Assessment and consequences of the constant-volume attribute of the four-chambered heart

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Bowman, Andrew W., and Sándor J. Kovács. Assessment and consequences of the constant-volume attribute of the four-chambered heart. Am J Physiol Heart Circ Physiol 285: H2027–H2033, 2003. First published July 17, 2003; 10.1152/ajpheart.00249.2003.—The constant-volume hypothesis regarding the four-chambered heart states that total pericardial volume remains invariant throughout the cardiac cycle. Previous canine studies have indicated that the pericardial volume remains constant within 5%; however, this hypothesis has not been validated in humans using state-of-the-art technology. The constant-volume hypothesis has several predictable functional consequences, including a relationship between atrial ejection fraction and chamber equilibrium volumes. Using cardiac magnetic resonance imaging (MRI), we measured the extent to which the constant-volume attribute of the heart is valid, and we tested the accuracy of the predicted relationship between atrial ejection fraction and chamber equilibrium volumes. Eleven normal volunteers and one volunteer with congenital absence of the pericardium were imaged using a 1.5-T MR scanner. A short-axis cine-loop stack covering the entire heart was acquired. The cardiac cycle was divided into 20 intervals. For each slice and interval, pericardial volumes were measured. The slices were stacked and summed, and total pericardial volume as a function of time was determined for each subject. In the normal subjects, chamber volumes at ventricular end diastole, end systole, and diastasis were measured. Pericardial volume remained invariant within 5 ± 1% in normal subjects; maximum variation occurred near end systole. In the subject with congenital absence of the pericardium, total heart volume, defined by the epicardial surface, varied by 12%. The predictions of the relationship between atrial ejection fraction and chamber equilibrium volumes were well fit by MRI data. In normal subjects, the four-chambered heart is a constant-volume pump within 5 ± 1%, and constant-volume-based modeling accurately predicts previously unreported physiological relationships.

cardiac magnetic resonance imaging; mathematical modeling; diastasis; pericardial motion

FULL UNDERSTANDING of the cardiovascular system at the organ, tissue, and cellular levels represents a continued challenge (27). To facilitate analysis of physiological data in the context of broad, conceptual ideas, both computational and theoretical models have been developed (18, 19). We (19) have previously defined and validated a conceptual and mathematical model that all ventricles obey when they fill. One beneficial consequence is that if a model is formulated appropriately, new physiological relationships can be predicted and validated, and seemingly unrelated physiological or clinical observations can be related and causally explained (21, 23, 25).

Although physiologically profound, the constant-volume pump attribute of the four-chambered heart is both conceptually and mathematically simple, yet it has received insufficient attention. It states that the total volume of the pericardial sack, containing the atria, ventricles, myocardium, coronary arteries, and roots of the aorta and pulmonary artery, remains constant throughout the cardiac cycle.

The constant-volume heart concept was first proposed in 1932 by Hamilton and Rompf (8), who invoked teleological arguments. In the 1980s, Hoffman and Ritman (12, 13) performed a series of pioneering experiments using the dynamic spatial reconstructor (DSR). They found that in dogs, pericardial sack volume varied by ~5% between end systole and end diastole. They also concluded that, independently, the left and right sides of the heart were relatively constant two-chamber pumps. However, the DSR was unable to validate the constant-volume attribute in humans due to technological limitations of X-ray imaging in conjunction with anatomic differences between dogs and humans (11). Later studies used magnetic resonance (MR) imaging (MRI) to evaluate pericardial volume in humans at several discrete timepoints (9–11) and in Fontan procedure candidates (4), but lacked sufficient resolution to measure chamber size accurately and required long scan times. A detailed human study, using the most recent MRI technology to determine pericardial volumes and cardiac chamber volumes simultaneously, has not been performed.

Mathematical modeling of the constant-volume pump attribute of the four-chambered heart predicts specific and testable physiological consequences. Selected examples include 1) a model of left ventricular (LV) filling that accurately predicts transmural flow patterns in normal and pathological states (19, 20); 2) the reciprocity of atrial and ventricular volumes and...
redirection of blood momentum and flow during the cardiac cycle (16); 3) the relation between the Doppler E-to-E’ ratio and LV end-diastolic pressure (21); 4) maximal LV wall thinning-to-Doppler E-wave relation (3); and 5) the compensatory changes of right ventricular (RV) and LV stroke volumes caused by acute perturbations in left (LA) or right atrial (RA) volumes (7). Additionally, the constant-volume attribute model predicts a specific, MRI-testable relationship between diastatic chamber volumes (17) and the atrial ejection fraction (EF\textsubscript{A}).

Because of its high spatial (<1 mm) and temporal (<30 ms) resolution, cardiac MRI has become the gold standard for LV mass and chamber size (volume) determination (33). The availability of a true steady-state gradient echo technique [balanced fast-field echo (bFFE)] (2, 29) makes MRI ideally suited for quantifying cardiac anatomy, function, and flow (1, 6, 33). Cardiac MRI can image the heart in any plane at any instant of the cardiac cycle. We are not aware of any prior MRI study that investigated the functional (dynamic) interrelationships of all cardiac chambers throughout the cardiac cycle and sought to validate model-predicted relationships between chamber volumes and function.

**METHODS**

**Imaging.** After appropriate informed consent was obtained (consistent with the Washington University Medical Center Human Studies Committee guidelines), 11 normal subjects (6 men and 5 women) and 1 (male) subject with congenital absence of the pericardium were scanned with a 1.5-T Philips Gyroscan MRI system (Release 9.0, Philips Medical Systems; Best, The Netherlands). Survey images and standard planes for ventricular four-chamber, short-axis, and LV outflow tract (LVOT) views were obtained. Once determined, high-resolution cine loops of the four-chamber and LVOT views were obtained during subject breathholds (duration of ~10 s each). These cine loops were divided into 20–27 cardiac phases triggered from the ECG R wave covering the entire cardiac cycle.

The initial four-chamber view was used to plan a short-axis cine-stack protocol of between 18 and 20 slices, 9 mm thick with zero gap, spanning the apex of the ventricles through the superior-posterior wall of the LA. Image slices were obtained during 10-s breathholds per slice, and each cine loop was divided into 20 cardiac phases triggered from the ECG R wave covering the entire cardiac cycle. For the short-axis stack image acquisition, the repetition time, echo time, and flip angles were 4.0 ms, 1.47 ms, and 50°, respectively. In-plane resolution of 1.41 mm was obtained with a field of view of 36 cm and a matrix size of 192 × 256 interpolated to 256 × 256.

Upon completion of the exam, the data was archived to 4.1-GB magneto-optical disks and transferred to a remote Sun Microsystems workstation running EasyVision analysis software (Philips Release 5.1). All image analysis was performed off-line using EasyVision or on a remote personal computer using fFilm 1.5.3 (eFilm Medical; Toronto, Ontario, Canada), Paint Shop Pro 7 (Jasc Software; Minnetonka, MN), and Scion Image (Scion; Frederick, MD).

In all subjects, the pericardial contour was manually traced in each slice at each phase of the three-dimensional (3-D) dataset (Fig. LA), and the corresponding segmental volume was determined. For each phase, the segmental volumes of the pericardial traces were summed and compared over the cardiac cycle. To compare hearts of different sizes, the pericardial volumes were normalized to the volume measured at ventricular end diastole (phase 1) in all subjects. Volumes of the individual cardiac chambers were measured in a similar manner (Fig. 1, B and C).

**Modeling.** In the context of the constant-volume hypothesis, we assume steady state; hence, cardiac output, ejection fraction, and stroke volume remain constant on a beat-to-beat basis. In analogy to the LV ejection fraction (EF\textsubscript{LV}), defined as (stroke volume)/LV end-diastolic volume, the atrial ejection fraction EF\textsubscript{A} is defined by

\[
EF\textsubscript{A} = \frac{A_D - A_m}{A_D} \quad (1)
\]

where \(A_D\) is the (left + right) atrial volume at diastasis (immediately before atrial contraction) and \(A_m\) is the (constant) minimal (left + right) atrial volume (after atrial contraction). According to the constant-volume attribute of the heart (ignoring the roots of the aorta and pulmonary artery for simplicity)

\[
V_D + A_D = C \quad (2)
\]

where \(V_D\) is the (left + right) ventricular volume at diastasis and \(C\) is the (constant) total volume of the LV and RV plus the LA and RA. Rearranging Eq. 2 and dividing both sides by \(A_D\) yields

**Fig. 1.** Typical balanced fast-field echo magnetic resonance imaging (MRI) images (short-axis view). A: pericardial trace at midventricular level. B: endocardial traces of the left ventricle (LV) and right ventricle (RV). C: endocardial traces of the left atrium (LA), right atrium (RA), aorta (Ao), and pulmonary artery (PA). S, superior; I, inferior; A, anterior, P: posterior; R, right; L, left.
and solving Eq. 3 for $A_D$ in terms of $V_D/A_D$ gives

$$A_D = \frac{C}{1 + \frac{V_D}{A_D}}$$  \hspace{1cm} (4)

Substituting Eq. 4 into Eq. 1 yields

$$\frac{V_D}{A_D} = \frac{C}{1 + \frac{V_D}{A_D}} - A_m$$

$$EF_A = \frac{\frac{V_D}{A_D} - A_m}{1 + \frac{V_D}{A_D}}$$  \hspace{1cm} (5)

which, when rearranged in the $y = mx + b$ form, generates

$$EF_A = -\left(\frac{A_m}{C}\right)\left(\frac{V_D}{A_D}\right) + \left(1 - \frac{A_m}{C}\right)$$  \hspace{1cm} (6)

Therefore, Eq. 6 predicts that as $EF_A$ increases, $V_D/A_D$ decreases linearly. This prediction can be tested by measuring the volumes of the atra and ventricles at ventricular end diastole and diastasis. Chamber volumes were also measured at ventricular end systole, and 3-D determined LV ejection fractions were compared with those obtained using the areal-length method from the LVOT view to corroborate the 3-D measurement. Intra- and interobserver variability for measurements were determined using 10 randomly selected images.

RESULTS

Demographics for all subjects are listed in Table 1. The normalized total pericardial volume measurements as a function of time for all subjects are displayed in Fig. 2. Data from the subject with congenital absence of the pericardium are shown separately (Fig. 2, open circles). In normal subjects, the maximum change in total pericardial volume over the cardiac cycle is $\approx 45$ ml, or $5 \pm 1$% (mean $\pm$ SD), relative to a total end-diastolic pericardial volume of $\approx 800$ ml and $\approx 25$% compared with a combined (right + left) ventricular stroke volume of $\approx 180$ ml. In eight subjects, the maximum pericardial volume change occurred at ventricular end systole. In the three other normal subjects, the maximal pericardial change occurred within 75 ms of end systole. In these subjects, however, the total pericardial volume change during the 75-ms interval from end systole was $< 1$% of the end-diastolic pericardial volume and essentially negligible (data not shown). During ventricular systole, the combined (left + right) atria filled by $\approx 105$ ml, and the combined (aortic and pulmonary artery) roots filled by $\approx 25$ ml. In the subject with congenital absence of the pericardium, the maximum change in total epicardial surface heart volume was 12% of the end-diastolic heart volume and also occurred at end systole.

For the $V_D/A_D$ and $EF_A$ measurements, the values obtained for each parameter are listed in Table 2. The plot of $EF_A$ versus $V_D/A_D$ is shown in Fig. 3A. Linear regression analysis yielded $EF_A = -0.23(V_D/A_D) + 0.79$ ($r = -0.84$). Similar analysis of the left and right sides of the heart individually yielded the plots shown in Fig. 3, B and C, respectively. For the left side of the heart, $EF_LA = -0.11(LV_D/LA_D) + 0.64$ ($r = -0.48$); for the right side of the heart, $EF_RA = -0.23(RV_D/RA_D) + 0.67$ ($r = -0.79$).

Table 2. Calculated MRI parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_D/A_D$</td>
<td>2.13 ± 0.37</td>
</tr>
<tr>
<td>$EF_A$, %</td>
<td>30 ± 10</td>
</tr>
<tr>
<td>$C$, ml</td>
<td>353 ± 85</td>
</tr>
<tr>
<td>$A_m$, ml</td>
<td>81 ± 24</td>
</tr>
<tr>
<td>$A_m/C$</td>
<td>0.23 ± 0.02</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SD; $n = 11$ subjects. $V_D$, (left + right ventricular volume at diastasis); $A_D$, (left + right) atrial volume at diastasis; $EF_A$, atrial ejection fraction; $C$, (constant) total volume of the left and right ventricles plus the left and right atrial; $A_m$, (constant) minimal (left + right) atrial volume. Chamber volumes at ventricular end diastole were used to calculate $C$. 

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Intra- and interobserver variability for tracings were 1.3% and 8.7%, respectively.

**DISCUSSION**

The findings of this study are significant because they demonstrate in humans that the volume of the normal four-chambered heart is rather constant (within 5%) throughout the cardiac cycle. As the ventricles contract, the epicardial surface slides within the pericardial sack and follows its contour (see animations 1 and 2; http://ajpheart.physiology.org/cgi/content/full/00249.2003/DC1). The individual volumes composed of the blood-filled cavities (ventricles \(V_{\text{ventr}}\), atria \(V_{\text{atria}}\), roots of the outflow tracts \(V_{\text{roots}}\)), muscle, and connective tissue \(V_{\text{tissue}}\) must add up to the total volume of the pericardial sack \(V_{\text{pericard}}\) and hence must obey the following summation rule

\[
V_{\text{pericard}} = V_{\text{ventr}} + V_{\text{atria}} + V_{\text{roots}} + V_{\text{tissue}} \tag{7}
\]

This rule has predictable consequences concerning normal heart function. Most importantly, when differentiated, it implies conservation of flow over the pericardial boundaries and requires that as the ventricles empty during systole, the atria and the roots of the great vessels within the pericardial sack must simultaneously fill (8). Specifically, when differentiated with respect to time \([\text{change in volume over time} (dV/dt)]\), we obtain

\[
dV/dt_{\text{pericard}} = dV/dt_{\text{ventr}} + dV/dt_{\text{atria}} + dV/dt_{\text{roots}} + dV/dt_{\text{tissue}} \tag{8}
\]

This expression defines the required reciprocation of volumes of structures below the atrioventricular plane (ventricles) to those above the plane (atria and great vessel roots), a feature consistent with the findings of other recent MRI studies (16, 32).

In the subject with congenital absence of the pericardium, the total heart volume change throughout the cardiac cycle was 12%, or 7SD above the normal mean. This suggests that the presence of the normal pericardium itself is required for the heart to maintain its constant-volume feature within normal limits (see animations 3 and 4; http://ajpheart.physiology.org/cgi/content/full/00249.2003/DC1). Previous findings have demonstrated that the intact pericardium directly affects chamber pressures (24) and volumes (7), consistent with the notion that the normal pericardium has a functional effect on cardiac physiology.

Contrasting the constant (four-chamber heart)-volume concept in the setting of simultaneous ejection and filling using a quantitative example helps to elucidate the dynamic nature of the physiology, as illustrated in animation 1. The combined (left + right) ventricular stroke volumes in the normal subjects sum to \(\sim 180\) ml. This is the total blood pumped out of the four-chambered heart during systole, lasting 0.33 s. This yields an average ventricular ejection rate of \(180/0.33 = 545\) ml/s. The total pericardial volume change during this time interval is \(\sim 45\) ml, and this 45-ml change is attained (effectively) by the time ventricular end sys-
tore is reached. Accordingly, the average rate of change for the entire pericardial volume is \(-45/0.33 = 136\) ml/s, or one-quarter the rate of change of the (left + right) ventricular volumes during ejection. The difference between the ventricular ejection rate and total pericardial volume decrease rate is accounted for by simultaneous filling of the atria and great vessel roots by 130 ml, yielding an inflow rate of \((105+25)/0.33 = 394\) ml/s. In the context of Eq. 8, using the sign convention that volume decrease is negative and volume increase is positive, these rates yield

\[
\frac{-45/0.33}{\text{pericard}} = \left(\frac{-180/0.33}{\text{ventr}} + \left(\frac{105/0.33}{\text{atria}} + \frac{25/0.33}{\text{roots}} + \frac{dV}{dt_{\text{tissue}}}\right)\right)
\]

or

\[
-136 \text{ ml/s} = -545 \text{ ml/s} + 318 \text{ ml/s} + 78 \text{ ml/s} + \frac{dV}{dt_{\text{tissue}}}
\]

and assuming the tissue to be incompressible \((dV/dt_{\text{tissue}} = 0)\) or, at the least, negligible \((dV/dt_{\text{tissue}} < 100 \text{ ml/s})\), we get

\[
-136 \text{ ml/s} \approx -149 \text{ ml/s}
\]

When expressed in words, Eq. 11 means

Average rate of pericardial

(four-chamber heart) volume decrease

\(\approx\) Difference between ventricular emptying

and simultaneous atrial + great vessel root filling

Combining the ventricular outflow volume and (atrial + root) inflow volume yields a net four-chamber heart volume decrease of 50 ml (from 800 to 750 ml), which closely approximates the 45-ml change observed when measuring total pericardial volume rather than integrating over individual chamber volume changes. Therefore, as the above numerical example illustrates, whether measuring the total pericardial volume or integrating over the rate of change of volume throughout the cardiac cycle, one concludes that the four-chambered heart is (within \(\approx 5\%\)) a constant-volume pump. The meaning of Eqs. 7–11 underscores this feature and highlights that the ventricles empty slightly faster than the atria and roots are able to fill. This results in a small (\(\approx 5\%\)) end-systolic overall decrease in four-chamber volume that keeps the four-chambered heart at (essentially) constant volume. Stated another way, in normal subjects, due to motion and shape changes as a result of ventricular systole, the inanimate pericardial sack develops a remarkably low 5% “ejection fraction,” underscoring the nearly constant-volume pump attribute of the four-chambered heart! As shown in Fig. 2, the small four-chamber volume decrease is made up during the next diastolic interval.

Using the constant-volume attribute of the four-chambered heart, we derived a mathematical relation predicting that the ratio of ventricular volume to atrial volume at diastasis decreases as atrial ejection fraction increases. In vivo measurements using cardiac MRI validated this prediction. Note the close agreement between the value of \(A_{\text{V}}/C\) in Table 2 and the magnitude of the slope of the linear regression equation.

A benefit of this approach is that it may be applied to hearts that vary substantially in size: even though the values for \(A_{\text{V}}\) and \(C\) vary widely among the population studied, the ratio of \(A_{\text{V}}/C\) is remarkably fixed, again as predicted by the constant-volume relationship. This ratio may have physiological significance in describing the proper anatomic relationship between atria and four-chamber heart volume. It is also of interest to note that the four-chambered heart as a whole obeys the constant-volume prediction more closely than does either the left or right side of the heart individually. This underscores the importance of evaluating global four-chamber heart function instead of restricting study to just the left- or right-sided chambers.

Additionally, the lower correlation coefficient between \(E_{\text{FA}}\) and \(V_{\text{P/A}}\) for the left heart \((-0.48)\) compared with the right heart \((-0.79)\) and the knowledge that the maximum deviation from the ideal constant-volume condition occurs at ventricular end systole is of physiological interest. We note that there appears to be little change in the longitudinal (apex to base) dimension of the heart throughout the cardiac cycle compared with the change in the radial (short axis) dimension (compare Animations 1 and 2), a distinction that is particularly striking in the subject with congenital absence of the pericardium (compare Animations 3 and 4). This observation combined with the substantially different correlation coefficients of the data presented in Fig. 3, B and C, implies that the normal small \((-45\) ml) change in total pericardial volume may be due primarily to systolic contraction and subsequent radial displacement of the LV epicardial surface directed toward the centroid of the chamber rather than radial displacement of the RV epicardial surface. Further studies to address this kinematic issue are in progress.

Limitations. The cine loops obtained in the present study were obtained during 10-s breathholds, so the resulting “cardiac cycle” loop represents data obtained over multiple heartbeats. However, during the exam, subjects remain in a physiological steady state at rest, so the resulting cine loop reflects this physiology. Indeed, the fact that identical (breathhold) cine loops comprise the standard used in cardiac MRI imaging (28) underscores that beat-to-beat variability is insignificant.

During breathhold scans prospectively gated by the QRS, it is impossible for the scanner to continuously scan from R wave to R wave; therefore, the scanner often does not obtain data during all of the atrial contraction phase of late diastole. This effect is exacerbated when the actual heart rate and the heart rate that the scanner “expects” do not match well. Other scanning techniques were available, such as retrospective gating, where the scanner acquires images continuously throughout the cardiac cycle and reconstructs them in order after the scan is completed. However, this technique may substantially increase scan time,
rendering breathholds less feasible. Free-breathing scans typically exhibit increased motion artifacts, making tracing of the pericardial and endocardial contours more challenging. Because breathhold images are substantially less noisy, the breathhold method was chosen for this study, even if parts of the atrial contraction phase were omitted. To minimize this atrial contraction loss, particular care was taken to input the correct heart rate into the triggering algorithm. Future studies using other imaging techniques may overcome the current limitations of prospectively gated cardiac MRI. Specifically, multidetector spiral computed tomography scanning (5, 26) may not only cover a larger percentage of the cardiac cycle but also provide higher resolution of cardiac chamber volumes. It suffers from its own limitations, however, including increased radiation exposure to the subject as well as an intravenous contrast administration, both of which were avoided by the use of MRI in this study.

Because the volumetric data were acquired using 9-mm-thick slices, there is the possibility of systematic error in the volumes reported in the present study. This error is most likely the largest when the chamber to be measured is the smallest and has the thinnest walls (i.e., the atria and outflow tract roots). However, previous MRI studies evaluating atrial size have used a similar if not larger slice thickness (14, 15, 30, 32). Manual tracings of the chambers may also raise concerns, but it has been the standard approach for chamber volume determination, and a recently developed automated edge detection method for volume measurement showed high agreement to segmental volumes traced manually (32).

It should be noted that the contents of the pericardial sack includes both the blood (including lymph) and tissue of the heart. Despite evidence for changes in bulk myocardial tissue volume over the cardiac cycle (12, 31), in the absence of changes in cellular volume, it is most likely that the majority of the volume change in pericardial sack content is accounted for by the change in total blood (fluid) volume rather than cellular (tissue) volume. This implies that because of shifts in coronary arterial, capillary, and venous volumes, the total chamber volumes in the pericardium may be less constant throughout the cardiac cycle than the blood pool content of the entire pericardial sack. This may explain why the correlation coefficient in Fig. 3A is −0.84 rather than a value closer to unity. Further MRI studies investigating the accuracy of the constant-volume attribute applied to the blood volumes of individual chambers are currently in progress.

We presume in the subject with congenital absence of the pericardium that the absence of the pericardium is the only cardiac anomaly. Frequently, patients with congenital absence of the pericardium have other genetic defects (22); however, nothing in the clinical history of the patient or MRI dataset indicated that there were any other cardiac malformations or dysfunction.

In conclusion, this study evaluated the constant-volume attribute of the four-chambered heart throughout the cardiac cycle in a sample of normal human subjects using state-of-the-art cardiac MRI. We conclude that in normal subjects, the four-chambered heart defined by the contents of the pericardial sack (of ~800 ml) behaves as a constant-volume pump within 5 ± 1% and that an intact pericardium is required for this degree of constancy to be maintained. We also showed that mathematical modeling of the constant-volume attribute accurately predicts a novel relationship that simultaneously demonstrates coupling between chamber diastasis volumes and atrial function. New insight was provided regarding how global four-chamber heart function differs from constant-volume left or right heart function and the importance of longitudinal ( apex to base) versus radial (short-axis) degrees of freedom. Application of this approach to intrapericardial dynamics and selected pathological states is in progress.

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DISCLOSURES
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