PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 161, 515-518 (1979)

A New Technique for Production of Chronic Atrial Septal Defect in Cat without Thoracotomy (40586)[1]

GANGAIAH NATARAJAN, RITA A. CAREY, RICHARD L. COULSON,[2] ALFRED A. BOVE,[3] AND JAMES F. SPANN

Section of Cardiology, Department of Medicine, Temple University Health Sciences Center, Philadelphia, Pennsylvania 19140

Cardiac hypertrophy resulting from pressure overload and from volume overload differ considerably in many respects. For example, pressure overload leads to concentric hypertrophy while volume overload leads to eccentric hypertrophy (1). Systolic contractile function is depressed in pressure overload hypertrophy (2) but is normal in volume overload hypertrophy (3). Studies utilizing experimentally produced pressure overload hypertrophied right ventricular papillary muscles of small mammals like cats (3–6) and rabbits (7, 8) have contributed considerably to the understanding of changes in myocardial function in cardiac hypertrophy. A surgically produced atrial septal defect in cats has been shown by Cooper *et al.* (3) to cause volume overload right ventricular hypertrophy which is another useful model for the study of cardiac hypertrophy. However, the surgical technique requires thoracotomy and pericardiotomy. A nonsurgical technique to create an atrial septal defect would facilitate further studies of volume overload cardiac hypertrophy. Accordingly, a new technique using a flexible bronchoscopy biopsy forceps was developed.

Methods. The cat is lightly anesthetized with sodium pentobarbital, 30 mg/kg administered intraperitoneally, and allowed to breathe spontaneously. The left femoral vein and the external jugular vein and carotid artery in the neck are exposed. The ascending aorta and the right ventricle are catheterized with a 5 F NIH catheter and a 5 F Goodale Lubin catheter, respectively, via the vessels in the neck. Dye dilution curves are recorded by injecting indocyanine green in the right ventricle and sampling continuously from the ascending aorta. A flexible bronchoscopy biopsy forceps (Olympus F B 1C) is then advanced via the left femoral vein to the right atrium under fluoroscopy. With the cat in a slight left anterior oblique position, the limits of the right atrium, particularly its junction with the superior venacava and the inferior venacava are defined using small amounts of a radioopaque contrast material injected through the right heart catheter. The tip of the right heart catheter is positioned at the junction of the superior venacava and the right atrium for reference. The mouth of the biopsy forceps is opened in the right atrium and advanced cephalad until it is resisted by the interatrial septum. The mouth of the forceps is closed, and it is gently pulled down. This traction will result in slight downward displacement of the catheter in the ascending aorta if the atrial septum is engaged by the forceps. After observing such a displacement of the aortic catheter, the biopsy forceps, with its mouth still closed, is pulled down forcibly, thereby pinching off a part of the septum. This maneuver is repeated several times until an adequate ASD is produced. The magnitude of the resulting ASD is assessed by repeated recording of the dye dilution curves as described above (Fig. 1), and calculating the pulmonary blood flow to systemic blood flow ratio (QP/QS) by the method of Carter *et al.* (9).

Results. Immediate outcome of the attempts to produce an atrial septal defect using the biopsy forceps in the first 16 cats is summarized in Table I. Among the 10 cats documented to have developed a left to right shunt as a result of the procedure, the presence of an atrial septal defect was confirmed

[1] Supported in part by NIH Grants HL 07198-02, HL 17631-05, and HL 19425-02.

[2] Present address: Cardiovascular Unit, School of Medicine, Southern Illinois University, Carbondale, Ill. 62901.

[3] Dr. Bove is an Established Investigator, American Heart Association.

0037-9727/79/090515-04$01.00/0

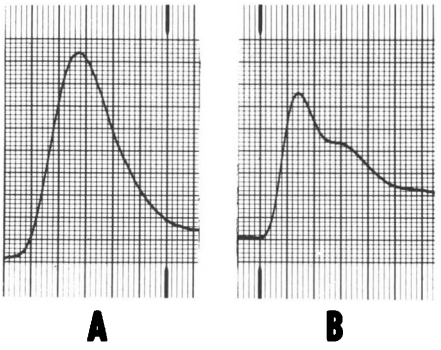

FIG. 1. Dye dilution curves recorded by injecting indocyanine in the right ventricle and sampling from the ascending aorta. (A) Before, and (B) after creating atrial septal defect with the biopsy forceps.

in each animal after it was sacrificed (Fig. 2). One cat was sacrificed immediately after the production of atrial septal defect, and the remaining 9 cats after 21 to 67 days. The right ventricular pressure, QP/QS ratio, and the heart weight ratios at the time of the terminal study in those 9 cats with chronic atrial septal defect are tabulated in Table II. The right ventricular pressure in all the 9 cats with chronic atrial septal defect was similar to the right ventricular pressure recorded in a group of 6 normal cats in this laboratory. Six of the nine cats (cats 1 through 6 of Table II) had QP/QS ratio of 1.77 or higher at the end of 35 to 67 days (50 days ± 5 SEM) and also significant right ventricular hypertrophy when compared to the group of 6 normal cats, as judged by increased right ventricle to body weight ratio (ASD = 1.09 g/kg ± 0.01, normal = 0.67 g/kg ± 0.04, $P < 0.01$) and right ventricle to left ventricle weight ratio (ASD = 0.47 ± 0.02, normal = 0.28 ± 0.01, $P < 0.001$). One cat with QP/QS ratio of 2.02 had no evidence of right ventricular hypertrophy, and two cats with QP/QS ratio of 1.12 and 1.38 had only mild right ventricular hypertrophy. There was no sign of congestive heart failure in any cat.

Complications. Four of the sixteen cats died during the procedure, three of them due to perforated right atrium and one due to perforated inferior venacava in the supradiaphragmatic region. In two cats, attempts to create atrial septal defect were abandoned, because of inability to advance the biopsy forceps beyond midabdominal level in one cat and damage to the forceps in another cat.

Discussion. Atrial septal defect produced by the nonsurgical technique described in this communication leads to volume overload and right ventricular hypertrophy of similar degree to that reported by Cooper *et al.* (3) who used a surgical technique to create the same lesion. In Cooper's study, the right ventricular weight to body weight ratio was 0.97 g/kg ± 0.03 for the atrial septal defect group, and 0.59 g/kg ± 0.03 for the sham-operated group. The extent of the right ventricular hypertrophy resulting from volume overload produced by the current technique also agrees favorably with that due to pressure overload induced by pulmonary arterial constriction (2, 10). For example, in a group of nine cats (weight = 2.28 ± 0.10 kg) with pressure overload right ventricular hypertrophy produced by pulmonary arterial constriction with 3.5-mm-internal-diameter clips in this laboratory during the period of current investigation, the average right ventricular weight to body weight ratio was 1.14 g/kg ± 0.06 and right ventricle to left ventricular weight ratio was 0.48 ± 0.02, values similar to those values of cats 1 through 6 in Table II.

Suitability of the cat right ventricular papillary muscle for studying cardiac muscle mechanics of the normal (11) and hypertrophied state (2, 3) has already been established. There have been many studies correlating the contractile function of normal and pressure-overload-hypertrophied cat right ventricular papillary muscles with biochemical and energetics measurements (2, 4–6, 12). In contrast, there has been only one study involving volume-overload-hypertrophied cat right ventricular papillary muscle. Systolic contractile function and energetics of volume-overload right ventricular hypertrophy have been studied by Cooper *et al.* (3). The nonsurgical technique to produce atrial septal

TABLE I. IMMEDIATE OUTCOME OF THE ATTEMPTS TO PRODUCE ASD USING THE BIOPSY FORCEPS TECHNIQUE IN THE FIRST 16 CATS

Outcome	Number
Successful ASD creation	10
Mortality	4
Inability to advance the BF beyond midabdomen	1
Broken BF	1

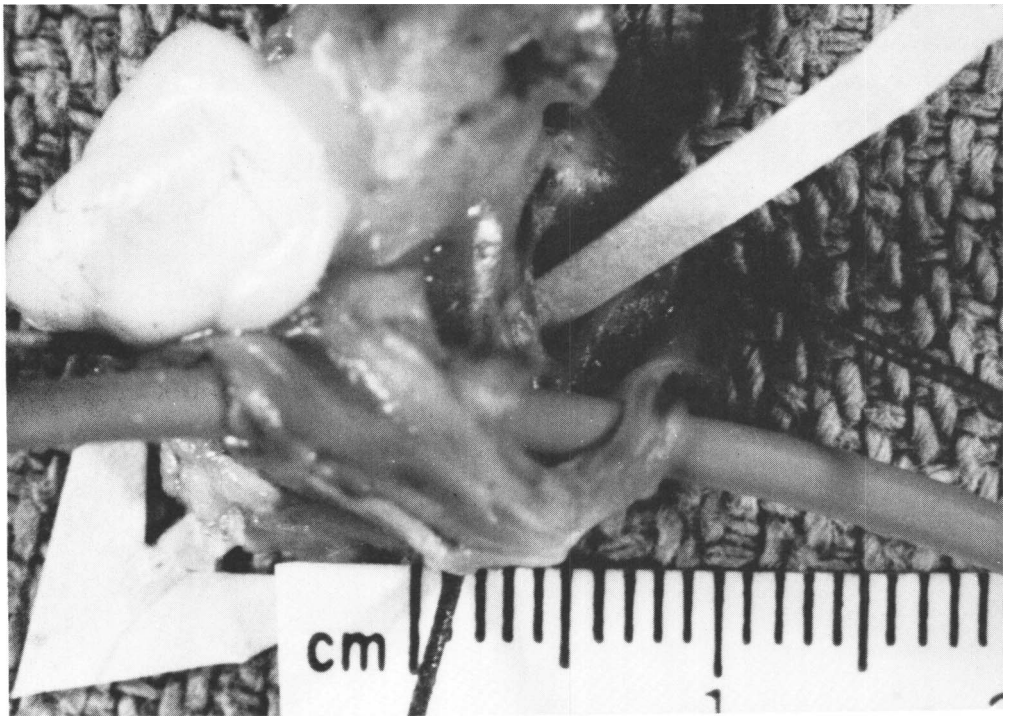

FIG. 2. Atrial septal defect confirmed at autopsy. The arrow is shown passing through the defect in the interatrial septum. The catheter below is positioned in the venacavae.

TABLE II. SIGNIFICANT FINDINGS IN THE NINE CATS WITH CHRONIC ASD[a]

Cat No.	Duration of ASD (days)	RV syst (mm Hg)	RV edp (mm Hg)	QP/QS	RV weight (g/kg BW)	RV weight / LV weight
1	35	30	5	7.55	1.14	0.52
2	54	25	1.5	3.54	0.71	0.38
3	47	24	1	1.77	1.04	0.41
4	38	26	3	4.52	0.92	0.47
5	56	30	3	1.81	1.20	0.50
6	67	23	2	3.70	1.50	0.51
7	41	21	2	2.02	0.68	0.32
8	41	15	1	1.12	0.85	0.35
9	21	24	1	1.38	0.87	0.36
Normal group		24.33 ± 2.27	1.83 ± 0.48	1.14 ± 0.02	0.67 ± 0.04	0.28 ± 0.01

[a] Mean values ± SEM of similar measurements in a group of six normal cats are given at the bottom for comparison. RV, right ventricular; syst, systolic pressure; edp, end diastolic pressure; BW, body weight; LV, left ventricular.

defect described in this communication will facilitate further investigation of volume-overload cardiac hypertrophy. Although this new technique requires using a fluoroscopy unit and familiarity with the use of catheters, it obviates the need for thoracotomy and pericardiotomy.

The authors with to thank Mrs. JoAnn Green and Miss Maxine Blob for their excellent secretarial support in the preparation of this manuscript.

1. Linzbach, A. J., Amer. J. Cardiol. **5,** 370 (1960).
2. Spann, J. F., Buccino, R. A., Sonnenblick, E. H., and Braunwald, E., Circ. Res. **21,** 341 (1967).
3. Cooper, G., IV, Puga, F. J., Zujko, K. J., Harrison, C. E., and Coleman, H. N., III, Circ. Res. **32,** 140 (1973).
4. Buccino, R. A., Harris, E., Spann, J. F., and Sonnen-

blick, E. H., Amer. J. Physiol. **216,** 425 (1969).
5. Gunning, J. F., and Coleman, H. N., J. Mol. Cell. Cardiol. **5,** 25 (1973).
6. Cooper, G., Satava, R. M., Harrison, C. E., and Coleman, H. N., Circ. Res. **3,** 213 (1973).
7. Alpert, N. R., Hamrell, B. B., and Halpern, W., Circ. Res. **34/35** (Suppl II), 71 (1974).
8. Hamrell, B. B., and Alpert, N. R., Circ. Res. **40,** 20 (1977).
9. Carter, S. A., Bajec, D. F., Yannicelli, E., and Wood, E. H., J. Lab. Clin. Med. **55,** 77 (1960).
10. Coulson, R. L., Yazdanfar, S., Rubio, E., Bove, A. A., Lemole, G. L., and Spann, J. F., Circ. Res. **40,** 41 (1977).
11. Sonnenblick, E. H., Amer. J. Physiol. **202,** 931 (1962).
12. Carey, R. A., Bove, A. A., Coulson, R. L., and Spann, J. F., Amer. J. Physiol. **234** (3), H253 (1978).

Received November 10, 1978. P.S.E.B.M. 1979, Vol. 161.