Recruitment of cardiac parasympathetic activity: effects of clonidine on cardiac vagal motoneurones, pressure lability, and cardiac baroreflex slope in rats

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Background. Association of low cardiac vagal activity and poor outcome is demonstrated in the cardiology setting. This has not been addressed in the postoperative setting. Cardiac vagal motoneurones (CVMs) in the brain stem generate sinus arrhythmia. They may reduce blood pressure (BP) variability ('pressure lability'). An alpha-2 agonist, clonidine, was administered to assess whether cardiac vagal activity could be recruited from a very low baseline activity, increase the sensitivity of the cardiac baroreflex and sinus arrhythmia, and reduce the pressure lability.

Methods. In ventilated anaesthetized rats, single-unit activity from antidromically identified CVMs was recorded. Given complex interactions within the cardiac ganglion, a peripherally acting beta-blocker, atenolol, was administered before clonidine.

Results. Atenolol 2 mg kg$^{-1}$ i.v. did not change systolic BP (SBP), CVM firing rate and slope of the cardiac baroreflex analysed at CVM (SBP—CVM unit activity relationship) level, or at the heart level (SBP–RR interval relationship) but evoked a significant bradycardia. In the presence of atenolol 2 mg kg$^{-1}$ h$^{-1}$, clonidine 10–100 μg kg$^{-1}$ i.v. evoked a significant reduction in SBP, a large increase of CVM firing rate from a very low baseline [0.16 (SD 0.28) to 1.37 (1.21) spikes s$^{-1}$, n=7 cells], and increased the slope of the cardiac baroreflex analysed at the CVM level or at the heart level. SDS of SBP were reduced, and that of RR interval was increased.

Conclusions. Following peripheral beta-blockade, clonidine activated CVMs from a very low baseline, increased the slope of the cardiac baroreflex and sinus arrhythmia, and reduced pressure lability.


Keywords: atenolol; clonidine; single unit activity; cardiac vagal motoneurons; baroreflex; sinus arrhythmia; blood pressure variability

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In the cardiology setting, an association between low para-
sympathetic drive to the heart ('cardiac vagal activity') and poor outcome was demonstrated following myocardial infarction.1 Trauma or surgery is associated with low cardiac vagal activity and low cardiac baroreflex sensitivity.2–4 A large beat-by-beat systolic blood pressure (SBP) variability ('pressure lability') is associated with poor outcome following cardiac surgery;5 6 brisk changes in pressure may increase shear stress, and plaque rupture, leading to target-organ ischaemia. Low cardiac vagal activity and high pressure lability are associated.4 7 At variance with the accepted view of a link between high sympathetic activity and poor outcome, only logic, but no evidence, suggests an association between low cardiac vagal activity and poor outcome following trauma or major surgery.

Cardiac vagal motoneurones (CVMs) located in the brain stem (external formation of the nucleus ambiguus, NA) generate cardiac vagal activity8 and sinus arrhythmia. Study of these neurones may be the key to understanding the low postoperative cardiac vagal activity. Furthermore, rats present with a low baseline cardiac vagal activity, especially under anaesthesia, mimicking low preoperative cardiac vagal activity, and a surgical approach to CVMs
involves extensive neuro- and thoracic surgery, mimicking major trauma. Such a setting is highly favourable to study a possible recruitment of cardiac vagal activity related to trauma or major surgery. An alpha 2 agonist, clonidine, reduces pressure lability and increases sinus arrhythmia in hypertensive patients recovering from major surgery. However, no data delineate the core mechanism, which co-generates sinus arrhythmia and reduced pressure lability. Given the clinical significance of parasympathetic recruitment and its relevance to the perioperative setting, we investigated whether clonidine activates CVMs from a low baseline activity and whether CVM activation associated with enhanced cardiac baroreflex sensitivity increases sinus arrhythmia and reduced pressure lability.

Sympathetic/parasympathetic interactions within the cardiac ganglion or in the presence of heart failure or elevated plasma catecholamine concentrations are complex. Thus, to suppress any sympathetic input on instantaneous heart rate and simplify interpretation, a beta-blocker which does not cross the blood–brain barrier, atenolol, was administered before clonidine.

**Methods**

**Anaesthesia**

Experiments followed the *NIH Guide for the Care and Use of Laboratory Animals* and were approved by the Rhône-Alpes Committee for the Care of Animals and performed on Sprague–Dawley male rats (Harlan, Gannat, France, 325–400 g), as detailed. Anaesthesia was maintained with isoflurane during surgery and switched over to urethane 1.4 g kg$^{-1}$ i.v. administered over 15–30 min before searching for CVMs. During recordings, the animal was paralysed with metocurine (0.2 mg i.v., Metubine®, Lilly, Indianapolis, IN, USA) only once, a stable plane of anaesthesia had been established to abolish the pedal withdrawal reflex. Saline was used to ascertain corneal reflex hourly. If the corneal reflex was positive, urethane (10–20% of original dose) was re-administered. After tracheostomy, rats were mechanically ventilated [f $\sim$72 min$^{-1}$, O$_2$–40%; end-tidal CO$_2$–25–30 (surgery), then 30–35 mm Hg (recording); Engström Elisa Duo, Gambro-Engström, Bromma, Sweden]. The rectal temperature was regulated to ~37.5°C with a warming blanket (Harvard, Edenbridge, KY, USA). The bladder was drained, and the right femoral vein was catheterized. A percutaneous transulminal coronary angioplasty catheter with an inflatable balloon at its tip (PTCA catheter 2–3 mm, Boston Scientific, Galway, Ireland) was inserted through the right femoral artery up to the thoracic level, to drain, and the right femoral vein was catheterized. The bladder was then checked by stimulating (20–50 Hz, 2–7 V, 0.05 ms). Occasionally, a small sheet of polyethylene was inserted beneath the branch to insulate it. A pair of electrodes made from Teflon-coated (125 ±m) silver wire, bared at the tips, was placed under the branch and secured in contact with silicon gel (Wacker, Munich, Germany). The wires were tied to avoid pulling on the branch. During surgery, the branch was kept wet with saline. The rat was fixed in a stereotaxic frame, with the tail under mild tension to stabilize the medulla. The head was ventroflexed so the medulla was horizontal. The viability of the branch was checked by stimulating (20–50 Hz) through the implanted electrodes: if this failed to give a bradycardia, the experiment was discontinued. Opening the dorsal neck muscles and part of the occipital bone exposed the medulla.

**Single-unit recording**

Carbon fibre electrodes were prepared, so the fibre will protrude by 10–15 μm. Electrical contact was made through a silver chloride wire and 2 M NaCl. Electrodes were lowered vertically through the dorsal surface of the medulla [L=1.5–2.2 mm to the right of the calamus scriptorius (caudal end of area postrema), depth corresponding to the external formation of the NA (−1.5–2.5 mm)]. Unit activity was recorded differentially between the carbon fibre electrode and a reference silver wire on the medullary surface using a preamplifier (Grass P16, Quincy, MA, USA). The signal was amplified (×10 000) and band-pass-filtered (300–3000 Hz) before display on an oscilloscope (Tektronix 5111A, Beaverton, OR, USA). For storage, the unit signal was digitized at 18.5 kHz (Instrutech, New York, NY, USA) along with BP, ECG, CO$_2$ (digitized at 4.5 kHz), stimulus, vocal messages and event markers on magnetic tape (JVC, Friedberg, Germany). On-line spike discrimination was performed with a time amplitude window discriminator (FHC, Brunswick, ME, USA). CVMs were identified by their antidromic response (fixed latency <5% relative variation; stimulation 0.5–5 mA, 0.05 ms, ~1 Hz). Spike detection software (Spike2 v3.21, CED, Cambridge, UK) revealed distant constant-latency unit responses and warned the
experimenter when successive electrode tracks were approaching or moving away from a particular CVM. Once a unit recording of sufficient amplitude and stability had been isolated (Fig. 1A), it was subjected to time-controlled collision testing (Fig. 1B). The unit activity was redigitized (15 kHz) off-line to check extensively the discrimination and edit it using a computer-based system (‘Micro 1401’, CED). At odds with a previous report, 18 cells were selected on the basis of their absence of spontaneous firing or their low baseline firing rate (<2 Hz; Table 1).

**Protocol**

Atenolol was administered (2 mg kg\(^{-1}\) i.v. over 5–10 min, 1.4 mg ml\(^{-1}\) in saline, Sigma-Aldrich, Steinheim, Germany) and then the balloon was inflated two or three times (pressure increases \(\leq\) 30–40 mm Hg), and atenolol was infused up to the end of the experiment (2 mg kg\(^{-1}\) h\(^{-1}\) i.v.). Such a regimen allows minimal changes in HR during nitroprusside challenges. Then clonidine (5 or 50 \(\mu\)g ml\(^{-1}\) in saline, Sigma, St Louis, MO, USA) was infused in 10, 30, 100 \(\mu\)g kg\(^{-1}\) i.v. cumulative doses, over

~10 min. Balloon inflations were generated for each dose of clonidine. At least 2 min were allowed to elapse between balloon inflations for full recovery of BP and HR to baseline values. CVM and HR responses were measured. Only one CVM was recorded in each animal.
Analysis

Barosynchronicity (‘cardiac rhythmicity’, ‘pulse-locked character’) of neurones was tested on-line, by generating pulse-triggered correlation histograms of single-unit activity (Spike2). Five millisecond periods were used at an interval ranging from 0.5 s to 0.5 s from the trigger point. Barosynchronicity was considered present if the histogram showed regular peaks and troughs locked to pulse pressure (Fig. 1 C). The stored BP and EKG signals were digitized at 1 and 4 kHz, respectively (Keithley KPCMCIA 16AIAO, Cleveland, OH, USA). SBP–RR interval and SBP–CVM relationships were generated with custom-made software (RECAN®, Alpha-2 Ltd, Lyon, France). The detected spikes of the single-unit activity were imported in RECAN from the Spike2 files and transformed into a frequency signal (CVM, Hz; Fig. 2B). As the firing pattern of CVM was transformed from single spike to volley of action potentials (‘doublet’) following clonidine administration, attention was paid to the firing pattern.

Cardiac baroreflex measured at the CVM level (SBP–CVM relationship, pressure–unit relationship)

In order to study the SBP–CVM relationship, SBP and the CVM activities were averaged over three respiratory cycles (~2.5 s), to avoid oscillations arising from respiratory patterns in the single-unit activity. Series of points coming from the beginning of the balloon inflation until BP reached again its baseline value were considered. For every series of data points, linear regression was applied for calculating the slope of the baroreflex. The variation of the correlation coefficient r was analysed while increasing the number of heart beats (latency τ) between the averaged SBP and the averaged CVM activities. The slope and the latency generating the maximal r-value were taken into consideration. For the analysis of the cardiac baroreflex measured at the CVM level or at the heart level, slope and latency for which the regression coefficient r<0.7 were discarded. When several balloon inflations were considered valid for the same condition in the same rat, values were averaged.

Cardiac baroreflex analysed at the heart level (SBP–RR interval relationship)

SBP and RR signals were filtered at 0.8 and 0.3 Hz, respectively, using a 201-coefficients low-pass finite impulse response filter. The ascending part of pressure increases was considered for calculating the slope of the SBP–RR interval relationship. As the parasympathetic component of the baroreflex is fast, and as the sympathetic component of the baroreflex takes over after 5 s, only the first 5 s following the SBP increase was considered for the analysis. Thus, only the parasympathetic-mediated cardiac vagal activity was considered. First, the latency τ between SBP and RR increases was computed by measuring the number of heart beats between the mid-height of SBP and RR increases. Then, linear regression was applied for calculating the SBP–RR interval slope.

Statistical analysis

Data are expressed as mean (SD) (when normally distributed) or median and range (non-normal distribution). SBP, RR, and SBP–CVM relationship data were analysed using one-way repeated measures ANOVA (STATISTICA 5.1, Statsoft, Tulsa, OK, USA), after verifying visually the normal distribution using log-normal plots. If ANOVA suggested significance, the post hoc LSD test was used. SD of RR interval, SD of SBP, the firing rate and the normalized firing rate, and SBP–RR interval relationship did not present normal distributions. Therefore, non-parametric Friedman analysis followed by Wilcoxon paired test was used. P<0.05 was chosen as significant.

Clonidine, atenolol, and cardiac vagal activity

Fig 2 Typical traces of RR interval (top), CVM activity (middle), and SBP (bottom) in one animal following atenolol 2 mg kg⁻¹ (A) and clonidine 100 μg kg⁻¹ i.v. (B). Note the reduction in pressure lability, increase in CVM activity, and increase in sinus arrhythmia after clonidine.
Results

A total of 75 rats were used for these experiments. Twelve cells were electrophysiologically identified and isolated in 12 rats (Table 1). All these 12 units could not be discriminated long enough throughout the experiments. Thus, results are presented from 7–9 cells according to the quality of the recordings. In some instances, circulatory variables could not be accurately determined because of noise on the EKG signal or dampening on BP signal. Thus, the data presented here are aggregated only from good-quality signals. The characteristics of the cells are identical to those described previously, except for the low baseline firing rate when compared with previous reports. Pontamine sky-blue ejection sites were recovered in the external formation of the NA (n=5), most often at the level of the obex or caudal to the obex (Fig. 1d).

Atenolol

A peripherally acting beta-blocker, atenolol (2 mg kg\(^{-1}\) followed by 2 mg kg\(^{-1}\) h\(^{-1}\)), was associated with a reduction in HR [365 (23) to 326 (24) bpm, n=11 rats, P<0.05], little changes in SBP [141 (15) to 138 (19) mm Hg, n=11 rats], and no changes in firing rate of CVM [median (range): 0.5 Hz (2) to 0.4 Hz (2.5), n=9 cells]. Non-significant changes were observed when the slope of the cardiac baroreflex was calculated either at the CVM level [0.06 (0.03) to 0.08 (0.04) spikes s\(^{-1}\) mm Hg\(^{-1}\), n=9 cells] or at the heart level [0.05 Hz (0.15) to 0.03 Hz (0.14) ms mm Hg\(^{-1}\), n=11 rats]. Finally, the sd of SBP (pressure lability) was reduced (P<0.05). In contrast, the sd of RR interval was not modified (Fig. 3c and d).

Clonidine

Following atenolol pretreatment and during continuous atenolol infusion, cumulative doses of clonidine 10–100 \(\mu g\) kg\(^{-1}\) were administered to evoke cardiac vagal activation (n=7 cells in 10 rats). Clonidine 100 \(\mu g\) kg\(^{-1}\) was associated with minimal changes in HR [324 (22) to 317 (22) bpm, n=10 rats, all values given for the highest dose of clonidine, i.e. 100 \(\mu g\) kg\(^{-1}\); Fig. 4a], but with significant reduction in SBP [142 (17) to 114 (10) mm Hg, n=10 rats; P<0.05; Fig. 4a]. The sd of SBP and RR interval was, respectively, reduced and increased (P<0.05; Figs 2 and 4c and d). This occurred together with CVM activation (Fig. 2n, 4c and d). From a low baseline-firing rate, a large increase occurred [0 (0.7) to 1 (3.3) spikes s\(^{-1}\), P<0.05, n=7 cells; Fig. 4e]. This was even more prominent when firing was normalized to the initial pressure [0 (0.7) to 1.2 (4.0) spikes s\(^{-1}\), P<0.05, n=7 cells; Fig. 4e]. This did achieve significance even if one cell was silent before and after clonidine. Four cells out of seven cells were silent before clonidine and were activated by clonidine 100 \(\mu g\) kg\(^{-1}\). Two out of seven cells were active before clonidine and increased their firing rate following clonidine (0.4–1 Hz; 0.7–2.7 Hz). One cell out of seven cells, which was inactive before clonidine, transformed its firing pattern from single spike to volley of action potentials (doublet). Finally, the slope of the cardiac baroreflex analysed at the CVM level [0.07 (0.04) to 0.12 (0.04) spikes s\(^{-1}\) mm Hg\(^{-1}\), n=7 cells, P<0.05] and at the heart level [0.03 (0.03) to 0.08 (0.13) ms mm Hg\(^{-1}\), n=10 rats, P<0.05] were both significantly increased (Fig. 4e).

Discussion

Atenolol had no effect on the activity of CVMs and on the slopes of the cardiac baroreflex analysed at the level of both CVMs and the heart. Clonidine increased the activity of CVMs which were either silent or with a low baseline firing rate, increased the slope of the cardiac baroreflex analysed at the level of CVMs and the heart, increased sinus arrhythmia, and reduced pressure lability.

Atenolol poorly crosses the blood–brain barrier at variance with propranolol. The absence of the effect of atenolol on CVM activity and pressure–unit relationship is in line with the absence of the effect of atenolol on the slope of the cardiac baroreflex analysed at the heart level in supine healthy volunteers.

One key difference of the present vs previous data is the low firing rate of CVMs observed here [2.9 (3.3) Hz\(^{18}\) vs 0.5 (0.7) Hz]. In agreement with other data, most CVMs were silent (66–84\%\(^{18}\) 14). Thus, the deliberate bias does not invalidate the data unless previous recordings, with a low baseline activity or following the use of an excitatory amino acid to increase the firing rate of the CVMs, including the characterization itself of CVMs, are also invalid. All but one silent cell were activated by clonidine; this is the major finding and confirms a preliminary finding. Our impression is that CVMs identified after a long surgery present with a low baseline firing, suggesting that greater trauma occurred here than the one observed upon shorter surgery. This was observed in a murine preparation, which exhibits low parasympathetic activity even in conscious animals.

One cell out of seven cells was not activated at all by clonidine. Urethane is an unlikely contributor, as its CVM activation was suppressed in only one cell. Rather it is more likely that this reflects altered reactivity or baseline activity. With respect to baseline activity, a muscarinic M1 antagonist, pirenzepine, evokes a much reduced bradycardia in aged volunteers as opposed to young volunteers. In a similar manner, clonidine did not elicit any bradycardia in middle-aged hypertensive patients. Our opinion is that young adult rats following major surgery mimic elderly humans, in the ambulatory setting, in whom cardiac vagal activation cannot be achieved with a 100% success rate.

A key difference between present and previous\(^{18}\) data is that the increase in the slope of the pressure–RR interval relationship (slope of the cardiac baroreflex) achieves
significance. In contrast, it did not without atenolol pre-treatment. The significant increase in both the pressure–unit and the pressure–RR interval relationships is in line with the following facts: (i) when vagal stimulation precedes immediately sympathetic stimulation, the bradycardia occurs with no delay; (ii) when sympathetic stimulation precedes vagal stimulation, the bradycardia is delayed; (iii) when administration of propranolol is followed by sympathetic stimulation and then vagal stimulation, the bradycardia occurs again without delay. Thus, atenolol was administered before clonidine to simplify the interpretation. Secondly, (i) sympathetic stimulation reduces vagally induced bradycardia; (ii) propranolol suppresses this reduction in bradycardia; (iii) with propranolol present, clonidine prevents this reduction of vagally induced bradycardia. Thirdly, atenolol enhances respiratory sinus arrhythmia in conscious supine volunteers: the sympathetic system exerts restraint on the parasympathetic system. Fourthly, the amplitude of the sinus arrhythmia is associated with increase in the slope of the cardiac baroreflex analysed at the heart level. Thus, suppression of sympathetic restraint on cardiac vagal activity, by atenolol, may explain our findings.

Pressure lability is increased upon light anaesthesia, emergence from anaesthesia, or in conscious hypertensive patients recovering from major surgery, but not under adequate anaesthesia. Thus, reduction in pressure lability following atenolol is quite remarkable and it is possible that this could translate into reduced postoperative pressure lability following beta-blockade in patients presenting for surgery. Secondly, the further reduction in pressure lability by clonidine is even more remarkable, given the low lability already achieved following adequate anaesthesia and atenolol. A link exists between the increase in pressure–unit

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**Fig 3** Effect of atenolol 2 mg kg⁻¹ i.v. on circulatory parameters, CVM unit activity, and derived data [mean (SEM)]. (A) SBP; (B) RR interval; (C) SD of SBP; (D) SD of RR interval; (F) cardiac baroreflex analysed at the CVM level (SBP–CVM slope; pressure–unit relationship); (G) cardiac baroreflex analysed at the heart level (SBP–RR interval slope; pressure–RR interval relationship).
relationship, increased sinus arrhythmia, and reduced pressure lability. Such a link was not observed in a previous report. Thus, the present and previous data bring us three steps ahead in our understanding of beat-by-beat perioperative circulatory stability in that an inhibitor of catecholamine synthesis, alpha-methylparatyrosine, suppresses pressure lability upon emergence in rats, suggesting sympathetic vascular activity as a cause of pressure lability, and atenolol suppresses pressure lability, suggesting sympathetic cardiac activity as a cause of pressure lability. A mechanistic link, that is, CVM activation, exists between increased sinus arrhythmia and reduced pressure lability following clonidine, but not atenolol. This calls for an effect of cardiac parasympathetic activity on pressure lability. Previously, reduced pressure lability was observed simultaneously to increased sinus arrhythmia in a clonidine-treated patient upon early recovery from major surgery. Thus, reduction in pressure lability may be linked to a reduction in sympathetic, vascular and cardiac, nervous activity combined with an increase in cardiac vagal activity.

It is important to recognize the limitations in our study. First, stringent electrophysiological and anatomical criteria for the identification of CVMs were met. Secondly, urethane was chosen, as isoflurane suppresses entirely CVM motoneurone activity (Toader, unpublished data). Thirdly, the low success rate confirms the difficulty in recording CVMs in vivo. This technically demanding experiment explains the design; as is standard for integrative physiologists during difficult experiments, we did not dare attempt to match these experiments with a proper control group.

Fig 4 Effect of cumulative doses of clonidine 10–100 μg kg$^{-1}$ i.v. following pretreatment with atenolol 2 mg kg$^{-1}$ i.v. followed by infusion of 2 mg kg$^{-1}$ h$^{-1}$ [mean (SEM)]. (A) SBP; (B) RR interval (n=10 rats); (C) sd of SBP; (D) sd of RR interval; (E) CVMs firing rate (n=7 cells; thick line: raw data; dashed line: data normalized for SBP); (F) slope of cardiac baroreflex analysed at the CVM level (SBP–CVM slope; pressure–unit relationship); (G) slope of the cardiac baroreflex analysed at the heart level (SBP–RR interval slope; pressure–RR interval relationship). *P<0.05 at the considered interval.

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over time challenged by saline. However, saline injected before each dose of atenolol 2 mg kg\(^{-1}\) or clonidine 100 μg kg\(^{-1}\) did not modify either firing rate or circulatory variables, and a control group challenged by vehicle would be very unlikely to show an improvement in cardiac vagal activity over time. This animal study points to further clinical data which showed increased sinus arrhythmia, preserved baroreflex slope and reduced pressure lability in hypertensive patients after major surgery,\(^4\) and improved outcome in high-risk patients following alpha-2 administration.\(^{38,39}\) Thus, no clinician will ever select alpha-2 agonists on the basis of the present data, given or not a control group over time, but only on previous clinical data.\(^{38,39}\)

Fourthly, a dose-dependent reduction of MAC\(_{\text{bar}}\) following alpha-2 agonist is irrelevant, as this study does not deal with sympathetic nervous activity or depth of anaesthesia but cardiac vagal activity. Fifthly, these data can hardly be viewed as confirmatory; even with hindsight, a clinician would have difficulties to infer a change in cardiac vagal activity, sinus arrhythmia, and pressure lability from previous clinical observations.\(^{4,38,39}\) All previously published data point towards sympathetic inhibition but not towards cardiac parasympathetic recruitment and certainly not towards their combination in reducing pressure lability.\(^{35}\) So far no monitor in the anaesthesia/critical care setting allows following pressure lability and sinus arrhythmia on-line on a beat-by-beat basis. Finally, the present data do not imply that CVMs are the only site of action of clonidine within the cardiac baroreflex.\(^{40}\)

The discrepancy in firing rate (high\(^{18}\) vs low: Table 1) increases the clinical relevance of the present data. As silent CVMs may be recruited by clonidine, this suggests recruiting cardiac vagal activity either in patients following major surgery\(^2\) or in elderly patients who present to surgery with low baseline cardiac vagal activity. Ageing patients in the ambulatory setting with advanced congestive heart failure are another target.\(^{11}\)

Pressure lability, or its surrogate, pulse pressure variation, is an independent factor of outcome both in the ambulatory\(^{41–45}\) and critical care\(^5\)\(^\text{6}^\) settings, as opposed to the mean level of SBP. Major surgery in high-risk patients appears to be associated with a high incidence for plaque rupture. The mechanism leading to plaque rupture may be the shear stress caused by beat-by-beat changes in pressure, during the postoperative period. Thus, attention to mean SBP level should go hand in hand with the reduction of pressure lability in the critical care setting. At variance with a demonstration in the cardiology setting,\(^1\) the association, postulated here, between increased vagal activity and improved perioperative outcome seems logical but remains speculative. In this respect, baroreflex failure, that is simultaneous hypertension and tachycardia, can be controlled uniquely\(^44\) with centrally acting agents in the cardiology\(^{45}\) or critical care\(^4\) setting. A reduced pressure lability and increased sinus arrhythmia in hypertensive humans\(^2\) were observed upon early recovery after major surgery. In contrast, increased pressure lability and poor outcome were observed in the ambulatory\(^{41–43}\) and critical care\(^5\)\(^\text{6}^\) setting. This preclinical study may stimulate interest in seeking a link between increased cardiac vagal activity, increased sinus arrhythmia, reduced pressure lability, and improved outcome following major trauma or surgery. In this respect, a comparison between beta-blockers and alpha-2 agonists is needed.

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### References

1. La Rovere MT, Bigger JT, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet* 1998; 351: 475–84
10. Levy MN. Neural control of the heart: the importance of being ignorant. *J Cardiovasc Electrophysiol* 1995; 6: 283–93
Deering AH, Harron DWG, Riddell JG, Shanks RG. Effect of
Coleman TG. Arterial baroreflex control of heart rate in the
Gilbey MP, Jordan D, Richter DW, Spyer KM. Synaptic mechanisms
Hall GT, Potter EK. Attenuation of vagal action following sym-
Elghozi J-L, Laude D, Janvier F. Clonidine reduces blood pressure
Cividjian A, Rentero N, Quintin L. Reduced blood pressure
during emergence from anesthesia in rats: a pilot study
Cividjian A, Rentero N, Pequinot JM, Quintin L. Effect of
catecholamine depletion on increased blood pressure
liability upon emergence from halothane anesthesia in rats. J Anesth (Tokyo) 2008; 140–8
liability and cardiac baroreflex in normotensive patients
Nosaka S, Yamamoto T, Yasunaga K. Localization of vagal
cardioinhibitory preganglionic neurons within rat brain stem. J Comp Neural 1979; 186: 79–92
Mendelowitz D. Advances in parasympathetic control of heart
cardiovascular morbidity and mortality after non cardiac surgery. Anesthesiology 2004; 101: 284–93