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# EFFECTS OF SURGICAL STIMULATION ON AUTONOMIC REFLEX FUNCTION: ASSESSMENT BY CHANGES IN HEART RATE VARIABILITY

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## SUMMARY

*Analysis of small oscillations in heart rate (known as heart rate variability or HRV) associated with the activity of homeostatic reflexes can provide a non-invasive measure of autonomic reflex function. We have investigated the effects of surgical stimulation on autonomic reflex function by assessment of changes in HRV. Healthy female patients undergoing laparoscopic tubal ligation were anaesthetized with either thiopentone–nitrous oxide–isoflurane (group I; n = 13) or continuous propofol infusion (group P; n = 13). Power spectral measurements of HRV (HRVtot = total HRV power; %HRVlo = percent of HRV power in the low frequency range) were obtained at the following times: control; before incision; after incision (3 min, 10 min and before skin closure). Compared with control values, measurements of HRVtot before incision were reduced significantly in both groups (group P: 16 (SEM 3)% of control; group I: 2.5 (0.7)% of control). With surgical stimulation, mean HRVtot in group P was restored to 55 (13)% of control (P < 0.01 compared with measurement before incision), whereas mean HRVtot in group I remained at less than 4% of control (ns). %HRVlo increased also in group P, from 49 (7)% to 75 (3)% (P < 0.05), consistent with a shift in sympathetic–parasympathetic balance towards sympathetic dominance. These results suggest that surgical stimulation may have significant effects on the autonomic reflexes mediating HRV, and that such effects vary with anaesthetic technique.* (Br. J. Anaesth. 1993; **70**: 301–305)



### KEY WORDS

*Heart: heart rate variability Surgery. Sympathetic nervous system.*


Although "hyperadrenergic" responses to surgical stimulation may be deleterious, less intense responses to such stimulation may be beneficial in reversing anaesthetic-induced circulatory depression [1]. "Stress induced" release of vasoactive hormones (e.g., catecholamines, ADH)[2, 3] is one mechanism which antagonizes circulatory depression. As suggested by Marti, alteration of baroreflex responses during general anaesthesia may be related in part to non-specific effects of anaesthetics on CNS function [1]. The ability of noxious stimulation to cause arousal in lightly anaesthetized subjects suggests that noxious stimulation may be able to modify some of the effects of anaesthetics on CNS function. In an analogous manner, such stimulation might partially reverse anaesthetic depression of homeostatic autonomic reflexes.

The purpose of the present study was to examine the effects of surgical stimulation on autonomic reflexes by assessment of changes in heart rate variability. "Heart rate variability" (HRV) is a term used to describe small oscillations in beat-to-beat heart rate. HRV is thought to result from the interplay of multiple homeostatic reflexes involved with respiration, arterial pressure, venous return, regional vasomotor tone and thermoregulation [4, 5]. Power spectral analysis of HRV provides frequency-specific measures of oscillation amplitude (similar to EEG analysis) which correlate with sympathetic and parasympathetic reflex activity [4]. The effects of surgical stimulation on HRV were assessed during both propofol and isoflurane–nitrous oxide anaesthesia. Our results suggest that surgical stimulation may have significant effects on the autonomic reflexes mediating HRV, and that such effects vary with anaesthetic technique.

## PATIENTS AND METHODS

After Institutional Review Board approval and informed consent, we studied 26 female patients undergoing laparoscopic tubal ligation. Subjects were ASA class I or II, and ranged in age from 18 to 40 yr. No premedication was administered before arrival of the patient in the operating room. Patients were allocated to two groups on an alternating basis. For patients in the isoflurane–nitrous oxide group (group I; $n = 13$), anaesthesia was induced with fentanyl 100 μg i.v. followed by thiopentone 4 mg $kg^{-1}$, and maintained with 0.5–1% end-tidal isoflurane and 60% nitrous oxide in oxygen. For patients in the propofol group (group P; $n = 13$),

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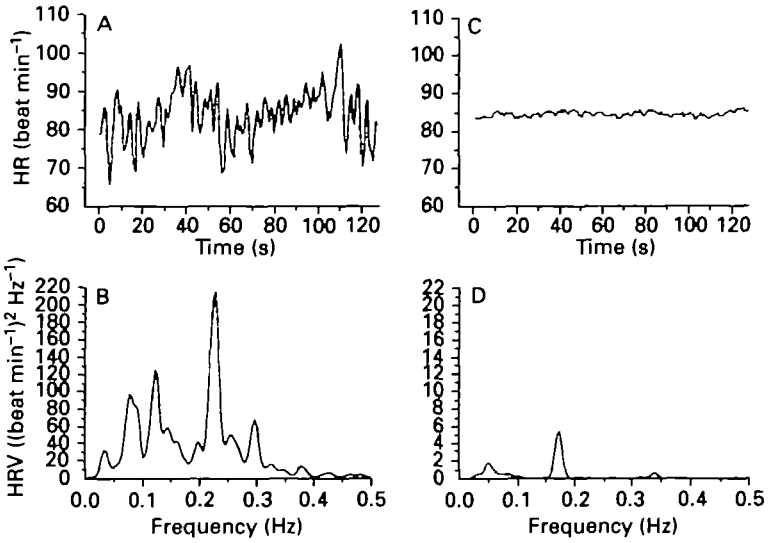


FIG. 1. Beat-to-beat heart rate (HR) signals and derived heart rate variability (HRV) power spectra from a patient anaesthetized with isoflurane and nitrous oxide. A, B: Control measurements. C, D: Measurements before incision. (Note change in scale between B and D).

anaesthesia was induced with fentanyl 100 μg i.v. followed by propofol 1–3 mg $kg^{-1}$ i.v. and maintained with a propofol infusion (initial rate 150 μg $kg^{-1}$ $min^{-1}$). Supplementary fentanyl (up to a total dose of 300 μg) was allowed for treatment of light anaesthesia in both groups. Total fentanyl dose in group I was 2.4 (SEM 0.3) μg $kg^{-1}$, and in group P was 3.1 (0.2) μg $kg^{-1}$. Vecuronium was used for neuromuscular block in both groups (intubating dose 0.1 mg $kg^{-1}$).

Non-invasive arterial pressure measurements were obtained at least once every 5 min using a Dinamap model No. 845. Digital ECG recordings for subsequent HRV analysis were obtained with an Intel 80386-based computer equipped with a Metrabyte analog-to-digital signal acquisition board. Digital recordings at 250 Hz were obtained by sampling the analog ECG output from a Tektronix model No. 414 operating room monitor. These ECG recordings were begun as soon as the ECG electrodes were placed, and continued until the end of surgery.

In order to derive HRV measurements, each QRS complex in the recorded ECG signal was located using a cross-correlation technique (in conjunction with a QRS template). A beat-to-beat heart rate signal was then constructed from measured R–R intervals utilizing the methods described by Berger [6]. This heart rate signal was then prefiltered to remove signal components of less than 0.0312 Hz and greater than 0.5 Hz using standard digital filtering techniques. Spectral analysis was then performed on 128-s segments of this filtered heart rate signal using a windowed periodogram technique [7]. Specific segments of the heart rate signal analysed in the present study were: control (obtained before fentanyl administration); before incision (obtained immediately before incision); after incision No. 1 (obtained 3 min after incision); after incision No. 2 (obtained 10 min after incision); after incision No. 3 (obtained shortly before skin closure).

Examples of heart rate signals and derived HRV power spectra are shown in figure 1. The power spectra (units: $(beat\ min^{-1})^2\ Hz^{-1}$) describe HRV power as a function of frequency (Hz). HRV power (units: $(beat\ min^{-1})^2$) within a specific frequency range was obtained by integration of the area under the power spectral curve over the defined frequency range. These power measurements (often termed "absolute" power measurements) represent the variance ((SD)²) of the heart rate about a given mean. Specific HRV variables examined in this study were: total HRV power between 0.03 and 0.5 Hz (HRVtot); low-frequency HRV power between 0.03 and 0.125 Hz expressed as a percentage of HRVtot (%HRVlo). This latter type of measurement (%HRVlo) is designated frequently in the literature as a "normalized" HRV measurement, where the HRV power in a specific frequency range is normalized by total HRV power [4, 8].

Significance of changes in HRV was assessed by the Mann–Whitney $U$ test for unpaired data, and the Wilcoxon signed ranks test for paired data. $P < 0.05$ was considered significant. All results are reported as mean (SEM). Changes in HRVtot are reported as the group mean of the percent change from control in each patient.

## RESULTS

There were no significant differences in control measurements of either HRVtot or %HRVlo between groups (table I). HRVtot before incision was significantly reduced from control in both groups (fig. 2). The decrease in group I was significantly greater than the decrease in group P (−97.5 (0.7)% compared with −84 (3)%) ($P < 0.002$). This decrease in HRVtot after induction of anaesthesia is evident in the example heart rate signals and power spectra shown in figure 1. With surgical stimulation, HRVtot significantly increased in group P, but not in group I. Mean HRVtot in group P was restored to 55 (13)% of control, but mean HRVtot in group I remained at less than 4% of control. HRVtot was significantly greater in group P than group I at all measurements after incision (table I).

TABLE I. *Group mean values for heart rate variability measurements obtained at each sampling point (mean (SEM)). Significant differences: * P < 0.05, ** P < 0.01 compared with control; † P < 0.05, †† P < 0.01 compared with before incision; § P < 0.05, §§ P < 0.01 compared with propofol*

| | Control | | Before incision | After incision | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | No. 1 | | No. 2 | | No. 3 | | Mean | |
| Total HRV power (% of control) | | | | | | | | | | | |
| Propofol | 100 | 16 | (3)** | 38 | (9)† | 55 | (19)†† | 70 | (22)† | 55 | (13)†† |
| Isoflurane–$N_2O$ | 100 | 2.5 | (0.7)**§§ | 2.9 | (0.5)§§ | 3.1 | (0.7)§§ | 3.1 | (0.6)§§ | 3.1 | (0.5)§§ |
| %HRVlo | | | | | | | | | | | |
| Propofol | 53 (6) | 49 | (7) | 76 | (5) | 77 | (3)†† | 71 | (5)† | 75 | (3)† |
| Isoflurane–$N_2O$ | 58 (7) | 38 | (4)* | 54 | (5)†§ | 45 | (7)§§ | 45 | (7)§ | 48 | (5)§§ |

TABLE II. *Group mean values of mean arterial pressure (MAP) and mean heart rate (HR) at each sampling point (mean (SEM)). Significant differences: ** P < 0.01 compared with control; † P < 0.05, †† P < 0.01 compared with before incision; § P < 0.05, §§ P < 0.01 compared with propofol*

| | Control | Before incision | After incision | | | |
|---|---|---|---|---|---|---|
| | | | No. 1 | No. 2 | No. 3 | Mean |
| MAP (mm Hg) | | | | | | |
| Propofol | 95 (3) | 91 (4) | 111 (5)†† | 109 (5)†† | 107 (4)†† | 109 (4)†† |
| Isoflurane–$N_2O$ | 93 (4) | 68 (2)**§§ | 81 (5)†§§ | 89 (4)††§§ | 89 (3)††§ | 87 (4)††§§ |
| Mean HR (beat $min^{-1}$) | | | | | | |
| Propofol | 76 (5) | 69 (2) | 76 (3)†† | 74 (3)† | 73 (2)† | 75 (2)† |
| Isoflurane–$N_2O$ | 74 (3) | 74 (3) | 74 (3) | 74 (3) | 76 (3) | 75 (3) |

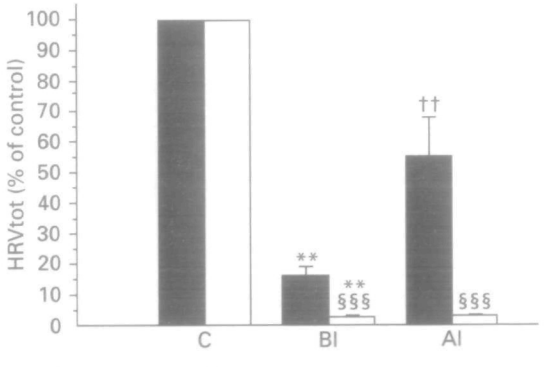


FIG. 2. Changes in total HRV power expressed as a percent of control measurements (C). Error bars indicate SEM. ■ = Propofol; □ = isoflurane. BI = Before incision; AI = after incision. ** $P < 0.01$ compared with control; †† $P < 0.01$ compared with measurement before incision. §§§ $P < 0.001$ compared with propofol.

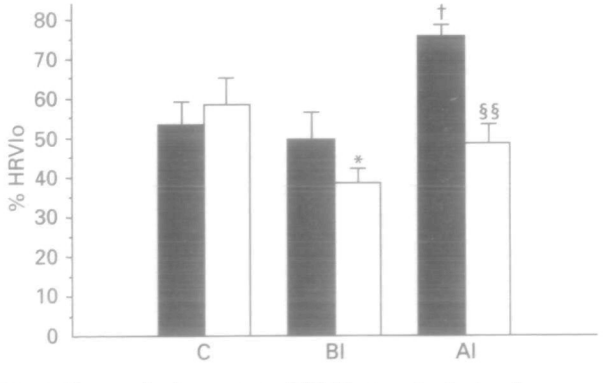


FIG. 3. Changes in the percent of HRV power in the low frequency range (0.03–0.125 Hz). Error bars indicate SEM. ■ = Propofol; □ = isoflurane. C = Control; BI = before incision; AI = after incision. * $P < 0.05$ compared with control; † $P < 0.05$ compared with measurement before incision; §§ $P < 0.01$ compared with propofol.

Before incision, group I showed a significant decrease in %HRVlo (from 58 (7)% to 38 (4)%) ($P < 0.05$), whereas group P showed no significant change (fig. 3). With surgical stimulation, group P showed a significant increase in %HRVlo (49 (7)% to 75 (3)%) ($P < 0.05$), whereas the average measurement after incision in group I was not significantly different from the measurement before incision. %HRVlo was significantly greater in group P than group I at all measurements after incision (table I).

Measurements of mean arterial pressures and heart rates for both groups are shown in table II. There were no significant differences in control measurements between groups. There was a significant decrease in arterial pressure before incision in group I, but arterial pressure before incision in group P was unchanged from control. After incision, there was a similar increase in mean arterial pressure (from 91 (4) mm Hg to 109 (4) mm Hg for group P and from 68 (2) mm Hg to 87 (4) mm Hg for group I). There was no significant change in mean heart rate from control at the measurement before incision in both groups. With surgical stimulation, there was a small but significant increase in heart rate in group P (from 69 to 75 beat $min^{-1}$) ($P < 0.05$), but no change in group I. There were no significant differences between groups in heart rates after incision.

Close examination of the beat-to-beat heart rate tracings revealed that patients in the isoflurane–nitrous oxide group had a high incidence of decelerations in heart rate (5–15 beat $min^{-1}$) with initial surgical stimulation. Decelerations were of two types. The first type was a transient, sudden deceleration in heart rate not preceded by any prior increase in heart rate. Maximal heart rate slowing occurred within 2 to 10 beats, and the rate returned

rapidly to the baseline within a similar time. This type of response occurred frequently with initial skin incision, abdominal trochar insertion, or both. Other patients showed a more gradual and prolonged decrease in heart rate as the initial response to surgical stimulation (and some patients showed both types of response). This more prolonged response appeared to coincide with abdominal insufflation of carbon dioxide. Eight of 13 patients in the isoflurane–nitrous oxide group had heart rate deceleration in response to initial surgical stimulation, whereas none of the 13 patients in the propofol group had such a response ($P < 0.002$, Fisher exact test).

## DISCUSSION

Although the mechanisms responsible for the genesis of HRV are complex, a functional explanation for HRV measurements has been obtained from observational studies (as with the EEG) [4]. These studies have shown consistent correlations between HRV variables and alterations in sympathetic and parasympathetic activity induced by both experimental interventions and various disease processes. These studies suggest that measurements of low frequency HRV provide an index of sympathetic activity, and measurements of high frequency HRV provide an index of parasympathetic activity [4, 9]. During conditions in which total HRV is significantly altered, normalized measurements of HRV (e.g., %HRVlo) are thought to provide a better index of changes in sympathetic–parasympathetic balance than do absolute power measurements of HRV [4, 8].

We found that surgical stimulation significantly increased HRVtot in the propofol group, but had no significant effect on HRVtot in the isoflurane–nitrous oxide group. This finding indicates that the effect of surgical stimulation on autonomic control of beat-to-beat heart rate differed with these two anaesthetic techniques. The different effects of surgical stimulation on %HRVlo also suggest important differences in these autonomic responses. The increase in %HRVlo in the propofol group suggests a shift in autonomic "balance" towards sympathetic dominance, whereas no such shift was evident in the isoflurane–nitrous oxide group. These different effects of surgical stimulation on HRV may present a significant limitation to the use of HRV for monitoring depth of anaesthesia [10].

In this initial study, we did not specifically examine the effects of altered anaesthetic concentrations, altered intensities of surgical stimulation, or altered anaesthetic "depth". The surgical stimulation applied in the present study was of fairly limited intensity and anaesthetic concentrations were adjusted as indicated clinically. We believe that the equivalent increase in mean arterial pressure in response to a standardized surgical stimulus, and the identical mean heart rates after incision, suggest similar anaesthetic "depths" for both groups. However, different results might be obtained with different anaesthetic concentrations or intensities of surgical stimulation. Earlier studies have suggested that the depth of anaesthesia may influence high frequency HRV (i.e. amplitude of the respiratory sinus arrhythmia) [10, 11], but these studies did not examine changes in other frequency-specific measurements of HRV.

The changes in HRV in response to surgical stimulation in the propofol group (increases in HRVtot and %HRVlo) are consistent with results from a study by Sellgren, Ponten and Wallin on changes in muscle sympathetic nerve activity [12]. Both studies suggest that induction of anaesthesia with propofol causes significant depression of homeostatic reflex activity, but that subsequent noxious stimulation causes significant augmentation of sympathetic activity. The lack of a significant change in HRV in the isoflurane–nitrous oxide group with surgical stimulation is consistent with baroreflex studies by Takeshima and Dohi [13].

The increase in HRVtot in group P may indicate partial reversal of the depression of autonomic reflexes caused by propofol. Noxious stimulation may cause this reversal via unspecified effects on CNS function, similar to the effects of noxious stimulation on arousal and depth of anaesthesia. Because of the multiple factors which influence HRV, these results should not be extrapolated as definitive evidence for increases in baroreflex function. Although studies in awake subjects indicate that depression of baroreflex sensitivity is associated with depressed heart rate variability, these two measurements are correlated only moderately ($r$ values of 0.5–0.6) [14]. Factors other than baroreflex sensitivity which may affect HRV include: sympathetic and parasympathetic "tone" [4, 9, 15]; cerebral function [16]; interrupted autonomic pathways [17, 18]. The increase in HRVtot could also represent a response to the haemodynamic effects of noxious stimulation, rather than restoration of depressed reflexes.

The absence of any concomitant changes in HRV (or mean HR) with the increase in mean arterial pressure after incision in the isoflurane–nitrous oxide group suggests a possible differential effect of surgical stimulation on reflex responses affecting heart rate and arterial pressure in this group. Possible mechanisms include a decrease in sympathetic influence on heart rate compared with sympathetic influence on vascular tone and a non-adrenergic cause for the increase in arterial pressure. In support of this first mechanism, baroreflex studies by Ebert suggest that nitrous oxide attenuates sympathetic influence on heart rate, but does not alter sympathetic influence on vascular tone [19]. With respect to the second mechanism, it has been demonstrated that very large increases in vasopressin occur in response to surgical stimulation [3]. This hormone causes significant increases in systemic resistance without any direct effects on heart rate.

Both propofol and isoflurane–nitrous oxide anaesthesia caused significant changes in HRV before incision (compared with control measurements). Latson has suggested that the effects of anaesthetics on HRV (in the absence of surgical stimulation) may be caused by both anaesthetic depression of baroreflexes and non-specific effects of general anaesthesia on cerebral function [8]. Changes in the

normalized measurements of HRV (e.g., %HRVlo) appeared to reflect changes in sympathetic–parasympathetic balance for induction with etomidate–nitrous oxide, thiopentone–nitrous oxide and sufentanil. In the present study, the reduction in HRVtot was significantly greater in the isoflurane–nitrous oxide group (−97.5 (0.7)%) compared with the propofol group (−84 (3)%), suggesting a lesser depression of autonomic reflexes in the propofol group even before surgical incision. The decrease in %HVRlo before incision in the isoflurane–nitrous oxide group is similar to the results reported by Galletly [20]. This decrease in %HRVlo suggests a shift in sympathetic–parasympathetic control of heart rate towards greater parasympathetic influence, and is consistent with studies by Seagard and colleagues [21].

Retrospective review of all heart rate signals derived from ECG recordings revealed a high incidence of heart rate deceleration with surgical stimulation in the isoflurane–nitrous oxide group. This high incidence of deceleration may be related to the following changes in HRV observed in this group: decrease in %HRVlo before incision, suggesting a shift in sympathetic–parasympathetic control of heart rate towards parasympathetic dominance; lack of change in %HRVlo with surgical stimulation, suggesting that expected sympathetic responses to noxious stimulation were not evident by analysis of beat-to-beat changes in heart rate; the large, persistent reduction in total HRV. Taken together, these observations suggest significant attenuation of sympathetic influences on heart rate control in the patients anaesthetized with isoflurane–nitrous oxide.

The ideal anaesthetic would attenuate reflex responses to noxious stimulation, but leave homeostatic circulatory reflexes intact [1]. In the absence of such an ideal anaesthetic, the interplay between anaesthetic effects on reflex responses to noxious stimulation, compared with reflex responses involved with circulatory homeostasis, may be an important consideration in selection of anaesthetic techniques. We have shown that this interplay differs significantly with different anaesthetic techniques.

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