

## Supraventricular escape rhythms during transient episodes of bradycardia in preterm infants

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**Abstract Objective:** To evaluate the origin of transient episodes of sinus bradycardia, atrial escape rhythm, and atrioventricular nodal escape rhythm in preterm infants. **Material and methods:** The study was observational, and was carried out in a third level neonatal intensive care unit. We studied 19 spontaneously breathing infants born healthy but prior to term, the examinations being carried out between the ages of 3 and 28 days. The mean gestational age was  $29.2 \pm 1.9$  weeks, and the mean birth weight was  $1154 \pm 264$  g. Transient episodes of bradycardia were defined as a decline in heart rate equal to or greater than 25% from baseline, lasting for at least 3 successive RR-intervals. To discriminate between different types of escape mechanisms, we used the P wave and the P axis of the electrocardiogram. Sinus bradycardia was diagnosed when the P axis was from +0 to +90 degrees; atrial escape rhythm when it was from +91 to +359 degrees, and atrioventricular nodal escape rhythm when the P wave was absent, hidden, or followed the QRS complex. **Results:** The mean P axis was  $+50 \pm 11$  degrees. We observed 60 transient episodes of bradycardia in 11 of the 19 infants. Of these, 34 (57%) were classified as sinus bradycardia, and 13 (22%) as atrial escapes. Atrioventricular nodal escapes developed during 6 episodes (10%), while 7 episodes (11%) could not be classified. **Conclusions:** Atrial excitation as evidenced by the P axis during sinus rhythm is similar in very preterm infants to that seen in children and adults. Escape rhythms with different origins occur during transient episodes of bradycardia in healthy preterm infants. In at least one third, the episodes are due to atrial or atrioventricular nodal escape.

Keywords: Infant; premature; arrhythmia; bradycardia

TRANSIENT EPISODES OF BRADYCARDIA ARE common in preterm infants, and have been studied most frequently in association with apnea.<sup>1–3</sup> The rapid development of hypoxaemia in this setting suggests that the slowing is due to a chemoreceptor reflex.<sup>3</sup> This is supported by the observation that the bradycardic response to vagal stimulation can be attenuated by hyperoxaemia.<sup>4</sup> Others believe that the relative maturity of the

parasympathetic efferents, and relative immaturity of the sympathetic efferents, both in experimental animals and the newborn human infant, predispose to bradycardia.<sup>5–7</sup> The association of bradycardia with vagal stimulation leads to the notion that transient episodes of bradycardia are the result of a decelerating firing rate of the sinus node.<sup>3,7</sup> No information is available, however, with regard to the pacemaking function of the sinus node during such episodes. In addition, as yet no thorough analysis has been made of the different types of escape mechanisms during transient episodes of bradycardia in preterm infants. One study suggested “ectopic arrhythmias” in both term and preterm infants.<sup>8</sup> Nodal escape, and wandering pacemaker, were the

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Accepted for publication 14 May 2001

commonest alterations in rhythm. The definition of a wandering pacemaker was based on the temporary inversion of the P wave in one bipolar lead. Meberg reported one patient in which different types of arrhythmia occurred during bradycardia,<sup>9</sup> again using one bipolar extremity lead. These findings stimulated our interest in the occurrence and the origin of escape mechanisms during transient episodes of bradycardia in healthy preterm infants. To discriminate between different sites of escapes, we used *two* leads to identify the atrial excitation wave and the P axis.

## Materials and methods

### *Subjects*

We examined 19 healthy preterm infants, 9 female and 10 male. All were breathing room air spontaneously. There were no signs or symptoms of respiratory insufficiency or sepsis, nor of patency of the arterial duct, at the time of the study. All infants had a normal position of the heart on the chest X-ray. Echocardiography revealed no structural abnormalities. Preceding the study itself, a standard 12 lead electrocardiogram (MAC 6, Marquette Electronics Inc., Milwaukee, USA) had been recorded in each infant during normal sinus rhythm and regular breathing. None had echoencephalographic evidence of cerebral haemorrhage. Values of sodium, potassium, calcium, phosphate and magnesium were all within the normal range. The mean gestational age was  $29.2 \pm 1.9$  weeks, and birth weight was  $1,154 \pm 264$  g. The age at the time of the study ranged from 3 to 28 days. During recording, the infants were all studied in the prone position, and were not fed. All infants received caffeine to prevent apnea. The levels of caffeine in the blood were within the therapeutic range (15–20 mg/l). Cardiotropic drugs or doxapram were not used.

### *Data acquisition*

Electrocardiograms were registered using a Hewlett Packard monitor (Waltham, USA). The mean recording time was 2.5 hours per infant. In order to register lead I and lead aVF simultaneously, we placed 5 electrodes on the chest and the abdomen. The gain and off-set were identical for each signal. All electrocardiograms were digitised at a sample rate of 400 Hertz, and all data were stored and were available for off-line analysis.

During the recordings, the oxygen saturation was measured by means of a pulse oximeter. We defined hypoxaemia as a saturation below 86%. Respiration was recorded by measurement of transthoracic electric impedance.

### *Analysis of data*

R waves were detected from the electrocardiogram, after which a RR-interval sequence was obtained. A transient episode of bradycardia was defined as a period of 3 or more RR-intervals being at least 25% longer than the preceding 400 RR-intervals measured during baseline sinus rhythm. The duration of a transient episode of bradycardia was defined as the total number of prolonged RR-intervals. The longest RR-interval during a transient episode of bradycardia was expressed as the lowest instantaneous heart rate in beats per minute.

The simultaneously registered leads I and aVF were visualised by means of a spreadsheet program. In most recordings, the P wave and the QRS complex could be clearly detected. During transient episodes of bradycardia, the P axis was determined complex-to-complex, and semi-quantified in one of the four quadrants: left lower quadrant (axis +0 to +90 degrees), right lower quadrant (axis +91 to +180 degrees), right upper quadrant (axis +181 to +270 degrees) and left upper quadrant (axis +271 to +359 degrees).<sup>10</sup> A transient episode of bradycardia with a P wave preceding each QRS complex, and a P axis in the left lower quadrant, was classified as sinus bradycardia. A P wave preceding each QRS complex, and the P axis outside the left lower quadrant, indicated an atrial escape. Absence of the P wave, or a P wave following the QRS complex, indicated an atrioventricular nodal escape. Thus, transient episodes of bradycardia could show sinus bradycardia, atrial escapes, or atrioventricular nodal escapes.

### *Informed consent*

Informed consent was obtained from the parents of each infant, and the study was approved by the hospital ethical committee.

### *Statistical analysis*

Values were expressed as means  $\pm$  standard deviation or medians and ranges. Comparisons were made with the Mann-Whitney U test for unpaired non parametric values. A p value  $<0.05$  was considered significant.

## Results

In all 19 infants, the P axis was determined during sinus rhythm at a mean heart rate of  $148 \pm 12$  beats per minute, and during regular breathing at a mean rate of  $50 \pm 10$  per minute. The mean of P axes in the standard 12-lead electrocardiogram was  $+50 \pm 11$  degrees.

Table 1. Characteristics of escape beats during transient episodes of bradycardia.

Type	Duration of episode (number of RR-intervals)	Number of escape beats	Lowest instantaneous heart rate (beats per minute)
Sinus bradycardia (n = 34)	12 (3–59)	–	79 (46–111)
Atrial escape rhythm (n = 13)	15 (3–77)	6 (2–40)	67 (39–90)*
Atrioventricular nodal escape rhythm (n = 6)	19 (5–51)	2 (1–5)	48 (38–55)†‡@

The table displays the characteristics of the different transient episodes of bradycardia: sinus bradycardia, atrial escape rhythm and atrioventricular nodal escape rhythm. All values are expressed as medians and ranges in brackets.

The lowest instantaneous heart rate was significantly slower during atrioventricular nodal escape rhythm than during sinusbradycardia or atrial escape rhythm (Mann-Whitney U test). \*Atrial escape rhythm versus sinusbradycardia  $p < 0.05$ ; †atrioventricular nodal escape rhythm versus sinusbradycardia  $p < 0.005$ ; ‡atrioventricular nodal escape rhythm versus atrial escape rhythm  $p < 0.005$

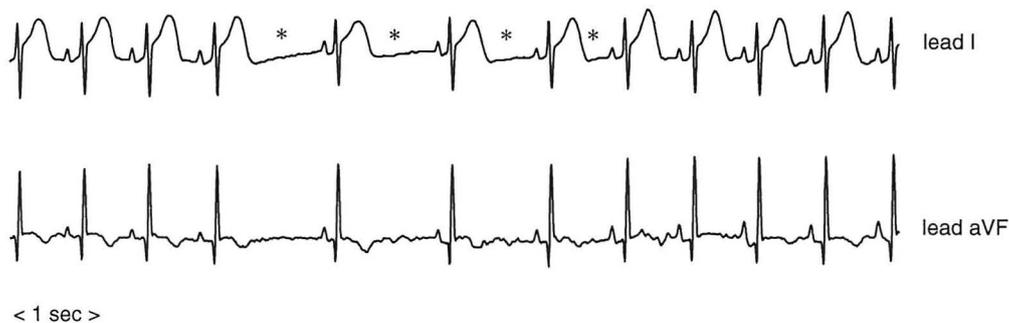


Figure 1.

Tracing of a short transient episode of bradycardia with a duration of 4 RR-intervals (marked by asterisks) being at least 25% longer than the preceding RR-intervals of the baseline rhythm (135 beats per minute). The P wave in both lead I and aVF remains positive indicating sinus bradycardia.

In 8 of 19 infants, we found no bradycardia during the period of recording. In the other 11 infants, we observed 60 episodes of transient bradycardia, with a median of 5 episodes per infant, and a range from 3 to 8. We were able to classify 53 episode on the basis of the P axis and the relation between the P wave and the QRS complex. The median duration of these episodes was 14 RR-intervals, with a range from 3 to 77. Seven episodes could not be classified because of artefacts. The instantaneous heart rate was slower during atrioventricular nodal escape rhythm than during sinus bradycardia (Mann-Whitney U test:  $p < 0.005$ ) or atrial escape rhythm ( $p < 0.005$ ). The characteristics of the transient episodes of bradycardia with respect to duration, number of escapes, and lowest instantaneous heart rate are shown in the Table 1.

In 8 of these 11 infants, we found different types of escape other than sinus bradycardia (Figs 1–3). Ventricular escapes were not observed.

The mean oxygen saturation dropped from  $97 \pm 3\%$  to  $87 \pm 12\%$  in the whole group. Hypoxaemia was associated with 32% of episodes of sinus bradycardia, and 37% of cases with escape rhythms.

During 34 episodes of bradycardia, with median RR-intervals of 12, and a range from 3–59, the P axis remained between +0 and +90 degrees. These were therefore classified as sinus bradycardia. We classified 13 episodes, with a median RR-interval of 15, and range from 3 to 77, as atrial escape rhythms. The median number of escapes was 6, with a range of 2 to 40. During 7 of these 13 periods, the P axis shifted leftwards from the left lower quadrant to the left upper quadrant and returned back to the left lower quadrant. During 2 episodes, the P axis wandered between the left lower and left upper quadrants. During 4 episodes, it wandered between the left lower, left upper, and the right upper quadrant.

During 6 episodes of bradycardia, with median RR-intervals of 19, and a range from 5 to 51, we found atrioventricular nodal escape rhythms. The median number of escapes was 2, with a range from 1–5. During 3 episodes in 3 infants, atrioventricular nodal escapes were seen together with atrial escapes. These episodes were relatively long, lasting a median of 42 RR-intervals, with a range from 25–51. They were associated with hypoxaemia, with a median oxygen saturation of 60%, and a range from 50–75%.

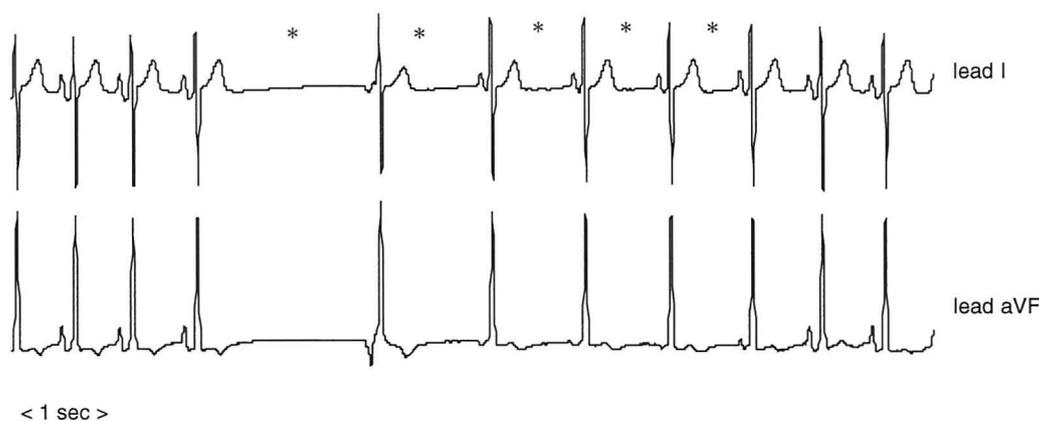


Figure 2.

Tracing of a short transient episode of bradycardia with a duration of 5 RR-intervals (marked by asterisks) being at least 25% longer than the preceding RR-intervals of the baseline rhythm. The baseline rhythm (136 beats per minute) is sinus rhythm with positive P waves in lead I and aVF. After a long pause of sinus arrest the first escape complex is characterised by a very short PR-interval and negative P wave in both lead I and aVF, indicating that the origin of the escape is in or near the atrioventricular node. The next complexes have a positive P wave in lead I and negative P wave in lead aVF, indicating an ectopic atrial focus. The following complex has a biphasic P wave, although slightly positive, in lead aVF and positive in lead I. Thereafter sinus rhythm is restored.

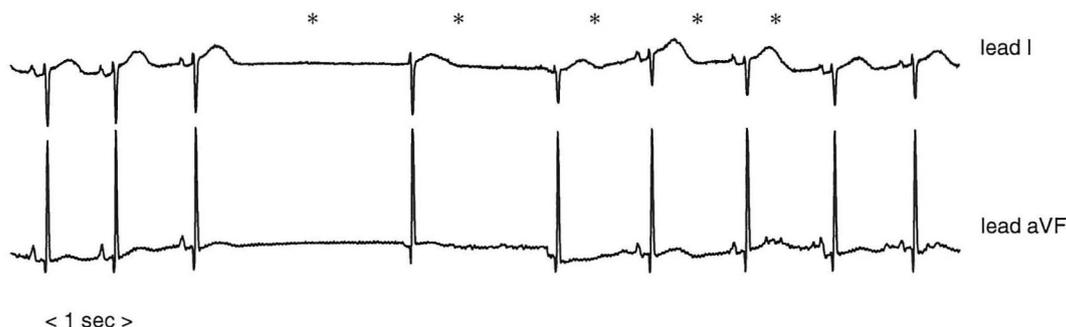


Figure 3.

Tracing of a short transient episode of bradycardia with a duration of 5 RR-intervals (marked by asterisks) being at least 25% longer than the preceding RR-intervals of the baseline rhythm (163 beats per minute). The first 3 complexes are normal sinus rhythm. After a long pause of sinus arrest the first 2 escapes are almost certainly of atrioventricular nodal origin (absence of a P wave). Thereafter clear P waves are visible indicating the return of sinus rhythm.

The observed sequence was sinus bradycardia, with subsequent atrial escape rhythm, and ultimately atrioventricular nodal escape rhythm. In 3 other episodes, however, atrioventricular nodal escapes occurred abruptly (Fig. 3) and without hypoxaemia. In these, the median oxygen saturation was 94%, with a range from 93–98%. The heart rate during atrioventricular nodal rhythm, determined in two periods each with 5 consecutive atrioventricular escape complexes, was 49 ventricular depolarisations per minute.

## Discussion

The human cardiac output depends, amongst other features, on the ability of the heart to vary its rate and stroke volume. The circulation of the newborn

at rest is characterised by a relatively high cardiac output.<sup>11</sup> This output is very sensitive to changes in heart rate.<sup>12</sup> Because of the great impact of such changes on cardiac output we, like others, took into account the baseline rate for each infant.<sup>13</sup> We defined bradycardia as a fall in heart rate of greater than 25% from baseline, lasting for at least 3 successive RR-intervals. Episodes of bradycardia may be associated with significant reduction in cerebral blood flow and therefore be a predisposing factor in the development of periventricular leucomalacia.<sup>14</sup> Most studies concerning apnea, bradycardia, and hypoxaemia in preterm infants investigate the association between apnea and bradycardia and their temporal relationship.<sup>1–3,13,15–18</sup> Systematic electrocardiographic analysis of different types of bradycardias occurring during these events is not available.

Some authors have noticed a change in the P wave recorded in one electrocardiographic lead during transient episodes of bradycardia.<sup>8,9</sup> The P axis represents the direction of the atrial depolarisation. During sinus rhythm, the wave of atrial depolarisation spreads in a leftward and downward direction.<sup>19</sup> The normal P axis ranges from +0 to +90 degrees in infants at term and in children, being positive or isoelectric in leads I and aVF.<sup>20</sup> Using a standard 12 lead electrocardiogram, we found a mean P axis of +50 degrees, with a range from 29 to 68 degrees, in our 19 healthy preterm infants. Thus, the P axis in very preterm infants is similar to that seen in older infants and children. Atrial excitation seems to be well established in these tiny preterm infants.

The P wave is useful in identifying the site of the pacemaker.<sup>10</sup> During 34 transient episodes of bradycardia, the axis of the P wave was between +0 and +90 degrees. This suggested sinus nodal bradycardia. If the cells of the sinus node are suppressed, other regions of the node take over and depolarise the atrium in a slightly different, but still leftward and downward, direction.<sup>10,20</sup> If the sinus node is further suppressed, an escape depolarisation will ultimately result from the next highest hierarchical pacemaking tissue.<sup>19</sup> The lowest instantaneous heart rate demonstrated this hierarchy in pacemaker frequency. Atrioventricular escape was significantly slower in comparison with atrial escape, while the atrial escape rhythm was slower than sinus nodal rhythm.

The next highest pacemaking tissue after sinus node tissue is the atrial myocardium. In atrial escapes, atrial excitation does not originate from the sinus node, and a negative P wave is seen in either lead I or lead aVF. We observed 13 transient episodes of bradycardia in which a P wave preceded each QRS complex and the P axis deviated outside the left lower quadrant. In 7 episodes, the P axis was temporarily directed superiorly and leftward. This could fit with a temporarily coronary sinus rhythm, in which an abnormal pacemaker in the lower part of the right atrium produces atrial depolarisation directed superiorly.<sup>10</sup> This results in a P axis directed superiorly, with a positive P wave in lead I and a negative P wave in lead aVF. Another observation was a shift of the P axis between different quadrants. This is known as a wandering atrial pacemaker, in which the pacemaking site varies within the atrium.<sup>10,20</sup> This produces a change in the shape of the P waves and the P axis varies in subsequent depolarisations.

If sinus nodal tissue and atrial myocardium are both suppressed, the atrioventricular node will ultimately depolarise and give rise to atrioventricular nodal escapes. In atrioventricular nodal escapes, P waves are positive or isoelectric in lead I, and negative

in lead aVF, so-called "retrograde" P waves, following a narrow QRS complex. Alternatively, the P waves are hidden in the QRS complex. We observed 6 transient episodes of bradycardia associated with atrioventricular nodal escapes. The measured heart rate during these escapes, at 49 beats per minute, is slightly higher than in adults, who show 40 beats per minute, and is consistent with the hierarchy in frequency of pacemaking myocardial tissue.<sup>19</sup> Three of them were associated with hypoxaemia. In 3 relatively short episodes, nonetheless, we observed a sinus arrest with atrioventricular nodal escapes. This was not associated with hypoxaemia. Although mean oxygen saturation in the whole group dropped from 97% before to 87% after a transient episode of bradycardia, no relationship could be found between the hypoxaemia and type of bradycardia.

We were surprised at the relatively high incidence of escape rhythms during transient episodes of bradycardia in healthy preterm infants. Electrophysiological changes have been studied in myocardial cells during embryonic development in the chick heart.<sup>21</sup> Myocardial cells in the young embryonic heart resemble the cells of the adult sinus node. This indicates that atrial and ventricular myocardial cells possess automaticity when they are young, but that this capability diminishes as the cells age. One may assume that the sinus node of the very preterm infant is less mature than in full term neonates. In these hearts, other atrial areas may have more capability to assume automaticity whenever the sinus node fails to fire. This possibly results in various escape origins during bradycardia.

A methodological consideration concerns the determination of the P wave axis in leads I and aVF as a means of identifying sinus rhythm. Patients with ectopic atrial rhythms can have a P wave axis that is between 0 and 90 degrees due to early depolarisation from any area high in the right atrium, but may not be in sinus rhythm.<sup>22,23</sup> One of the most commonly found sites of early activation in these patients is the right atrial appendage. Only careful review of the P wave morphology in multiple leads, in addition to data concerning the axis, can conclusively determine a P wave to be "sinus" in origin. This means that some ectopic atrial rhythms may be erroneously labelled as sinus.

Methylxanthines, caffeine for example, are frequently used to treat apnea in preterm infants. Caffeine leads to an increase in left ventricular output, but does not increase heart rate.<sup>24</sup> In another study, caffeine in a maintenance dosage of 2.5 mg/kg/day, demonstrated no chronotropic effect.<sup>25</sup> In this study, we administered caffeine in a dosage of 2.5 mg/kg/day, and all levels were within the therapeutic range. For these reasons, we assume that the

escape rhythms were not triggered by the administration of caffeine.

In conclusion, during sinus rhythm, the pattern of atrial depolarisation is similar in very preterm infants to that of children and adults. A relatively high incidence of supraventricular escape rhythms occur in these healthy preterm infants. This may be due to immature pacemaking by the sinus node, and is probably a physiological variant of normal sinus rhythm in early life. Continuous electrocardiographic recordings show similar patterns in healthy full term infants and children.<sup>18,26</sup> On the other hand, 24-hour continuous electrocardiographic monitoring showed a high incidence of arrhythmia in healthy infants with a history of apparent life-threatening events.<sup>27</sup> Our study was not designed to determine the incidence and variation of cardiac rhythms in the individual patient. Future studies should focus on the follow-up of supraventricular escape mechanisms in preterm infants. It is not inconceivable that escape mechanisms as found in this study may prevent life threatening events in infancy, or even sudden infant death.

## References

- Krauss AN, Solomon GE, Auld PAM. Sleep state, apnea and bradycardia in preterm infants. *Dev Med Child Neurol* 1977; 19: 160–168.
- Vyas H, Milner AD, Hopkin IE. Relation between apnea and bradycardia in preterm infants. *Acta Paediatr Scand* 1981; 70: 785–790.
- Henderson-Smart DJ, Butcher-Puech MC, Edwards DA. Incidence and mechanism of bradycardia during apnea in preterm infants. *Arch Dis Child* 1986; 61: 227–232.
- Cabal L, Siassi B, Blanco C, Plajstek C, Hodgman J. Cardiac and beats changes during airway suctioning in premature infants with RDS. *J Calif Perinatal Assoc* 1984; 4: 45–48.
- Kralois FA, Millar CK. Functional development of cardiac sympathetic nerves in newborn dogs: evidence for asymmetrical development. *Cardiovasc Res* 1978; 12: 547–554.
- Vapaavouri EK, Shinebourne EA, Williams RL, Heymann MA, Rudolph AM. Development of cardiovascular responses to autonomic blockade in intact fetal and neonatal lambs. *Biol Neonate* 1973; 22: 177–188.
- Church SG, Morgan BC, Oliver TK, Guntheroth WG. Cardiac arrhythmias in premature infants: an indication of autonomic immaturity? *J Pediatr* 1967; 71: 542–546.
- Välimäki I, Tarlo PA. Heart rate patterns and apnea in newborn infants. *Am J Obstet Gynecol* 1971; 110: 343–349.
- Meberg A. Transient bradycardia in early infancy. *Arch Pediatr Adolesc Med* 1994; 148: 1231–1232.
- Garson A. Systematic interpretation of cardiac arrhythmias. In: Gillette PC, Garson A, (eds). *Pediatric Arrhythmias: Electrophysiology and Pacing*. WB Saunders, Philadelphia, 1990, pp 118–204.
- Teitel DF. Physiologic development of the cardiovascular system in the fetus. In: Polin RA, Fox WW (eds). *Fetal and Neonatal Physiology*, 2nd edition. WB Saunders, Philadelphia, 1998, pp 827–836.
- Kaufman TM, Rudolph AM. The effect of heart rate on the atrial contribution to stroke volume in newborn and one month old lambs. *Pediatr Res* 1988; 24: 434A.
- Poets CF, Stebbens VA, Samuels MP, Southall DP. The relationship between bradycardia, apnea, and hypoxemia in preterm infants. *Pediatr Res* 1993; 34: 144–147.
- Perlman JM, Volpe JJ. Episodes of apnea and bradycardia in the preterm infant: impact on cerebral circulation. *Pediatrics* 1985; 76: 333–338.
- Hodgman JE, Hoppenbrouwers T, Cabal LA. Apnea, transient episodes of bradycardia, and periodic breathing in preterm infants. *Am J Dis Child* 1990; 144: 54–57.
- Upton CJ, Milner AD, Stokes GM. Apnoea, bradycardia, and oxygen saturation in preterm infants. *Arch Dis Child* 1991; 66: 381–385.
- Upton CJ, Milner AD, Stokes GM. Episodic bradycardia in preterm infants. *Arch Dis Child* 1992; 67: 831–834.
- Hodgman JE, Hoppenbrouwers T, Cabal LA. Episodes of bradycardia during early infancy in the term-born and preterm infant. *Am J Dis Child* 1993; 147: 960–964.
- van der Kooi MW, Durrer D, van Dam RTh, van der Tweel LH. Electrical activity in sinus node and atrioventricular node. *Am Heart J* 1956; 51: 684–700.
- Park MK, Guntheroth WG. Normal ECG values and deviations from normal. In: Park MK, Guntheroth WG, (eds). *How to Read Pediatric ECGs*, 3rd edition. St Louis: Mosby-Year Book, 1992, pp 42–55.
- Sperelakis N, Pappano AJ. Physiology and pharmacology of developing heart cells. *Pharmac Ther* 1983; 22: 1–39.
- Wellens HJ, Brugada P. Mechanisms of supraventricular tachycardia. *Am J Cardiol* 1988; 62: 10D–15D.
- Tang CW, Scheinman MM, van Hare GF, et al. Use of P wave configuration during atrial tachycardia to predict site of origin. *J Am Coll Cardiol* 1995; 26: 1315–1324.
- Walther FJ, Erickson R, Sims ME. Cardiovascular effects of caffeine therapy in preterm infants. *Am J Dis Child* 1990; 144: 1164–1166.
- Romagnoli C, De Carolis MP, Muzii U, et al. Effectiveness and side effects of two different doses of caffeine in preventing apnea in premature infants. *Ther Drug Monit* 1992; 14: 14–19.
- Southall DP, Johnston F, Shinebourne EA. 24-hour electrocardiographic study of heart rate and rhythm patterns in population of healthy children. *Br Heart J* 1981; 45: 281–291.
- Woolf PK, Gewitz MH, Preminger T, Stewart J, Vexler D. Infants with apparent life threatening events. Cardiac rhythm and conduction. *Clin Pediatr* 1989; 28: 517–520.