

# Non-invasive assessment of cardiovascular autonomic activity induced by brief exposure to 50% nitrous oxide in children

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**Background.** The use of the equimolecular mixture of oxygen and nitrous oxide is widely recommended for relief of pain in children undergoing minor procedures. Although the benefits and adverse effects of the clinical use of nitrous oxide seem well known, its effects on the autonomic nervous system have never been studied in children. The aim of this study was to evaluate changes in autonomic cardiovascular activity induced by brief exposure to 50% nitrous oxide in children. This study was based on non-invasive continuous recordings of RR-interval and non-invasive arterial pressure. Vascular and cardiac sympathetic activity and cardiac parasympathetic activity were investigated using spectral analysis of systolic arterial pressure variability (SAPV) and RR-interval variability (RRIV). In addition, the sensitivity of the spontaneous baroreflex (SBR) was assessed using the sequences and the cross-spectral analysis methods.

**Methods.** Sixteen non-pre-medicated pre-pubertal children undergoing middle-ear surgery, were studied. Data analysis was performed at three points: baseline, when the end-tidal concentration of nitrous oxide was stabilized at 50%, and after withdrawing nitrous oxide. Low (0.04–0.14 Hz) and high frequency (0.2–0.6 Hz) components of the spectral power of RRIV and SAPV, and SBR sensitivity were calculated using these 2-min data epochs.

**Results.** Our results show that brief exposure to 50% nitrous oxide in children results in: (1) absence of effect on mean AP and SAPV; (2) attenuation of the low frequency component of heart rate variability with a shift of the sympathetic–parasympathetic cardiac balance toward a parasympathetic predominance; and (3) absence of alteration of spontaneous baroreflex sensitivity.

**Conclusions.** Unlike the results demonstrated in adults, our findings show very few cardiovascular effects of nitrous oxide in children. Furthermore, whereas in adults nitrous oxide is associated with an excitatory cardiovascular profile, in children this agent seems to be associated with a depressant cardiovascular profile. The rapid return to baseline after discontinuation of administration and the absence of baroreflex changes are positive attributes for the use of nitrous oxide in children.

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Nitrous oxide is potent enough to provide sedation and analgesia for minor painful procedures with a wide safety margin. Nitrous oxide can be administered in a very controllable manner because of its favourable kinetics,<sup>1</sup> and can be monitored easily on-line. In the operating theatre, nitrous oxide is a useful adjuvant that allows a reduced dose of analgesic and/or hypnotic agents, although

concerns about occupational exposure have been reported.<sup>2</sup> Furthermore, the introduction of a stable equimolar mixture of oxygen and nitrous oxide used with an inhalation system (EMONO), has allowed nitrous oxide to be administered by non-anaesthetists.<sup>3</sup> Consequently, this technique has spread rapidly outside the operating theatre and it is administered to children for relief of pain related to procedures such as

dental care, venipunctures, bladder catheterizations, lumbar punctures, bone marrow aspirations, nasogastric tube placement, laceration repair, and others.<sup>4</sup>

The benefits and adverse effects of nitrous oxide have been reviewed recently.<sup>5</sup> However, to our knowledge there are no data regarding the autonomic cardiovascular effects of nitrous oxide in children. Ebert and colleagues<sup>6</sup> have demonstrated an increase in the peripheral sympathetic nerve activity associated with a moderate alteration of the cardiac baroreflex-mediated tachycardia in healthy adults breathing a mixture of 40% nitrous oxide and 60% oxygen. As pre-pubertal children show different autonomic cardiovascular profiles with a higher parasympathetic cardiac drive and lower sympathetic vascular tonus compared with adults,<sup>7</sup> their haemodynamic response to nitrous oxide inhalation might differ from that of adult subjects. To investigate cardiovascular autonomic activity and the spontaneous baroreflex sensitivity in pre-pubertal children receiving nitrous oxide, we conducted a study based on non-invasive continuous recordings of RR-intervals and finger arterial pressure (AP). Vascular and cardiac sympathetic activities and cardiac parasympathetic activity were assessed using spectral analysis of systolic arterial pressure variability (SAPV) and RR-interval variability (RRIV). Data analysis was performed at three points: baseline, when the end-tidal concentration of nitrous oxide was stabilized at 50% and after withdrawing nitrous oxide. In addition, the baroreceptor-heart rate reflex was evaluated by calculating the spontaneous baroreflex slope using the beat sequences method<sup>8</sup> as well as the cross-spectral analysis method.<sup>9</sup>

## Methods

### *Subjects*

We studied children (ASA PS I or II) undergoing middle-ear surgery. Patients with a history of cardiovascular disease, arrhythmia, or autonomic nervous system disease were excluded from the study. None of the patients was taking concurrent medication. The study procedure was approved by our institutional ethics committee, and informed consent was obtained from parents and children.

### *Study procedure*

Children were not pre-medicated and atropine was not given. Before nitrous oxide inhalation, a Finapres (model 2300, Ohmeda, Trappes, France) probe was placed on the middle phalanx of the third finger of the right hand, which was passively maintained at heart level during the study. This non-invasive device is widely used in adults and children in laboratory settings for physiological studies. In children, its reliability to assess non-invasively the main components of short-term systolic and diastolic AP variability has been demonstrated in intensive care<sup>10</sup> and during the perioperative period.<sup>11</sup> To ensure optimal AP measure-

ment, we used appropriate cuff sizes (S or M) according to the manufacturer's instructions.

The electrocardiogram was recorded using disposable electrodes attached to the thorax and placed to provide clear R-waves, and connected to a Datex cardiocap II monitor (Instrumentation Corp, Helsinki, Finland). RR-interval and AP were recorded continuously from baseline to the end of the recovery period. Expired gases and oxygen saturation were continuously recorded (Capnomac Ultima, Datex, Instrument Corporation Helsinki, Finland). This study took place in an anaesthetic area, nitrous oxide was delivered through an anaesthetic machine using an open circuit with a non-rebreathing valve. Nitrous oxide administration was standardized as follows: a comfortable-fitting face mask was applied and all subjects started to breathe air delivered at 6 litre min<sup>-1</sup> for a control period. Five minutes after application of the mask, when heart rate and AP were stable, a 2-min data sample was obtained (baseline). Then the subjects received nitrous oxide in oxygen to achieve a steady-state end-tidal concentration of 50%. When the expired concentration of nitrous oxide was stabilized at 50%, the second 2-min data sample was obtained (nitrous oxide inhalation). The i.v access was then obtained where the local anaesthetic cream (EMLA) had been applied. Nitrous oxide was then discontinued and the mixture of nitrous oxide and oxygen was replaced with air. The third 2-min data sample was obtained when the expired concentration of nitrous oxide returned to below 1%.

### *Data processing*

#### *Analysis of autonomic cardiovascular activity*

The details of data sampling and analysis have already been described.<sup>12</sup> The analogue outputs of the Datex monitor and of the Finapres device were connected to an analogue-to-digital converter to permit data acquisition, storage, and analysis using a microcomputer. AP and ECG signals were digitized (300 Hz) and processed by an algorithm based on feature extraction to detect and measure the characteristics of an AP cycle and a R-wave (Acqknowledge v3.25, Biopac Systems, Inc, Santa-Barbara, CA). Systolic AP was extracted from the AP signal, and RR-interval was calculated as time in milliseconds (ms), measured between successive R-waves. A re-sampling rate of 10 Hz was chosen without interpolation, that is systolic AP and RR-interval values were replicated every 0.1 s until a new AP cycle or R-wave occurred within a 0.1 s window. The evenly spaced sampling allowed direct spectral analysis using fast Fourier transformed algorithm on a 1024-point stationary time series. This corresponded to a period of 102.4 s at our sampling rate. Power of the RR-interval or systolic AP spectrum had units of (ms)<sup>2</sup> or (mm Hg)<sup>2</sup>. The integration of the values of consecutive bands was computed to estimate the various components of the variability. The total area under the curve (AUC) was taken as the overall variability

**Table 1** Average data of systolic AP (SAP), diastolic AP (DAP), RR-interval (RRI), ventilatory frequency (VF), end-tidal carbon dioxide ( $E'_{CO_2}$ ), and end-tidal nitrous oxide ( $E'_{N_2O}$ ) obtained at the three points of data analysis. \*\*\* $P < 0.001$ , nitrous oxide inhalation vs baseline and recovery

	Baseline	Nitrous oxide inhalation	Recovery
SAP (mm Hg)	109.0 (15.7)	104.0 (18.8)	104.5 (20.0)
DAP (mm Hg)	59.7 (17.4)	62.3 (9.0)	62.2 (8.7)
RRI (ms)	680.7 (119.7)	689 (94.5)	695 (102.0)
VF (bpm)	20.4 (4.7)	22.8 (5.0)	21.4 (4.6)
( $E'_{CO_2}$ ) (mm Hg)	35.3 (1.5)	34.2 (1.3)	35.1 (1.2)
( $E'_{N_2O}$ ) (%)	0.0 (0.0)	51.3 (1.6)***	0.5 (0.2)

and was obtained by integration of all the spectral bands after exclusion of the first one. The low frequency component was obtained by integration of the values of consecutive bands from 0.049 to 0.147 Hz of systolic AP or RR-interval spectrum, in order to include the 10-s rhythm (0.1 Hz). The high frequency oscillation was obtained by integration of consecutive bands from 0.205 to 0.598 Hz in order to include those corresponding to the spontaneous breathing rate of all children. The normalized low and high frequency power (LFnu and HFnu), calculated as a percentage of the overall variability (AUC), were used for calculations and statistical analysis, as previously suggested.<sup>13</sup>

#### Assessment of spontaneous baroreflex

The technique of spontaneous baroreflex analysis was used to calculate sensitivity of the cardiac baroreflex during spontaneous fluctuations of AP and heart rate.<sup>14</sup> The computer software examined each 2-min data set to select all sequences of three or more successive heart beats in which there were concordant increases or decreases in systolic AP and RR-interval. A linear regression was applied to each of the sequences, and an average regression slope was calculated for the sequences detected during each recording period. The slope of this regression (expressed as ms mm Hg<sup>-1</sup>) represents the mean cardiac baroreflex sensitivity for that time period and has been shown to reflect values obtained at the resting AP using the vasoactive drug method.<sup>15</sup>

The baroreflex was also determined by the closed-loop spectral analysis method described by Pagani and colleagues.<sup>9</sup> The cross-power spectral density was derived from the power spectra of RR-interval and systolic AP obtained as described previously. Following Pagani and colleagues<sup>9</sup> only frequencies in which the squared coherence function of the cross spectrum of RR-interval and systolic AP was greater than 0.5 were used to calculate the gain of the baroreflex index. There were two regions where this level of squared coherence could be found that have been described as low (below 0.15 Hz) and high frequency (above 0.15 Hz). We calculated the baroreflex gain in these two spectral bands.

#### Statistical analysis

Data are expressed as mean (SD). Significant differences between anaesthesia and recovery were analysed by one way analysis of variance (ANOVA) for repeated measures, followed by paired *t*-test with Bonferroni's correction to adjust for multiple comparisons.

Differences were considered to be statistically significant when the *P* value was  $< 0.05$ .

## Results

Sixteen children (ASA PS I or II) were included in the study. Mean (SD) age was 8.2 (1.7) yr (range 6–11) and mean weight 27.0 (5.1) kg (range 19–39). The mean time to reach a steady-state end-tidal concentration of 50% nitrous oxide was 215 (18) s, the total duration of nitrous oxide inhalation was 344 (74) s, and after discontinuation of nitrous oxide the mean time for the end-tidal concentration of nitrous oxide to return to below 1% was 107 (9) s. The administration of nitrous oxide did not produce significant alterations in mean ventilatory frequency, end-tidal carbon dioxide, systolic AP, diastolic AP, and RR-interval (Table 1). No desaturation (oxygen saturation  $< 94\%$ ) was observed during the study.

#### AP variability

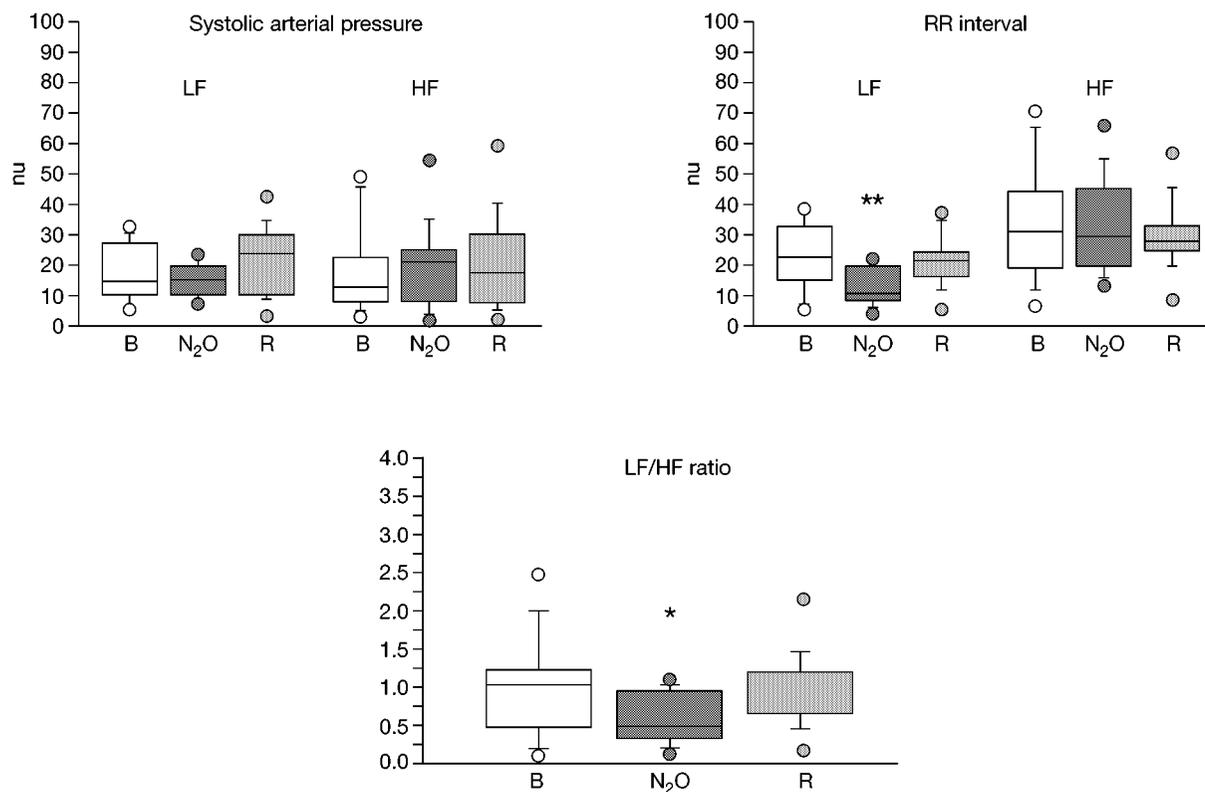
At baseline, children showed typical SAPV spectra with a low frequency component of SAPV accounting, on average, for 20% of the total spectral power. Neither the overall variability assessed by the variance of the signal (29.6 (18.0) vs 40.3 (30.3) mm Hg<sup>2</sup>,  $P = 0.2$ ), nor the organized variability assessed by the spectral low and high frequency components (Fig. 1) were not significantly modified during nitrous oxide administration.

#### RRIV

At baseline children exhibited a large degree of RRIV, as estimated by the SD of the distribution of the corresponding heart rate values, ranging between 4 and 10 beats min<sup>-1</sup>. Frequency domain analysis of this variability revealed classical components, mainly assessed by the low frequency peak and the respiratory high frequency peak of the power spectra. Inhalation of nitrous oxide resulted in significant changes in spectral components of RRIV with a decrease in the low frequency component associated with a decrease in the low to high frequency ratio (Fig. 1).

#### Spontaneous baroreflex analysis

Data relating to the non-invasive assessment of the spontaneous baroreflex are summarized in Tables 2 and 3. The sensitivity of the spontaneous baroreflex, as assessed either by the sequences method or by the cross-correlation of the spectral components of heart rate and systolic AP was not



**Fig 1** Effect of nitrous oxide on the spectral components of systolic AP variability (in normalized units), RRIV (in normalized units), and sympathovagal balance (LF/HF ratio). \* $P<0.05$ , \*\* $P<0.01$ , baseline vs nitrous oxide inhalation. B, baseline; nitrous oxide, end-tidal concentration of nitrous oxide stabilized at 50%; R, end-tidal concentration of nitrous oxide less than 1%.

**Table 2** Effect of 50% nitrous oxide inhalation on average values of sensitivity (mean slope of the systolic AP (SAP)–RR-interval relationship) of spontaneous baroreflex (SBR) and percentage of beats involved in baroreflex sequences out of total number of beats in the data sample (% sequence). Results of up and down sequences are detailed

	BRS total		–RR/–SAP		+RR/+SAP	
	% sequences	Mean slope (ms mm Hg <sup>-1</sup> )	% sequences	Mean slope (ms mm Hg <sup>-1</sup> )	% sequences	Mean slope (ms mm Hg <sup>-1</sup> )
Baseline	24.6 (13.6)	21.9 (11.3)	10.3 (5.2)	19.9 (11.9)	14.3 (6.1)	24.8 (14.0)
Nitrous oxide inhalation	16.2 (10.0)	20.2 (15.7)	8.2 (4.3)	21.7 (16.3)	8.2 (4.9)	20.0 (12.3)
Recovery	22.7 (11.3)	21.5 (13.2)	10.7 (4.9)	18.7 (12.0)	10.8 (5.1)	22.1 (14.3)

affected by nitrous oxide inhalation. As expected, values of spontaneous baroreflex sensitivity assessed by the sequences method were highly correlated to those derived from the cross-spectral method both in the low frequency band ( $r=0.5$ ,  $P<0.001$ ) and the high frequency band ( $r=0.8$ ,  $P<0.001$ ).

#### Side effects

In four out of 16 children, nitrous oxide inhalation was associated with vomiting occurring at the end of the nitrous oxide inhalation period. These subjects showed a specific profile of RRIV during inhalation of nitrous oxide (before

vomiting) with a marked increase of the vagally mediated high frequency component resulting in a decrease in the low/high frequency ratio, compared with the others (Table 4). Moreover, at baseline those subjects who vomited showed a higher high frequency component of RRIV reflecting stronger parasympathetic drive on the sinus node compared with the non-vomiting subjects (48.5 (23.0) vs 29.1 (13.0) nu,  $P=0.05$ ).

During inhalation of nitrous oxide, four out of 16 children showed moderate and brief agitation but this did not prevent them from inhaling the gas. The haemodynamic responses of these children were no different from those of the other children.

**Table 3** Effect of 50% nitrous oxide inhalation on average values of sensitivity of spontaneous baroreflex estimated by the gain of the cross-spectral analysis of systolic AP and RR-interval in the low frequency (LF) and high frequency (HF) bands. The coherence and the phase resulting from the cross-spectral analysis are also indicated

	LF coherence	LF gain (ms mm Hg <sup>-1</sup> )	LF phase	HF coherence	HF gain (ms mm Hg <sup>-1</sup> )	HF phase
Baseline	0.6 (0.1)	9.9 (4.1)	-1.4 (0.4)	0.9 (0.1)	18.8 (8.1)	-1.5 (0.6)
Nitrous oxide inhalation	0.6 (0.1)	9.2 (4.3)	-1.4 (0.6)	0.9 (0.1)	16.9 (7.0)	-1.8 (0.5)
Recovery	0.6 (0.1)	9.8 (5.9)	-1.2 (0.8)	0.8 (0.1)	21.3 (14.0)	-1.6 (0.5)

**Table 4** Spectral component of RRIV (in normalized units, nu) of vomiting and non-vomiting children during nitrous oxide inhalation. LF=low frequency; HF=high frequency

	Vomiting (n=4)	Non vomiting (n=12)	P
LF nu	7.2 (2.5)	15.3 (5.1)	0.0012
HF nu	51.6 (10.2)	24.6 (11.3)	0.009
LF/HF	0.1 (0.1)	0.7 (0.3)	0.0032

## Discussion

To our knowledge, the influence of nitrous oxide inhalation on cardiovascular autonomic activity in children has not been reported previously. The major findings of this research are that brief exposure to 50% nitrous oxide in children: (1) has no effect on mean AP levels or SAPV profiles; (2) attenuates selectively the low frequency component of heart rate variability, resulting in a shift of the sympathetic-parasympathetic cardiac balance toward a parasympathetic predominance; and (3) does not alter spontaneous baroreflex sensitivity.

These results differ noticeably from those reported in adult subjects. Earlier studies performed in adults, have provided indirect evidence that brief exposure to nitrous oxide enhances sympathetic nervous system activity.<sup>16–18</sup> Ebert and co-workers<sup>19</sup> have provided direct evidence of sympathetic activation produced solely by nitrous oxide in healthy adults. They have shown that brief exposure to nitrous oxide results in augmentation of sympathetic outflow with increasing concentrations (25–40%) of nitrous oxide. Indeed 15–20 min of exposure to 40% nitrous oxide was associated with a 59% increase in efferent sympathetic traffic directed to vascular smooth muscle in skeletal muscle in adults.<sup>6</sup> In the present study, we evaluated the efferent sympathetic activity using the low frequency component of SAPV. This low frequency component was calculated between 0.05 and 0.15 Hz, and therefore included the Mayer waves (0.1 Hz). The low frequency component calculated in this frequency band was increased in conditions associated with sympathetic activation such as the tilt test,<sup>20</sup> the cold-pressor test,<sup>21</sup> or mental stress.<sup>22</sup> Moreover, Pagani and colleagues<sup>23</sup> have demonstrated that the low frequency

component of SAPV was positively correlated with the low frequency component of muscular sympathetic nerve activity (MSNA) variability. They have provided more direct support for the concept of using changes in the low frequency component of SAPV as a marker of changes in the sympathetic efferent activity to the peripheral vasculature. In our paediatric study, we failed to demonstrate any effect of nitrous oxide inhalation on the spectral power of SAPV. As reported previously, baseline MSNA correlates directly and vagal baroreflex gain correlates inversely with age.<sup>24</sup> The lack of sympathetic excitation in children breathing nitrous oxide might be a result of lower peripheral sympathetic vasomotor tone, as has been suggested in young animals<sup>25</sup> and pre-pubertal children.<sup>7–26</sup> In accordance with this hypothesis, we have reported previously that healthy pre-pubertal children showed few 0.1 Hz oscillations of AP in the supine and standing positions, although standing is classically assumed to cause sympathetic nervous system excitation.

The power-spectral analysis of RRIV is routinely used as a non-invasive means of quantifying the cardiac autonomic input. The high frequency peak represents respiratory sinus arrhythmia and is a reliable indicator of parasympathetic efferent activity. The low frequency oscillations of the RR-interval seem to be subject to both sympathetic and parasympathetic influences.<sup>27</sup> Despite its mixed origin, some studies indicate that the low frequency component, when measured in normalized units, may be an adequate reflection of sympathetic drive on the sinus node. Indeed Pagani and colleagues<sup>23</sup> reported a very tight correlation between the low frequency component of RR and the low frequency component of MSNA variability. The concept of sympatho-vagal balance reflects the autonomic state resulting from the sympathetic and parasympathetic influences on the sinus node. The low to high frequency ratio was proposed to assess the fractional distribution of power when algorithms such as fast Fourier transformation were used. This new approach was tested with subtractive strategies<sup>28</sup> and observational studies.<sup>29</sup>

We have demonstrated a decrease in the low frequency component of the RRIV without any significant changes in the high frequency component, leading to a decrease in the low to high frequency ratio in children breathing 50% nitrous oxide. These findings suggest that in children, inhalation of 50% nitrous oxide induces a decrease in

sympathetic cardiac tone, leading to a shift of the sympatho-vagal balance towards the parasympathetic influence in accordance with the closed-loop conditions and the reciprocal relationship between low and high frequency components.<sup>30</sup> Gallety and co-workers<sup>31</sup> have shown a significant decrease in high frequency power leading to a rise in the low to high frequency ratio of heart rate variability in supine adults breathing 30% nitrous oxide; in addition, they showed that enhanced sympathetic dominance as a result of the standing position was blunted under nitrous oxide. The latter result suggests that nitrous oxide may exert a sympathetic inhibitor effect as we have demonstrated in children.

The healthy children we studied showed considerable baseline heart rate variability, which is more pronounced than that observed in adults. The respiratory contribution to RRIV in our subjects, taken at baseline, was higher than the low frequency contribution, in contrast to the findings described in adults. The data reflect a high vagal modulation of the RR-interval in children, as we have demonstrated previously.<sup>26</sup> This specific RRIV profile might explain the different features observed in children breathing nitrous oxide compared with the results described in adults.

In our study, four out of 16 children vomited during exposure to nitrous oxide. It is well known that nitrous oxide may induce nausea and vomiting when administered as the sole anaesthetic drug in volunteers.<sup>32</sup> An interesting finding in our study is the marked vagal predominance demonstrated in children who vomited compared with the others. This vagal predominance was observed not only under nitrous oxide, but also at baseline. We suggest that in children, nitrous oxide inhalation may induce an increase in parasympathetic system output associated with emesis in some predisposed children who have a high level of basal vagal tone. This effect might be related to interactions of nitrous oxide with opioid receptors in the brain.<sup>33</sup>

The spontaneous baroreflex method was used to calculate the sensitivity of the cardiac baroreflex by measuring the chronotropic responses to arterial pressure fluctuations.<sup>34</sup> This method has been shown to yield a reliable index of parasympathetic responsiveness of the baroreflex within its resting operating range.<sup>15</sup> The baroreflex sensitivity is defined by the ratio of change in RR-interval to change in systolic AP. It has been established that these variations in RR-interval are brought about by changes in parasympathetic and sympathetic efferent influences on the heart. However, the relative roles of the two efferent pathways that control the RR-interval are not strictly simultaneous and reciprocal. In particular it has been shown that in supine resting conditions the parasympathetic pathway plays the major role in heart rate control, whereas the sympathetic system has a minor modifying influence.<sup>34</sup> Thus, in our study, the baroreflex sensitivity was probably influenced primarily by the parasympathetic drive. Ebert, studying adult volunteers,<sup>6</sup> found a decrease in baroreflex-mediated tachycardia induced by nitroprusside injection during brief

exposure to 40% nitrous oxide in oxygen. Ostlund and co-workers,<sup>35</sup> studying the whole range of baroreflex stimuli using neck pressure and suction, found no change in carotid cardiac chronotropic responses to hypertensive stimuli with 39% nitrous oxide but found, at the same time, that the sensitivity of tachycardic responses to hypotensive stimuli tended to be lower than when breathing air. However, in our study we failed to demonstrate any effect of nitrous oxide on cardiac baroreflex response in children, either using the sequences method that allows to separate the up and down sequences of RR-interval and AP, or using cross-spectral analysis that is based on concordant AP and RR-interval changes independent of their direction. These discrepancies may be explained either by the differences between the baroreflex assessment methods or by the autonomic physiological differences between children and adults discussed previously.

In our study a maximum of 50% nitrous oxide was chosen because it is the nitrous oxide concentration delivered with the EMONO system. Previous human studies suggest that sympathetic excitation is most prevalent during the first 15–30 min of exposure to nitrous oxide. Our experimental procedure was kept brief to stimulate typical duration of exposure found in clinical practice. However, it is possible that some time-related factors in adult studies such as gastric distension and stimulation, have not been taken into account in our study.

In summary our non-invasive study documents autonomic cardiovascular changes induced by brief exposure to 50% nitrous oxide in children. Unlike the results demonstrated in adults, our findings show very few cardiovascular effects of nitrous oxide. In children, this agent seems more associated with depressant cardiovascular profiles than with excitatory profiles such as those demonstrated in adults. The rapid return to baseline after discontinuation of nitrous oxide and the absence of baroreflex alterations is reassuring if nitrous oxide is to be used in children.

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