35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Application of Cardiovascular Models in Comparative Physiology and Blood Pressure Variability*

Alberto P Avolio, Ke Xu, Mark Butlin

Abstract— **The usefulness of cardiovascular models is determined by their intended function with respect to elucidating underlying hemodynamic concepts and to enable simulations that will assist in understanding the effects of specific parameters. Models can take different forms, including mock circulatory constructs with physical components, mathematical representations of parameter space relations employing constitutive equations, or closed form representations of electrical circuit analogs described in the time or frequency domain. This investigation describes the use of cardiovascular models based on electrical analogs of mechanical hydrodynamic systems to elucidate two different physiologic concepts: (i) the use of distributed vascular impedance to investigate comparative physiology of optimal design and features related to body size across a broad range of animal species; (ii) use of lumped parameter models to assess the role of arterial stiffness in blood pressure variability. The impedance model shows that an allometric relationship between body weight and aortic effective length can be determined by using the frequency of minimum input impedance and aortic pulse wave velocity. This concept provides a background for optimal matching of body size and hemodynamic load on the heart. The lumped parameter model indicates that arterial stiffness, simulated by the total arterial compliance term, has a significant impact on variability of arterial pressure when changes are due to dynamic alterations of peripheral resistance. In addition, the known pressure dependency of arterial stiffness results in a curvilinear relationship between blood pressure variability and mean pressure. This has implications in hypertensive treatment where there are marked changes in arterial stiffness, as occurs with aging.**

I. Introduction

Early studies in hemodynamics were aimed at reducing the complexities of the fluid dynamic problem of blood flow in arteries so as to be able to compute flow velocity from the measurable pressure gradient [1], [2]. This lead to the broader consideration of the relatively small effects of the non-linear properties [3] so that the relationship between pulsatile arterial pressure and flow can be described by the concept of the electrical analogy of impedance, a quantity described in the frequency domain [1]. When the relationship is determined as input impedance of the systemic and pulmonary arterial trees, it becomes the complete description of the hydraulic load on the ejecting ventricles. The impedance concept, such that it can be described by physical elements, advanced the modeling of hemodynamic phenomena and lead to implementation of physical and mathematic models to describe the underlying concepts of arterial design [4]–[9].

This paper aims to present the use of models that are based on the impedance concepts to illustrate their use in describing the pulsatile arterial load and to assess fundamental quantities of arterial design over a large range of animals of body size as well as quantifying the effect of a fundamental arterial property, arterial stiffness, on the dynamic variability of arterial pressure.

* This work was supported in part by a grant from the Australian Research Council (MB; ARC Discovery DP110101134) and by a Macquarie University Research Postgraduate Scholarship (KX)

A.P. Avolio, K. Xu and M. Butlin are with the Australian School of Advanced Medicine, Macquarie University, Sydney, NSW, AUSTRALIA. phone: +61 2 9812 3500; fax +61 2 9812 3600; e-mails: alberto.avolio@mq.edu.au; ke.xu1@students.mq.edu.au; mark.butlin@mq.edu.au;

II. Arterial impedance

A. Calculation of impedance spectra

Impedance is defined in the frequency domain and relates oscillatory components of the time-varying signals of pressure, P(t) and flow Q(t). Assuming that P(t) and Q(t) are periodic functions and the system is stationary, the harmonic components, Pk(ω) and Qk(ω) are obtained by Fourier decomposition of P(t) and Q(t) and the impedance spectrum is calculated (1).

$$Z_k(\omega) = \frac{P_k(\omega)}{Q_k(\omega)};\ (k = 1, 2, \ldots N) \qquad (1)$$

This is a complex quantity with modulus ($|Z|_k(\omega)$) and phase ($Zphs_k(\omega)$) plotted as function of frequency for the N harmonics. For physiological signals the impedance spectrum can be completely specified for N = 10.

Fig 1 shows aortic impedance in two animals, rabbit and guinea pig, with markedly different body size. Both show a frequency of impedance minimum and phase zero crossing, but the smaller size guinea pig (and higher heart rate (HR)) is at a higher frequency (10-11 Hz) compared to the rabbit (5-6 Hz). From this spectrum, association with single tube behavior led to considerations of arterial effective length (L_{eff}), determined from the 'resonance' frequency of minimum impedance modulus (f_{min}) and the pulse wave velocity (c) by equating it to a quarter wavelength ($L_{eff} = c/(4 \cdot f_{min})$) [6], [10]–[12].

This concept was used in comparing impedance spectra across a range of species of different body size (Fig 2, Table I).

B. Allometric relations

The allometric concepts employed in scaling laws [17]–[20] were used to assess whether an invariant relation exists between L_{eff} and body weight (2), where c is a scalar quantity and k is the power exponent.

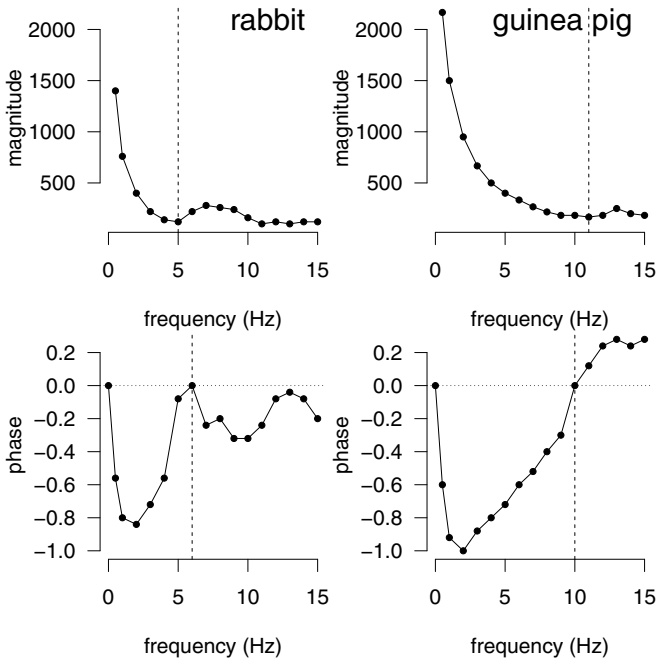

Fig. 1. Input impedance in rabbit and guinea pig [13], [14], showing a higher frequency for the minima of magnitude and phase zero crossing (dashed lines) for the lower body weight animal (rabbit).

TABLE I

ALLOMETRIC SCALING DATA FOR VARIOUS ANIMAL SPECIES ACROSS A RANGE OF BODY WEIGHTS.

species	weight (kg)	HR (Hz)	PWV (cm·s^{-1})	f_{min} (Hz)	L_{eff} (cm)
rat	0.45	5.8	600	14.0	10.7
guinea pig	0.70	3.9	480	14.0	10.0
rabbit	3.0	3.5	450	4.5	25
snake	5.6	0.67	593	3.0	49
dog	5.8	2.4	590	4.0	31
kangaroo	23.3	1.4	469	2.5	47
sheep	33	2.1	520	2.0	65
human	72	1.2	600	3.5	43

$$log(L_{eff}) = k \cdot log(body\ weight) + c \qquad (2)$$

From the data in Table I, the relationship is shown in Fig. 3, with a high correlation, indicating that the known allometric parameters related to body size in terms of optimizing metabolism [17], [18] are also relevant with respect to matching of arterial impedance to ventricular ejection, since they were determined from the frequencies corresponding to impedance minima.

III. LUMPED PARAMETER 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 inertia (L), total peripheral resistance (TPR) and aortic compliance (C), which is also a function of pressure ($C(P)$) (Fig. 4). The nominal values for the circuit elements are: Z_c: 0.05

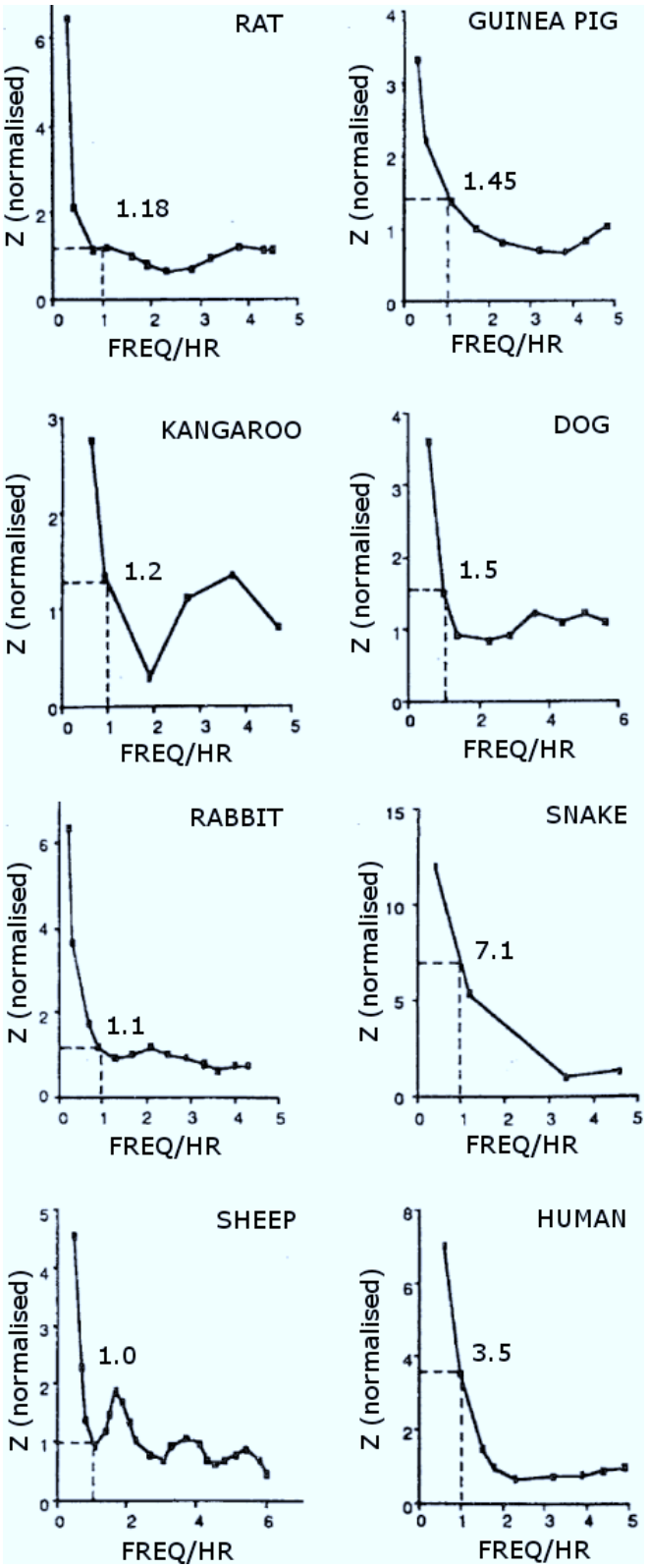

Fig. 2. Impedance modulus normalised for characteristic impedance and resting HR for each species. The figure indicates the normalized modulus value at the equivalent resting HR. Note that some mammalian species (human) have a comparatively higher relative impedance at the normal HR, indicating reduced matching based on allometric data (Fig. 3) (Data obtained from previous studies [4], [13]–[16]).

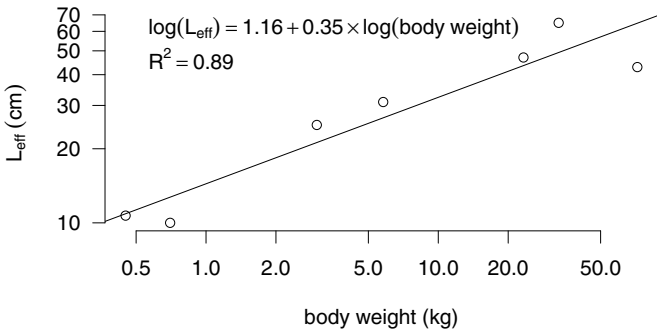

Fig. 3. Allometric relationship between aortic effective length (L_{eff}) and body weight determined for mammalian species (ie. snake not included), as per Table I, expressed on log axes.

mmHg·m^{-1}·s; L: 0.008 mmHg·ml^{-1}·s^2; C: 2 ml·mmHg^{-1}; TPR: 1.2 mmHg·ml^{-1}·s.

The input to the model is a physiological flow wave at a nominal HR of 60 beats/min. All simulations were performed in Simulink and Matlab.

IV. Simulation of Blood Pressure Variability

A. Blood pressure variability index

The importance of blood pressure variability (BP$_v$) is being increasingly recognized with evidence emerging of the association of BP$_v$ with cardiovascular risk, independent of average levels of BP [21]. In addition, BP$_v$ has also been shown to be associated with large artery stiffness, as measured by pulse wave velocity [22].

For this analysis, the index for BP$_v$, SBP$_v$ (%), was determined from the standard deviation (SD) and mean of systolic pressure (SBP$_m$) over 5 minute epochs (3).

$$SPB_v(\%) = 100 \cdot \frac{SD}{SBP_m} \tag{3}$$

B. Variation of peripheral resistance

The variation in blood pressure is brought about by variation in TPR or in stroke volume. 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 (4). The random generator function uses real constants (a and c) and a seed value (x).

$$TPR_v = a \cdot exp\left[\frac{-(x - TPR_c)^2}{2c^2}\right] \tag{4}$$

C. Pressure dependency of arterial compliance

The pressure dependency of the stiffness of the arterial wall is modeled by assigning an exponential relation between aortic compliance (C) and mean BP (MBP), using a constant (k) that varies with age [23] (eg. 0.022, 0.016, 0.07 for ages 30, 50 and 80 years respectively), and a constant compliance coefficient (C_0) (5).

$$C = C_0 \cdot exp\,(-k \cdot MBP) \tag{5}$$

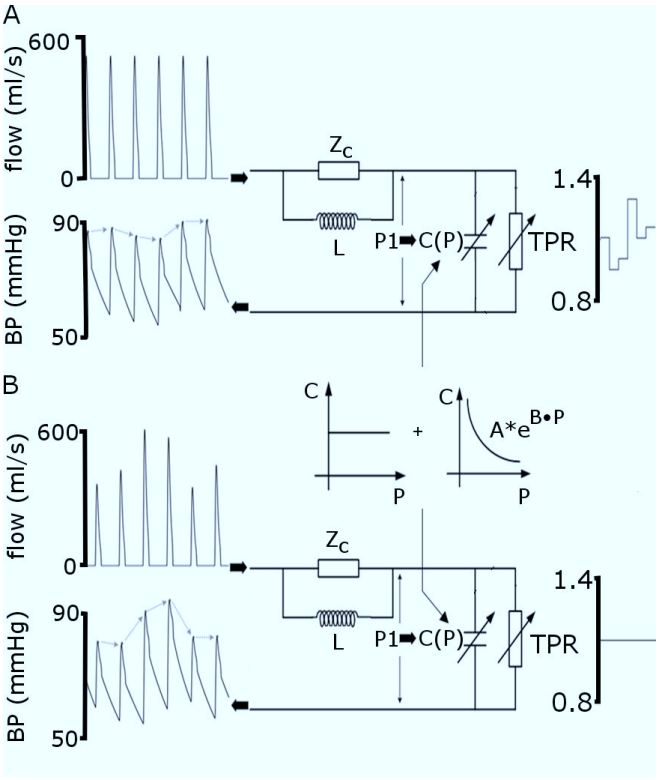

Fig. 4. Circuit representation of a 4-element windkessel model: aortic characteristic impedance (Z_c), blood inertia (L), TPR and aortic compliance (C), which is also a function of pressure ($C(P)$), the exponential relation shown in the center. A. The flow input is constant (upper trace) and the blood 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 stroke volume (upper trace).

D. Characterization of blood pressure variability

Simulations were conducted using the model to quantify the relation between SBP$_v$ (%) and the causal variable for variability in BP. Fig. 5 shows SBP$_v$ (%) when variability is due to random variation in TPR using 5 min epochs at varying values of mean TPR, for pressure independent and pressure dependent arterial compliance. Since when TPR is varied, stroke volume (SV) and HR are constant, the change in TPR is proportional to mean BP.

The random variation in TPR (simulating neurogenic activity) resulting in BP$_v$ has different effects for pressure dependent and pressure independent compliance. For constant compliance, BP$_v$ decreases with increasing mean BP, but with pressure dependent compliance, the relationship is curvilinear, indicating an 'optimal' value of mean BP where BP$_v$ is minimal.

V. Discussion

The models presented in this paper illustrate the potential for closed form representation of the arterial system to investigate underlying concepts ranging from evolutionary adaptations for optimal cardiovascular function to effects of basic parameters on dynamic changes in blood pressure. Comparative physiology allows investigations of fundamental laws governing physiological function [12]. The

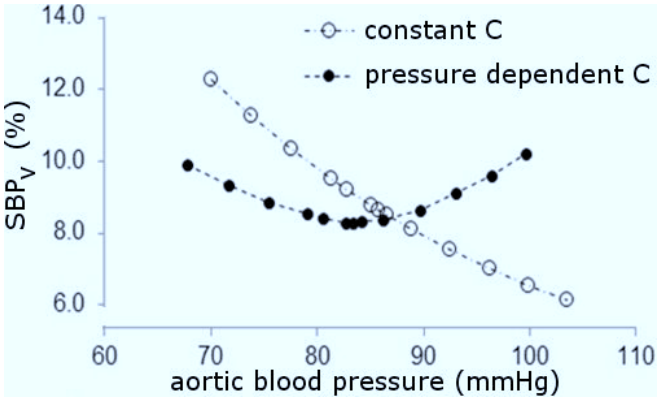

Fig. 5. Blood pressure variability index (SBP$_v$ (%)) as a function of mean aortic blood pressure for a constant (pressure independent) compliance and for a pressure dependent compliance.

impedance concepts using distributed models [24] uncover possible maladaptive changes across animal species. For example, the human arterial system has a relatively higher impedance, and so pulsatile load at the normal cardiac frequency compared to other species.

Lumped parameter models enable implementation of realistic hemodynamic load for cardiac experimentation [25]. Our recent simulations on the effects of arterial stiffness on BP$_v$ has illustrated a further optimal function where a given value of mean pressure exists for minimal variability in systolic pressure, for a given variability in peripheral resistance. This has significant implications in the optimization of antihypertensive treatment. Currently, hypertension guidelines recommend similar BP targets for all age groups [26]. However, given the known decrease in pressure dependency of arterial stiffness with age [23], the optimal value of blood pressure for minimal variability would not be similar across ages. And this may be one of the explanations for different risk profiles among treated hypertensives, given the increasing importance of BP$_v$ in cardiovascular risk [27].

REFERENCES

[1] 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.

[2] J. R. Womersley, "Method for the calculation of velocity, rate of flow and viscous drag in arteries when the pressure gradient is known," *J Physiol*, vol. 127, no. 3, pp. 553–563, 1955.

[3] D. E. Dick, J. E. Kendrick, G. L. Matson, and V. C. Rideout, "Measurement of nonlinearity in the arterial system of the dog by a new method," *Circ Res*, vol. 22, no. 2, pp. 101–111, 1968.

[4] A. P. Avolio, "Multi-branched model of the human arterial system," *Med Biol Eng Comput*, vol. 18, no. 6, pp. 709–718, 1980.

[5] J. Lefevre, "Teleonomical optimization of a fractal model of the pulmonary arterial bed," *J Theor Biol*, vol. 102, no. 2, pp. 225–248, 1983.

[6] M. F. O'Rourke, "Pressure and flow waves in systemic arteries and the anatomical design of the arterial system," *J Appl Physiol*, vol. 23, no. 2, pp. 139–149, 1967.

[7] M. G. Taylor, "The input impedance of an assembly of randomly branching elastic tubes," *Biophys J*, vol. 6, no. 1, pp. 29–51, 1966.

[8] N. Westerhof, F. Bosman, C. J. De Vries, and A. Noordergraaf, "Analog studies of the human systemic arterial tree." *Journal of biomechanics*, vol. 2, no. 2, pp. 121–43, May 1969.

[9] N. Westerhof, G. Elzinga, and P. Sipkema, "An artificial arterial system for pumping hearts," *J Appl Physiol*, vol. 31, no. 5, pp. 776–781, 1971.

[10] R. Burattini and S. Di Carlo, "Effective length of the arterial circulation determined in the dog by aid of a model of the systemic input impedance," *IEEE Trans Biomed Eng*, vol. 35, no. 1, pp. 53–61, 1988.

[11] W. R. Milnor, "Aortic wavelength as a determinant of the relation between heart rate and body size in mammals." *The American journal of physiology*, vol. 237, no. 1, pp. R3—-6, Jul. 1979.

[12] A. Noordergraaf, J. K. Li, and K. B. Campbell, "Mammalian hemodynamics: a new similarity principle." *J Theor Biol*, vol. 79, no. 4, pp. 485–489, Aug. 1979.

[13] A. P. Avolio, "Haemodynamic studies and modeling of the mammalian arterial system," 1976.

[14] A. P. Avolio, F. O'Rourke M, K. Mang, P. T. Bason, and B. S. Gow, "A comparative study of pulsatile arterial hemodynamics in rabbits and guinea pigs," *Am J Physiol*, vol. 230, no. 4, pp. 868–875, 1976.

[15] A. P. Avolio, M. F. O'Rourke, and M. E. Webster, "Pulse-wave propagation in the arterial system of the diamond python Morelia spilotes," *Am J Physiol*, vol. 245, no. 6, pp. R831–6, 1983.

[16] W. W. Nichols, A. P. Avolio, and M. F. O'Rourke, "Ascending aortic impedance patterns in the kangaroo: their explanation and relation to pressure waveforms." *Circulation research*, vol. 59, no. 3, pp. 247–55, Sep. 1986.

[17] B. Gunther, "Dimensional analysis and theory of biological similarity," *Physiol Rev*, vol. 55, no. 4, pp. 659–699, 1975.

[18] S. B. Heymsfield, D. Childers, J. Beetsch, D. B. Allison, and A. Pietrobelli, "Body size and human energy requirements: reduced mass-specific resting energy expenditure in tall adults," *J Appl Physiol*, vol. 103, no. 5, pp. 1543–1550, 2007.

[19] G. S. Kassab, "Scaling laws of vascular trees: of form and function," *Am J Physiol Heart Circ Physiol*, vol. 290, no. 2, pp. H894–903, 2006.

[20] M. Zamir, "On fractal properties of arterial trees," *J Theor Biol*, vol. 197, no. 4, pp. 517–526, 1999.

[21] 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.

[22] 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.

[23] 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.

[24] A. P. Avolio, "Input impedance of distributed arterial structures as used in investigations of underlying concepts in arterial haemodynamics." *Medical & biological engineering & computing*, vol. 47, no. 2, pp. 143–51, Feb. 2009.

[25] G. Elzinga and N. Westerhof, "Matching between ventricle and arterial load. An evolutionary process," *Circ Res*, vol. 68, no. 6, pp. 1495–1500, 1991.

[26] 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. 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. 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, and B. Williams, "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)," *J Hypertens*, vol. 25, no. 6, pp. 1105–1187, 2007.

[27] 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.