Effect of ventricular contraction, pressure, and wall stretch on vessels at different locations in the wall

MARTIJN A. VIS, PETER H. M. BOVENDEERD, PIETER SIPKEMA, and NICOLAS WESTERHOFF. Effect of ventricular contraction, pressure, and wall stretch on vessels at different locations in the wall. Am. J. Physiol. 272 (Heart Circ. Physiol. 41): H2963–H2975, 1997.—A cylindrical model of the heart was used to calculate the influence of ventricular filling and (isovolumic and isobaric) contraction on the cross-sectional area and resistance of a subendocardial and subepicardial maximally dilated arteriole and venule. Contraction is defined as the difference between static diastole and static systole. Furthermore, a small piece of rectangular myocardium containing the vessel was modeled to distinguish between the individual contributions of contractility (i.e., myocardial elastic properties), ventricular pressure, and local circumferential stretch to the changes in vascular area and resistance during contraction. Calculations were performed assuming the muscle fibers ran in either an apex-to-base or a circumferential direction. The results were similar for the two directions. Assuming constant, physiological arteriolar and venular pressures of 45 and 10 mmHg, respectively, coronary blood vessels were predicted not to collapse during ventricular contraction. Moreover, vascular area reduction was found to be larger for the arteriole (≈50%) than for the venule (≈30%) during both isovolumic and isobaric contractions. Consequently, arteriolar resistance was found to increase more than venular resistance (≈340 and 120%, respectively). Subendocardial area reductions were found to be somewhat smaller than subepicardial area reductions for the venule (by ≈10%) but not for the arteriole. Contractility was found to be the main contributor to the changes in vascular area and resistance in the subepicardium but to contribute by <50% to the changes in the subendocardium. Because pressure does, but stretch does not, contribute to the area change during isovolumic contraction and the reverse is true during isobaric contraction, it was concluded that although changes in vascular area and resistance may be similar for different contractions, the causes for these changes are very different.

arteriole; venule; subendocardial; subepicardial; isovolumic contraction; isobaric contraction; stress; finite-element method

THE DECREASE IN CORONARY ARTERIAL INFLOW (1, 8, 10, 25) and the increase in coronary venous outflow (1, 26) during cardiac contraction were originally thought to be caused by the increase in ventricular pressure. This idea was based on the assumption that ventricular pressure generates an intramyocardial pressure that decreases linearly from the endocardium to the epicardium. The well-known “vascular waterfall mechanism” (8) and “intramyocardial pump model” (1, 25) were based on this concept.

Later experiments on isobarically (constant left ventricular pressure) and isovolumically (constant left ventricular volume) contracting cat (16) and rabbit hearts (17), however, showed similar decreases in coronary arterial inflow despite the differences in developed left ventricular pressure. This led Krams and colleagues (16, 17) to propose that the varying material properties of cardiac muscle (“contractility”) rather than ventricular pressure are responsible for the influence of contraction on coronary flow.

Vascular area and shape changes stand at the basis of changes in resistance and thus flow. Vis et al. (31) recently proposed a model to predict the area changes in arterioles and small veins embedded in the isolated contracting papillary muscle. The varying material properties during contraction resulted in a decrease in vessel area without the presence of a ventricular pressure.

In the whole heart, however, the situation is more complex. Not only do the material wall properties change during contraction, but wall stretch and ventricular pressure vary also. Moreover, wall stretch depends on the location in the ventricular wall. The effects of both ventricular wall stretch (24) and pressure (2, 15, 32) on the vasculature have been recently suggested.

Contractility, pressure, and (local) wall stretch cannot be uncoupled experimentally in the left ventricle because it is not possible to change one of these variables while keeping the other two constant. We therefore used the finite-element method to calculate the influence of ventricular filling (stretch) and ventricular pressure in static diastole and static systole on the area and resistance of a subendocardial and subepicardial maximally dilated arteriole and venule in a cylindrical model of the left ventricle. This model predicts the integrated influence of the three mechanical components, ventricular contractility, pressure (related to local radial stress), and local circumferential wall stretch, on the vascular area. In another set of calculations, a small piece of rectangular myocardium contain-
ing the vessel was modeled to distinguish among the individual contributions of contractility (i.e., myocardial elastic properties), ventricular pressure, and local circumferential stretch to the differences in vascular area between static diastole and static systole.

**METHODS**

**General Outline**

Two models are described here. Model 1, concerning an equatorial ring from the ventricular wall, is used to determine the influence of ventricular inflation in diastole and systole on the luminal cross-sectional area and shape of a subendocardial or subepicardial coronary blood vessel. Model 2 concerns a local myocardial environment of the blood vessel and is used to determine the individual contributions of ventricular contractility, pressure, and circumferential wall stretch on the change in vascular luminal area and shape between static diastole and static systole (contraction).

**Material Properties**

The myocardium. As in the previous study by Vis et al. (31), the myocardial tissue (i.e., muscle fibers + collagen + interstitial fluid) was assumed to be incompressible. Total Cauchy stress \( \sigma \) in the tissue can then be written as

\[
\sigma = \sigma^e - \mu I
\]

where \( \sigma^e \) is the "extra stress" tensor that is related to the deformation of the tissue, \( \mu \) is the Lagrange multiplier that represents the part of the tissue stress that originates from the incompressibility of the tissue, and \( I \) is the unity tensor. Furthermore, the myocardium was assumed to be homogeneous, (nonlinearly) elastic in both diastole and systole, and transversely isotropic with respect to the fiber direction.

The strain-dependent \( \sigma^e \) was modeled with a strain-energy density function \( W \)

\[
W = C \left[ \varepsilon + E_{11} + E_{22} + E_{33} + 2E_{12} + 2E_{23} + 2E_{31} \right] - 1
\]

where \( E_{ij} (i, j = 1, 2, 3) \) and \( \varepsilon \) are the components of the Green-Lagrange strain matrix (see APPENDIX A for mathematical background) and \( C, D, \alpha, \beta, \theta_1, \) and \( \theta_2 \) are the material parameters discussed below. The first term of this strain energy function describes the passive material. Its form was taken from Bovendeerd (3). The second term represents the developed (active - passive) energy. The form for this term was chosen by analogy with the description of active material reported previously (31). First, developed (active - passive) stress is assumed to be an exponential function of strain. Second, the active myocardium (like the passive myocardium) is assumed to be transversely isotropic with respect to the fiber direction. Third, active stress is assumed to develop also in cross-fiber direction. Equation 1, which must be regarded as an empirical relationship, contains the full description of the material properties of the myocardium, and from it, Cauchy stress-strain relationships can be obtained for all possible stretching protocols and in all directions (APPENDIX A).

The following values for the parameters were used: \( \alpha = 15.82, \beta = 1.5, \) and \( C = 0.042 \) kPa for the passive material, and \( \theta_1 = 2.53, \theta_2 = 0.39, \) and \( D = 19.07 \) kPa for the active material. With the use of these parameter values, Fig. 1 shows the Cauchy stress-strain relationships for the uniaxial stretch in fiber direction, fitting the experimental data of Schouten et al. (23). Figure 1 also shows the Cauchy stress-stretch relationships for cross-fiber stretch with fiber length fixed at a slack length and at 90% of maximal fiber length \( L_{\text{max}} \).

The value for \( \beta \), which controls anisotropy in diastole, was set at 1.5, in accordance with measures of anisotropy reported in the literature (12, 19). Values for \( \alpha \) and \( C \) (for the myocardium in diastole) were chosen so as to reproduce the systolic Cauchy stress-stretch relationships used in the previous study by Vis et al. (31) (see Fig. 1). Analogously, values for \( \theta_1, \theta_2, \) and \( D \) (for the myocardium in systole) were chosen so as to reproduce the systolic Cauchy stress-stretch relationships as presented in the previous study by Vis et al. (31) (see Fig. 1). An important feature in our study is the incorporation of active stress not only in the fiber but also in the cross-fiber direction, which is in accordance with recent experimental findings (4, 11, 19).

The vessels. A maximally dilated arteriole and a maximally dilated venule were considered. Maximal vasodilation was chosen to avoid changes in the pressure-area relationships of the vessels due to autoregulation between diastole and systole. The vessel wall tissue was assumed to be incompressible. Vascular transmural pressure-area relationships for the isolated arteriole and venule were taken from the literature (see Ref. 31) and were (least squares) fitted by an empirical two-parameter inverse tangent function adapted from Lange-wouters (18) (see Ref. 31 for details). The ratio of outer to inner radius of the vessels at zero vascular transmural pressure was taken to be 1.6 for the arteriole (28) and 1.1 for the venule (22). Physiological working pressures for the arteriole and venule are 45 and 10 mmHg, respectively (6).

Vessels and surrounding myocardium. Embedded coronary blood vessels were assumed to fit exactly in the cavity in the wall of the undeformed ventricle (i.e., in diastole and at zero ventricular pressure). Furthermore, the blood vessels were assumed to remain tightly connected to their surrounding myocardial tissue during deformations.

**Geometry**

Model 1: Left ventricular equatorial ring. An equatorial ring from the rat left ventricle was modeled (see Fig. 2). In the reference situation (i.e., in diastole and at zero left ventricu-
Ventricular contraction and coronary blood vessels

Fig. 2. Finite-element mesh of one quarter of an equatorial ring from left ventricle containing a cylindrical, subendocardial (subendo) cavity pertaining to a coronary blood vessel. Measurements shown are for rat heart. Note that mesh density (no. of elements per unit of ring volume) is highest near cavity. An analogous mesh was used for ventricle containing a subepicardial (subepi; vascular) cavity. Inset: a local rectangular environment of cavity is subject to circumferential stretch on one hand and (compressive) radial stress on the other.

Local compressive radial stress

70 μm

1.0 mm

local circumferential stretch

2.5 mm

Y Z X

Model 2: Local rectangular vessel environment. Calculations were also performed for a rectangular piece of myocardial tissue containing the above-defined (vascular) cavity (see Fig. 2, inset). Length (4.5 mm) and width (2.5 mm) of the rectangle were chosen to be large with respect to the size of the cavity; height was taken as equal to that of the ventricular ring (1.0 mm) and kept constant during the calculations. Considering the rectangular piece of myocardial tissue as a representation of the direct environment of the cavity, rectangular length, width, and height directions correspond to left ventricular circumferential, radial, and longitudinal directions, respectively. In analogy with the ventricular equatorial ring, myocardial fibers were assumed to run either in a "longitudinal" or in a "circumferential" direction. The vascular cavity in the myocardium and the pertaining coronary blood vessels were of the same sizes as in the ventricular equatorial ring.

Computational Procedure

Governing equations. The finite-element method was used to solve the partial differential equations describing the equilibrium of a continuum (see Ref. 3). These equations are 1) conservation of mass, which, under the assumption of incompressibility, gives

\[ \det(F) = 1 \] (3)

where \( F \) is the deformation gradient tensor, describing the (local) deformation of a piece of material, and \( \det \) denotes the determinant; 2) equilibrium of force

\[ \nabla \cdot \sigma = \nabla \cdot \sigma^e - \nabla \mu = 0 \] (4)

where \( \nabla \) denotes the gradient operator and inertial and gravitational effects are neglected, and 3) conservation of angular momentum, implying symmetry of the Cauchy stress tensor. This is fulfilled by the choice of the constitutive relationships of the material expressed in Eq. 1.

The boundary conditions completing this set of equations are 1) \( \sigma \cdot n = P_n \), where \( n \) is the normal vector to the (endocardial, epicardial, or vascular cavity) surface and \( P \) is the left ventricular pressure at the endocardium, \( P = 0 \) at the epicardial surface, or \( P \) is the (vascular) cavity pressure at the surface of the muscle cavity pertaining to the blood vessel; and 2) the prescription of some displacements at the remaining surfaces, which is described in Mesh for model 1.

The finite-element calculation. Calculations were performed with the finite-element package NONSYS (not commercially available). Details are given by Bovendeerd (3). Briefly, with a Galerkin-type finite-element formulation of Eqs. 2 and 3, the conservation equations are converted into algebraic equations on 20-node brick elements. In these
elements, integration is carried out using a 14-point integration rule. The displacement field is approximated quadratically in each of the isoparametric coordinates, with displacements defined in all 20 nodes. The pressure field is approximated linearly in each of the isoparametric coordinates, with pressures defined only at the eight corner nodes. A Newton-Raphson iterative solution method is used to solve the algebraic equations.

Mesh for model 1. One quarter of the left ventricular ring, containing the longitudinally directed cavity, was used for the finite-element mesh (see Fig. 2). The mesh consists of 184 elements and contains 1,164 nodes. Element and node densities were made highest in regions of expected highest gradients (i.e., near the endocardium and near the cavity).

The quarter ring is bounded by the x-z and y-z planes. Points on these planes, connecting the quarter to the rest of the ventricle, were forced to remain in those planes during the calculations but were allowed to shift along them. The radial and longitudinal displacements of corresponding nodes in the x-z and y-z planes were forced to be identical, i.e., the vertical planes through the x- and y-axis are planes of symmetry. Together with the placement of the center of the cavity in the x = y plane, this implies that the entire left ventricle may be regarded as consisting of four identical quarters, each quarter containing one longitudinally directed cavity.

Computation of a complete vascular cavity pressure-area-shape relationship for one ventricular pressure took ~6 h of computation with a Silicon Graphics Challenge L computer (4xR4400, 175 MHz) in single-processor mode. This was repeated for a range of ventricular pressures in diastole and in systole.

Mesh for model 2. The mesh for the rectangular piece contained the same number of elements and nodes as the mesh of the quarter ring and had the same element and node densities near the cavity (see Fig. 2, inset). A uniform pressure was applied to the surfaces normal to the "radial" direction and a uniform stretch, corresponding to local circumferential stretch in the ventricular wall, was applied to the surfaces normal to the circumferential direction.

Incorporating a blood vessel. The pressure-area relationship of a cavity in the ventricular wall, as calculated with the finite-element method, together with the pressure-area relationships of the isolated blood vessels, were used to calculate the pressure-area relationships of the embedded vessels (see Ref. 31).

When the ventricular wall deforms, the cavity in the wall and consequentially the embedded blood vessel will not remain circular. The "aspect ratio" of the cavity was determined by dividing the cavity diameter in the left ventricular circumferential direction by the cavity diameter in the left ventricular radial direction and was converted into the aspect ratio \(a/b\), where \(a\) and \(b\) are the vessel diameters in the left ventricular circumferential and radial direction, respectively) of the pertaining blood vessel by assuming uniform vessel wall thickness. Note that an aspect ratio of 1.0 implies a circular lumen. If the vessel is assumed to be elliptical, vascular (steady-state) hydraulic resistance is proportional to \((a^2 + b^2)/a^3b^3\). (29).

Determining the individual contributions of ventricular contractility, pressure, and wall stretch to the changes in vascular area, shape, and resistance. When changes in contractility, radial stress, and circumferential stretch in model 2 are applied independently, the influence of these three factors on the pressure-area relationship of an embedded coronary blood vessel could be studied separately. This was done for an isovolumic and for an isobaric ventricular contraction when the diastolic ventricular pressure was 5 mmHg. The values of radial stress and circumferential wall stretch, corresponding to a certain ventricular mechanical state (diastole or systole), were calculated analytically from the theory given in Appendix: local circumferential wall stretch follows from ventricular luminal volume and the assumption of incompressibility of the ventricular wall (the element in Eq. B1 in the 2,2 position), and local radial stress follows from Eq. B3.

Figure 3 demonstrates how the individual contributions of ventricular contractility (E) and ventricular pressure (P, directly related to radial wall stress) to the area reduction in a subendocardial arteriole during ventricular isovolumic contraction were determined. The thin and thick solid lines represent the arteriolar pressure-area relationships in diastole (ventricular pressure 5 mmHg) and systole (ventricular pressure 99 mmHg), respectively, as calculated with model 1. The same relationships are found in diastole (solid circles) and systole (open circles) when using model 2. This shows that the small rectangle is sufficient to describe local behavior. The dashed line in Fig. 3 represents the arteriolar pressure-area relationship in a rectangular piece of myocardium when only contractility changes from diastole to systole. The subsequent transition from the dashed line to the thick solid line gives the influence of ventricular pressure per se on the arteriolar pressure-area relationship. Assuming a constant vascular pressure, the influence of ventricular contractility, pressure, and stretch on the area is expressed as a percentage (termed the "contributions") of the total vascular area reduction during contraction.

Note that the dashed and diastolic solid lines in Fig. 3 intersect at ~10 mmHg. This means that at this pressure contractility does not contribute to the decrease in vascular area. At a lower arteriolar pressure, the contribution of the contractility is even reversed; i.e., the increase in contractility during contraction results in an increase in vascular area. Note that in this example concerning an isovolumic contraction, the contribution of circumferential stretch (\(\lambda\)) to vascular area reduction is zero. In reverse, during an isobaric contraction, the contribution of pressure is negligible.

RESULTS

Only those results that were obtained from calculations with the fibers running in a longitudinal (i.e.,
Ventricular contraction and coronary blood vessels

Fig. 4. Ventricular pressure-volume relationships in diastole (●) and systole (○). Solid lines, pressure-volume data calculated analytically from theory in APPENDIX B; symbols, pressure-volume data obtained from finite element calculations.

apex-to-base) direction are shown. The results were found to be qualitatively and quantitatively similar to those obtained if the fibers were assumed to be directed circumferentially.

Left Ventricular Equatorial Ring

Ventricular pressure-volume relationships. Figure 4 shows the ventricular pressure-volume relationships in diastole and systole calculated analytically (lines; see APPENDIX B) and from finite-element calculations (symbols). Analytic and finite-element results can be seen to be in close agreement.

Local radial stress. Figure 5 shows how the “compressive radial stress” (defined as radial stress times \(-1\)) varies throughout the ventricular wall in diastole at a pressure of 5 mmHg (Fig. 5A) and in systole after isovolumic contraction at a ventricular pressure of 99 mmHg (Fig. 5B). It can be seen that compressive radial stress decreases from left ventricular pressure at the endocardium to external pressure at the epicardium in a curvilinear fashion.

Cavity area. Figure 6 shows the pressure-area relationships of a subendocardial and a subepicardial cavity in the ventricular wall for the myocardium in diastole and systole and for a range of ventricular pressures. In diastole, it can be seen that left ventricular inflation has a strong effect on the pressure-area relationship of a subendocardial cavity (Fig. 6A) but has almost no effect on the pressure-area relationship of a subepicardial cavity (Fig. 6C). For cavity pressures larger than \(-1.5\) mmHg, the cavity area reduces during ventricular inflation. For pressures smaller than \(-1.5\) mmHg, the cavity area increases during ventricular inflation. For cavity pressure equal to \(-1.5\) mmHg, there is a “crossover” region where the cavity area hardly varies during ventricular inflation.

In systole, ventricular inflation has a small effect on the pressure-area relationship of a subendocardial cavity (Fig. 6B) and a somewhat larger effect on the pressure-area relationship of a subepicardial cavity (Fig. 6D). In systole, the cavity area increases during ventricular inflation except for a subendocardial cavity (at a cavity pressure larger than \(-10\) mmHg) during an increase in ventricular pressure from 80 to 120 mmHg.

Cavity shape. Ventricular inflation not only affects cavity area but also cavity shape, both of which determine hydraulic resistance. Figure 7 shows the influence of ventricular inflation on the aspect ratio-area relationship of a subendocardial cavity in diastole and systole (cf. Fig. 6, A and B, for the area ranges in diastole and systole, respectively). It can be seen that for zero ventricular pressure in both diastole and systole, the cavity is circular for all areas (i.e., aspect ratio = 1.0). During ventricular inflation, the aspect ratio increases (i.e., the cavity becomes more elliptical). This deformation is larger in diastole than in systole at lower ventricular pressures. This is due to the fact that ventricular wall stretch is also larger in diastole when the wall material is more compliant. At a ventricular pressure of 120 mmHg, cavity aspect ratios are about the same in diastole and systole. It can also be seen that during an increase in cavity area (cavity inflation), the cavity becomes more circular (the aspect ratio decreases).

Local Rectangular Vessel Environment

Changes in arteriolar area and resistance. Figure 8 shows the relative contributions of the three components (E, P, and \(\lambda\)) to the decrease in area of a subendocardial and a subepicardial arteriole during an isovolumic contraction and during an isobaric contraction.
H2968

VENTRICULAR CONTRACTION AND CORONARY BLOOD VESSELS

Fig. 6. A: pressure-cross-sectional area relationships of a subendocardial coronary cavity in diastole (D) for different ventricular pressures \( P_{cv} \). (During calculations, muscle fibers were longitudinally directed and ring height was fixed.) B: as in A but for systole (S). C and D: as in A and B, respectively, but for a subepicardially situated cavity.

Fig. 7. Cavity area-aspect ratio relationships of a subendocardial coronary cavity in diastole (thin lines) or systole (thick lines) for different ventricular pressures (nos. on left, pressure in systole; nos. on right, pressure in diastole; in mmHg). Ranges in cavity area at each ventricular pressure correspond to those in Fig. 6, A and B. Note that most left and most right points of each line piece correspond to cavity pressures of 0 and 50 mmHg, respectively.

Arteriolar pressure was assumed to remain constant during contraction.

Because the contribution of \( \lambda \) is zero during isovolumic contraction, the contributions of \( E \) and \( P \) during isovolumic contraction can be seen to be complementary (Fig. 8, A and C). Analogously, the contributions of \( E \) and \( \lambda \) can be seen to be complementary during isobaric contraction (Fig. 8, B and D) because the contribution of \( P \) is negligible then. Comparison of Fig. 8, A and C, with Fig. 8, B and D, thus shows that \( P \) and \( \lambda \) “switch roles” during an isovolumic vs. an isobaric contraction. During both isovolumic and isobaric contractions, the contribution of \( E \) can be seen to increase with arteriolar pressure.

During isovolumic contraction, \( E \) and \( P \) contribute almost equally to the decrease in subendocardial arteriolar area at arteriolar pressures above \( \sim 25 \) mmHg (Fig. 8A). During isobaric contraction, the contribution of \( E \) to the decrease in area of a subendocardial arteriole (Fig. 8B) is somewhat smaller than during isovolumic contraction (Fig. 8A). For a subepicardial arteriole, it can be seen that at arteriolar pressures \( > 10 \) mmHg \( E \) is the major contributor to the area decrease during both isovolumic and isobaric contractions (Fig. 8, C and D). This is, however, most prominent during isovolumic contraction (Fig. 8C) when the contribution of \( E \) is \( > 90\% \).

Figure 9 is similar to Fig. 8, but here the individual contributions of \( E \), \( P \), and \( \lambda \) to the change in arteriolar resistance are shown, accounting for both area and shape (aspect ratio). The results are qualitatively similar to those in Fig. 8, although it can be seen that the contribution of \( E \) to the increase in arteriolar resistance is smaller than its contribution to arteriolar area reduction. In the subendocardium, \( E \) can be seen to contribute much less than \( P \) (during isovolumic contraction) or \( \lambda \) (during isobaric contraction). In the subepicardium, the contribution of \( E \) is still considerable at pres-
sures > 10 mmHg and most prominently so during isovolumic contraction when the contribution of E is >80%.

The results for an arteriole at its physiological working pressure. Figure 10A shows the area reduction during isovolumic and isobaric contractions of a subendocardial and a subepicardial arteriole at a constant physiological pressure of 45 mmHg. Figure 10 shows how E, P, and \( \lambda \) contribute to these arteriolar area reductions.

It can be seen that area reductions are somewhat smaller during isovolumic contraction (~45%) than during isobaric contraction (~57%). On the other hand, area reductions are similar in the subendocardium vs. the subepicardium during both isovolumic and isobaric contractions. In the subendocardium, E contributes by ~50% to the arteriolar area reduction during isovolumic and isobaric contractions. In the subepicardium, E is the major contributor to arteriolar area reduction, most prominently during isovolumic contraction (by 94%) but also during isobaric contraction (by 70%).

Figure 10B is similar to Fig. 10A, but now arteriolar resistance is presented. It can be seen that subendocardial increases in arteriolar resistance are similar during isovolumic and isobaric contractions (~340%). In the subepicardium, however, arteriolar resistance increases much less during isovolumic contraction (229%) than during isobaric contraction (460%). E is the major contributor to the increase in subepicardial arteriolar resistance during isovolumic contraction (88%).

Results for a venule at its physiological working pressure. Figure 10C is similar to Fig. 10A, but now a venule is considered, kept at a physiological pressure of 10 mmHg. It can be seen from a comparison of Fig. 10, A and C, that arteriolar area reductions are 16–25% larger than venular area reductions. Furthermore, area can be seen to be less reduced during isovolumic than during isobaric contraction, as was also the case for the arteriole. Subendocardial area reductions are found to be smaller than subepicardial area reductions during both isovolumic and isobaric contractions, which is different from what was found for the arteriole. The contributions of E, P, and \( \lambda \) are qualitatively similar to those found for the arteriole. In the subendocardium, however, the contribution of E to the area reduction is considerably less for the venule (~10%) than for the arteriole (~50%).

Figure 10D is similar to Fig. 10B, but here the venule is considered at its working pressure of 10 mmHg. It can be seen that the increase in venular resistance during contraction (~120%) is much less than the increase in arteriolar resistance (~340%). The contributions of E, P, and \( \lambda \) are qualitatively similar for the venule and the arteriole, although the contribution of E in the subendocardium is much less for the venule (12%) than for the arteriole (31%).

DISCUSSION

Discussion of Methods

Stability and convergence of the finite-element calculations. Element and node densities were chosen high
Fig. 9. Individual contributions of $E$, $P$, and $\lambda$ to increase in arteriolar resistance of a subendocardial (A and B) and subepicardial arteriole (C and D) during isovolumic (A and C) or isobaric contraction (B and D). During contraction, arteriolar pressure is assumed constant.

Fig. 10. Subendocardial and subepicardial arteriolar area reduction (A) and resistance increase (B) during isovolumic (iv) and isobaric (ib) cardiac contraction, assuming a constant (physiological) arteriolar pressure of 45 mmHg. Area and resistance changes are caused by changes in $E$ (open bars), $P$ (crosshatched bars), and $\lambda$ (hatched bars). C and D: as in A and B, respectively, but for a venule at a constant (physiological) pressure of 10 mmHg.
in regions of expected high gradients to ensure numerical stability and convergence during the calculations. Pressure-volume relationships of the ventricular lumens, calculated with model 1, were accurately described (with an error of < 1%) by the theory in Appendix B (see Fig. 4). The pressure-volume relationships of the (vascular) cavity in the wall of the ventricle, as calculated for zero ventricular pressure and for muscle fibers running in the longitudinal direction, were found to correspond with the analytic pressure-volume relationship of a thick-walled cylinder of myocardial tissue. (The ratio of outer to inner radius of the thick-walled cylinder was taken as 25, corresponding to the distance of the vascular cavity to the ventricular surface divided by the cavity radius.) That these relationships should indeed be expected to be similar was discussed in the previous study by Vis et al. (31). Moreover, the deformations and the value of the Lagrange multiplier were found to vary smoothly in the mesh during all calculations. These findings show that the present mesh was good enough to ensure stability and convergence during the finite-element calculations.

The order of applying changes in contractility, stress, and stretch. In the real ventricle, ventricular pressure development and deformation both result from the change in ventricular contractility. Therefore, the individual contributions of the three components during contraction were determined by applying the change in contractility first, followed by the change in local circumferential wall stretch and finally by the change in local radial stress. The order of application of the components is important because, even in the rectangular configuration, there is a complex interaction of muscle elastic properties, material stresses, and stretch. For example, the influence of local circumferential stretch on the cross-sectional area of the cavity depends on the contractile state of the myocardium. In Fig. 11A, the area of a cavity (at zero cavity pressure) in systolic myocardium increases more with circumferential stretch than does the area of a cavity in diastolic myocardium. This means that the contribution of wall stretch, as calculated from applying a change in wall stretch after applying a change in contractility, is different from that calculated from applying a change in wall stretch before applying a change in contractility. Similarly, the influence of local radial stress on the area and resistance of the cavity depends on the contractile state of the myocardium. Figure 11B shows the influence of compressive radial stress (radial stress \( X - 1 \)) on the area of a cavity (at zero cavity pressure) in a rectangular piece of diastolic or systolic myocardium. It can be seen that whereas radial stress hardly affects the cavity area in the stiff systolic myocardium, it strongly affects the area of the cavity in the compliant diastolic myocardium.

From our modeling results, it can thus be concluded that we need precise knowledge about the sequence of events in the wall of the contracting heart to predict the influence of the different mechanical components in that situation.

Sensitivity analysis. Because of the extremely long computation times, it was only possible to perform sensitivity analysis for the most important parameters: muscle material properties, cavity size, blood vessel direction, muscle fiber direction, and ring height fixation.

The elastic properties of the diastolic myocardium. Studies on the multiaxial elastic properties of the passive myocardium (cf. Refs. 12, 19) show that the properties in fiber direction are qualitatively similar to those in the cross-fiber direction. For an equibiaxial stretch (i.e., equal and simultaneous in the fiber and in one of the cross-fiber directions) of 1.1 and 1.3, passive stress ratios of 0.5 and 0.9, respectively, can be found from the data of Humphrey et al. (12) and ratios of 0.8 and 0.9, respectively, were found by Lin and Yin (19). Parameter \( \beta \) in Eq. 2 was set to 1.5, giving passive stress ratios in our model of 0.8 and 0.7, respectively, for these two stretches.

The elastic properties of the systolic myocardium. The presence of \( E_{11} \) and \( E_{22} \) in the second (developed) term of Eq. 2 implies active cross-fiber stress development. For the tetanized dog diaphragm, Strumpf et al. (27) found an average active stress ratio of \( \sim 1.0 \). Lin and Yin (19) found an active stress ratio of 0.5 for equibiaxial stretches of 1.1 and 1.3. For both these stretches, Eq. 2 gives an active stress ratio of 0.7, which is in between the values given in the literature.

To our knowledge, we are the first to use an active component in the cross-fiber direction in a model for

![Fig. 11. A: influence of circumferential stretch on area of a cavity at zero cavity pressure in a rectangular piece of diastolic (thin line) or systolic (thick line) myocardium. Radial stress is kept at zero. B: influence of compressive radial stress (radial stress times \( X - 1 \)) on area of a cavity at zero cavity pressure in a rectangular piece of diastolic (thin line) or systolic (thick line) myocardium. No circumferential stretch is applied.](image-url)
myocardial mechanics. In other modeling studies (1, 3, 13, 32), the myocardium was assumed to remain passive in the cross-fiber direction even during muscle activation. Nevertheless, recent studies on the multi-axial elastic properties of cardiac (11, 19) and skeletal muscles (4, 27) clearly show that there is considerable force development perpendicular to the fibers during muscle activation. The existence of an active cross-fiber component is of major importance for the modeling results, especially in the case where the muscle fibers run in the longitudinal (apex-to-base) direction with ring height fixed. In that case, all deformations result from cross-fiber stretch and stress only, so that omitting the active cross-fiber component would abolish the effect of cardiac contraction. When the fibers run in the circumferential direction, a reduction in vascular area will occur, even when the active cross-fiber component is omitted. The individual contributions of contractility, ventricular pressure, and wall stretch may, however, be different then.

Cavity size. Figure 3 shows that the influence of ventricular mechanics can be represented accurately by the effect of a local environment on the cavity. However, radial stress and wall stretch vary throughout the ventricular wall so that this approximation is only reasonable for small cavities in the wall. To determine the influence of cavity size on the modeling results, calculations were also performed with a cavity with a cross-sectional area that was five times larger. The approximation was found to be equally good. Therefore, because only local stress and stretch were used, the results as shown in Figs. 3, 6, and 7 can be scaled (with respect to cavity area) to apply to smaller and up to five times larger cavities and can thus be used for smaller and moderately large blood vessels as well.

The direction of blood vessels and muscle fibers. In reality, blood vessels run not only in the apex-to-base direction, such as studied here, but also circumferential, obliquely, and transmurally (from epicardium to endocardium and vice versa). The influence of cardiac contraction on the resistance of transmural vessels was not studied here but may play a role in the differences between subendocardial and subepicardial flows (5).

Because our model shows no significant qualitative or quantitative differences in the results for the two extreme fiber directions chosen (longitudinal and circumferential), it may be expected that incorporating a through-the-wall variation of fiber direction (26) would have no large effect on the results.

Ring height fixation. Allowing changes in ring height was found to have a small quantitative (but not qualitative) effect on cavity cross-sectional area (changes) and on cavity ellipticity. Cavity resistance was calculated to be smaller without fixation of ring height than with fixation by ~5 and 15% in diastole and systole, respectively. These changes are much less than the changes in resistance during contraction (Fig. 10). During calculations, ring height was therefore kept fixed for conceptual simplicity.

**Discussion of Results**

**Ventricular pressure-volume relationships.** The magnitude and shape of the calculated pressure-volume relationships (Fig. 4) were found to be similar to those found in the literature (2, 21). For comparison, if an end-diastolic pressure of 5 mmHg was assumed, the calculated end-systolic pressure for isovolumic ventricular contraction was 99 and 120 mmHg for the muscle fibers directed in the apex-to-base and circumferential directions, respectively. During isobaric contraction at a ventricular pressure of 5 mmHg, ventricular volume was reduced by 37 and 41%, respectively, for these two muscle fiber directions.

**The role of intramyocardial pressure.** Earlier models concerning the influence of cardiac contraction on coronary vascular mechanics and coronary flow assumed an essential role of intramyocardial pressure. Intramyocardial pressure, whether resulting from left ventricular pressure (1, 8, 25) or from local muscle mechanics (32), was supposed to act as the compressive pressure on the outside of the blood vessels ("extravascular pressure") independent of the pressure or volume loading of the vessels. We are the first to abandon this concept. In our model, extravascular pressure is not necessarily equal to the intramyocardial pressure in the surrounding myocardial tissue but opposes the normal component of the total stress at the inner surface of the (vascular) cavity (i.e., \( n \cdot \sigma \cdot n \)). Moreover, extravascular pressure itself depends on vascular pressure in a direct way: increasing vascular pressure is associated with increasing vascular luminal area, which implies an increase in extravascular (cavity) pressure (30).

Analogously, left ventricular pressure is not necessarily equal to the intramyocardial pressure at the endocardium but opposes the normal total stress component at the endocardium. This was also recently shown by Huyghe et al. (13). These researchers distinguish between solid (muscle fibers, collagen) and fluid and assume that the Lagrange multiplier (\( \mu \) in Eq. 1) represents intramyocardial pressure. When this is also done in our model, systolic intramyocardial pressures are predicted to be (much) higher than left ventricular pressure [in accordance with Mihalcescu and Abel (20)], and even negative intramyocardial pressures are predicted in diastole. Unfortunately, in practical stretch experiments, we know only \( \sigma \). We chose a constitutive law that describes the measured relationship between the total stress and the deformation. Then, it is not guaranteed that \( \mu \) is indeed the intramyocardial pressure.

**Systolic myocardium protects the vessels against the influence of ventricular pressure.** In accordance with the suggestion of Kouwenhoven et al. (15), our model predicts that the stiffened myocardium in systole protects the coronary blood vessels from the effects of left ventricular pressure. This can be seen in Fig. 11B: at positive compressive radial stresses, the cavity area is larger in systole than in diastole. To our knowledge, we are the first to show this phenomenon in a modeling study.

Changes in subendocardial and subepicardial vessel area during cardiac contraction: comparison with the
literature. There exist a number of studies on the influence of cardiac contraction on the cross-sectional area of coronary vessels. Most of them, however, cannot be used for comparison with the present results because they either report on hearts with intact vasomotor tone or on beating hearts. In the beating heart, the area and pressure of a vessel depend on capacitive effects, the (change in) resistance in other parts of the coronary vasculature, and the viscoelastic behavior of the vessel wall and the myocardium. The results of our model can be compared with the literature on the maximally diluted vasculature in hearts arrested in diastole and systole (9, 14). Judd and Levy (14) measured total coronary intravascular volume in different layers of the diastolically arrested and barium-contracted (“sustained systole”) rat heart. From their results, we estimated the total vascular area reduction in the subendocardium and subepicardium during the transition from diastole to systole, accounting for systolic fiber shortening in the ventricular wall. Assuming a fiber shortening of 16% in the subendocardium and 14% in the subepicardium (7), we estimated that the total vascular area is similarly reduced in the subendocardium and subepicardium by 23 and 21%, respectively. Because ~80% of the intramyocardial blood volume is found in the venous part of the vascular tree (14), these values can best be compared with the area reductions that we found for the venule (~28% in the subendocardium vs. ~35% in the subepicardium). The differences in subepicardial to subendocardial venular area reduction that we calculated were found to vanish when we accounted for the finding of Chilian (5) that venular pressures are ~10 mmHg larger in the subendocardium than in the subepicardium. The results for the venule are thus in good agreement with the findings of Judd and Levy (14).

Goto et al. (9) found that, in the rabbit heart, reductions in the area of terminal arterioles (inner diameter in diastole ~10 µm) and capillaries (inner diameter in diastole ~7 µm) during the transition from diastolic arrest (at zero ventricular pressure) to sustained systole (barium contracture; at a ventricular pressure of 55 mmHg) were considerably larger in the subendocardium than in the subepicardium. Area reductions in subendocardial terminal arterioles and capillaries were found to be 79 and 72%, respectively. In the subepicardium, terminal arteriolar area was reduced by 14%, whereas capillary area was increased by 12%. The large differences in the area reductions of subendocardial vs. subepicardial vessels are not corroborated by our study. Namely, considering a capillary as a vessel having a negligibly thin wall and assuming a constant, physiological capillary pressure of 27 mmHg (6), we calculated from our model that the capillary area reductions during isovolumic and isobaric contractions were similar in the subendocardium (34 and 39%, respectively) and subepicardium (34 and 43%, respectively). The findings of Goto et al. (9), however, are also not in agreement with the findings by Judd and Levy (14) that the total vascular volume decreases by ~35% in both the endocardium and the epicardium. These differences in experimental findings may be due to difficulties caused by the use of barium in simulating a normal contraction (14). Moreover, difficulties may arise from a possible constricting action of the barium on the blood vessels, overriding the dilation by adenosine (9). For future evaluation of our modeling results, it is therefore necessary to get more insight into the characteristics of barium contraction.

Changes in vessel shape during cardiac contraction: comparison with the literature. Goto et al. (9) also measured the capillary aspect ratio (longest diameter divided by shortest diameter) before and after contraction. Aspect ratios of subendocardial or subepicardial vessels were not significantly different and ranged from 1.0 to 2.3. Our model predicts the capillary aspect ratio to be somewhat larger in the subendocardium (between 1.0 and 2.2; cf. Fig. 5) than in the subepicardium (between 1.0 and 1.5). These values compare well with the values reported by Goto et al.

Comparison of calculated area reductions in the ventricular wall and the papillary muscle. Vis et al. (31) calculated the area reductions in an embedded arteriole, small vein, and capillary during isometric contraction of an (isolated) rat papillary to be ~50, 40, and 35%, respectively. Because the isolated papillary muscle is not subjected to an external pressure, myocardial contractility is then the only contributor to the area reductions. Calculations on these vessels in the ventricular wall, where contractility is not the only contributor, gave area reductions of ~50, 30, and 38%, respectively. It can thus be concluded that the reduction in vascular area during cardiac contraction is similar in the ventricular wall and the papillary muscle, although the causes for the area reductions are very different.

Comparison with earlier models. Earlier models, assuming intramyocardial pressure to work as an extravascular pressure independent of the vascular pressure or volume loading, would predict a larger area reduction for the compliant, low-pressure capillaries, venules, and veins than for the less compliant, higher pressure arterioles (1, 25, 32). Capillaries and veins would even be predicted to collapse during isovolumic contraction, predominantly in the subendocardium where high intramyocardial pressures are thought to exist. Our model, however, predicts that the compliant, low-pressure small veins, venules, and capillaries do not collapse, in accordance with the findings of Goto et al. (9) and Judd and Levy (14). Moreover, our model predicts that the area reduction during contraction is (much) larger for the arterioles than for the venules and capillaries. In a previous study, Vis et al. (31) showed that this is mainly the result of the larger relative wall thickness of the arterioles.

Cardiac contraction and coronary blood flow. Krams and colleagues showed that the reduction in coronary arterial inflow was similar during isovolumic and low afterloaded isobaric contractions in isolated cat (16) and rabbit hearts (17). We estimated overall coronary flow by considering a subendocardial vascular system (consisting of one arteriole in series with two parallel
venules) in parallel with a similar subepicardial system to decrease by 69% during isovolumic contraction and by 77% during isobaric contraction. Although these flow reductions are quite similar, the causes are different for the reasons mentioned above. Our model thus shows that although changes in coronary flow are very similar for isovolumic or isobaric contractions, it is not justified to conclude that contractility is the major determinant of coronary flow impediment.

In conclusion, a static model was described for the influence of ventricular contraction on the area and shape of subendocardial and subepicardial blood vessels. The model predicts that coronary blood vessels decrease in diameter but do not collapse during contraction and that isovolumic and isobaric contractions have similar overall effects. The model also predicts that ventricular contractility, pressure, and wall stretch all contribute to blood vessel deformation but that their individual contributions depend on the type of ventricular contraction, the type of vessel, and the location in the ventricular wall.

APPENDIX A

**Strain, Strain Energy, and Stress**

The deformation gradient tensor $\mathbf{F}$ describes the (local) deformation of a piece of material. The elements of the deformation gradient matrix $\mathbf{F}$ are defined by

$$ F_{ij} = \frac{\partial x_i}{\partial X_j} \quad (A1) $$

($i, j = 1, 2, 3$), where $x_i$ and $X_j$ are the corresponding material coordinates in the deformed and undeformed configuration, respectively.

The Green-Lagrange strain matrix $\mathbf{E}$ is defined as

$$ E_{ij} = \frac{1}{2}(F_{ik} F_{kj} - 1) \quad (A2) $$

($i, k, j = 1, 2, 3$), where Einstein’s summation convention is assumed (i.e., summation is performed over repeated subscripts).

The second Piola-Kirchhoff stress matrix $\mathbf{S}$ is calculated from the strain-energy density function $W(\mathbf{E})$ as follows

$$ S_{ij} = \frac{\partial W(\mathbf{E})}{\partial H_{ij}} \quad (A3) $$

The second Piola-Kirchhoff stress matrix $\mathbf{S}$ is related to $\sigma^e$, the (“extra”) Cauchy stress related to the deformation of the tissue per se according to

$$ \sigma^e = \frac{1}{\det(\mathbf{F})} \mathbf{F} \cdot \mathbf{S} \cdot \mathbf{F}^T \quad (A4) $$

where $T$ denotes matrix transposition.

APPENDIX B

**Inflation and Stretch of a Thick-Walled Myocardial Cylinder: Analytic Approach**

Assume a cylinder of incompressible myocardium with an initial inner radius $R_{i0}$, outer radius $R_{o0}$, and height $L_0$ when undeformed. When the fibers are directed in a longitudinal, circumferential, or radial direction, deformation due to an increase in cavity volume is axisymmetric without torsion. Deformation to a height $L$ and inner radius $R$, leads to the following local deformation gradient tensor at radius $r$

$$ F(r) = \begin{pmatrix} \rho & 0 & 0 \\ \frac{\lambda r}{2} & 0 & 0 \\ 0 & \frac{r}{\rho} & 0 \end{pmatrix} \quad (B1) $$

where $\lambda = L/L_0$, $\rho = \sqrt{L_0^2 - R^2}$, and new inner radius $< r <$ new outer radius. The second Piola-Kirchhoff stress matrix $\mathbf{S}(r)$ will also be diagonal and the extra stress $\sigma^e$ can be written as $Eq. A4$

$$ \sigma^e(r) = \begin{pmatrix} \Sigma_{rr} & 0 & 0 \\ 0 & S_{\phi\phi} & 0 \\ 0 & 0 & S_{zz} \end{pmatrix} \quad (B2) $$

where $rr$, $\phi\phi$, and $zz$ denote radial, circumferential, and longitudinal direction, respectively. Local radial Cauchy stress $[\sigma_{rr}]$ follows from the local force equilibrium (Eq. 3) in the radial direction

$$ \sigma_{rr}(r) = -\int_{R_{i0}}^{r} \frac{\sigma^e_{rr} - \sigma^e_{\phi\phi}}{r} \, dr \quad (B3) $$

and the local value for the Lagrange multiplier $[\mu(r)]$ then follows from Eq. 1

$$ \mu = \sigma_{rr} - \sigma_{\phi\phi} \quad (B4) $$

Left ventricular pressure ($P_{lv}$) is found from the force equilibrium in the radial direction

$$ P_{lv} = \int_{R_{i0}}^{R_{i0}} \frac{\sigma^e_{rr}}{r} \, dr \quad (B5) $$

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