

# Quantification of the Contribution of Cardiac and Arterial Remodeling to Hypertension

Patrick Segers, Nikos Stergiopoulos, Nico Westerhof

**Abstract**—The study aim was to quantify the individual and combined contributions of both the arterial system and the heart to systolic blood pressure in hypertension. We assessed the parameters of a heart–arterial model for normotensive control subjects and hypertensive patients with left ventricular adaptation patterns classified as normal, concentric remodeling, concentric hypertrophy, or eccentric hypertrophy. The present simulations show that vascular stiffening alone increases the pulse pressure without increasing systolic blood pressure. It is only in combination with an increased peripheral resistance that arterial stiffening leads to systolic hypertension in concentric remodeling and concentric hypertrophy. The contribution of cardiac pump function to the increase in blood pressure depends on cardiac remodeling, hypertrophy, or both. In hypertensive patients with a normal left ventricle, the heart is responsible for 55% of the increase in systolic blood pressure. In concentric remodeling, concentric hypertrophy, and eccentric hypertrophy, the cardiac contribution to the increase in systolic blood pressure is 21%, 65%, and 108%, respectively. We conclude that along with arterial changes, cardiac remodeling and hypertrophy contribute to hypertension. (*Hypertension*. 2000;36:760-765.)

**Key Words:** hypertrophy ■ arteries ■ compliance ■ models ■ remodeling

Aortic pressure and flow arise from the interaction between the left ventricle (LV) and the systemic arterial load. Factors that affect LV pump function are preload (venous filling pressure or LV end-diastolic volume [LVEDV]) and contractile properties of the heart muscle (LV contractility). The 2 main mechanical afterload parameters that determine systolic blood (SBP) and pulse pressure (PP) are total peripheral resistance (R) and total arterial compliance (C).<sup>1,2</sup> Arterial blood pressure is thus determined by a limited number of cardiac and arterial mechanical factors. In hypertension, each of these parameters may change and thus contribute, to a different degree, to the elevated blood pressure.

Blood pressure in hypertension, measured *in vivo*, reflects the combined effects of alterations in cardiac and arterial parameters. In this work, we use a mathematical heart–arterial interaction model<sup>1</sup> to unravel and quantify the specific contribution of arterial and cardiac changes. Cardiac and arterial model parameters for normotensive control subjects and for hypertensive patients with different LV adaptation patterns were taken directly from the literature or calculated from data given in the literature.<sup>3</sup> The effect of individual changes in arterial and cardiac properties in hypertension was evaluated, and the relative contribution of cardiac and arterial remodeling to the increase in SBP was quantitatively assessed.

## Methods

### Heart–Arterial Interaction Model

Aortic blood pressure is computed with a heart–arterial interaction model<sup>1</sup> (Figure 1). Heart function is described with a time-varying elastance model<sup>4</sup> and is coupled to a 4-element lumped-parameter windkessel model that represents the arterial load.<sup>5</sup> The systemic arterial model parameters are total peripheral resistance (R), total arterial compliance (C), total inertance (L), and aortic characteristic impedance ( $Z_0$ ). Time-varying elastance is calculated as  $E(t) = P_{LV} / (V_{LV} - V_d)$ , where  $P_{LV}$  and  $V_{LV}$  are LV pressure and volume, respectively.<sup>4</sup> Cardiac parameters are the slope ( $E_{max}$ ) and intercept ( $V_d$ ) of the end-systolic pressure-volume relation,<sup>4</sup> the slope of the diastolic pressure-volume relation ( $E_{min}$ ) and venous filling pressure ( $P_v$ ), heart rate, and the time to reach maximal elastance ( $t_p$ ).<sup>4,6</sup>  $E_{max}$  is a measure for LV contractility, whereas  $E_{min}$  and  $P_v$  determine LV filling. Cardiac valves are simulated as frictionless, perfectly closing devices, that allow only forward flow.

### Estimation of Model Parameters

Values of R for control subjects and hypertensives are taken from a clinical study by Ganau et al.<sup>3</sup> Hypertensives are classified according to 4 different LV adaptation patterns: normal LV (LV mass index <111 g/m<sup>2</sup> in men and 106 g/m<sup>2</sup> in women and relative LV wall thickness of <0.44), concentric remodeling (normal LV mass index but elevated relative LV wall thickness), concentric hypertrophy (both LV mass index and relative LV wall thickness elevated), or eccentric hypertrophy (elevated LV mass index but normal relative LV wall thickness) (for details, see Ganau et al<sup>3</sup>). Total arterial compliance is calculated from given pressure and flow data as follows. Stroke volume (SV) is given, and PP is calculated as the

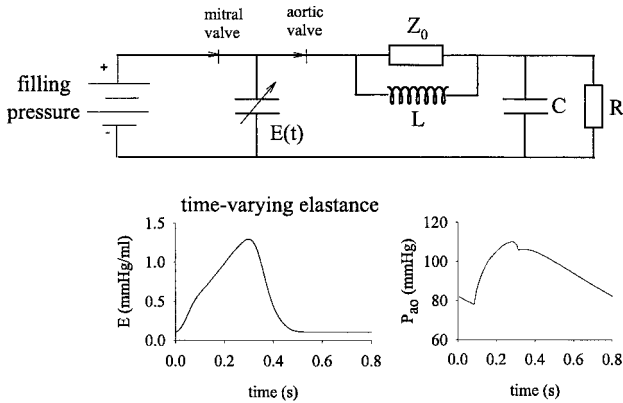
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From the Laboratory for Physiology (P.S., N.W.), Institute for Cardiovascular Research, Free University of Amsterdam, the Netherlands; and Biomedical Engineering Laboratory (N.S.), EPFL, Lausanne, Switzerland.

Correspondence to Dr Patrick Segers, Laboratory for Physiology, Institute for Cardiovascular Research, Free University of Amsterdam, Van Der Boerhorstlaan 7, 1081 BT Amsterdam, the Netherlands. E-mail [patrick.segers@navier.rug.ac.be](mailto:patrick.segers@navier.rug.ac.be)

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**Figure 1.** In the heart–arterial interaction model, the heart function is modeled as a time-varying elastance function [E(t)]. The arterial model is a lumped parameter model that consists of total compliance (C), total peripheral resistance (R), characteristic impedance of the aorta (Z<sub>0</sub>), and the inertia of blood in the systemic arteries (L). The model directly yields aorta pressure.

difference between SBP and diastolic blood pressure (DBP). The ratio of SV to PP is a measure of compliance but tends to overestimate windkessel compliance by a factor of ≈1.6 in dogs<sup>7</sup>; we therefore estimate C as 0.64 times SV/PP. In control subjects, Z<sub>0</sub> is taken 33 mm Hg · L<sup>-1</sup> · s<sup>2</sup>; to calculate values for Z<sub>0</sub> in patients, we make use of the fact that Z<sub>0</sub> varies in proportion to 1/√C.<sup>9</sup> L is a parameter that represents the inertia of blood and is related to arterial dimensions and blood density. We assume L=5 mm Hg · L<sup>-1</sup> · s<sup>2</sup> for control subjects and patients.<sup>5</sup>

In the approximation of end-systolic aortic pressure with LV SBP, effective arterial elastance (E<sub>a</sub>) is given as SBP/SV.<sup>10</sup> For the control population, E<sub>a</sub>=1510 mm Hg/L (1.51 mm Hg/mL). In normal subjects, the ratio of E<sub>a</sub> and E<sub>max</sub> is close to 1.<sup>11</sup> We therefore assume E<sub>max</sub>=1500 mm Hg/L in the control group. Further, LVEDV values are computed from given end-diastolic diameters and the minor/major hemiaxis ratio, with the assumption of an ellipsoidal model. With SV in each subgroup known, LV end-systolic volume (LVESV) can then be calculated as LVESV=LVEDV–SV. E<sub>max</sub> is approximated as E<sub>max</sub>=SBP/(LVESV–V<sub>d</sub>). In solving this equation for V<sub>d</sub> with appropriate values for controls (E<sub>max</sub>=1500 mm Hg/L, SBP=124 mm Hg, and LVESV=29×10<sup>-3</sup> L), V<sub>d</sub> is estimated as -53.7×10<sup>-3</sup> L in the control group. With P<sub>v</sub>=5 mm Hg, E<sub>min</sub> is

calculated as P<sub>v</sub>/(LVEDV+53.7), giving a value of 30 mm Hg/L (0.030 mm Hg/mL) in the control group.

To the best of our knowledge, there are no data on the variation of the intercept of the end-systolic pressure-volume relation in the different cardiac adaptation scenarios. Therefore, we use a constant V<sub>d</sub> for all patient groups. E<sub>max</sub> can then be calculated directly from the data reported by Ganau et al.<sup>3</sup> Heart rate (70 bpm) and the timing of maximal contraction (t<sub>p</sub>=0.32 second) are taken as constant. The changes in LV volume and wall thickness have a similar effect on passive (E<sub>min</sub>) and active (E<sub>max</sub>) properties. We thus assume that E<sub>min</sub> changes in proportion to E<sub>max</sub>; P<sub>v</sub> then follows from E<sub>min</sub>, measured LVEDV, and V<sub>d</sub>. The validity of the heart–arterial model and the assumptions that lead to the model parameter setting is evaluated by comparing computed pressure and flow with the reported, measured values.

**Contribution of Arterial and Cardiac Changes to Blood Pressure in Hypertension**

To study the individual contribution of alterations in cardiac properties, arterial model parameters are given the values assessed for the control group, whereas cardiac model parameters are given the appropriate values that we assessed in the hypertensive patients. Isolated changes in R (or C) are studied in an analogous way, with control cardiac parameters and control C (or R). The difference between the control and the newly obtained hemodynamic data yields the contribution of each individual parameter to SBP, PP, and SV. We further consider combined changes in R and C to quantify the overall contribution of arterial changes to SBP.

**Results**

**Estimation of Model Parameters**

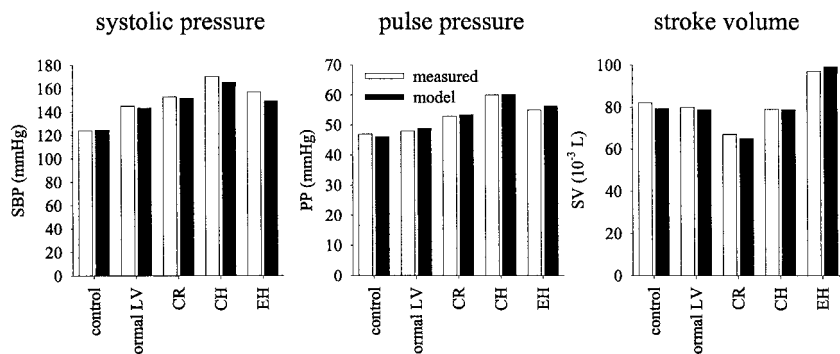
Hemodynamic data and model parameters for control subjects and hypertensives, taken directly or derived from the work of Ganau et al.,<sup>3</sup> are summarized in Table 1. Venous filling pressure, calculated from measured LVEDV and estimated E<sub>min</sub>, varies between 5.6 (normal LV group) and 7.0 (concentric hypertrophy) mm Hg. Measured PP and SV are predicted within 3% of data reported in literature<sup>3</sup>; SBP is estimated within 5% (5% underestimation in eccentric hypertrophy group) (Figure 2). We conclude that the model predicts the human data well.

**TABLE 1. Hemodynamic Data and Arterial and Cardiac Model Parameters in Normotensive Control Subjects and Hypertensive Patients With Different Cardiac Remodeling Patterns Taken From the Literature**

	Normotensive Subjects (n=125)	Hypertensive Patients			
		Normal LV (n=87)	Concentric Remodeling (n=21)	Concentric Hypertrophy (n=13)	Eccentric Hypertrophy (n=44)
Age, y	44±13	43±11	50±10	50±15	45±11
Heart rate, bpm	NC	70±13	70±10	71±10	71±10
SBP, mm Hg	124±10	145±16	153±21	170±34	157±22
DBP, mm Hg	77±7	97±12	100±13	110±20	102±12
LVEDV, 10 <sup>-3</sup> L*	111	115	92	103	146
SV, 10 <sup>-3</sup> L	82±17	80±17	67±15	79±16	97±16.2
Wall thickness, 10 <sup>-2</sup> m	0.84±0.10	0.9±0.09	1.1±0.07	1.3±0.09	1±0.09
Relative wall thickness	0.33±0.04	0.36±0.04	0.49±0.03	0.52±0.04	0.38±0.04
LV mass index, g/m <sup>2</sup>	75±17	85±17	93±9	144±23	136±27

NC indicates not communicated.

\*Calculated value with data given in the literature.<sup>3</sup>



**Figure 2.** Agreement between measured and predicted SBP, PP, and SV in control subjects and in hypertensive patients with normal LV, concentric remodeling (CR), concentric hypertrophy (CH), or eccentric hypertrophy (EH). The simulations are obtained with the model parameters given in Table 2.

### Contribution of Arterial and Cardiac Changes to Blood Pressure in Hypertension

In the group of hypertensives with normal LV, the data in Table 2 show modest alterations in R (increase), C (decrease), and LV pump function ( $E_{\max}$  and  $P_v$  increase). R and cardiac function both contribute positively to SBP; C has little effect (Figure 3, top row). The increase in R decreases PP, whereas the changes in C and pump function increase PP. The increase in R lowers SV, whereas the increase in pump function increases SV.

In the concentric remodeling group, R and LV pump function both increase, whereas C decreases (Table 2). The only parameter that contributes significantly to the increase in SBP is R (Figure 3, second row). The decrease in C has the greatest effect on PP (increase), whereas the increase in R has the greatest effect on SV (decrease).

In the concentric hypertrophy group, R and LV pump function have increased, whereas C has decreased (Table 2). The changes in cardiac function and R both contribute to the higher SBP (Figure 3, third row). The increase in R results in a lower PP and SV; the increase in pump function results in a higher PP and SV. The decrease in C increases PP and lowers SV.

In the eccentric hypertrophy group, only cardiac preload parameters change (Table 2). The increase in preload results in higher SBP, PP, and SV values (Figure 3, bottom row).

The mathematical model simulations indicate that in the normal LV group, the SBP increment is about equally due to arterial (46%) and cardiac (54%) remodeling (Figure 4). In the concentric remodeling group, arterial changes are the main factors that contribute to blood pressure (82%). In both the concentric and eccentric hypertrophy groups, cardiac geometric alterations are the main contributor to SBP and are responsible for 58% and 108% of the increase in SBP, respectively. The 108% increase in SBP in eccentric hypertrophy is due to the fact that the arterial changes have a small negative effect (−8%) on SBP.

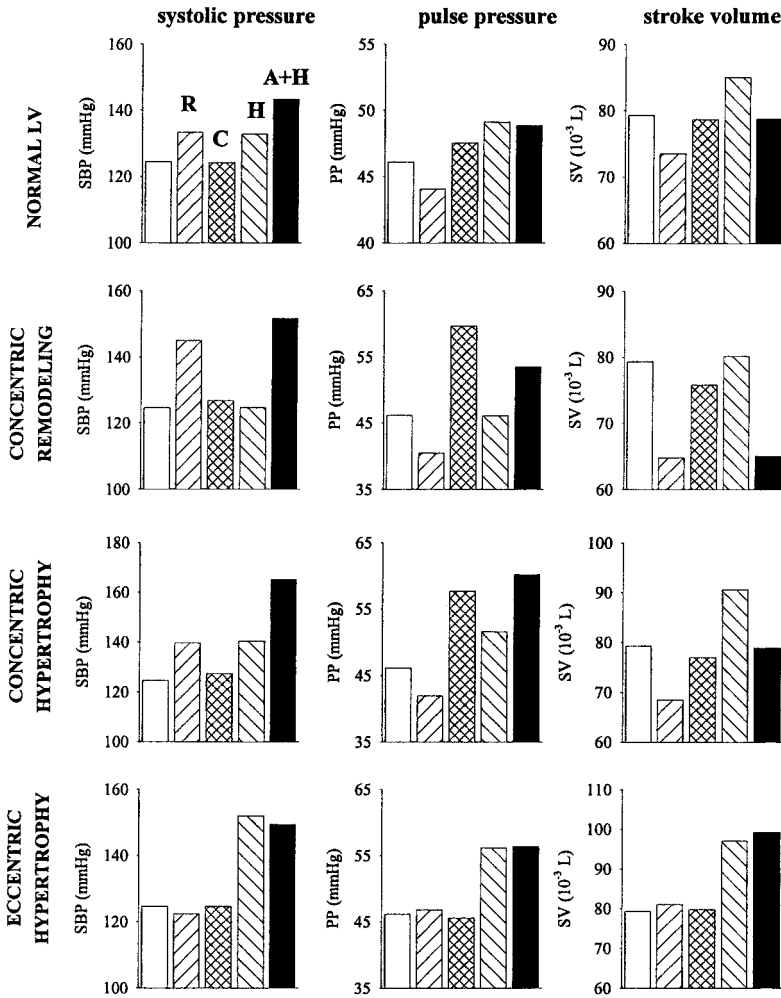
### Discussion

The present study is based on data presented in the literature of measurements in 125 normal and 165 hypertensive subjects who are classified into 4 groups, depending on measured LV mass and increase in LV wall thickness.<sup>3</sup> Quantitative analysis that is based on a mathematical model indicates that depending on the specific patient group, the heart contributes between 18% and 108% to the increase in SBP. In patients with a normal LV, there are modest alterations in cardiac and arterial properties. Individually, none of the changes leads to hypertension, but their combination does. The concentric remodeling group is the only patient group in whom the high blood pressure is almost exclusively attributable to arterial changes (ie, the increase in peripheral resistance). In the

**TABLE 2. Arterial and Cardiac Model Parameters Used for the Simulation of Hemodynamics in Normotensive Control Subjects and Hypertensive Patients With Different Cardiac Remodeling Patterns**

	Normotensive Subjects (n=125)	Hypertensive Patients			
		Normal LV (n=87)	Concentric Remodeling (n=21)	Concentric Hypertrophy (n=13)	Eccentric Hypertrophy (n=44)
$E_{\max}$ , mm Hg/L	1500	1640	1950	2200	1530
$V_d$ , $10^{-3}$ L	−53.7	−53.7	−53.7	−53.7	−53.7
$E_{\min}$ , mm Hg/L	30	33	39	44	31
$P_v$ , mm Hg	5.0	5.6	5.7	7.0	6.2
R, mm Hg · L <sup>−1</sup> · s	1110	1310	1660	1490	1060
C, $10^{-3}$ L/mm Hg	1.13	1.08	0.81	0.86	1.15
$Z_0$ , mm Hg · L <sup>−1</sup> · s	33	34	39	38	33
L, mm Hg · L <sup>−1</sup> · s <sup>2</sup>	5	5	5	5	5

Model parameters were calculated or estimated from the literature.<sup>3</sup> See the text for details on the assessment of model parameters.



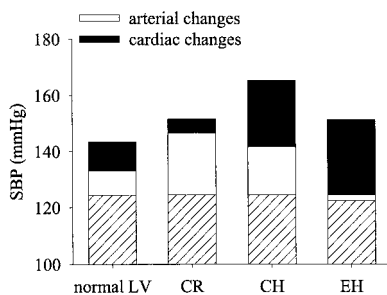
**Figure 3.** Effect of isolated changes in compliance (C), resistance (R), or cardiac parameters (H) on SBP, PP, and SV. Data are shown for the different cardiac remodeling patterns. The open bar represents data in the control condition; filled bar, data obtained with changes in the arterial and cardiac parameters together (ie, with model parameters from Table 2, A+H).

concentric hypertrophy group, arterial changes yield borderline hypertension only, whereas the heart is the major contributor to the increase in blood pressure. The high blood pressure in the eccentric hypertrophy group can be attributed almost exclusively to the heart. Overall, increased arterial load (reduced compliance, increased resistance, or both) results in a lower SV and lower cardiac output when the pump function of the heart is unchanged. Our simulations show that the development of hypertension requires an increase in

peripheral resistance or an increased pump function ( $E_{max}$ , LVEDV) to generate a higher cardiac output<sup>12</sup> and elevated SBP.

Parallel changes in arterial and cardiac structure and function have been observed.<sup>11,13</sup> Roman et al<sup>14</sup> studied carotid artery structure and function in the same 4 left ventricular phenotypes. They found that although blood pressure was the same in the concentric and eccentric hypertrophy groups, carotid artery dimensions, intima-media thickness, and stiffness were most abnormal in the concentric hypertrophy group.<sup>14</sup> The data used for our simulations show reduced total arterial compliance in the concentric hypertrophy but also the concentric remodeling group (Table 2). SV was considerably lower in the latter group than in all others, leading to higher values for peripheral resistance and lower values for total arterial compliance. Unfortunately, Roman et al<sup>14</sup> did not report SV, limiting a more detailed and direct comparison of both data sets.

The LV response to hypertension is a complex dynamic process, with mechanical, molecular, genetic, and biochemical factors involved.<sup>15</sup> In the present study, we do not speculate on the mechanisms that trigger arterial or cardiac remodeling. We simply use reported arterial and cardiac mechanical parameters, measured at a particular moment during the disease process, to calculate their effect on blood



**Figure 4.** Contribution of arterial (resistance and compliance) and cardiac changes to systolic blood in hypertension, according to the different cardiac remodeling patterns (normal LV, concentric remodeling [CR], concentric hypertrophy [CH], or eccentric hypertrophy [EH]). The hatched bar represents SBP under control conditions.

pressure elevation. When possible, we determined mechanical properties directly from the data (R and C); other parameters were varied in a relative sense, starting from the parameters in the control group ( $E_{\min}$ ). There was a good agreement (Figure 2) between measured and predicted arterial pressure and flow, which supports that the model parameter values we used are correct. The only arbitrary parameter we entered was venous filling pressure in the control group. As LVEDV was measured,  $P_v$  determines the slope of the diastolic pressure-volume relation in the control group. In the patients, we assumed that changes in wall thickness and volume, changing  $E_{\max}$ , proportionally affected diastolic stiffness. Together with measured LVEDV, we thus obtained estimations for the increase in venous filling pressure. Impaired diastolic function in LV hypertrophy has been described,<sup>16,17</sup> and the elevated venous filling pressure in concentric hypertrophy is well documented in studies on chronic pressure overload of the heart.<sup>18,19</sup>

The outcome of the present study, however, does not depend on the assumptions we made on the diastolic filling properties of the LV. Our model couples the LV to the arterial load and is suitable to study LV systolic function. The preload parameters  $E_{\min}$  and  $P_v$  are important because they yield LVEDV, the extent to which the LV is loaded at the onset of contraction. In the present study, however, we used the actual measured values for LVEDV; the choice of either  $P_v$  or  $E_{\min}$  yields the other parameter through the definition of  $E(t)$ , but their value is only indicative. For the same reason, the model is not suited to study the effects of impaired LV relaxation of LV filling hemodynamics.

Recently, much attention was paid to the role of vascular stiffening in hypertension.<sup>20,21</sup> Our model predicts that compliance changes alone have a limited effect on SBP, confirming experimental results in isolated feline heart preparation<sup>22</sup> and in the intact mammal.<sup>23,24</sup> Randall et al<sup>23</sup> concluded that compliance changes alone do not lead to (isolated systolic) hypertension. Kelly et al<sup>24</sup> found a 47% increase in SBP after lowering compliance by 60% to 80%, but in their study, peripheral resistance (+17%) and venous filling pressure (+38%) were also increased, with both effects contributing to the elevation of blood pressure.

The classification of LV adaptation patterns allows a better characterization of the hypertensive population. It is, however, still unclear whether it provides a prognostic value in addition to LV mass.<sup>25,26</sup> Our approach, which enables the quantification of vascular versus heart components to blood pressure on a per-patient basis, has the potential to lead to a better prognostic marker for cardiovascular risk.

The present mathematical model study has some inherent limitations. Both the heart and the arterial tree were simulated with linear models; thus, nonlinear properties were neglected. However, with appropriate model parameters, both models are good mechanical representations of both physiological systems, incorporating principal features of both.<sup>1,5,27</sup> We compared aortic blood pressure, given by the model, with measured sphygmomanometer brachial blood pressure. Due to wave travel and wave reflection, SBP is higher in the brachial artery than in the aorta.<sup>9</sup> Further, we assumed that an increase in contractility ( $E_{\max}$ ) proportionally affects passive

diastolic filling properties ( $E_{\min}$ ). However, given the uncertainties in the assessment of these parameters and the fact that we studied relative differences between different groups, these assumptions do not affect the validity of our results. We also assumed a constant intercept ( $V_d$ ) of the end-systolic pressure-volume relation. Especially in eccentric remodeling, where the LV pressure-volume loop is shifted to the right, this assumption may not hold. However, there still is a significant overlap with the pressure-volume loops measured or simulated in the control group. The rightward shift thus is much smaller than that seen in patients with cardiac failure, with severely dilated hearts and LVEDV in the range of 200 to  $300 \times 10^{-3}$  L,<sup>28</sup> where  $V_d$  is expected significantly elevated.

In summary, we have shown that vascular stiffening widens the arterial pulse without increasing SBP. It is only in combination with an increased resistance that arterial remodeling can lead to hypertension. However, the most important contribution to blood pressure in hypertension comes from cardiac remodeling and, thus, altered pump function. Depending on the remodeling pattern, the cardiac contribution is responsible for 21% to 108% of the increase in SBP in hypertension.

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