Cardiac Performance During Exercise in Dogs with Constricted Pulmonary Artery

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Numerous studies on the acute response to obstruction of the right ventricular outflow of animals with open and closed chests have been reported. However, little information is available on cardiac performance in preparations of long duration and on the response of the right ventricle under increased stress, such as can be induced by exercise. Donald and Kirklin reported right ventricular pressures of 95 mm Hg, systolic, and 1 mm Hg, diastolic, in one anesthetized, resting dog that was studied 17 days after constriction, and Barger and associates reported elevation up to 335 mm of water in the mean right atrial pressure in exercising dogs with constricted pulmonary arteries.

The object of the present investigation was twofold: (1) to study the cardiovascular response to exercise of intact dogs in which chronic right ventricular hypertension had been previously induced by constricting the main pulmonary artery, and (2) to determine cardiovascular performance over a period of months.

Methods

PRIMARY OPERATIVE PROCEDURE

Mongrel dogs, weighing 12 to 18 kg, were anesthetized with pentobarbital and the main pulmonary artery of each was constricted by tightening a double-cellophane band around the pulmonary artery. In the open chest animal undergoing positive pressure ventilation the band was fixed at the point at which right ventricular diastolic pressure just failed to increase (systolic pressure, 40 to 55 mm Hg). An Ivalon sponge strip was placed loosely around the cellophane band to prevent erosion of the pulmonary artery; erosion was not seen in any of the dogs. After recovery, the dogs were trained on a treadmill, and the maximal rate at which each animal was capable of running was roughly determined.

Six dogs (dogs 1 to 6) were studied two and one-half to three months after operation. One of these (dog 6) was studied again two weeks after the first study. Three of the six dogs (dogs 3, 4, and 6) were restudied six to nine months after the initial operation.

EXERCISE PROCEDURE

The dogs were exercised on a horizontal treadmill running at different but constant speeds for three or four successive bouts, of six-minute duration each, without intervening rest periods. The treadmill speed was increased by increments of 2 or 3 kilometers per hour (km/hr) up to a maximal speed between 9 and 10 km/hr which was maintained for three or six minutes. The maximal speed for two dogs was 7.6 km/hr. In the second study (nine months), the plane of the treadmill was tilted to 10 degrees to increase the severity of exertion. Dragging on the shoulders of the dog on the treadmill indicated that the limit of tolerance had been reached. None of the dogs fainted under the maximal strain.

DETERMINATION OF DEGREE OF NARROWING OF PULMONARY ARTERY

The cross-sectional area of the constricted portion of the pulmonary artery was determined from an angiocardiogram made with a Westinghouse Cinefluorax while the animal was anesthetized and lying on the right side. Test injections were made during fluoroscopy to obtain the optimal projection, and filming was carried out with injection of sodium diatrizoate and mebrofenine diatrizoate (60% Renovist) (2 ml/kg of body wt). Assuming the orifice to be circular, the cross-sectional area was calculated from the diameter (fig. 1) corrected for magnification by means of a steel bar notched at 1-cm intervals and inserted into the X-ray beam at the level of the pulmonary artery. The constriction was expressed as a fraction of the mean cross-sectional area of the pulmonary artery before constriction, determined as one-half the sum of systolic area and...
diastolic area. Following constriction there was no change in diameter with the cardiac cycle. The measurements of orifice size at necropsy agreed within 10% with those determined from the angiocardiogram.

PREPARATION OF DOGS FOR EXERCISE STUDY WITHOUT GENERAL ANESTHESIA

The animals were placed on a worktable on which they had been restrained previously for one to two hours on several occasions. One carotid artery was exposed after administration of a local anesthetic, and needles of large diameter were placed percutaneously in one or both jugular veins. Catheters were introduced and, under fluoroscopic and manometric control, manipulated into the right ventricle, the right atrium, and the carotid artery. The catheters were secured by means of a few stitches to the skin to prevent them from slipping out of position. A Kifa Teflon catheter with an outer diameter of 2.3 mm and an inner diameter of 1.2 mm was present in a wide loop so that its tip was maintained in the outflow tract of the right ventricle. On no occasion was this catheter displaced from the ventricle. The other catheters were no. 6 Lehman catheters, 80 cm long.

PRESSURE MEASUREMENTS

Statham strain-gauge transducers were used to measure simultaneously right ventricular, right atrial, and systemic arterial pressures. To avoid artifact due to high frequency motion, the catheter-manometer systems provided a flat response to frequencies of 5 to 12 cycles/sec with a rapid cut-off to components of higher frequency. The zero reference point was set at midchest while the dog was standing on the treadmill and changes in zero were monitored by encircling the chest with a hose filled with water to the zero level and connected to a strain-gauge manometer. To compensate for apparent changes in intravascular pressures associated with movement in the vertical plane, hydrostatic pressure variations in the tube relative to the established zero during exercise were recorded and added to or subtracted from the intravascular pressures.

Cardiac output was measured using the dye-dilution technique. Indocyanine green dye (Cardio green) was injected into the right atrium in a concentration of 1.25 mg/ml. Arterial blood was sampled continuously from the carotid artery by a vacuum suction system and drawn through a densitometer for recording the dilution curves. After the experiment, the densitometer was calibrated with aliquots of the animal's blood containing known concentrations of indocyanine green. Flow values were related to surface area calculated according to Meeh's formula.

Stroke work \((W)\) (pressure \(\times\) volume \([P \cdot V]\)) was calculated from the formula:

\[
W = \frac{SV' \times P_{RV}}{100} \quad \text{for the right ventricle} \\
W = \frac{SV' \times P_{LV}}{100} \quad \text{for the left ventricle (LV)}.
\]

\(SV'\) = stroke volume (grams),
\(P_{RV}\) = mean right ventricular systolic pressure (cm H\(_2\)O),
\(P_{LV}\) = mean aortic pressure (cm H\(_2\)O).

The kinetic component \(\left(\frac{MV^2}{2g}\right)\) of the ventricle.

\*Recordings at rest of pulmonary artery pressure proximal to the constriction were identical to right ventricular pressure.
First study of cardiovascular variables during exercise after banding of the pulmonary artery in one dog. The solid area at the bottom of the graph shows running speed. The period of observation was 30 minutes, with measurements taken between the second and third minutes, and at three-minute intervals thereafter. At the fastest rate pulsus alternans occurred with a marked difference between strong and weak beats for the right ventricle (solid circles joined by vertical lines). Note the prompt return to control values at the end of exercise.

Right ventricular stroke work was calculated from:

$$W_{RV} = \frac{SV \times V}{E \times g};$$

where

- $V$ = acceleration work for right (RV) and left (LV) ventricles (grammeters).
- $SV$ = stroke volume (milliliters).
- $A$ = area ($cm^2$) of the constricted segment of pulmonary artery for $W_{RV}$ and mean area of the aortic root ($systolic area + diastolic area$)

for $W_{LV}$. These cross-sectional areas were calculated from angiograms for both great arteries.

$E$ = ejection time (seconds). For reasons to be presented later, $E$ for the calculations of the $W_{RV}$ was taken as the duration of the entire cardiac cycle and for $W_{LV}$ from the beginning of the upstroke to the dicrotic notch of the aortic pressure pulse.

$$q = 980.6 \text{ cm/sec}^2$$

Results

First study after pulmonary artery constriction

The first study was carried out two and one-half to three months after banding. For the dogs at rest, the average right ventricular systolic pressure was 89 mm Hg (range, 53 to 111 mm) and the end diastolic right ventricular pressure was less than 5 mm Hg in three dogs, between 5 and 10 mm in two dogs, and between 10 and 15 in one. The average cross-sectional area of the constricted segment of pulmonary artery was 0.28 cm$^2$ (range, 0.18 to 0.49 cm$^2$). The average degree of constriction was 84% (range, 80 to 87%).

Figure 2 demonstrates a representative response obtained in one dog in which the area after constriction was 0.18 cm$^2$. Right ventricular systolic pressure (94 mm Hg at rest) increased steadily throughout exercise and stroke volume remained virtually constant. At the maximal tolerated speed, a regular pulsus alternans supervened, the strong beat reaching 228 mm Hg and the weak beat, 118 mm Hg. The diastolic right ventricular pressure increased from 2 to 20 mm Hg. The arterial pressure changed from 135/88 (mean, 104) at rest to 172/73 (mean, 106) mm Hg during the most severe bout. Right ventricular stroke work ($P.V$) increased from 11 to 23 grammeters (fig. 2). The kinetic component represents 36% at rest, and 70% during maximal effort of the total right ventricular stroke work. Because of difficulty in determining the precise end of right ventricular systole at faster heart rates (fig. 3), the time of the entire cardiac cycle was used for ejection time. These figures for the kinetic work component for the right ventricle ($W_{RV}$) are therefore minimal values. However, since the fraction of the cardiac
Intravascular pressure pulses during the transition from rest to 7.6 km/hr in a dog with banded pulmonary artery. Note the development of a pulsus alternans of progressive severity over 30 seconds. Thereafter the difference between strong and weak beats is constant. b. Pressures recorded at higher chart rate during pulsus alternans.

Heart rate = 180 beats/min.

cycle occupied by systole certainly decreases during exercise, the relative change in \( W_a \) cannot be stated. Since mean aortic blood pressure is unchanged, the total left ventricular stroke work (\( W_{LV} + W_{aLV} \)) was not significantly altered by exercise (18.90 to 20.75 grammeters). The acceleration work accounted for 0.7% of the total figure at rest, and 4% during maximal effort.

Values for cardiac index, heart rate, and
First study after banding of pulmonary arteries. Values for cardiac index, heart rate, and stroke volume for all six dogs (dogs 1 to 6). The superscripts I and II refer to studies separated by two weeks on dog 6. Running speed is indicated at the bottom of each graph. The value for each variable is the average of two determinations. The broken line indicates that no observation was made at the intermediate running speed.
stroke volume in all dogs are given in figure 4. The cardiac index increased by an average of 102% and the heart rate by 90%. Stroke volume was not significantly affected by exercise, the average increase being 12% (range +46 to −17%). Since the duration of systole is greatly shortened, the rate of cardiac ejection is increased. The peak right atrial pressure averaged 3.5 mm Hg at rest and 24 mm Hg during exercise (fig. 5). Three animals (dogs 2, 4, and 6) in which atrial pressures greater than 20 mm Hg were developed during exercise were unable to run at treadmill rates exceeding 7.6 km/hr. Dog 2 showed evidence of tricuspid regurgitation with a resting pressure of 17 mm Hg which increased during exercise to a peak atrial pressure of 39 mm Hg. The right ventricular systolic pressure increased greatly in all of the dogs. The right ventricular end diastolic pressure changed in the manner of the right atrial pressure.

The average increase in right ventricular stroke work was 100% (fig. 6), mainly due to the increase in its kinetic fraction.

Pulsus alternans appeared in four of the six dogs during exercise. Dog 6, which was studied on two occasions, two weeks apart, showed evidence of pulsum alternans only during the first study. Pulsus alternans was never seen while the dogs were at rest; it started at the first bout of exercise in two dogs (dogs 2 and 6) but did not immediately hinder the continuance of exercise. The difference between the strong and the weak beat increased with the severity of the exertion. Pulsus alternans was not observed in any dog with a heart rate of less than 180 beats/min nor with a systolic right ventricular pressure of less than 140 mm Hg, and did not occur in two dogs even with heart rates of 276 and 221 beats/min and with right ventricular sys-
Comparison of cardiac indices obtained two and one-half to three months (I) and nine months (II) after banding. The values are similar.

Systolic pressures of 158 and 146 mm Hg, respectively. The greatest pressures seen in any animal with pulsat alternans were 228 and 118 mm Hg for the strong and the weak beat, respectively (dog 2).

Pulsus alternans was not accompanied by electrocardiographic change and therefore was thought to occur on a mechanical basis. The aortic pressure showed concordant pulsat alternans with the difference between strong and weak beats never in excess of 25 mm Hg. There was no obvious relationship between right ventricular end diastolic pressure and the pressure generated by the next beat. Pulsus alternans promptly disappeared with the cessation of the exercise.

SECOND STUDY AFTER PULMONARY ARTERY CONSTRICTION

For the three dogs (dogs 3, 4, and 6) re-studied six to nine months after pulmonary artery constriction, an attempt was made to increase the severity of the exercise by increasing the treadmill speed of the first study and by inclining the treadmill to an angle of 10 degrees from the horizontal.

One dog was unable to improve its performance; another ran at a higher rate than previously, and the third accepted the additional stress of the inclined treadmill. The cardiac index of dog 6 decreased during the highest degree of exercise. Dog 3, although running at 7.6 km/hr at the increased treadmill angle, did not increase its cardiac index.

Data obtained from the second study correlate well with data from the first study (fig. 7). The stroke volume showed slight variations, which are similar to those observed during the first study. The right ventricular systolic pressure (fig. 8) averaged 106 mm Hg (range, 120 to 88) at rest, an average increase of 9 mm Hg compared with the values for the same dogs at the first study.

The right atrial pressure, right ventricular stroke work, and systemic arterial pressure during exercise in the second study, showed changes similar to those observed in the first study.

Discussion

These dogs, with significant obstruction to right ventricular outflow, were capable of performing substantial levels of work as evidenced by exercising on a treadmill. The average resting stroke volume in our animals was less than that found by Wang and associates, and the animals with the least exercise tolerance (lowest maximal treadmill speed) showed the lowest cardiac output. However, the increment during exercise was of the same order of magnitude as that reported for normal animals studied under similar conditions. During exercise, the increase in cardiac output was paralleled by the increase in heart rate, resulting in values for stroke volume that did not change significantly. Heart rate rather than stroke volume is a major variable in these, as in normal dogs under conditions of exercise. The myocardial component of such a response appears to lie in the more rapid ejection of the same stroke volume.
between the right ventricular pressure and stroke volume during pulsus alternans, calculation of stroke work \((P\cdot V)\) based on average values for stroke volume and right ventricular mean systolic pressures seems reasonably valid. However, \(W_a\) is related to the cubic power of \(SV\), and thus \(W_{aRV}\) is underestimated significantly in the presence of right ventricular pulsus alternans.

Changes in atrial and venous pressures and cardiac output during exercise in dogs with tricuspid and pulmonary valve lesions have been described.\(^\text{16}\) In regard to right ventricular function a few factors are deserving of brief comment:

1. Associated with the increase in heart rate, the systolic time was shortened markedly, although the precise end of systole could not be determined with certainty (fig. 3). In order to eject an unchanged stroke volume, the ventricle must have contracted more effectively as evidenced by the rate of increase in intraventricular pressure.

2. The right atrial pressure prior to exercise was within the normal range in five of the six dogs (dog two had mild tricuspid incompetence) but became abnormally elevated in all exercising animals. Difficulties of measurement and compensation for zero shift notwithstanding, the magnitude of the changes were such that increases of at least 15 mm Hg in right atrial pressure occurred. The performance of each dog was inversely related to its initial atrial pressure as observed by Barger and associates\(^\text{18}\) in dogs with valve lesions of varying severity; that is, animals with a higher atrial pressure before or in the early phases of exercise had less change in cardiac output and lower maximal running speeds. Individual animals showed a progressive increase in both cardiac output and right atrial pressure at faster running rates. At maximal running rate, each animal had a right atrial pressure exceeding 15 mm Hg. This level of pressure was usually, but not always, attained when right ventricular systolic pressure approached left ventricular systolic pressure. At these faster heart rates and increased pressure within the wall of the greatly hypertrophied right ventricle, coronary blood flow may well be impaired.\(^\text{17}\)

3. At faster heart rates and increased atrial pressure levels the animals appeared distressed, tended to drag on their chains, and frequently urinated and defecated. On cessation of exercise, the dogs recovered imme-
No animals had a syncopal reaction similar to that seen in certain forms of heart disease characterized by right ventricular outflow obstruction. Acute venous distention due to the inability of the right ventricle to transmit the returning blood may have produced the limiting symptoms.

4. That a cyclical metabolic debt is the basis for the pulsus alternans is an attractive hypothesis. Right ventricular myocardial blood flow may be continuous during the weak beat to permit the establishment of biochemical conditions for the strong, forceful contraction of the succeeding beat. During this cardiac cycle the coronary flow might be reduced to a level at which only a weak contraction is metabolically possible. The reproducible level of pressures for strong and weak beats for a given heart rate and stroke volume may favor such reasoning.

5. From the three animals studied at two and one-half to three months and at six to nine months after banding, it is evident that no significant change in cardiovascular status occurred during the intervening months and that the compensatory change in right ventricular function had occurred in the first eight to ten weeks after banding. This is in accord with the experience of Donald and Kirklin who demonstrated electrocardiographic changes in dogs indicative of progressive right ventricular hypertrophy 17 days after banding. No evidence of cardiac failure of late onset was seen either in the six dogs of the present study or in 14 dogs that were observed up to 14 months in another study. The values given by Davis and co-workers suggest that a reduction of 90% in the cross-sectional area of the pulmonary artery was necessary to produce chronic heart failure in unanesthetized dogs.

Summary

In dogs, the pulmonary artery was constricted by banding; the cross-sectional area of the pulmonary artery after banding averaged 16% of the prebanded area. The right ventricular pressure in six unanesthetized dogs at rest averaged 89 mm Hg two and one-half to three months following constriction and 106 mm Hg in three of these when studied nine months following constriction.

All animals were studied during exercise on a treadmill. A doubling of the cardiac output during exercise was achieved by increasing the heart rate, while the stroke volume remained unchanged. The duration of systole decreased. Right ventricular systolic pressure increased markedly during exercise. The highest right ventricular pressure in dogs free of pulsus alternans was 158 mm Hg. A regular pulsus alternans usually supervened at heart rates in excess of 180 beats/min. Under these circumstances the maximal pressure generated was 228 mm Hg. Average right atrial pressure increased from 3.5 to 24 mm Hg. The right ventricular stroke work was somewhat less than that of the left ventricle at rest but exceeded it during exercise in these experiments.

The compensation for chronic obstruction to right ventricular outflow was fully operative two and one-half months after banding, and no significant change in performance was observed later.

References


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Circ Res. 1963;13:410-419
doi: 10.1161/01.RES.13.5.410

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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