a pronounced increase in the unidirectional efflux of calcium ions. The addition of acetylcholine or a high potassium medium enhances the tone of a muscle that is partially contracted in a calcium-free medium. The addition of 1.8 mM $CaCl_2$ depresses it. However, when the same concentration of $CaCl_2$ is added in the presence of acetylcholine or a high potassium medium it enhances muscle tone even more. We inferred from these data that acetylcholine, a high potassium medium, and a calcium-free medium, by increasing membrane permeability, accelerate the migration of calcium ions from an intracellular depot to the cytoplasm. The results suggest that they also accelerate the movement of calcium ions between the external solution and the cytoplasm of the muscle fiber.

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Production of Right Ventricular Hypertrophy With and Without Congestive Heart Failure in the Cat. (32137)

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Ventricular hyperthrophy and congestive heart failure have been induced in dogs(1), guinea pigs(2), and rabbits(3) and such experimental models have provided considerable insight into these pathologic states. However, a quantitative description of the contractile state of cardiac muscle isolated from the hypertrophied or failing heart is not available. The cat offers unique advantages for analyzing the contractile state of the myocardium in these conditions because the papillary muscle from the right ventricle is small enough to permit *in vitro* oxygenation and its fibers are oriented in parallel and thus allow definition of heart muscle function per unit of muscle cross-sectional area and length. Further, the functional characteristics of the cat papillary muscle preparation have been described in detail(4) and are sufficiently uniform to allow meaningful comparison of the myocardial contractile state of one group of cats to that of another group(5). To provide the animal model for such studies, a method for production of right ventricular hypertrophy with and without congestive heart failure in the cat has been developed and is the subject of this report. This was accomplished by imposing a chronic pressure load on the right ventricle by reduction of the lumen of the supravalvular portion of the main pulmonary artery.

Methods. The pulmonary artery of the cats was constricted by a circular clip(6) (Fig. 1) which was applied in the following manner. Animals were anesthetized with intravenous sodium methohexital (15 mg/kg). To permit endotracheal intubation and control of respiration intravenous succinylcholine (1 mg/kg) was then given and intermittent positive pressure ventilation was applied by a Harvard respirator* using air. Under sterile conditions, the chest was opened through the anterior one-third of that left intercostal space lying 2 cm cephalad from the apical impulse, the pericardium was widely excised, and a 5 mm segment of the main pulmonary artery just distal to the pulmonic valve was dissected free of the ascending aorta. This

* Harvard Apparatus Co. model 672.

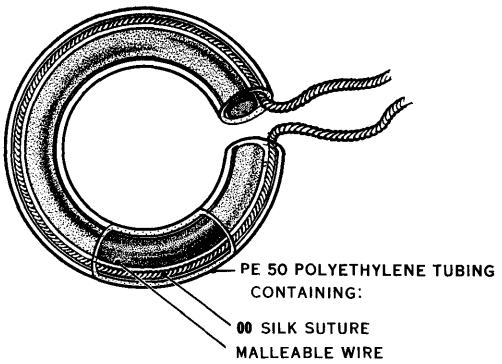

FIG. 1. Clip used to constrict the pulmonary artery. It consists of malleable wire and silk suture within polyethylene tubing. The slot which interrupts the circumference of the clip is 0.5 mm wide.

segment of the pulmonary artery was cleaned of adipose and connective tissue and a curved hemostat passed from left to right behind the pulmonary artery so that its tip was exposed between this vessel and the aorta. One free end of the suture threaded through the tubing of the clip (Fig. 1) was then picked up by this hemostat and pulled around the pulmonary artery as the hemostat was removed. The clip was then positioned posterior to the pulmonary artery and this vessel was insinuated through the opening in the circle into the clip. The ends of the clip were approximated by slight tension on the two ends of the suture which were then tied together. After the clip was in place, the respiratory gas mixture was changed to 95% oxygen and 5% carbon dioxide, the incision closed, the endotracheal tube removed, and the animal allowed to recover for 30 minutes in a chamber containing 95% oxygen and 5% carbon dioxide.

The clips were made in the following manner. PE-50 polyethylene tubing was wound in a spiral around a rod with a diameter equal to that desired as the internal diameter of the clip. A single cut was then made through the spiral of tubing in the long axis of the rod so as to result in several pieces of tubing of appropriate length. Copper wire (0.016 inch diameter) and a 20 cm length of #00 silk suture were inserted into each segment of tubing and the wire was cut to correspond to the length of the polyethylene. The tubing, wire, and suture were bent around the rod until the cut ends of the tubing were brought together, thus forming an open circle with shape maintained by the stiffness of the wire. Clips with an internal diameter of either 2.8 or 3.5 mm were used in adult cats weighing between 1.8 and 2.4 kg.

One to 90 days after the pulmonary banding procedure, right heart catheterization was carried out under light intravenous nembutal anesthesia (20 mg/kg). A cannula was placed in the descending aorta *via* the femoral artery, the electrocardiogram was monitored, and a #5 Birdseye catheter was placed in the body of the right ventricle *via* the right external jugular vein. Right ventricular and aortic pressures were measured by Statham force transducers (P23AA) and all signals were recorded on a multichannel Sanborn oscillograph. The zero reference point was taken as the mid-chest position, corresponding to the level of the right atrium. Cardiac output was determined by the dye dilution technique(7) with the injection of 1.25 mg indocyanine (lcc) into the right ventricle and sampling from the abdominal aorta. Mixed venous and arterial blood samples were obtained from the right ventricle and aorta respectively and analyzed for oxygen content by the Van Slyke technique(8).

Results. The pulmonary artery was constricted to an average residual lumen of 10% of normal by the 2.8 mm clips and to 20% of normal by the 3.5 mm clips. Pulmonary banding by either clip produced right ventricular systolic hypertension and resulted in right ventricular hypertrophy. The increment increase in weight of the right ventricular free wall was 80% of the control weight or greater in every animal, from either group, studied one week or longer after constriction of the pulmonary artery. In addition to right ventricular hyperthrophy, overt congestive heart failure was present in 20 of 26 cats sacrificed at 1 to 77 days (average 26 days) following constriction with 2.8 mm clips. Evidence of overt congestive heart failure included pleural fluid, hepatic congestion, ascites, elevation of right ventricular end-diastolic pressure (Fig. 2), reduction of cardiac index, and increase in arterio-venous oxygen difference. Gross pleural and (or) ascitic fluid were present in 15 of these 20 animals with heart failure and two or more of the criteria of failure were present in

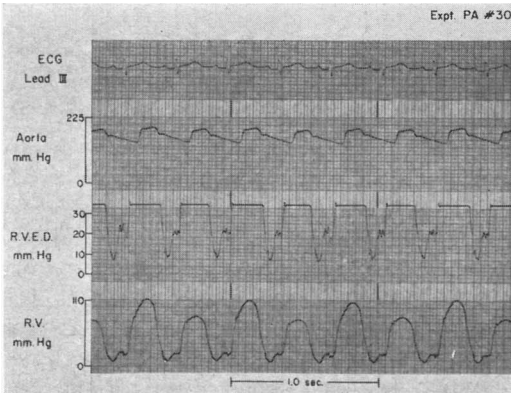

FIG. 2. Electrocardiographic (ECG), aortic pressure (Aorta), high gain (RVED) and low gain (RV) right ventricular pressure recordings from a cat with right ventricular hypertrophy and overt congestive heart failure. The high right ventricular end-diastolic pressure (21 mm Hg), the elevated right ventricular peak systolic pressure (up to 110 mm Hg), and the pulsus alternans in the right ventricle are characteristic of the hemodynamic findings in the cats with overt congestive heart failure.

15 animals. The cats with 2.8 mm clips were also noted to have marked dilatation of the right ventricular chamber and several had right ventricular pulsus alternans (Fig. 2). Sixty per cent of animals with 2.8 mm clips died before catheterization or sacrifice for study and all showed evidence of severe congestive heart failure.

Discussion. Partial constriction of the main pulmonary artery in the cat resulted in right ventricular hypertrophy in all animals. Reduction of vessel lumen to approximately 20% of normal was associated with right ventricular hypertrophy without overt failure in surviving animals, while reduction of the lumen to 10% of normal resulted in severe congestive heart failure. Thus, by varying the degree of pulmonary artery constriction, right ventricular hypertrophy could be obtained with or without overt congestive heart failure.

Since the cat is suitable for hemodynamic measurements in the intact state(9), this preparation will permit such studies to be performed in animals with hypertrophy of the right ventricle in the presence and absence of heart failure. More importantly, since the contractile properties of cat right ventricular papillary muscles have been described in detail(4) and the function of muscles from one group of cats can be meaningfully compared to the function of a second group(5), the contractile state of cardiac muscle from hypertrophied and failing hearts can be examined in detail under isolated and controlled conditions.

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