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Cardiogenic Hypertension in Maturing Dogs

FABIO MAGRINI, NERYS ROBERTS, GIOVANNA BRANZI,
CRISTINA MONDADORI, PAOLO REGGIANI, MICHELE CIULLA,
AND ROBERTO MEAZZA

SUMMARY   The purpose of this study was to evaluate whether the heart can induce high blood pressure by maintaining an inappropriately elevated cardiac output/body weight ratio during growth. Direct (femoral artery) mean arterial pressure (MAP), heart rate, cardiac output/body weight ratio (as defined by M-mode echocardiography), and total peripheral vascular resistance were measured and calculated every 2 months in nine conscious dogs during development from 2 to 10 months of age. In four dogs a J-shaped catheter for atrial pacing was chronically implanted at the age of 3 months, and their hearts were permanently paced at 130 beats/min until maturity. The aim of atrial pacing was to prevent the natural slowing of the heart rate and, consequently, to maintain a cardiac output/body weight ratio that was inappropriately high in relation to age during growth. Five dogs were studied as controls. No hemodynamic differences were observed until the age of 4 months. From the age of 5 to 10 months heart rate was kept at 130 beats/min by atrial pacing in the atrially paced group, and the mean cardiac output/body weight ratio did not decrease (196 ± 24 vs 191 ± 34 [SE] ml/min/kg). MAP rose from 62 ± 4 to 116 ± 8 mm Hg, and total peripheral resistance increased from 0.34 ± 0.07 to to 0.61 ± 0.09 mm Hg/ml/min/kg. In the control group heart rate decreased with age from 170 ± 8 to 76 ± 6 beats/min, the cardiac output/body weight ratio was reduced from 195 ± 18 to 118 ± 22 ml/min/kg, MAP increased from 65 ± 6 to 92 ± 8 mm Hg, and total peripheral resistance rose from 0.32 ± 0.09 to 0.77 ± 0.08 mm Hg/ml/min/kg. In summary, inappropriate elevation of the cardiac output/body weight ratio during growth caused a deviation toward higher levels of the blood pressure maturation curve and inhibited the natural rise in total peripheral resistance. We conclude that the heart may generate high blood pressure during development, but this pure cardiogenic hypertension does not trigger a secondary rise in total peripheral resistance. (Hypertension 12: 295–300, 1988)

THE concept of cardiogenic hypertension is based on the simple hypothesis that, since arterial blood pressure is determined by both cardiac output (CO) and total peripheral resistance (TPR), the heart may play an *active* role in the development of some types of hypertension.[1-3] Theoretical objections to such a mechanism are based on the facts that under normal conditions CO is controlled primarily by peripheral factors and the heart itself has little to do with CO regulation and that the role of the kidney in controlling blood pressure appears critical.[4] Indeed, studies in both animals and humans have shown a wide spectrum of hemodynamic variations ranging from increased TPR with a normal or low CO, to increased CO with normal TPR, to a transitional pattern with a later progressive rise in TPR.[5]

Nonetheless, the finding of a rise in CO of about 15% in borderline hypertension revived interest in the suggestion that an augmented force of the heartbeat could play a role in the genesis of hypertension, although most investigators have been unable to show that such an increase will *necessarily* result in *chronic* hypertension.[3, 6]

Difficulties in design and differences in methodology may account for some of the uncertainties and conflicts reported in the literature. Several techniques have been used to augment flow (e.g., hypervolemia, increased myocardial contractility, and decreased capacitance leading to central redistribution of blood volume), and CO has been measured using a variety of techniques, such as dye dilution and ultrasonic and electromagnetic flowme-

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ters. Furthermore, a recent review concluded that greater attention to the effects of circadian rhythm and of aging, as well as the use of adequate controls, is necessary in further evaluation of the concept of cardiogenic hypertension.[3]

This study represents a novel approach to this problem, aiming to overcome some of the methodological shortcomings of previous work. First, the study was performed *during growth,* so that the effects of aging were intertwined. A previous study of rapidly growing mongrel dogs showed that the infantile cardiovascular system, which is characterized by high blood flow, low precapillary resistance, and possibly low venous capacitance and designed to provide a high degree of tissue perfusion in accordance with the high metabolic needs of growing tissues, is gradually remodeled during tissue growth to the adult pattern of lower blood flow and higher blood pressure.[7] Furthermore, analysis of the rate of change of hemodynamic variables indicates that the rate of weight gain acts as a natural stimulus to the cardiovascular system, resulting in a natural rise in mean arterial pressure (MAP), with reduced peripheral metabolic needs, that may mediate the fall in heart rate (HR), possibly through baroreceptor stimulation, and hence in CO/body weight (in kilograms) during extrauterine development.

Second, instead of producing an elevated CO, the aim of this study was to *prevent* the physiological fall in CO, thus maintaining with increasing age a CO that becomes inappropriately elevated in relation to age. By inserting an atrial pacemaker to regulate HR and by monitoring the CO by noninvasive echocardiography, we evaluated the response of the cardiovascular system to this single hemodynamic error in the presence of intact neural, humoral, and renal control mechanisms to determine whether this experimental error alone was sufficient to induce a deviation from the physiological blood pressure maturation profile to hypertensive levels and, if so, whether a rise in CO is an important step in the progression of hypertension to a stage of chronic peripheral resistance.

Materials and Methods

Animals and Anesthetics

Nine mongrel dogs were maintained in relative freedom with no major restriction of diet or physical activity. Dogs were studied hemodynamically from the age of 1 month (infancy) to 10 months (maturity). The first study was performed at 1 month of age because at this age there is sufficient distance from the acute cardiac and respiratory adjustments of the perinatal period. The dogs were considered mature at 10 months because they did not show significant increases in body weight in comparison with their parents over the preceding 2 months.

At 3 months, four dogs were chronically implanted with a J-shaped catheter or atrial pacing.[8] Implantation of the catheter was performed under local

anesthesia (lidocaine; 2% Xylocaine) using the jugular approach with fluoroscopic control. Animals were paced continuously at 130 beats/min until the age of 10 months (Figure 1) using a Cordis Chronocor M Standby Pacer (Model 156B, Miami, FL, USA) that was attached to each dog's back by means of a dog jacket and crepe bandages. A frequency of 130 beats/min was chosen because it was lower than the natural frequency at implantation but became functional when the physiological reduction in frequency reached 130 beats/min.

Periodic electrocardiograms were performed to document atrial capture of the pacemaker, and the threshold was adjusted as necessary to avoid escape with increasing age, from an initial threshold of 3 mA to a maximum of 7 mA.[9]

Hemodynamic Measurements

Hemodynamic measurements were determined every 2 months in control and atrially paced dogs from infancy to maturity, and in the 2 weeks before the first study the puppies were taken to the laboratory daily to familiarize them with the instruments and investigators. Following commencement of the study proper, the dogs were taken to the laboratory as frequently as possible (approximately three times per week) to maintain this familiarization. The dogs were weighed before the study. All the hemodynamic measurements were performed on conscious dogs in a quiet laboratory while the dogs rested on a padded bench. The average time required for the hemodynamic evaluation was 30 to 40 minutes.

With the dogs under local anesthesia (lidocaine; 2% Xylocaine), the femoral artery was cannulated with a 4F polyurethane radiopaque needle introduced percutaneously using a 21-gauge butterfly needle and a Teflon guidewire (Seldinger tech-
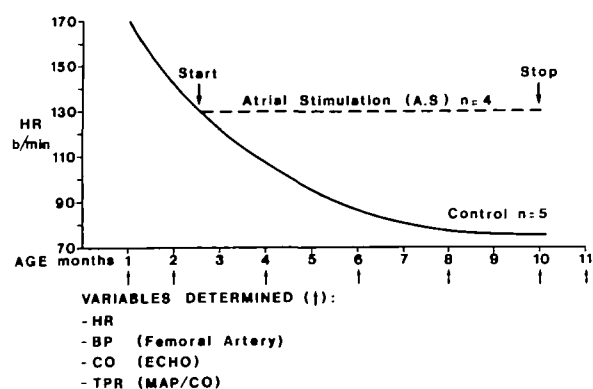

FIGURE 1. *Design of study. Arteriovenous oxygen difference was also determined during each hemodynamic study. The continuous curve represents the physiological reduction in frequency with age, while the interrupted line projects the anticipated effect of atrial pacing at a constant frequency. HR = heart rate; BP = blood pressure; CO = cardiac output; TPR = total peripheral resistance; ECHO = echocardiography.*

nique). In isolated cases, surgical exposure of the femoral vessels was necessary by means of a 1-cm cutdown through the skin of the inguinal region. The cannula was connected to a Statham P23Db strain gauge transducer (Oxnard, CA, USA). In nonpaced dogs ($n = 5$), a 4F cannula was introduced into the femoral vein.

Blood pressure was monitored directly in the femoral artery for 30 to 45 minutes until the pressure was stable, and MAP was measured from the arterial tracing taken over a 30-second period using an electronic integrator (Model K0300, Battaglia Rangoni, Bologna, Italy). HR was measured from the arterial tracing taken over a 30-second period. CO was deduced from echocardiographic measurements. With the dog in the right lateral decubitus position, bidimensional echocardiographic screening was used to find the optimal probe position and M-mode echocardiography (ATL MK 400, Advanced Technology Laboratories, Bellevue, WA, USA) was used to determine left ventricular systolic and diastolic diameters. The validity of this technique in awake dogs has been addressed previously. In particular, echocardiographic estimates of stroke volume (SV) have been shown to correlate closely with dye dilution technique measurements.[10, 11] Hence, left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were calculated, from which SV was deduced (SV = LVEDV − LVESV). CO (SV × HR) and ejection fraction (SV/LVEDV × 100) were then derived. TPR was calculated by dividing MAP by the CO/body weight (in kilograms) ratio.

Blood samples were taken from the femoral artery and femoral vein (in nonpaced dogs) or through the pacing catheter (in paced dogs) at each study to determine oxygen saturation. The arteriovenous oxygen ($A-V_{O_2}$) difference was subsequently calculated (IL CO oximeter system, Lexington, MA, USA).

Statistical Evaluation

The statistical significance of the results was evaluated with paired or unpaired Student's t test. Probability values (p) less than 0.05 were accepted as significant. The results are expressed as means ± SE.

Results

The paced dogs did not suffer any adverse effects from the chronically implanted pacemaker, and body weight, taken as an index of body growth, did not differ significantly from that in control (nonpaced) dogs.

No significant difference in any hemodynamic parameter was observed between control and paced dogs until 4 months of age (Figures 2 and 3). The expected physiological reduction in HR was observed in the control dogs (from 170 ± 8 beats/min at 1 month to 76 ± 6 at 11 months), whereas the pacemaker maintained the frequency of the paced
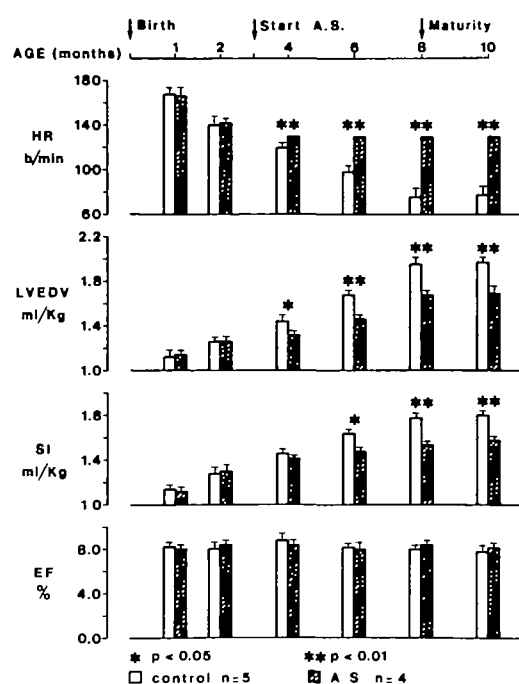

FIGURE 2. *Cardiac changes during normal growth and their modification by the maintenance of a frequency of 130 beats/min. The physiological rise in left ventricular end-diastolic volume (LVEDV), taken as an index of cardiac dimension, was reduced. HR = heart rate; SI = stroke index; EF = ejection fraction; AS = atrial stimulation.*

dogs at 130 beats/min throughout the period of growth.

The maintenance of a fixed, inappropriately high frequency for age was not sufficient to prevent the physiological increase in cardiac volume, as evidenced by the progressive rise in LVEDV per kilogram of weight, although it was sufficient to significantly reduce the increments in LVEDV in comparison to normally developing dogs. Similar findings were observed for stroke index. Ejection fraction, taken as an index of ventricular performance, was essentially equal in paced and control dogs and relatively independent of age. Therefore, the net result of maintaining a frequency that became inappropriate for age, was the generation of a supraphysiological cardiac index, which in paced dogs remained essentially unchanged (196 ± 24 ml/min/kg at 4 months, 191 ± 34 ml/min/kg at 10 months), while normal dogs exhibited a gradual, progressive reduction in cardiac index with growth (from 195 ± 18 ml/min/kg at 4 months to 113 ± 22 ml/min/kg at 10 months).

In the paced dogs, MAP rose from 62 ± 4 to 116 ± 8 mm Hg and TPR increased from 0.34 ± 0.07 to 0.61 ± 0.09 mm Hg/ml/min/kg (see Figures 2 and 3). In control dogs MAP increased from 65 ± 6 to 92 ± 8 mm Hg and TPR increased from 0.32 ± 0.09 to 0.77 ± 0.08 mm Hg/ml/min/kg (see Figures 2 and 3). Although the methodology restricted measurement
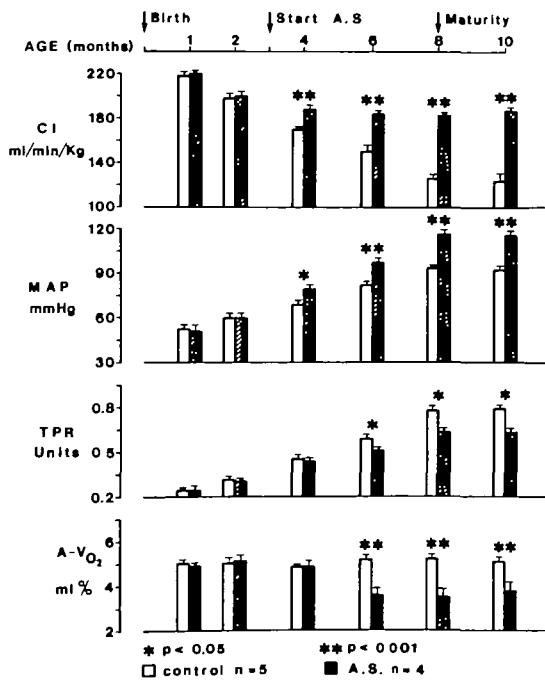
FIGURE 3. *Systemic hemodynamics during growth with and without fixation of heart rate. Chronic atrial pacing maintained a physiological but inappropriately high cardiac output (CO) in relation to age and prevented the physiological fall in CO with growth. AS = atrial stimulation; CI = cardiac index; TPR = total peripheral resistance; $A\text{-}V_{O_2}$ = arteriovenous oxygen difference.*

of blood pressure to short periods, it is unlikely that the elevation in blood pressure observed in paced dogs was a transient effect due to the stress of the study, as this rise was not seen in the control animals undergoing the same investigations.

Chronic pacing produced no significant change in $A\text{-}V_{O_2}$ difference until 6 months of age. Before the age of 6 months the control and paced dogs had essentially equal and constant values of $A\text{-}V_{O_2}$ difference; thereafter, however, while the $A\text{-}V_{O_2}$ difference remained stable with further growth in normal animals, in those that underwent chronic atrial pacing there was a sharp, sustained reduction in $A\text{-}V_{O_2}$ difference between 4 and 6 months that was statistically highly significant ($p < 0.001$).

After cessation of atrial pacing, the values of $A\text{-}V_{O_2}$ difference remained constant (3.9 ± 0.2 and 4.1 ± 0.3 ml%, respectively, after 15 and 30 minutes) in spite of the acute reduction in CO. One month later (at the age of 11 months) no differences were observed in the $A\text{-}V_{O_2}$ values between control dogs and dogs that underwent atrial pacing.

In summary, atrial pacing of dogs from the age of 3 months to maintain an elevated CO/body weight ratio during maturation resulted in a slight increase in MAP after 4 months compared with that in controls. Furthermore, atrial pacing and subsequent elevation of the CO/body weight resulted in

an inhibition of the natural rise in TPR observed during the maturation of control dogs (see Figure 3). Cessation of atrial pacing at 10 months of age resulted in complete reversal of all hemodynamic effects of the inappropriately high frequency by 11 months of age (Figure 4).

Discussion

The experimental design of this study provides a new model of cardiogenic hypertension. In contrast to control dogs whose cardiovascular systems underwent physiological maturation to achieve higher blood pressure with a lower CO/body weight ratio with increasing age, insertion of a pacemaker in dogs at 2 months of age prevented the fall in CO/body weight and was a sufficient stimulus to the deviation of the blood pressure curve to hypertensive levels. Thus, in contrast to the hypothesis that an increase in CO alone would not sustain an increase in arterial pressure because the kidneys would respond to the augmented perfusion pressure by increasing urine output (pressure-diuresis),[12] these data suggest that elevation of blood pressure results from an inappropriately high CO despite the presence of normal renal function.

Many other investigators have observed an elevation in blood pressure in a number of models after maneuvers that augment CO, with an initial phase of high CO and low TPR, followed by a phase in which the elevated blood pressure was maintained by TPR with a gradual normalization of CO.[13-15] These find-
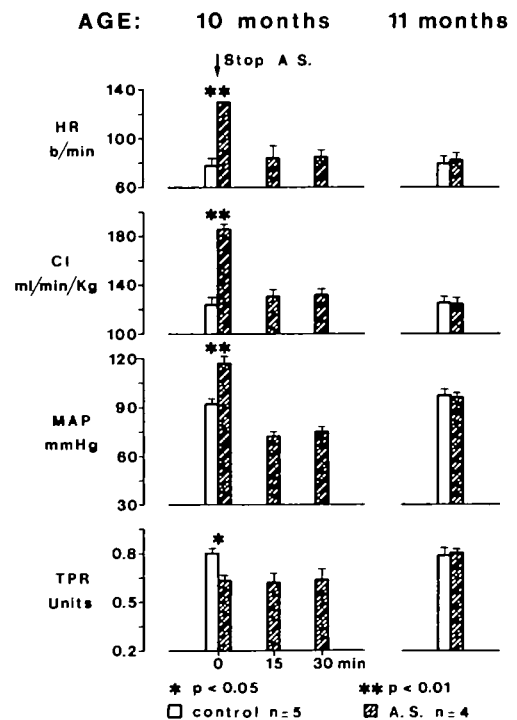

FIGURE 4. *Reversibility of systemic hemodynamic changes induced by pacing. HR = heart rate. See Figure 3 for key to other abbreviations.*

ings are consistent with an initial baroreceptor-mediated fall in TPR and a subsequent rise in TPR with adaptation of the baroreceptor reflex, together with the activation of autoregulatory mechanisms in response to the increased tissue perfusion.

In contrast, in this study, the elevated CO was maintained and was associated throughout with a failure of the TPR to increase in the usual manner with age (Figure 5). Since the dogs were studied throughout the growth period, it seems unlikely that these findings represent only the initial phase of hypertension and that further follow-up would have been associated with the development of augmented TPR.

The possibility that the baroreceptor reflex and autoregulatory mechanisms were not mature in the study population can also be ruled out by the observation of normal hemodynamic development in the control population. Clearly, a study of maturing animals introduces the complexity of the physiological changes occurring in the parameters studied; however, the data do not represent a simple arrest of maturation, as removal of the pacemaker was associated with reversal of all parameters to values that were appropriate in relation to age. Therefore, it may be postulated that, although present, the mechanisms of autoregulation are not triggered by a situation of excess tissue perfusion per se under these experimental conditions or that, if they are triggered, they may be masked by independent regulation of flow to meet metabolic demands rather than blood volume status.

The other salient features of this study were the reversibility of the hypertension, the reduction in vascular resistance, and the reestablishment of a CO and HR appropriate to age within 1 month of cessation of pacing. Thus, a rise in CO per se is not sufficient to initiate chronic hypertension. This conclusion is in agreement with the observation of increased CO resulting from electrical stimulation of the stellate ganglion for periods of 1 week up to 2 months, with peripheral constriction disappearing soon after the stimulation is stopped.[1] Furthermore, the structural changes in vascular architecture, with changes in wall thickness and length and growth or retardation of new and existing vessels, postulated to underlie long-term autoregulation did not occur in the present study.

The observation of increased CO with low TPR in these healthy dogs in which reversible hypertension developed is consistent with the suggestion that the subgroup of hypertensive patients with increased CO and normal peripheral resistance actually represent an inappropriate response to increased CO (i.e., that the normal TPR is inappropriately high and that this is essential for the maintenance of high blood pressure). Thus, to conclude, atrial pacing at an early age provides a novel animal model for purely cardiogenic juvenile hypertension, and this study seems to suggest that although augmenting the CO results in abnormally high blood pressure, these changes are reversible, thus negating a primary role for the heart in the pathogenesis of juvenile hypertension.

Acknowledgments

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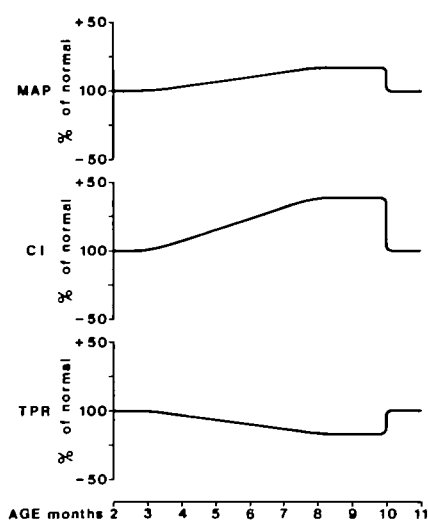
FIGURE 5. *Percent changes in basic hemodynamic parameters during atrial pacing and after the interruption of electrical stimulation (10 months of age). See Figure 3 for key to abbreviations.*

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