Rapid Attenuation ("Fade") of the Chronotropic Response During Vagal Stimulation in the Canine Newborn: Evidence for a Prominent Neuropeptide Y Effect

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We studied the time-dependent changes in the response of heart rate (sinus cycle length) to 30-second trains of vagal stimulation (8 Hz), repeated every 2 minutes, in canine neonates aged 7.1±2.5 (mean±SD) days. The first vagal train prolonged the sinus cycle length by 58±35%, but the response was attenuated during subsequent trains (98±5% inhibition of the vagal response after only 6.4±1.7 trains). After 40 minutes, complete restoration of the chronotropic response could be demonstrated. Receptor desensitization could be excluded as the reason for the attenuation by demonstrating preserved responses to exogenous acetylcholine. Neuropeptide Y, a sympathetic cotransmitter that has been shown to attenuate parasympathetic responses (thought to be the result of inhibition of the release of acetylcholine from parasympathetic nerve terminals), was administered (50 µg/kg) to eight newborns. Exogenous neuropeptide Y resulted in a complete inhibition of the chronotropic response to vagal stimulation, with restoration of the chronotropic response occurring after 60 minutes. Thus, exogenous neuropeptide Y mimicked the effect of repetitive vagosympathetic trunk stimulation; this finding suggested that neuropeptide Y release from sympathetic nerves during repetitive vagosympathetic trunk stimulation may have resulted in the observed attenuation of the vagal chronotropic response. To test this hypothesis, seven other newborns underwent chemical sympathectomy (50 mg/kg i.p. 6-hydroxydopamine for 3 days, tyramine verified), and in these newborns, stable chronotropic responses to repetitive vagosympathetic trunk stimulation were observed (inhibition of vagal response was 0±18% after 10 stimulus trains). These data suggest that in the newborn neuropeptide Y is a potent inhibitor of cardiac vagal responses and that relatively low levels of sympathetic activity may, through a nonadrenergic mechanism, attenuate or even eliminate the ability of the parasympathetic nervous system to modulate neonatal cardiac function. (Circulation Research 1991;69:406–413)

It is recognized that parasympathetic cardiac responses are to some extent time dependent.1 That is, the magnitude of the response evoked by either an initial brief burst of vagal stimuli or during the first seconds of a continuous vagal train can be observed to be significantly larger than what is observed in response to an appropriately timed sec-

Onond stimuli train or after steady state is reached during tonic stimulation. This time dependency, or "fade phenomenon," has been documented for heart rate, atrioventricular nodal conduction, and cardiac inotropic responses.2–4 It is generally believed, but not certain, that the mechanism of this fade is a post-receptor-desensitization process and is not related to any alteration in the kinetics of acetylcholine release or uptake, although more than one mechanism may be involved.1,4,5 Characteristically, full restoration of the initial response is observed within 1–2 minutes after cessation of vagal stimulation.4 In the course of evaluating the effects of tonic and brief vagal stimuli in newborn dogs,6,7 we frequently encountered a sudden diminution or even loss of cardiac vagal responses that occurred early during the course of the experiments (generally within min-

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utes of beginning vagal stimulation) and that seemed to persist for a longer time (i.e., >30 minutes) than would be normally ascribed to the post-receptor-desensitization process. In the present report, we characterize the time-dependent changes in the response of heart rate (measured as sinus cycle length) to repeated trains of vagal stimulation in the canine newborn. A rapid attenuation ("fade") of the chronotropic response is demonstrated and evidence is provided that suggests that this inhibition may be the result of the liberation of the nonadrenergic sympathetic cotransmitter neuropeptide Y8–12 from adrenergic nerve fibers contained within the canine vagosympathetic trunk (VST).13

Materials and Methods

General Preparation

Experiments were performed in a total of 29 newborn (aged 7.1±2.5 days and weighing 566±168 g) mongrel dogs. All newborns were anesthetized with 30 mg/kg pentobarbital given intraperitoneally and were mechanically ventilated. Arterial blood pressure and blood gases were monitored by a left femoral artery cannula. Via a right femoral vein cutdown, a quadrupolar 4F electrophysiological catheter was placed under fluoroscopic visual guidance in the region of the right high atrium. The high right atrial electrogram was filtered at 30–1,000 Hz, amplified, and displayed along with the blood pressure and surface electrocardiographic lead II using a Gould TA-2000 thermal array chart recorder (Gould, Cleveland, Ohio). Paper speeds of 50–100 mm/sec were used for recording data. In all subjects, the right and left cervical VSTs were isolated and divided, and the caudal end of the right VST was prepared for stimulation with bipolar, platinum/iridium electrodes. The nerve was kept constantly moistened with physiological saline to prevent drying. Electrical stimulation of the right VST was accomplished with a programmable stimulator (model DTU-210, Bloom, Reading, Pa.), which delivered 2-msec impulses at a frequency of 8 Hz at constant current. Stimulation threshold was defined as that current output, in milliamperes, at which maximum lengthening of the sinus cycle length occurred, without producing atrioventricular block, after stimulating for 15 seconds. In all experiments, changes in the sinus cycle length during VST stimulation were measured as changes in the high right atrial electrogram interval (AA interval), in milliseconds, and were expressed as the percent change from the control resting sinus cycle length: ΔAA=100(AA−AAcontrol)/AAcontrol. Attenuation of the effects of vagal stimulation observed over the course of the experiments was expressed as a percent change (% inhibition) in the effect of stimulation on sinus cycle length observed for trial n compared with the initial (i) response: % inhibition = 100 (ΔAA−ΔAA_i)/ΔAA_i. During any given stimulation train, the AA interval was always measured 4–5 seconds after the start of stimulation.

Experimental Protocols

Evaluation of the time-dependent changes in sinus cycle length during stimulation of the right vagosympathetic trunk in neonates with intact sympathetic nervous systems (sympathetically intact). To evaluate the time dependency of the response of sinus cycle length to vagal stimulation, 30-second trains of stimuli (8 Hz) were repeatedly delivered every 2 minutes at threshold to the right VST in seven neonates (aged 6.9±2.3 days). This mode of stimulation was continued until either 1) the chronotropic response, measured 4 seconds after the start of each stimulation train, was inhibited by at least 80% ("fade") or 2) shortening of the sinus cycle length was observed during VST stimulation. Stimulating electrodes were then repositioned more caudally on freshly exposed nerve, and a brief stimulation train was repeated to confidently exclude local nerve trauma or drying as a possible cause of "fade." After documenting the attenuation of the chronotropic response ("fade"), test stimulus trains were then delivered 10 and 40 minutes after the cessation of vagal stimulation to characterize the time course of recovery of the chronotropic response to vagal stimulation. To test for possible changes in the responsiveness of the cardiac muscarinic receptors to acetylcholine during the course of these experiments, in four newborns (separate experiments), the maximum change in sinus cycle length (ΔAA) was measured in response to exogenously administered acetylcholine (100 μg/kg i.v.) before repetitive vagal stimulation and then again after "fade" of the chronotropic response was observed.

Since "fade" was rapidly achieved and long lasting in these newborns (see "Results") and since we speculated that this was possibly related to concomitant sympathetic stimulation, we wished to document that sympathetic stimulation was occurring in our model during VST stimulation. Thus, in four of these seven newborns and in an additional three newborns (aged 6.9±2.1 days), we evaluated the changes in sinus cycle length during right VST stimulation after the administration of atropine (1 mg/kg i.v.). Vagal stimuli were delivered at threshold in an attempt to elicit a shortening of sinus cycle length. When a shortening of cycle length was observed, 1 mg/kg propranolol was then administered intravenously to document that the change in sinus cycle length was mediated through β-adrenergic mechanisms. Right VST stimulation after propranolol administration was performed initially at threshold and then at progressively higher outputs for a minimum of 30 seconds.

Evaluation of the time-dependent changes in sinus cycle length during vagal stimulation in chemically sympathectomized neonates. To evaluate the possible role of the sympathetic nervous system in mediating the observed time-dependent changes in parasympathetic responses of the newborn, seven canine newborns (aged 8.9±2.3 days) were chemically sympathectomized by administering 50 mg/kg i.p. 6-hydroxydopamine hydrobro-
mide, dissolved in 0.9% NaCl plus 0.1% ascorbic acid, for 3 days before the study. In all, on the day of study, the adequacy of chemical sympathectomy was verified by observing the response of sinus cycle length and blood pressure to a test dose of tyramine (100 μg/kg i.v.). Their response to tyramine was compared with that observed in seven newborns (aged 7.1±2.2 days) not given 6-hydroxydopamine.

In the sympathectomized newborns, the same protocol of repetitive 30-second stimulus trains to the right VST was then performed. After the ninth 30-second train, a long 3-minute train of vagal stimulation was delivered to further assess the stability of the vagal response over time. Finally, 2 minutes after the long vagal train was ended, a final 30-second vagal train was delivered.

Effect of exogenous neuropeptide Y on vagal chronotropic responses. The effect of the sympathetic cotransmitter, neuropeptide Y, on the magnitude and time course of the vagal chronotropic response in the newborn was evaluated in 15 newborns; eight were sympathetically intact, and seven were chemically sympathectomized as described above. In these newborns, a 10-second test train of vagal stimulation (8 Hz) was delivered to the right VST before and 5, 10, 30, 60, and 90 minutes after the intravenous administration of 50 μg/kg neuropeptide Y9 (Peninsula Laboratories, Inc., Belmont, Calif.) The change in sinus cycle length during vagal stimulation was measured at each time interval and compared with the response measured just before neuropeptide Y administration. Thus, the magnitude and time course of recovery of any inhibition of the parasympathetic chronotropic response due to neuropeptide Y could be determined. Additionally, the effect of neuropeptide Y in sympathetically intact and sympathectomized newborns could be compared to assess whether the response to neuropeptide Y is altered by sympathetic denervation.

Statistical Analysis
Changes in sinus cycle length (ΔAA) or the percent inhibition of vagal response (% inhibition), defined previously, were plotted as a function of the stimulus train number or as a function of time when the recovery of the vagal response was being assessed. One- or two-way analyses of variance for repeated measurements (ANOVAs) were used to assess the statistical significance of changes observed in the course of an experiment. Where ANOVA was significant (p<0.05), Bonferroni multiple comparison tests were used to determine the train number and/or time where observed values differed significantly from control.14 Student’s t tests were performed for statistical comparisons of paired data. All data are presented as mean±SD.

Results
Time-Dependent Changes in the Vagal Chronotropic Response in Sympathetically Intact Newborns
Changes in sinus cycle length in response to the first 30-second train of right VST stimulation in seven newborns are shown in Figure 1, which plots the percent change in sinus cycle length as a function of time. In these neonates, the control sinus cycle length was 334±26 msec; after 4 seconds of vagal stimulation, it was 532±141 msec, representing a 58±35% prolongation. As shown in Figure 1, in four of the seven newborns sinus cycle length remained either unchanged or decreased slightly over the course of the 30-second stimulus train, whereas in three newborns a slow, gradual increase in the magnitude of sinus cycle length slowing was noted. On cessation of vagal stimulation (not shown in Figure 1), the sinus cycle length decreased in all newborns to values less than the control sinus cycle length (mean decrease in cycle length, 20±5%). This relative tachycardia lasted less than 2 minutes and likely represents the phenomenon of “postvagal tachycardia” described by other investigators.15
The response to VST stimulation became progressively diminished in these newborns as 30-second stimulus trains were repeated. Representative data from one newborn are shown in Figure 2. As illustrated in this figure, when 30-second vagal trains were repeated, the change in sinus cycle length gradually diminished. Near total “fade,” or inhibition of the vagal response, occurred after only five vagal trains in this newborn. For the group (Figure 3), the vagal chronotropic response “faded” after only 6.4±1.7 trains. Furthermore, 40 minutes after cessation of vagal stimulation, the chronotropic response was completely restored (60±33% prolongation at 40 minutes). Only a partial recovery of the vagal response was noted at 10 minutes (n=5, Figure 3). Thus, the response of sinus cycle length to repeated vagal stimulation was labile in these newborns with a rapid “fade” of the chronotropic response noted. The recovery of the vagal response was relatively slow, requiring between 10 and 40 minutes to completely recover. In separate experiments (n=4), acetylcholine (100 μg/kg) was administered intravenously both before vagal stimulation and after “fade”
had occurred. Before vagal stimulation, the maximum increase in sinus cycle length after acetylcholine administration was 26±10%. After "fade," the response to acetylcholine was fully preserved (maximum change in sinus cycle length, 33±15%, p=0.228). Thus, although stimulation of the VST after "fade" produced no increase in the sinus cycle length in these newborns (and actually a small decrease of 18±4% in cycle length over the 30-second train), exogenously administered acetylcholine produced a bradycardia that was comparable to that observed before "fade." Thus, it is not likely that a post-receptor-desensitization mechanism was responsible for the observed lack of response to VST stimulation.

Contribution of the Sympathetic Nervous System to Chronotropic Responses During Vagosympathetic Trunk Stimulation

To assess whether sympathetic nervous system activation was demonstrable during cervical VST stimulation in our model, the effects of VST stimulation after pretreatment with intravenously administered atropine (1 mg/kg) were assessed. In seven newborns (aged 6.9±2.1 days), right vagal stimulation after atropine resulted in a significant shortening of the sinus cycle length from 329±18 to 231±19 msec (p<0.001). That the observed shortening of sinus cycle length during right vagal stimulation was mediated via the sympathetic nervous system was proven, since the positive chronotropic response was abolished by the administration of propranolol (1 mg/kg i.v.) (354±24 msec resting sinus cycle length, 343±30 msec with VST stimulation, p=0.066). These observations are consistent with the known mixed sympathetic and parasympathetic makeup of the canine VST and demonstrate that in the newborn the sympathetic component is functional and intact. That propranolol completely eliminated the positive chronotropic response to VST stimulation in these atropinized newborns stands in contrast to the findings in atropinized adult dogs, in which β-blockade was reported to only partially block the positive chronotropic response.16

Time-Dependent Changes in the Vagal Response in Chemically Sympathectomized Newborns

Tyramine was used to assess the adequacy of chemical sympathectomy in this group of seven newborns (aged 8.9±2.3 days). In a group of control neonates (n=7, aged 7.1±2.2 days), 100 µg/kg of tyramine resulted in a significant shortening of sinus cycle length (from 384±34 to 290±27 msec, or 24±6%, p<0.001) and increased the systolic blood pressure by 88±19% (from 57±8 to 106±11 mm Hg).
In contrast, in the sympathectomized newborns, the change in sinus cycle length with tyramine (although statistically significant) was only 2% (from 333±19 to 326±21 msec), and blood pressure rose by only 10±8% (from 69±15 to 75±17 mm Hg), providing evidence that a significant if not total sympathectomy had been achieved.

The response of sinus cycle length in these sympathectomized newborns to repeated trains of vagal stimulation was fundamentally different from that observed in the sympathetically intact newborns. In response to the first 30-second train, sinus cycle length was prolonged from 346±34 to 611±116 msec, or 76±24%, and in most, the degree of sinus cycle length slowing increased gradually over the course of the 30-second train (Figure 4). However, in contrast to the sympathetically intact group, the chronotropic response was stable during subsequent trains and did not “fade” even after nine full 30-second trains plus a 10th train, which was delivered as a longer 3-minute stimulus train (Figure 5). After nine full 30-second trains plus the additional 3-minute train, sinus cycle length still prolonged from 339±29 to 578±108 msec, or 71±27%, in response to a test stimulus train (train 11). These findings suggest that the sympathetic nervous system is responsible for the profound inhibition of the vagal chronotropic response observed in the sympathetically intact newborns.

**Effects of Exogenous Neuropeptide Y on Vagal Chronotropic Responses in the Newborn**

Since integrity of the sympathetic nervous system appeared to be necessary for “fade” of the vagal chronotropic response to occur and since the duration of inhibition was long lasting and similar to the time course noted by others for the inhibitory effects of the sympathetic cotransmitter neuropeptide Y, we evaluated the effects of exogenous neuropeptide Y (50 μg/kg i.v.) on the chronotropic response to 10-second trains of vagal stimuli in groups of sympathetically intact (n=8, aged 6.9±3.0 days) and sympathectomized (n=7, aged 8.9±2.3 days) newborns. In the sympathetically intact group, before neuropeptide Y administration, vagal stimulation prolonged the sinus cycle length from 338±23 to 482±86 msec, or 43±25%, and in the sympathectomized group, the sinus cycle length was prolonged from 329±22 to 556±94 msec, or 69±26%. Exogenous neuropeptide Y significantly inhibited the chronotropic effect of vagal stimulation in both groups 5 minutes after administration (p<0.01 in both sympathetically intact and sympathectomized newborns), and the inhibitory effect was long lasting (Figure 6). The degree of vagal inhibition and the duration of inhibition appeared to be somewhat greater in the sympathectomized newborns (p<0.05, comparing the degree of inhibition 30 minutes after neuropeptide Y administration). Finally, in both groups, a modest increase in systolic blood pressure was noted after the administra-
Concerning the possible mechanism for the marked inhibition of the vagal response in the newborn, several observations are pertinent. First, there are two important arguments against an exaggeration of the classically described “receptor desensitization”\(^1\)-\(^5\) as a mechanism for the loss of vagal responses in these experiments. One argument against this mechanism in our model is that the bradycardia response to exogenously administered acetylcholine remains fully intact even after the chronotropic response to vagal stimulation (8 Hz) is completely abolished. Second, and important, the time course of recovery of the attenuated chronotropic response in these experiments (>10 minutes) is significantly longer than the time course of recovery of attenuated or faded vagal responses in the adult dog (attenuated by repetitive stimulation and believed to represent muscarinic receptor desensitization), which is generally complete within 1–2 minutes.\(^6\) Thus, receptor desensitization seems an unlikely mechanism for the inhibition of vagal responses observed in this study and suggests that a prejunctional mechanism may be more likely.

During the past 6 years, it has become evident that the nonadrenergic sympathetic cotransmitter neuropeptide Y can profoundly inhibit cardiac vagal responses. This neuropeptide is stored along with norepinephrine in sympathetic nerve terminals, can be demonstrated by histochemical techniques in the hearts of many species, is thought to inhibit the release of acetylcholine from parasympathetic neurons, and can be shown to markedly attenuate cardiac vagal responses in vivo.\(^8\)-\(^12,17\) We believe that our study strongly implicates the sympathetic nervous system as the mediator of the inhibition of cardiac vagal responses in our newborns and believe that neuropeptide Y release is the most likely mechanism of this inhibition.

That the sympathetic nervous system is involved in the mechanism of the observed “fade” of the vagal response in our study is clearly demonstrated by the stability of vagal responses (i.e., lack of “fade”) in those newborns subjected to chemical sympathectomy. Although many preadrenergic and postadrenergic sympathetic/parasympathetic interactions have been described,\(^22\) it is the release of neuropeptide Y that best accounts for our observations in the canine newborn. In addition to requiring functional integrity of the sympathetic nervous system for release of the cotransmitter, the demonstration that exogenously administered neuropeptide Y profoundly inhibits cardiac vagal responses in our model and that the time course of recovery of the inhibition closely mimics the recovery of the “fade” induced by repetitive VST stimulation strongly suggests that the inhibition of vagal responses is mediated by neuropeptide Y. That exogenously administered neuropeptide Y in our study resulted in a greater degree of inhibition of the vagal response in the chemically sympathectomized newborns compared with the sympathetically intact newborns 30 minutes after admin-

![Figure 6](http://circres.ahajournals.org/)

**Figure 6.** Plot showing effect of neuropeptide Y on cardiac vagal responses in sympathetically intact and sympathectomized canine newborns. Control ΔAA, change in sinus cycle length during vagal stimulation before neuropeptide Y administration. A profound inhibition of cardiac vagal responses is noted as early as 3 minutes after intravenous infusion of neuropeptide Y. Partial recovery is noted by 30 minutes, and complete recovery occurs 60–90 minutes after intravenous infusion. C, control (pre–neuropeptide Y administration); SYMP. INTACT, sympathetically intact group; SYMPATHECT. chemically sympathectomized group. (See text for further discussion.)

Discussion

The first important observation of this study is that the chronotropic response of the newborn sinus node to repetitive vagal stimulation is extremely labile. Using a relatively standard and nonaggressive vagal stimulation protocol (repeated 30-second trains, 8 Hz), we observed near complete “fade” of the chronotropic response in the newborn after only six or seven stimulation trains (~3 minutes total of vagal stimulation). We were confident that this near total “fade” of the chronotropic response was not related to local nerve damage, since repositioning of the electrodes to a fresh stimulation site did not restore the response. Additionally, with time, the response did eventually fully recover. This lability of the response of the newborn to vagal stimulation stands in contrast to the relatively stable responses that can be observed over many hours of vagal stimulation in the adult dog.\(^18\) Interestingly, there is no mention of difficulties in maintaining stable vagal responses in previous studies of the effects of vagal stimulation in young animals.\(^19-21\) This may, in part, be due to the older ages of the puppies (1–2 months) used in these studies.
istration of neuropeptide Y is consistent with the observations of Mabe et al.,23 who demonstrated an enhanced pressor effect of neuropeptide Y in chemically sympathectomized rats. Although adrenergic blocking agents were not evaluated in this study, the long time course of inhibition of the vagal response as well as the nature of the interaction would argue against a norepinephrine-mediated inhibition of vagal effects. Furthermore, we know from previous experience in our laboratory, where propranolol was routinely administered before vagal stimulation, that at least β-blockade does not prevent the rapid “fade” of the vagal chronotropic response from occurring. In these previous studies, stable vagal responses were difficult to maintain (which was thought at first to be the result of nerve damage) and prevented the completion of experimental protocols in all subjects.7

Finally, our data suggest that the newborn parasympathetic nervous system may be quite sensitive to the effects of endogenously released neuropeptide Y. In most previously published reports, significant inhibition of cardiac vagal responses due to neuropeptide Y release has required the direct stimulation of major cardiac sympathetic nerves (i.e., the stellate ganglia or the ansa subclavia) at generally high intensities of stimulation (10–20 Hz) and for durations of up to 5 minutes for an effect to be demonstrated.8 (There are two notable exceptions to this. The first is the study of Potter,9 in which it was shown that reflex activation of sympathetic tone, through such maneuvers as bilateral carotid occlusion, can result in a measurable inhibition of cardiac vagal responses. The second is the study of Warner and Levy,10 in which it was shown that modest stimulation frequencies of sympathetic nerves of ~2–5 Hz can result in a measurable inhibition of cardiac vagal responses in vivo.) Significantly, in our study, profound inhibition of cardiac vagal responses was observed in the newborn without direct stimulation of the stellate ganglia or ansa subclavia and at a stimulation frequency (8 Hz) and duration (~3 minutes) that have been previously associated with no more than a 20% inhibition of the cardiac vagal response.10 Thus, in the newborn it appears that even the relatively low levels of sympathetic stimulation that occur during stimulation of the VST are sufficient to totally inhibit the chronotropic response of the newborn heart to parasympathetic stimulation. To our knowledge, this is one of only a few demonstrations of a probable neuropeptide Y-mediated inhibition of parasympathetic function that did not require at least direct, if not intense, stimulation of the major sympathetic cardiac nerves to elicit. Although we believe that the inhibition of the vagal chronotropic response in our study was most likely mediated through the release of neuropeptide Y from sympathetic nerves contained within the VST, it is possible that some inhibition of parasympathetic function could have resulted from neuropeptide Y released during reflex activation of the sympathetic nervous system (during vagal stimulation, systolic blood pressure decreased by 18±8% in the sympathetically intact newborns). Finally, it is also possible that other substances released during parasympathetic or sympathetic stimulation (perhaps other neuropeptides) may also have played a role in the observed inhibition of the vagal chronotropic response in the newborn.

The reason for the apparent heightened sensitivity of the newborn to neuropeptide Y will require further study for elucidation. It is possible that neuropeptide Y storage in sympathetic nerve terminals and/or release is greater in the newborn than in the adult. Alternatively, the parasympathetic neuron of the newborn may be more sensitive to neuropeptide Y by virtue of an increased number of neuropeptide Y receptors or because of a greater affinity of binding sites. Possibly more than one mechanism is involved.

Finally, there are some important implications of these findings. Although the precise physiological role of neuropeptide Y remains to be determined, the fact that even physiological levels of sympathetic stimulation10 and physiologically induced increases in sympathetic tone9 can result in a measurable inhibition of the cardiac vagal response suggests that neuropeptide Y may in fact function as a true neurotransmitter in vivo. If the parasympathetic nervous system of the newborn is particularly vulnerable to inhibition by neuropeptide Y, this could conceivably result in a different kind of “autonomic imbalance” in the newborn, one of sympathetic rather than parasympathetic dominance. This could be of importance in understanding the initiation of certain dysrhythmias in the newborn and the response of the newborn to pharmacological agents, such as digoxin, whose therapeutic effect is mediated, in part, via the parasympathetic nervous system.

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