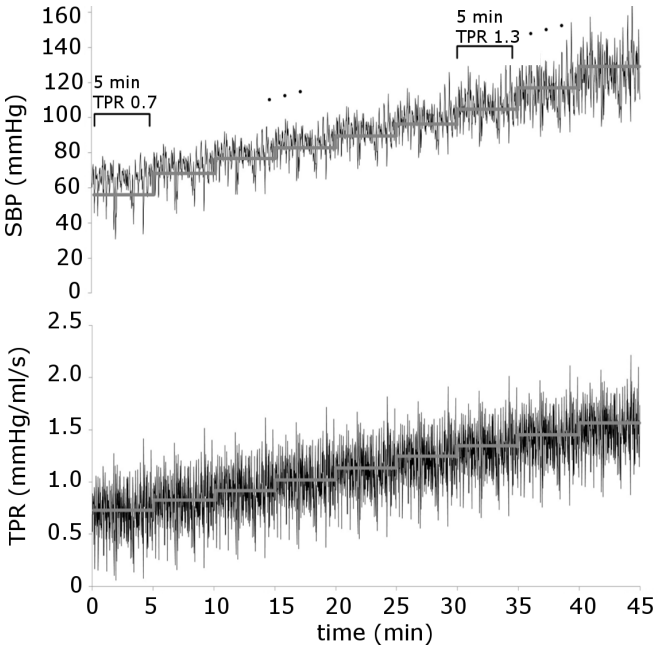

Fig. 3. The response of SBP to step changes in TPR for 5 minute epochs. Each epoch of TPR step has an identical random variability function. The simulation is run with a pressure dependent compliance in the model. Note the increased variability in SBP at higher values of TPR, and therefore at higher mean BP.

The simulation for a step change in mean TPR resulting in increase in mean BP is shown in Fig. 3.

Further simulations were conducted using the model to quantify the relation between SBP$_v$ (%) and the causal variable for variability in BP. Fig. 4 shows SBP$_v$ (%) when variability is due to random variation in TPR, SV and heart rate (HR) for pressure independent and pressure dependent arterial compliance. When TPR is varied, SV and HR are constant, so change in TPR is proportional to mean BP.

This shows that for a pressure independent compliance, SBP$_v$ (%) decreases monotonically with increase in mean BP. However, for a pressure dependent compliance, the relationship is curvilinear, with a critical value of mean BP where SBP (%) is minimal. This curvilinear relationship is not seen when BP variability is due to variability in SV or HR.

IV. EFFECTS OF AGE

A hallmark of arterial aging is the increase in arterial stiffness, resulting in reduced aortic compliance [6]. In

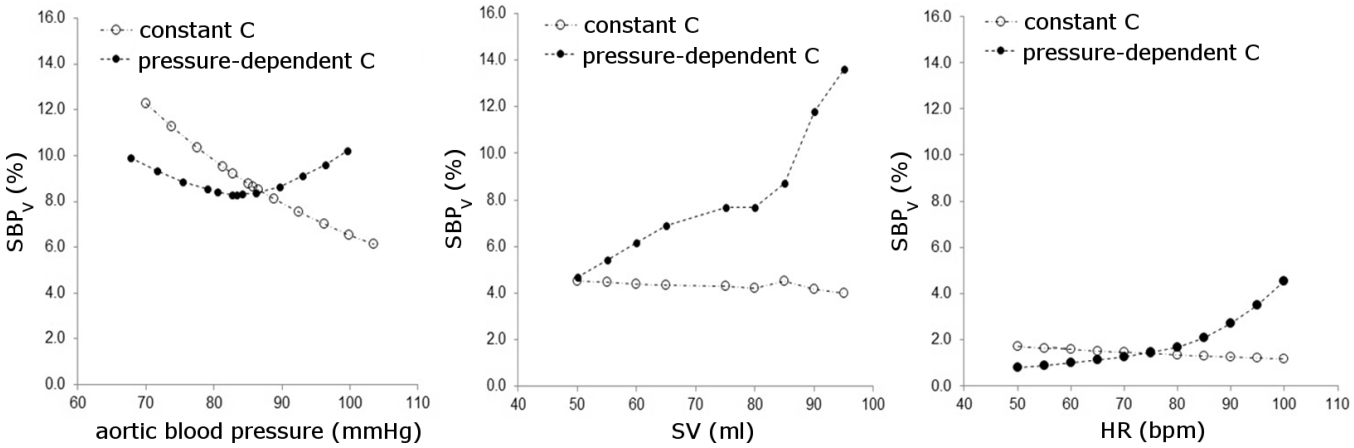

Fig. 4. BP variability (SBP$_v$ (%)) due to changes in TPR (left), SV (center) and heart rate (right). Simulations were conducted with and without pressure dependency of arterial compliance (C). SBP$_v$ (%) values are of the same order as those in epidemiological studies [4], [7].

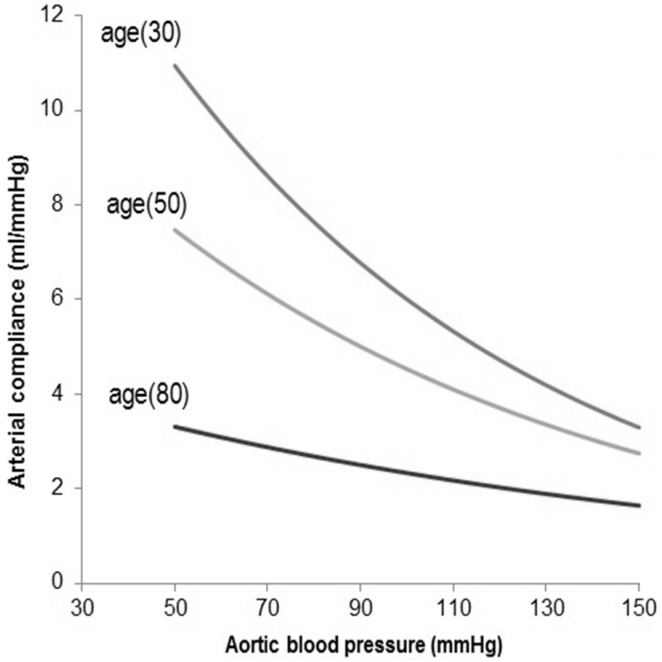

Fig. 5. Exponential relationship between total arterial compliance in the 4-element windkessel model and mean BP. Data obtained from Wesseling et al [8].

addition, there is also a loss of pressure dependency of aortic compliance with age [8]. The effect is modeled for 3 ages, 30, 50 and 80 years using an exponential relation (3) between aortic compliance (C) and mean BP (MBP) [8] (Fig. 5), where k is 0.022, 0.016, 0.007 for ages 30, 50 and 80 years respectively. C_0 is a constant coefficient derived from the mean across all ages.

$$C = C_0 exp(-kMBP) \tag{3}$$

To test the effects of pressure dependency of arterial stiffness on BP variability without the confounding effect of change in overall compliance, the relationships described in Fig 5 were used for simulation comparing the BP variability for the range of exponents in (3) and when the value of compliance (C) is similar for a specific pressure. The reference pressure chosen was 100 mmHg and comparison was made in relation to a constant value of compliance with no pressure dependency (Fig. 6).

When compliance was not pressure dependent, the BP variability, when due to random beat-to-beat variation in TPR, decreases with increasing mean BP. However, when compliance is pressure dependent, the curvilinear relation between BP variability and mean BP was found for all ages. In addition, with increasing age the critical pressure where BP variability is minimal is higher (Fig. 6).

V. Discussion

This study aimed to quantify the effects of large artery stiffness on the variability in arterial pressure due to changes in vascular (TPR) or cardiac (SV and HR) properties. This was aimed at addressing only the passive effects of arterial mechanical properties (as separate from the active mechanisms involved in closed loop control [2], [5]) using a lumped parameter arterial model.

Simulations show that BP variability is dependent on the degree of pressure dependency of arterial compliance. For no pressure dependency, BP variability has a much greater sensitivity to changes in TPR than SV or HR. However, for pressure dependency of arterial compliance, BP variability increases monotonically with SV and HR, but shows a curvilinear relation with TPR and mean BP for changes in TPR. The implication of this is that there is a mean BP where BP variability is minimal. The novel finding using this model is that the optimal mean BP for minimal BP variability is also age dependent due to the known changes of pressure dependency of aortic stiffness [8].

This finding has potentially important implications in treatment of hypertension. Presently, all hypertension guidelines prescribe similar target values irrespective of age [9]. However, from the findings of this modeling study, the effect of age-related changes in large artery stiffness is to increase

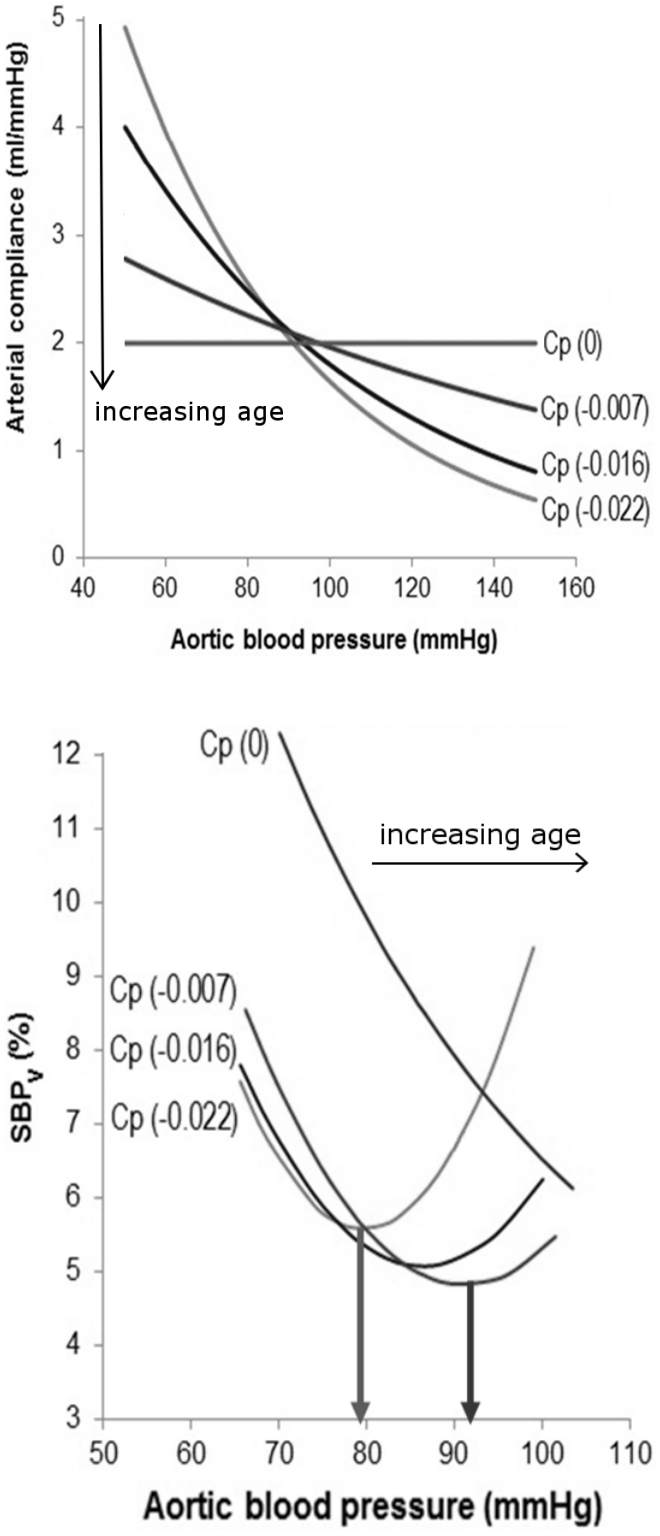

Fig. 6. *Upper panel.* Effect of age on loss of pressure dependency of arterial compliance (C) with age in comparison with a nominal value of C of 2 ml/mmHg independent of pressure ($C_p(0)$). Compliance curves $C_p(-0.022)$, $C_p(-0.016)$, $C_p(-0.007)$ refer to ages 30, 50 and 80 years respectively as described in (3) and Fig. 5. *Lower Panel.* Simulation of systolic BP variability (SBP$_v$(%)) as a function of mean blood pressure with change in pressure dependency of arterial compliance. The arrows indicate the critical mean pressure form minimal SBP$_v$ (%) for age 30 (left arrow) and 80 years (right arrow)

the relative BP variability in the elderly at pressures corresponding to those in the young. Indeed, this phenomenon may also play a role in the apparently increased range of hazard ratio for increased small vessel disease in the brain for those with increased values of arterial stiffness as measured by aortic PWV, even when hypertension is controlled [10].

REFERENCES

[1] S. Lewington, R. Clarke, N. Qizilbash, R. Peto, and R. Collins, "Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies." *Lancet*, vol. 360, no. 9349, pp. 1903–13, Dec. 2002.

[2] M. Ursino and E. Magosso, "Short-term autonomic control of cardiovascular function: a mini-review with the help of mathematical models." *Journal of integrative neuroscience*, vol. 2, no. 2, pp. 219–47, Dec. 2003.

[3] G. Parati, L. R. Krakoff, and P. Verdecchia, "Methods of measurements: home and ambulatory blood pressure monitoring." *Blood pressure monitoring*, vol. 15, no. 2, pp. 100–5, Apr. 2010.

[4] P. M. Rothwell, S. C. Howard, E. Dolan, E. O'Brien, J. E. Dobson, B. Dahlöf, P. S. Sever, and N. R. Poulter, "Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension." *Lancet*, vol. 375, no. 9718, pp. 895–905, Mar. 2010.

[5] A. C. Guyton, "Long-term arterial pressure control: an analysis from animal experiments and computer and graphic models." *The American journal of physiology*, vol. 259, no. 5 Pt 2, pp. R865–77, Nov. 1990.

[6] W. W. Nichols, M. F. O'Rourke, and C. Vlachopoulos, *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*, 6th ed. Oxford University Press, 2011.

[7] G. Schillaci, G. Bilo, G. Pucci, S. Laurent, I. Macquin-Mavier, P. Boutouyrie, F. Battista, L. Settimi, G. Desamericq, G. Dolbeau, A. Faini, P. Salvi, E. Mannarino, and G. Parati, "Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from 2 large databases." *Hypertension*, vol. 60, no. 2, pp. 369–77, Aug. 2012.

[8] K. H. Wesseling, J. R. Jansen, J. J. Settels, and J. J. Schreuder, "Computation of aortic flow from pressure in humans using a nonlinear, three-element model." *Journal of applied physiology*, vol. 74, no. 5, pp. 2566–73, May 1993.

[9] G. Mancia, G. De Backer, A. Dominiczak, R. Cifkova, R. Fagard, G. Germano, G. Grassi, A. M. Heagerty, S. E. Kjeldsen, S. Laurent, K. Narkiewicz, L. Ruilope, A. Rynkiewicz, R. E. Schmieder, H. A. J. S. Boudier, A. Zanchetti, A. Vahanian, J. Camm, R. De Caterina, V. Dean, K. Dickstein, G. Filippatos, C. Funck-Brentano, I. Hellemans, S. D. Kristensen, K. McGregor, U. Sechtem, S. Silber, M. Tendera, P. Widimsky, J. L. J. L. Zamorano, S. Erdine, W. Kiowski, E. Agabiti-Rosei, E. Ambrosioni, L. H. Lindholm, M. Viigimaa, S. Adamopoulos, V. Bertomeu, D. Clement, C. Farsang, D. Gaita, G. Lip, J.-M. Mallion, A. J. Manolis, P. M. Nilsson, E. O'Brien, P. Ponikowski, J. Redon, F. Ruschitzka, J. Tamargo, P. van Zwieten, B. Waeber, B. Williams, H. a. J. Struijker Boudier, H. a. J. Struijker-Boudier, The task force for the management of arterial hypertension of the European Society of Hypertension, and The task force for the management of arterial hypertension of the European Society of Cardiology, "2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)." *Journal of Hypertension*, vol. 25, no. 6, pp. 1105–87, Jun. 2007.

[10] M. M. F. Poels, K. Zaccai, G. C. Verwoert, M. W. Vernooij, A. Hofman, A. van der Lugt, J. C. M. Witteman, M. M. B. Breteler, F. U. S. Mattace-Raso, and M. A. Ikram, "Arterial stiffness and cerebral small vessel disease: the rotterdam scan study." *Stroke*, vol. 43, no. 10, pp. 2637–42, Oct. 2012.