Published in : American Heart Journal (2002), vol. 144, iss. 4, pp. 568-578
Status : Postprint (Author's version)

Arterial elastance and heart-arterial coupling in aortic regurgitation are determined by aortic leak severity[1]

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Background In aortic valve regurgitation (AR), aortic leak severity modulates left ventricle (LV) arterial system interaction. The aim of this study was to assess (1) how arterial elastance (E_a), calculated as the ratio of LV end-systolic pressure and stroke volume, relates to arterial properties and leak severity and (2) the validity of E_a/E_{max} (with E_{max} the slope of the end-systolic pressure-volume relation) as a heart-arterial coupling parameter in AR. **Methods and Results** Our work is based on human data obtained from a study on vascular adaptation in chronic AR. These data allowed us to assess the parameters of a computer model of heart-arterial interaction. In particular, total peripheral resistance (R) and aortic leak severity—expressed as leak resistance ($R_{L,ao}$)—were quantified for different patient subgroups (group I/IIa/IIb: E_{max} = 2.15/0.62/0.47 mm Hg/mL; E_a = 1.24/0.66/0.90 mm Hg/mL; R = 1.9/0.6/0.85 mm Hg·s/mL, $R_{L,ao}$ = 0.35/0.05/0.20 mm Hg·s/mL). A parameter study demonstrated that $R_{L,ao}$ was the main determinant of E_a. With all other parameters constant, valve repair would increase E_a to 2.81, 1.08, and 1.54 mm Hg/mL in groups I, IIa, and IIb, respectively. For a given E_a/E_{max}, LV pump efficiency (estimated as the ratio of stroke work and LV systolic pressure-volume area) was lower than the theoretical predicted value, except for the simulations with intact aortic valve. **Conclusions** In AR, E_a is determined by aortic leak severity rather than by arterial system properties. Using E_a/E_{max} as a coupling parameter in general or as a mechanico-energetic regulatory parameter in particular is questionable.

Effective arterial elastance (E_a), introduced as a measure of the arterial load on the heart,[1] is considered a surrogate of arterial input impedance[2] and a measure of arterial stiffness.[3] It is approximated by the ratio of left ventricular (LV) end-systolic pressure and stroke volume and combines steady and pulsatile load components.[1] E_a can be combined with E_{max} (the slope of the LV end-systolic pressure-volume relation) to form the heart-arterial coupling parameter E_a/E_{max}. The E_a/E_{max} parameter is extensively used in studies considering mechanico-energetic aspects of heart-arterial coupling.[2] [12] In the normal heart, the E_a/E_{max} ratio is within the range of 0.5 to 1, and the LV operates close to its optimal efficiency (E_a/E_{max} = 0.5) or stroke work (E_a/E_{max} = 1).[3] [10] In heart failure, with dilated hearts, E_a/E_{max} becomes larger than 1.[7] [8] It is therefore tempting to see E_a/E_{max} as a regulated parameter that is kept at a value close to or below 1 in the normally functioning heart.

In aortic valve regurgitation, the normal heart-arterial interaction is disturbed by the leaking aortic valve. In such circumstances, the mechanical interaction between the LV and the arterial system takes place during both systole and diastole, with the severity of the aortic leak being an important modulator of cardiovascular hemodynamics. Although E_a and E_{max} can still be calculated from measured pressure-volume (P-V) loops,[13] the pattern of these P-V loops is in part determined by the aortic regurgitation itself, and aortic leak severity should therefore interfere with the E_a/E_{max} concept.

Our study is based on human data obtained from a study on heart-arterial coupling (E_a/E_{max}) and vascular adaptation in chronic aortic regurgitation. [13] Devlin et al[13] classified the patients in 3 groups on the basis of LV performance and characterized arterial function by means of E_a. We used these data to assess the parameters of a computer model that allows simulation of heart-arterial coupling in control and aortic regurgitation conditions. As such, we (1) expanded the information contained in E_a into important clinical parameters, such as total peripheral resistance and aortic leak resistance, uniquely quantifying aortic leak severity. Making further use of the data sets derived from the 3 patient subgroups, we (2) quantified the impact of changes in total peripheral resistance, aortic leak severity, and total arterial compliance on cardiovascular hemodynamics in general and on

[1] Supported by a postdoctoral grant of the Fund for Scientific Research-Flanders, Belgium (FWO-Vlaanderen), and by a postdoctoral grant of the National Fund for Scientific Research, Belgium.

E_a in particular; and (3) assessed how far the theoretical E_a/E_{max} mechanico-energetic heart-arterial coupling framework holds in aortic regurgitation.

Methods

Human data

Data were obtained from a patient study on chronic aortic regurgitation.[13] In this study, 45 patients (aged 50 ± 14 years) were classified into 3 subgroups according to LV contractility (E_{max}) and ejection fraction (EF). Group I consisted of 24 patients with normal contractility (E_{max} ≥1 mm Hg/mL). Group IIa consisted of 10 patients with impaired LV contractility (E_{max} <1 mm g/mL) but normal EF (EF ≥0.5), whereas group IIb (11 patients) had both impaired contractility and EF (EF <0.5). Hemodynamic patient data, as reported by Devlin et al,[13] are given in Table I.

Table I. *Hemodynamic data as reported by Devlin et al[13] and calculated and estimated computer model parameters for the 3 subgroups of aortic regurgitation data*

	Group I	**Group IIa**	**Group IIb**
HR (beats/min)	80	78	84
P_{ed} (mm Hg)	19	12	22
P_s (mm Hg)	153	136	153
P_{es} (mm Hg)	146	134	151
V_{ed} (mL)	202	383	514
V_{es} (mL)	84	179	347
EF (-)	0.59	0.55	0.34
SV (mL)	118	204	167
RI (-)	2.81	2.53	2.19
E_{max} (mm Hg/mL)	2.15	0.62	0.47
CO (L/min)*	3.36	6.29	6.41
E_a (mm Hg/mL)*	1.24	0.66	0.90
E_a/E_{max} (-)*	0.57	1.06	1.92
E_{min} (mm Hg/mL)*	0.102	0.029	0.045
V_d (mL)*	16	-37	26
T (s)	0.75	0.77	0.71
t_{Emax} (S)	0.26	0.27	0.25
R (mm Hg · s/mL)‡	1.9	0.6	0.85
C (mL/mm Hg)†	1.15	1.15	1.15
L (mm Hg · s^2 /mL)†	0.005	0.005	0.005
Z_0 (mm Hg · s/mL)†	0.033	0.033	0.033
$R_{L.ao}$ (mm Hg · s/mL)‡	0.35	0.05	0.20

The lowest $R_{L,ao}$ corresponds to the most severe aortic leak. Compared to Devlin's reported E_a (1.50, 0.70 and 1.36 mm Hg/mL for group I, IIa and IIb, respectively), the values we found for E_a are somewhat lower. It is not clear why our E_a, calculated from the reported average values of SV and end-systolic pressure, differ this much from their values.
* Calculated directly from data reported by Devlin et al.[13]
†Assumed fixed values.
‡Estimated values.

Cardiac output (CO; L/min) was calculated from the data as (HR/1000)·(SV/RI), with heart rate (HR, beats/min), stroke volume (SV, mL), and regurgitation index (RI) being the ratio of LV stroke volume to the forward stroke volume. Devlin et al[13] calculated RI from radionuclide LV and right ventricular counts, the latter representing the forward stroke volume. Arterial elastance was calculated as the ratio of end-systolic pressure and stroke volume.[1]

Published in : American Heart Journal (2002), vol. 144, iss. 4, pp. 568-578
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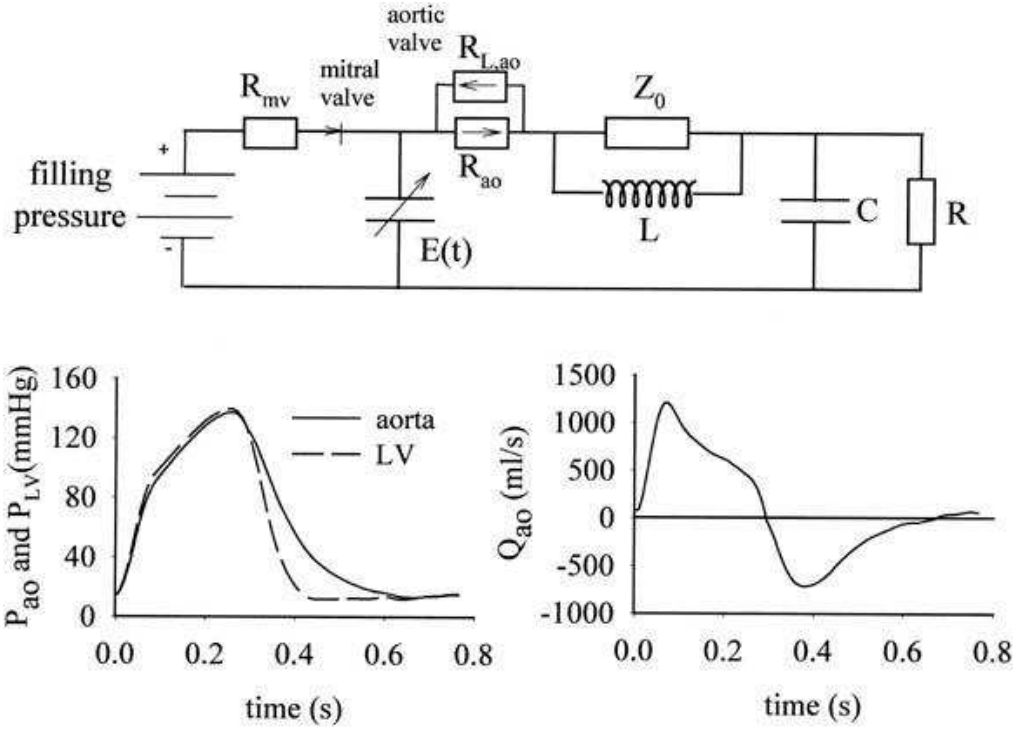
Computer model of heart-arterial interaction

LV pressure (P_{LV}) and volume (V_{LV}) and aortic pressure (P_{ao}) and flow (Q_{ao}) are computed with the use of a heart-arterial interaction model (Figure 1).[14] [15]

Fig. 1. *In the heart-arterial interaction model, heart function is modeled as a time-varying elastance function, E(t). Arterial model is a lumped parameter model consisting of total arterial compliance (C), total peripheral resistance (R), aortic characteristic impedance (Z_0), and the inertia of blood in the systemic arteries (L). The model directly yields LV and aortic pressures and aortic flow (Q_{ao}).*



Heart function is described by a time-varying elastance model[16] [17] and is coupled to a 4-element, lumped-parameter Windkessel model representing the arterial load.[18] 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 $E(t) = P_{LV}/(V_{LV} - V_d)$. Cardiac parameters are the slope (E_{max}) and intercept (V_d) of the end-systolic pressure-volume relation, the slope of the diastolic pressure-volume relation (E_{min}), and LV end-diastolic pressure (P_{ed}), heart rate (HR), and the time to reach maximal elastance (t_{Emax}). The mitral valve is simulated as a frictionless, perfectly closing device. To allow for aortic regurgitation simulations, the aortic valve is modeled as a linear resistor with a low resistance value (0.005 mm Hg·s/mL) during forward flow and a value for the leak resistance ($R_{L,ao}$) that will be determined for the different subgroups. When the LV-aorta pressure difference is positive, the forward valve resistance is used in the computations, whereas $R_{L,ao}$ is used when this difference becomes negative. The model is programmed in Matlab 5.3 (The Mathworks, Inc, Natick, Mass) and runs on standard PC configurations.

Estimating cardiac and arterial properties and aortic valve leakage in the 3 subgroups

Cardiac parameters

Values for all heart-related parameters for the 3 subgroups, obtained or calculated from the published clinical study by Devlin et al,[13] are given in Table I. The time to reach E_{max} (t_{Emax}) was estimated as 35% of the cardiac cycle. With $E_{max} = P_{es}/(V_{es} - V_d)$ and LV end-systolic pressure (P_{es}) and volume (V_{es}) given, this equation can be solved for V_d by using appropriate values for the 3 subgroups, yielding V_d = 16, −37, and 26 mL in groups I, IIa, and IIb, respectively. E_{min} is calculated from the data as $P_{ed}/(V_{ed} - V_d)$, with V_{ed} the LV end-diastolic volume.

Arterial parameters and aortic valve leakage

The report by Devlin et al[13] contains no data allowing a direct calculation of the arterial parameters of the 4-element Windkessel model. Therefore, these data must be estimated in an indirect way. Fixed values are

Published in : American Heart Journal (2002), vol. 144, iss. 4, pp. 568-578
Status : Postprint (Author's version)

assumed for L (0.005 mm Hg·s^2 /mL) and Z_0 (0.033 mm Hg·s/mL),[15] 2 parameters that have been shown to have limited impact on pressure and flow.[14] It is further assumed that total arterial compliance does not differ between the subgroups, being 1.15 mL/mm Hg, a value that we have found in another study for age-matched hypertensive patients.[15] The impact of total arterial compliance on hemodynamics will be further assessed.

Thus, at this stage, all parameters are known, except total peripheral resistance (R) and aortic valve leak resistance ($R_{L,ao}$). We then performed model simulations by use of different combinations of R and $R_{L,ao}$ and calculated LV systolic blood pressure ($P_{s,sim}$), cardiac output (CO_{sim}), and regurgitation index (RI_{sim}) from the data, with RI_{sim} calculated as $SV/(V_{fwd} - V_{bwd})$, with V_{fwd} and V_{bwd} being the forward and backward flow volumes through the aortic valve during one cycle, respectively. The (R, $R_{L,ao}$) parameter combination yielding the closest match between measured and calculated values for LV systolic pressure (P_s), CO, and RI, evaluated as $\Delta = ([P_s - P_{s,sim}]/LVSP)^2 + ([CO - CO_{sim}]/CO)^2 + ([RI - RI_{sim}]/RI)^2$, is taken as the optimal parameter set.

Contribution of total peripheral resistance, aortic leak resistance, and total arterial compliance to E_a, E_a/E_{max} stroke work, and LV pump efficiency

We further assessed the effect of isolated changes in total peripheral resistance or valve leak severity (as sort of sensitivity analysis) on hemodynamics and derived parameters such as E_a, stroke work, or pump efficiency. To study, for instance, the impact of R in group I, we first performed a "reference" simulation for this subgroup (ie, using all reference model values for group I) and 2 extra simulations with new values for R, being the values that were found for groups IIa and IIb. The impact of $R_{L,ao}$ in group I is studied in a similar way, and these procedures are repeated to study the impact of R and $R_{L,ao}$ in groups IIa and IIb.

In all 3 subgroups, additional simulations are done with all respective reference model parameters, except for total arterial compliance, which is given a value 50% lower (0.57 mL/mm Hg) or higher (1.72 mL/mm Hg) than the assumed reference value.

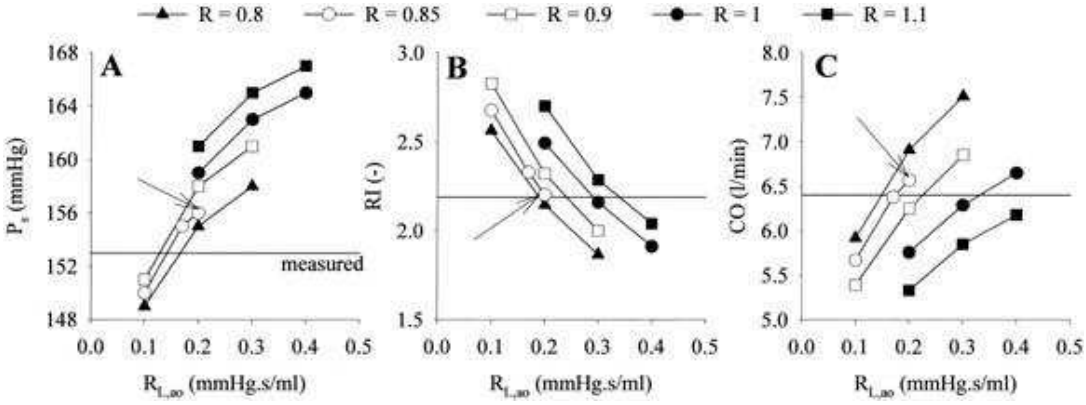
For all these simulations, E_a is calculated as P_{es}/SV, whereas heart-arterial coupling is characterized by E_a/E_{max}. Stroke work (SW) is calculated as the area enclosed by the LV pressure-volume loop, and the pressure-volume area (PVA) is defined as the area enclosed by E_{max}, the diastolic pressure-volume curve (E_{min}), and the systolic portion of the pressure-volume loop. The ratio of SW/PVA is then calculated as a surrogate of LV pump efficiency.[5] [6]

Results

Estimating cardiac and arterial properties and aortic valve leakage in the 3 subgroups

An overview of directly derived and estimated cardiac and arterial model parameters is given in Table I. The effect of R and $R_{L,ao}$ on LV systolic pressure, cardiac output, and regurgitation index for the data of subgroup IIb is shown in Figure 2.

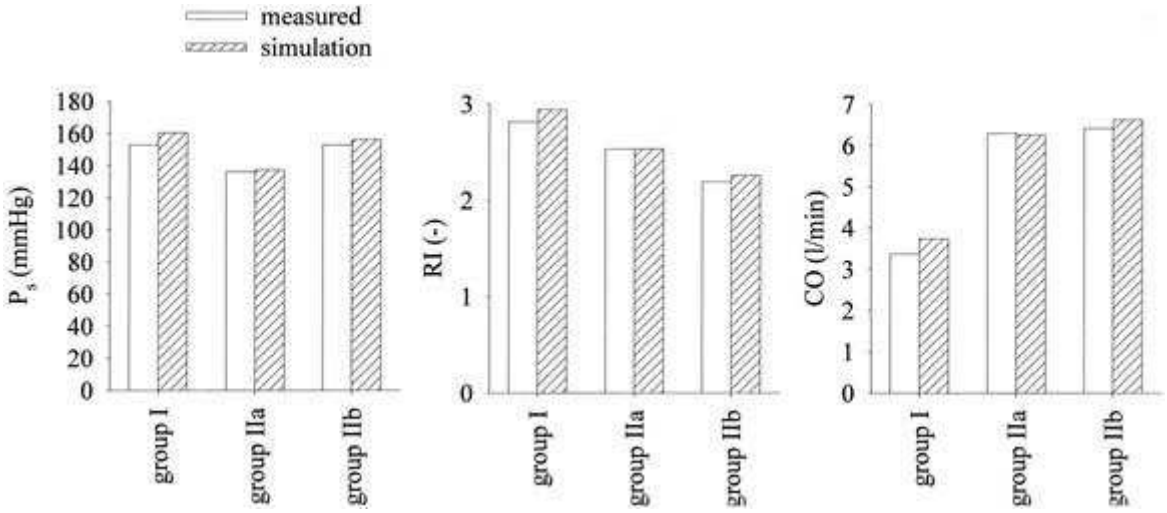
Fig. 2. *To assess the values for total peripheral resistance (R) and aortic valve leak resistance ($R_{L,ao}$), the R-$R_{L,ao}$ parameter space is scanned and the combination of R and $R_{L,ao}$ yielding the best agreement between measured and predicted LV systolic pressure (**A**), regurgitation index (**B**), and cardiac output (**C**) is taken as the optimal parameter set. For patient group IIb, the best solution (indicated by arrows) is obtained for R = 0.85 and $R_{L,ao}$ = 0.2 mm Hg·s/mL.*



For a given aortic leak resistance, an increase in total peripheral resistance yields a higher systolic pressure, higher regurgitation index, and lower cardiac output. For a given R, an increase in $R_{L,ao}$, that is, a less severe

leak, yields higher P_s, lower RI, and higher CO. For subgroup IIb, optimal parameters that fit the measured data are R = 0.85 mm Hg·s/mL and $R_{L,ao}$ = 0.2 mm Hg·s/mL, giving Δ = 0.001. For subgroups I and IIa, Δ is 0.016 and 0.00007, respectively. Values for all model parameters are given in Table I; comparison between measured (reported by Devlin et al[13]) and simulated systolic pressure, cardiac output, and regurgitation data is given in Figure 3.

Fig. 3. *Comparison between measured and predicted LV systolic pressure (**A**), regurgitation index (**B**), and cardiac output (**C**) for the 3 patient subgroups. See Tables I and II for model parameter values.*



Hemodynamic impact of R, C, and aortic valve leakage

Data showing the impact of isolated changes in total peripheral resistance, total arterial compliance, and valve leak resistance are given in Figure 4 and in Table II.

Table II. *Overview of simulations using the computer model*

Group	R	$R_{L,ao}$	C	CO	SV	RI	SBP	DBP	MAP
I	1.9	0.35	1.15	3.7	140.9	2.94	160.5	63.3	116.5
I	0.6	0.35	1.15	7.7	140.6	1.47	112.8	32.8	75.7
I	0.85	0.35	1.15	6.2	137.8	1.77	126.7	42.3	88.1
I	1.9	0.05	1.15	2.0	133.7	5.58	114.3	20.9	62.6
I	1.9	0.20	1.15	3.0	148.4	3.89	145.9	41.6	96.9
I	1.9	0.35	0.57	3.4	107.8	2.45	181.9	33.6	105.7
I	1.9	0.35	1.72	3.9	157.4	3.14	152.8	82.4	123.3
I	1.9	-	1.15	6.5	80.9	1.00	228.5	178.0	205.3
IIa	0.6	0.05	1.15	6.3	200.2	2.53	137.1	12.9	61.8
IIa	0.85	0.05	1.15	4.6	193.3	3.33	141.2	13.3	63.8
IIa	1.9	0.05	1.15	2.1	182.9	7.04	146.4	13.6	66.7
IIa	0.6	0.20	1.15	8.1	195.6	1.88	146.3	24.4	81.0
IIa	0.6	0.35	1.15	9.2	188.2	1.59	151.4	36.7	91.4
IIa	0.6	0.05	0.57	6.7	146.6	1.71	170.0	11.7	66.7
IIa	0.6	0.05	1.72	6.1	239.3	3.14	117.6	15.4	59.8
IIa	0.6	-	1.15	12.2	154.6	1.00	166.2	78.3	121.5

Published in : American Heart Journal (2002), vol. 144, iss. 4, pp. 568-578
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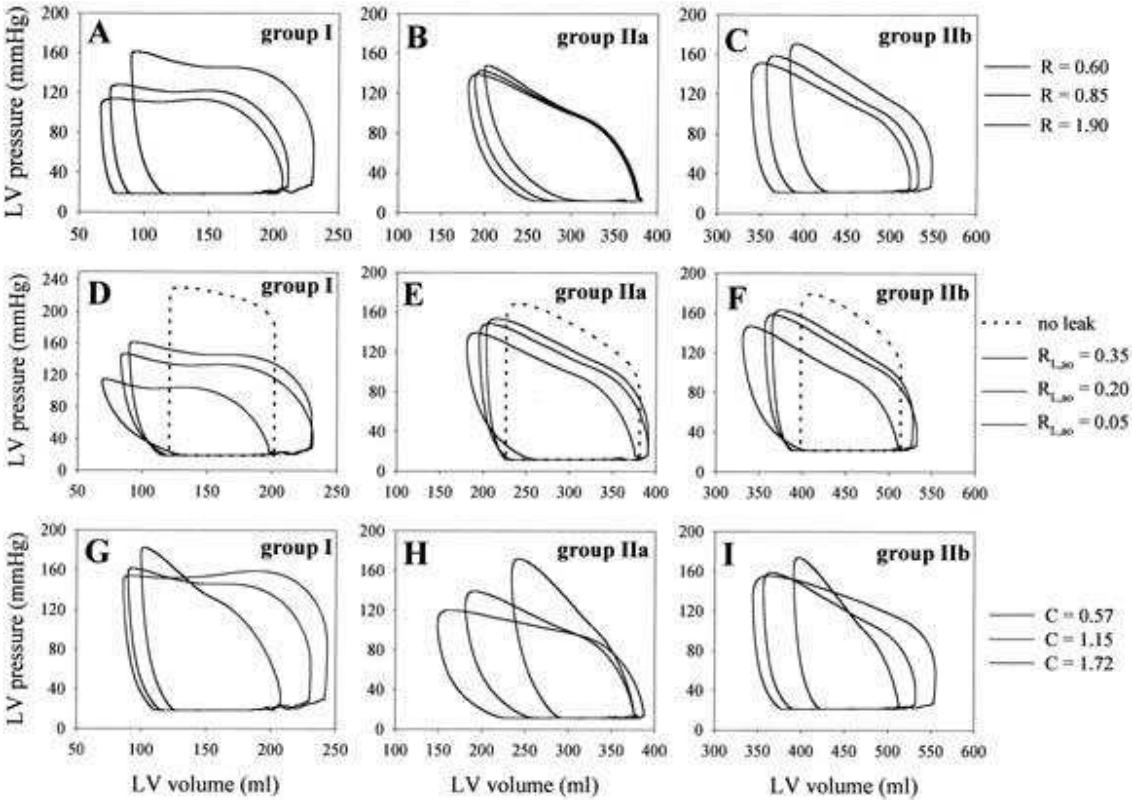
Group	R	$R_{L,ao}$	C	CO	SV	RI	SBP	DBP	MAP
IIb	0.85	0.20	1.15	6.6	176.2	2.26	156.2	39.3	93.0
IIb	0.6	0.20	1.15	8.6	183.8	1.79	148.8	33.8	85.9
IIb	1.9	0.20	1.15	3.3	165.2	4.13	168.5	49.0	104.7
IIb	0.85	0.05	1.15	5.0	183.8	3.12	144.3	23.4	69.9
IIb	0.85	0.35	1.15	7.4	162.8	1.85	160.5	54.2	104.2
IIb	0.85	0.20	0.57	5.9	123.7	1.77	172.2	23.8	83.3
IIb	0.85	0.20	1.72	7.2	211.2	2.45	151.9	56.6	101.4
IIb	0.85	-	1.15	9.9	116.0	1.00	176.2	103.9	138.0

SBP, Systolic arterial pressure; *DBP*, diastolic arterial pressure; *MAP*, mean arterial pressure.

***Fig. 4. A** through **C**, Effect of isolated changes in total peripheral resistance (R) on simulated pressure-volume loops in the 3 subgroups. The 3 simulations for group I **(A)**, for instance, are obtained using (1) all reference model parameters for group I (as given in Table I) and (2) the same parameters except for R that is given the values of groups IIa and IIb, respectively. Similarly, **D** through **F** show the impact of the severity of the aortic leak for all subgroups. **G** through **I** illustrate the effect of a change in total arterial compliance on the pressure-volume loops.*



For all groups, an increase in resistance leads to higher systolic pressures and a rightward shift of the P-V loops, but the effect is most outspoken for group I, that is, the subgroup with the less severe aortic leak (Figure 4, *A-C*). Increasing resistance lowers cardiac output and increases regurgitation index (Table II).

An increase in total arterial compliance (Figure 4, *D-F*) yields lower LV systolic pressure and a rightward shift of the P-V loop with a large increase in stroke volume. Effects are most outspoken for subgroup IIa, that is, the subgroup with the most severe aortic leak. A higher compliance leads to higher mean arterial pressures in groups I and IIb (and thus higher cardiac output) but not in group IIa. RI increases in all groups (Table II).

The more severe the aortic leak is (ie, the lower its resistance $R_{L,ao}$), the lower are systolic pressure (Figure 4, *G-I*) and end-systolic volume. Obviously, more severe leaks yield higher RI and lower cardiac output (Table II).

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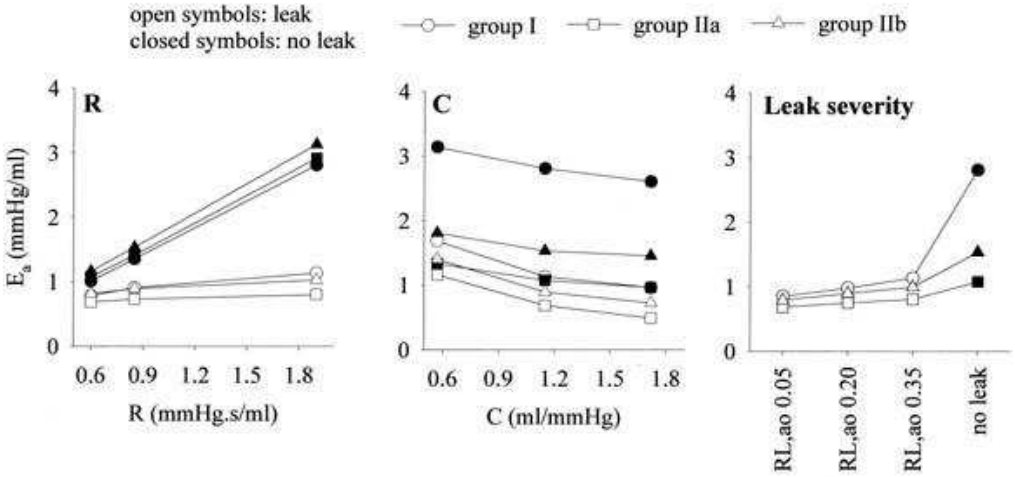
Figure 4 (*D-F*) and Table II also contain no-leak simulations, which are hypothetical post-valve repair data, assuming that all cardiac and arterial properties remain constant, whereas $R_{L,ao}$ approximates infinity (no leak). In groups IIa and IIb, valve repair would lead to high cardiac output (≥10 L/min) with only modest increases in systolic blood pressure. In contrast, cardiac output would be normalized in group I (6.5 L/min), with a high increase in systolic pressure.

Contribution of R, C, and aortic valve leakage to arterial elastance

An increase in R, a decrease in C, and less severe aortic leaks (higher $R_{L,ao}$) lead to higher E_a (Figure 5).

Comparing the reference simulations for the 3 groups with the hypothetical no-leak simulations, it follows from Figure 5 that repairing the aortic valve would instantly increase E_a from 1.14 to 2.81, from 0.69 to 1.08, and from 0.90 to 1.54 mm Hg/mL in groups I, IIa, and IIb, respectively.

Fig. 5. *Contribution of total peripheral resistance (R), total arterial compliance (C), and leak severity to arterial elastance in conditions of aortic regurgitation and for identical cardiac and arterial conditions but with an intact aortic valve (closed symbols).*

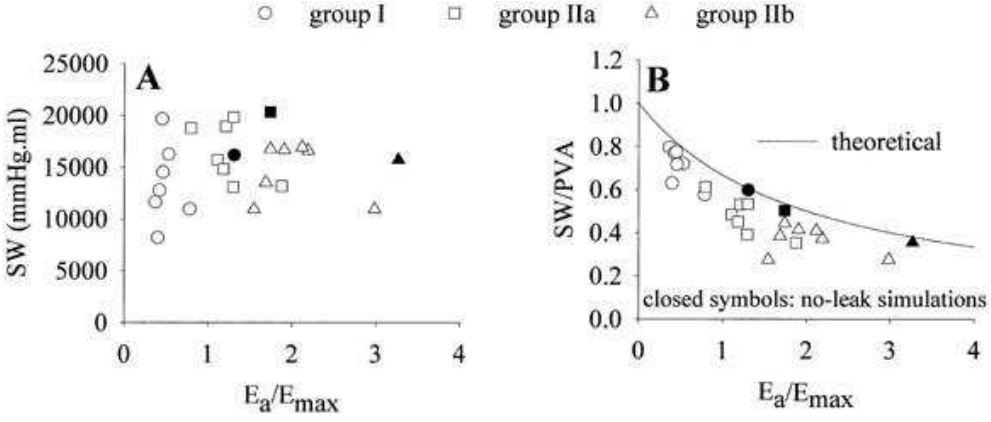


Mechanico-energetics and E_a/E_{max}

The relations between E_a/E_{max} and stroke work and between E_a/E_{max} and SW/PVA are depicted in Figure 6.

Within each subgroup, there is no obvious relation between SW and E_a/E_{max}. Concerning SW/PVA, all data points are below the theoretical relation between pump efficiency and E_a/E_{max}, that is, $SW/PVA = 1/(1 + 0.5\ E_a/E_{max})$, except for the hypothetical no-leak simulations for which the results adhere to this relation.

Fig. 6. *Relation between E_a/E_{max} and LV stroke work (**A**) and between E_a/E_{max} and SW/PVA (**B**), a surrogate measure of LV pump efficiency for the 3 patient subgroups. **B** also shows the theoretical relation between E_a/E_{max} and SW/PVA. It is observed that the no-leak simulations are the only data points adhering to this theoretical relation.*



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Discussion

In this study, we explored hemodynamic data obtained from patients with chronic aortic regurgitation by means of a (relatively) simple computer model describing heart-arterial interaction. The 3 patient subgroups as defined by Devlin et al[13] on the basis of LV performance criteria show distinct values for total peripheral resistance and aortic leak severity. E_a is highest in group I (E_{max} ≥1 mm Hg/mL) due to the high total peripheral resistance (1.9 mm Hg·s/mL) and the less severe aortic leak ($R_{L,ao}$ = 0.35 mm Hg·s/mL). Group IIa (E_{max} <1 mm Hg/mL, EF ≥0.5) has the lowest E_a because of low R (0.6 mm Hg·s/mL) and a severe aortic leak ($R_{L,ao}$ = 0.05 mm Hg·s/mL). Group IIb, which has the poorest LV performance (E_{max} < 1 mm Hg/mL, EF < 0.5) has intermediate values for E_a (R = 0.85 and $R_{L,ao}$ = 0.2 mm Hg·s/mL).

Because direct data necessary to calculate arterial parameters or aortic leak resistances are lacking, such as time course of LV and aortic pressures and aortic flow, R and $R_{L,ao}$ had to be estimated in an indirect way, thereby making use of a heart-arterial interaction model. All cardiac parameters used are obtained from Devlin et al[13] and are directly implemented in our model. Concerning the arterial model parameters, we assumed constant reference values for Z_0 and L, parameters that have a negligible impact on blood pressure and cardiac output in their physiological range,[14] [19] as well as a constant compliance. We have done a coarse scan of the R-$R_{L,ao}$ parameter space for the solution that yields the closest match between measured and predicted cardiac output, systolic pressure, and regurgitation index. This procedure yields distinct R-$R_{L,ao}$ combinations for the 3 subgroups, with the best results obtained in subgroup IIa (Figure 3). Possibly, other R-$R_{L,ao}$ combinations in the vicinity of our solution may further improve the fitting results, but parameter values will not differ by >0.05 mm Hg·s/mL for R or $R_{L,ao}$.

We have assumed identical total arterial compliance in the 3 subgroups (1.15 mL/mm Hg), with the value obtained from a study on hypertensive patients with the same age range as the patients in this study.[15] Another choice for the value of total arterial compliance would lead to different R-$R_{L,ao}$ solutions in the 3 subgroups. To assess the impact of this assumption, extra simulations are done with all parameters kept constant, except that C is increased and decreased by 50%. On average, a 50% lower compliance decreases cardiac output by 4% and RI by 23%, but increases systolic pressure by 16%. The 50% increase in compliance leads to 4% increase in CO, 13% increase in RI, and 7% decrease in systolic pressure. Therefore, another choice of C within the physiological range would only minimally affect the obtained results and still maintain the clear discrepancy between the different subgroups.

The effect of arterial parameters (R and C) on arterial elastance is illustrated in Figure 5. It has been shown earlier that—assuming that mean arterial pressure approximates LV end-systolic pressure—E_a can be approximated as R/T, with T the duration of the cardiac cycle.[6] In aortic regurgitation, this assumption is clearly violated, as apparent from Figure 5: increasing R only moderately increases E_a . The higher the valve leakage is (group IIa), the lesser the effect of an increase in total peripheral resistance. To better illustrate this effect, we performed some extra simulations with a nonleaking aortic valve while also changing R (and C) over the same range as with the leaking valves (Table II). These data are represented by the filled symbols in Figure 5, where it can be seen that the relation is linear, as expected. Concerning total arterial compliance, the opposite is true. Whereas the contribution of total arterial compliance to E_a is only marginal, its effect is somewhat stronger in aortic regurgitation, with higher compliances leading to lower E_a.

Having observed the relative insensitivity of E_a to R in aortic regurgitation, it is difficult to see E_a as an "active" regulatory arterial property. Total arterial compliance is mainly a passive property of the large elastic arteries, and the major determinant of E_a, that is, aortic leak severity, is a given noncontrollable "property." Thus, if E_a/E_{max} is indeed a regulatory parameter, it can only be controlled through changes in cardiac contractility and heart rate in aortic regurgitation.

In a theoretical study, it has been shown that for a given preload (V_{ed}) and inotropic state (E_{max} and V_d) of the LV, stroke work is determined by E_a/E_{max} and maximal when E_a/E_{max} = 1.[6] This relation was derived under the assumption that SW can be approximated by the product of SV and end-systolic pressure, which, obviously, is an assumption violated in case of aortic regurgitation. The relation between SW and E_a/E_{max} for the aortic regurgitation simulations is given in Figure 6, and it can be seen that there is no straightforward relation between E_a/E_{max} and SW, not even after normalization of the data, and SW is not maximal for E_a/E_{max} = 1. Note that "violation" of the predicted theoretical relation between E_a/E_{max} and SW was also observed in experimental studies with intact aortic valves. De Tombe et al[20] reported that E_a/E_{max} corresponding to maximal SW is <1, whereas SW remains close to its maximum (>90% of optimal value) for a wide range of E_a/E_{max} ratios (0.3 to 1.3).

The efficiency of the heart as a pump is quantified by the ratio of total heart oxygen consumption and stroke work. It has been demonstrated that ventricular systolic pressure-volume area, PVA, is strongly correlated to myocardial oxygen consumption. [21] As such, SW/PVA is a surrogate index of cardiac pump efficiency that can

be calculated from the pressure-volume loop. Moreover, there is a theoretical relation between SW/PVA and E_a/E_{max} , given by $SW/PVA = 1/(1 + 0.5\ E_a/E_{max})$.[6] In aortic regurgitation, however, this theoretical E_a/E_{max} heart-arterial coupling framework does not hold, as illustrated in Figure 6, where the relation between SW/PVA and E_a/E_{max} for the simulated data is shown. The only data points adhering to the theoretical relation are the simulations with the intact aortic valve. For all other cases, pump efficiency is lower than the theoretically predicted value based on E_a/E_{max}.

The use of effective arterial elastance and of E_a/E_{max} has been promoted by theoretical and experimental studies linking E_a/E_{max} to LV mechanico-energetics.[3] [4] [6] [10] [12] Note, however, that E_a/E_{max} is mainly a "geometrical" parameter related to ventricular volume. With $E_a = P_{es}/SV$ and $E_{max} = P_{es}/(V_{ed} - SV - V_d)$ and assuming V_d small enough so that it can be neglected, $E_a/E_{max} = V_{ed}/SV - 1 = 1/EF - 1$.

For ejection fractions of 0.5 to 0.7, E_a/E_{max} is 1 to 0.42. In failing, dilated hearts, the EF decreases (mainly because of the increase in V_{ed}) and E_a/E_{max} thus increases. The validity of the relation between E_a/E_{max} and EF in aortic regurgitation is confirmed by regression analysis on all simulated cases of Table II, which yields a regression equation $1/EF - 1 = 1.02\ E_a/E_{max} - 0.02$; $r^2 = 0.96$.

The reason LV ejection fraction is around 0.5 ($E_a/E_{max} = 1$) in the normal heart can be argued on mechanical-energetic grounds, but it has also been shown that this value is explicable on the basis of evolutionary arguments.[22] Also, the human body has no sensors or receptors being sensitive to stroke work or mechanical efficiency. It is therefore unlikely that there are control mechanisms maintaining constant E_a/E_{max} to operate at optimal power or optimal efficiency. It seems more plausible that cardiovascular control mechanisms are based on (coronary perfusion) pressure, wall stress (or strain), or flow.

It should be emphasized that this is a mathematical model study with some inherent limitations. The heart and the arterial tree are simulated with linear models, thus neglecting nonlinear properties. However, it has been shown earlier that the combination of such linear models yields accurate predictions of cardiovascular hemodynamics. [14] [19] [23] In addition, the aortic valve is simulated as a simple linear resistor. Incorporating a more complex nonlinear aortic valve model may generate patterns of aortic forward and regurgitant flow better matching in vivo observations, but we do not have the data necessary to derive better constitutive laws for the aortic valve. Also, total arterial compliance is given a constant value. With the large alterations of arterial pressure in aortic regurgitation, a nonlinear pressure-dependent compliance model would be a more accurate representation of the arterial system. It should, however, be stressed that the aim of this work is to illustrate the limitations of the conceptual E_a/E_{max} heart-arterial coupling framework in aortic regurgitation and not to fine-tune the computer model for a perfect simulation of the human data, which is impossible with the data provided by the work of Devlin et al. To our knowledge, such data, which would consist of simultaneously measured LV pressure and volume and aortic pressure and flow, are currently not available.

There is a growing clinical interest in vascular properties in general and arterial stiffness in particular. E_a, being termed arterial elastance and having stiffness units, appears to be an attractive parameter to characterize the arterial system,[1] [3] [13] [24] especially in studies relating cardiac and arterial function (heart-arterial coupling). However, E_a is hardly related to arterial elasticity, and instead of an arterial parameter, it is a heart-arterial coupling parameter in itself. In fact, the main determinants of E_a are total peripheral resistance and cardiac frequency[5] [6] and not arterial stiffness. E_a cannot be used as a substitute of arterial impedance,[5] which becomes most obvious in aortic regurgitation where aortic leak severity is an important determinant of E_a.[25]

In particular in aortic regurgitation, the arterial system should be quantified by specific system properties (total peripheral resistance, total arterial compliance, valve leakage resistance) rather than by a global parameter such as E_a. The combined use of clinical data and computer models can help the clinician in this process of identifying and quantifying the true mechanical properties of both the arterial system and the aortic leak, as illustrated in this study. Furthermore, these computer models allow to predict the impact of, for instance, vasodilator/vasoconstrictive drugs or valve repair on hemodynamics and cardiac load.

Though not numerous, there are several studies reporting E_a in aortic regurgitation.[13] [25] [26] It is nevertheless important to heighten the awareness of cardiovascular practitioners and researchers for the correct use of E_a, in particular in aortic regurgitation. We have shown that aortic leak is an important modulator of E_a and that the assumptions leading to the conceptual heart-arterial coupling framework linking E_a/E_{max} to mechanico-energetic parameters are violated. As such, the use of E_a as an arterial function parameter and of E_a/E_{max} as a coupling parameter in general or as a mechanico-energetic regulatory parameter in particular is questionable in these conditions.

Published in : American Heart Journal (2002), vol. 144, iss. 4, pp. 568-578
Status : Postprint (Author's version)

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