Early Changes in Left Ventricular Regional Dimensions and Function during Chronic Volume Overloading in the Conscious Dog

F.R. Badke and J.W. Covell

SUMMARY As the left ventricle dilates during chronic volume overloading, it assumes a more spherical configuration, suggesting a nonuniform regional myocardial response. Accordingly, we studied early alterations in left ventricular geometry and regional function induced by chronic volume overloading in the canine heart subjected to an aortocaval fistula. Nine mongrel dogs were instrumented with ultrasonic crystal pairs placed perpendicularly to the long axis to measure instantaneous segment lengths in the apical, midventricular, and basal portions of the left ventricle; another pair monitored an apical internal diameter. We obtained control measurements of end-diastolic dimensions and percent shortening in the conscious state. An aortocaval fistula was then constructed, resulting in an increase in resting end-diastolic pressure (EDP) from 11 ± 1 (SEM) to 22 ± 2 mm Hg and resting heart rate from 100 ± 4.9 to 131 ± 5.0 beats/min at 1 month (P < 0.01). At 10–20 days, mid-basal regional end-diastolic dimensions were significantly greater than control (8.8 ± 2.4% increase, P < 0.01), while there were no significant increases in apical dimensions when compared at the same EDP. However, by 20–40 days, all dimensions were significantly increased (11.4 ± 3.3% increase at the mid-base, P < 0.01), 7.8 ± 1.6% at the apex (P < 0.01), and 11.2 ± 4.5% at the diameter (P < 0.05). Regional function as measured by percent shortening at the same EDP exhibited early augmentation in all segments by 2 weeks compared to control (3.8 ± 1.3% increase at the diameter, 3.8 ± 1.9% at the base, 7.2 ± 2.2% at the middle, and 12.2 ± 4.7% at the apex, P < 0.05). From 4 to 6 weeks, however, function was not different from control, with a slight reduction in all regions from the peak values obtained at 2 weeks. We conclude that in the canine heart there are regional differences in the rate of left ventricular dilation to chronic volume overload, suggesting differential regional hypertrophy, with the earliest response at the mid-basal level. Furthermore, despite dilation, regional function is preserved or even augmented, although to varying degrees in each region.

FOR many years, pathologists and clinicians have appreciated that the shape of the left ventricle is quite spherical late during the course of chronic volume overload (Kirch, 1920, 1930; Grant, 1953). Since the normal heart is ellipsoidal in shape, this progressive change in geometry implies regional differences in the rate of left ventricular dilation and hypertrophy, the meaning and implications of which have been unclear. Since the geometry of the heart is an important determinant of ventricular function measured by mean circumferential fiber shortening rate was preserved in these dogs (McCullagh et al., 1972). Fischl (1977) and Vokonas (1973) examined ventricular shape angiographically in patients with chronic aortic and mitral regurgitation and showed that eccentricity decreased compared to a control population, also suggesting a more globular heart with volume-overload lesions. In contrast, however, Lin et al. (1977) demonstrated conflicting data in the volume-overloaded rat heart model produced by 3 months of a low iron diet resulting in significant anemia. They found essentially no difference in the ratio of the minor to major axis in volume-overloaded hearts compared to controls. Changes in left ventricular shape suggest regional differences in the rate of cardiac dilation and perhaps hypertrophy. In particular, if the ventricle is changing from an ellipsoidal to a spherical shape...
during chronic volume overload, this suggests a more rapid increase in apical than in basal dimensions. The development of small implantable ultrasonic crystals for chronic length measurements has provided a method for more precisely investigating in the conscious animal these regional dimension and function changes during cardiac adaptation to certain pathological lesions. Thus the objective of the current study was to examine in dogs differential changes in apical, midventricular, and basilar dimensions during chronic volume overload imposed by a large arteriovenous fistula, using ultrasonic crystals implanted at these levels to define the regional variations in diastolic lengths and systolic function.

**Methods**

Eight adult mongrel dogs weighing 25–31 kg were the subjects for this study. Each dog was instrumented with sterile technique and, after recovery, control measurements were obtained. During a second sterile procedure, chronic volume overloading was produced by an aortocaval fistula; serial weekly follow-up studies then were performed from 14 to 100 days afterward.

Specifically, at the first operation, the dogs were anesthetized with sodium pentobarbitol (25 mg/kg) and the heart was exposed through a thoracotomy in the left fifth interspace. Four pairs of ultrasonic crystals were implanted in the left ventricle. Each crystal pair consisted of two 5-mHz piezoelectric crystals, two mm in diameter with two 35-gauge stainless steel wires soldered to either side, and a 1-mm thick spherical resin lens. One set served as an anteroposterior endocardial diameter but was situated more toward the apex of the left ventricle than the true minor axis (Fig. 1). The other three crystal pairs were placed in small segments of myocardium—one near the base, one near the apex, and the other midway between the basal and apical pairs at the midventricular level. These crystal pairs were oriented perpendicular to the major axis of the ventricle and therefore parallel to the hoop fiber direction (Streeter et al., 1969). The crystals were inserted 2.5 mm from the endocardial surface (i.e., approximately 8–12 mm from the epicardial surface). Crystal location was confirmed later by autopsy examination of each dog. Two polyethylene catheters for measurement of left ventricular pressure were inserted into the tip of the left ventricular apex via small stab wounds. The chest was closed, the wires and tubes tunneled subcutaneously to the back of the neck, and the dogs allowed to recover.

Control studies were carried out from 1 to 3 weeks postoperatively in the conscious unanesthetized state with the dogs trained to lie quietly on the floor. The polyethylene tube was connected to a Statham P23Db transducer for measurement of left ventricular pressure which was recorded, along with the dimension signals and a suitable electrocardiographic lead, on a Brush-Clevite model 2000 polygraph at a paper speed of 100 mm/sec. Transit time of 5 mHz sound between each crystal pair was determined using the electronics of Franklin and Kemper (Franklin et al., 1973) and converted to distance, assuming a constant velocity of sound in myocardium of 1.55 mm/sec. All measurements were taken from the beat with the lowest end-diastolic pressure (EDP) in a given respiratory cycle. By this method the following data could be obtained: heart rate, left ventricular pressures, and
instantaneous dimension of each crystal pair throughout the cardiac cycle. Following measurements in the resting state, EDP was varied between 5 and 25 mm Hg by bleeding, retransfusion, and volume expansion with dextran, and the corresponding changes in heart rate, left ventricular pressure, and crystal dimensions were recorded. Repeat control studies also were performed on different days to ensure that individual dimensions did not vary more than 2.5%. In particular, the mean percent change in length during the control period was 

\[ -0.34 \pm 0.86\% \text{(SEM)} \] (range, -2.5% to 1.5%). Previous work from Theroux et al. (1976, 1977) has indicated that these measurements remain stable over a 20- to 30-day period following implantation. Furthermore, careful histological examination of myocardium around the crystals reveals that they are contained in a thin rim of fibrous tissue (<1 mm) and that normal myocardium is present between each crystal pair.

Once control data had been obtained, the dogs were re-operated to create a large arteriovenous fistula as previously described (Taylor et al., 1968). In brief, through a midline abdominal incision, the aorta and inferior vena cava were exposed below the level of the renal arteries and above the aortic bifurcation. A 1-cm side-to-side aortocaval anastomosis was constructed and, once again, the dog allowed to recover. Studies similar to the control study were performed in the conscious state at 1-week intervals following the operation. By 6 weeks, overt evidence of volume overload had developed in all dogs as manifested by an elevation of the resting left ventricular end-diastolic pressure (LVEDP), pulmonary rales, ascites, and peripheral edema. Most dogs were followed for at least 6 weeks following construction of the shunt (average, 50 days; range, 15–126 days). The dogs were then killed with sodium pentobarbital anesthesia and examined at autopsy; the fistula was demonstrated to be patent in all dogs, and crystal location was confirmed by dissection of the left ventricle.

Comparison of dimensions in both control and shunted dogs was made at a uniform EDP of 15 mm Hg. This was done in an attempt to compare dimensions of both control and shunted dogs at the same ventricular distending pressure, and hence to obviate automatic increases in end-diastolic length secondary to the increase in EDP in the volume overload dogs. However, comparisons also were made at the resting or “operating” EDP’s. Statistical significance was assessed by analysis of variance of repeated measures of the same parameter (Wiener, 1971).

Regional peak systolic wall stresses were calculated according to the method of Wong and Rautahargu (1968), assuming the ventricle to be a thick prolate spheroid and the myocardium to be an elastic, isotropic, and homogeneous material and neglecting shears and bending moments. For the calculations, long axis measurements were taken from the previous data of Ross et al. (1967, 1971), and regional wall thickness from the computations of Streeter et al. (1973). Myocardial segment lengths were transposed into a regional radius, r, by assuming that the angle subtending the arc length, s, was constant throughout the course of the study; this assumption is correct if and only if dilation of the left ventricle is uniform around its circumference at any level along the long axis.

The mean percent distance from the base of the left ventricle to its apex for the mid-point of the basal ventricular crystal pair was 28 ± 1.2% (SEM); for the midventricular crystals, 49 ± 0.9%; and for the apical crystals, 80 ± 1.8%. The average depth of each crystal was 2.5 mm from the endocardial surface, so that each crystal pair presumably represented subendocardial behavior during the course of chronic volume overloading. The anterior diameter crystal was located on the endocardial surface at a mean percent distance from the base to the apex of 65 ± 2.7% and its counterpart on the posterior wall 70 ± 3.4% of the base-to-apex distance. Thus, the diameter measured during the course of the experiments was more an “apical” chord than a true minor axis of the left ventricle.

The mean distance between each crystal at the base at autopsy was 11.6 ± 1.8 mm (SEM) at the midwall 16.1 ± 3.6 mm, and at the apex 14.0 ± 2.9 mm. The mean distance measured by the diameter crystals at autopsy was 46.03 ± 2.4 mm.

Finally, the mean angle subtended by a line through each crystal pair and a plane perpendicular to the long axis of the left ventricle was 70 ± 4° for the large crystals, 75 ± 5° for the midwall crystals, and 70 ± 3° for the apical crystals (range, 65° to 80° for all locations). This would indicate that the crystals were parallel to the direction of the hoop fibers in all locations (Streeter et al., 1969).

![Figure 2](http://circres.ahajournals.org/)

**Figure 2** Resting hemodynamic data (heart rate, peak left ventricular pressure (LVP) and LVEDP) during the control period and one month after creation of an aortocaval fistula. Heart rate and LVEDP are significantly different from control (P < 0.001).
Results

Hemodynamic Data

The effects of the aortocaval fistula on hemodynamic parameters 4 weeks after the shunt was created are presented in Figure 2. The mean heart rate increased from 100 ± 49 beats/min pre-fistula to 131 ± 5.0 beats/min post-shunt (P < 0.001). Peak left ventricular pressure did not change significantly (mean pressure of 125 ± 5 mm Hg at control compared to 126 ± 2.0 mm Hg 4 weeks post-shunt). However, resting LVESP rose markedly from a level of 11 ± 1 to 24 ± 2 mm Hg post-shunt (P < 0.001). Heart rate changes generally were apparent

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* For each dog, top row = operating EDP; bottom row = EDP of 15 mm Hg.
† Blank spaces indicate that adequate signals could not be obtained.
within 1 week after operation but LVEDP changes were gradual, and values were not significantly different from controls until 20–30 days (Table 1).

End-Diastolic Length (EDL) Changes

Figure 3 represents a typical example of the serial changes observed in EDL and shortening over a 5-week period in one dog. Each length corresponds to an EDP of 15 mm Hg defined by the Z point of the left ventricular pressure trace. The diameter increased by 7.5 mm over the course of 4 weeks post-shunt; this increase was first detectable at 14 days. Similarly, increases in the individual segments occurred over 4 weeks, and detectable changes were present in the midventricular and basal regions at 2 weeks. In contrast, no increase is evident at the apex by 2 weeks. However, by 4 weeks, the apical crystal is 1.7 mm longer at end diastole compared to control. Viewed three-dimensionally, this suggests that the ventricular shape at 2 weeks is conical as opposed to the spherical configuration normally associated with the volume-overloaded heart.

Similar behavior was exhibited by other dogs (Table 1). In particular, there was a mean increase of $0.9 \pm 0.3$ mm ($P < 0.05$) in the basal end-diastolic length at LVEDP = 15 (EDL$_{15}$) at 10–20 days post-shunt, and a $1.5 \pm 0.5$ mm ($P < 0.05$) increase in the midsegment EDL$_{15}$. These changes persisted but were not significantly greater at 3–4 weeks. In contrast, there was no increase in EDL$_{15}$ at the apex until 20–30 days after shunt when EDL$_{15}$ was $0.9 \pm 0.2$ mm greater than control ($P < 0.01$). The diameter exhibited behavior similar to the apex in that length did not significantly increase until 3–4 weeks when there was a mean increase of $4.4 \pm 1.5$ mm ($P < 0.06$, $n = 5$).

Because of similar location and behavior, the midventricular and basal data have been combined in Figure 4. At 10–20 days, there is a mean increase of $1.1 \pm 0.3$ mm ($P < 0.01$) above control EDL$_{15}$.

![Figure 3](http://circres.ahajournals.org/)

**Figure 3** Typical tracing obtained from one dog followed through the study protocol. Arrows indicate end diastole. Note increases in the mid ventricular and basilar segment lengths at 14 days when the apex is essentially unchanged from control. EKG = electrocardiogram, LV = left ventricular.
and a $1.6 \pm 0.6$ ($P < 0.03$) increase in EDL at 3-4 weeks. Thus there is a $8.8 \pm 2.4\%$ increase in the mid-base region by 2 weeks which persists at 4 weeks ($11.4 \pm 3.3\%$). In contrast, the apical region demonstrates no change at 2 weeks, but a $7.8 \pm 1.6\%$ increase above control at 3-4 weeks. These results suggest a fundamental difference in the early response of these two regions to volume overload.

End-diastolic lengths also were compared at the operating EDP to assess whether this early difference between the basal and apical dilation was present at the dog's working level of EDP. In general, the results were not significantly affected. Thus, there was no statistically significant increase in the diameter or apical segment until 20-30 days, at which time $6.1 \pm 1.8\ mm$ and $1.2 \pm 0.3\ mm$ mean increases were apparent. In contrast, at 10-20 days, there were significant increases ($P < 0.03$) in the basal and midventricular EDL's ($1.2 \pm 0.4\ mm$ and $2.0 \pm 0.7\ mm$ mean increases, respectively). Thus, the regional differences apparent when comparing end-diastolic lengths at an EDP of 15 mm Hg are also present when comparing them at the operating EDP.

**Function Changes**

Regional function as measured by percent shortening of a given segment at an EDP of 15 mm Hg was followed serially in a subgroup of five dogs (Fig. 5). Control values revealed $20.7 \pm 2.3\%$ shortening for the diameter, $17.4 \pm 3.2$ for the base, $14.2 \pm 3.5$ for the midventricular region, and $22.4 \pm 5.5$ for the apex. By 10-20 days, there was augmentation of function in all segments with percent shortening rising to $24.5 \pm 2.4$, $21.2 \pm 3.3$, $26.6 \pm 5.0$, and $33.3 \pm 7.2$ in the diameter, basal, midventricular, and apical segments, respectively. In all cases except for the diameter, these are statistically significant increases ($P < 0.05$). Late post-shunt (30-40 days), there appears to be a reduction in shortening compared to the 2-week values with the diameter, basal, midventricular, and apical percentages falling to $21.8 \pm 2.8$, $17.6 \pm 1.9$, $19.7 \pm 5.2$, and $31.0 \pm 6.4$, respectively. However, these reductions are not statistically different from either control or the 2-week data.
Heart rates at an EDP of 15 (achieved by transfusion in control dogs and bleeding in shunted dogs) were not significantly different when 2-week or 5-week shunted dogs were compared to controls [110 ± 6.1 (control) vs. 136 ± 21.0 (2 weeks) vs. 137 ± 14.4 (5 weeks)]. Also, calculations of peak regional wall stress based on the equations of Wong et al. (1968) revealed no difference between the control and early or late shunted state. Table 2 contains the average peak wall stress data for the five dogs in which regional function was studied. Here a wall thickness of 10.0 mm at the base and 0.9 mm at the apex was assumed throughout the course of the experiment based on the data and calculations of Streeter (1973). Although peak basilar wall stress is significantly higher than apical wall stress during each time frame of comparison, serial changes in a given region are not significantly different (392 ± 17 × 10^3 dynes/cm^2 at control vs. 392 ± 12 × 10^3 at 2 weeks vs. 387 ± 24 × 10^3 at 5 weeks at the base; 360 ± 23 × 10^3 at control vs. 353 ± 10 × 10^3 at 2 weeks vs. 369 ± 18 × 10^3 at 5 weeks at the apex). Also since all measurements of function were made at an EDP of 15 mm Hg, end-diastolic wall stresses also were not serially different. Thus, at the comparison EDP of 15 mm Hg, three determinants of cardiac performance—local preload, local afterload, and heart rate—were not significantly different throughout the course of the experiment, despite significant changes in regional performance.

### Discussion

The major finding of this study is that there are regional differences in the response of the left ventricle to chronic volume overload. In particular, we have shown that early after the creation of the lesion (2-3 weeks), basal dilation occurs without a noticeable apical response, as measured by dimensional changes on the anterior surface of the left ventricular wall. If these alterations are representative of changes along the left ventricular circumference, then this suggests a more conical ventricle at 10-20 days. In support of this geometric construct is the serial apical diameter data which show no significant increase in size until 20-30 days. Because the diameter crystals were placed more in the apical region of the left ventricle, this is consistent with the absence of early apical dilation and early transition from an ellipsoid to a cone. By 4-5 weeks, however, the rate of apical elongation has increased while the rate of change at the base has tapered off. Persistence of this trend would suggest that the ventricle has become more spherical, the shape generally associated with this lesion.

Previous investigators have not appreciated a similar pattern in the regional responses to chronic volume overloading but generally have not specifically examined basal vs. apical changes or have not looked at this model early after creation of the lesion. However, our work is in contrast to the results of Lin et al. (1977) who have shown in the rat that apparently there are no regional dimensional differences 3 months after volume overloading by anemia. However, species differences, and the gradual onset of volume overload in this preparation, may account for this disparity. Since all dimensions were assessed at an EDP of 15 mm Hg, it might be questioned whether these shape changes are the result of varying EDP from the normal operating EDP in the conscious animal. However, comparing EDL's at operating EDP (mean 11 mm Hg in the control animals and 22 mm Hg in the late shunted animals) does not significantly affect the results. This is presumably because (1) there are no regional differences in diastolic stiffness (Kent, 1978) and (2) the pressure-dimension curves for pressures in the 10 to 25 mm Hg range are relatively steep (i.e., little change in dimension for a large change in EDP) (Kent et al., 1978; Bishop et al., 1969; Boettcher et al., 1978). Accordingly, these changes in regional dimensions at 1-2 weeks after shunt appear to be a true change in geometrical configuration.

It is interesting to speculate as to the meaning of these different regional changes. An increase in the distance between the two crystals of a given pair suggests one of the following changes on a structural level: either there is an increase in diastolic sarcomere length at end diastole, or slippage of parallel fibers with respect to each other, or actual addition of sarcomeres in series (i.e., hypertrophy) with maintenance of normal sarcomere length. Previous work by Ross et al. (1971) has shown sarcomere length in this volume-overloaded preparation to be relatively normal. Furthermore, although fiber slippage cannot be excluded entirely, a slight increase in wall thickness and an increase in the LV to body weight ratio at autopsy (both in our data and that of Ross) suggests that hypertrophy, with addition of sarcomeres in series, is the primary mechanism for these increases in EDL. Accordingly, our data indicating differential base to apex changes in dilation suggest differential regional hypertrophy with earliest hypertrophy occurring in the mid-base region, followed by a later apical response.

It has been proposed that hypertrophy may be a response to an increase in myocardial wall stress brought about by dilation and/or pressure elevation and that hypertrophy continues until wall stress is normalized by the resultant increase in wall thickness, as reflected in the LaPlace relation. Indeed, recent work by Sasayama et al. (1976) in the chronic
pressure-overloaded heart has demonstrated this tendency for wall stress to return to control as hypertrophy ensues. The same phenomenon has been hypothesized for the chronically volume-overloaded heart, although careful serial investigations have not been done. At any rate, differential regional hypertrophy might be predicted by this theory if differential regional wall stresses are present. Although direct measurements are not available, the formulations of a number of individuals who assume the left ventricle to be a prolate spheroid predict that basal and midventricular wall stresses are greater than apical stresses, presumably because of a smaller radius of curvature at the apex (Wong and Rautahargu, 1968; Minsky, 1969). Hence, even though stresses at all levels in the ventricle are increased early after creation of a large arteriovenous fistula, basal stress should be higher than apical stress. Thus, if a certain value of wall stress must be exceeded to stimulate hypertrophy, one would expect the midventricular and basal regions to respond initially and a conical ventricle, as suggested by our data, to result early in the compensatory process. However, later with a continued rise in EDP and a continued increase in EDL, the critical level of wall stress eventually might be exceeded at the apex and hypertrophy stimulated there. Presumably, the process ceases when increases in wall thickness are sufficient to balance the increases in radius, and wall stress returns to normal.

Our calculations of regional wall stresses according to the work of Wong et al. are in agreement with this formulation, suggesting that basilar wall stresses are indeed higher than apical stresses. However, the absence of regional and serial wall thickness measurements to include in these computations make this construct still highly speculative.

In this study we have also examined regional ventricular function in the chronically volume-overloaded heart. Previous studies in the volume-overloaded heart have emphasized that ventricular function, as measured by mean velocity of circumferential fiber shortening, is preserved for at least up to 6 weeks post-shunt (Ross, 1972). Our data would support this with the extension that regional ventricular function as measured by percent shortening of myocardial segments is also preserved—in fact, augmented. Furthermore there are differences in regional function (i.e., more shortening at the apex compared to the base) existing in the normal canine heart, and these disparities are also present throughout the course of the study in the volume-overloaded heart. For the normal heart, these observations are consistent with the data of LeWinter et al. who also documented higher levels of apical shortening (LeWinter et al., 1976).

This augmentation of regional function appears to be present despite relatively comparable levels of preload, afterload, and heart rate during the course of the study. In particular at the apex, there is an 11% increase in shortening despite no measurable increase in EDL at an EDP of 15 mm Hg and no change in peak left ventricular wall stress. This would suggest that the augmentation of function is due to the third determinant of ventricular performance, namely, inotropic state. The mediator of this change in contractile state is uncertain, although it may be related to increased levels of circulating catecholamines (Chidsey, 1967).

Although our and Ross's data support preservation of function early in the volume-overloaded heart, some clinical data suggest that eventually ventricular performance deteriorates (Gault et al., 1970). The later data on regional shortening in our study suggest that there indeed appears to be a gradual fall-off in function, although this is not statistically significant. Furthermore, this fall-off is evident despite a continued increase in EDL. One might suggest that such a reduction is a result of afterload mismatch, but our calculations of peak systolic regional wall stress indicate comparable levels throughout the course of the study; presumably this results because by 6 weeks the hemorrhage necessary to reduce the EDP to 15 mm Hg also reduces systolic pressure, and hence peak wall stress, even though heart size is greater. Furthermore, wall thickness was assumed constant through the course of the study, and since in reality there probably are increases in wall thickness which accompany hypertrophy, this would tend to lower our 30-40-day calculations of regional wall stress even further. Thus, it seems unlikely that any apparent deterioration in shortening in these late studies is due to an excess of afterload, but rather to a reduction in contractile state. We note in particular that this reduction is more pronounced in the mid-basilar level than at the apex, suggesting that the area to respond first to the lesion is also the first to be depressed. However, since these results do not achieve statistical significance, we prefer to emphasize that mechanical performance in this condition is maintained, and that the hypertrophied, chronically volume-overloaded heart represents in effect a larger "normal" heart, in which initial sarcomere length and amount of sarcomere shortening are preserved, but a larger number of sarcomeres in series effects a greater stroke volume.

In summary, we have examined the early changes in canine left ventricular geometry and regional function following chronic volume overloading by an aortocaval fistula. By means of chronically implanted ultrasonic crystals, we have shown that increases in EDL in the midventricular and basilar regions occur by 10-20 days post-shunt, whereas apical dilation does not take place until 20-30 days. There findings suggest a cone-shaped ventricle exists early after chronic volume overloading, as a transition state between the normal ellipsoidal ventricle and the spherical ventricle seen late after volume overload. Since past work has demonstrated
normal sarcomere lengths and increased wall thickness in this preparation, we suggest that this early shape change represents differential regional hypertrophy.

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