Experimental Chronic Right Ventricular Failure Produced by Endocardial Application of Dilute Iodine Solution.* (31301)

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Experimental chronic congestive cardiac failure has been produced by various methods (1-7). This paper describes a new one-stage method by which this can be accomplished.

Previous experiments have shown that the application of dilute Lugol's solution to the canine right ventricular endocardium causes an extensive intraventricular conduction defect and destruction of the Purkinje-net system(8,9). During these experiments it was noted that the animals developed signs of congestive cardiac failure. The present experiments were undertaken to evaluate this phenomenon further.

Method. Experiments were performed on 12 medium sized mongrel dogs. Two animals died during the surgical procedure and one animal died 5 days post-operatively with dyspnea, massive hydrothorax and breakdown of the chest incision. The data which will be presented were collected from the 9 surviving animals.

Under pentobarbital anesthesia (25 mg/kg) the following control studies were obtained: right heart catheterization, cardiac output, arterial pressure, 12 lead electrocardiogram, blood urea nitrogen, hematocrit, serum proteins and body weight.

The heart was then exposed through a fourth right intercostal incision while the animal was maintained on artificial respiration. The right ventricular cavity was approached by retraction of the tricuspid valve through an atrial incision during temporary cardiac inflow and outflow occlusion. The right ventricular cavity was irrigated for 15 seconds with dilute Lugol's solution (diluted 1:5 or 1:10 with saline solution). The right atrial appendage was amputated.

Following the surgical procedure daily body weights and urinary outputs were obtained. Serial right heart catheterizations and electrocardiograms were performed at weekly intervals for the first 3 weeks and then at 2- to 3-week intervals, depending on the rate of development of cardiac failure. When severe failure developed, the cardiac output, arterial pressure, blood urea nitrogen, serum proteins and hematocrit measurements were repeated. All post-operative studies were performed with the animal in the unanesthetized state to eliminate the risk of anesthesia in the presence of cardiac failure.

When death occurred, autopsy examination was performed with particular reference to the cardiovascular system. Histologic studies of the heart, liver, spleen, lungs and kidneys were obtained.

Cardiac catheterizations were performed with a small polyethylene catheter under pressure monitoring with a P23D Statham strain gauge. All recordings were made on a multichannel Sanborn direct writing machine. The right ventricle was difficult to enter by this method when failure became marked so that the right ventricular and pulmonary artery pressures were then obtained by direct percutaneous needle puncture of the right ventricle and passage of a polyethylene catheter into the pulmonary artery.

Cardiac outputs were measured by the dye dilution method. Two animals died unexpectedly and a follow-up cardiac output was not obtained.

Results. All animals surviving the surgical procedure developed findings consistent with congestive cardiac failure, and eventually succumbed. The average survival period of the 9 dogs that survived the surgical procedure was 61 days. Ascites became clinically evident about mid-way in the survival period and usually became massive. Edema of the

* Supported by U.S.P.H.S. Research Grant HE-07483-03 and Moody Fund of Evanston Hospital.

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extremities often was evident. The weight gain with advanced cardiac failure averaged 5 pounds. Actual weight gain was minimized by loss of fat tissue. The animals became emaciated as failure developed. Urinary output became scant in the terminal state. Dyspnea developed rather suddenly and indicated a terminal state.

The main data are summarized in Table I. The control central venous pressures were normal. A slight increase in the mean central venous pressure was usually evident one week following the operation. This became progressively elevated and reached an average level of 17 mm Hg with advanced cardiac failure. Right ventricular end-diastolic pressure progressively increased, with levels approaching the mean right atrial pressure. The pressure tracings with advanced failure revealed tricuspid insufficiency, pronounced atrialization of the right ventricular and pulmonary artery pressures and an early diastolic "dip" in the ventricular pressure curve. The pulmonary artery mean pressure and right ventricular systolic pressure did not show a consistent change.

The average control cardiac output was 2.2 liters/minute. The cardiac output decreased to an average of 1.2 liters/minute after cardiac failure developed. This decrease was minimized by the rather low control outputs which had been obtained in the anesthetized state just before the surgical procedure. The repeat cardiac outputs were obtained with the animals awake.

The control electrocardiograms were normal. Following the surgical procedure the electrocardiogram showed a permanent QRS pattern of extensive intraventricular conduction defect as described previously(8). The QRS duration increased from .03-.04 second to .09-.11 second. The QRS interval widened further in most animals as cardiac failure became severe (to .10-.14 second).

The arterial pressure, blood urea nitrogen, and hematocrit were not significantly altered with the development of heart failure. The serum protein concentration decreased slightly in some animals.

Autopsy revealed marked serous pleural effusion and ascites in all dogs. The fluid was

TABLE I. Summary of Data Collected from Animals with Congestive Cardiac Failure.

Dog No.	Post-operative survival period, days	Post-operative day clinical ascites first observed	Abdominal fluid at autopsy, ml	Pleural fluid at autopsy, ml	Maximum mean central venous pressure during cardiac failure, mm Hg	Maximum right ventricular end-diastolic pressure during heart failure, mm Hg	Cardiac output, l/min	
							Control	Cardiac failure
1	60	20	1600	1300	23	11	4.9	.5
2	48	36	400	1700	23	19	1.7	.6
3	145	80	1930	700	14	10	2	.7
4	51	30	550	1200	16	13	2	1.5
5	14	no clinical ascites	200	1800	8 (at 7 days)	7 (at 7 days)	1.5	not obtained
6	61	27	2675	1400	14	14	1.9	1.2
7	34	20	2500	1000	21	20	1.4	2.8
8	28	no clinical ascites	400	1700	6 (at 12 days)	4 (at 12 days)	——not obtained——	
9	105	40	7400	600	24	20	2.1	1.3

usually straw colored except in several animals which exhibited serosanguineous fluid. The pericardium was somewhat adherent to the epicardium, but constriction was not present. The right ventricle appeared dilated without increase of mural thickness. Endocardial sclerosis was always extensive, though the ventricle was still pliable. This process usually involved the tricuspid valve which was then thickened and quite rigid. Two animals exhibited pliable tricuspid valves with minimal involvement by the sclerotic process. Tricuspid stenosis did not appear to be present, although this could not be excluded when the valve was very rigid. Four hearts had thrombi close to the tricuspid valve which may have caused some degree of right ventricular inflow obstruction. Microscopic examination indicated that these were of recent origin (probably about 2 weeks of age), well after the appearance of failure. Two animals (#5 and #8) had large thrombi near the atrial incision which appeared to produce significant obstruction to the superior vena cava. These animals also had the shortest duration of life following the surgical procedure. Several animals exhibited small organized thrombi at the site of the atrial incision which did not appear to have been hemodynamically significant.

Histologic studies of the heart revealed marked endocardial sclerosis and loss of the Purkinje-net system. Fibrosis predominantly involved the immediate subendocardial muscle. However, some patchy intramural involvement of the right ventricle was often seen.

The lungs of 4 animals were found to have small pulmonary emboli and infarctions of recent origin. The involvement was not extensive except in one animal (#5). Pulmonary edema was not found.

The liver was always enlarged and markedly congested.

Discussion. The procedure which has been described appears to be a reliable one-stage operation for producing a syndrome of experimental chronic congestive right sided cardiac failure. It should be useful for studying the pathophysiology of failure. The mechanism is most likely an inadequate propulsion of blood through the right side of the heart due to inadequate pumping action of the right ventricle. Autopsy and catheterization findings revealed tricuspid insufficiency and a generalized endocardial and subendocardial fibrotic process. The extensive intraventricular conduction defect might further have compromised right ventricular function. This requires further investigation. Failure was not due to the surgical procedure alone: previous experiments in which the right ventricular cavity was entered in identical fashion to produce right bundle-branch block caused no signs of heart failure(10).

The hemodynamic significance of the thrombi which formed in some animals is difficult to evaluate. Since autopsy showed them to be definitely of more recent origin than the failure, and since failure occurred in dogs without thrombi, it must be assumed that their role is contributory but not primary.

Two dogs exhibited a fulminating postoperative course with death in 5 and 14 days. Dyspnea and massive pleural effusion with little ascites were present in both of these animals. The mechanism may have been somewhat different in these cases and is suggestive of a similar condition produced in rabbits by the intrapericardial injection of tincture of iodine(1,11).

Application of dilute Lugol's solution to the left ventricular endocardium produces a "left sided" cardiac failure with dyspnea and pulmonary edema. This procedure, however, has been associated with a high operative mortality in our experience.

Summary. A method has been described for production of experimental chronic congestive cardiac failure. Elevation of the central venous pressure becomes evident in one to two weeks. The process is progressive and results in eventual death of the animal. The average survival period following the surgical procedure was 61 days.

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Received December 3, 1965. P.S.E.B.M., 1966, v122.

Effect of Hydrochlorthiazide on Renal Blood Flow and Clearance of Para-Aminohippurate and Creatinine.* (31302)

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The introduction of chlorthiazide and its congeners has led to considerable research on the renal handling of these compounds. All of the thiazides investigated thus far seem to be secreted by similar mechanisms and at the same tubular site as para-aminohippurate (PAH), penicillin and phenol red, *i.e.*, the proximal tubule(1-5). If two of the above organic acids are administered to dogs simultaneously, it is possible in some instances, by elevating the plasma level of one of the drugs, to depress the clearance of the other. Thus, when the plasma concentration of PAH is increased to self-depression levels, the clearance of hydrochlorthiazide (HCT) may be depressed(2). Similarly, depression of both HCT and PAH by probenecid has been demonstrated(1,2). Although suggestions have been made(1,2) that thiazides depress the clearance of PAH, we are not aware that such a depression has actually been demonstrated. Depression of PAH clearance when diuretic doses of HCT are administered would certainly invalidate the use of PAH clearance for a measure of effective renal plasma flow if the depression in clearances were due to a decrease in the extraction ratio for PAH. It is the purpose of this brief report to show the effect of 3 diuretic doses of HCT on the clearance of PAH as well as on renal blood flow as measured by an electromagnetic flowmeter.

* Supported by contract AF 41 (609)-2421.

Materials and methods. Sixteen mongrel dogs of both sexes were anesthetized with sodium pentobarbital (30 mg/kg) intravenously. One femoral artery was isolated and cannulated for blood pressure measurements; the other for blood sampling. A catheter was also placed in a femoral vein for infusions, and in each ureter for measurement of urine flow. The left renal artery was exposed by retroperitoneal approach and an electromagnetic flow probe placed around the artery. In 2 animals bifurcation of the left renal artery necessitated use of the right renal artery.

All animals were hydrated by stomach with 50 ml/kg tap water. Creatinine (50 mg/kg) and PAH (8.4-42 mg/kg) were given as priming doses intravenously one hour prior to collection of urine samples, followed by constant infusion of creatinine (3.0 mg/ml) and PAH (1.0-3.2 mg/ml) in saline at 6 ml/min. Two 20-minute urine collections were made for control clearance measurements. HCT (5, 10 or 30 mg/kg prepared in a volume of 10-20 ml of equimolar NaOH) was then infused by vein over a 10-minute period. Two additional 20-minute urine collections were made immediately after infusion of the drug. Arterial blood was withdrawn into syringes, the dead spaces of which were filled with mepesulfate (Roche) at the mid points of the urine collection periods. It was established in early experiments that the kidney on which the flowmeter probe had been placed cleared