IN THIS REVIEW we examine how the Frank-Starling relationship operates in normal man, and summarize earlier investigations. There is good evidence to show that the left ventricle actually works near the peak of its function curve at the filling pressure encountered in normal man. This is surprising, since it is generally accepted that the normal ventricle operates on a prolonged ascending portion of its function curve, where there is a close relationship between the amount of energy produced by the contracting ventricle and the pressure or volume of the ventricle just before contraction. The strongest evidence describing this limitation of the Starling mechanism in the intact circulation is from two recent sources. In this laboratory, infusions of whole blood or dextran in normal man in amounts sufficient to double left ventricular filling pressure have resulted in only small increases in stroke volume, stroke work and cardiac output. The recent investigation by Boettcher and co-workers, in which the diameter of the left ventricle was continuously measured in the conscious dog by ultrasonic crystals, is also important. Elevation of left ventricular end-diastolic pressure to more than 30 mm Hg by saline infusion, increase in afterload with methoxamine, or global ischemia, resulted in only a slight increase in left ventricular end-diastolic diameter. The ventricle is near its maximal end-diastolic volume in the normal, reclining, conscious dog, and is thus on a relatively stiff part of the ventricular pressure-volume curve in which further slight increases in volume are accompanied by marked rises in left ventricular end-diastolic pressure. While these observations must be interpreted cautiously relative to the human heart, the results are analogous to those we have obtained in man, in which traditional measures of the energy of ventricular contraction indicated that little reserve in the Starling mechanism was available for the normal left ventricle. Also, a recent echocardiographic study showed only minor changes in the dimensions of the normal human ventricle after dextran infusion, which was associated with significant elevations in left ventricular end-diastolic pressure.

While these studies show a limitation in the normal ventricle, the usefulness and validity of the Starling relationship in left ventricular failure or myocardial infarction has been repeatedly affirmed. Using volume challenges in patients with ischemic disease and failure, it has been possible to substantially increase the energy of ventricular contraction as measured by stroke work, stroke volume or cardiac output. Peak ventricular function in these conditions has been reported at a left ventricular filling pressure of 14–18 mm Hg or 18–24 mm Hg. The use of volume expansion to increase left ventricular filling pressure, and thus cardiac output, has become a common mode of therapy in low-output states. This validation of the Starling relationship and its clinical usefulness during left ventricular dysfunction has been made possible by the easy access to left ventricular filling pressure by means of the flotation catheter, although earlier measurements using the wedged pulmonary artery catheter produced valuable information. The therapeutic approach of increasing cardiac output by the use of an afterload reducing agent, such as nitroprusside, has provided further evidence of the importance of the Starling relationship in cardiac failure. This maneuver finds a clear basis in the experimental work of Sarnoff 20 years ago. By regarding the filling pressure-stroke work relationship as a "family of curves" rather than one rigid curve, Sarnoff showed that the ventricle delivered a larger stroke work at a reduced afterload at any left ventricular filling pressure. Thus, the clinical acceptance and validity of the Starling relationship in the failing or ischemic left ventricle is unquestioned. However, this is not the case for the normal left ventricle, where there is little reserve remaining in the Starling relationship.
The application of the Starling relationship to man was hotly debated 20 years ago. Then, excellent evidence from several laboratories\textsuperscript{10-16} clearly showed that the energy developed by the contracting ventricle was a function of its late diastolic pressure or volume. The constraints under which the system operated were carefully defined by Sarnoff in 1955\textsuperscript{19} and in a subsequent group of studies from his laboratory as summarized in 1961.\textsuperscript{27} Despite this evidence, several investigators still believed that the Starling relationship did not have an active role in the control of the circulation in the intact organism. Evidence for the Starling relationship was accumulated almost entirely in anesthetized dogs subjected to thoracotomy and extensive surgical procedures, or in isolated hearts. Technical capabilities at that time required these procedures in order to obtain the essential information, but Rushmer\textsuperscript{18} contended that experimental data thus obtained in animals in support of the Starling relationship were largely invalid for the intact organism, since these data were obtained under the effects of hypovolemia and the myocardial depressant effect of anesthesia. Using a gauge providing left ventricular diameter, Rushmer\textsuperscript{18} found that this measurement was greatly reduced as a result of either anesthe-sia or thoracotomy, although he could not further define the cause. In retrospect, the tachycardia that appeared at this time, as well as the effect of venous pooling and blood loss, were most probably responsible for the decreased ventricular volume. In a later study in 1959,\textsuperscript{20} which was remarkably sophisticated for that time, he continuously measured left ventricular diameter in the conscious dog using opposed ultrasonic crystals; intraventricular pressure and left ventricular dp/dt were also recorded, as well as a computerized integral of stroke work based on instantaneous left ventricular pressure and ventricular diameter changes. He found little evidence for the application of the Starling relationship to the circulation of the conscious, intact dog, using a variety of maneuvers such as exercise and volume load. His results are similar to the recent data of Boettcher and associates,\textsuperscript{5} in that an infusion of whole blood produced a rise in left ventricular filling pressure up to 20 mm Hg, but there was only a minimal increase in left ventricular end-diastolic diameter. Rushmer believed that normal circulatory control occurred primarily through extracardiac mechanisms, such as reflex neural and hormonal mechanisms, and the Starling mechanism was a less important factor.\textsuperscript{19-21}

In 1960–1965, Braunwald investigated the applicability to man of the Starling relationship; he and his associates have been credited with the demonstration of the validity of Starling's law in man, and its subsequent general acceptance. The studies were usually conducted in patients without a diseased ventricle. Their investigations have been presented in summary form.\textsuperscript{22, 23} They found in man that 1) with a mercury-in-rubber gauge sewn to the left ventricle, the arterial pulse pressure correlated with myocardial segment length and left ventricular end-diastolic pressure in patients with atrial fibrillation;\textsuperscript{24} 2) isometric contractile force as determined by a strain gauge sewn to the right ventricle varied with the length of the segment under the gauge;\textsuperscript{25} 3) during atrioventricular dissociation, the arterial pressure and pulse pressure varied with left ventricular filling pressure;\textsuperscript{26} 4) with silver clips sewn to the heart, reduction in right ventricular dimensions during the Valsalva maneuver correlated positively with similar changes in systolic excursions;\textsuperscript{27} and left ventricular dimension changes were less prominent; 5) during left ventriculography, stroke volume was positively correlated with changes in end-diastolic volume which occurred at that time.\textsuperscript{28} While these particular investigations show a basic relationship between determinants of fiber length and energy release in man, they do not bear directly on the applicability of the Starling mechanism during circulatory control. Through an increase in afterload with angiotension\textsuperscript{29} it was possible to increase stroke work, but this is not comparable to a volume overload.

In the crucial experiments of volume overload, Frye and Braunwald infused 1500 ml of autologous blood and observed only minor changes in cardiac output and left ventricular stroke work.\textsuperscript{30} To relate this lack of change to a compensatory reflex mechanism, they found that after ganglionic blockade, such an infusion increased stroke work by over 100%. No left ventricular pressures were reported in that investigation. In a subsequent study,\textsuperscript{31} left ventricular filling pressure was measured during a 1500-ml blood transfusion after ganglionic blockade, but no control filling pressures before blockade were reported. It is important in the present study to note that the left ventricular filling pressure after ganglionic blockade, before blood transfusion, was only 5 cm H$_2$O (3.5 mm Hg), and that systolic arterial pressure had been reduced by an average of 42 mm Hg by the blockade. While Braunwald and co-workers concluded that ganglionic blockade interrupted a reflex which interfered with the Starling response, we believe that an alternative explanation must be considered. The reduced afterload and preload resulting from the trimethaphan, used for ganglionic blockade, would have the observed effect of decreasing left ventricular filling pressure to its low value, and thus reduce left ventricular volume and pressure to a more active portion of the Starling relationship. This interpretation is consistent with the concept presented here.

In retrospect, a better demonstration of the Starling relationship was observed later by Ross and Braunwald by impeding venous return.\textsuperscript{32} In normal subjects, in the absence of ganglionic blockade, reduction in left ventricular filling pressure to a low level by inflation of a balloon in the inferior vena cava was associated with a major decline in cardiac index and stroke work. This was interpreted as evidence that the left ventricle operates on the ascending limb of the Starling curve. Similar results were obtained by Sachner and associates.\textsuperscript{33} These findings are clearly in accord with the thesis presented here, but a more appropriate interpretation would be that the left ventri-
cle normally operates at the peak of the Starling curve and that this relationship comes into play only at reduced filling pressures.

Further information indicates that the active portion of the Starling relationship is present at a left ventricular filling pressure below that found in normal, supine man. We have reviewed all catheterization studies from this laboratory over the past 12 years in which heart disease was excluded, and in which proper hemodynamic studies were made while left ventricular end-diastolic pressure was reduced through various interventions, including nitroglycerin administration, atrial pacing, and phlebotomy (reported here). The mean values for each group of data relating left ventricular stroke work and left ventricular end-diastolic pressure have been combined on a plot with values from volume expansion. This results in a composite description (fig. 1, table 1) of ventricular function, with data from 75 patients and consisting of 102 separate observations of stroke work and left ventricular end-diastolic pressure over a wide range. Each point in figure 1 is a mean for the particular investigation quoted. The points roughly describe an initial positive relationship between filling pressure and stroke work, followed by a plateau beginning near a left ventricular end-diastolic pressure of 10 mm Hg. Information from several different studies presented in a composite curve such as this lacks the strength of an individual set of data, but it has value in that a large number of observations for the normal human ventricle become available over a wide range of left ventricular filling pressures. Its validity is increased because all data were collected in one laboratory under similar conditions. To provide additional validity to these observations, we have obtained a complete ventricular function curve in a few patients, using alterations in blood volume and pacing as interventions. One of these is presented in figure 2, showing the relationship of left ventricular stroke work to left ventricular end-diastolic pressure. The relationship is similar to that of the composite curve, in that there is initially a sharply rising limb, followed by a plateau in stroke work which is reached near a left ventricular end-diastolic pressure of 10 mm Hg. These curves show that there is a close relationship between filling pressures and stroke work, but at values below the normal in the supine subject. They confirm the existence of the Starling relationship in normal man but predict that it will only come into play when left ventricular end-diastolic pressure is reduced below 10 mm Hg.

While data describing ventricular function curves have usually been expressed in stroke work, this expression of ventricular energy has been criticized on the basis that it will lead to an erroneously low value for the energy of ventricular contraction, in particular at higher filling pressures. The standard hydraulic expression for calculation of work by a pump requires the energy at the beginning of the cycle to be subtracted. In the case of the ventricle, this means subtraction of left ventricular end-diastolic pressure, and at high values for filling pressure, this will lead to mathematical reductions in the calculated stroke work, according to the relationship \( \text{LVWSI} = (\text{BAm} - \text{LVEDP}) \) (SI) 0.136, where \( \text{LVWSI} \) = left ventricular stroke work index (g-m/m²), \( \text{BAm} \) = brachial artery mean pressure (mm Hg), \( \text{LVEDP} \) = left ventricular end-diastolic pressure (mm Hg), and SI = stroke volume index (ml/m²). At a low left ventricular end-diastolic pressure, subtraction of filling pressure would have little effect on calculated stroke work, and the expression is valid as a measure of total energy delivered during contraction. At a higher filling pressure, this can lead to a more flattened or depressed function curve.

**Figure 1.** A composite graph for 75 patients in whom left ventricular end-diastolic pressure (LVEDP) was modified as shown. Each point represents the mean value for a particular intervention and includes from four to 21 patients, with a total of 102 interventions. Left ventricular stroke work index (LVSWI) is positively related to LVEDP up to 10 mm Hg (LVSWI = 24.4 + 2.70 LVEDP); thereafter, there is little increase in LVSWI as LVEDP increases further. NTGO = nitroglycerin ointment with observations made after 15, 30 and 60 minutes; NTG = sublingual nitroglycerin. See table 1.
TABLE 1. Effects of Alterations of Left Ventricular Filling Pressure in Normal Subjects

<table>
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<tr>
<th>Conditions</th>
<th>n</th>
<th>LVEDP (mm Hg)</th>
<th>CI (l/min/m²)</th>
<th>SI (ml/m²)</th>
<th>LVSWI (g·m/m²)</th>
<th>BAm (mm Hg)</th>
<th>HR (beats/min)</th>
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<td>51.6 ± 1.2</td>
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<td>28 ± 1.7</td>
<td>95 ± 4.9</td>
<td>147 ± 2.8</td>
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*New data presented in this paper. Data shown are mean values ± SEM.
Abbreviations: LVEDP = left ventricular end-diastolic pressure; CI = cardiac index; SI = stroke index; LVSWI = left ventricular stroke work index; BAm = brachial arterial mean pressure; HR = heart rate; NTG = sublingual nitroglycerin; NTGO = nitroglycerin ointment (at 15, 30, and 60 minutes).

of the Starling relationship requires that a measure of the energy of ventricular contraction be related to the ventricular filling pressure. Measurement of total ventricular work delivered per contraction is a proper measure of energy delivered by the ventricle, although it is not hydraulically correct regarding analysis of the heart as a mechanical pump, and the question of the proper manner in which to view the work of the ventricle has never been resolved. In view of this problem, the data presented here were analyzed without subtraction of left ventricular filling pressure (fig. 3), and there is little difference in the calculated stroke work compared with the traditional method of calculation using filling pressure subtraction (fig. 2). The filling pressures encountered here were not high enough to make a significant difference in work calculation, so either form may serve to define the energy of contraction.

Another way to resolve the issues raised by stroke work calculation is to use only stroke volume as a measure of the energy of ventricular contraction. Presentation of the data in this form (fig. 4) yields a ventricular function curve similar to those using stroke work (figs. 2 and 3), with the plateau beginning near a left ventricular end-diastolic pressure of 10 mm Hg. Similar curves are available in other patients.
While mean brachial artery pressure is traditionally used for the calculation of stroke work, this is not completely accurate. The correct expression for ventricular work is obtained from an integration of the instantaneous value for ventricular pressure and volume rate of flow from the ventricle during the contraction phase of the cardiac cycle. Calculations of mean systolic pressure have been made, and these lead to minor changes in calculated stroke work, but this would not alter the results sufficiently to modify the concepts presented here.

Atrial pacing is a good method of reducing left ventricular filling pressure in a controlled and stepwise fashion. Since stroke volume is inversely related to heart rate, and arterial pressure and cardiac output are unchanged, the relation between filling pressure and stroke work or stroke volume can be readily examined under controlled conditions, thus performing a "pacing-function curve." We and others have described such curves, and it has been possible to obtain appropriate shifts in the ventricular function curve using factors that increase (digitalis and isoproterenol) or decrease (propranolol and ischemia) contractility. At that time it was believed that the "pacing-function curve," which could only examine the left ventricular end-diastolic pressure below the control value, was describing only the lower portion of the ventricular function curve, but in retrospect, it was describing the active portion of the curve and starting near the peak. While it was recognized that heart rate might affect the type of curve generated, subsequent studies with volume changes as seen here (fig. 2), produced curves similar to those of pacing; also, pacing during phlebotomy did not alter the distribution of data on the function curve (fig. 2). Moreover, studies with an isometric strain gauge sewn directly to the right ventricle in man do not show an increase in peak contractile force as rate is increased from 72 to 145 beats/min, although the rate of force generation is increased. It might be suspected that a pacing ventricular function curve is cutting across a number of curves of varying contractility, but this does not seem to be the case. But even if pacing should be discarded as an invalid way to measure ventricular contractility, the use of blood volume changes alone characterizes the function curve as described above, with an early ascending limb and a peak at 10 mm Hg.

Filling pressure may also be lowered simply by adopting the upright posture, in which case left ventricular end-diastolic pressure will fall by an average of 4 mm Hg, presumably through venous pooling. Thus, it seems reasonable that in the upright position, the normal left ventricle acts in the midportion of the ascending limb. This assumption is supported by the finding that an infusion of 1000 ml of blood will significantly increase cardiac output in men at rest in the upright position.

Current opinion subscribes to the importance and validity of the Starling relationship. Illustrations of this relationship for man are, however, invariably presented diagrammatically, rather than with direct evidence, or more commonly by reproduction of...
animal experiments demonstrating this point. It is implied, or stated directly, that the normal ventricle functions on the ascending limb of the Starling curve. Sonnenblick recently commented that in man "the normal heart is operating in that portion of the Starling curve where stroke volume is highly dependent on filling pressure," but this does not appear to be the case for supine man. However, there has been surprisingly little factual information for the human ventricle; most of it has been obtained recently with the flotation catheter in the failing or ischemic ventricle, and very little information other than that discussed here has been available. The implication of the information presented here is that sarcomere length has reached a limiting value at the upper limits of normal left ventricular filling pressure. In fact, Sonnenblick and associates found that near a distending pressure of 12 mm Hg in the excised cat and dog ventricle, sarcomere length reached 2.2 μ, a value associated with maximal tension generation in the papillary muscles. Thereafter, there was little increase in sarcomere length as distending pressure rose to higher levels, although some additional volume increase occurred. The explanation for the early peak and plateau for the normal ventricular function curve must lie in the configuration of the ventricular pressure-volume realtionship and its influence on sarcomere length. Unfortunately, little information is available regarding the pressure-volume relationships in man to document this assumption, other than in the limited range obtained during normal diastole; these results often hint that a rapidly rising left ventricular pressure is present near the end of diastole, but are insufficient for any meaningful conclusion.

Figure 5 is a diagrammatic representation of the probable normal left ventricular pressure-volume relationship in man, with filling pressures obtained for interventions at various levels on this curve. The configuration has been made similar to that reported for the canine left ventricle and indicates that large volume changes accompany decreases in filling pressure below homeostatic levels. Observations from this laboratory have indicated that during infusions of dextran in normal subjects, only minor changes in echocardiographically determined left ventricular volume occurred despite large increases in left ventricular filling pressures. Using a programmed pacemaker with left ventriculography, it has been shown by Morton and associates that ventricular volume decreases with a decrease in RR interval, but with the longer RR intervals, end-diastolic volume increased only slightly. These direct measurements of left ventricular volume provide support for the concept of the early peak of the Starling relationship.

While the pericardium must be considered a contributing factor in limiting left ventricular distensibility, the studies of Spotnitz and co-workers and Sonnenblick and associates, showing that maximal sarcomere length occurs near a distending pressure of 12 mm Hg, indicate that the pericardium does not play an important role in limiting left ventricular distensibility.

The present considerations should be related to previous animal experiments in which the Starling relationship was developed. Burton, while supporting the importance of the Starling concept, has commented that it is unlikely that Starling's law would have been discovered if studies had been done in the intact animal. As Rushmer has said, the effects of anesthesia and surgery tend to lower ventricular...
volume. This in itself would not seem to have an important effect on left ventricular function. However, it could alter completely the position on the ventricular function curve by reducing ventricular volume. Furthermore, the nature and duration of the animal studies, extending from the isolated heart preparation of Starling to the open-chest preparation of Sarnoff, result in varying and progressive degrees of left ventricular failure. In animal studies with various degrees of failure, peak stroke work is reached at increasingly higher values for filling pressure, varying from 15–30 mm Hg, as the failure becomes more severe. Also, the presumably “normal” left ventricular function curves in the anesthetized, open-chest dog probably contain a certain degree of reduced contractility, since these curves become progressively less steep and resemble failure curves as the experiment progresses. This may explain the delayed peak encountered in some experiments. Thus, it appears from experimental data, for reasons that are not clear, that the failing heart, in contradistinction to the normal heart, follows the Starling relationship and peaks at filling pressures in excess of normal values. Administration of a positive inotrope will result in both a steeper ascending limb and an earlier peak. The considerations presented here do not deny the existence of a Starling mechanism; indeed, they confirm the strong relationship between left ventricular filling pressure and stroke work or stroke volume. However, they do show that this relationship exists at filling pressures below 10 mm Hg for the normal human ventricle as well as for other mammalian species. They do indicate that cardiac output is normally controlled by extracardiac factors, probably peripheral vascular resistance, heart rate, and hormonal stimulation of contractility. The Starling mechanism would then only come into play during situations in which left ventricular end-diastolic volume is reduced and left ventricular filling pressure is lowered, such as tachycardia, drug therapy, or physiological influences associated with a lowered left ventricular volume. The most obvious of these would be the assumption of the upright posture.

When the extensive literature on the Starling relationship is examined from the point of view expressed here, many of the extreme differences of opinion fall into place. Boettcher and associates, in their instrumented conscious dog, found essentially no increase in ventricular end-diastolic diameter with volume expansion, but showed that this measurement could be increased substantially with volume expansion when the dog was anesthetized and the chest opened. Their results and conclusions are almost identical to those Rushmer expressed some 25 years previously — that the ventricle is normally operating near its maximal end-diastolic volume.

In summary, the normal ventricular function curve is much different from that usually portrayed, in that the sensitive portion of the curve lies below the normal supine filling pressure and that peak performance is achieved near a filling pressure considered to be normal at rest. This should be considered when performing hemodynamic studies in the catheterization laboratory. However, in the upright position, with a reduced left ventricular filling pressure, cardiac output is sensitive to volume changes, and in this situation, normal man is operating along the ascending limb of the ventricular function curve. Also, filling pressure can easily be altered by relatively minor changes in heart rate and other influences. The ventricular function curve in the failing or noncompliant ventricle differs from the normal in that the failing ventricle reaches its peak performance at a much higher filling pressure.

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Left Axis Deviation
A Reassessment

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SUMMARY This report deals with the ramifications of the concept of left axis deviation. In early life, the leftward shift of the frontal plane QRS axis is determined chiefly, if not solely, by the relative weights of the ventricles. Once adult ventricular weight ratios are reached, there is a long period of axis stability, then a gradual leftward drift of the QRS, governed principally by left anterior fascicular conduction. Thus, the normal QRS axis is age-dependent, and left axis deviation must be considered accordingly.

THE DIRECTION of the mean frontal QRS axis has been studied since derivation of the Einthoven triangle from bipolar leads I, II and III. With the advent of augmented unipolar limb leads, measurement of the QRS axis became more precise. Normal ranges were established, and deviations from normal designated "left" and "right," according to the direction of the shift. The normal QRS axis is age-dependent. Thus, left axis deviation exists when the mean frontal plane axis is equal to or less than 0° in very premature infants (weights below 1000 g), +90° or less in full-term newborns, +75° or less at 3 months, +45° or less in infants older than 6 months and in children, and −30° or less in adults.1 In early life, the relationship between axis and age is related primarily to the relative weights of the ventricles. In the fetus, up to approximately 30 weeks gestation, the left ventricle outweighs the right.2 The right ventricle then grows disproportionately so that at 32 weeks it is about the same thickness as the left, and at 36 weeks, slightly thicker.2,3 After birth, the right ventricle continues to gain weight, but at a much slower rate than the left. By the end of 4 weeks, the left ventricle is heavier; adult ratios are reached before age 6 months.2

The causes and clinical significance of left axis deviation have been controversial since the early days of electrocardiography. The concept of interruption of the anterior fascicle of the left bundle branch — commonly designated "left anterior hemiblock" — as a cause of left axis deviation dominated interest in the past decade.4,5 Evolution of the theory of fibrotic or degenerative left anterior fascicular block resulted in clarification of many misconceptions previously applied to the left superior QRS axis. Concurrently, the term "left axis deviation" was reapplied to several old designations and to some new ones not related to unifascicular block. This progress has generated a considerable amount of information on left axis deviation. Most, if not all, the various patterns can now be separated by applying strict analytical electrocardiographic criteria, thus avoiding the limitations inherent in inappropriate concentrations on left anterior fascicular block.

Despite lively interest, the diverse ramifications of acquired and congenital left axis deviation have not been condensed into a single current essay. It is to this end that our remarks are directed.

Historical Perspective
As early as 1937, Ashman and Hull ascribed left axis deviation to coronary artery disease and left ventricular hypertrophy,6 and a decade later Wilson reinforced the latter concept.7 Shortly thereafter, the idea of "peri-infarction block" was introduced,8 and attention was called to Wilson's comments on intraventricular block.9 The notion of peri-infarction block emphasized the importance of coronary artery disease as a cause of left axis deviation, and provided a seemingly rational explanation for it.10 Although in 1951 Grant and Estes elaborated on focal intraventricular block of the peri-infarction type, they stated, "There is evidence that the left bundle bifurcates early

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Received August 29, 1978; revision accepted January 31, 1979.

Circulation 60, No. 1, 1979.

Normal left ventricular function.
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Circulation. 1979;60:4-12
doi: 10.1161/01.CIR.60.1.4

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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