Epinephrine in the Treatment of Cardiac Failure due to Shunts

By Abraham M. Rudolph, M.D., Emmanuel Mesel, M.D., and Jay M. Levy, M.D.

Cardiac failure frequently occurs in infants with congenital heart lesions associated with left-to-right shunts. The development of cardiac failure may be correlated chronologically with the postnatal changes in the pulmonary vasculature, resulting in a decreased pulmonary vascular resistance. The presence of a moderate or large communication between the pulmonary and systemic circulation permits a left-to-right shunt, the magnitude of which increases as pulmonary vascular resistance falls. Since the left ventricular output is increased in an attempt to maintain an adequate systemic blood flow, a marked increase in the volume load on the ventricle ensues. Left ventricular end-diastolic and left atrial pressures increase, and cardiac failure may supervene.

The accepted therapeutic measures for cardiac failure include digitalization and administration of diuretics and oxygen. Although most infants respond to these measures, occasionally cardiac failure persists, necessitating surgical intervention, such as division or ligation of a patent ductus arteriosus or pulmonary arterial banding. Symptoms and signs of failure may, however, progress so rapidly with increasing pulmonary edema that the infant may succumb before a surgical procedure can be accomplished.

The effects of various therapeutic measures in the management of acute cardiac failure due to shunts have been studied in animals with an induced aorto-pulmonary communication. The size of the shunt could be controlled by a balloon device incorporated into a silicone rubber prosthesis that was used to produce the aorto-pulmonary communication. In many animals, acute cardiac failure could be induced by widely opening the shunt to its full diameter; and, if not controlled, death of the animal ensued within a few minutes. Cardiac failure could be rapidly corrected by closing the shunt completely. The effectiveness of a number of pharmacologic agents in preventing the development of failure on opening the shunt, or reversing the failure once established, has been evaluated. Epinephrine was found to be the most promising, and the results of epinephrine administration in this experimental preparation are presented in this paper.

In view of the beneficial effect of epinephrine infusion in the experimental studies, the usefulness of this agent in the management of cardiac failure due to similar physiologic derangement in the infant was considered. Its success in the management of three infants with cardiac failure due to shunts is discussed.

Material and Methods

Experimental Studies

The shunt is manufactured from silicone rubber (Dow-Corning). It is U-shaped with an inside diameter of 12 mm. The length is 5 cm. and each end is 3 cm. A flange on each limb facilitates suture onto the aorta and pulmonary artery. The

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center portion is very thin, and covered by a short length of rigid acrylic tube, so as to form an enclosed space. A polyvinyl tube leads from the acrylic jacket and injection of 0.8 to 1.0 ml. of fluid collapses the thin center portion, completely closing the lumen. Removal of the fluid opens the shunt to its full diameter of 12 mm.

Eighteen mongrel dogs weighing 19 to 23 Kg. were investigated in this study. The animals were anesthetized with intravenous sodium pentobarbital in doses of 25 to 30 mg./Kg. Left thoracotomy was performed through the fourth intercostal space, positive pressure respiration being maintained by a Harvard respirator pump. An end-expiratory pressure of 3 cm. of water was maintained to prevent complete collapse of the lung.

A cuff electromagnetic flowmeter probe was applied around the ascending aorta just above the origin of the coronary arteries. The descending aorta just beyond the origin of the left brachiocephalic artery was then mobilized, and a partially occlusive arterial clamp was applied along its anterolateral portion. A longitudinal incision was made, and one limb of the shunt was attached to the edges of this incision by interrupted sutures. The other end of the shunt was similarly applied to the anterior portion of the main pulmonary artery. Air was removed from the shunt through a small needle inserted into the lumen. The shunt was partially opened, the clamps were removed from the aorta and pulmonary artery, and hemorrhage was achieved.

Polyvinyl catheters for pressure measurement were inserted into the left atrium, left ventricle, pulmonary artery, and right ventricle by methods previously described and into the ascending aorta through the left internal mammary artery. All catheters, including that for control of the shunt, and the leads from the flowmeter probe, were passed subcutaneously and exteriorized at the back of the neck. The chest was closed, the lung was re-expanded, and the animal was allowed to breathe spontaneously. After the responses to opening and closing of the shunt were studied, epinephrine was infused into the right ventricular catheter at varying doses, and the effects of opening and closing were restudied.

Pressures were measured by means of Statham P23D transducers, and instantaneous flow tracings were obtained with a gated, sine-wave, electromagnetic flowmeter of the Kolin type. All pressures and flows were recorded by an 8-channel Grass direct-writing oscillograph.*

The flow tracing obtained from the ascending aorta represents total left ventricular output, excluding coronary flow. Since the transducer is proximal to the shunt from the aorta, the total flow measured includes shunt flow and systemic flow when the shunt is opened, and thus is equal to total pulmonary flow.

**Results**

The findings were consistent in all animals studied. Rapid opening of the aorto-pulmonary communication could be accomplished in 1 to 2 seconds, and resulted in the hemodynamic changes demonstrated in figure 1. The aortic systolic and diastolic pressures dropped within one to two beats, and pulse pressure widened markedly. Left ventricular systolic pressure dropped immediately, and left ventricular end-diastolic pressure and left atrial pressure rose rapidly. Pulmonary arterial systolic and diastolic pressures, and right ventricular systolic and end-diastolic pressure all increased. The ascending aortic flow showed a marked increase in stroke volume as measured by integrating the flow tracing over each beat. Heart rate increased moderately. These changes have been described in greater detail elsewhere.

Following these immediate changes, one of two major types of responses occurred. When the animal tolerated the shunt well, there was a slow rise in left ventricular, aortic, pulmonary arterial, and right ventricular systolic pressures, and a gradual fall of left ventricular end-diastolic, left atrial, and right ventricular end-diastolic pressures. Ascending aortic peak flow velocity gradually increased, and a further increase in heart rate occurred.

Closure of the shunt resulted in an immediate increase of left ventricular and aortic systolic pressures above control level, followed by a gradual return to control pressure. Left atrial and left ventricular end-diastolic pressures dropped precipitously and then more slowly to control levels. These changes have been described in detail and are demonstrated in figure 1. This response occurred in about half of all the animals investigated and is described in order to clarify the sequence of events when the shunt is well tolerated.

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*Harvard Apparatus Company, Dover, Massachusetts.

1Grass Instrument Company, Quincy, Massachusetts.
EPINEPHRINE IN CARDIAC FAILURE

Figure 1
Response of pressures to opening and closing of shunt is well tolerated. LV, left ventricular; Ao, aortic; LA, left atrial; RV, right ventricular; and PA, pulmonary arterial pressures. Left ventricular pressures recorded at two levels of amplification to show systolic and diastolic pressure. RV and PA pressures recorded alternately on same pressure transducer. The apparent artifacts seen about 20 seconds after opening the shunt are due to ventricular ectopic beats.

Animals showing this type of response were not used for the purpose of this study. The group of animals investigated developed acute cardiac failure within a few minutes after the shunt was opened widely (fig. 2). After the immediate changes on opening described above, there was a continued slow decrease in left ventricular, aortic, pulmonary arterial, and right ventricular systolic pressures, and a gradual further rise of left ventricular end-diastolic, left atrial, and right ventricular end-diastolic pressures. Ascending aortic stroke volume showed the initial increase on opening the shunt, and then gradually fell, paralleling the slow decrease of left ventricular systolic pressure. Closure of the shunt resulted in only a slow return of all parameters to control levels. Left ventricular systolic pressure showed either no immediate increase or a small rise, and then gradually rose to control over 30 to 90 seconds. Left ventricular end-diastolic and left atrial pressures also declined gradually over a similar period of time. Aortic stroke volume also only gradually returned to normal.

Neglecting to close the shunt when this "failure" type of response was manifested resulted in a continuing rise of left and right ventricular end-diastolic and left atrial pressures, a persistent decrease of left and right ventricular systolic pressures, and a marked reduction in aortic blood flow, culminating in pulmonary edema and death of the animal (fig. 3).

During the course of studies of the effects of various pharmacologic agents on the acute circulatory response to the aorto-pulmonary shunt, it was observed that sympathetic block-
ing agents could precipitate a failure-type of response in animals previously tolerating the shunt well. Figure 4A demonstrates the effects of opening and closing the shunt, in an animal that showed no failure after numerous manipulations of the size of the shunt. Following the intravenous administration of 100 mg. of tetraethylammonium chloride, the dog showed a typical failure response (fig. 4B). Similar adverse effects on the ability of animals to tolerate a large shunt have been observed during the administration of halothane anesthetic agents, such as 1/2 to 1 per cent Fluothane (unpublished observations).

In view of the deleterious results produced by the sympathetic blocking agents, the effects of epinephrine in reversing or preventing the failure response were examined. Epinephrine hydrochloride was infused continuously into the right ventricular catheter in gradually increasing doses from 0.01 to 3.0 µg./Kg./min. Infusions were given by means of a constant infusion pump (Harvard Apparatus Company).

After the failure response on opening the shunt was demonstrated on several occasions, the shunt was closed; the epinephrine infusion was commenced and the effects of opening were observed after a 3- to 5-minute period. At levels of infusion below 0.3 µg./Kg./min., no changes were observed in pressures or flows with the shunt closed, and the failure response to opening the shunt was not affected. At infusion rates of 0.5 to 1.5 µg./Kg./min., pressures with the shunt closed showed a variable change, depending on the amount of epinephrine administration. Left ventricular systolic and aortic pressures, as well as pulmonary arterial pressure, increased; left ventricular end-diastolic and left atrial pressures showed no consistent change, sometimes decreasing slightly, sometimes increasing slightly, and sometimes not changing. Heart rate and aortic stroke volume increased. In some

![Figure 2](image-url)  
Response to opening and closing of shunt with development of failure. Symbols as in figure 1.
EPINEPHRINE IN CARDIAC FAILURE

animals with infusion rates of 0.5 to 0.6 μg./Kg./min. no changes in pressure or flow occurred in the control state. When epinephrine was infused at rates above 1.5 to 2.0 μg./Kg./min., ventricular ectopic beats frequently occurred, and occasionally bigeminy was encountered.

The shunt was again suddenly opened when pressures and flows had stabilized. The results observed were consistent in all animals studied. The failure response was prevented, and the changes in pressures and flows noted in the animals that tolerated the shunt well were now observed. The responses to closure were also similar to those that occurred when the shunt was well tolerated (fig. 5).

Numerous observations in the 18 dogs indicated that the optimal infusion rate to prevent the development of failure on opening the shunt with avoidance of ectopic beats was 0.5 to 1.5 μg./Kg./min., with 0.5 to 1.0 μg./Kg./min. giving a good response in the large majority of animals.

Attempts were also made to reverse an established failure response by epinephrine infusion. This resulted in variable success, depending on the degree of deterioration of hemodynamic factors that had occurred before epinephrine infusion. If epinephrine infusion was instituted as soon as peak aortic flow velocity began to decline, 0.5 to 1.0 μg./Kg./min. usually prevented or reversed the failure response. If the failure response was well developed, it was necessary to infuse 1.5 to 2.0 μg./Kg./min. to reverse the response. Ectopic beats were not observed under this circumstance until left ventricular systolic pressures and ascending aortic flows had again risen to near control levels. When left ventricular and aortic systolic pressures and aortic stroke volume had dropped to very low levels, it was necessary rapidly to infuse 15 to 25 μg. of epinephrine initially, and then to continue with the flow infusion to reverse the failure response. For periods of 5 to 15 minutes after the epinephrine infusion had been discontinued, opening the shunt did not result in failure although pressures and flows with the shunt closed had returned to normal.

The effect of digoxin in preventing the failure response was examined in four animals. Digoxin was administered intravenously in doses up to 50 μg./Kg. as a single injection. This agent was ineffective in preventing the failure response on opening the shunt for as long as 70 minutes after administration. In these same animals in which digitalis did not succeed, subsequent epinephrine infusion was effective in preventing the failure response.

In view of the dramatic effect of epinephrine in prevention or reversal of cardiac failure due to experimental patent ductus arteriosus, it was decided to evaluate this agent as therapy for critically ill infants with similar hemodynamic derangement.

Clinical Observations

Intravenous epinephrine infusions have been administered to three infants in extreme left ventricular failure due to large left-to-right shunts.

Case 1

K.M. (B.M.H.C. no. 209255), a baby girl, was delivered 2 weeks prematurely of an otherwise normal pregnancy. At 6 weeks of age the child became
A. left. Opening of shunt is well tolerated before administration of tetraethylammonium chloride (TEA). B, right. Failure response following TEA. LV, left ventricular; PV, pulmonary venous; LA, left atrial; and PA, pulmonary arterial pressures in mm. Hg. PV and LA mean pressures recorded.

Figure 4

Prevention of failure response following epinephrine administration. Prior to epinephrine infusion, opening of shunt results in rapid development of failure. After epinephrine, opening shunt is very well tolerated for long period of time.

Figure 5
EPINEPHRINE IN CARDIAC FAILURE

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extremely irritable, and had frequent bouts of tachycardia and a continual hacking cough. At 12 weeks of age, she was admitted to the Bronx Municipal Hospital Center in frank congestive failure. She was in severe distress with a heart rate of 160/min., and respiratory rate of 70/min., with marked intercostal retraction. The liver was enlarged 3 cm. below the right costal margin. Crepitant rales were audible at both lung bases. The cardiac rhythm was regular; the first sound was normal, and the second sound was accentuated at the pulmonic area. A harsh grade-IV systolic murmur was present at the lower left parasternal region and a mid-diastolic rumble was heard at the apex. Chest films showed biventricular enlargement and pulmonary hypervascularity. The electrocardiogram showed left ventricular hypertrophy. The clinical impression was of congestive heart failure secondary to a large left-to-right shunt, probably through an interventricular septal defect. She was rapidly digitalized with digoxin and stabilized over the following 2 weeks.

A definitive diagnosis was established by right heart catheterization. There was a marked increase in blood oxygen saturation on entering the right ventricle, with no further consistent rise in the pulmonary artery. Pulmonary arterial pressure was almost at systemic levels. The pulmonary to systemic flow ratio of 3.5:1 indicated an enormous left-to-right intracardiac shunt (table 1).

Over the next week the infant's condition worsened considerably, and she again developed acute pulmonary edema with coarse rales and marked liver enlargement. Despite vigorous treatment, consisting of increasing digoxin dosage, mercurial diuretics, and chlorothiazide, she failed to respond satisfactorily.

Five weeks after admission the condition rapidly deteriorated and the child was in extremis. The skin was gray and clammy and the eyes had a vacant glassy stare. The pulses were barely palpable. The heart sounds were almost inaudible and the murmur had decreased markedly in intensity. Bubbling rales were heard throughout the chest and she produced frothy sputum. It was thought that any therapy holding the least promise for relief of the intractable cardiac failure was justified. Accordingly, a decision was made to give this child an intravenous infusion of epinephrine in an attempt to improve cardiac tolerance of the enormous volume and pressure overload, prior to and during an attempt to perform palliative surgery.

An intravenous epinephrine infusion at the rate of 0.9 μg./Kg./min., body weight/min. was started. This was prepared by adding 1 ml. of 1:1000 epinephrine hydrochloride to 19 ml. of 5 per cent dextrose, and infusing at the rate of 0.1 ml./min. This was equivalent to the dose of 0.9 μg./Kg./min. in this infant.

Within 5 to 10 minutes after the infusion had started the infant showed marked clinical improvement. Heart rate increased from 100 to 140/min., the peripheral pulse became readily palpable and strong, respiration improved, and over a 15- to 20-minute period bubbling rales disappeared, and only a few fine crepitant rales were heard. Respirations became less labored, and peripheral circulation improved. Two hours later, the infant withstood general anesthesia and surgery remarkably well. The pulmonary artery was isolated and a constrictive band was applied. Immediately after the operation, pulmonary rales were no longer audible. The epinephrine infusion was continued for 2½ hours following surgery, a total of about 4 hours. Faint generalized cyanosis was present in the immediate postoperative period, but this disappeared within

Table 1

<table>
<thead>
<tr>
<th>Cardiac Catheterization Findings</th>
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</table>

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<tr>
<th>Patient</th>
<th>K.M.</th>
<th>R.O.</th>
<th>M.P.</th>
<th>Patent ductus arteriosus</th>
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</thead>
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<td>Diagnosis</td>
<td>Ventricular septal defect</td>
<td>Ventricular septal defect</td>
<td>Patent ductus arteriosus</td>
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<tr>
<td>Catheter position</td>
<td>Pressure mm. Hg</td>
<td>m</td>
<td>O₂ sat. %</td>
<td>Pressure m. Hg</td>
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<td>Superior vena cava</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right atrium</td>
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<td>58</td>
<td>3</td>
<td>49</td>
</tr>
<tr>
<td>Right ventricle</td>
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<td>70</td>
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<td>68</td>
</tr>
<tr>
<td>Pulmonary artery</td>
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<td>7</td>
<td>79</td>
<td>60</td>
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<tr>
<td>Aorta</td>
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<td>86</td>
<td>70</td>
<td>38</td>
</tr>
<tr>
<td>Femoral artery</td>
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<td>44</td>
<td>61</td>
<td>93</td>
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<tr>
<td>VO₂ (assumed)</td>
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<td>130 ml.</td>
<td>130 ml.</td>
<td></td>
</tr>
<tr>
<td>O₂ cap. vol. %</td>
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<td>10.1</td>
<td>13.0</td>
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<td>Qp/M.²</td>
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<td>16.2 L.</td>
<td>16.6 L.</td>
<td></td>
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<tr>
<td>Qs/M.²</td>
<td>5.2 L.</td>
<td>3.2 L.</td>
<td>2.3 L.</td>
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</tbody>
</table>

Circulation, Volume XXVIII, July 1958
48 hours after surgery. By the third postoperative day, digoxin was withdrawn and the infant made an uncomplicated recovery.

She has been observed at frequent intervals, and 13 months postoperatively is growing well and thriving normally.

**Case 2**

R.O. (B.M.H.C. no. 218738), a boy, was born following a 34-week pregnancy. Transient cyanosis was present during the first day of life. At 3 weeks of age a loud prerooidal systolic murmur was heard. The infant reportedly became cyanotic on crying, had a tachycardia of 224/min. and an enlarging liver, and was therefore digitalized with improvement.

At 6 weeks of age he again suddenly developed tachypnea, intercostal retractions, and tachycardia.

On the night of admission the liver was palpated 3 cm. below the right costal margin. The resting respiratory rate was 45 to 80/min. The cardiac apex was at the anterior axillary line. The second sound at the pulmonic area was extremely loud and snapping. A grade-III blowing systolic murmur was audible over the entire precordium but loudest at the lower left parasternal line. A short mid-diastolic rumble was present at the apex.

Radiographic examination showed biventricular enlargement and considerable pulmonary hyperaemia with diffuse congestive changes. The electrocardiogram was normal for the age.

Cardiac catheterization was performed on the third hospital day. Right ventricular and pulmonary arterial systolic pressures were equal and elevated to systemic level. Pulmonary blood flow was markedly increased with a pulmonary-to-systemic flow ratio of 5:1 (table 1). Cineangiography revealed a dilated enlarged left ventricle, a large ventricular septal defect, and tricuspid regurgitation.

Over the ensuing week the child's condition followed a steadily deteriorating course, in spite of intensive therapy with digalis and diuretics. Pulmonary congestion supervened and rales appeared in the right base. Within a few hours the condition rapidly worsened and the infant now looked mortified. Diffuse bubbling rales were heard in both lungs, and peripheral pulses could not be palpated.

It was obvious that the patient would soon succumb unless more active therapy were given. A decision was made to perform an emergency banding of the pulmonary artery, but the risks of anesthesia and surgery were considered to be overwhelming. In view of the experience in the previous infant, an intravenous infusion of epiinephrine was started, at a rate of 0.75 µg./Kg./min. Within about 5 minutes, the infant showed dramatic improvement, with considerable relief of respiratory distress; pulse rate increased and pulse volume was much improved. The rales decreased, and the fingers and toes became pink, indicating an improvement in peripheral circulation.

The infusion was continued throughout the surgical procedure, which was performed under light ether anesthesia 2 hours later. The pulmonary artery was banded to approximately one third of aortic diameter. The procedure was very well tolerated and the child recovered rapidly. The epinephrine infusion was continued for 2 hours after surgery. Respirations were normal within 6 hours, and digoxin was withdrawn over the 10-day postoperative period.

The infant has been observed at regular intervals in the out-patient department for 1 year. The cardiorespiratory status has been quiescent and weight has steadily increased.

**Case 3**

M.P. (B.M.H.C. no. 221469), a baby girl, was delivered prematurely after an otherwise normal pregnancy. Mild respiratory distress with scattered rales in both lungs was present after birth. No murmurs were audible. The condition worsened, and severe respiratory distress and cyanosis, with diffuse pulmonary infiltration on x-ray, suggested the diagnosis of hyaline membrane disease. Improvement slowly occurred over the next few days. On the twentieth day symptoms reappeared, with respiratory distress, retraction, and cyanosis, even with oxygen. The pulse rate rose to 200/min., crepitant rales were heard at both lung bases, and the liver was palpated 3 cm. below the right costal margin. A grade-II blowing systolic murmur at the upper left sternal border appeared for the first time. Radiologic examination revealed a markedly enlarged heart with increased pulmonary vascularity. Digoxin, chlorothiazide, oxygen, and mercurial diuretics produced only mild temporary relief. Two days later the infant became cyanotic even in oxygen, with extremely severe respiratory distress, and opisthotonus was noted. She was transferred to the Bronx Municipal Hospital Center for further diagnosis and treatment.

Cardiac catheterization and angiocardiography were performed as an emergency procedure; the findings are summarized in table 1. This confirmed the presence of a patent ductus arteriosus with large left-to-right shunt and pulmonary arterial hypertension at systemic levels.

In view of the desperate clinical condition of the infant, an epinephrine infusion was begun as soon as the diagnosis was established. An intravenous infusion of 0.5 µg./Kg./min. was administered resulting in immediate improvement with relief of respiratory distress, and increased pulse volume and heart rate. The ductus arteriosus was
EPINEPHRINE IN CARDIAC FAILURE

ligated; epinephrine was continued through the surgical procedure, and for about 2 hours after surgery. The procedure was well tolerated, and the infant had an uneventful recovery and has progressed very favorably.

Discussion

The dramatic effect of epinephrine in preventing cardiac failure in animals and patients warrants a discussion of the mechanism of the cardiac failure due to left-to-right shunts, and the possible mode of action of epinephrine. The mechanism for the development of cardiac failure in infancy associated with large systemic-pulmonary communications has not been well understood. Most descriptions of cardiac failure in infancy have stressed the importance of liver enlargement as one of the early signs.\(^5\)\(^,\)\(^6\) Relatively little attention has been directed toward the respiratory distress associated with pulmonary congestion and edema as the earliest evidence of left ventricular failure. The three infants presented all demonstrated severe left ventricular failure as evidenced by pulmonary edema, low cardiac output with weak pulses, and poor peripheral circulation. Hepatomegaly, although present, was not a striking feature of the clinical picture.

The manifestations of acute left ventricular failure associated with a large left-to-right shunt were reproduced in the animal preparation with an artificially induced, controlled aorto-pulmonary shunt. Acute cardiac failure could be precipitated repeatedly in the same animal, and could be reversed by rapid closure of the shunt. This provided a unique opportunity to study the adverse or beneficial effects of various agents on cardiac failure in the closed-chest, spontaneously breathing animal.

The development of failure was characterized by a continuing fall of left ventricular systolic and aortic pressures, a rise of left ventricular end-diastolic and left atrial pressures, and, after the initial increase, a continuing fall of ascending aortic stroke volume. The phasic flow tracings recorded from the ascending aorta are flow-velocity tracings (figs. 1 and 2), and stroke volume is represented by the area under the curve. The ascending aortic flow is monitored just above the aortic valve and represents left ventricular output, which, since the flowmeter probe is proximal to the shunt, also indicates total pulmonary blood flow.

The actual mechanisms responsible for left ventricular failure in large shunts have not been fully investigated. The left-to-right shunt places a large volume load on the left ventricle. The systemic arterial pressure drops when the shunt is open, and this may interfere with coronary blood flow. This mechanism may be particularly important in aorto-pulmonary communications, since diastolic pressure is markedly affected. The effect of sympathetic blocking agents in precipitating failure in an animal previously tolerating the shunt could be related to their effect on the heart itself, resulting in decreased contractility.\(^7\) The peripheral vascular effect of vasodilatation may be important in allowing a very striking decrease of diastolic blood pressure when the shunt is opened, interfering with coronary flow.

The dramatic effect of epinephrine in preventing or reversing the cardiac failure due to shunts was consistently demonstrated in all animals. The optimal dose level was 0.5 to 1.5 \(\mu\)g./Kg./min. Intravenous infusion of lesser amounts produced no measurable effects on the circulation. It was of interest that in some animals, infusion of 0.5 \(\mu\)g./Kg./min. produced no hemodynamic changes in the control animal, but prevented the development of failure on opening the shunt. When amounts greater than 1.5 to 2.0 \(\mu\)g./Kg. were infused, numerous ventricular ectopic beats occurred.

The cardiac inotropic effect of epinephrine is well documented. The direct action on improving myocardial contractility has been demonstrated in the isolated heart-lung preparation\(^8\) and also in the intact animal.\(^9\) This may be the major mechanism by which epi-

Circulation, Volume XXVIII, July 1963
the peripheral circulation and coronary circulation. In the doses used epinephrine usually produces vasodilatation; however, vasoconstriction may occur, and a peripheral vasoconstrictor effect may prevent the marked fall in systemic blood pressure coincident with opening the shunt, and thus maintain an adequate coronary perfusion. Also, the direct vasodilator effect of epinephrine on the coronary vessels may improve myocardial perfusion.

Although the effects of epinephrine in maintaining adequate coronary perfusion after opening the shunt have not been investigated, some preliminary observations suggest that the direct effect of epinephrine on myocardial contractility is the more important factor in preventing failure. An infusion of acetylcholine during the epinephrine administration resulted in a marked decrease in systemic arterial pressure to levels well below those recorded after opening the shunt in the control animal. Should inadequate coronary perfusion due to low arterial pressure be the important factor in producing failure, the failure should have been precipitated. The animals tolerated opening of the shunt quite well while under acetylcholine, however, and left ventricular failure did not occur.

The remarkable effectiveness of epinephrine in preventing left ventricular failure in animals with induced shunts, prompted a trial of this "therapy" in infants with severe left ventricular failure. The three infants presented all had large left-to-right shunts documented by cardiac catheterization; two had a ventricular septal defect with pulmonary arterial hypertension and the other a patent ductus arteriosus with pulmonary hypertension. Left ventricular failure with persistent pulmonary edema was the predominant feature of the clinical picture. Although all three infants responded moderately well to digitalization initially, their condition gradually deteriorated, and in spite of vigorous therapy, which included chlorothiazide, mercurial diuretics, oxygen, and increasing digitalis dosage, they regressed into a critical condition. The decision to institute epinephrine therapy was made when the infants showed evidence of severe left ventricular failure with low cardiac output, poor peripheral circulation, and severe pulmonary edema.

Epinephrine hydrochloride was infused intravenously in doses of 0.5 to 0.9 μg./Kg./min. in small volumes of 5 per cent dextrose to attempt to improve the condition of the patients prior to surgery. The infusion was carefully administered by means of a constant infusion pump to achieve a steady infusion rate. The electrocardiogram was monitored to detect changes in rate and rhythm and presence of ventricular ectopic beats. As described under the individual case reports, the infants all showed dramatic clinical improvement, with increase in heart rate, improved peripheral circulation, increased pulse volume, and decrease in pulmonary rales and respiratory distress.

Anesthesia and surgery were remarkably well tolerated in all three infants, even though performed within a few hours after starting the epinephrine. Epinephrine was administered for periods of 4 to 6 hours with no adverse effects. The amounts given did not appear to interfere with urinary output.

We would like to stress that epinephrine infusion has thus far been observed to be effective only in cardiac failure due to left-to-right shunts. The effect on cardiac failure due to obstructive lesions has not been examined. Some preliminary observations on chronic experimental pulmonary stenosis indicate, however, that epinephrine may be dangerous, since a marked bradycardia with decreased cardiac output occurred, presumably as a baroreceptor response to a rise of systemic arterial pressure.

The use of epinephrine is not recommended for routine management of cardiac failure in infants. Its use should be reserved for the treatment of the desperately sick infant with left-to-right shunt in which other measures have failed.

**Summary**

A technic for establishing a controlled
EPINEPHRINE IN CARDIAC FAILURE

aorto-pulmonary shunt in closed-chest, spontaneously breathing dogs has been developed. Wide opening of the shunt is well tolerated in some animals, but others develop acute left ventricular failure. Administration of sympathetic blocking agents may induce a failure response on opening the shunt, in an animal that previously tolerated it well.

Epinephrine infusion during the control period consistently prevented cardiac failure when the shunt was widely opened. Epinephrine was also capable of reversing the failure, if rapidly infused before left ventricular systolic pressure had dropped to extremely low levels. It was also effective in countering the adverse effects of sympathetic blocking agents. The optimal rate of infusion was found to be 0.5 to 1.5 μg./Kg./min. of epinephrine hydrochloride.

A constant infusion of epinephrine hydrochloride was administered to three infants with large left-to-right shunts who had failed to respond to intensive decongestive measures, and who manifested severe cardiac failure with severe pulmonary edema. Marked clinical improvement resulted, and anesthesia and surgery were well tolerated while the infusion was continued.

Epinephrine should be administered with a constant infusion apparatus to avoid induction of ventricular ectopic beats due to overdosage. Its use is reserved, at present, for the management of the desperately sick infant with acute left ventricular failure due to systemic-pulmonary shunts.

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