Left Ventricular Dilatation and Diastolic Compliance Changes during Chronic Volume Overloading

By William H. McCullagh, M.D., James W. Covell, M.D., and John Ross, Jr., M.D.

SUMMARY
The magnitude and time course of alterations in left ventricular size, end-diastolic pressure (LVEDP), and stiffness consequent to chronic volume overloading were examined in conscious dogs. A large infrarenal aortocaval shunt was produced surgically, left ventricular dimensions were measured by cineradiography using radiopaque beads implanted subendocardially, and LVEDP was measured via an indwelling catheter. In nine experimental and seven control animals, LVEDP was related to the left ventricular end-diastolic diameter (LVEDD) over a range of LVEDP produced by transfusion and bleeding. In control studies LVEDP averaged 6.7 ± 1.42 (SEM) mm Hg, LVEDD determined at 15 mm Hg LVEDP averaged 4.8 ± 1.13 cm, and the mean slope of linear stiffness curves was 45.9 ± 2.3 mm Hg/cm. Time-dependent changes in all of these parameters were observed following creation of the shunt: A progressive increase of LVEDP reached a maximum by 2 to 3 weeks, and when early postshunt studies (mean 5.2 days) were compared with late postshunt studies (mean 6.8 weeks) LVEDP had increased from 9.7 ± 1.2 to 18.9 ± 1.1 mm Hg (P < 0.01). There was a progressive, more gradual, increase in left ventricular size, LVEDD being 4.81 ± 2.4 cm in early postshunt and 5.34 ± 2.8 cm in late postshunt studies (P < 0.01). Left ventricular diastolic stiffness showed an increase from 50.2 ± 5.6 to 96.6 ± 10.7 mm Hg/cm between early and late postshunt studies, respectively (P < 0.01), and functional compliance was reduced. In six animals the shunts were closed; at approximately 1 week there was a substantial drop in LVEDP (9.5 ± 1.9 mm Hg), and although LVEDD were unchanged stiffness decreased to 58.6 ± 12.2 mm Hg/cm (P < 0.01). Observations up to 4 months after shunt closure suggested further progressive return toward normal of these parameters. It is concluded that chronic volume overloading in the normal dog causes a time-dependent shift to the right of the diastolic left ventricular pressure-dimension relation accompanied by a progressive reduction of diastolic compliance, and that these changes are at least in part reversible following correction of the shunt.

Additional Indexing Words:
Aortocaval shunt Animal studies LV pressure-dimension relations

ALTERATIONS in left ventricular size and filling pressure accompanying chronic volume overloading are important phenomena in human disease. However, few data are available concerning the time course and extent of such changes in an experimentally controlled setting, and associated changes in left ventricular pressure-volume

Address for reprints: Dr. John Ross, Jr., Department of Medicine, University of California, San Diego, PO Box 109, La Jolla, California 92037.

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relations and diastolic compliance have not been quantified. Accordingly, in conscious dogs left ventricular dimensions and pressure have been measured serially during and following correction of chronic volume overloading produced by means of a large arteriovenous fistula.

**Methods**

**Surgical Procedures**

Mongrel dogs weighing 16–32 kg were prepared in advance for study using sterile surgical technic. A left thoracotomy was performed under Sodium Thiopental-Halothane anesthesia, and after opening the pericardium radioopaque beads (1.6-mm [1/16-in] stainless-steel ball bearings) were inserted into the wall of the left ventricle to a subendocardial position with a 14-gauge needle and trochar as described by Mitchell et al. To outline the left ventricular cavity, beads were placed in the following positions: at the apex and base, and at the septal, anterior, posterior, and lateral aspects of the circumference at the minor equator. A small vinyl tube (0.44-mm od) was implanted into the left ventricular cavity near the apex and brought out via a small incision in the neck. The pericardium was left open, the chest closed, and the animal allowed to recover.

The second operative procedure was performed through an abdominal incision and following administration of heparin a side-to-side aortic-inferior vena caval anastomosis (10–12 mm in length) was constructed. The abdomen was closed and intravenous fluids and antibiotics given for several days, as necessary. In each instance, a large shunt was evidenced by vena caval dilatation, a thrill, and a subsequent murmur. In a few animals, control studies were performed at 3–10 days following the first operation. However, in most of the animals the two operative procedures were performed at one stage. A substantially higher survival rate was achieved by the latter approach.

In six animals the shunts were closed at 4–10 weeks. A repeat laparotomy was performed, the aorta and vena cava opened, and the shunt orifices sutured closed. After recovery (4–7 days), repeat serial studies were performed.

**Cineangiographic Technics**

The animals were trained to lie quietly on an X-ray table without medication. Most of the cineradiographic films were obtained in single plane using a Philips unit (type X63000/11); in two animals serial biplane cines were performed. Films were exposed at 200 frames/sec using 16-mm Eclair cameras. During each study the beads were aligned under fluoroscopic control to a repeatable configuration. The animal was positioned so that the apical-to-base axis and the medial-to-lateral axis were aligned, the anterior or posterior bead serving as the center of a cross. Since single-plane data were used for most of the studies, accurate alignment was necessary to avoid changes in apparent dimensions introduced by rotation of the heart.

By the careful reproduction of a specific bead configuration fluoroscopically at each serial study, changes of position of the heart of less than 5° lateral rotation could be readily detected, and hence the nearly exact position of the heart relative to the X-ray beam could be reproduced at each study. Analysis of control animals in three separate studies showed a variation of LVEDD of only 0.05 cm. After each study, a grid made of crossed rows of beads of known distance apart was filmed at the level of the ventricle at a constant X-ray tube to image intensifier distance. This calibration allowed correction for X-ray magnification and spherical distortion on the cine films.

After each study, the film was processed in a Huston-Fearless A-11 Automatic Processor and projected using an L. W. Photo Co. Motion Analyzer 900 16-mm movie projector. The image was directed by means of a mirror to a ground-glass screen oriented horizontally under an electronic X-Y plotter. Travel on the pointer of the X-Y plotter produced a change in the voltage on a potentiometer, and this voltage was accessed to an EAI 580 analog computer. The analog signal was then A/D converted and processed on an EAI 640 digital computer. The computer was calibrated by digitizing the projected grid, filmed at each study. To gain the dimension desired (usually the LVEDD) at a given left ventricular pressure, the film was positioned at the appropriate frame, determined by counting the frame markers inscribed on the pressure recording, the pointer moved between the appropriate beads, and the true distance obtained using an appropriate computer program.

Left ventricular pressure at low and high gains was measured with a Statham P23Db transducer and recorded on Clevite Brush Mark 200 oscillograph. Pressure and radiographic data were correlated by the simultaneous recording of pressure and a pulse generated by each opening of the camera shutter.

**Design of Individual Studies**

During the course of each cineangiographic study, left ventricular dimensions and pressures were obtained at the control, or operating, level and then over a spectrum of left ventricular end-diastolic pressures (LVEDP). This range was
obtained by infusion of saline or dextran, or by controlled hemorrhage if the initial filling pressure was elevated. Cineradiography was carried out at each new pressure level. Each study usually was comprised of 4-5 such runs. If the heart rate in the control study was low compared to the usual postshunt values, a small dose of atropine sometimes was given.

In each study, the LVEDD was calculated over a range of LVEDP values from approximately 5 to 20 mm Hg. LVEDP was then plotted against LVEDD to describe the diastolic pressure-circumference relation. Some investigators have employed pressure-volume and pressure-circumference curves using the filling curve of a single beat. This approach was not employed in the present study, since, with the instrumentation used, artifacts in the pressure tracing during the filling cycle were noted. Therefore, a series of determinations made at end-diastole comprised the pressure-circumference curves. The curves often were partially exponential and could be fitted by the exponential equation employed by Noble et al. However, we chose to compare the curves by a linear fit, using the mean-squares method (calculated by an appropriate computer program), an index of diastolic stiffness being defined as the slope (Δpressure/Δcircumference) of the calculated linear curve. This ratio, then, represents the reciprocal of diastolic compliance. A linear analysis was favored over the exponential-fit method, since it is difficult statistically to compare exponential curves. It should be noted that the values calculated for LVEDD may not precisely equal the actual LVEDD, due to differences in distances of the beads from the endocardium and slight variations from perpendicular of the plane of the measured dimension to the X-ray beam. However, the beads were within 2 mm of the endocardium in all autopsied specimens, and since each animal was compared to itself when changes in heart size were analyzed, and since stiffnesses were compared by slopes, these factors should not have played a major role.

The term "operating LVEDP" is defined as that LVEDP level, averaged over a normal respiratory cycle, which existed in the animal prior to infusions or hemorrhage. Diastolic stiffness is considered as the slope of the entire pressure-circumference curve. However, when the whole pressure-dimension curve (LVEDP-LVEDD) is considered, changes in operating LVEDP may sometimes alter the effective stiffness and compliance (e.g., an animal operating at an LVEDP of 20 mm Hg often is on a somewhat steeper portion of the normal curve than one operating at 5 mm Hg). Therefore, in discussing the experimental animals we also have used the term "functional compliance" (FC), calculated by dividing the change in LVEDD (ΔLVEDD) in mm by the pressure range from 5 mm Hg below up to the animals' operating LVEDP (FC = ΔLVEDD/5 mm Hg). In animals with operating LVEDP less than 10 mm Hg, FC is defined as the slope of the curve between LVEDP 5 and 10 mm.

Serial Studies

Studies were carried out serially (intervals of 1 week or more) in 13 animals. Five animals had control studies only (no second [shunt] operation); two animals had control studies followed by a second operation, postshunt studies, and postshunt-closure studies; three animals had studies after the second operation only; and four animals had both postshunt and postshunt-closure studies. Thus, there were seven control studies and nine animals in the postshunt group studied serially for between 4 and 10 weeks postshunt. Following shunt closure, at least one study was obtained in six animals and in three animals additional serial studies were obtained for up to 4 months.

A Student's t test was used for statistical analyses in comparisons with control animals and a t test for paired observations in comparisons during serial studies.

Results

Control Studies

In control studies in the seven animals without arteriovenous shunt, the operating left ventricular end-diastolic pressures (LVEDP) averaged 6.7 ± 0.42 (SEM) mm Hg, and the end-diastolic diameters (LVEDD) determined at 15 mm Hg LVEDP averaged 4.8 ± 0.13 cm. Stiffness (LVEDP/LVEDD) curves were plotted over a mean pressure range of 6.7 to 21.6 mm Hg, and the mean slope was 45.9 ± 2.3 mm Hg/cm (table 1).

Serial Studies

Early Postshunt Studies. The data are summarized in all dogs in table 2. An example is shown in figure 1 of serial studies in dog F, in which control, early, and late postshunt, as well as postshunt-closure data were obtained. Data from control animals and from serial studies in all dogs are shown in figure 2. Studies in nine animals from 2 to 9 days (mean 5.2 days) following creation of the arteriovenous shunt are summarized in figure 3. The operating LVEDP averaged 9.7 ± 1.2

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mm Hg, a value not significantly different from control. The LVEDD at 15 mm Hg LVEDP was 4.81 ± 0.24 cm, and stiffness curves plotted over a mean pressure range of 8 to 20.9 mm Hg gave a mean slope 50.2 ± 5.6 mm Hg/cm, again not different from the control group (fig. 3). However, in the two animals in which paired control and early postshunt data were obtained, the LVEDD had increased slightly by 2.9 and 0.6%, the slopes had increased from 56 to 70 and 40 to 63 mm Hg/cm, and the operating LVEDP had increased from 8 to 11 and 6 to 10 mm Hg, respectively.

Late Postshunt Studies. There was a progressive, gradual increase in heart size (LVEDD at 15 mm Hg) for the first 4–5 weeks after creation of the shunt. The increase in operating LVEDP tended to be more abrupt and to plateau at 2–3 weeks (figs. 1, 2). In some animals the rise in the operating LVEDP was quite abrupt (fig. 1) occurring long before the plateau was reached in the LVEDD. Late postshunt studies were carried out at 4–10 (mean 6.8) weeks in the same nine animals having early postshunt studies. There was a significant increase in operating LVEDP from 9.7 ± 1.2 to 18.9 ± 1.1 mm Hg (P < 0.01) and also a significant increase in left ventricular size (LVEDD at 15 mm Hg) from 4.81 ± 0.24 to 5.34 ± 0.28 cm, a mean increase of 12.4% (P < 0.01).

Examples of stiffness curve changes are shown in figure 4. Such curves plotted over a mean range of 8.1 to 21.2 mm Hg in all animals showed a significant increase in slope from a mean of 50.2 ± 5.6 mm Hg/cm in the early postshunt studies to 96.6 ± 10.7 mm Hg/cm in the late postshunt studies (P < 0.01). This change indicates a substantial increase in diastolic stiffness (table 2; figs. 2, 3).

Average diastolic functional compliance (FC) decreased between early and late studies from 0.28 ± 0.03 to 0.12 ± 0.04 mm/mm Hg (P < 0.02; table 2; figs. 2, 3).

Studies following Shunt Closure. In six animals the fistulae were successfully closed, and postclosure studies were carried out 4–7 days postoperatively. There was a significant drop in operating LVEDP from 18.5 ± 1.3 to 9.5 ± 1.9 mm Hg (P < 0.01), but there was no significant change in heart size, the LVEDD at 15 mm Hg being 5.45 ± 0.21 cm at the initial postclosure study and 5.54 ± 0.21 cm prior to closure. In one animal (fig. 1) with prolonged survival, the LVEDD diminished further from 5.11 to 4.85 cm, although it had not reached control (4.51 cm) by 4 months.

Stiffness curves plotted over a mean LVEDP range of 8 to 20.2 mm Hg showed a

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Table 1

<table>
<thead>
<tr>
<th>Dog</th>
<th>HR (beats/min)</th>
<th>Operat LVEDP (mm Hg)</th>
<th>LVEDP* (mm Hg)</th>
<th>Operat LVEDD (cm)</th>
<th>LVEDD at 15 mm Hg (cm)</th>
<th>LVEDD/LVEDD slope (mm Hg/cm)</th>
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</table>

Averages | 6.7 | 4.8 | 45.9 |
Averages | 1.1 | 0.35 | 5.9 |
Averages | 0.42 | 0.13 | 2.3 |

Abbreviations: HR = heart rate; operat LVEDP and LVEDD = operating left ventricular end-diastolic pressures and dimensions, respectively.

*Low and high refer to the extremes of the indexed LVEDP-LVEDD relation.
Table 2

Summary of Data for All Dogs

<table>
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<tr>
<th>Dog</th>
<th>Days postshunt (min)</th>
<th>HR (beats/min)</th>
<th>Operat LVEDP (mm Hg)</th>
<th>LVEDP* (mm Hg)</th>
<th>Operat LVEDD (cm)</th>
<th>LVEDD at 15 mm Hg/cm</th>
<th>LVEDP/LVEDD slope (mm Hg/cm)</th>
<th>FC (mm/min Hg)</th>
<th>Inc LVEDD (%)</th>
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<tr>
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</table>

Early postshunt data

| Av  | 5.2                | 154            | 9.7                  | 8.0           | 20.9            | 4.69                | 4.81                      | 50.2           | 0.28         |
| sd  | 2.6                |                | 3.7                  |               |                 | 0.71                | 16.8                      | 0.07           | —            |
| SEM | 0.9                |                | 1.2                  |               |                 | 0.24                | 5.6                       | 0.03           | —            |

Late postshunt data

| Av  | 47.3               | 157            | 18.9                 | 8.1           | 21.2            | 5.38                | 5.34                      | 98.9           | 0.12         |
| sd  | 17.0               |                | 3.1                  |               |                 | 0.85                | 29.4                      | 0.04           | 5.0          |
| SEM | 5.7                |                | 1.1                  |               |                 | 0.28                | 9.8                       | 0.01           | 1.7          |

Postshunt-closure data

| Av  | 5.3                | 9.5            | 8.0                  | 20.2          | 5.34            | 5.45                | 58.6                      | 0.36           | —            |
| sd  | 1.5                |                | 4.8                  |               |                 | 0.51                | 29.9                      | 0.02           | —            |
| SEM | 0.6                |                | 1.9                  |               |                 | 0.21                | 12.2                      | 0.08           | —            |

Abbreviations: HR = heart rate; operat LVEDP and LVEDD = operating left ventricular end-diastolic pressures and dimensions, respectively; FC = functional compliance; Inc = increase.

*Low and high refer to the extremes of the indexed LVEDP-LVEDD relation.

significant decrease in slope from 105.3 ± 13.1 to 58.6 ± 12.2 mm Hg/cm (P < 0.01), and the latter value was not significantly different from the early postshunt slope in these six animals, 55.1 ± 8.6 mm Hg/cm (figs. 3, 4B). In the animal having further postshunt-closure studies, LVEDP and LVEDD tended to fall slowly, and the stiffness decreased further from 86 to 66 mm Hg/cm (fig. 2). Since all animals were operating at a substantially lower LVEDP after shunt closure, the increase in functional compliance further emphasized this change (fig. 3).

Discussion

The results of this study demonstrate that chronic volume overloading is associated with
Examples of the changes in the diastolic properties of the left ventricle before (dashed vertical line), during, and after (solid vertical line) volume overloading by means of an arteriovenous fistula. EDP = left ventricular end-diastolic pressure; EDD = left ventricular end-diastolic dimension. Both functional compliance (FC) and stiffness changes are shown in the lower panel.

A time-dependent shift to the right of the pressure-diameter relation and a large increase in left ventricular diastolic stiffness, indicating a reduction in diastolic compliance. The finding that the operating LVEDP was only mildly elevated in the early postshunt studies may in part have been due to the postoperative status, with relative hypovolemia; however, the technic used to assess stiffness changes should have obviated potential effects of operating LVEDP on this factor. After reversal of the shunt, filling pressure and compliance rapidly returned toward normal although left ventricular size changes appeared to occur more slowly.

The shift to the right in the pressure-dimension relation found in this study could be considered analogous to "creep," although ventricular enlargement due to hypertrophy also undoubtedly played some role. Creep has been observed acutely in isolated muscle held isotonically at a fixed tension, a change in length occurring initially rapidly and then progressively more slowly as a function of time. The observed shift to the right of the pressure-length relation occurred in a progressive manner for the first 5 or 6 weeks following induction of the shunt, at which time the increase in LVEDD tended to plateau (figs. 1, 2). This phenomenon emphasizes the unreliability of end-diastolic pressure as an indicator of end-diastolic volume in the presence of chronic heart disease, since LVEDP usually reached a maximum considerably earlier (fig. 2). In earlier studies on animals with chronic arteriovenous fistul ae, we demonstrated an increased left ventricular volume in ventricles fixed in diastole at their operating filling pressures compared to control animals fixed acutely at similarly elevated LVEDP; however, in those studies it was not possible to draw conclusions concerning the time course of these changes or the slopes of pressure-volume relations.

In addition to a rightward shift, a substantial increase in the slope of the pressure-diameter relation occurred; i.e., an increase in left ventricular end-diastolic stiffness and a compliance decrease were demonstrated. Although many studies continue to explore the controversy as to whether or not compliance changes are induced acutely by various interventions, chronic diastolic compliance changes of this type have received little quantitative experimental study. Noble et al. recently analyzed left ventricular pressure-volume relations acutely in the conscious normal dog and obtained curves resembling those in the present investigation. Their data were obtained throughout the filling phase of single cardiac cycles, rather than over a range of LVEDP values, and it was possible to show acute compliance variations during the phases of rapid ventricular filling. Because diastolic compliance was estimated only at end-diastole
in the present study, we were unable to assess possible dynamic compliance changes occurring during cardiac filling. It seems likely that the compliance changes reported herein reflect alterations in the properties of the ventricular myocardium, since the pericardium was opened widely at the time of the initial operation, but the mechanism of the compliance reduction remains uncertain. Although rapid heart rates have been shown to decrease diastolic compliance, presumably because of incomplete relaxation, this is unlikely to have been a significant factor since the heart rates in the early postshunt animals compared to the late postshunt were practically identical. Clinical studies support the view that hypertrophy is associated with a reduction in left ventricular diastolic compliance, as assessed from diastolic pressure-volume relations. It has been disputed, however, whether or not experimental hypertrophy causes an alteration in the resting stiffness of cardiac muscle. Thus, Spann and co-workers studying right ventricular papillary muscles from cats subjected to chronic pulmonary artery constriction found no change, whereas Bing et al. recently have documented an increased resting stiffness of such papillary muscles normalized for muscle cross-sectional area. Our previous experimental studies indicate that a mild degree of left ventricular hypertrophy has occurred.

Figure 2

Data in all nine experimental animals following creation of an arteriovenous fistula and following its closure (vertical dashed lines). Data from control animals are indicated by large open circles, bars indicating SEM.
Averaged data on diastolic properties of left ventricle in control dogs and in nine dogs subjected to large arteriovenous fistula. Abbreviations are the same as in figure 1. Both stiffness and functional compliance (FC) changes are shown in the lower panels. P values refer to changes in stiffness.

by 6 weeks following creation of experimental arteriovenous fistulae identical to those of the present study, although sizeable variations between animals did not permit a definite conclusion concerning the presence of significant hypertrophy in the present study.

We also observed in those studies that wall stress at end-diastole was not significantly different at comparable filling pressures in chronically and acutely dilated hearts, and it seems certain that the diastolic stress-circumference relation, as well as the pressure-circumference relation, also was abnormal in the present chronic studies. Therefore, it is possible that hypertrophy per se, or some other structural change, was responsible for the compliance change. That compliance tends to diminish in the normal heart as ventricular volume is increased seems accepted, and the compliance changes could be in part related to this phenomenon. The striking decrease in compliance between the early and late postshunt studies cannot be solely explained on this basis, however, since the same ranges of end-diastolic pressures were induced.

There have been several clinical reports concerning pressure-volume, or pressure-length, relations in cardiac patients. Dodge and co-workers using angiographic methods have constructed pressure-volume loops in patients with a variety of cardiac lesions and shown differences in the slopes of these curves at comparable diastolic volumes, as well as scatter of diastolic volumes at comparable diastolic pressures, and vice versa. Gault et al., studying patients with volume overloading due to free aortic regurgitation,
found that the left ventricular diastolic pressure-circumference relation was shifted rightward from the normal. Six months to 1 year following aortic valve replacement, patients with evidence of depressed myocardial inotropic state preoperatively had lower LVEDP values but appeared to be operating on the same pressure-circumference curve as that existing before operation. However, when myocardial inotropic state was normal preoperatively, the diastolic pressure-circumference curve shifted leftward into the normal range after operation. Jarmakani et al. demonstrated directionally similar changes in pressure-volume relations after corrective operations in children with ventricular septal defect, most of whom did not have evidence of left ventricular failure.

These studies in patients considered to have relatively normal myocardial function, and the present experiments in normal dogs, suggest that cardiac enlargement induced by chronic volume overload, as well as the associated compliance changes, are reversible with time. It would have been desirable to assess this reversibility more fully in the present experiments, but a relatively high mortality in the early weeks following closure of the shunt precluded serial long-term studies. Likewise, the question of when, and by what mechanism, changes in heart size and compliance appear to become irreversible (as noted in the clinical study on aortic regurgitation) seems amenable to experimental study and could have important clinical implications. The fact that functional compliance became normal in the very early postshunt-closure period suggests that favorable effects on the impedance to left ventricular filling and, in turn, on the mean pulmonary venous pressure can occur rapidly postoperatively, whether or not a concomitant reduction in heart size has taken place.

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