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The balance of the autonomic nervous system is normal in colicky infants

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Excessively crying, hard-to-soothe infants are described as colicky. The self-limiting course of infantile colic during early infancy suggests an etiology of transient developmental dysmaturation. It has been proposed that emotional characteristics such as temperament and self-soothing ability are correlated with the balance of the autonomic nervous system. Heart rate variability (HRV) analysis was used for evaluating the balance of the autonomic nervous system in colicky and control infants during and after the colicky period. HRV analysis was carried out on 12 colicky infants and 14 control infants at the age of 2 mo, and repeated on 10 colicky and 11 normal infants at the age of 7 mo. Measurements were performed during polygraphically confirmed slow-wave sleep (sleep stages 3 and 4). Three HRV frequency bands were defined, including a high (0.2–1.0 Hz), middle (0.12–0.2 Hz) and low (0.025–0.12 Hz) frequency variability. There were no differences between the study groups in any of the three HRV frequency bands analyzed. The high frequency variability increased significantly with age in both study groups ($p = 0.009$).

Conclusion: The findings suggest that imbalance between the parasympathetic and the sympathetic nervous system is not associated with infantile colic and that, in accordance with previous findings, control of HRV shifts in a parasympathetic direction with increasing age during the first year of life.

Key words: *Autonomic nervous system, cry, infantile colic, heart rate variability, spectral analysis*

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It is suggested that 10–20% of infants suffer from infantile colic (1, 2), but despite active research the etiology of colic has remained obscure (3). Transient developmental dysregulation of the nervous system has been suggested since colic presents during the first few weeks of life (4). One hypothesis for the etiology has been an imbalance between the parasympathetic system (PNS) and the sympathetic nervous system (SNS).

A predominance of the PNS as well as the SNS has been suggested. The early literature refers to colic as "hypertonia of infancy", which was thought to be a consequence of a predominance of the vagal system (or vagotonia) (5–7). This conception is indirectly supported by the findings that colic symptoms are relieved by anticholinergic medication (8) and that motilin levels are higher in colicky infants (9). Some behavioral studies also suggest that neonates with higher vagal tone are more irritable and exhibit greater difficulty in self-soothing (10). Newborns with higher vagal tone had lower cry frequencies in response to pain caused by a surgical procedure (11). On the contrary, acoustic cry analysis supports sympathetic predominance in colicky infants (12, 13). In healthy infants, the balance of the autonomic nervous system (ANS) has been shown to change during the first 6 mo of life. Vagal tone reaches its nadir at 1 mo of age and increases thereafter (14). The relative reduction of vagal tone from birth to the age of 1 mo suggests relative sympathetic predominance at the age when colic symptoms present.

Heart rate variability analysis (HRV) can be used to estimate function, balance and maturation of the ANS (15). Heart rate (HR) fluctuates periodically due to different physiological mechanisms. High-frequency variability (0.2–1.0 Hz) has been shown to reflect the influence of the PNS and is related to the respiratory cycle (respiratory sinus arrhythmia) (16). Middle-frequency variability (0.12–0.2 Hz) and low-frequency variability (0.025–0.12 Hz) depend on both the sympa-

Table 1. Group characteristics.

		Colic	Control
Number	1. Recording	12	14
	2. Recording	10	11
Sex (female/male)	1. Recording	7/5	6/8
	2. Recording	5/5	5/6
Age (wk)	At the beginning of 1 wk diary	4.4 (1.2)	4.6 (1.0)
	1. Recording	8.6 (1.7)	8.8 (1.3)
	2. Recording	30.4 (1.9)	29.9 (1.5)
Gestational age (wk)		40.1 (1.3)	39.8 (1.1)
Birthweight (g)		3612 (336)	3471 (331)
Daily crying times (min/d)		229 (73)	39 (30)*
	Range (min)	130–390	2–105

* $p < 0.001$, to all other variables $p > 0.2$. Standard deviation is given in parentheses.

thetic and parasympathetic branches of the ANS. Low-frequency variability is mainly affected by thermoregulation and baroreceptor function (16).

We studied HRV in colicky and control infants to evaluate whether the imbalance of the ANS is associated with colic. Since sleep state has a strong influence on HRV (14), all recordings were done exclusively during polygraphically confirmed slow-wave sleep (sleep stages 3 and 4). An overnight sleep polygraphy and HRV analysis was performed at the age of 2 mo and a follow-up study was performed at 7 mo of age.

Patients and methods

Study design and patients

Colicky infants were recruited to this study after informing the mothers of newborn babies at the postpartum wards of Turku University Hospital and at the well-baby clinics in Turku town district. The study information included a description of colic: intensive crying (despite consoling efforts) for 3 h or more a day on 3 d or more a week in an otherwise healthy and thriving infant. The parents contacted the researchers if their infant had shown symptoms of colic consistent with the definition for at least 1 wk and the symptoms had begun before 1 mo of age. Control infants were recruited from the same population by telephone. The infants included: (i) were born at more than 37 wk of gestation, (ii) were neither small nor large for gestational age, (iii) had Apgar scores equal to or more than 7 at 5 min and equal to or more than 8 at 15 min, (iv) were healthy, (v) younger than 6 wk of age, and (vi) were not administered any vasoactive or sedative drugs. A medical and abdominal ultrasound examination was performed at the beginning of the study and at age 6 mo to exclude other reasons for crying. After referral, the parents kept a daily diary (2) in which they recorded their infant's crying in 15-min epochs for 1 wk. The colicky infants recruited were perceived as colicky by parents, except in the case of one infant who was transferred from the control group to the colic group due to excessive crying based on the diary recording. All control infants were perceived as non-colicky by parents.

Sixteen colicky and 18 control infants were enrolled in the study between September 1995 and September 1996. Because of technical errors, good quality data were obtained from 12 colicky and 14 control infants first at the age of 2 mo and 10 colicky and 11 control infants at the age of 7 mo. Demographic data of these infants are presented in Table 1. The study groups differed only in the amount of crying.

This study was part of a larger study protocol in which colicky infants were randomized into the two treatment groups (crib vibrator or infant massage). No differences were observed in the reduction in crying with age between the groups, and therefore these two treatments were considered to be ineffective and treatment was not taken into account in the analysis (17).

All families gave written consent for participation. The study protocol was approved by the Joint Commission on Ethics of Turku University and Turku University Hospital.

Signal acquisition

Before sleep and the HRV study night, all the infants were examined and were found to be healthy. The whole-night sleep recordings were performed at a constant 24°C room temperature in a low light sleep laboratory between 2100 h and 0700 h. One parent slept and took care of the infant in the same room. Overnight videorecording was obtained. Electrocardiogram (ECG, Olli® Monitor Company, Finland) and respiration signals derived from a static-charge-sensitive bed (SCSB, Biomatt®, Biorec, Turku, Finland) were recorded continuously and stored on magnetic tape (Racal Thermionic Store 4DS®, Racal Recorders Ltd, Hythe, Southampton, UK). Disposable ECG electrodes (Blue Sensors®, Medicotest Inc.) were placed on the left and right side of the trunk and on the lower back to obtain optimal R-peaks. At the same time sleep polygraphic signals were recorded using the Alice3® sleep recording system (Healthdyne Technologies, USA). The sleep polygraphy recordings included two electroencephalograms (C3A2, C4A1, according to the international 10–20 placement system), two electro-oculograms, chin-electromyogram, ECG, airflow (thermistor), thoracic and abdominal strain gauges and pulse oximetry (Ohmeda 3700c®, Datex, Finland).

Signal analysis

For the HRV analysis the recorded heart and respiration signals were divided into 3-min segments and fed into a personal computer (Eclipse MV4000, Data General Corp., Southboro, MA) for further analysis. The ECG

Table 2. Heart rate variability in colicky and control infants during S3–S4 sleep stage.

		Colic			Control		
Age	Frequency band	Arbitrary units	SEM	%	Arbitrary units	SEM	%
2 mo	LF	5.02	(1.24)	48	6.09	(1.57)	51
	MF	1.93	(0.35)	21	1.92	(0.39)	19
	HF	2.68	(0.39)	31	2.86	(0.62)	30
7 mo	LF	4.19	(0.77)	34	3.81	(0.58)	34
	MF	1.96	(0.48)	14	2.10	(0.35)	17
	HF	8.20*	(2.17)	52	7.29*	(1.93)	49

LF = Low-frequency variability (0.025–0.12 Hz); MF = middle-frequency variability (0.12–0.20 Hz); HF = high-frequency variability (0.20–1.0Hz). SEM = standard error of the mean. % = Proportion of a frequency band of the total variability. *$P = 0.009$ for difference in the two age points. All other comparisons were insignificant ($p > 0.05$).

was subjected to R-wave detection using a voltage threshold trigger. Time intervals between detected R waves were measured using an interval counter operating at a clock frequency of 1 kHz offering a measurement accuracy of 1 ms. The total accuracy of the R-R interval was about 2 ms. The interval series were interpolated to derive an instantaneous HR signal. The respiration signal was low-pass filtered and digitized at a sampling frequency of 33 Hz. The data were resampled at 4.125 Hz. A trend correction was performed by computing the 4th order polynomial least squares approximation and subtracting the polynomial trend from the original data. The auto-covariance functions of HR and respiration were derived using the fast Fourier transformation algorithm. The magnitude of periodic HRV was studied by integrating the power spectral density function over three frequency bands: (i) 0.025–0.12 Hz (low-frequency variability), (ii) 0.12–0.20 Hz (middle-frequency variability) and, (iii) 0.20–1.0 Hz (high-frequency variability). Relative distribution was calculated for each frequency band as a percentage of the 0.025–1.0 Hz variability. Before spectral analysis, all signals were plotted for inspection of the data quality and artifacts were excluded. Two 3-min segments of each infant were selected for further analysis. Sleep stages were scored as described by Guilleminault and Souquet (18). To avoid the influence of the different sleep states and circadian rhythm, all selected segments were originally recorded while the infants were in S3–S4 sleep and between 2300–2400 h and 0300–0400 h.

Statistical methods

HRV indices were logarithmically transformed to normalize data distribution. The difference in HR and HRV between groups was tested using analysis of variance for repeated measurements (SPSS® for Windows®, Release 6.1). Expression mean ± SEM was used. *P*-values < 0.05 were considered to be statistically significant. The sample size of this study can detect a difference of 8 heart beats or 12 percentage units in the HF band at 2 mo of age with a power of 0.80 at the significance level of 0.05.

Results

Heart rate

The mean HR did not differ significantly between colicky and control infants at the age of 2 mo (122 2.0 bpm vs 120 1.9 bpm; $p = 0.83$) or 7 mo (111 2.5 bpm vs 110 1.6 bpm; $p = 0.09$). HR decreased significantly with increasing age in both groups ($p < 0.001$).

Heart rate variability

The low (0.025–0.12 Hz), middle (0.12–0.2 Hz) and high (0.2–1.0 Hz) frequency oscillations of HRV did not differ significantly between colicky and control infants—neither at 2 mo nor at 7 mo of age (Table 2). High-frequency oscillation increased with age in all infants, indicating increased vagal influence on HRV (Table 2; $p = 0.009$).

Discussion

These results show no differences in the balance of the autonomic nervous system controlling HRV between colicky and control infants. The parasympathetic tone increased with age in both groups (Table 2), which is consistent with earlier findings (14).

Since HRV is strongly related to sleep state (14), the recordings were made exclusively during slow-wave sleep confirmed by sleep polygraphy. A possible effect of circadian rhythm was eliminated by taking one sample at the beginning of the night and another at the end of the night. All artifacts were excluded with visual examination of signal quality. The recordings were performed in a sleep laboratory, which might have had an influence on an infant's behavior but the circumstances were the same in both study groups. The gastrointestinal system is mainly innervated by the PNS through the vagus nerve. The PNS, with its ganglions located in close proximity to an end organ, is thought to provide specific regulation, in contrast to the SNS, which acts in a systemic way. It is possible that the balance of the ANS between the heart and the intestine is not the same at a given time. Therefore the results of this study provide indirect evidence of the balance of the ANS in the intestine. The sample size of this study was fairly small, but, as shown, it was strong enough to show an increasing parasympathetic tonus with age.

The treatment effect of anticholinergic dicyclomine medication in colic gives some indirect evidence that colicky infants have an imbalance of the ANS (8, 19–21). However, it is not clear which specific action of dicyclomine is responsible for its effects. It has been thought to relieve intestinal spasms (19) but also to have sedative central nervous system effects (21). Another finding suggestive of parasympathetic predominance among colicky infants is elevated levels of motilin (9). Motilin, which enhances gastric emptying, is secreted in higher amounts under parasympathetic stimulus. Gut hypermotility in colicky infants has also been described (22). However, no difference has been found in mouth-to-cecum transit-time between infants with or without colic (23). Furthermore, gall-bladder hypocontractility has been described in colicky infants (24). Since gall-bladder contraction is vagally stimulated, hypocontractility argues more towards low parasympathetic tone, although factors such as cholecystokinin may be involved. However, there are also many suggestions of the other kind of intestinal abnormalities such as food allergy and abnormal intestinal permeability that may cause the symptoms of colic (25).

Porges and colleagues (10) have proposed the hypothesis of a vagal circuit of emotion regulation. According to this theory, baseline levels of cardiac vagal tone and vagal tone reactivity abilities are associated with behavioral measures of reactivity, the expression of emotion and self-regulation skills. Generally, higher vagal tone correlated to better organized behavioral skills in infants and toddlers. Baseline vagal tone correlated to temperamental reactivity in young children in a study by Calkins and colleagues (26). Also, a study of 3-mo-old infants showed a significant positive correlation between vagal tone and soothability (27). The opposite effect has been described in newborns. In both full-term and preterm newborns, the ability to self-soothe was inversely related to vagal tone. The neonates with higher vagal tone were more irritable and exhibited greater difficulty in self-soothing (10). It has been suggested that the colicky infants react more intensively to the normal stimuli from the internal and external environment (28). If colicky babies have higher reactivity to environmental stimuli, the results of this study suggest that the baseline vagal tone is not the etiology for this difference.

In conclusion, this study did not show any difference in the HRV between colicky and control infants. The hypothesis that colicky infants have either increased vagal or sympathetic tone was not supported by these findings. The first recording at 2 mo of age was timed to examine for differences related to the colicky period. None was observed at this time, nor at the 7-mo follow-up study. However, the increased HRV in the high frequency band with age supports the previous findings that parasympathetic tone increases during the first year of life.

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References

1. Canivet C, Hagander B, Jakobsson I, Lanke J. Infantile colic—less common than previously estimated? Acta Paediatr 1996; 85: 454–8
2. Lehtonen L, Korvenranta H. Infantile colic. Seasonal incidence and crying profiles. Arch Pediatr Adolesc Med 1995; 149: 533–6
3. Lehtonen LA, Rautava PT. Infantile colic: natural history and treatment. Curr Probl Pediatr 1996; 26: 79–85
4. Brazelton TB. Crying and colic. Infant Mental Health J 1990; 11: 349–56
5. Wessel MA, Cobb JC, Jackson EB, Harris GS, Detwiler AC. Paroxysmal fussing in infancy, sometimes called "colic". Pediatrics 1954; 14: 421–34
6. Breslow L. An analysis of etiology of colic in infants. Pediatrics 1956; 18: 838–43
7. Illingworth RS. Three months colic. Arch Dis Child 1954; 29: 165–74
8. Illingworth RS. Evening colic infants: a double-blind trial of dicyclomine hydrochloride. Lancet 1959; 2: 1119–120
9. Lothe L, Ivarsson SA, Ekman R, Lindberg T. Motilin and infantile colic. A prospective study. Acta Paediatr Scand 1990; 79: 410–6
10. Porges SW, Doussard-Roosevelt JA, Maiti AK. Vagal tone and the physiological regulation of emotion. Monogr Soc Res Child Dev 1994; 59: 167–86
11. Porter FL, Porges SW, Marshall RE. Newborn pain cries and vagal tone: parallel changes in response to circumcision. Child Dev 1988; 59: 495–505
12. Zeskind PS, Barr RG. Acoustic characteristics of naturally occurring cries of infants with "colic". Child Dev 1997; 68: 394–403
13. Lester BM, Boukydis CFZ, Garcia-Coll CT, Hole WB. Colic for developmentalists. Infant Mental Health J 1990; 11: 321–33
14. Schechtman VL, Harper RM, Kluge KA. Development of heart rate variation over the first 6 months of life in normal infants. Pediatr Res 1989; 26: 343–6
15. van Ravenswaaij-Arts CM, Kollée LA, Hopman JC, Stoelinga GB, van Geijn HP. Heart rate variability. Ann Int Med 1993; 118: 436–47
16. Akselrod S, Gordon D, Medwed JB, Snidman ND, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. Am J Physiol 1985; 249: H867–75
17. Huhtala V, Lehtonen L, Heinonen R, Korvenranta H. Infant massage compared with crib vibrator in the treatment of colicky infants. Pediatrics 2000; 105: 84
18. Guilleminault C, Souquet M. Scoring criteria. In: Guilleminault C, editor. Sleeping and waking problems: indications and techniques. Menlo Park, CA: Addison-Wesley Publishing Co.; 1982
19. Lucassen PL, Assendelf WJ, Gubbels JW, van Eijk JT, van Geldrop WJ, Knuistingh Neven A. Effectiveness of treatments for infantile colic: systematic review. Br Med J 1998; 316: 1563–9
20. Weissbluth M, Christoffel KK, Davis AT. Treatment of infantile

colic with dicyclomine hydrochloride. J Pediatr 1984; 104: 951–5
21. Hardoin RA, Henslee JA, Christenson CP, Christenson PJ, White M. Colic medication and apparent life-threatening events. Clin Pediatr Phila 1991; 30: 281–5
22. Jorup S. Colonic hyperperistalsis in neurolabile infants. Acta Paediatr Scand 1952; 85: 1–111
23. Hyams JS, Geertsma MA, Etienne NL, Treem WR. Colonic hydrogen production in infants with colic. J Pediatr 1989; 115: 592–3
24. Lehtonen L, Svedstrom E, Korvenranta H. Gallbladder hypocontractility in infantile colic. Acta Paediatr 1994; 83: 1174–7
25. Lindberg T. Infantile colic and small intestinal function: a nutritional problem? Acta Paediatr 1999; 88: 56–60
26. Calkins SD. Cardiac vagal tone indices of temperamental reactivity and behavioral regulation in young children. Dev Psychobiol 1997; 31: 125–35
27. Huffman LC, Bryan YE, del Carmen R, Pedersen FA, Doussard-Roosevelt JA, Porges SW. Infant temperament and cardiac vagal tone: assessments at twelve weeks of age. Child Dev 1998; 69: 624–35
28. Carey WB. "Colic"—primary excessive crying as an infant—environment interaction. Pediatr Clin North Am 1984; 31: 993–1005

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