Mechanism of Congestive Heart Failure Following Aorta Constriction in Rabbits

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With the technical assistance of Marjorie DeCuir

Severe constriction of the abdominal aorta in rabbits caused congestive heart failure and death in 4 to 7 days. Expansion of total plasma volume suggested that aortic narrowing increases the vascular bed distal to the stricture. Reduction of total body fluids did not prevent total plasma volume expansion, unless it caused severe dehydration. A large percentage of dietary sodium was retained. Expansion of extracellular volume occurred even when sodium intake was reduced. The early, gradual post-operative rise in arterial pressure probably depends, in part, on development of an effective circulating plasma volume. A tentative answer is given to the question of what factors determine the exact time that heart failure will occur.

AN EARLIER paper from this laboratory described a method for producing congestive heart failure in rabbits. Constricting the abdominal aorta proximal to the superior mesenteric artery induces hypertension and within 2 weeks, in most cases, respiratory distress and death ensues. After the aorta is narrowed there is a period of 4 to 7 days during which the animal is active and the appetite returns, then the average rabbit develops signs of congestive heart failure and death may follow within 1 or 2 days. Why does the heart fail at a particular time in the postoperative course? The present study was part of a broad program designed to answer this question.

The working hypothesis for the present study of body fluid and arterial pressure changes was that aorta narrowing elicits an increase in size of the vascular bed distal to the stricture and that the homeostatic response to this should be expansion of the circulating blood volume. We wished to learn whether an increase in blood volume was related to the rising arterial pressure and to renal retention of sodium and water.

The general procedure was to subject aorta-constricted rabbits to several different dietary regimens designed to alter total body fluids. The relatively short survival times of the experimental animals, 5 to 15 days, made it necessary to distinguish between the effects of surgery per se and narrowing of the aorta. Control rabbits were subjected to laparotomy only and were placed on similar dietary regimens. Measurements were made of plasma volume, blood pressure, and water and sodium balance.

METHODS

Operation. The method for narrowing the aorta has been described in detail elsewhere. It consists of clearing the aorta just proximal to the superior mesenteric artery and placing a 3 mm. wide, 6 mm. long, Goldblatt clamp on the vessel. By means of a movable plate the diameter of the aorta is reduced to about one-fourth the original size. Control rabbits were subjected to a laparotomy which included the same surgical procedure used for experiments except that a clamp was not placed on the aorta.

Routine Procedure. Each rabbit was placed in a metabolism cage, and the particular dietary regimen under study was started 1 or 2 weeks before operation. Ingesta and excreta along with body weight were measured and recorded every day. To facilitate the operative procedure, all animals were fasted 1 to 3 days before the day of operation. On that day, the urinary bladder was catheterized and blood pressure and plasma volume measured. After operation, body weight and blood pressure were recorded daily along

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with ingesta and excreta. At 2 or 3 day intervals throughout the survival time, plasma volumes were determined. Other determinations, such as urinary sodium excretion and sodium thiocyanate (NaSCN) space, were usually carried out on the same day as a plasma volume determination. Any signs of respiratory distress or other changes in condition of the animal were noted during the postoperative course.

Evans blue dye (T-1824) was used to measure plasma volume. A single, 5 to 6 min. plasma sample was obtained from the marginal ear vein. To check the reproducibility of the 5 to 6 min. sampling method, 34 repeat plasma volume determinations were made 30 to 60 min. after the initial one in 24 normal and aorta constricted animals. The mean variation between the first and second determination of total plasma volume (TPV) was 2.2 per cent, with a range of —14 to +7 per cent. Day to day variations of plasma volume from 20 determinations on 10 normal rabbits (when food and water intake was constant) were no greater than those found within 1 hour.

Systolic blood pressure readings were obtained from the central car artery by an indirect method first introduced by Grant and Rothchild. These readings are about 20 mm. Hg less than mean carotid pressure.

Sodium balance was studied in a number of experimental and control rabbits at intervals throughout the postoperative course. The urinary bladder was catheterized and washed with water and air at the beginning and end of a period which was not less than 48 hours and up to 96 hours. Sodium content of the urine was quantitated by Consolazio's gravimetric procedure. A Beckman flame spectrophotometer was used to determine sodium in food and water. Fecal sodium was not measured.

Body weights were measured with an accuracy of ±5 Gm. The change in body weight during periods of a week reflect closely the change in total body water for an adult animal. Other workers have also found that the daily body weight changes in rabbits reflect changes in body water.

Extracellular fluid space of some animals was estimated with NaSCN, using a single plasma sample obtained 1 hour postinjection. Values for NaSCN space were corrected for gastrointestinal water which in rabbits represents 8 to 10 per cent of the body weight.

At autopsy, the volume of fluid collected from chest and abdomen was recorded along with weights of lungs, liver, kidneys and ventricles. Cut surfaces of unopened and described.

Henceforth aorta-constricted rabbits will be designated a.c.(s) or experimental, and laparotomized animals will be referred to as lap.(s) or controls.

**Dietary Regimens.** The rabbits used in this study ranged in size from 1.8 to 3.0 Kg. Initial studies were carried out in 9 a.c. and 14 lap. animals which received stock food and water ad lib., Group I. Food was commercial dry rabbit pellets containing 530 mg. Na/100 Gm. food, and water was tap water. Postoperatively, lap.s would consume greater quantities of food and water than a.c.s when ingesta was available ad lib. For this reason the food and water of 6 lap.s in group I was matched to that of 6 a.c.s. With this procedure the a.c. member of each pair gained weight, but the lap. generally lost. Thus, in order to have weight gains in lap.s comparable to a.c.s in group I, free access to ingesta was allowed in 8 other lap.s.

Two dietary regimens were used to reduce body weight and will be referred to as group II and group III. Group II was restricted water, 100—900 ml./day. This amount of water was slightly less than that calculated to meet insensible water loss and minimal urine formation. Rabbits automatically reduced food intake when water was restricted so that this group of 7 a.c. and 7 lap. rabbits consumed less sodium than those in group I. Group III was on low sodium pellets and water ad lib. The food was dry pellets containing only 58 mg. Na/100 Gm. food. This low sodium food was rejected by some rabbits, and only those eating normal quantities pre-operatively were used, totaling 5 a.c.s and 4 lap.s. The ingesta of several lap.s in both group II and III was matched to that of a.c.s.

A fourth group (Group IV) of 7 a.c.s was severely dehydrated 3 to 6 days pre- and 3 days postoperatively, by limiting drinking water to 0 or 40 cc. ml./day. Two lap.s were run on this regimen. Rabbits do not eat when water is not given.

**RESULTS**

**Unoperated Rabbits.** We found that values for plasma volume ranged from 32 to 56 ml./Kg. in 85 unoperated, fasting, 1.7 to 3 Kg. rabbits. Because of this relatively wide range of values we have presented plasma volume data as per cent change in TPV from the preoperative fasting value to give a clearer picture of the magnitude of change for each individual rabbit.

At 1 to 3 day fast in 27 unoperated animals cause the following: an average decrease in TPV of 10 per cent (range +10 to −22 per cent), a negative sodium balance, a diuresis and loss in total body weight of approximately 4 to 5 per cent/day, and a 20 to 40 per cent decrease in NaSCN space. These were the conditions present at time of operation.

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This was established by comparing weight change alone to calculated values for net gain or loss of body water in a large number of rabbits in our laboratory.
TABLE 1.—Total Plasma Volume and Blood Pressure the First and Second Day After Aorta Constriction

<table>
<thead>
<tr>
<th>Postoperative day</th>
<th>Control</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.P. mm. Hg</td>
<td>TPV ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>85</td>
<td>97</td>
<td>85</td>
<td>100</td>
</tr>
<tr>
<td>95</td>
<td>107</td>
<td>—</td>
<td>108</td>
</tr>
<tr>
<td>110</td>
<td>165</td>
<td>100</td>
<td>115</td>
</tr>
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</tr>
<tr>
<td>95</td>
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</tr>
<tr>
<td>100</td>
<td>101</td>
<td>115</td>
<td>105</td>
</tr>
</tbody>
</table>

Fig. 1. The per cent change of TPV 3 or 4 days after operation in a.c. (●) and lap. (X) rabbits. A Animals which lost body weight; B. Animals which gained body weight. ○, □ averages.

**TPV and Blood Pressure Changes in Operated Rabbits.** Plasma volumes were measured 2 days after operation in 11 rabbits from groups I, II, and III, and these values along with blood pressures are shown in table 1. One day after operation, blood pressure was the same, lower, or slightly higher than the control pressure. No plasma volumes were measured at 1 day. By the second day blood pressure was increased in all animals and so was TPV.

All a.c. rabbits in group I, and 2 from group III gained weight postoperatively while the other 3 from group III, and all from group II lost body weight. The per cent change in body weight and TPV at 3 or 4 days postoperatively for both a.c. and lap. rabbits appear in figure 1.

A.c. rabbits that gained weight after operation (fig. 1B) had TPV increases which averaged 29 per cent, and those a.c.s which lost body weight (fig. 1A) had TPV increases which averaged 38 per cent. Of those losing weight, only 3 were remeasured at 7 or 8 days, and the average TPV increase was 26 per cent. Two other rabbits which lost weight had increases of 40 and 30 per cent in TPV at the fifth and sixth postoperative day, respectively. These results show that a loss in total body fluid (weight loss) brought about by low water (group II) or sodium intake (group III) did not prevent expansion of TPV in a.c. rabbits. The maximum per cent increase in TPV of any of the 21 a.c.s in groups I, II and III was 88 per cent and 10 of them had increases over 40 per cent at some time during the first 8 postoperative days.

The lap.s did not show any further average change in TPV after the first 3 or 4 days. At that time the average per cent increase in TPV was 9.0 and 20 per cent for those which lost body weight and gained, respectively.

Blood pressure changes proximal to the aorta stricture at 3 or 4 and 7 or 8 days for a.c. rabbits are shown in table 2 along with the per cent change in TPV for each animal. Figure 2 shows the complete course of arterial blood pressure and percent increase of total plasma volume of 4-a.c. rabbits...
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CONGESTIVE HEART FAILURE FOLLOWING AORTA CONSTRICTION

TABLE 2—Total Plasma Volume and Blood Pressure at 8 or 4 and 7 or 8 Days After Aorta Constriction

<table>
<thead>
<tr>
<th>Group*</th>
<th>Control</th>
<th>3 or 4 Days</th>
<th>7 or 8 Days</th>
<th>Day of Death</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>B.P. mm. Hg</td>
<td>B.P. mm. Hg</td>
<td>TPV Per cent change</td>
<td>B.P. mm. Hg</td>
</tr>
<tr>
<td>I</td>
<td>95</td>
<td>128</td>
<td>38</td>
<td>105</td>
</tr>
<tr>
<td>I</td>
<td>115</td>
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<td>130</td>
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<td>98</td>
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<td>85</td>
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</tr>
<tr>
<td>III</td>
<td>105</td>
<td>140</td>
<td>17</td>
<td>115</td>
</tr>
<tr>
<td>III</td>
<td>103</td>
<td>124</td>
<td>142</td>
<td>115</td>
</tr>
</tbody>
</table>

* Those above the line gained body weight; those below, lost.

Comparison between per cent change in TPV and blood pressure elevation shows no regular correlation between the height of blood pressure and increase in TPV. Both increased during the first part of the postoperative course, although the increases were not necessarily proportional to each other. During the last 2 or 3 days of survival, arterial pressure and plasma volume might continue to rise or fall together or blood pressure might fall and plasma volume remain the same (fig. 2).

The low sodium diet (group III) did not prevent a rise of blood pressure. A.c. animals in group III had the same amount of elevation in pressure as those receiving 10 times the quantity of sodium in their diet (table 2).

During the first part of the postoperative course blood pressure elevation might be, in part, dependent on an expanding plasma volume. This is suggested by the blood pressure findings in those animals whose regimen produced severe dehydration (group IV). The 7 a.c.s in this group had body weight losses from 8 to 18 per cent, averaging 12 per cent on the third postoperative day. At this time their changes in TPV ranged from +11 to —12 per cent (average +3 per cent) and 6 of the 7 animals had blood pressures ranging from 85 to 111 mm. Hg, i.e., within normal limits, and only 1, above normal values, 140 mm. Hg. The latter had a TPV increase of +11 per cent.

In all other groups plasma volume increases ranged from +16 to +63 per cent on the third postoperative day and blood pressures ranged from 115 to 155 mm. Hg (see table 2). It would seem then that expansion of TPV is associated with an elevation of arterial blood pressure in the upper half of the body during the first part of the postoperative course in a.c.s. Rehydration of animals in group IV caused large increases in TPV and death occurred within 7 days. Figure 3 is a plot of blood pressure and TPV changes for a rabbit representative of those in group IV.

Sodium Thiocyanate Space. NaSCN space, like plasma volume, increased even though total body water decreased as a result of water (group II) or salt (group III) restriction, and the increase represented a greater percentage of the body weight in a.c.s than in lap.s.

Sodium and Water Balances. Sodium and water balance studies carried out in 10 a.c.s and 11 lap.s showed that a.c.s retained 3 times as much sodium as lap.s and 20 to 30 per cent more water throughout the first postoperative week. Tabular details of experiments can be obtained from authors on request.

Signs of Congestive Failure and Postmortem Findings. A definite decrease in blood pressure, along with signs of respiratory distress, distended jugular veins, increased central venous pressure and sometimes tachycardia would often precede death by several days. On the
other hand, onset of death could be much more acute, and then blood pressure would be elevated and respiration normal within a few hours of death.

Tabular details of autopsy findings can be obtained from authors on request.

All animals in groups I and II had heavy livers and ascites. Over half of these animals had fluid accumulations (ascites plus pleural effusion) which totaled 1½ to 3 times the normal TPV of a rabbit. All animals in group III had heavy livers but died without significant ascites. Seemingly, low sodium intake causes ascites to be reabsorbed, by lymphatics and/or directly from peritoneal surfaces, at a rate exceeding that of formation.

A consistent autopsy finding was lung edema which, along with pleural effusion, explains the dyspnea before death and was undoubtedly the immediate cause of death. Animals with the largest pleural effusion volumes had the lowest lung weights. Apparently the lung is compressed by large volumes of fluid in the chest and less is held in the lung tissue proper.

Comparison of ventricle/body weight ratios of a.c. rabbits and normal or lap. rabbits showed that hypertrophy occurred in most of the a.c.s. This is additional evidence that hypertension was present proximal to the aorta stricture as was indicated by the high blood pressure readings.

DISCUSSION

Aorta constriction does not produce an immediate, persistent hypertension, but rather a gradual rise of arterial pressure to some definite level in each animal. One possible mechanism which could affect the rate of blood pressure elevation is the rate of adaptation of the buffer nerve reflex system. If there were a lag in adaptation after operation, buffer nerves would act to oppose a large rise in blood pressure. Figure 4 presents the changes in central ear artery pressure and heart rate during the first 5 postoperative days in 5 representative rabbits. Notice that the trend is for an increase in heart rate on the first day, followed by a tendency to level off at rates exceeding preoperative ones, 3 to 4 days after operation. Blood pressure on the other hand shows a gradual elevation. If the buffer nerves had been opposing the rise in pressure, heart rates would have been below normal. There was no definite correlation between blood pressure and heart rate in individual cases or the group.

Another mechanism which could influence the rate of rise in pressure is an increase in plasma volume, and the present work was concerned with this mechanism. The finding of plasma volume expansion supports the hypothesis, as mentioned in the introduction to this paper, that aorta constriction initiates an increase in size of the vascular bed distal to the narrowing. Expansion of total plasma volume takes place even though total body fluids are being reduced as the result of low water or sodium intake. When severe dehydration prevented plasma volume from expanding above 11 per cent on the third postoperative day, blood pressure did not go up in 6 of 7 animals. In the other groups on the third day, the least relative increase in total plasma volume was 16 per cent and all animals had
elevations in pressure. It is not implied that plasma volume expansion means the presence of hypervolemia in our animals. On the contrary, the increased size of the vascular bed would result in reduction of effective circulating blood volume so that subsequent expansion of plasma volume merely brings about a proper effective circulating volume. However, observations on cardiac output made in our laboratory indicate that the expanded plasma volume is not entirely meeting the needs of the circulation and in this way delays the rise in pressure. Cardiac outputs were measured by the dye dilution technic in 24 unanesthetized normal rabbits and 6 a.c. unanesthetized rabbits on the first, second, and third postoperative day. The average for normals was 196 ml. whole blood/Kg./min., S.D. ±33 ml./Kg./min. None of the 6 a.c.s showed signs of respiratory distress and all had a decline in cardiac output, ranging from −2 to −33 per cent of their control preoperative value, average −17 per cent, which represented an average decrease of 33 ml/Kg.min. (or 1 S.D.). A probable explanation for reduced cardiac output is that plasma volume expansion is not sufficient to maintain adequate venous return and also meet the requirements of an expanded vascular bed which resulted from aorta narrowing.

We are now in a position to answer tentatively the question proposed in the introduction: Why does the heart fail at a particular time in the postoperative course and why is there a period of recovery after aorta narrowing and then a sudden failure of the heart? The answer lies in the fact that arterial pressure does not rise immediately but instead builds up over a period of days to a level which will precipitate heart failure in each individual animal. The reason that a critically high pressure does not develop immediately after operation is because of the reduced cardiac output, and the latter condition exists because plasma volume has not increased sufficiently to maintain the venous return. It is probable, that although the size of the vascular bed has increased beyond the stricture, the vascular resistance in the fore part of the body is increased to regulate the distribution of blood. Blood pressure must go up to the critical level at a rate dependent on continued expansion of blood volume and achievement of normal cardiac output, as well as increased vascular resistance.

**Summary**

Rabbits were subjected to severe aorta constriction. The average rabbit has a 4 to 7 day period of recovery, then develops signs of congestive heart failure, and death may follow within a day or two. The postoperative changes of TPV, arterial blood pressure proximal to the stricture, and water and sodium balance were studied in aorta-constricted (a.c.) rabbits and in laparotomy (lap.) controls. Some animals were placed on normal diets, others, on regimens designed to decrease body fluids—restriction of water or sodium intake.

The working hypothesis that aorta narrowing induces an increase in size of the vascular bed distal to the stricture was supported by finding that TPV expanded both early and late in the survival period. Except for the regimen producing severe dehydration, TPV increased as much in a.c. rabbits losing body weight (body fluids) as in those which gained. Average TPV increased about 25 to 40 per cent above preoperative values. Total extracellular fluid volume (NaSCN space) was also increased even when sodium intake was reduced. Lap. rabbits had average increases in TPV of 9 and 20 per cent.

By the second postoperative day arterial pressure was increased along with TPV and both continued to rise for the next 1 or 2 days. After this time blood pressure and TPV did not necessarily take the same direction. Of the 7 severely dehydrated rabbits, none had increase in TPV above 11 per cent on the third postoperative day, and 6 had blood pressures which were within normal limits at that time.

A.c. rabbits retained sodium and water throughout the first postoperative week.

Why the heart fails at a particular time in the postoperative course was discussed. It was tentatively proposed that this will depend on the time for arterial pressure to reach the critical level. The latter is not reached immedi-
ately after operation because of reduced cardiac output. This results because plasma volume is inadequate to maintain venous return and meet the requirements of the increased vascular bed.

**SUMMARY IN INTERLINGUA**

Conilios esseva subjicite a sever grados de constriction del aorta. In le caso typic, le sequente periodo de recovramento dura 4 a 7 dies. Postea le animal disvelloppa signos de congestive disfallimento cardiac. Morte pote evenir intra un die o duo. Le alterationes post-operatori del volumine total de plasma, del presion de sanguine arterial proximal al sito del constriction, e del balancias de aqua e de natrium esseva studiate in conilios a constriction aortic e in conilios laparotomisate que serviva como controlo. Certes del animales recipeva dietas normal. Alteres esseva subjicite a regimes planate a reducer le fluidos corporee per restringer le ingestion de aqua o de natrium.

Le hypothese provisori que le restriction del aorta resulta in un aggrandimento del vasculatura distal al sito del constriction esseva supportate per le constatation que le volumine total de plasma accresce al initio e al fin del periodo de superviventia. A parte le casos in que le animales recipeva dietas resultant in sever dishydratation, le volumine de plasma total accresceva tanto in le conilios con constriction aortic le quale suffriva perditas de peso corporee (fluidos corporee) como in le conilios le quale ganiava in peso. Le augmento medie del volumine de plasma total amontava a circa 25 a 40 pro cento del valores pre-operatori. Le volumine del fluido extracellular total (spatio de NaSCN) se augmentava mesmo igualmente, mesmo quando le ingestion de natrium esseva reducite. Conilios laparotomisate habeva augmentos del volumine de plasma total amontante a 9 e 20 pro cento.

Le secunde die post le operation, le pression arterial e etiam le volumine de plasma total se monstrava augmentate, e ambe iste valores continuava montar le sequente 1 a 2 dies. Postea, le pression sanguine e le volumine de plasma total non sequeva necessarmente le mesme direction. Septe conilios esseva severmente dishydratate, e nulle de illos habeva augmentos del volumine total de plasma de plus que 11 pro cento le tertie die post le operation, e 6 habeva pressiones sanguinee que esseva intra le limites del norma.

Conilios a constriction aortic reteneva natrium e a qua quarte le integreprime septimana post le operation.

Es discutite proque le corde disfalle a un specific tempore in le curso post-operatori. Es proponite tentativemente que isto depende del tempore quando le pression arterial attinge le nivello critic. Iste nivello critic non es attingite immediamente post le operation a causa del reduce rendimento cardiac. Le reduction del rendimento cardiac es un consequentia del facto que le volumine del plasma non suffice pro manten te retorno venose e pro satisfacer simultaneamente le requerimentos del augmentate vasculatura.

**REFERENCES**

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