Induced Pressure Gradients Across Infundibular Zone of Right Ventricle in Normal Dogs

By John R. Tobin, Jr., M.D., Peter E. Blundell, M.D., Ralph G. Goodrich, and H. J. C. Swan, M.B., Ph.D., M.R.C.P.

During investigations of the effects of sympathomimetic amines on ventricular function in normal dogs, significant pressure gradients were observed frequently across the right ventricular outflow tract. The magnitude of these pressure gradients was greatest in anesthetized animals infused with isopropylarterenol. Since no detailed description of such functional right ventricular outflow-tract pressure gradients was found in the literature, studies on the occurrence and mechanism of this phenomenon were initated.

These experiments demonstrated that infusions of isopropylarterenol induce pressure gradients, which are largest in late systole, between the sinus of the right ventricle and the pulmonary artery; that the magnitude of these pressure gradients always is increased by the prior administration of either acetyl strophanthidin or calcium chloride, and that the genesis of these pressure gradients apparently depends on early vigorous contraction of the infundibulum of the right ventricle.

Methods

PREPARATION OF DOGS

Mongrel dogs weighing 12 to 18 kg were anesthetized with pentobarbital and restrained in the supine position. One carotid artery and both jugular veins were exposed. Number 6 Lehman catheters were introduced and, under fluoroscopic and manometric control, manipulated into the pulmonary artery, the sinus of the right ventricle, and the aortic arch. Number 5 Lehman catheters were introduced into the superior vena cava for the injection of indocyanine green and into a jugular vein for the infusion of drugs.

INSTRUMENTATION

Statham strain-gauge transducers with equal sensitivities were used to measure simultaneous pressures which were recorded on the same base line. The assembly for calibration of zero reference levels at midthorax and the sensitivities of multiple manometers in situ have been described. The catheter-manometer systems used have frequency responses which are uniform to between 15 and 20 cycles/sec.

When three pressure pulses were recorded simultaneously and at the same sensitivities from three sites (the sinus and infundibulum of the right ventricle and the pulmonary artery) in open-chest dogs, special catheter-manometer systems were used. These consisted of flanged, 19-gauge, thin-walled needles, 1 cm long; nylon tubing with an internal diameter of 0.039 inch and a length of 12 cm; P23DB Statham strain-gauge transducers; and 40-350 Heiland galvanometers which were electrically damped by 300 ohms resistance. The frequency response of such systems is uniform to 35 cycles/sec with variability of ± 10%.

Cardiac output was measured by the indicator dilution technic. Indocyanine green (cardio-green), 1.0 to 1.5 ml, was injected into the superior vena cava in a concentration of 1.25 mg/ml. Arterial blood was sampled continuously from the aortic arch by a vacuum suction system and drawn through a densitometer, model XC-100, Waters Corporation, for recording of the dilution curves. After each experiment, the densitometer was calibrated with aliquots of the animal's blood containing known concentrations of indocyanine dye. Values for cardiac output were calculated by standard methods.

Stroke volume was obtained by dividing the cardiac output by the heart rate.

To determine the exact time of pulmonary valve closure, a phonocardiogram was recorded from the right parasternal area at the level of the third interspace by means of a Sanborn impedance.
microphone with a diaphragm, a Sanborn logarithmic amplifier, and a Heiland-C galvanometer with a frequency response from 0 to 225 cycles/sec and a variability of ± 4%. Lead II of the electrocardiogram was recorded and used as an additional timing reference to the cardiac cycle.

**EXPERIMENTAL PROCEDURE**

When relative stability was attained, control observations (control 1), which included the recording of indicator dilution curves and pressure pulses, were made during a ten-minute period. Then, isopropylarterenol (Isuprel hydrochloride, Winthrop Laboratories) was infused at a constant rate of 2.5 μg/min by means of a Harvard syringe. After six minutes of infusion, indocyanine green-dye curves and pressure pulses were again recorded. The rate of infusion was increased to 5.0 μg/min, and after a second six-minute interval of infusion, the same variables were recorded. An exact twelve-minute time interval was permitted to elapse and another set of records (control 2) was obtained.

When acetyl strophanthidin or calcium chloride was used, control 2 was followed by the injection of 0.5 mg of acetyl strophanthidin or 40 mg/kg of calcium chloride. A twelve-minute interval was permitted to elapse and variables were recorded again (control 3). Isopropylarterenol infusions and subsequent experimental procedures were done also in the manner just described.

**CALCULATIONS**

Figure 1 illustrates the method used to measure the systolic ejection period. The mean right ventricular (sinus) pressure (RVsm) and the mean pulmonary arterial pressure (PAsm) during systolic ejection were calculated by conventional planimetry. The mean pressure gradient during systolic ejection (SGm) was obtained by subtraction of the mean pulmonary arterial pressure from the mean right ventricular (sinus) pressure. The mean pressure gradient was divided by the mean right ventricular (sinus) pressure to express the magnitude of the pressure gradient in relationship to the ventricular pressure.

**Results**

**ISOPROPYLARTERENOL (TABLE 1)**

The effects of isopropylarterenol infusion on right ventricular outflow-tract pressure gradients in a normal dog are illustrated in figure 2.
Responses of this magnitude were found in one third of the studies. The data which describe the effects of isopropylarterenol infusion in nine normal dogs are listed in table 1.

The infusion of isopropylarterenol at 2.5 μg/min increased right ventricular pressure by an average of 6.0 mm Hg and increased the mean pressure gradient by an average of 6.0 mm Hg. The pulmonary arterial pressure was unaltered. A significant increase of heart rate resulted in an average increase of cardiac output by 0.62 liter/min. The systolic ejection period was unchanged. When the infusion rate of isopropylarterenol was increased to 5.0 μg/min, the average increase of the outflow-tract pressure gradient during systolic ejection was 8.0 mm Hg.

**ACETYL STROPHANTHIDIN AND ISOPROPYLARTERENOL (TABLE 2)**

The effects of isopropylarterenol infusion on right ventricular outflow-tract pressure gradients in a normal dog 12 minutes after the infusion of 0.5 mg of acetyl strophanthidin are illustrated in figure 3. The data which describe the effects of isopropylarterenol infusion in four normal dogs, after the infusion of 0.5 mg of acetyl strophanthidin, are listed in table 2.

The infusion of isopropylarterenol at a rate of 2.5 μg/min increased right ventricular pressure by an average of 21 mm Hg and increased the mean pressure gradient by an average of 19 mm Hg. There was a small and inconsistent increase of pulmonary arterial pressure (average 3.0 mm Hg). A consistent increase of heart rate (average 36 per minute) was primarily responsible for the average increase in cardiac output of 0.65 liter/min and for a shortened systolic ejection period. When the infusion rate of isopropylarterenol was increased to 5.0 μg/min, the average increase...
INFUNDIBULAR PRESSURE GRADIENTS IN DOGS

of the outflow-tract pressure gradient during systolic ejection was 26 mm Hg.

CALCIUM CHLORIDE AND ISOPROPYLAERENOL (TABLE 3)

The effects of isopropylarlenol infusion on right ventricular outflow-tract pressure gradients in a normal dog 12 minutes after the infusion of 40 mg/kg of calcium chloride are illustrated in figure 4. The data which describe the effects of isopropylarlenol infusion in three normal dogs after the infusion of 40 mg/kg of calcium chloride are listed in table 3.

The infusion of isopropylarlenol at a rate of 2.5 μg/min increased right ventricular pressure by an average of 20 mm Hg and increased the mean pressure gradient by an average of

![Diagram](image)

**FIGURE 2**
Isopropylarlenol-induced right ventricular outflow-tract pressure gradients in normal dog weighing 12.5 kg. Two control gradients also shown.

![Diagram](image)

**FIGURE 3**
Effects of acetyl strophanthidin on isopropylarlenol-induced right ventricular outflow-tract pressure gradients in normal dog weighing 12.5 kg. Infusion of isopropylarlenol administered 12 minutes after infusion of acetyl strophanthidin, 0.5 mg.
<table>
<thead>
<tr>
<th>Experimental period</th>
<th>Heart rate</th>
<th>Stroke volume</th>
<th>Cardiac output</th>
<th>Systolic ejection period</th>
<th>RVsm*</th>
<th>PAsm*</th>
<th>Pressure gradient % of RVsm*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Control</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Average</td>
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<td>2.50</td>
<td>0.176</td>
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<td>16</td>
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<td>Range</td>
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<td>13.9 to 21.1</td>
<td>1.90 to 3.30</td>
<td>0.158 to 0.200</td>
<td>18</td>
<td>14</td>
<td>1 to 12</td>
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<td></td>
<td></td>
<td></td>
<td>5 to 46</td>
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<tr>
<td>B. Isopropylarterenol, 2.5 μg/min</td>
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<td></td>
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<tr>
<td>Average</td>
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<td>19</td>
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<td>-1</td>
<td>5 to 12</td>
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<td></td>
<td>12 to 24</td>
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<td>C. Isopropylarterenol, 5.0 μg/min</td>
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<tr>
<td>Average</td>
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<td>18.6</td>
<td>3.34</td>
<td>0.150</td>
<td>46</td>
<td>15</td>
<td>31</td>
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<td>0.137 to 0.158</td>
<td>38</td>
<td>12</td>
<td>25 to 41</td>
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<td>60 to 73</td>
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<tr>
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<td>0.74</td>
<td>-0.027</td>
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<td>26</td>
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<td>Range</td>
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<td>-0.09 to 1.20</td>
<td>-0.045 to -0.007</td>
<td>14</td>
<td>-7</td>
<td>3 to 21 to 37</td>
</tr>
</tbody>
</table>

*RVsm is the mean systolic right ventricular (sinus) pressure; PAsm is the mean systolic pulmonary arterial pressure.

†Discrepancies between the mean of individual differences and the apparent arithmetic mean differences are the result of rounding numbers for average values.
<table>
<thead>
<tr>
<th>Experimental period</th>
<th>Heart rate</th>
<th>Stroke volume</th>
<th>Cardiac output</th>
<th>Systolic ejection period</th>
<th>RVsm*</th>
<th>PAsm*</th>
<th>Pressure gradient</th>
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<tr>
<td></td>
<td>ml</td>
<td>liters/min</td>
<td>sec</td>
<td>mm Hg</td>
<td>mm Hg</td>
<td>mm Hg</td>
<td>% RVsm</td>
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<td>A. Control</td>
<td></td>
<td></td>
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<td></td>
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<td>0.182</td>
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<td>132 to 156</td>
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<td>1.70 to 2.95</td>
<td>0.174 to 0.188</td>
<td>12 to 24</td>
<td>11 to 17</td>
<td>1 to 7</td>
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<tr>
<td>B. Isopropylarterenol, 2.5 μg/min</td>
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<td></td>
<td></td>
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<tr>
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<td>3.71</td>
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<td>3.43 to 3.98</td>
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<td>38 to 40</td>
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<td>18 to 24</td>
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<td>1.42</td>
<td>-0.022</td>
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<td>-0.033 to -0.011</td>
<td>14 to 28</td>
<td>1 to 5</td>
<td>13 to 23</td>
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<tr>
<td>C. Isopropylarterenol, 5.0 μg/min</td>
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<td></td>
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<tr>
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<td>170</td>
<td>22.1</td>
<td>3.81</td>
<td>0.153</td>
<td>38</td>
<td>15</td>
<td>23</td>
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<tr>
<td>Range</td>
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<td>19.9 to 24.0</td>
<td>3.08 to 4.90</td>
<td>0.137 to 0.170</td>
<td>29 to 43</td>
<td>11 to 17</td>
<td>18 to 27</td>
</tr>
<tr>
<td>Difference between A and C</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean of differences</td>
<td>28</td>
<td>6.0</td>
<td>1.51</td>
<td>-0.023</td>
<td>19</td>
<td>1</td>
<td>19</td>
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<tr>
<td>Range</td>
<td>-18 to 66</td>
<td>3.0 to 11.7</td>
<td>0.13 to 3.20</td>
<td>-0.046 to 0.18</td>
<td>5 to 31</td>
<td>-6 to 5</td>
<td>11 to 26</td>
</tr>
</tbody>
</table>

*RVsm is the mean systolic right ventricular (sinus) pressure; PAsm is the mean systolic pulmonary arterial pressure.
†Discrepancies between the mean of individual differences and the apparent arithmetic difference are the result of rounding numbers for average values.
16 mm Hg. There was a small but consistent increase of pulmonary arterial pressure (average, 4.0 mm Hg). A larger cardiac output was the product of consistent increases of heart rate and stroke volume. When the infusion rate of isopropylarterenol was increased to 5.0 µg/min, the average increase of the outflow-tract pressure gradient during systolic ejection was 19 mm Hg.

The means of the differences between values obtained at the two levels of isopropylarterenol infusion were evaluated for all experiments. In each instance the differences were small and inconsistent excepting for the small increases in the outflow-tract pressure gradients.

Comment

"... I do not think that either clinicians or physiologists have yet fully perceived the bearings which this theory (incorporation of the bulbus cordis into the right ventricle as the infundibulum) has on the constitution and action of the normal heart."—Sir Arthur Keith

At the conclusion of our initial experiments (table 1), it was apparent that right ventricular outflow-tract pressure gradients could be induced by isopropylarterenol in normal dogs; but if the genesis of such pressure gradients was to be investigated, an invariably successful method of producing them was desirable. The infusion of epinephrine or norepinephrine at 10 µg/min induced significant right ventricular outflow-tract pressure gradients in 10% of studies, but the magnitudes of such responses were invariably less than those attained with isopropylarterenol. Left ventricular outflow-tract pressure gradients have been induced in normal dogs by several investigators. These investigators either infused sympathomimetic amines or combined such infusions with a procedure which reduced the stroke volume. Our right ventricular outflow-tract pressure gradients were not effectively magnified by either prior phlebotomy or infusion of massive concentrations of isopropylarterenol.

Isopropylarterenol enhances the rate and force of myocardial contraction. If the inotropic effect were primarily responsible for the development of the right ventricular outflow-tract pressure gradients in normal dogs, other agents which enhance the force of myocardial contraction might be additive and magnify those pressure gradients. The experi-
ments detailed in tables 2 and 3 showed that the right ventricular outflow-tract pressure gradients induced by isopropylarterenol in normal dogs are indeed enhanced by the prior administration of either acetyl strophanthidin or calcium chloride.

Figure 5 summarizes graphically the average results of these experiments. The pressure gradients varied for different experimental periods, with respect to both the absolute values and their percentage relationship to the ventricular pressures. When the pressure gradient increased, right ventricular pressure increased simultaneously, but the pulmonary arterial pressure did not rise.

The infusion of isopropylarterenol at 5.0 μg/min produced responses which did not differ substantially from those obtained with 2.5 μg/min. The infusion of acetyl strophanthidin or calcium chloride alone did not induce right ventricular outflow-tract pressure gradients which differed significantly from those observed during control periods. Yet, the administration of either acetyl strophanthidin or calcium chloride, prior to the infusion of isopropylarterenol at 2.5 μg/min, resulted in responses which greatly exceeded those accompanying the infusion of isopropylarterenol alone. These observations indicate that isopropylarterenol was primarily responsible for the genesis of these gradients and its effect was probably maximal, but pretreatment with acetyl strophanthidin and calcium chloride resulted in a substantially greater infundibular contraction. Thus, a mechanism other than simple inotropic stimulation may be induced by the addition of these substances. The data indicate that the relatively small increases in cardiac output were not major factors in the genesis of these pressure gradients.

Braunwald and co-workers, in reporting studies of hypertrophic subaortic stenosis in man, emphasized the variable nature of the pressure gradients between the left ventricle and the brachial artery and suggested that this variability depends on changes in the

<table>
<thead>
<tr>
<th>MEAN PRESSURES (mm Hg)</th>
<th>Calcium Chloride</th>
<th>Acetylstrophanthidin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (9, Mean and ± S.D.)</td>
<td>Isopropyl-arterenol (μg)</td>
<td>Isopropyl-arterenol (μg)</td>
</tr>
<tr>
<td>Control 2.5 5.0</td>
<td>Control 2.5 5.0</td>
<td>Control 2.5 5.0</td>
</tr>
</tbody>
</table>

Hemodynamic features of isopropylarterenol-induced right ventricular outflow-tract pressure gradients in normal dogs (average values).

Circulation Research, Vol. XVI, February 1965
Simultaneously recorded pressure pulses from sinus and infundibulum of right ventricle and from pulmonary artery during filming of cineangiogram of outflow tract of right ventricle of a 14-kg dog. Cineangiogram marker (above) identifies timing of individual frames (I-IV) reproduced to right. Note the contraction of infundibulum (frame III) associated with rising sinus pressure and falling infundibular pressure. Diagonal line traversing record indicates syringe travel during injection of Renovist (mixture of sodium and methylglucamine diatrizoates) 30 ml.

Simultaneously recorded pressure pulses from sinus and infundibulum of right ventricle and from pulmonary artery during filming of cineangiogram of outflow tract of right ventricle of the right ventricle during systole and that the cross-sectional area of the lowest portion of the outflow tract is smallest in late systole.

The classic studies of Keith\textsuperscript{3} demonstrated that the bulbus cordis appears in a developmental stage of the heart in all vertebrate embryos and that it does not disappear from the mammalian heart but becomes incorporated into the right ventricle, forming the outflow tract or infundibulum. There is ample evidence that in normal sequence the sinus of the right ventricle is activated and contracts before the infundibulum.\textsuperscript{12} If the sequence of right ventricular activation or contraction were altered, premature contraction of the infundibulum might be responsible for the right ventricular outflow-tract pressure gradients induced in these normal dogs.

The sequence of ventricular activation was
Effects, in a 20-kg dog, of isopropylarterenol-induced pressure gradients on temporal relationships of peak electromyographic potentials recorded directly from body (A) and infundibulum of right ventricle (B).

investigated by implanting bipolar electrodes in the right ventricular wall of two open-chest dogs (fig. 7). One electrode (A) was placed in the anterior wall in the region of the anterior papillary muscle, and the second (B) was placed in the outflow tract immediately beneath the pulmonary valve. Under controlled conditions, the maximum peak potential recorded from electrode A preceded the maximum peak potential from electrode B by 19 msec. When large gradients were produced in the manner previously described, the sequence of ventricular activation was not altered.

The nature of right ventricular contraction was also investigated by analysis of the pressure pulses recorded directly from the sinus and infundibulum of the right ventricle and from the pulmonary artery in open-chest dogs (fig. 8). When pressure gradients were induced, the initiation sequence of contraction was not altered, but the contours of the pressure pulses and the time intervals between them were altered. The interval between the onset of contraction in the sinus and in the infundibulum decreased to 10 msec, and the interval between the peak pressures (infundibular peak preceding sinus peak) increased to 46 msec. The infundibular systolic pressure became similar to the systolic pulmonary arterial pressure, rising sharply to an attenuated peak and falling abruptly to the level of pulmonary arterial diastolic pressure as the pressure in the sinus of the ventricle continued to rise to a delayed peak. These pressure pulse contours are similar to those described by Rodbard and Shaffer and Johnson in patients with muscular (functional) infundibular stenosis.

Altered tonus of the infundibular portion of the right ventricle has been suggested as a mechanism involved in the "cyanotic spells" associated with tetralogy of Fallot, in the reduction of left-to-right shunts associated with ventricular septal defects, and in the persistence of right ventricular outflow-tract pressure differences after pulmonary valvulotomy. It has been assumed that these findings were characteristic of the hypertrophied infundibulum of the diseased heart. However, our experiments demonstrate that severe right ventricular outflow-tract pressure gradients
can be induced in normal dogs by drugs which alone or in combination alter the rate and force of cardiac contraction.

**Summary**

In these experiments we have demonstrated that:

1. Right ventricular outflow-tract pressure gradients of significance can be induced in normal dogs by a sympathomimetic amine which increases the rate and force of ventricular contraction.

2. Such outflow-tract pressure gradients are magnified by the addition of other inotropic drugs, such as acetyl strophanthidin and calcium chloride.

3. These outflow-tract pressure gradients are not the result of an increase in the volume and rate of blood flow but are due to forceful contraction of the infundibulum.

**References**


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