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In Vivo Demonstration of Maturational Changes of the Chronotropic Response to α-Adrenergic Stimulation[1]

JORGE McCORMACK, HENRY GELBAND, JUAN VILLAFAÑE, HUI XU, ADRIENNE STOLFI, AND ARTHUR S. PICKOFF

Division of Pediatric Cardiology, Department of Pediatrics, University of Miami School of Medicine, Miami, Florida; the Division of Pediatric Cardiology, Department of Pediatrics, University of Louisville School of Medicine, Louisville, Kentucky [J.V.]; and the Division of Pediatric Cardiology, Department of Pediatrics, Tulane University School of Medicine, New Orleans, Louisiana [A.S.P.]

ABSTRACT. ***In vitro* studies suggest that neonates and adults may have different cardiac chronotropic responses to α-adrenergic stimulation. To investigate these differences *in vivo*, three groups of dogs were studied. Group I = 12 puppies, ages 3–7 days; group II = 12 puppies ages 8–15 days, and group III = seven adult dogs. Heart rate and blood pressure determinations were made in the control setting and then after combined β-adrenergic and parasympathetic blockade (propranolol 0.6 mg/kg and bilateral vagotomies). Alpha-stimulation was then achieved with phenylephrine given in doses of 0.5, 1.0, and 10.0 μg/kg/min. A second, high dose of propranolol (1.0 mg/kg intravenously) was administered after the highest phenylephrine infusion dosage to assure complete β-blockade. Finally, α-blockade was achieved with phentolamine (groups I and II: 0.5 mg intravenously; group III: 5.0 mg intravenously). An α-mediated positive chronotropic effect was observed in 42 and 100% of subjects in groups I and II, respectively, but never observed in the adults. Whereas α-blockade with phentolamine resulted in a large decrease in heart rate of all puppies (groups I and II), it had no effect on adults. Blood pressure responses were similar in all three groups. Thus, there are important maturational changes in the chronotropic response to α-adrenergic stimulation and blockade demonstrable in the intact neonatal canine. (*Pediatr Res* 24, 50–54, 1988)**

In vivo and *in vitro* studies in the adult human and mature animal have suggested that stimulation of myocardial α-adrenoceptors results in a decrease in myocardial chronotropy (1–5). However, studies using intracellular microelectrodes in neonatal Purkinje fibers (6, 7) and spontaneously beating cultured neonatal cardiocytes (8), have suggested that α-adrenergic stimulation in these immature cells often results in an increase in their spontaneous rate. Other studies have found an increased binding of radioactive ligands to α-adrenoceptors in the immature myocardium, suggesting that these receptors either are increased in absolute numbers or have an increased affinity for these drugs (9).

Because of the potential physiological and clinical importance of these observations, we undertook this study to determine whether differences in the responses of the neonatal and adult sinus node to α-adrenergic stimulation could be demonstrated in the intact animal. Specifically, this study was designed to examine the chronotropic effects of α-adrenergic stimulation and blockade on the neonatal sinus node and to assess the influence of maturation on the observed response.

METHODS

Experimental preparation. To investigate the chronotropic response to α-stimulation and to assess the role of maturation in modulating this response, three groups of dogs were studied. Group I consisted of 12 neonatal puppies, ages 3–7 days; group II consisted of 12 older puppies, ages 8–15 days; and group II consisted of seven adult dogs.

All animals were anesthetized with Na pentobarbital (30 mg/kg) intraperitoneally in groups I and II and intravenously in group III. Na pentobarbital supplementation (15 mg/kg) was given intravenously when spontaneous movement occurred or when there was a response to painful stimuli. All animals were intubated and mechanically ventilated with a Harvard ventilator. Arterial blood gases were monitored to assure adequate acid base status and oxygenation.

ECG surface lead II and femoral artery blood pressure (Gould Statham blood pressure transducer) were constantly monitored. A catheter was introduced in each femoral vein and positioned in the inferior vena cava for drug administration.

Protocol. After the above preparation, 15 min were allowed before "control" heart rate and "control" blood pressure determinations were obtained. Heart rate was determined by measuring and averaging at least three cycle lengths. To eliminate β-adrenergic-mediated and parasympathetic modulation of the heart, combined β-adrenergic and parasympathetic blockade was performed. This was achieved with the administration of racemic propranolol 0.6 mg/kg intravenously and by performing bilateral cervical vagotomies. We have previously shown that this dose of propranolol is sufficient to completely block the tachycardia caused by drug induced catecholamine release (McCormack J, Stolfi A, Pickoff AS, unpublished observations). Also, in other experiments, the adequacy of bilateral cervical vagotomies for parasympathetic blockade was verified by observing a lack of heart rate response to atropine after bilateral vagotomies (10). After these procedures, an additional 15 min were allowed for stabilization and "blockade" heart rate and blood pressure meas-

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Correspondence and reprint requests Jorge McCormack, M.D., Pediatric Cardiology, Department of Pediatrics (R-76), University of Miami School of Medicine, P.O. Box 016960, Miami, FL 33101.
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urements were then obtained. At this point, the only possible autonomic modulation of the heart rate and blood pressure is via α-adrenoceptors being stimulated either by circulating catecholamines or sympathetic nerve terminals.

Alpha-adrenergic stimulation was achieved with phenylephrine, administered at increasing constant infusion doses of 0.5, 1.0, and 10.0 μg/kg/min. Infusion rate was constant at 10 ml/h and dosages adjusted by changing the concentration of phenylephrine in each infusate. Each infusion dose was maintained for 15 min. Repeat measurements of heart rate and blood pressure were obtained at the end of each 15-min interval, just before the next increase in phenylephrine dosage. Fifteen min after the highest phenylephrine infusion was started heart rate and blood pressure were measured and the infusion was continued during the remainder of the experimental manipulations described below. Unless otherwise stated, the "phenyl" heart rate and blood pressure values reported in the text are those obtained with the highest phenylephrine infusion dosage.

To exclude the possibility that any of the observed effects of phenylephrine were due to β-adrenergic stimulation (11), a second, high dose of propranolol (1.0 mg/kg intravenously) was administered after the highest dose of phenylephrine. The heart rate and blood pressure were determined 15 min after the second dose of propranolol was administered ("prop 2").

Finally, α-adrenergic blockade was achieved with phentolamine, 0.5 mg intravenously in groups I and II and 5.0 mg intravenously in group III. Because of phentolamine's known rapid onset of action and its short half-life (12) only 5 min were allowed for equilibration and the phentolamine ("phentol") heart rate and blood pressure data were obtained.

Data analysis. Animals were classified according to the type of heart rate responses exhibited after phenylephrine infusions and by the response to the second dose of propranolol. The types of responses were defined as follows. Type A: phenylephrine induced an increase in the sinus rate that was not reversed to baseline values by the second dose of propranolol, indicating that the phenylephrine-induced acceleration is α mediated. Type B: phenylephrine induced an increase in sinus rate that is completely reversed by the second dose of propranolol. Thus, the phenylephrine induced cardioacceleration is a β effect. Type C: phenylephrine administration resulted in a decrease in sinus rate, suggesting this is an α-mediated cardiodeceleration.

Statistical analysis. To determine whether a specific manipulation resulted in a significant change, statistical analysis were performed with analysis of variance followed by the Tukey honestly significant difference test for multiple comparisons between paired means. Results are presented as mean ± 1 SD.

RESULTS

Heart Rate Responses to Combined β-Adrenergic and Parasympathetic Blockade. In group I, the combined β-adrenergic and parasympathetic blockade resulted in a statistically insignificant decrease in the mean heart rate (172 ± 23 bpm, control; 166 ± 25 bpm, blockade; NS), whereas in group II, the mean heart rate remained unchanged (164 ± 18 bpm, control; 163 ± 19 bpm, blockade; NS) However, combined β-adrenergic and parasympathetic blockade resulted in a 21% decrease in the heart rate of the adult dogs (151 ± 15 bpm, control; 118 ± 10 bpm, blockade; $p < 0.05$).

Heart Rate Responses to Phenylephrine Infusions. Group I (3–7 days old). Five of the 12 neonates in this age group exhibited a type A response, in which the phenylephrine-induced increase in heart rate was not reversed by propranolol (Table 1; Fig. 1). In these neonates, phenylephrine resulted in a dose-related increase in the mean heart rate of 18%, although this did not achieve statistical significance (169 ± 27 bpm, blockade; 201 ± 43 bpm, phenyl; NS). As a type A response, in this group, the second dose of propranolol resulted in only a small decrease in heart rate (201 ± 43 bpm, phenyl; 188 ± 32 bpm, prop 2; NS)

Table 1. *Heart rate response**

	Group I ($n = 12$)						Group II ($n = 12$)				Group III ($n = 7$)			
	A ($n = 5$)		B ($n = 4$)		C ($n = 3$)		A ($n = 12$)		B ($n = 4$)		C ($n = 3$)	
Type of Response:	HR (bpm ± SD)	% Change	HR (bpm ± SD)	% Change	HR (bpm ± SD)	% Change	HR (bpm ± SD)	% Change	HR (bpm ± SD)	% Change	HR (bpm ± SD)	% Change
Control	176 ± 24		172 ± 30		165 ± 13		164 ± 18		146 ± 6		157 ± 22	
Prop. + vagot.	169 ± 27		152 ± 25		180 ± 21		163 ± 19		117 ± 14		118 ± 3	
Phenylephrine (0.5 μg/kg/min)	173 ± 30	+2	155 ± 22	+3	168 ± 18	−7	166 ± 21	+1	116 ± 17	−1	116 ± 5	−2
Phenylephrine (1.0 μg/kg/min)	178 ± 36	+5	158 ± 20	+4	159 ± 10	−11	170 ± 21	+4	122 ± 13	+4	113 ± 5	−4
Phenylephrine (10.0 μg/kg/min)	201 ± 43	+18	166 ± 25	+10	164 ± 3	−8	187 ± 17	+15	128 ± 18	+9	115 ± 6	−2
Propranolol 2 (1.0 mg/kg)	188 ± 32	+12	148 ± 24	−2	148 ± 9	−17	182 ± 20	+12	107 ± 10	−9	113 ± 15	−5
Phentolamine	138 ± 18	−18	116 ± 19	−24	117 ± 3	−35	156 ± 21	−5	105 ± 4	−10	109 ± 4	−8

* Prop. + vagot., propranolol (0.6 mg/kg) plus bilateral vagotomies. HR, heart rate, expressed as beats per minute bpm ± 1 SD; % change, the change from the prop. + vagot. value.

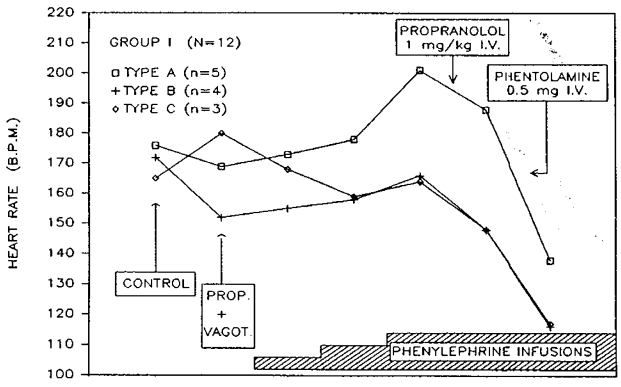

Fig. 1. Heart rate responses in group I (ages 3–7 days). Heart rate is expressed in beats per minute. Combined β-adrenergic and parasympathetic blockade had a minor effect on heart rate. Type A, phenylephrine-induced increase in heart rate was only partially reversed by the second dose of propranolol and completely abolished by phentolamine. Type B, phenylephrine induced increase in heart rate was completely reversed by the second dose of propranolol. Type C, phenylephrine administration resulted in a decrease in heart rate.

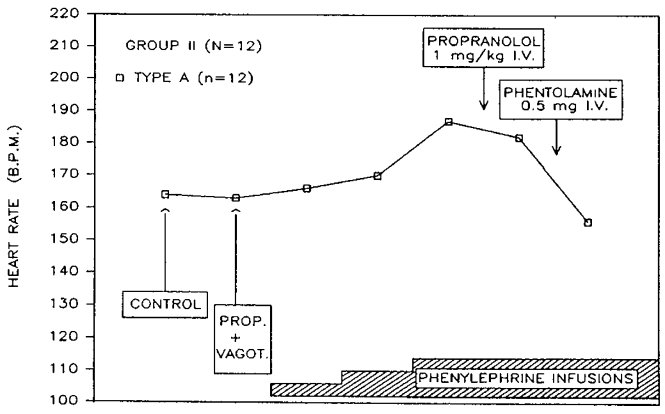

Fig. 2. Heart rate responses in group II (ages 8–15 days). Heart rate is expressed in beats per minute. Combined β-adrenergic and parasympathetic blockade had no significant effect on heart rate. All of the subjects in this group had type A response. The phenylephrine-induced increase in heart rate was not affected by the second dose of propranolol but was completely reversed by phentolamine.

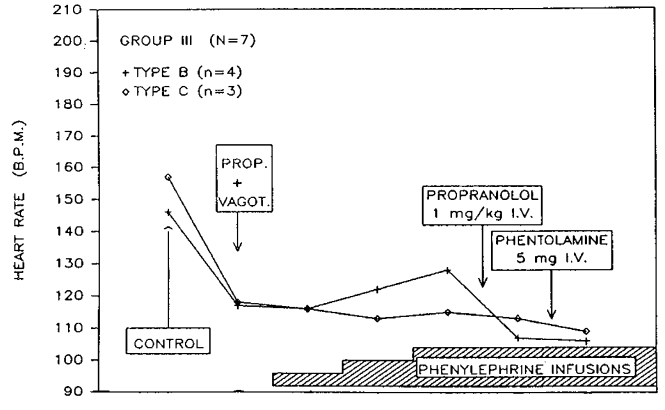

Fig. 3. Heart rate responses in group III (adults). Heart rate is expressed in beats per minute. Combined β-adrenergic and parasympathetic blockade resulted in a significant decrease in heart rate. Type B, the phenylephrine-induced increase in heart rate was abolished by the second dose of propranolol. Type C, phenylephrine administration results in a decrease in heart rate. Phentolamine had no effect on heart rate in either subgroup.

and the heart rate remained 12% faster than that before the phenylephrine infusion. Finally α-blockade with phentolamine caused a significant deceleration of the heart rate (188 ± 32 bpm, prop 2; 138 ± 18 bpm, phentol; $p < 0.05$). Thus, in these puppies, phenylephrine resulted in a slight tendency to increase heart rate, suggesting an α-mediated positive chronotropic effect.

Four of the 12 puppies in this group had a type B response, in which the phenylephrine-induced acceleration is reversed by propranolol. Specifically, phenylephrine caused a dose related increase (10%) in heart rate (152 ± 25 bpm, blockade; 166 ± 25 bpm, phenyl; $p < 0.05$). The second dose of propranolol, however, completely abolished the phenylephrine induced acceleration (166 ± 25 bpm, phenyl; 148 ± 24 bpm, prop 2; $p < 0.05$). In these puppies, the administration of phentolamine caused a further 24% reduction of the mean heart rate (148 ± 24 bpm, prop. 2; 116 ± 19 bpm, phentol; $p < 0.01$). Thus, in these puppies, whereas the phenylephrine-induced cardioacceleration is likely to have been mediated via β-receptor stimulation, α-blockade with phentolamine still resulted in a decrease in their sinus rate, suggesting a tonic, α-mediated positive chronotropic effect.

Three of the 12 puppies in group I had a type C response, in which decreases in heart rate were observed after phenylephrine. In this subgroup, after the 1.0 μg/kg/min dose of phenylephrine a tendency of decrease in heart rate was observed (the mean heart rate decreased by 11%) (180 ± 21 bpm, blockade; 159 ± 10 bpm phenyl 1.0 μg/kg/min; NS). During the 10.0 μg/kg/min infusion of phenylephrine, the heart rate remained unchanged in two of the puppies and increased in one. After the second dose of propranolol the mean rate of all three puppies seemed to decrease (164 ± 3 bpm, high phenyl 10.0 μg/kg/min; 148 ± 9 bpm, prop 2; NS). Interestingly, α-blockade with phentolamine seemed to result in a further 35% reduction of the heart rate of these three puppies, although this did not achieve statistical significance (148 ± 9 bpm, prop 2; 117 ± 3 bpm, phentolamine; NS). Thus, in this subgroup, both α-agonist and α-antagonist drugs appear to result in a decrease in heart rate.

Group II (8–15 days). In contrast to the youngest neonates, all of the responses observed in this group were type A, where a positive chronotropic effect from alpha stimulation could be demonstrated (Table 1; Fig. 2). Phenylephrine caused a dose-related 15% increase in heart rate (163 ± 19 bpm, blockade; 187 ± 17 bpm, phenyl; $p < 0.05$). The second high dose of propranolol resulted in only a small decrease in heart rate (187 ± 17 bpm phenyl; 182 ± 20 bpm prop 2; NS), but the mean heart rate still remained 12% above values obtained after the combined β-adrenergic and parasympathetic blockade and before the phenylephrine infusion. In this group, α-blockade with phentolamine resulted in an additional decrease in the heart rate of all puppies (182 ± 20 bpm, prop 2; 156 ± 21 bpm, phentol; $p < 0.001$). Thus, in all of the older puppies, a positive chronotropic effect due to α-stimulation could be demonstrated.

Group III (adult dogs). In this group, a very different pattern of responses was observed (Table 1; Fig. 3). In contrast to the neonates, a positive chronotropic effect due to α-adrenergic stimulation was never demonstrated in the adult dogs.

Four of seven adult dogs had a type B response, where the phenylephrine-induced increase in heart rate was blocked by propranolol. In these animals, the pattern of observed responses was as follows: phenylephrine resulted in a dose dependent 9% increase in heart rate (117 ± 14 bpm, blockade; 128 ± 18 bpm, phenyl; NS). The second dose of propranolol resulted in a complete reversal of the phenylephrine-induced acceleration, their heart rate now becoming 9% slower than after the combined blockade (128 ± 18 bpm, phenyl; 107 ± 10 bpm prop 2; NS). Phentolamine had no effect in these animals (107 ± 10 bpm prop 2; 105 ± 4 bpm phentol; NS)

Table 2. *Blood pressure response**

		Group I (n = 12)		Group II (n = 12)		Group III (n = 7)	
		BP (mm Hg ± SD)	% Change	BP (mm Hg ± SD)	% Change	BP (mm Hg ± SD)	% Change
Control	Sys./Dias.	55 ± 9		69 ± 10		141 ± 19	
		27 ± 5		32 ± 5		106 ± 11	
Prop. + vagot.	Sys./Dias.	57 ± 7		64 ± 6		144 ± 20	
		27 ± 3		30 ± 3		101 ± 13	
Phenylephrine (0.5 μg/kg/min)	Sys./Dias.	75 ± 15	+32	73 ± 10	+15	158 ± 19	+11
		34 ± 7	+27	33 ± 6	+7	112 ± 21	+12
Phenylephrine (1.0 μg/kg/min)	Sys./Dias.	88 ± 17	+55	79 ± 15	+24	178 ± 34	+27
		39 ± 9	+44	36 ± 8	+17	131 ± 30	+32
Phenylephrine (10.0 μg/kg/min)	Sys./Dias.	113 ± 18	102	115 ± 17	+80	219 ± 22	+55
		64 ± 13	+141	64 ± 19	+107	172 ± 22	+73
Propranolol 2 (1.0 mg/kg)	Sys./Dias.	103 ± 15	+84	104 ± 21	+63	154 ± 42	+9
		60 ± 12	+127	59 ± 18	+91	122 ± 35	+24
Phentolamine	Sys./Dias.	42 ± 9	−25	61 ± 17	−4	109 ± 28	−24
		19 + 3	−30	28 ± 9	−8	76 ± 20	−24

* Sys., systolic blood pressure in mm Hg ± 1 SD; dias., diastolic blood pressure in mm Hg ± 1 SD; Prop. + vagot., propranolol (0.6 mg/kg) plus bilateral vagotomies; % change, the change from the prop. + vagot. value.

Three of seven adult dogs had a type C response. The phenylephrine infusions resulted in an insignificant (2%) decrease in the mean heart rate of these dogs. In this group, the administration of the second dose of propranolol and the dose of phentolamine resulted in no change in their mean heart rate.

Blood Pressure Responses. The observed changes in blood pressure were similar within each group regardless of the type of heart rate response observed (Table 2).

Blood pressure responses observed were similar in groups I and II. Specifically, no changes in systolic and diastolic blood pressure were observed after the combined β-adrenergic and parasympathetic blockade. Phenylephrine infusion resulted in a dose-dependent increase in both the systolic (group I: 57 ± 7 mm Hg, blockade; 113 ± 18 mm Hg, phenyl; $p < 0.01$) (group II: 64 ± 6 mm Hg, blockade; 115 ± 17 mm Hg phenyl $p < 0.01$) and diastolic (group I; 27 ± 3 mm Hg blockade; 64 ± 13 mm Hg phenyl; $p < 0.01$) (group II: 30 ± 3 mm Hg blockade; 64 ± 19 mm Hg phenyl; $p < 0.01$) blood pressure. The second dose of propranolol resulted in only a slight decrease in blood pressure. However, phentolamine caused a large decrease in systolic (group I: 103 ± 15 mm Hg prop 2; 42 ± 9 mm Hg phentol; $p < 0.01$) (group II: 104 ± 21 mm Hg prop 2; 61 ± 17 mm Hg phentol; $p < 0.01$) and diastolic (group I: 60 ± 12 mm Hg prop 2; 19 ± 3 mm Hg phentol; $p < 0.01$) (group II: 59 ± 18 mm Hg prop 2; 28 ± 9 mm Hg phentol; $p < 0.01$) blood pressure.

In group III, small and variable changes were observed after the combined β-adrenergic and parasympathetic blockade. As with groups I and II, phenylephrine infusion resulted in dose-related increases in both systolic (144 ± 20 mm Hg blockade; 219 ± 22 mm Hg phenyl; $p < 0.01$) and diastolic (101 ± 13 mm Hg blockade; 172 ± 22 mm Hg phenyl; $p < 0.01$) blood pressures. However, unlike groups I and II, the second dose of propranolol resulted in a large decrease of systolic blood pressure (219 ± 22 mm Hg phenyl; 154 ± 42 mm Hg prop 2; $p < 0.05$) whereas decreases in diastolic blood pressure did not achieve statistical significance (172 ± 22 mm Hg phenyl; 122 ± 35 mm Hg prop 2; NS). Phentolamine caused a further reduction in both systolic (154 ± 42 mm Hg prop 2; 109 ± 28 mm Hg phentol; $p < 0.001$) and diastolic (122 ± 35 mm Hg prop 2; 76 ± 20 mm Hg phentol; $p < 0.05$) blood pressures becoming substantially lower than the baseline values.

It is interesting to note that the phenylephrine induced increase in blood pressure was substantially greater in the neonatal than in the adult groups.

DISCUSSION

Several studies have described significant differences in the function of the β-adrenergic and parasympathetic systems between neonates and adults (13–17). These studies have suggested that the autonomic nervous system is immature at birth. Specifically, studies have suggested that the parasympathetic system is relatively more "mature" at birth than the β-adrenergic system (14, 15). Whereas there is decreased cardiac sympathetic innervation at birth, it has also been suggested that the neonatal β-adrenoceptors are "supersensitive" to circulating catecholamines (13, 15, 17). These studies, however, did not evaluate the role of α-adrenergic system in the autonomic modulation of the neonatal heart.

In the mature heart, stimulation of myocardial α-adrenergic receptors results in a negative chronotropic effect. This has been well documented with *in vitro* as well as *in vivo* studies (1–5).

The chronotropic effects of α-adrenergic stimulation in the immature heart, however, have not been extensively studied. That the chronotropic effect of α-stimulation may be different in the immature heart was first suggested by the studies of Rosen and coworkers (6, 7) who found that 76% of adult but only 50% of neonatal Purkinje fibers showed an initial decrease in automaticity with increasing phenylephrine concentrations. Lane *et al.* (8) described that spontaneously beating cultured neonatal cardiocytes increased their "beat rate" when perfused with phenylephrine in the presence of propranolol.

More recently, sophisticated tissue culture studies have suggested that the change in the effect of α-stimulation from positive to negative chronotropism is related to the increase in autonomic innervation of the myocardium that occurs postnatally (3). Other investigations have found this may be related to the acquisition of a guanine nucleotide binding protein in the myocardial cells (18, 19), which is involved in the regulation of intracellular cAMP metabolism. It is unclear, however, whether these phenomena are related to a specific α-adrenoceptor subtype.

Our experimental model was designed to evaluate the maturational changes in sinus node responses to α-adrenergic stimu-

lation *in vivo*. This is in contrast to the previous studies that studied Purkinje fibers *in vitro*. In our model, the anesthetic agent used was Na pentobarbital. Although this drug has some vagolitic effect, no interactions with the sympathetic nervous system have been described. Inasmuch as our studies are concerned with the effects of α-adrenergic stimulation after a combined parasympathetic and β-adrenergic blockade, the vagolitic properties of Na pentobarbital did not affect our findings.

The most important observation of our study was that in the intact neonatal canine, an α-mediated positive chronotropic response was demonstrated (42% of the younger neonates and 100% of the older neonates) whereas this was never observed in the adult canine (Fig. 4). Furthermore, all neonates in which α-stimulation resulted in a type B or C response, had a large decrease in heart rate after α-blockade with phentolamine. This is in sharp contrast to the adult dogs in which phentolamine had no significant effect. That phentolamine decreased the heart rate to a rate that was slower than after the combined blockade (and before the administration of phenylephrine) suggests to us that the endogenous catecholamines and/or the basal sympathetic tone were indeed stimulating the myocardial α-adrenoceptors and increasing the sinus rate. The possibility exists that this phentolamine-induced cardiodeceleration is due to direct effects of phentolamine (*i.e.* not via α-receptor blockade). However, studies that have investigated the direct effects of phentolamine (20), used large, nonpharmacologic doses of this drug whereas the doses we used were in the pharmacologic range (12). Thus, the data presented suggest that, in the intact neonatal heart, α-stimulation has a positive chronotropic effect and, accordingly, α-blockade has a negative chronotropic effect.

Whereas 57% of adult dogs had the type B response, it is important to note that the magnitude of the phenylephrine-induced acceleration was less than in the neonates. This difference is possibly due to a combined β-receptor stimulation (with a positive chronotropic effect) and α-receptor stimulation (with a negative chronotropic effect). Indeed, once the phenylephrine-induced β-stimulation was eradicated with the second dose of propranolol, the heart rate in adult dogs became considerably slower. In these subjects phentolamine had no effect.

The data presented corroborate in the intact neonatal canine what has been suggested with *in vitro* studies: that stimulation of myocardial α-adrenoceptors results in a positive chronotropic effect in the immature heart. Furthermore, our studies suggest that not only does α-adrenoceptor stimulation have a chronotropic effect opposite to that observed in the adult heart but the magnitude of the increase of the neonatal heart rate is considerable.

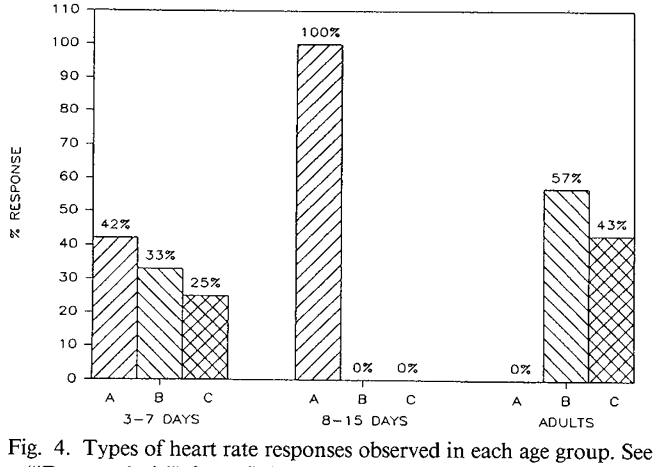

Fig. 4. Types of heart rate responses observed in each age group. See text ("Data analysis") for definition of each type of response.

These observations are of potential importance in the understanding of neonatal cardiac physiology. If the neonatal heart is indeed being stimulated by α-adrenoceptors and these same receptors inhibit the adult heart, the transition between the neonatal and adult function of α-adrenoceptors could possibly be related to certain physiologic and pathophysiologic processes in the neonatal heart. The age at which this transition occurs, as well as the characteristics of this transition period, remain to be established.

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