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Effect of catecholamine depletion on increased blood pressure lability upon emergence from halothane anesthesia in rats: the role of sympathetic nervous activity in postanesthetic circulatory instability

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Abstract
Purpose. Circulatory instability is often observed upon emergence from general anesthesia. The increased blood pressure (BP) lability has been associated with poor clinical outcome. However, its underlying mechanisms are not fully understood. Thus, we investigated a possible role of the sympathetic nervous system (SNS) and cardiac baroreflex in the increased pressure lability observed upon emergence from general anesthesia.
Methods. Male rats (n = 16) were allocated to two groups, i.e., (1) a control group (n = 8) and (2) an α-methylparatyrosine (α-MPT; an inhibitor of tyrosine hydroxylase)-treated group (n = 8). In the α-MPT-treated group, in order to deplete catecholamines both in the central nervous system and in the SNS, α-MPT (300 mg·kg^{-1}) was injected intraperitoneally (i.p.), administered twice, 4 and 2 h before halothane discontinuation (total dose, 600 mg·kg^{-1} i.p.). In the control group, saline was administered at identical time-points. Systolic BP (SBP) lability was evaluated on a beat-by-beat basis, using the coefficient of variation of SBP, and the occurrence of slow and rapid rises in SBP and their amplitude, while the cardiac baroreflex slope was calculated using the "sequences" method.
Results. In the control group, heart rate, SBP, and the three indices of BP lability (i.e., the 3 indices of BP lability are: coefficient of variation of SBP, number of slow and rapid rises in pressure, amplitude of slow and rapid rises in pressure) all increased upon emergence from anesthesia ($P < 0.05$). Such increases were all blunted in the α-MPT-treated group, with the increases in the three indices of BP lability almost entirely suppressed ($P < 0.05$). The cardiac baroreflex slope was similarly decreased in both groups ($P < 0.05$).
Conclusion. The postanesthetic increase in pressure lability seems largely a consequence of increased sympathetic activity, irrespective of any change in cardiac baroreflex sensitivity.

Key words Rat · Blood pressure variability · Emergence from anesthesia · Immobilization · Stress · α-Methylparatyrosine · Sympathetic nervous system

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Introduction

Postoperative circulatory instability is generated by the sympathetic, angiotensin, and vasopressin systems, which concur to increase the *mean* level of blood pressure (BP). Accordingly, elevated arterial pressure in the postoperative period is treated to lower BP to a desired level. However, this clinical approach totally ignores *beat-by beat* pressure instability, called BP variability or *pressure lability*. In the ambulatory setting, increased pressure lability is associated with poor outcome in a manner independent of the level of systolic pressure itself [1–4]. In the perioperative setting, heightened pressure lability was associated with poor outcome [5]. Thus, pressure lability carries a prognostic factor in itself, possibly by increasing the incidence of shear stress, *plaque* rupture, and downstream ischemia, e.g., in the heart or the brain. Given the mortality associated with pressure lability [1–4] and its importance for anesthesiologists and critical-care physicians [5], this study analyzed the mechanism behind pressure lability. As increased baroreceptor-heart rate reflex ("cardiac baroreflex") sensitivity is inversely related to pressure lability [6], the sensitivity of the cardiac baroreflex was calculated.

A sympatholytic agent, clonidine, blunted postoperative hypertension and tachycardia in hypertensive patients recovering from abdominal aortic [7] or coronary surgery. Alpha-2 agonists administered to high-risk patients improve outcome [8–9]: whether this improved outcome is related to blunted tachycardia, or blunted hypertension or blunted pressure lability is unknown. Clonidine reduced pressure lability in hypertensive patients [10,11] following major surgery (see Fig. 3D in [12]). However, this demonstration [12] was only *qualitative*. Furthermore, clonidine is nonselective and presents both as a sympatholytic [13] and as a parasympathomimetic [14]. Thus, these data [12] leave open the question of whether pressure lability is linked only

to sympathetic inhibition. An alternative explanation could be that reduced pressure lability might be secondary to increased parasympathetic activity to the heart ("cardiac vagal activity"), and increased baroreflex sensitivity. Such increased sensitivity would lead to a rapid buffering of pressure changes within one or two beats, and reduced lability.

Alpha-methylparatyrosine (α-MPT) inhibits tyrosine hydroxylase, the rate-limiting enzyme for the synthesis of catecholamines. Thus, α-MPT depletes central and peripheral catecholamines in the sympathetic nervous system (SNS). However, unlike clonidine, α-MPT can inhibit sympathetic activity without increasing cardiac vagal activity. α-Methylparatyrosine was previously reported to reduce perioperative pressure lability upon removal of pheochromocytoma [15]: thus, the reduced circulatory instability may have been due only to the inhibition of sympathetic activity. In order to investigate the mechanism underlying the beat-by-beat pressure lability upon emergence from general anesthesia, we observed the effects of α-MPT on circulatory variables, beat-by-beat pressure lability, and cardiac baroreflex sensitivity during the postanesthetic period after the discontinuation of halothane in rats under myorelaxation. Emergence combined with paralysis was used as a model to generate increased pressure lability. The working hypothesis was that α-MPT would reduce the beat-by-beat pressure lability independently of any increase in the sensitivity of the cardiac baroreflex.

Methods

The experiments were approved by the Rhône-Alpes Animal Care Committee and adhered strictly to the guidelines of the National Institute of Health [16]. Male Sprague-Dawley rats (350–400 g; Iffa-Charles River, L'Arbresle, France) were anesthetized with halothane: its concentration was monitored using a gas monitor (Siemens GM 120; Siemens-Elema AB, Sweden). Mechanical ventilation was established (f, $68 \cdot min^{-1}$; fractional inspired oxygen [$F_{I_{O_2}}$], 0.40; end-tidal CO_2 [$CO2_{et}$], 30–35 mmHg). Rectal temperature was maintained at 37 ± 0.5°C, using a warming blanket (Harvard; Edenbridge, KY, USA). Blood pressure (BP) was recorded with a calibrated Bentley Trantec 800 transducer-Gould pressure processor (Gould, Cleveland, OH, USA), through a femoral arterial catheter. Surgical staples located at the four limbs allowed us to derive an electrocardiogram (EKG; Biotach Gould amplifier; Gould) and the heart rate (HR). Signals were displayed on an oscilloscope and recorded on paper (Gould Brush 2600; Gould). EKG and BP were sampled (4 and 1 kHz respectively) using a 12-bit analog/digital (A/D) converter (DAS 16G; Metrabyte, Taunton, MA, USA) fed into a computer. Chloral hydrate 500 $mg \cdot kg^{-1}$ i.v was used for euthanasia.

Care was taken to minimize pain and discomfort inflicted on the animals upon emergence [17, 18]: (a) the rectal probe and tracheotomy tube were covered with pramocaine 1% (Tronothane; Abbott, Rungis, France), (b) swabs soaked in a long-acting local anesthetic (bupivacaine 0.25%; Aguettant, Lyon, France), were inserted in all surgical incisions, (d) corneal drying was prevented by the application of saline before halothane discontinuation, and (e) all visual and auditory stimuli were kept to the minimum compatible with recording following halothane discontinuation. Before baseline recording and the injection of metocurine 500 $\mu g \cdot kg^{-1}$ i.v., the monitoring of withdrawal movements or increases in pressure upon tail pinch allowed us to assess the adequacy of halothane concentration [18, 19]. If tail pinch evoked a withdrawal movement or an increase in systolic BP (SBP) of more than 20 mmHg, the halothane concentration was increased by 0.2% until the SBP increase was less than 10 mmHg, indicative of adequate anesthesia. To evaluate the interval necessary for emergence from halothane anesthesia without muscle paralysis, one group of rats did not receive myorelaxation and had halothane readministered immediately following withdrawal movements (mean, 26 ± [SD] 10 min; range, 13–38 min; $n = 4$; data not shown). This group was not further analyzed or reported.

Rats were allocated to two groups (Fig. 1): (1) *control*: anesthesia was induced with halothane (induction, 5%; surgery, 1.5%). After 30 min of baseline recording under a stable halothane concentration, halothane was discontinued for 60 min. (2) α-MPT: as α-MPT takes several hours to produce catecholamine depletion, α-MPT 300 $mg \cdot kg^{-1}$ i.p. was administered 4 and 2 h before halothane discontinuation (total dose, 600 $mg \cdot kg^{-1}$), i.e., before the induction of anesthesia. In the control group, saline was administered at identical time points. After 30 min of baseline recording under stable halothane concentration, halothane was discontinued for 60 min.

The cardiac baroreflex slope was calculated using the "sequence" technique [20,21] (Fig. 4): the software (RECAN; Alpha-2, Lyon, France) we used selects all sequences of successive beats in which there a four or more concordant increases or decreases in SBP, and the interval between the R waves of the EKG (RR interval). A linear regression was applied to each sequence. Given all these regressions, to avoid emphasis on outliers, the median of all these slopes (millisecond per mmHg: ms/mmHg) was calculated for each considered interval (–20–0 min; 10–20 min; 20–40 min; and 40–60 min) and taken as the cardiac baroreflex sensitivity for the considered interval. The coefficient of variation of SBP was calculated as the ratio between the SD in

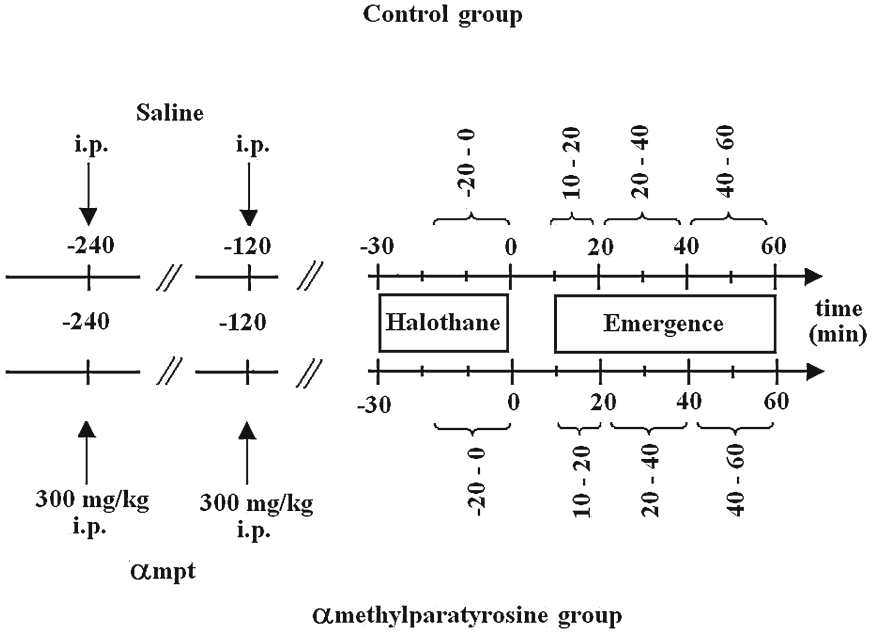

Fig. 1. Study protocol. α-MPT, α-Methylparatyrosine

1-min periods and the considered variable (SBP) multiplied by 100 [(SD/X)*100]. To delineate pressure lability, slow pressure rises were defined as oscillations in the smoothed SBP signal having a rise time (aperiodic waves) of less than 90 s and amplitude arbitrarily greater than 5 mmHg. To delineate slow pressure rises, SBP raw data were low-pass filtered (Fig. 3B). Rapid pressure rises were defined as oscillations in the smoothed SBP signal having a period of 2.5–20 s and amplitude arbitrarily greater than 7.5 mmHg. To delineate rapid pressure rises, SBP raw data were low-pass filtered (Fig. 3C).

Data were analyzed (a) at baseline (–20–0 min before halothane discontinuation) and (b) at 10–20 min, 20–40 min and 40–60 min after halothane discontinuation. Data were checked for normality using lognormal plots. Data were log-transformed to present comparable SDs in each group. Then a two-way (time and treatment) analysis of variance (ANOVA) for repeated measurements was performed. When the ANOVA showed significance ($P < 0.05$), a post-hoc least significant difference test was used. Values for results are presented as mean ± SEM and as mean ± SD in the Figures and text, respectively.

Results

Before halothane discontinuation (stable anesthesia) and 60 min after the discontinuation of halothane inhalation (interval, +60 min, i.e., end of study), respectively, the end-tidal halothane concentrations were: control group, 0.85 ± 0.09% and 0.14 ± 0.04%; α-MPT group, 0.79 ± 0.21% and 0.17 ± 0.05% ($P < 0.05$ within groups; not significant [NS] between groups).

In the control group ($n = 8$), increased SBP (Fig. 2C) and HR (i.e. decreased RR interval; Fig. 2D) were observed following halothane discontinuation. In the α-MPT group ($n = 8$), hypertension was reduced, albeit nonsignificantly (Fig. 2C) and tachycardia was partially blunted ($P = 0.05$ vs control at 40 to 60-min interval; Fig. 2D).

In the control group, the following circulatory profile was observed, (a) increased coefficient of variation of SBP (Fig. 2E), and (b) increased number and amplitude of slow and rapid rises in pressure (Fig. 3D–G). By contrast, α-MPT (a) suppressed the increase in the coefficient of variation of SBP (Fig. 2E; $P < 0.05$ vs control at 20 to 40 and 40 to 60-min intervals), (b) reduced the number of slow and rapid rises in pressure ($P < 0.05$ vs control at 20 to 40 and 40 to 60-min intervals; Fig. 3D, E), and (c) reduced the amplitude of slow and rapid rises in pressure by around 50% (rapid, 48.5%; slow, 49.3% at 40 to 60-min interval). Furthermore, this reduction was significant at 20 to 40 and 40 to 60-min intervals for rapid rises and at 40 to 60-min interval for slow rises in pressure (Fig. 3F, G). The sensitivity of the cardiac baroreflex was lowered in a similar manner upon emergence in the control and α-MPT-treated rats (Fig. 4D).

Discussion

α-Methylparatyrosine (α-MPT) largely blunted the increase in *beat-by-beat* pressure lability generated by

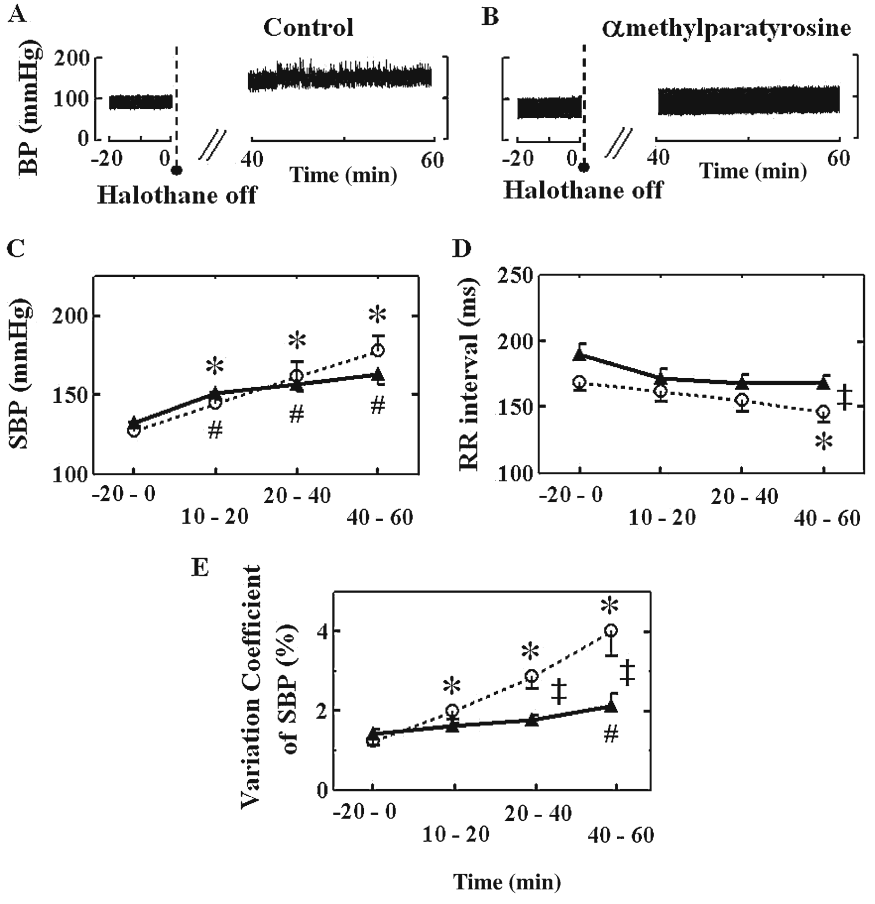

Fig. 2A–E. Typical examples of changes in pressure lability observed for 20 min before discontinuation of halothane inhalation (*left traces* in **A** and **B**) and 40–60 min after its discontinuation (*right traces* in **A**, **B**) in the control (**A**) and α-MPT-treated (**B**) paralyzed rats. The *dotted lines* indicate the time points when halothane was discontinued (*halothane off*). A different time scale was used in the *right* and *left parts* of **A** and **B**, to better display peaks of systolic blood pressure (SBP) during late emergence (+40–+60 min). The slow and rapid rises in pressure were largely reduced in α-MPT-treated rats as compared to findings in the control rats; contrast the beat-by-beat peaks in systolic blood pressure (SBP) in **A** (*right*) with their near total suppression in **B** (*right*). **C–E** Aggregated data for intervals (–20–0; baseline), 10–20, 20–40, and +40 to +60 min. **C** SBP for control (*open circles*, $n = 8$) and α-MPT-treated (*closed triangles*; $n = 8$) rats. **D** RR intervals for control and α-MPT groups. **E** Coefficient of variation of SBP over 1-min periods. **C–E** Data values are shown as mean ± SEM. $^{*}P < 0.05$ vs baseline within control group; $^{\#}P < 0.05$ vs baseline within α-MPT; $^{\ddagger}P < 0.05$ between control and α-MPT groups at corresponding interval

immobilization stress combined with emergence from anesthesia. The mechanism of this reduced pressure lability is entirely via sympathetic inhibition, as the sensitivity of the cardiac baroreflex is reduced. However, α-MPT only partially blunted the tachycardia and the hypertension generated by emergence from anesthesia under paralysis.

This study presents shortcomings. Firstly, no dose-response relationship was constructed: a high dose of α-MPT was selected based on the literature [22,23]. Secondly, no plasma or tissue catecholamine determination was performed: this was reported extensively earlier [22,23]. Thirdly, no sympathetic nerve recording was performed: this mechanistic study did not look at biochemical or electrophysiological markers but *only* at physiological indices (pressure lability in itself, i.e., coefficient of variation of SBP, etc.). Sympathetic nerve recording or tissue/plasma determinations would not add any further insight, given the limited objective of this communication, which is, in itself, a mere follow-up of previous studies [7,12,17,19,24]. Fourthly, this communication simply builds upon existing literature (see below), but does not delineate the effects of various combinations of ganglionic blockers or alpha/beta blockers. Fifth, this report has only a mechanistic purpose and does not promote α-MPT for the treatment of postoperative hypertension. Sixth, nowadays, halothane is seldom used, except for pediatric anesthesia. However, as this experiment was only mechanistic, and as recent halogenated agents do not lead to better postoperative circulatory stability, halothane was selected as the prototype of all halogenated agents. Finally, both pressure and pressure lability were found to be stable over time under anesthesia ($n = 8$; data not shown).

Firstly, in our animal model, care was taken to reduce pain in the animals, as extensively described [17,18]. Indeed, infiltrations of local anesthetic in each surgical wound inhibit the responsiveness of *locus coeruleus* neurons when strong pressure or a pinch is delivered to any of the locally anesthetized areas [17]. This suggests that the present model is virtually free of nociceptive inputs. Secondly, this model combines immobilization stress [25] with emergence from anesthesia. In contrast to the immobilization stress usually employed in behavioral studies, immobilization was produced by paralysis to make it relevant to anesthesia and critical care. However, that emergence from anesthesia is combined with paralysis makes this experimental model crude or even muddy: two different stimuli (emergence, paraly-

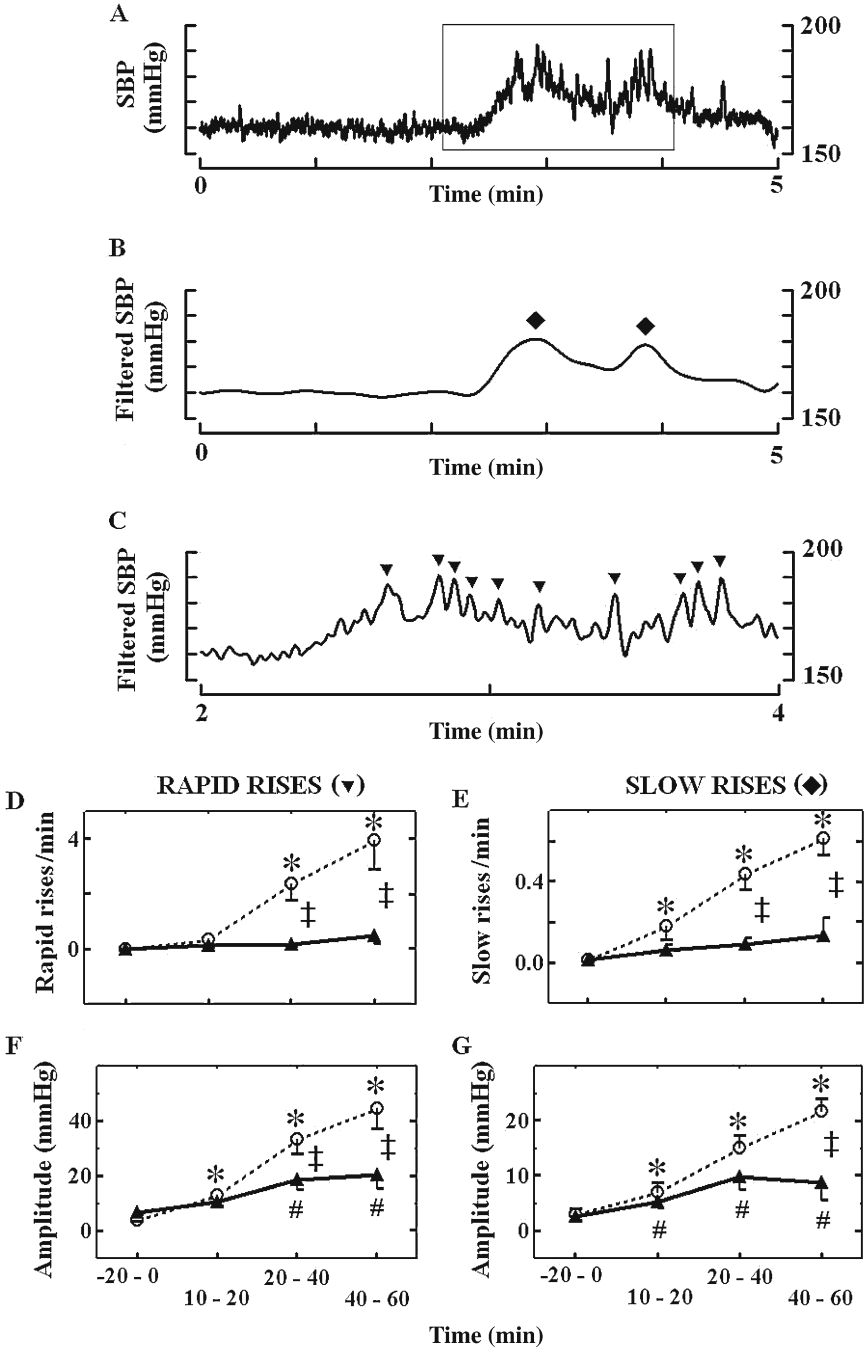

Fig. 3A–G. Blood pressure lability during emergence from anesthesia under paralysis: **A** Typical trace for raw SBP. The data included *within the box* are shown in **C**. **B** Delineation of slow rises in pressure (*diamonds*; duration > 20 s, rise time < 90 s, amplitude > 5 mmHg) observed on a filtered BP trace with time scale as in **A**. **C** Delineation of rapid rises in pressure (*triangles*; duration 2.5 s–20 s, amplitude >7.5 mmHg) observed on a filtered BP trace. The data included *within the box* in **A** are displayed using a *larger* time scale (2–4 min). **D, E** Number of rapid and slow rises in pressure; **F, G** amplitude of rapid and slow rises in pressure. Data values are shown as mean ± SEM. $^{*}P < 0.05$ vs baseline within the control group (*open circles*; $n = 8$); $^{\#}P < 0.05$ vs baseline within α-MPT group (*filled triangles*; $n = 8$); $^{\ddagger}P < 0.05$ between control and α-MPT groups at corresponding interval

sis) are combined, as discussed earlier [17,19,25]: this is the biggest shortcoming. But, *this shortcoming is in fact the strength of the study, because of its daily clinical relevance*. Emergence from anesthesia and weaning from ventilatory support following major surgery, or in the critical care unit, involves a degree of coercion: during this interval—lasting from minutes to hours—from the end of sedation and extubation itself, patients may present residual paralysis or have, either their hands attached or have strong and repeated instructions to refrain from any movement. State-of-the-art emergence is achieved under controlled conditions (temperature, analgesia, etc . . .). The patient returns to ventilatory and airway self-sufficiency and consciousness before extubation. However, weaning remains challenging: the longer the ventilatory support, the longer this weaning period lasts. Thus, immobilization stress *and* emergence from anesthesia are inextricably intertwined, with a consequence: pressure lability. Given this clinical relevance, and the present results, the reduction in pressure

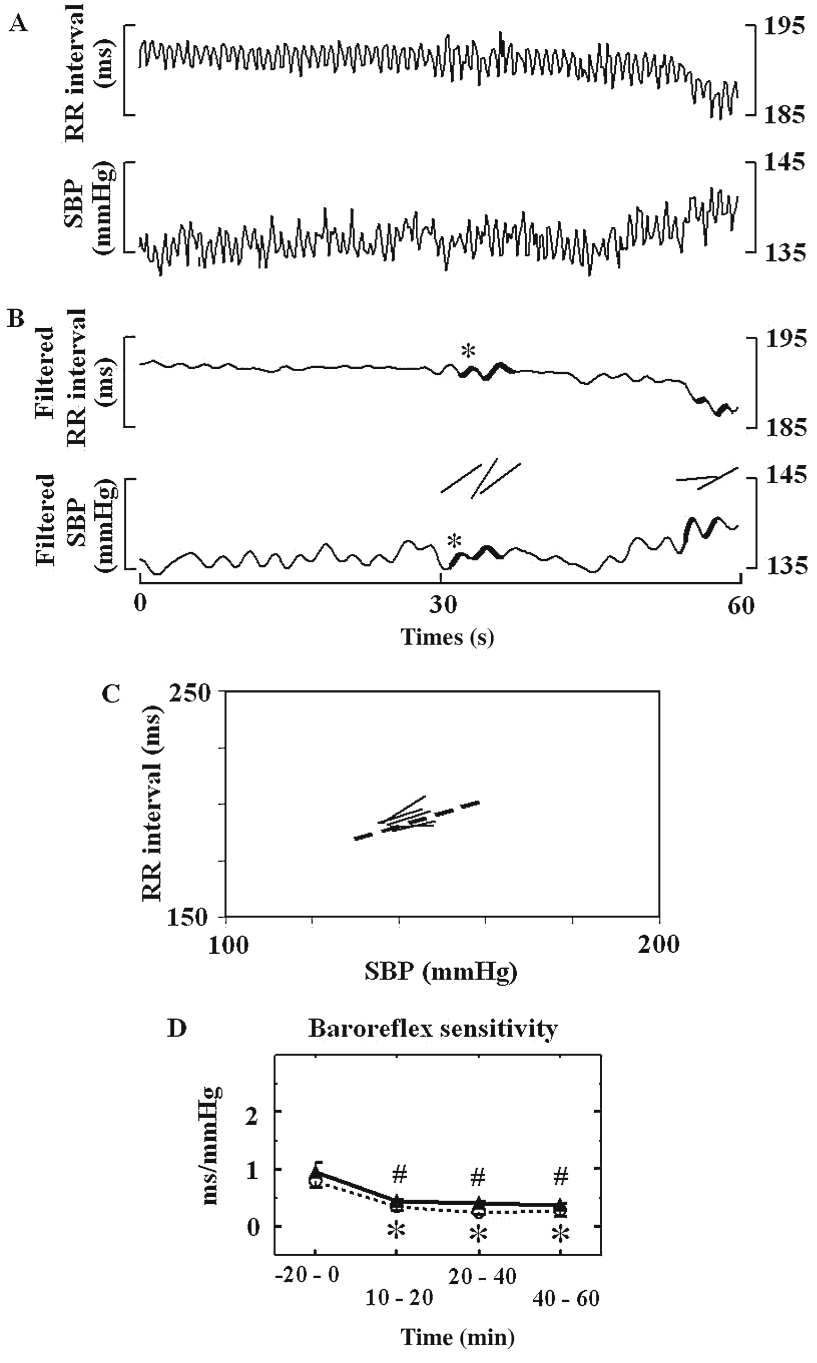

Fig. 4A–D. Baroreflex sensitivity upon emergence from anesthesia under paralysis in rats. **A** Raw systolic blood pressure (*SBP*) and RR interval in one rat. **B** Filtered BP and RR series over time: the software scans the data for all sequences of at least four consecutive increases in SBP and RR intervals (hypertension-bradycardia; *heavy lines*) or decreases in SBP and RR intervals (hypotension-tachycardia: *light lines*) called "sequences" [20]. A linear regression (*middle panel*) between filtered SBP and RR interval is applied to each of the sequences. **C** Plot shows the slopes of the individual sequences for the considered interval. The median value (*broken line*) of the slopes is taken as the baroreflex sensitivity for the considered interval. **D** Baroreflex sensitivity. Data values are shown as mean ± SEM. $^{*}P < 0.05$ vs baseline within control group (*open circles*; $n = 8$); $^{\#}P < 0.05$ vs baseline within α-methylparatyrosine α-MPT group (*closed triangles*; $n = 8$). *RR*; interval between the R waves of the EKG

lability observed in hypertensive humans following major surgery and clonidine [12] may be, presumably, linked to reduced sympathetic activity evoked by stress and immobilization during the recovery period, but not primarily linked to parasympathetic activation. Thirdly, care was taken in our model to reduce the length of the full emergence period to a minimum (30 min or less), compatible with ethics [16–26]: the circulatory profile observed in our present study 60 min after halothane discontinuation was similar to the one observed [19] after 150 min of halothane discontinuation. Previously, rapid rises in pressure were observed as temporally associated with bursts of action potentials recorded from *locus coeruleus* neurons [17]. Furthermore, attempts at voluntary movement in paralyzed human volunteers increased the pressure proportionally to the intensity of the effort (Figs. 5 and 6 in [27]). Therefore, the slow and rapid rises in pressure in the present study (Fig. 3B,C) are the likely circulatory counterparts associated with escape attempts.

Would lengthening of the period of observation beyond the 60-min interval change the result regarding reduced pressure lability? Indeed, sympatholytics reduce the minimal alveolar concentration of halothane [28]; therefore, the blunted lability may have been simply due to delayed emergence under residual halothane end-tidal concentration. This is unlikely: (a) escape movements in unparalyzed rats occurred 26 ± 10 min after halothane discontinuation ($n = 4$; data not shown), (b) the halothane concentrations measured 60 min after discontinuation of halothane were identical to concentrations measured previously at similar intervals [18–19], and (c) the tachycardia and hypertension observed in the present study 40–60 min after the discontinuation of halothane were identical to those observed 150 min after halothane discontinuation [19]. Therefore, the length of the observation period was the minimum required to achieve full emergence from anesthesia, but the maximum compatible with ethics [16–26]. Finally, pressure lability under *adequate* anesthesia is almost nonexistent (see BP trace in Fig. 2A before halothane discontinuation). Thus, a comparison between adequate anesthesia with no pressure lability and emergence from anesthesia under paralysis and full expression of pressure lability allowed the contrasting of full expression or full inhibition of pressure lability.

High-dose α-MPT led to a 73%–82% depletion of central and peripheral noradrenaline [23]. The turnover time of noradrenaline in the rat cervical sympathetic ganglia is 2 h [22]. A depletion of 80% of central and peripheral noradrenaline stores [22,23] was considered as a valid model; thus, an identical time scale was used in the present design: observation occurred roughly 5 h after α-MPT administration. The main result of sympatholysis is the simultaneous occurrence of a large suppression of pressure lability contrasting with a nonsignificant suppression of hypertension, and a significant reduction in tachycardia upon emergence. When the effect of α-MPT was compared with the effect of saline, tachycardia was more effectively blunted ($P < 0.05$ vs control at the 40 to 60-min interval) as opposed to hypertension: could the effect of circulating factors (e.g., vasopressin, angiotensin, plasma adrenaline) be less important than the effect of nervous factors on the sinus node? More remarkable, the set point of blood pressure (*mean* pressure) is only marginally affected, while pressure lability (*beat-by-beat*) is largely suppressed. The remaining hypertension cannot be linked to sympathetic *nervous* factors, but presumably, is linked to *circulating* factors: (a) depletion of catecholamines by reserpine did not alter spontaneous or evoked preganglionic sympathetic nervous activity [29], (b) the longer turnover in the adrenal gland [22] implies that adrenaline excretion may not be fully suppressed 5 h after α-MPT, (c) phentolamine suppresses Mayer waves during hemorrhage [30], and (d) a converting enzyme inhibitor suppresses compensatory rises in pressure *after* sympathectomy with guanethidine [31]. To sum up, sympatholysis suppresses pressure lability.

Sympathetic activity originates from adrenergic and glutamatergic rostral ventrolateral medulla (RVLM) barosensitive bulbospinal neurons in the brain stem. Adrenergic RVLM neurons are involved in the genesis of sympathetic *reflexes*, but not in the genesis of vasomotor *tone* [32]. This schema [32] is extended by the present findings to reflexes evoked by behavioral stimulation: (a) pressure lability appears to be controlled through the adrenergic RVLM neurons and pre- and postganglionic sympathetic neurons, while (b) by contrast, the *mean* pressure (set point) is under the control of glutamatergic RVLM neurons and/or circulating factors.

An inverse relationship has been reported between pressure lability, heart rate variability, and baroreflex sensitivity [6]. The inverse relationship between pressure lability and HR variability was illustrated in hypertensive patients recovering from major surgery following placebo/clonidine (see Fig. 3B,D in [12]): the placebo patient presented with high pressure lability and low heart rate variability ("fixed heart rate"). By contrast, the clonidine patient presented with low pressure lability and high heart rate variability. In the present study, α-MPT suppressed pressure lability without increasing baroreflex sensitivity, at variance with clonidine. Thus, in the present study, cardiac vagal activation cannot explain the beat-by-beat buffering of lability. Therefore, the inverse relationship between pressure lability and baroreflex sensitivity [6] may not be as straightforward as we previously thought [12].

In the ambulatory setting, a link exists between morbidity and mortality, on the one hand, and pressure lability, on the other hand [1–4]. Indeed, a morning blood pressure surge is associated with an unstable-*plaque* phenotype [33]. Furthermore, the alpha-adrenergic component of the morning blood pressure surge is associated with a high prevalence of silent cerebral ischemia [34]. Although the precise relation between pressure lability, shear stress, inflammation, and *plaque* rupture is not fully delineated yet, attention should be paid to these various factors in both the ambulatory and perioperative setting. For example, in addition to lowering blood pressure *mean* level, reduction in pressure *lability* is to be considered when choosing an antihypertensive drug in the ambulatory setting [35]. In the anesthesia/critical care setting, pressure lability is associated with perioperative mortality [5]. A putative link between pressure lability and increased mortality may be an increase in the incidence of *plaque* rupture following post-operative circulatory instability. Thus, antihypertensive treatment in the anesthesia/

critical care setting should target both the *mean* level of SBP and the *beat-by-beat* pressure lability. A direct clinical comparison of the effects of alpha-2 agonists, beta-blockers, and statins on pressure lability and outcome is needed in high-risk patients.

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