

The Yucatan Miniature Swine: An Improved Pig Model for the Study of Desoxycorticosterone-Acetate (DOCA) and Aldosterone Hypertension (41480)

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Abstract. Blood pressure responses to chronic desoxycorticosterone-acetate (DOCA) or *d*-aldosterone (Aldo) administration in the intact adult Yucatan miniature boar were investigated. Daily pressure measurements were made between 9:00 AM and noon from Tygon carotid artery catheters. Following several days of baseline observations, DOCA-impregnated silastic strips, Aldo-impregnated silastic strips, or silastic alone (control) were implanted subcutaneously in the right or left flank under light thiethylal (Surital) anesthesia. Observations were continued for 3 weeks. Blood pressures with either steroid were significantly different from control within one week postimplantation. They continued to rise throughout the study period from a preimplant level of 100-110 mm Hg to a mean of 140 mm Hg. These studies demonstrate that the Yucatan miniature boar, in contrast to other animal models previously described, will readily develop hypertension with either DOCA or Aldo and that such studies can be conducted in the intact adult animal.

It has previously been reported that young, uninephrectomized farm pigs respond to desoxycorticosterone-acetate (DOCA) implantation with a rapid and consistent rise in blood pressure (1, 2). While these animals responded more reliably than dogs and rats, the use of a rapidly growing, pediatric animal presented difficulty in the interpretation of data (1, 3). Since this model was really a characterization of juvenile hypertension, it was questioned whether the responses observed could be directly extrapolated to the adult hypertensive process. Adult domestic farm pigs can weigh 300 kg or more. Studies utilizing these animals in their adult stage were therefore not feasible. The present study was undertaken to determine whether the adult Yucatan miniature swine would be suitable for studies in this area. Mature Yucatan miniature boars have a mean weight of 83 ± 12 kg (range 59-105 kg) (4) and, when treated correctly, are extremely docile. These features of the breed permit

measurements to be made in the unrestrained adult animal, and, since it has been shown that uninephrectomy is not required (5, 6), hypertension studies can be conducted in the intact animal. Additionally, it was of interest to determine whether the intact adult animal would respond to the administration of *d*-aldosterone (Aldo) as well as DOCA with an increase in blood pressure and whether the responses would be similar. Significant aldosterone hypertension in an intact adult animal model has not been previously reported.

Materials and Methods. Experimental animals (18-28 months old, 70-100 kg), were housed in 4 × 6-ft metabolic cages for observation periods of 2-4 weeks before undergoing surgical procedures. Throughout the study all animals received a premeasured quantity of pig chow meal (Zeigler Brothers, Gardners, Pa.) supplemented with sodium chloride to allow a controlled sodium intake of 4.5 meq/kg/day. Water was provided *ad libitum*. All metabolic measurements had stabilized by the end of the observation period.

An indwelling carotid artery catheter (Tygon 0.040-in. i.d., 0.070-in. o.d.) was then placed in each experimental animal. Following preanesthesia with ketamine (20

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mg/kg), pigs were maintained at a surgical plane with a mixture of halothane, nitrous oxide, and oxygen. The tip of the catheter was advanced into the thoracic descending aorta. Catheters were passed subcutaneously to the back of the neck and secured to stainless steel suture wire looped under the skin for external access.

After a minimum of 10 days of stable baseline measurements had been obtained, silicone (control), DOCA-impregnated silicone, or Aldo-impregnated silicone rubber strips were placed subcutaneously in the left or right flank under thiamylal (Surital) 2% or 4% i.a. anesthesia. Thiamylal was administered as necessary. Implants were prepared by mixing DOCA or Aldo (Sigma Chemical) and rubber (Dow Corning) in a ratio of approximately 1:2, and were sterilized with ethylene oxide before implantation (1). Total dosage was 100 mg/kg DOCA and 2.7 mg/kg Aldo. Fifteen experimental animals were used, six controls, five DOCA, and eight Aldo (two control animals were subsequently implanted with DOCA and two with Aldo).

Pressure measurements were made between 9:00 AM and noon daily with Statham pressure transducers (Model P23Db) and recorded on a Gould recorder (Model 2400) or Hewlett Packard recorder (Model 7758). All animals were conscious, standing, and unrestrained during pressure measurements. When not in use, catheters were filled with sodium-heparin (1000 U/ml) and closed with obturators constructed from 18-gauge needles.

All values are reported as mean \pm SEM. An unpaired Student's *t* test was used to compare data between experimental and control groups for 5 days pre- and 1 week postimplantation to determine the day on which experimental mean blood pressures became significantly greater than control. Differences were considered significant if $P < 0.004$. This level was chosen to reduce the possibility of Type I error since multiple tests were used (7). Mean blood pressures were similarly compared between Aldo- and DOCA-implanted animals throughout the study period. An adjustment was made in the alpha level for multiple tests and dif-

ferences were considered significant if $P < 0.002$.

Results. Blood pressure rose rapidly following DOCA administration and was significantly different from control by Day +7 (Fig. 1). It continued to rise throughout the study period to approximately 140 mm Hg. No significant blood pressure differences were observed between the control and DOCA groups prior to implantation, and pressures in the control group remained unchanged after implantation. Similar results were obtained following Aldo implantation (Fig. 1), in contrast to all other large species previously reported. By Day +4 pressures were significantly greater than control. They increased to approximately 140 mm Hg by Day +20. There were no significant differences between the two experimental groups throughout the 3-week implantation period.

Discussion. It has been reported that induction of steroid hypertension in adult animals is difficult if not impossible (8). Studies with the domestic pig clearly demonstrated that this animal, in its pediatric stage, will respond to DOCA administration (1-3). Studies with adult domestic pigs, however, were impractical due to the rapid growth rate and large adult size. Our studies demonstrate that the adult Yucatan miniature pig will rapidly and consistently become hypertensive after implantation with DOCA or Aldo. Since these animals are not rapidly growing, difficulties encountered in previous studies can be avoided (1, 2). Additionally, uninephrectomy is unnecessary in this animal in order for DOCA or Aldo hypertension to be expressed. Difficulties encountered with this surgical procedure can therefore be avoided. It has been shown, for example, that rats receiving DOCA on the day of nephrectomy are less responsive than those receiving treatment 2 weeks following the reduction of renal mass, and that the response of the hypertrophying kidney to DOCA is dose related (9-11).

Although Aldo has been used in a number of studies with rats, the ability of this steroid to produce hypertension has been disappointing and the results have been

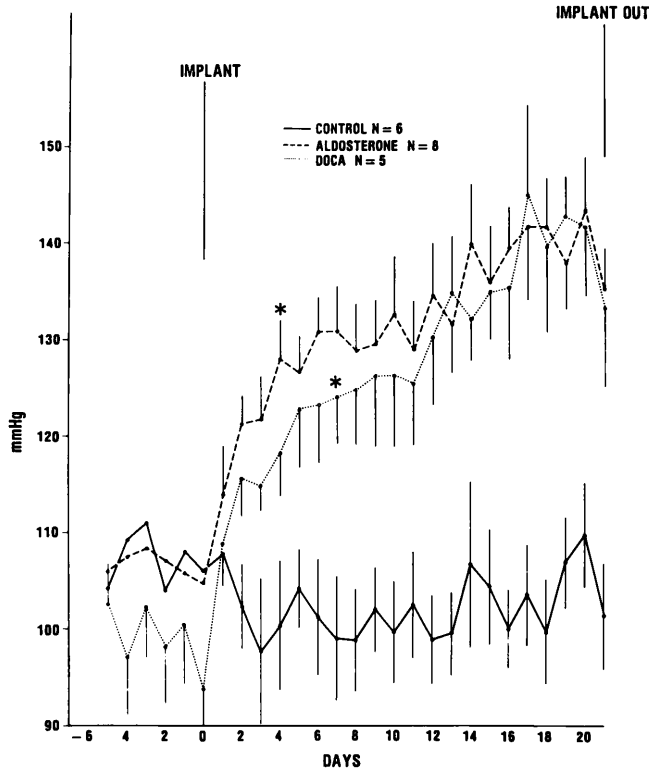


FIG. 1. Average mean arterial pressure of control, DOCA-hypertensive, and *d*-aldosterone-hypertensive pigs from 5 days before until 20 days after implantation of silastic (control), DOCA silastic, or *d*-aldosterone silastic. Pressures were measured using indwelling catheters advanced into the thoracic aorta via the left or right carotid artery. Data are presented as mean \pm SEM. Mean pressures increased regularly in the DOCA- and *d*-aldosterone-implanted animals, and were significantly different from control by 4 days postimplantation with *d*-aldosterone (*) and 7 days postimplantation with DOCA (*).

conflicting. It is possible that the use of the racemic mixture, *d,l*-aldosterone, rather than the *d*-isomer alone may have been the source of some of the problems encountered in attempting to produce Aldo hypertension in an animal model (12). In several cases the isomer used is not stated. In addition, the number of daily injections, vehicle used, and doses administered differ considerably from one study to another. The present studies demonstrate that an intact adult animal will respond to the administration of Aldo as well as DOCA with a rapid and consistent increase in blood pressure. The Yucatan miniature boar therefore provides an excellent opportunity for comparative studies of the actions of DOCA and Aldo in an intact animal in its adult stage.

It has been reported that captopril, an inhibitor of kininase II (angiotensin-I-converting enzyme) had no effect on the development of DOCA-salt hypertension or on established DOCA-salt hypertension when administered in the drinking water of rats (13, 14). However, the same investigators subsequently reported a decrease in blood pressure in established aldosterone-salt hypertension and an attenuation of the hypertension when captopril was given during the developmental phase (15). These findings imply mechanistic differences in the hypertensive process resulting from the administration of these two steroids. The authors speculated a difference in the importance of the vasodilator kinins. Vascular reactivity studies in the rat

also suggest that the mechanism(s) by which aldosterone produces hypertension may differ in certain important respects from that involved in DOCA hypertension (16, 17). Further studies of both DOCA and Aldo hypertension may provide additional insight into the underlying mechanistic differences of these two steroids. The results of such studies, now possible in an intact adult model of a large animal species, may afford a more realistic comparison to the hypertensive process in humans than has previously been possible.

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