The Effect of Bretylium Tosylate on the Pulmonary Arterial and Venous Circulations of the Intact Anesthetized Dog[1] (34963)

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Bretylium tosylate, a benzyl quaternary ammonium compound, was introduced in 1959 as a systemic arterial hypotensive agent (1). However, recently it has been used as a cardiac antiarrhythmic drug (2, 3). Knowledge of the action of this agent on the pulmonary arterial circulation is limited, and the effects of the drug on the pulmonary veins have not even been studied. While investigating the circulatory effects of bretylium given intravenously in man, Taylor and Donald (4) noted an increase in pulmonary arterial pressure unaccompanied by changes in pulmonary capillary wedge pressure. Systemic hypertension also followed for a few minutes the intravenous administration of bretylium. Halmagyi and Colebatch (5) studied aspects of the effects of bretylium on the pulmonary arterial circulation in sheep and found, in addition to an initial increase in pulmonary arterial pressure, an increase in pulmonary capillary wedge pressure. They were of the opinion that mild hypoxemia might have been responsible for the pulmonary arterial hypertension. McGaff and Leight (6) studied the effects of bretylium on the pulmonary arterial circulation of dogs and found that there was an increase in pulmonary arterial pressure without a significant rise in pulmonary capillary wedge pressure, left atrial pressure, or pulmonary blood volume. The mechanism for the pulmonary hypertension has remained obscure.

The following investigation was undertaken to define the effects of bretylium on the pulmonary veins and to determine if the small pulmonary veins play a role in the production of the pulmonary arterial hypertensive response to the drug. This study was considered especially important since no other investigations have considered the direct effects of the drug on the pulmonary veins. Previous investigators measured only pulmonary capillary wedge pressure which may or may not reflect satisfactorily pulmonary venous pressure (7–9).

Materials and Methods. Nine adult mongrel dogs (av wt, 17.6 kg) were lightly anesthetized with urethane (1.5 g/kg). The trachea was intubated and a small polyethylene catheter was placed in the endotracheal tube for administration of 100% oxygen (2–3 liters/min). Under fluoroscopic control, catheters were placed in the left atrium, small left lower pulmonary vein, pulmonary artery, right atrium, and aorta, as described in detail elsewhere (10). The small pulmonary vein catheter has not been found to obstruct venous flow sufficiently to interfere with experimental results (11). Following placement, the catheters were connected to P23Db Statham transducers, and pressures were recorded simultaneously on an Electronics for Medicine oscilloscopic recorder. Cardiac output and pulmonary blood volume were determined by the indicator dilution technique using indocyanine green (Cardiogreen) (12). Pulmonary mean transit time (PMTT) was calculated according to the formula:

$$PMTT = MTT_{(RA\ to\ LA)} - MTT_{(RA\ to\ PA)},$$

where MTT is mean transit time, RA is right atrium, LA is left atrium and PA is pulmonary artery. This method has been found to be

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reliable and reproducible in our laboratory (12). Systemic vascular resistance and total pulmonary vascular resistance were calculated by the standard method and expressed in resistance units. Pulmonary venous resistance, also expressed in resistance units, was calculated according to the formula:

$$\text{Pulmonary venous resistance} = \frac{P_{vs} - P_{la}}{CO},$$

where P_{vs} is pressure (mm Hg) in the small pulmonary vein, P_{la} is pressure (mm Hg) in the left atrium, and CO is cardiac output (liters/min).

When the dogs were in a "steady state," as determined by relatively constant pressures and cardiac output for 10 to 15 min, bretylium tosylate (150 mg) was rapidly injected through the right atrial catheter. Pressures were then recorded simultaneously and continuously except for brief interruptions at 5, 10, 15, 30, and 60 min for the indicator dilution studies.

Results. The results, summarized in Fig. 1, were essentially the same for all dogs.

Immediately following injection of bretylium, the pressure in the femoral artery decreased markedly, but within 5 min rose to above control levels (Fig. 1). This response in the femoral artery pressure occurred in every dog. The pressure in the femoral artery then declined slowly throughout the period of observation. The pulmonary artery pressure increased immediately after the injection of bretylium, returned to control levels, increased again at 15 min and then declined steadily (Fig. 1). The pressure in the left atrium decreased significantly at 10 min and continued to do so throughout the experimental period. Pressure recorded in the small pulmonary vein did not change significantly. Heart rate increased immediately after injection and remained above control levels throughout the study. Cardiac output increased markedly immediately after the injection of bretylium but returned to control levels by 10 min and remained there. Pulmonary blood volume did not change significantly during the experimental period. The pulmonary venous resistance increased significantly at 60 min. Total pulmonary vascular resistance decreased immediately following administration of bretylium, but returned to normal by 10 min and remained there throughout the experimental period.

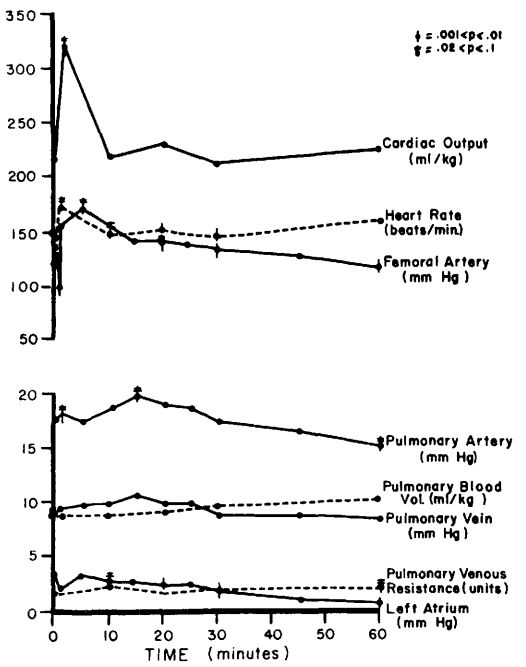

FIG. 1. Mean hemodynamic effects of bretylium tosylate (mean of 9 dogs).

Discussion. As noted by others (4–6), the intravenous injection of bretylium resulted in a transient rise in systemic arterial and pulmonary arterial pressures. Our finding of no change or a decrease in pressure in the small pulmonary veins and left atrium or in the pulmonary blood volume supports the contention of Taylor and Donald (4) that the transient increase in the pulmonary arterial pressure is due to the constriction of small arterial vessels. Although the initial increase in pulmonary artery pressure and decrease in pulmonary vascular resistance were related to an increase in cardiac output, this increase in cardiac output played no major role in the production of the increase in pulmonary arterial pressure at 10 min since the cardiac output had returned to normal by that time. After the initial "adrenergic" events had subsided, there was a progressive decline in the pulmonary arterial and venous pressures and pressure in the left atrium, reflecting a gener-

alized decrease in pulmonary vascular "tone." The significant increase in the "calculated" value for pulmonary venous resistance noted at 60 min was due to the relatively marked decrease in left atrial pressure. There may have been a localized relative constriction at the pulmonary vein–left atrial junction (13).

As in all studies in which an anesthetic agent is used, the role of the anesthetic agent in the observed changes must be considered. The initial "adrenergic" effects of bretylium would not be expected with urethane alone (14). However, the gradual decreases in pressures seen during the first hour are partly due to urethane anesthesia.

Summary. The effects of intravenous bretylium tosylate on the pulmonary circulation, including the small pulmonary veins, were studied in 9 intact dogs anesthetized with urethane. Bretylium produced a transient rise in femoral and pulmonary arterial pressures and in cardiac output and heart rate. The small pulmonary vein pressure did not change; and, since pulmonary blood volume did not change, there was no significant change in pulmonary venous tone. It is concluded that the initial pulmonary hypertensive effects of intravenous bretylium are primarily due to constriction of small arterial vessels.

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