Coherence analysis overestimates the role of baroreflex in governing the interactions between heart period and systolic arterial pressure variabilities during general anesthesia

Tito Bassani a, Vlasta Bari b,c, Andrea Marchi d, Maddalena Alessandra Wu e, Giuseppe Baselli b, Giuseppe Citerio f, Alessandro Beda g, Marcelo Gama de Abreu h, Andreas Güldner h, Stefano Guzzetti d, Alberto Porta a,⁎

a Department of Biomedical Sciences for Health, Galeazzi Orthopedic Institute, University of Milan, Milan, Italy
b Department of Electronics, Information, and Bioengineering, Politecnico di Milano, Milan, Italy
c Gruppo OSPedaliero San Donato Foundation, Milan, Italy
d Department of Emergency, L. Sacco Hospital, Milan, Italy
e Department of Biomedical and Clinical Sciences, Internal Medicine II, L. Sacco Hospital, University of Milan, Milan, Italy
f Neuroanaesthesia and Neurointensive Care Unit, Department of Perioperative Medicine and Intensive Care, San Gerardo Hospital, Monza, Italy
g Pulmonary Engineering Group, Department of Anesthesiology and Intensive Care Therapy, University Hospital Carl Gustav Carus, Dresden University of Technology, Dresden, Germany
h Department of Anesthesiology and Intensive Care Therapy, University Hospital Carl Gustav Carus, Dresden University of Technology, Dresden, Germany

ARTICLE INFO

Article history:
Received 30 October 2012
Received in revised form 7 January 2013
Accepted 19 March 2013

Keywords:
Baroreflex
Coherence analysis
Cardiovascular control
General anesthesia
Granger causality
Heart rate variability

ABSTRACT

During general anesthesia positive pressure mechanical ventilation (MV) profoundly affects intrathoracic pressure and venous return, thus soliciting cardiopulmonary reflexes and modifying stroke volume. As a consequence heart period, approximated as the temporal distance between two consecutive R peaks on the ECG (RR), and systolic arterial pressure (SAP) variability series are usually highly correlated at the MV frequency (MVF) and this significant correlation is commonly taken as an indication of an active baroreflex. In this study the involvement of baroreflex was tested according to a time-domain linear Granger causality approach accounting explicitly for MV in two experimental protocols. In the first protocol volatile (VA) or intravenous (IA) anesthetic was administered in humans during pressure controlled MV (PCMV). In the second protocol IA was administered in pigs during PCMV or pressure support MV (PSMV). Causality analysis was contrasted with RR-SAP squared coherence. Significant coherence values at MVF were always found in both protocols. On the contrary, a significant causal link from SAP to RR was less frequently found in humans independently of the anesthesiological strategy and in animals during PCMV, PSMV was superior to PCMV in animals because it was able to better preserve a link from SAP to RR. During general anesthesia the involvement of baroreflex in governing RR-SAP variability interactions is largely overestimated by RR-SAP squared coherence and causality analysis can be exploited to rank anesthesiological strategies and MV modes according to the ability of preserving a working baroreflex.

© 2013 Elsevier B.V. Open access under CC BY-NC-ND license.

1. Introduction

Baroreflex control of heart rate is an important short-term neural reflex aiming at guaranteeing the homeostasis of the organism through continuous adjustments of heart rate in response to arterial pressure changes (Smyth et al., 1969). Baroreflex sensitivity is usually depressed during general anesthesia. In particular, both volatile and intravenous anesthetics have been demonstrated to depress cardiac baroreflex sensitivity in humans (Tanaka and Nishikawa, 1999; Sato et al., 2005) and animals (Palmisano et al., 1991; Akine et al., 2001). Those studies evaluated the baroreflex sensitivity by administering a vasoactive agent capable to increase or decrease systolic arterial pressure (SAP) and by observing the magnitude of the evoked heart period changes. It was proposed that baroreflex sensitivity could be estimated without perturbing cardiovascular regulation from the analysis of the spontaneous beat-to-beat variability of heart period, approximated as the temporal distance between two consecutive R peaks on the ECG (RR), and SAP (Laude et al., 2004). The assessment of the “spontaneous” baroreflex sensitivity postulates a significant correlation between RR and SAP variabilities. Therefore, during general anesthesia it is common practice to check the significance of RR-SAP squared coherence at the rate of the mechanical ventilator.
(Beda et al., 2012) before estimating baroreflex sensitivity based on spectral or cross-spectral techniques (De Boer et al., 1985; Pagani et al., 1988) or to assess the significance of the RR-SAP correlation coefficient (Sato et al., 2005) when spontaneous baroreflex sequence method is exploited (Bertinieri et al., 1985).

Nevertheless, during general anesthesia positive pressure mechanical ventilation (MV) profoundly affects intrathoracic pressure and venous return and stimulates cardiopulmonary reflexes, thus influencing directly both SAP and RR variabilities (Beda et al., 2011). As a consequence RR and SAP series might be significantly correlated at the MV frequency (MVF) without any involvement of the baroreflex.

We hypothesize that causality analysis, specifically accounting for MV, provides different information about the involvement of the baroreflex during general anesthesia compared to squared coherence function and could be fruitfully exploited to assess the performance of anesthesiological treatments and MV modes in preserving a more physiological cardiovascular control.

The aim of this work is to compare a traditional tool for the assessment of the degree of linear association between RR and SAP (i.e. squared coherence) with a model-based linear approach for the estimation of Granger causality in the time domain. While coherence analysis does not take explicitly into account the temporal direction of the interactions, causality analysis assesses the statistical dependence only from SAP to RR and accounts for the confounding influences of MV on both RR and SAP variabilities. Comparison was carried out over two experimental protocols performed during general anesthesia. The first protocol compares in humans under pressure controlled MV (PCMV) two different anesthesiological strategies involving the utilization of different anesthetics: volatile anesthetic (VA) versus intravenous anesthetic (IA). The second protocol compares two different MV modes: PCMV versus pressure support MV (PSMV) in animals under IA administration.

2. Materials and methods

2.1. General anesthesia in humans

Data belong to a database recorded during the NeuroMorfeo trial (Citerio et al., 2009, 2012) designed to compare VA and IA strategies under PCMV during neurosurgical procedures for elective craniotomy. The details of the experimental protocol are reported elsewhere (Citerio et al., 2009). Briefly, thirty-seven subjects (aged from 18 to 75 years) gave their written informed consent and were scheduled for craniotomy for supratentorial lesion. All subjects did not exhibit signs of intracranial hypertension, were in good physical state (ASA I-III, Glasgow Coma Scale equal to 15) and were randomly assigned to one of two anesthesiological strategies. Anesthesia was induced with propofol, a sedative-hypnotic agent, and remifentanil, as analgesic. Animals were tracheally intubated with auffed tube (8 mm inner diameter) and instrumented with a catheter in the right femoral artery. Anesthesia was maintained through IA administration based on the continuous infusion of propofol (2–7 mg Kg⁻¹ h⁻¹) and sufentanil (0.3–1.5 μg Kg⁻¹ h⁻¹). MV was performed according to PCMV or PSMV modes. Only during PCMV muscle paralysis was achieved by infusion of atracurium (1 mg Kg⁻¹). During PCMV the respiratory cycle was initiated by the ventilator at a fixed rate, while during PSMV it was triggered by the animal when his initial spontaneous inspiratory airflow exceeded a predefined threshold (5–7 l min⁻¹). During PSMV the mean respiratory rate was 0.22 Hz. The MVF during PCMV was set in each animal according to the spontaneous respiratory rate observed during PSMV. In both modes, a positive driving pressure was delivered by the ventilator until a cycling-off condition occurred. More specifically, the positive driving pressure was terminated after a fixed time in the case of PCMV, while in the case of PSMV the cycling-off condition was reached when the airflow went below a given percentage of the peak inspiratory airflow (15–25%). These cycling off conditions were manually adjusted to achieve an inspiration/expiration ratio of 0.3. The inspiratory driving pressure was tuned cycle-by-cycle by an automatic control system (Beda et al., 2010) to achieve a target mean tidal volume of 12 ml kg⁻¹ in all modes. The inspiration was followed by passive expiration. The animals underwent 30 minutes of each MV modes in a randomized order. When randomization procedure imposed the completion of the PCMV session before the PSMV one, a brief session of PSMV was carried out to find out the spontaneous respiratory rate of the animal. Throughout the experimental protocol, anesthetic agents were administered at constant infusion rates, the inspired fraction of O₂ was 0.4 and the positive end-expiratory pressure was 5 cmH₂O. The protocol adhered to the principles of the Guide for Care and Use of Vertebrate Animals in Research and Training. All experimental procedures were approved by the Animal Care Committee of the Faculty of Medicine Carl Gustav Carus, Dresden University of Technology, and by the Government of the State of Saxony.

One non-standard ECG lead and arterial blood pressure from the femoral artery were acquired synchronously during the last 20 minutes of each MV mode with sampling frequency of 2 kHz. Airflow was acquired continuously from the ventilator. The respiratory volume signal was obtained by integrating in time the airflow signal.

2.2. Data processing

After locating the R apex on the ECG using parabolic interpolation, RR was computed. SAP(i), where i is the cardiac beat counter, was assessed as the maximum arterial pressure inside RR(i). In the experimental protocol involving animals the respiratory volume signal was sampled in correspondence to the first R apex delimiting RR(i). This measure was indicated as RESP(i) and expressed in liters (l). In the experimental protocol involving humans RESP(i) was derived from respiratory-related ECG
amplitude changes and it was expressed in arbitrary units (a.u.), RR(i), SAP(i) and RESP(i) measures were performed on a beat-to-beat basis, thus obtaining $RR = \{RR(i), i = 1, ..., N\}$, $SAP = \{SAP(i), i = 1, ..., N\}$ and $RESP = \{RESP(i), i = 1, ..., N\}$ where $N$ is the series length. $N$ ranged from 200 to 250 samples. We selected sequences without evident artifacts and non stationarities. RR and SAP mean ($\mu_{RR}$ and $\mu_{SAP}$) and variance ($\sigma_{RR}^2$ and $\sigma_{SAP}^2$) were evaluated and expressed in ms, mmHg, ms$^2$ and mmHg$^2$ respectively. Data sequences were linearly detrended before any successive analysis.

### 2.4. Granger-causality test

Given the set of series $\Omega = \{SAP, RR, RESP\}$, SAP is said to Granger-cause RR in $\Omega$ (i.e. $SAP \rightarrow RR$) if SAP can provide an unique information about the future evolution of RR that cannot be derived from any of the series present in $\Omega$ after excluding SAP (Granger, 1969). In other words, we say that SAP Granger-causes RR if RR can be better predicted in $\Omega$ than in $\Omega - \{SAP\} = \{RR, RESP\}$. The interactions among the series in $\Omega$ were described according to a linear time invariant parametric model (Lutkepohl, 2005). More specifically, the current sample of RR ($i.e. RR(i)$) depended on its own past values, i.e. the autoregressive (AR) part, plus the contributions of the present and past values of the remaining two signals ($i.e. SAP$ and $RESP$). Both SAP and RESP were considered as exogenous ($X$) signals for RR, thus modeling a double $X$ ($XX$) model. The number of past values of SAP, RR, and RESP was equal to $q$ and $p$ respectively, with $q$ and $p$ adjusted to the Akaike figure of merit for multivariate processes (Akaike, 1974). We checked that the mean square prediction error of the ARXX model on RR in $\Omega$ was significantly smaller than that of the ARX model on RR in $\Omega - \{SAP\}$ = $\{RR, RESP\}$. The interactions among the series in $\Omega$ were described according to a linear time invariant parametric model (Lutkepohl, 2005). More specifically, the current sample of RR ($i.e. RR(i)$) depended on its own past values, i.e. the autoregressive (AR) part, plus the contributions of the present and past values of the remaining two signals ($i.e. SAP$ and $RESP$). Both SAP and RESP were considered as exogenous ($X$) signals for RR, thus modeling a double $X$ ($XX$) model. The number of past values of SAP, RR, and RESP was equal to $q$ and $p$ respectively, with $q$ and $p$ adjusted to the Akaike figure of merit for multivariate processes (Akaike, 1974). We checked that the mean square prediction error of the ARXX model on RR in $\Omega$ was significantly smaller than that of the ARX model on RR in $\Omega - \{SAP\}$ = $\{RR, RESP\}$. The interactions among the series in $\Omega$ were described according to a linear time invariant parametric model (Lutkepohl, 2005). More specifically, the current sample of RR ($i.e. RR(i)$) depended on its own past values, i.e. the autoregressive (AR) part, plus the contributions of the present and past values of the remaining two signals ($i.e. SAP$ and $RESP$). Both SAP and RESP were considered as exogenous ($X$) signals for RR, thus modeling a double $X$ ($XX$) model. The number of past values of SAP, RR, and RESP was equal to $q$ and $p$ respectively, with $q$ and $p$ adjusted to the Akaike figure of merit for multivariate processes (Akaike, 1974). We checked that the mean square prediction error of the ARXX model on RR in $\Omega$ was significantly smaller than that of the ARX model on RR in $\Omega - \{SAP\}$ = $\{RR, RESP\}$. The interactions among the series in $\Omega$ were described according to a linear time invariant parametric model (Lutkepohl, 2005). More specifically, the current sample of RR ($i.e. RR(i)$) depended on its own past values, i.e. the autoregressive (AR) part, plus the contributions of the present and past values of the remaining two signals ($i.e. SAP$ and $RESP$). Both SAP and RESP were considered as exogenous ($X$) signals for RR, thus modeling a double $X$ ($XX$) model. The number of past values of SAP, RR, and RESP was equal to $q$ and $p$, and $r$ was optimized according to the Akaike figure of merit for multivariate processes (Akaike, 1974). We checked that the mean square prediction error of the ARXX model on RR in $\Omega$ was significantly smaller than that of the ARX model on RR in $\Omega - \{SAP\}$ = $\{RR, RESP\}$ with RESP as the unique X signal, thus indicating that the goodness of fit of the ARXX model was larger than that of the ARX one. The significance of the predictability improvement was tested according to the $F$ statistic with $p < 0.01$ (Porta et al., 2012). The coefficients of the ARXX and ARX models were estimated using traditional least-squares approach and Cholesky decomposition method (Baselli et al., 1997). The series were first demeaned and, then, divided by the standard deviation, before performing causality test.

### 2.5. Squared coherence function

Squared RR-SAP coherence function ($K_{RR-SAP}^2$) was exploited to measure the degree of linear association between RR and SAP as a function of the frequency ($K_{RR-SAP}^2(f)$). The squared RR-SAP coherence function was assessed as the ratio of the square RR-SAP cross-spectrum modulus to the product of the power spectra. $K_{RR-SAP}^2$ ranges from 0 to 1, indicating that SAP and RR are completely unrelated and perfectly linearly associated respectively. A parametric approach exploiting the bivariate AR model was chosen to estimate cross-spectrum and power spectra (Baselli et al., 1997). The model order was fixed to 10 and the coefficients of the model were identified via least squares approach (Baselli et al., 1997). $K_{RR-SAP}^2(f)$ was sampled in correspondence of the MVF as detected in correspondence of the dominant peak of the power spectrum of the RESP series. The significance of $K_{RR-SAP}^2(MVF)$ was assessed using the technique of surrogate data. Surrogate pairs were constructed simply by matching up the original RR series of a subject (or animal) with the original SAP series taken from another one. Only the matching of the RR series with the SAP one taken from the same subject (or animal) was prevented in the construction of the surrogate set; thus the number of surrogate pairs is equal to the number of subjects (or animals) minus 1. $K_{RR-SAP}^2(MVF)$ was assessed from all surrogate pairs in each protocol. The 95th percentile of $K_{RR-SAP}^2(MVF)$ distribution derived from surrogate was taken as the threshold for significance. If $K_{RR-SAP}^2(MVF)$ computed over the RR and SAP relevant to the same subject (or animal) was larger than the threshold, the strength of the RR-SAP relation was deemed as significant.

### 2.6. Statistical analysis

The unpaired t-test, or Mann–Whitney rank sum test when appropriate, was applied to check whether time domain parameters depended on the anesthesiological strategy in humans. The paired t-test, or Wilcoxon signed rank test when appropriate, was applied to check whether time domain parameters depended on the MV strategy in animals. The $\chi^2$ test was performed to check the difference between the percentage of the subjects (or animals) exhibiting a significant $K_{RR-SAP}^2(MVF)$ and that of the subjects (or animals) exhibiting a significant causal relation from SAP to RR. Values were reported as mean ± standard deviation. A $p < 0.05$ was always considered as significant.

### 3. Results

Table 1 reports time domain parameters obtained from humans in VA and IA groups. The RR mean, $\mu_{RR}$, and the RR variance, $\sigma_{RR}^2$, were similar in VA and IA groups. The SAP mean, $\mu_{SAP}$, and the SAP variance, $\sigma_{SAP}^2$, were significantly larger during IA.

|                      | VA       | IA       |
|----------------------|----------|----------|
| $\mu_{RR}$ [ms]      | 958.19 ± 161.13 | 925.00 ± 147.40 |
| $\sigma_{RR}^2$ [ms$^2$] | 582.59 ± 581.32 | 352.47 ± 744.93 |
| $\mu_{SAP}$ [mmHg]   | 107.13 ± 9.24  | 171.22 ± 162.2* |
| $\sigma_{SAP}^2$ [mmHg$^2$] | 11.40 ± 15.47 | 15.58 ± 14.81* |

VA = volatile anesthetic; IA = intravenous anesthetic. Values are expressed as mean ± standard deviation. The symbol * indicates a significant difference between VA and IA with $p < 0.05$.

### 4. Discussion

The main findings of this study can be summarized as follows:

1. RR-SAP squared coherence overestimates the role played by baroreflex...
in determining the association between RR and SAP during general anesthesia; 2) causality analysis accounting for MV is able to detect a causal link from SAP to RR during general anesthesia, thus suggesting a working baroreflex; 3) in humans accounting for MV decreases the probability of finding a significant causal relation from SAP to RR compared to a causality analysis based solely on RR and SAP variabilities, especially during PCMV under VA; 4) during PCMV mechanisms other than baroreflex are responsible for the high degree of association between RR and SAP at the MVF; 5) PSMV can preserve baroreflex control better than PCMV.

Under spontaneous closed loop conditions and in presence of small SAP changes it might happen that baroreflex contributes negligibly to the overall amount of RR variations especially in presence of a depressed baroreflex sensitivity. In this situation a sound procedure to assess baroreflex sensitivity based on spontaneous RR and SAP variabilities should advise that baroreflex sensitivity cannot be safely inferred. This warning is currently provided by the coherence function. If the coherence function is smaller than a threshold, RR and SAP series are irrelevance linked and, thus, the estimate of the baroreflex sensitivity might be unreliable (De Boer et al., 1985). Usually the threshold is set at an arbitrarily, even though large, value (i.e. 0.5) (De Boer et al., 1985), or calculated based on the distribution of the coherence values derived analytically under the null hypothesis of uncoupling between two series with well-known statistical properties (Barres et al., 2004) or computed based on the construction of a distribution of coherence values derived empirically according to a set of uncoupled iso-distributed iso-spectral surrogates (Porta et al., 2002; Faes et al., 2004). However, a significant association between RR and SAP series might be solely due to Starling’s law and diastolic runoff causing changes of SAP in response to modifications of RR (Baselli et al., 1994; Porta et al., 2002). Therefore, a

| PCMV | PSMV |
|------|------|
| μRR [ms] | 652.26 ± 44.56 | 651.30 ± 76.20 |
| σ²RR [ms²] | 48.09 ± 47.90 | 662.53 ± 936.40* |
| μSAP [mmHg] | 121.92 ± 15.75 | 120.21 ± 15.66 |
| σ²SAP [mmHg²] | 3.69 ± 2.71 | 5.76 ± 2.79 |

PCMV = pressure controlled mechanical ventilation; PSMV = pressure support mechanical ventilation. Values are expressed as mean ± standard deviation. The symbol * indicates a significant difference between PCMV and PSMV with p < 0.05.

Fig. 1. RR (a), SAP (b) and RESP (c) series in a human subject with no significant causal relation from SAP to RR during PCMV under IA.

Fig. 2. RR (a), SAP (b) and RESP (c) series in a pig with no significant causal relation from SAP to RR during PCMV under IA.

Fig. 3. Squared coherence function, $K^2_{RR,SAP}$, computed in a human subject (a) and a pig (b) with no significant causal relation from SAP to RR. RR and SAP series are shown in Figs. 1a,b and 2a,b respectively. Despite the virtually absent causal link from SAP to RR, $K^2_{RR,SAP}$ exhibits values close to 1 in correspondence of the MVF and its harmonics, as a likely effect of the common perturbation on both series due to MV. The conventional threshold of significance for $K^2_{RR,SAP}$ (i.e. 0.5) is shown as a dotted line.
coherence function value overcoming the threshold at a given frequency cannot be taken as a reliable proof of baroreflex involvement at that frequency. Conversely, only a causality test checking a specific temporal direction of the interactions (i.e. from SAP to RR) can provide a convincing evidence of the baroreflex involvement.

This study compares results of squared coherence analysis between RR and SAP variabilities with those provided by a causality test assessing the presence of a significant causal relation from SAP to RR in humans and animals during general anesthesia. We found that, regardless of the anesthetic administration mode and MV technique, in both humans and animals, RR and SAP variabilities were significantly correlated at the MVF. This finding is not surprising. Indeed, during general anesthesia under MV the amplitude of the RR and SAP oscillations at the MVF is not negligible (Beda et al., 2011). SAP changes at the MVF are the result of the modulation of the venous return, cardiac preload and afterload and stroke volume due to changes of intrathoracic pressure (Innes et al., 1993; Baselli et al., 1994) and of the link from RR to SAP due to diastolic runoff and Starling law (Baselli et al., 1994). RR changes at the MVF can be the result of the stimulation of cardiopulmonary receptors (Hakumaki, 1987), of the mechanical stimulation of sinus node due to changes of the intrathoracic pressure (Bernardi et al., 1989), of the coupling between respiratory centers and vagal outflow (Porta et al., 2000; Eckberg, 2003) and of baroreflex (De Boer et al., 1987). These mechanisms contribute to the raise of the values of RR-SAP squared coherence at the MVF above the threshold of significance observed in all cases in both protocols.

Conversely, causality analysis was able to recognize that RR variability was driven by SAP changes in a significantly smaller percentage of humans during PCMV under both IA and VA. The same observation held in animals under IA strategy during PCMV. Therefore, we conclude that during PCMV squared coherence overestimates the role of baroreflex in governing RR-SAP variability interactions and mechanisms other than baroreflex concur to determine the large RR-SAP correlation at the MVF. As a consequence of this finding we strongly advise that baroreflex sensitivity estimated from spontaneous RR and SAP variabilities during PCMV might be unreliable even in presence of a high value of squared coherence function at the MVF. In addition, this study supports the more physiological action of the PSVM mode compared to the PCMV one. Indeed, in animals under IA during PSVM the RR-SAP link was, at least partially, due to the solicitation of baroreflex. This finding is not in contrast with the possible action of mechanisms, different from baroreflex, capable of producing RR changes independent of SAP variations suggested in Beda et al. (2012). These mechanisms, working specifically at the MVF, might coexist with an active baroreflex working over different temporal scales (e.g. in the low frequency band), thus contributing all together to the overall amount of RR variability. A Granger causality analysis performed in the frequency domain (Baccalà and Sameshima, 2001; Kaminski et al., 2001; Porta et al., 2002) might be able to clarify this issue.

A previous study suggested that a significant causal relation from SAP to RR could be found in the majority of subjects during general anesthesia, thus suggesting that baroreflex was still working (Bassani et al., 2012) even though with a lower baroreflex sensitivity (Tanaka and Nishikawa, 1999; Sato et al., 2005). This finding was based on a Granger causality bivariate analysis performed solely over SAP and RR series. Since it was demonstrated that respiration is a latent confounder for RR-SAP causal interactions (i.e. disregarding respiration might introduce spurious causal links between RR and SAP series) (Porta et al., 2012), one of the major aim of this study was to verify if our previous conclusions about the relevance of the causal relation from SAP to RR (Bassani et al., 2012) were still valid even when accounting for MV. The present study confirms that causality from SAP to RR was still detectable even when the latent confounder of MV was accounted for. However, the percentage of subjects exhibiting causal relations from SAP to RR was decreased compared to our previous study (Bassani et al., 2012), especially during PCMV under VA, thus confirming the importance of accounting for MV when assessing RR-SAP causal relations.

5. Conclusions

This study exploits a time-domain approach to causality analysis, explicitly accounting for MV, as a tool to assess the performance of anesthesiological treatments and MV strategies. The analysis suggests a novel criterion for ranking anesthesiological treatments and MV strategies according to their ability to preserve the involvement of baroreflex in regulating RR-SAP variability interactions. According to this criterion PSVM ranked better than PCMV. In addition, the proposed analysis allows a more precise definition of the scope of applicability of the methods assessing spontaneous baroreflex sensitivity based on spectral and cross-spectral analyses during general anesthesia. Indeed, they should be applied only in those anesthesiological treatments and MV strategies capable to guarantee a significant causal relation from SAP to RR in a large percentage of cases, such as during PSVM, or, independently of the anesthesiological treatment and MV strategy, on an individual basis over those subjects preserving causality from SAP to RR. Future studies should compare different modalities utilized to acquire respiratory signal with the specific aim to understand if they lead to different conclusions in terms of causal relations among cardiovascular variables.

Acknowledgements

The NeuroMorfeo trial “Anaesthesiological strategies in elective craniotomy” (EudraCT 2007-005279-32) was fully financed by AIFA (FARM6FJJKK), the animal experiments were fully financed by the MedDrive Program of the Faculty of Medicine of the Technical University Dresden, and the Telethon Grant GGP09247 to A. Porta partially supported the study.

References

Akaike, H., 1974. A new look at the statistical novel identification. IEEE Trans. Autom. Control. 19, 716–723.
Akine, A., Suzuki, H., Hayashida, Y., Kato, Y., 2001. Effects of ketamine and propofol on autonomic cardiovascular function in chronically instrumented rats. Auton. Neurosci.-Basic Clin. 87, 201–208.
Baccalà, L., Sameshima, K., 2001. Partial directed coherence: a new concept in neural structure determination. Biol. Cybern. 84, 463–474.
Barres, C., Cheng, Y., Julien, C., 2004. Steady-state and dynamic responses of renal sympathetic nerve activity to air-jet stress in sinoaortic denervated rats. Hypertension 43, 629–635.
Baselli, G., Cerutti, S., Badilini, F., Blancardi, L., Porta, A., Pagani, M., Lombardi, F., Rimoldi, O., Furlan, R., Malliani, A., 1994. Model for the assessment of heart period

### Table 3

| VA | VA | IA | IA |
|---|---|---|---|
| $K^2_{RR-SAP}(MVF)$ | 100% | 100% |
| SAP $\rightarrow$ RR | 39%* | 63%* |

VA = volatile anesthetic; IA = intravenous anesthetic; MVF = mechanical ventilation frequency; $K^2_{RR-SAP}(MVF)$ = squared coherence at MVF. The symbol * indicates a significant difference between coherence and causality analyses within the same experimental condition with $p < 0.05$.

### Table 4

| PCMV | PSVM |
|---|---|
| $K^2_{RR-SAP}(MVF)$ | 100% | 100% |
| SAP $\rightarrow$ RR | 62%* | 100% |

PCMV = pressure controlled mechanical ventilation; PSVM = pressure support mechanical ventilation; MVF = mechanical ventilation frequency; $K^2_{RR-SAP}(MVF)$ = squared coherence at MVF. The symbol * indicates a significant difference between coherence and causality analyses with the same experimental condition with $p < 0.05$.
and arterial pressure variability interactions and respiratory influences. Med. Biol. Eng. Comput. 32, 143–152.

Baselli, G., Porta, A., Rimoldi, O., Pagani, M., Cerutti, C., 1997. Spectral decomposition in multi-channel recordings based on multivariate parametric identification. IEEE Trans. Biomed. Eng. 44, 1092–1101.

Bassani, T., Magagnin, V., Guzzetti, S., Baselli, G., Citerio, G., Porta, A., 2012. Testing the involvement of baroreflex during general anesthesia through Granger causality approach. Comput. Biol. Med. 42, 306–312.

Beda, A., Spith, P.M., Handszij, T., Pelosi, P., Carvalho, N.C., Koch, E., Koch, T., de Abreu, M.G., 2010. A novel adaptive control system for noisy pressure-controlled ventilation: a numerical simulation and bench test study. Intensive Care Med. 36, 164–168.

Beda, A., Carvalho, N.C., Guldner, A., Koch, T., Gama de Abreu, M., 2011. Mechanical ventilation during anaesthesia: challenges and opportunities for investigating the respiration-related cardiovascular oscillations. Biomed. Tech. 56, 195–206.

Beda, A., Guldner, A., Simpson, D.M., Carvalho, N.C., Franke, S., Uhlig, C., Koch, T., Pelosi, P., de Abreu, M.G., 2012. Effects of assisted and variable mechanical ventilation on cardiorespiratory interactions in anesthetized pigs. Physiol. Meas. 33, 503–519.

Bernardi, L., Keller, F., Sanders, M., Reddy, P.S., Griffith, B., Meno, F., Pinsky, R., 1989. Respiratory sinus arrhythmia in the deservated human heart. J. Appl. Physiol. 67, 1447–1455.

Bertinieri, G., Di Rienzo, M., Cavallazzi, A., Ferrari, A.U., Pedotti, A., Mancia, G., 1985. A new approach to analysis of the arterial baroreflex. J. Hypertens. 3, 579–581.

Citerio, G., Franzosi, M.G., Latini, R., Masson, S., Barlera, S., Guzzetti, S., Pesenti, A., 2009. Anaesthesiological strategies in elective craniotomy: randomized, equivalence, open trial — the NeuroMorpheo trial. Trials 10, 19.

Citerio, G., Pesenti, A., Latini, R., Masson, S., Barlera, S., Gaspari, F., Franzosi, M.G., 2012. A multicentre, randomised, open-label, controlled trial evaluating equivalence of inhalational and intravenous anaesthesia during elective craniotomy. Eur. J. Anaesthesiol. 29, 371–379.

De Boer, R.W., Karemaker, J.M., Strackee, J., 1985. Relationships between short-term blood pressure fluctuations and heart rate variability in resting subjects I: a spectral analysis approach. Med. Biol. Eng. Comput. 23, 352–358.

De Boer, R.W., Karemaker, J.M., Strackee, J., 1987. Hemodynamic fluctuations and baroreflex sensitivity in humans: a beat-to-beat model. Am. J. Physiol. 253, H680–H689.

Eckberg, D.L., 2003. The human respiratory gate. J. Physiol. 548, 339–352.

Faes, L., Pinna, G.D., Porta, A., Maestri, R., Nollo, G.D., 2004. Surrogate data analysis for assessing the significance of the coherence function. IEEE Trans. Biomed. Eng. 51, 1156–1160.

Granger, C.W.J., 1969. Investigating causal relations by econometric models and cross-spectral methods. Econometrica 37, 424–438.