The relationship between expired concentration of sevoflurane and sympathovagal tone in children.

Eric Wodey, Lotfi Senhadji, Patrick Pladys, François Carre, Claude Ecoffey

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Eric Wodey [1], MD, Ph.D.
Lotfi Senhadji [2], Ph.D.
Patrick Pladys [3], MD, PhD
François Carre [4], MD, Ph.D.
Claude Ecoffey [5], MD

1: Assistant Professor, Department of Anesthesiology and Surgical Intensive Care.
2: Professor, LTSI
3: Assistant Professor, Department of Pediatric and Neonatal Intensive Care.
4: Professor, Department of Physiology
5: Professor, Department of Anesthesiology and Surgical Intensive Care.

Received from the Departments of Anesthesiology and Surgical Intensive Care 2, Pediatric and Physiology Hôpital Pontchaillou and of LTSI, INSERM EMI 9934, Groupe de Recherche Cardio-vasculaire (EA 3194), Université de Rennes 1, Rennes, Inserm U127, Paris, France.

Corresponding author : Dr Eric Wodey, Service d'Anesthésie - Réanimation Chirurgicale 2, Centre Hospitalier Regional et Universitaire, 2 rue Henri le Guilloux, 35033 Rennes Cedex 9, France. E mail: eric.wodey@chu-rennes.fr

Abbreviated title: Sevoflurane and sympathovagal tone in children

Abstract

Recently, effects of sevoflurane on the autonomic nervous system have been investigated, during the induction time, by using the spectral analysis of both heart rate and blood pressure variabilities. It was reported that sevoflurane depresses more parasympathetic tone during induction than did halothane in children and a transitory increase in sympathetic vascular tone was also observed. This effect could be more dependent upon an indirect effect of the anesthetic procedure rather than a direct pharmacological effect. The purpose of this study is to determine the relationship between end tidal concentration of sevoflurane and respectively the sympathetic and parasympathetic drives, in children by using a spectral analysis of the RR intervals. Ten children ASA PS I who required elective surgery were studied. After a steady state at 8% of sevoflurane, recordings were started and inspired concentration of sevoflurane was decreased every minute by 1% until a 0% inspired concentration and the beginning of the clinical awakening. A time varying auto-regressive modeling of the interpolated RR sequences (i.e. the RR series) was performed for estimating its power spectrum ($msec^2$). The LF and HF bands were defined respectively by (0.04-0.15 Hz) and (0.15-0.55 Hz). Individual and mean heart rate decreased in the same way that expired sevoflurane concentration. Conversely, the decrease in expired concentration of sevoflurane led respectively SBP, SP, HF and LF/HF to increase. During the decrease of sevoflurane concentration, the increase in LF/HF appeared sooner than the increase in HF. These results demonstrated that heart rate alterations induced by sevoflurane could be more dependent on the parasympathetic tone withdrawal rather than on an increase on sympathetic tone.

Keywords: Heat rate variability; Anesthesia, Sevoflurane, Parasympathetic activity, Children

Introduction:

Several studies have been performed to determine cardiovascular effects of sevoflurane in children as well as in infants (1-4). In comparison to halothane, few cardiovascular side effects have been reported (5). Recently, effects of sevoflurane on the autonomic nervous system have been investigated, during the induction time, by using the spectral analysis of both heart rate and blood pressure variabilities (6). The analysis of heart rate variability (HRV) in frequency domain rely on the calculation of the power spectrum in two frequency bands. The high frequency band (HF) ranges usually from 0.15 to 0.4 Hz and the low frequency (LF) ranges from 0.04 to 0.15 Hz. Parasympathetic activity is usually described as the major contributor to the HF component. The physiological origin of the LF component appeared more controversial (7). Indeed both of sympathetic and parasympathetic activity appear to have components in the LF. Thus the power ratio between LF and HF, noted LF/HF, is considered by some investigators to mirror the sympathovagal balance and is often used in clinical studies (7). Using this method of analysis, Constant *et al.* have recently demonstrated that sevoflurane depresses more parasympathetic tone during induction than did halothane in children (6). Moreover, a transitory increase in sympathetic vascular tone was also observed. Both of these effects could explain the transitory increase in heart rate and the low incidence of bradycardia, classically reported with sevoflurane during induction in children.

In adults, it has been reported that sevoflurane did not increase sympathetic tone (8). Thus the transitory increase of sympathetic vascular tone, reported by Constant *et al.* in children during induction, could be more dependent upon an indirect effect of the anesthetic procedure rather than a direct pharmacological effect of the sevoflurane (6). Until now, few data concerning the pharmacological effect of this anaesthetic drug on the autonomic nervous system in children has been available. The purpose of this study is to determine in children the

relationship between end tidal concentration of sevoflurane and respectively the sympathetic and parasympathetic drives, by using a spectral analysis of the RR intervals.

Patients and Method:

Ten children ASA PS I who required elective surgery were studied after approval by the Human Studies Committee and informed parental consent obtained. The children were unpremedicated. Induction of anesthesia was started with sevoflurane at 8%, in oxygen without nitrous oxide, through an open circuit without soda lime absorber. Children breathed spontaneously during induction until endotracheal intubation. After placement of an intravenous line, the trachea was intubated and the lungs were ventilated at 30 $c.min^{-1}$. Anaesthetic gas concentrations and carbon dioxide concentrations were measured from gas samples continuously aspirated from an elbow connector subsequently attached to the endotracheal tube.

Recordings were started before induction (5 minutes) in order to determine control values. After 5 minutes of steady state at 8% inspired concentration of sevoflurane was decreased every minute by 1% until a 0% inspired concentration and the beginning of the clinical awakening (8%, 7%, 6%,5%, 4%, 3%, 2%, 1% and 0%). Recordings were then stopped and sevoflurane was increased, in order to perform the surgical procedure.

Capnograms as well as inspired and expired gas concentrations were recorded continuously in order to maintain normocapnia. Systolic blood pressure (SBP) was measured every minute using an automated blood pressure cuff. ECG was recorded continuously and digitized at 400 Hz. Heart rate was calculated using RR intervals.

Prior to power spectrum density estimation, the RR sequence, which is intrinsically a non evenly spaced data, is interpolated in order to obtain a series of uniformly sampled data. The retained sampling rate was set to 2 Hz and, using a sliding window of 50 seconds duration, a time varying auto-regressive modeling of the interpolated RR sequences (i.e. the RR series) was performed for estimating its power spectrum ($msec^2$) (7). The LF and HF bands were defined respectively by (0.04-0.15 Hz) and (0.15-0.55 Hz). The maximal range of HF, classically set to 0.4 Hz, was increased to 0.55 Hz as regards to the high breathing rate of children (30 $c.min^{-1}$, i.e. 0.5 Hz). The power spectrum analysis was performed

As described previously, the expired sevoflurane concentration (C) varied between 0 and 8%. For each child various interval of sevoflurane concentration were defined $[C_n, C_{n+1}[$, where $C_{n+1} = C_n+0.25\%$ and $C_1=0\%$. Median values of power in the HF and LF bands as well as median value of expired concentrations of gas were then calculated in each interval $[C_n, C_{n+1}[$. The classical spectral parameters were then derived for each value n : the power in the LF and HF bands, their ratio (LF/HF) and their sum (SP).

A Kruskal Wallis test was used to investigate the effect of sevoflurane on each parameter. A Wilcoxon test was used to establish change in values of parameter between various concentration of sevoflurane. Probability values less than 0.05 were considered significant. Calculation was performed with the BI LOGINSERM© 1979/1987 software.

Results: Age of children ranged from 21 to 76 months (median: 50 months). Maximal expired concentrations of sevoflurane recorded in children ranged from 4.6% to 5.81% (median 5.51%). The beginning of the clinical awakening appeared for expired concentrations of sevoflurane ranging from 0.38% to 0.9% (median 0.44%).

Then, eighteen windows of sevoflurane expired concentration were determined on the data recording. The first concentration window ranged from 4.5% to 4.25% (labeled 4.5) and the last concentration window ranged from 0.5% to 0.25% (labeled 0.5).

Individual and mean heart rate decreased in the same way that expired sevoflurane concentration (Figures 1, 3). Conversely, the decrease in expired concentration of sevoflurane led respectively SBP, SP, HF and LF/HF to increase (Figures 2, 3, 4). During the decrease of sevoflurane concentration, the increase in LF/HF appeared sooner than the increase in HF (Figure 4). For the lowest values of sevoflurane concentration, corresponding to the beginning of the clinical awakening, HF remained significantly lower than the control values.

Discussion

This study shown that in children, the decrease in expired concentration of sevoflurane induced a dose-effect increase in HRV. Although a large increase of parasympathetic activity appeared, we observed a simultaneous increase of sympathovagal balance, i.e. LF/HF ratio. However by contrast, the decrease in sevoflurane concentration slow down the heart rate in all individual cases. These results demonstrated that heart rate alterations induced by sevoflurane (pharmacological effect) during induction previously reported could be more dependant on the parasympathetic tone withdrawal rather than on an increase on sympathetic tone. The present results could explain the difference in heart rate change between infants and older children during induction with sevoflurane (9-13).

Parasympathetic tone

The sevoflurane HR alterations could be attributed to various determinants. Indeed an increase in sympathetic tone as well as a decrease in parasympathetic tone could lead HR to increase. In the present work, the HF component of HRV and the LF/HF ratio, remained at a low level for concentrations of sevoflurane respectively larger than 1.5% and 2% (Figure 4).

As sevoflurane concentration decreased, both HF and LF/HF increased progressively even though HR decreased (Figure 3). Several previous study results show that in healthy patients at rest the mean value of HR is mainly dependent on the parasympathetic tone. The decrease of HR linked to physical training is for the main part due to an increase in the parasympathetic tone (14). In children at rest, a positive relationship between mean RR intervals, i.e. HR, and HF power has been reported (15). It has been shown that the parasympathetic tone, i.e. HF power, increases from the early infancy to the preschool age (15,16). Thus, effects of sevoflurane on the parasympathetic activity could explain the difference in HR variation described between infants and children, during induction with this anaesthetic gas (9). Indeed, in regard to the withdrawal of parasympathetic activity induced by sevoflurane, its HR effect could be more pronounced in preschool children than was in infants. Similarly, the lack of significant variations in HR noted in adults with sevoflurane could be explained in part by a relative low level of the parasympathetic tone.

Sympathetic tone.

During induction in children, Constant et al have reported that the LF/HF ratio increased firstly at the time of the loss of eyelash reflex and secondly decreased at the central pupils time (6). This transitory increase in sympathetic activity could also explain the transitory increase in HR during induction. However in the same study, 5 minutes after intubation, heart rate remained higher to the baseline value even if an important decrease in the LF/HF ratio appeared. In contrast to the HRV parasympathetic activity, HRV analysis of the sympathetic activity as well as sympathovagal balance is more complex to perform. Indeed, increase in the LF/HF ratio can depend upon an increase in sympathetic tone or on a predominantly withdrawal of parasympathetic activity. Regarding our results, sevoflurane did not appear to induce a direct pharmacological activation of the sympathetic tone. The simultaneous decrease in LF/HF and in HF is in favor of an absence of significant sevoflurane sympathetic

activation. This analysis confirms the results of a previous study reported in adults (8). Thus, the transitory increase in sympathovagal balance, i.e. LF/HF, reported by Constant *et al* during induction could be due to the transitory indirect sympathetic activation induced by the anesthetic procedure (6).

Clinical implications

The pharmacological effect on parasympathetic activity at low concentrations of sevoflurane seems to be the main factor for the low incidence of bradycardia in children compared to other anaesthetics agent as halothane (17). The large and early withdrawal of parasympathetic activity, could be compared to the pharmacological effect of intravenous administration of an anticholinergic drug as atropine (18). Thus, administration of atropine before induction with sevoflurane in children appears probably less relevant than with halothane.

As previously described in the present study, a blood pressure decrease appeared for the higher value of sevoflurane. This is partly dependent on the decrease in afterload (4). The decrease in afterload induced by tilt test induces a significant increase of LF/HF in healthy patients, due to the sympathetic activation, i.e. baroreflex adaptation (7). According to our research, the higher values of HR associated to the higher value of sevoflurane concentration can not be attributed to the baroreflex adaptation. Indeed during the higher value of sevoflurane concentration, LF/HF did not increase even if HR increased. Thus, HR alterations should probably be considered with caution in order to assess of changes of loading conditions during pediatric surgery, especially for the higher sevoflurane concentration because it does not seem to reflect an adequate response of the baroreflex.

Limitations of HRV analysis

The evaluation of parasympathetic tone by using HF power can lead in some cases to misinterpretation. It has been demonstrated that changes in breathing rate could induce

significant alterations in HF power without any change in RR value (19). For example, during induction, the various values of breathing rates could influence HF power. Thus, in the present study we chose to perform our analysis only in intubated children with ventilated periods at a fixed frequency. In the present work, the absolute value of the HF power at the beginning of the clinical awakening appeared lower than control values. They are two possible explanations for this difference. Firstly, in our study all recordings were stopped at the occurrence of the initial signs of clinical awakening. Thus sevoflurane concentration did not decrease at the zero value and the residual pharmacological effect of this agent could maintain a significant depression on the parasympathetic tone. Secondly, as regard to the HF breathing effect, the higher range of breathing frequency used in our study could add an artificial decrease in HF value (19).

Finally, the delay between the expired sevoflurane concentration and the central nervous system concentrations must be taken into account in the analysis of the relationship between HRV and sevoflurane concentration. Thus, determination of an accurate threshold for expired sevoflurane concentration to maintain the autonomic nervous system activity should integrate the hysterisis phenomenon. However, analysis of the direct effect of sevoflurane on HRV in a steady state appeared difficult to perform from an ethical point of view in children as regard to the time needed for recording.

HR alteration induced by sevoflurane in children appeared mainly dependent on its pharmacological effect on the parasympathetic tone. This hypothesis could explain partially the difference in HR variation during induction previously described by other researchers between young and old children, as regard to their respective parasympathetic tone development. Further studies are required to improve the understanding of the complex relationship between sevoflurane and both autonomic system activity and HR.

Acknowledgements to: Mister James for his helpful English translation advice

Figure 1 : Example of recordings performed in a child. (Top) Sevoflurane concentration. (Middle) Change in RR interval (msec) during the same period of time. (Bottom) Change in RR interval minus the RR trend (msec).

Figure 2 : Variations of Systolic Blood Pressure (SBP) during the decrease in sevoflurane concentration as regard to the time. (Median; 70th percentile; 90th percentile and range (circle)). * $p < 0.05$ vs the first minute value, i.e. the higher concentration of sevoflurane.

Figure 3: Alteration of HR (top) and of the sum (SP) of high and low frequency power (bottom) during the progressive decrease of sevoflurane expired concentration. Median 70th percentile; 90th percentile and range (open circle) of the population; † $p < 0.05$ vs the higher concentration window of sevoflurane. * $p < 0.05$ vs Control.

Figure 4 : Variations of the high frequency (HF) power spectrum values (top) and of the HF to low frequency ratio (LF/HF) (bottom) during the progressive decrease of sevoflurane expired concentration. Median 70th percentile; 90th percentile and range (open circle) of the population; † $p < 0.05$ vs the higher concentration window of sevoflurane. * $p < 0.05$ vs Control.

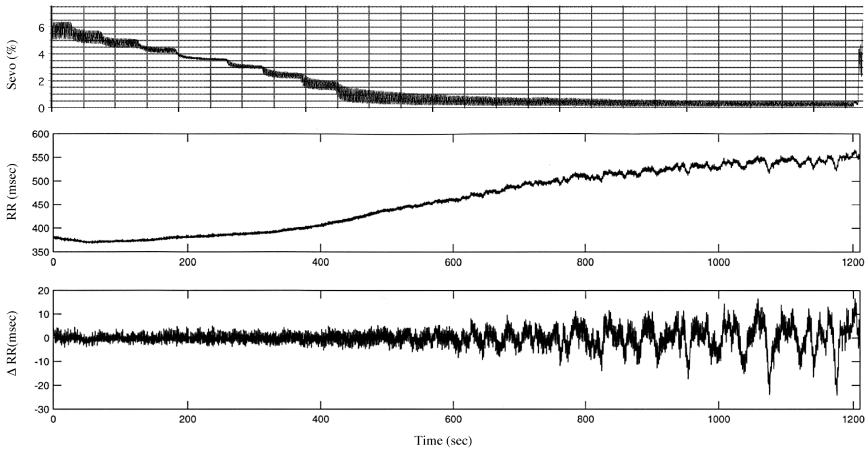
Servo (%)
6
4
2
0
RR (msec)
600
550
500
450
400
350
0
200
400
600
800
1000
1200
Δ RR(msec)
20
10
0
-10
-20
-30
Time (sec)

Figure 1

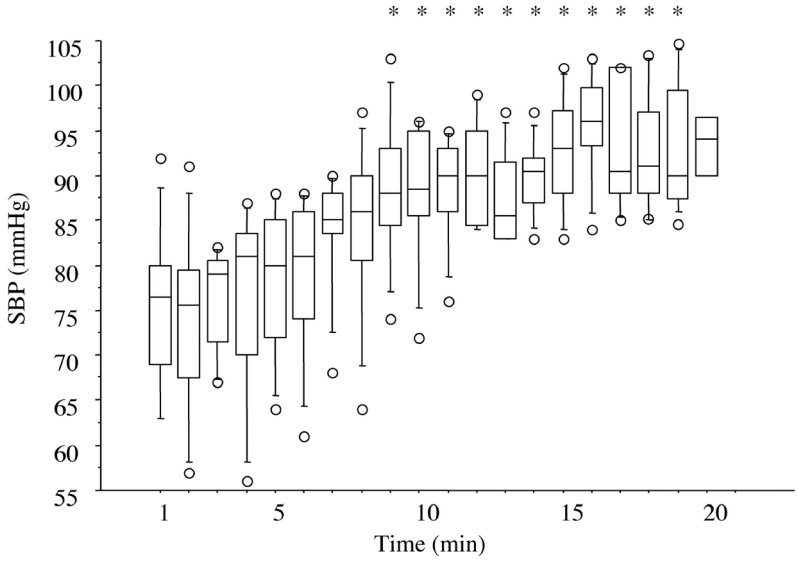

Figure 2

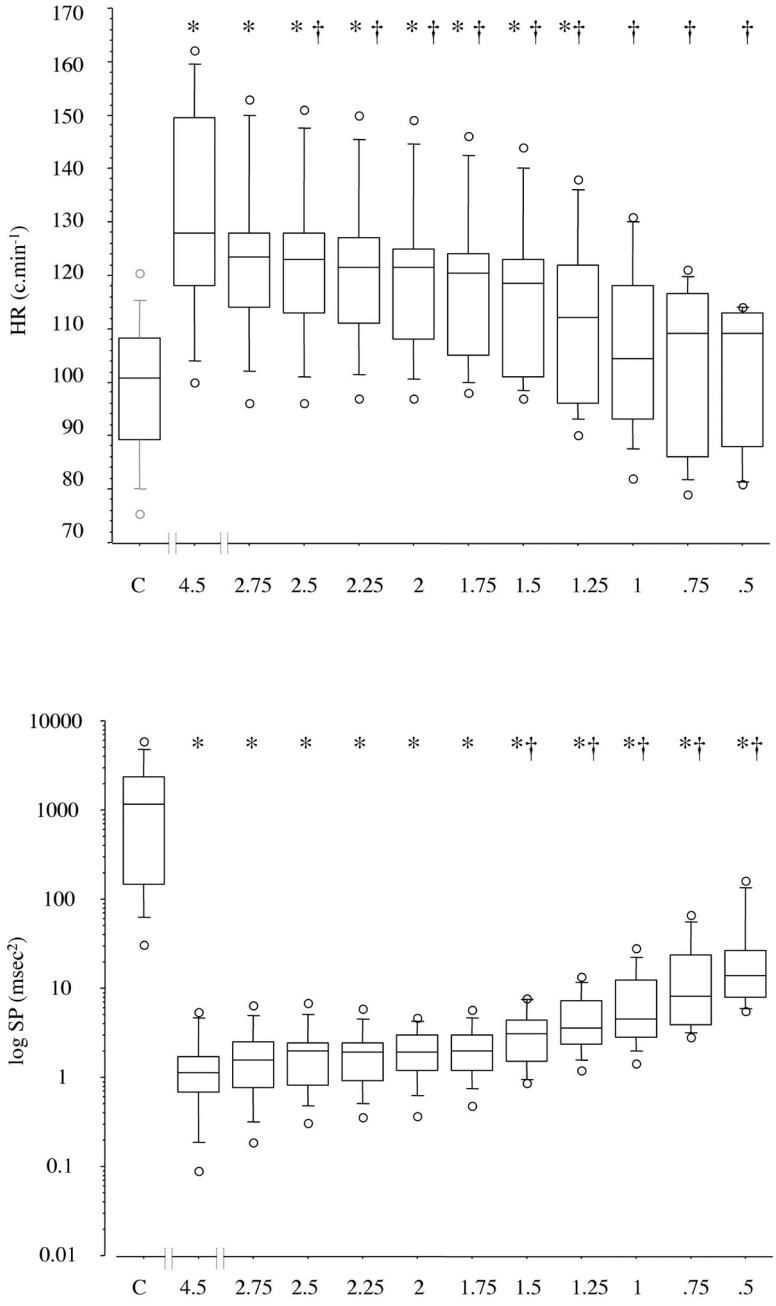
HR (c.min-1)
170
160
150
140
130
120
110
100
90
80
70
log SP (msec2)
10000
1000
100
10
1
0.1
0.01
C
4.5
2.75
2.5
2.25
2
1.75
1.5
1.25
1
.75
.5

Figure 3

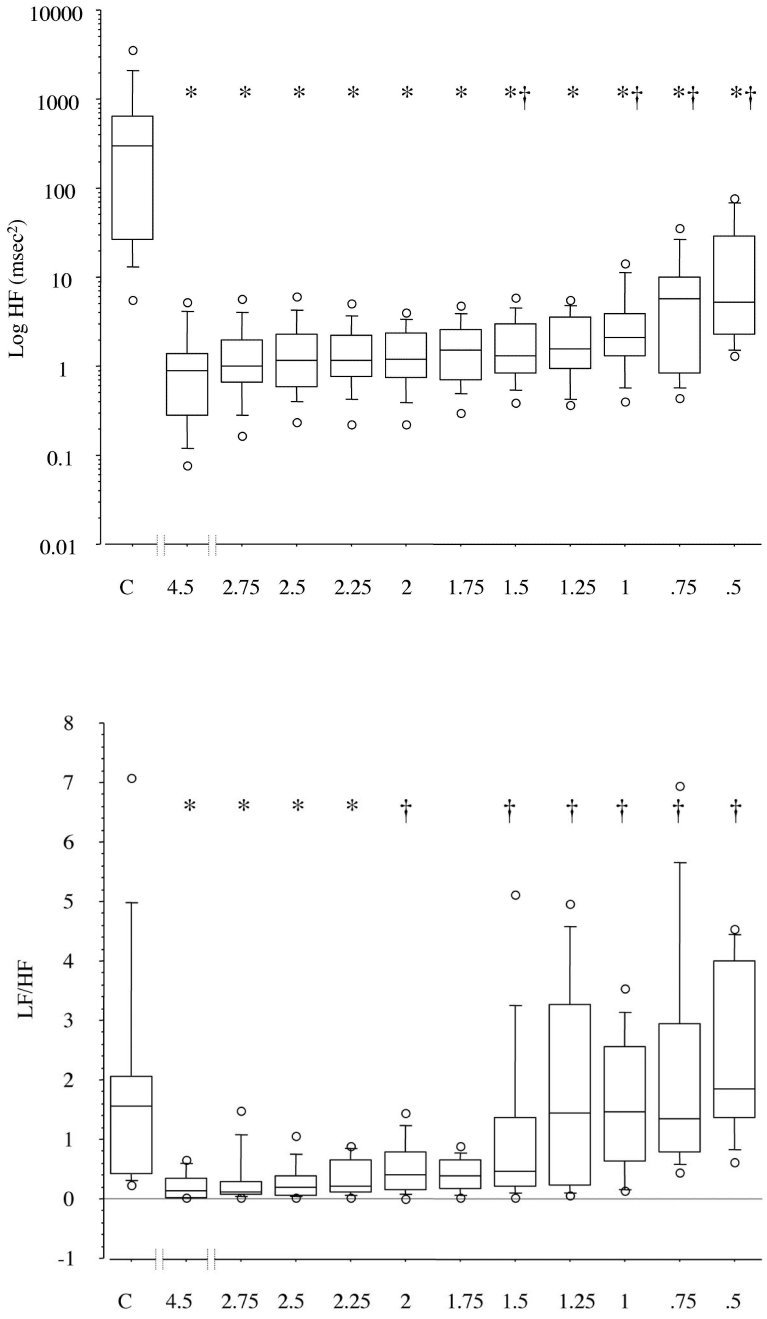
10000
1000
100
10
1
0.1
0.01
Log HF (msec²)
C 4.5 2.75 2.5 2.25 2 1.75 1.5 1.25 1 .75 .5
8
7
6
5
4
3
2
1
0
-1
LF/HF
C 4.5 2.75 2.5 2.25 2 1.75 1.5 1.25 1 .75 .5

Figure 4

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