Pericardial Modulation of Right and Left Ventricular Diastolic Interaction

JOEL SPADARO, OSCAR H.L. BING, WILLIAM H. GAASCH, AND RONALD M. WEINTRAUB

SUMMARY We studied the effects of the right ventricle (RV) and pericardium on left ventricular (LV) diastolic pressure-volume (P-V) relations in the normothermic isolated blood-perfused dog heart. Studies were performed at a constant heart rate (atrial pacing at 120 beats/min) with a coronary perfusion pressure of 100 mm Hg. LV volume was directly controlled by an intraventricular balloon, whereas RV filling pressure was increased stepwise from zero to 20 mm Hg. During progressive increases in RV filling pressure, with the pericardium intact, the LV diastolic P-V relations were shifted up and to the left; this leftward shift of the LV diastolic P-V relation was associated with an increase in the modulus of LV chamber stiffness. Closing the small pericardial incisions with sutures significantly increased this effect. In the absence of the pericardium, progressive filling of the RV resulted in minor changes in LV diastolic P-V relations. Only when the RV filling pressure was markedly elevated (20 mm Hg) was there a significant effect on LV diastolic pressure. The pericardium has a small but significant effect on LV diastolic P-V relations at physiological RV filling pressures, and this effect becomes considerable at high RV filling pressures. The RV influence on LV diastolic P-V relations is significantly modulated by the presence of tightness of the pericardium. Circe Res 48: 233-238, 1981

IN MANY STUDIES of left ventricular (LV) compliance, the pericardium is considered to be a flaccid sac which exerts important effects only at large diastolic volumes (Mirsksy, 1976; Grossman and McLaurine, 1976; Gaasch et al., 1976). On the other hand, numerous studies have been performed which demonstrate a direct mechanical coupling between the two ventricles through the intraventricular septum. Some investigators indicate that this coupling does not depend on the pericardium (Bemis et al., 1974; Elzinga et al., 1974; Santamor et al., 1976; Laks et al., 1967; Taylor et al., 1967; Ludbrook et al., 1979), and others note that an intact pericardium tightens the coupling (Berglund et al., 1955; Spotnitz and Kaiser, 1971; Hefner et al., 1961; Holt et al., 1970; Glantz et al., 1978).

In a recent publication, Glantz et al. (1978), used an in vivo dog heart preparation and studied the effects of infused volume on right ventricular (RV) and LV pressures and dimensions with and without the pericardium. They found that when RV pressure or volume was increased with the pericardium intact, the LV was smaller than without the pericardium. Furthermore, the RV and LV pressures appeared to be tightly coupled when the pericardium was closed. With the pericardium opened, the myocardial wall properties were found to be the major determinant of diastolic pressure-volume (P-V) relationships. In these studies, the pericardium was opened for placement of recording devices, and the borders were then reapproroximated with sutures. Although the authors indicate that the suturing process did not tighten the pericardial sac and impose an additional restriction on the ventricles, there is no experimental evidence to indicate that this is in fact the case. Minor degrees of artifactual pericardial restriction due to the sutures could be of considerable importance. Effects due to sutures have been suggested previously by Hefner et al. (1961) and more recently by Mirsky (1979). In this study, we evaluated the role of the RV and the pericardium on LV P-V relations using a preparation in which LV volume is directly controlled; this permitted an accurate determination of the LV diastolic P-V relationships. In addition, the effects of suturing the pericardium were studied.

Methods

Studies were performed in hearts from 12 mongrel dogs weighing 25-30 kg, using our modification (Gaasch et al., 1978) of a preparation described by Brown et al (1972). In each experiment, a support and donor dog were anesthetized with chloralose and urethane, given 500 U heparin per kilogram, iv, and ventilated mechanically. After a median sternotomy to expose the heart and vessels, small incisions (1.0-1.5 cm) were made in the pericardium of the donor dog to insert RV and LV drains. With the drains in place, the pericardium was not closed in six dogs, and several additional small holes (1-2
LV. The donor animal was exsanguinated by ligating the descending aorta and bleeding via the subclavian artery. When pressure had fallen to less than 100 mm Hg, the heart was perfused with blood (37°C) from the femoral artery of the support dog and removed without cessation of perfusion. A perfusion pump and Starling resistor were used to maintain a pressure of 100 mm Hg in the proximal aorta of the perfused heart. Coronary venous blood was drained from the RV and returned to the femoral vein of the support dog. After ventricular fibrillation had been induced, the pericardium and left atrium were opened widely, the chordae tendo- 
dae were cut, the papillary muscles were removed, and a balloon on a Silastic mount was placed in the LV through the mitral annulus and connected to a Statham P23Db pressure transducer via a 10- to 20-cm section of 1.5-mm (i.d.) polyethylene tubing. The Silastic mount was held in place by a purse-string suture sewn to the mitral annulus. The Silastic mount consisted of a 3-mm thick Silastic disc of varying diameter (15–30 mm varying in 3-mm increments to accommodate mitral valve orifices of differing sizes) connected to a Luer lock syringe barrel. During the performance of ventricular function curves, saline was injected through the syringe barrel and disc into the attached condom balloon. Vaseline was placed in the recessed rim of the Silastic disc to afford a leak-proof seal when the balloon was mounted on the Silastic disc with a rubber O-ring. The Silastic mount prevented prolapse of the highly compliant condom balloon into the left atrium while the perfusion pressure of 100 mm Hg prevented ejection of the balloon into the aorta. When the balloon subsequently was filled to perform ventricular function curves, balloon volume was limited so that total intraventricular pressure did not exceed 100 mm Hg (perfusion pressure). The condom balloon size was carefully selected; it was large enough so as not to contribute to filling pressure but so large that redundancy was a problem during the removal of the saline filling it. A drain placed in the apex of the ventricle prevented blood accumulation. The heart then was submerged in a blood bath maintained at a constant temperature of 37°C. After defibrillation, the atrial rate was maintained at 120 beats/min by atrial pacing, and the preparation was allowed to equilibrate for 30 minutes.

After the equilibration period, the right ventricular end-diastolic pressure was raised stepwise by changing the level of a reservoir to achieve RV end-diastolic pressures of 0, 5, 10, and 20 mm Hg. RV filling pressures were recorded from a no. 24 Urological catheter draining the RV. This catheter was connected to a P23Db Statham pressure transducer via a 10- to 20-cm length of polyethylene tubing with an internal diameter of 1.5 mm. After a 5-minute stabilization period at a given RV filling pressure, the left ventricular balloon was filled in increments and LV pressures were recorded. The zero reference level for both RV and LV was placed at the midpoint of the heart in each study. Baseline determinations were carried out with the RV diastolic pressure as zero. The volume of the left ventricle was increased stepwise so that a peak systolic pressure of 100 mm Hg was achieved. In each dog, this volume was assigned a value of 100%, and all other volumes related to it. Volume (expressed as percent) is the method for normalizing data from hearts of animals of differing size (Gaasch et al., 1978). Left ventricular P-V measurements were recorded at increments of 20% in the volume of the LV balloon. Thus, if the 100% volume for a given ventricle was 25 ml, volumes of 5, 10, 15, 20, and 25 ml were added stepwise to the balloon. Both systolic and diastolic pressures were quite stable after each change in left ventricular volume; 6–10 contractions were recorded 1 minute after a LV volume change and measurements were averaged. Pressures during the 6–10 contractions were extremely stable. Subsequent stepwise balloon inflations to this volume were carried out at the different RV end-diastolic pressures: 5, 10, 20 mm Hg. After the data had been collected with the pericardium closed, the pericardium was excised, and the protocol was repeated after a new equilibration period. In each heart, the LV volume used was the same with and without the pericardium so that comparisons could be made in the same heart at equal ventricular volumes. To test the effect of suturing the pericardium, the same protocol described above was repeated in six additional hearts, except that in these studies, the pericardium was reapproximated with 2-0 silk. Sutures were carefully placed around the openings made for the RV and LV drains and the Silastic LV balloon mount in the left atrium. Care was taken to avoid excessive constriction caused by suture placement.

LV P-V data were fit by a simple linear equation using the least squares technique, $P = kV + b$, where $P = LV$ diastolic pressure in mm Hg, $V = LV$ diastolic volume in milliliters, and $k$ and $b$ are variables to be fit to data. The $k$ value characterized the overall diastolic P-V relation and may be considered a modulus of chamber (or volume) stiffness; $b$ is the pressure intercepted 0 volume (Gaasch et al., 1976; Mirsky, 1976).

Statistical data were calculated using a multiple comparison technique (Dunnett’s test) in comparing LV filling pressures at varying RV filling pressures. Similar multiple comparison testing was used in evaluating $k$ and $b$ values in Table 2. The paired $t$-test was used to evaluate the effects of pericardium vs. no pericardium in the same heart.

**Results**

**Effect of RV Filling Pressure on LV Diastolic P-V Relationships; Intact Pericardium**

With the exception of low RV filling pressures at small LV volumes, higher values for LV diastolic P-
V points are seen at all RV filling pressures with the pericardium intact than without (Table 1, horizontal comparisons; Fig 1). Table 1 also shows (vertical comparison) that, with the pericardium intact, an increment in RV filling pressure is associated with a significant increase in LV diastolic pressure when the right ventricular filling pressures are increased from 10–20 mm Hg. With the pericardium intact, the LV P-V curve is shifted upward and to the left, with increasing RV filling pressures. From these data, an average increment in LV diastolic pressure caused by the pericardium was calculated. For a RV diastolic pressure of zero mm Hg, the average increment in LV diastolic pressure at different LV volumes (20–100%) was 1.6 ± 0.3 mm Hg (P < 0.05). For a RV diastolic pressure of 5 mm Hg, this value was 1.9 ± 0.2 mm Hg (P < 0.05). The increase in RV diastolic pressure to 10 mm Hg was associated with a rise in the LV diastolic pressure to 2.7 ± 0.1 mm Hg (P < 0.05), and finally, at a RV diastolic pressure of 20 mm Hg, the LV diastolic pressure increased 6.5 ± 0.1 mm Hg (P < 0.05) (Fig. 1).

**Effect of Placing Sutures in the Pericardium**

In six dogs, sutures were carefully placed to approximate the edge of the incisions in the pericardium. In comparison to the unsutured pericardium, a further parallel upward shift in LV diastolic P-V relations was seen at all RV filling pressures (Fig. 1).

**Effect of RV Filling Pressures on LV Diastolic P-V Relationships; Pericardium Removed**

With removal of the pericardium, increments in RV filling pressure did not change the LV P-V relationship significantly, except at a RV diastolic pressure of 20 mm Hg (Table 1; Fig. 2).

**The Modulus of LV Chamber Stiffness (k and b Values)**

Table 2 depicts LV chamber stiffness constants (k values) and pressure axis intercepts (b values) of the LV diastolic P-V relations. The k values were not different (parallel shift) when comparing the data with and without the pericardium (horizontal comparisons). Table 2 also demonstrates that, in the absence of the pericardium, increasing the RV filling pressure has little effect on the k value (ver-

<table>
<thead>
<tr>
<th>LVEDP* (mm Hg)</th>
<th>RV diastolic pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 mm Hg</td>
</tr>
<tr>
<td>20% Pericardium</td>
<td>-0.3 ± 0.46</td>
</tr>
<tr>
<td>No pericardium</td>
<td>-3.0 ± 1.89</td>
</tr>
<tr>
<td>40% Pericardium</td>
<td>1.6 ± 0.34</td>
</tr>
<tr>
<td>No pericardium</td>
<td>-0.3 ± 0.93</td>
</tr>
<tr>
<td>60% Pericardium</td>
<td>3.3 ± 0.38</td>
</tr>
<tr>
<td>No pericardium</td>
<td>2.1 ± 0.53</td>
</tr>
<tr>
<td>80% Pericardium</td>
<td>4.4 ± 0.46</td>
</tr>
<tr>
<td>No pericardium</td>
<td>3.5 ± 0.62</td>
</tr>
<tr>
<td>100% Pericardium</td>
<td>5.9 ± 0.56</td>
</tr>
<tr>
<td>No pericardium</td>
<td>4.8 ± 0.68</td>
</tr>
</tbody>
</table>

* Left ventricular end-diastolic pressure (mm Hg) at normalized LV volume (%).
† P < 0.05 in comparison to RV = 0.
‡ P < 0.001 in comparison to RV = 0.
FIGURE 2 Comparison of the effects of the pericardium on LV diastolic P-V relations over a range of RVEDP. The effect of RV filling pressures is considerably increased with the pericardium present.

tical comparison). With the pericardium closed, the $k$ values increased significantly with filling of the RV from an EDP of 10 to 20 mm Hg (Fig. 2, left).

The average $b$ values are listed in Table 2. In general, $b$ values tend to increase with parallel upward shifts of the LV diastolic P-V curve associated with the presence of the pericardium (horizontal comparisons). Where differences in magnitude of shifts were small (no pericardium, vertical comparisons), differences in $b$ values are nonsignificant. With the non-parallel shift in LV diastolic pressure-volume relations (pericardium intact 10 to 20 mm Hg RVEDP), a significant difference in $b$ at the $P < 0.05$ level was seen.

Discussion

The results of the present study clearly demonstrate that an analysis of LV P-V relationships requires both a consideration of the pericardium and the filling pressure of the RV.

Although the cross-over of information from studies on the isolated, isovolumic heart to the intact heart must be viewed with caution, advantages of such a preparation include a control of many of the variables which alter LV P-V relationships. It might also be pointed out that an isovolumic LV pressure of 100 mm Hg, as used in the present study, occurs at a small volume relative to that which is found in the in situ heart. Larger, more physiological volumes would only provide additional pressure-volume coordinates but would not alter the concept which is set forth. Previous studies undertaken to evaluate ventricular interaction used a variety of models. Mouloupolos et al. (1965), investigating an "in vivo" heart-lung preparation in which the pericardium was excised, found that an increase in the RV end-diastolic pressure (RVEDP) above 10 mm Hg caused a rise in LV EDP. They suggested mechanical interference through the interventricular septum to explain the fact that diastolic collapse of the RV caused an increase in the LV EDP. In studies on the arrested heart, Laks et al. (1967) and Taylor et al. (1967) found that the LV EDP may be a misleading index of volume or function of the left ventricle when RV filling pressures vary. In these studies, the pericardium was open or excised and the observed mechanical ventricular interaction was independent of the pericardium. Bemis et al. (1974) used an isolated beating heart preparation with independent right and left ventricular loading and found that the right ventricle alters left ventricular filling and geometry over the entire range of RV end-diastolic pressures. Although they closed the pericardium, these authors reported that the observed ventricular interaction was independent of the pericardium.

In a recent publication, Glantz and Parmley, (1978) used an "in situ" beating supported dog heart preparation and studied the effects of changes in volume, RV and LV pressures and dimensions with the pericardium open and closed. These authors disagree with the conclusions of Bemis et al. (1974) and state that, with the pericardium intact, the LV was smaller than without the pericardium, when RV pressure or volume was increased. The RV and LV pressures are tightly coupled when the pericardium is closed; however with the pericardium open, the ventricular wall is the major determinant of

<table>
<thead>
<tr>
<th>RVEDP (mm Hg)</th>
<th>k Values</th>
<th>b Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No pericardium</td>
<td>Pericardium*</td>
</tr>
<tr>
<td>0</td>
<td>0.10 ± 0.02</td>
<td>NS</td>
</tr>
<tr>
<td>5</td>
<td>0.10 ± 0.02</td>
<td>NS</td>
</tr>
<tr>
<td>10</td>
<td>0.10 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>20</td>
<td>0.13 ± 0.02</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Pericardium incised for placement of drains and recording devices but not sutured.
† $P < 0.01$ in comparison to RVEDP = 0 mm Hg.
‡ $P < 0.05$ in comparison to RVEDP = 0 mm Hg.
diastolic pressure. The preparation used in the present investigation differs from that of Bemis et al. (1974) and Glantz et al. (1978), where ventricular volumes were determined indirectly by means of markers (Bemis et al., 1974) and ultrasonic transducers (Glantz et al., 1978) implanted in myocardium. In the present study, a balloon in the left ventricle enabled us to determine directly the LV volume at any given RV filling pressure. This method is direct, simple, and avoids incision and/or damage to the myocardium. As in the studies cited above, sutures were placed carefully in the pericardium, and additional small incisions were placed in the pericardial sac to prevent artifactual pericardial blood accumulation and restriction or alteration of the LV configuration. Studies in which the incised pericardium was left unsutured also were carried out. Our data show that the unsutured pericardium affects the diastolic P-V relationships of the LV even when RV filling pressures are zero. Our findings for the contracting heart at a RVEDP of 0 mm Hg are similar to those of Spotnitz et al. (1971), who showed in the arrested canine heart with intact pericardium that pressures were elevated over the entire range of LV P-V relations. At larger RV volumes, the pericardial effect is increased substantially. As can be seen in Table 2 and Figure 1, there is a parallel downward shift of the LV P-V curve when the pericardium is removed. A similar parallel (but upward) shift is seen when the pericardium is closed with sutures. Parallel shifts in the P-V relations are identified by an unchanged k value when determinations are made at a given right ventricular volume (Table 2).

The magnitude of the pericardial effects is easily seen in Figure 2. Thus it appears that the pericardium has a small but significant effect on LV P-V curves at low RVEDP. This pericardial effect increases at higher RVEDP and reaches high values at a RVEDP of 20 mm Hg.

Suturing the pericardium considerably increases ventricular interaction. The effect of RV filling pressure on LV diastolic P-V relations in the absence of the pericardium is observed only at high RV filling pressures (20 mm Hg) and with the LV at a volume greater than 60%. Thus, in the absence of the pericardium, compliance changes due to the RV are seen at high RV filling pressures which presumably bulge the septum toward the LV.

The work of Ludbrook et al. (1979) raises an interesting point regarding the importance of the pericardium and RV filling on LV diastolic P-V relations. These authors report that the administration of nitroglycerin but not amyl nitrite to patients with angina leads to a downward displacement of the LV diastolic P-V curve. Although a similar fall in afterload was seen with amyl nitrite as with nitroglycerin, amyl nitrite did not decrease RVEDP. The decreased RVEDP in the nitroglycerin group was responsible, according to the authors, for the downward displacement of the LV diastolic P-V relation. This shift was not thought to be due to the pericardium because of the work of Bemis et al. (1974) and Taylor et al. (1967), whose studies are discussed earlier. Our studies indicate the importance of the pericardium in concert with the RV rather than RV filling pressure alone. This formulation is in accordance with previous data from Moulopoulos et al. (1965), Glantz et al. (1978), Ross (1979), and Shirato et al. (1978).

LV P-V relations are compared for the unsutured and sutured pericardium (Fig. 1). As can be seen, suturing the pericardium results in an upward shift in LV P-V relations, at any RV filling pressure, (even when the pericardium has been very carefully reapproximated). These data demonstrate that closing the pericardium augments the RV-pericardial effect on LV P-V relations. On the other hand, the unsutured pericardium may underestimate this relation; in either case, qualitative interference is seen with both the unsutured and sutured pericardium. It is clear, however, that the manner in which the pericardium is reapproximated considerably alters the pericardial effect in the present and previous studies. This “suturing effect” of pericardium has been considered previously by Hefner et al. (1961) and Mirsky (1979).

In summary, the pericardium affects the LV diastolic P-V relationship, even at low RV filling pressures, and the intensity of this effect is clearly augmented at increasing RV diastolic pressures. The effect of elevating RV diastolic pressure in the absence of the pericardium is small and manifest only at high RV filling pressures. We conclude that there is an important interaction between the right and left ventricles; particularly when the pericardium is closed. Thus, studies which seek to evaluate cardiac compliance in the presence of an intact pericardium must take the pericardium into consideration.

Acknowledgments

We gratefully acknowledge the technical support of Alvin Franklin, John Clement, and David Rhodes and the assistance of Ilene Burton in the preparation of this manuscript.

References


Gaasch WH, Bing OHL, Pine MB, Franklin A, Clement J, Rhodes D, Phear WP, Weintrub RM (1978) Myocardial...
THE sex differential in coronary heart disease is well documented but poorly understood. It is not explained totally by differences in the established risk factors. Estrogen lowers plasma lipid levels and is thought to be protective in women, but produces excess cardiovascular mortality when given to men. Oral contraceptives increase the risk of both coronary and cerebral vascular disease in women, apparently by mechanisms other than augmentation of atherosclerosis. After reviewing these and other paradoxical features of the relationship of sex to atherosclerosis and its sequelae (McGill and Stern, 1979), we concluded that the arteries might contain receptors for the sex steroid hormones. In preliminary studies, we found autoradiographic and biochemical findings which indicate that the heart and major arteries of several mammalian species contain androgen and estrogen receptors in distinctive patterns of distribution among muscle and connective tissue cells. The distribution patterns of these receptors may contribute to the sex differential in coronary heart disease.

**Nuclear Uptake of Sex Steroid Hormones in the Cardiovascular System of the Baboon**

**Henry C. McGill, Jr., and Peter J. Sheridan**

**SUMMARY** Cardiac and arterial tissues of six male and six female adult baboons were examined for nuclear uptake of tritiated 5α-dihydrotestosterone (5α-DHT) or tritiated estradiol-17β (H-E2) by autoradiography. 5α-DHT uptake occurred in nuclei of most atrial and ventricular myocardial fibers, no cardiac interstitial tissues, some arterial endothelial cells, smooth muscle cells of the intima and inner arterial media, and a few smooth muscle cells of the outer arterial media. 5α-DHT uptake occurred in nuclei of a few atrial and ventricular myocardial fibers, many cardiac interstitial cells, occasional arterial endothelial cells, a few smooth muscle cells of the intima and inner arterial media, smooth muscle cells of the outer arterial media, and nearly all adventitial cells. These observations are consistent with other autoradiographic and biochemical findings which indicate that the heart and major arteries of several mammalian species contain androgen and estrogen receptors in distinctive patterns of distribution among muscle and connective tissue cells. *Circ Res* **48**: 238–244, 1981

**CIRCULATION RESEARCH**

Vol. 48, No. 2, February 1981
Pericardial modulation of right and left ventricular diastolic interaction.
J Spadaro, O H Bing, W H Gaasch and R M Weintraub

Circ Res. 1981;48:233-238
doi: 10.1161/01.RES.48.2.233
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/48/2/233

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/