Frequency Domain Causal Analysis Allows the Detection of Baroreflex Control Recovery in Patients Undergoing Surgical Aortic Valve Replacement After a Three-Months Follow-up

Vlasta Bari[1,2], Francesca Gelpi[2], Beatrice Cairo[2], Noemi Cornara[1], Beatrice De Maria[3], Marco Ranucci[1] and Alberto Porta[1,2]

[1]Department of Cardiothoracic, Vascular Anesthesia and Intensive Care, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy
[2]Department of Biomedical Sciences for Health, University of Milan, Milan, Italy
[3]IRCCS Istituti Clinici Scientifici Maugeri, Istituto di Milano, Milan, Italy

Abstract

Surgical aortic valve replacement (SAVR) can impact on cardiovascular control as assessed via the analysis of heart period (HP) and systolic arterial pressure (SAP) variability. Frequency domain causality techniques allow to explore HP-SAP closed-loop relation in the typical frequency bands of the cardiovascular control.

A frequency-domain causality analysis was applied to HP and SAP variability acquired from 58 patients (age: 65±13 yrs, 39 males) before SAVR (PRE), within one-week post-surgery (POST) and after a three-month follow-up (POST3). Analyses were carried out at rest in supine position (REST) and during an active standing test (STAND). Causal squared coherence (K^2) analysis was performed along the baroreflex pathway from SAP to HP ($K^2_{SAP\rightarrow HP}$) and along the mechanical feedforward link from HP to SAP ($K^2_{HP\rightarrow SAP}$) in the low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.4 Hz) bands. Findings suggested that baroreflex control was depressed just after SAVR but recovered after a three-month follow-up while mechanical feedforward link was not affected. Future studies will be aimed to investigate a longer follow-up and to link results on the occurrence of post-surgery adverse outcomes.

1. Introduction

Cardiovascular control can be assessed by the analysis of spontaneous variability time series of heart period (HP) and systolic arterial pressure (SAP). The linear coupling between the two time series is generally assessed as a function of the frequency by the computation of squared coherence (K^2). Coherence analysis is usually evaluated in the two frequency bands typical of cardiovascular control regulation, low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.5 Hz) [1, 2]. Anyway, HP and SAP relation acts in closed-loop, being composed by two different mechanisms: the baroreflex, acting along the direction from SAP to HP and the mechanical feed-forward pathway along the opposite direction [3]. When signals are strongly related in closed-loop, K^2 could be considered not enough powerful since a high value can be found either in case a strong interaction occurs along both the arms of the closed-loop or when the interaction is strong along only one arm and the other is cut out. For this reason, it is advisable to take into account causality, and thus to compute causal K^2, respectively switching off one of the two arms of the closed-loop at a time [4].

Furthermore, cardiovascular control can be impaired by several pathologies and clinical conditions as in patients undergoing cardiac surgery and in particular surgical aortic valve replacement (SAVR), where it is known that autonomic and cardiovascular control is impaired already before surgery, it can worsen after the intervention but it could recovery after a follow-up [5-8]. Although different methods of analysis have already been exploited to assess cardiovascular control in these patients and how it is modified immediately post-surgery [9, 10], a causal approach exploiting casual coherence and considering also data acquired after a 3-months follow-up has never been proposed so far.

The aim of this work, thus, was to evaluate causal and non causal K^2 between HP and SAP in patients undergoing SAVR evaluated the day before intervention (PRE), within one week after surgery (POST) and after a 3-months follow-up (POST3). At all time points, patients were evaluated in supine position and during an active standing test, known to evoke sympathetic activation and baroreflex unloading.

2. Experimental protocol and methods of analysis

2.1. Experimental protocol

Fifty-eight patients scheduled for SAVR (age: 65±13

Table 1. Time domain markers derived from HP and SAP series.

Parameter	REST			STAND		
	PRE	POST	POST3	PRE	POST	POST3
μ_{HP} [ms]	933.8±132.1	757.7±110.6#	892.6±121.0§	825.3±125.4*	699.2±115.6*#	796.8±120.7*§
σ^2_{HP} [ms^2]	1189.4±1535.2	353.1±643.3#	976.2±2413.1	869.5±1151.3	350.4±602.4	1235.1±2644.4
μ_{SAP} [mmHg]	142.4±21.8	129.2±21.3	139.8±24.7#	136.6±23.0	132.8±21.9	131.8±26.5
σ^2_{SAP} [mmHg^2]	30.4±25.1	29.3±18.4	31.8±39.5	44.0±36.0	47.1±38.4	130.5±306.1*#§

HP: heart period; AP: arterial pressure; SAP: systolic AP;; μ_{HP} = HP mean; σ^2_{HP} = HP variance; HF: high frequency; μ_{SAP} = SAP mean; σ^2_{SAP} = SAP variance; REST = at rest in supine position; STAND = active standing; PRE = before surgery; POST = within 7 days from surgery; POST3 = 3–month follow-up. Results are reported as mean±standard deviation. The symbol * indicates p<0.05 versus REST within the same time point, # indicates p<0.05 versus PRE and § indicates p<0.05 versus POST within the same experimental condition.

yrs, 39 males) were enrolled at the Department of Cardiothoracic, Vascular Anesthesia and Intensive Care of IRCCS Policlinico San Donato [10]. The study was performed in keeping with Helsinki Declaration for studies involving humans, subjects signed an informed consent before participating. Acquisitions took place one day before surgery (PRE), within one week post-surgery (POST) and after a 3-months follow-up (POST3). Electrocardiogram (ECG) and arterial pressure (AP), non invasively recorded via a photoplethysmographic device (CNAP Monitor 500, CNSystems, Austria) were sampled at 400Hz and recorded for 10 minutes with patients lying in supine position (REST) and for 10 minutes during active standing (STAND). Since this is still an ongoing study, 58 patients were acquired in PRE, 38 in POST and only 16 in POST3. From the signals the time series of HP, approximated as the temporal distance between 2 QRS-complexes on the ECG and SAP, approximated as the maximum of AP inside the HP were extracted. 256-beats length stationary time series were extracted in all phases (PRE, POST, POST3) and conditions (REST and STAND). Series were checked and corrected via linear interpolation in case of ectopic beats. From the series, time domain indices in terms of mean and variance of HP and SAP were extracted and labeled respectively as $\mu_{HP,}$ σ^2_{HP}, $\mu_{SAP,}$ $\sigma^2_{SAP.}$

2.2. Non Causal and Causal coherence assessment

The relation between HP and SAP variability series was assessed via squared coherence K^2. K^2 was computed as the ratio between the cross-spectrum between HP and SAP divided by the product of the power of the autospectra. Bivariate autoregressive model was exploited to describe the dynamics of the target as a linear combination of its past values and of the past values of the driver plus a random white Gaussian noise. The model coefficients were identified via traditional least squares technique and the model order was optimized via the Akaike information criterion between 5 and 12 [11]. The latency from HP to SAP was set equal to 1 beat and that from SAP to HP equal to 0 beats. The computed spectral matrix allowed to define the K^2 as a function of the frequency. K^2 between HP and SAP, $K^2_{HP\text{-}SAP}$ was noncausal since $K^2_{SAP\text{-}HP} = K^2_{HP\text{-}SAP}$. The causal coherence from SAP to HP, $K^2_{SAP\rightarrow HP}$ was obtained forcing to 0 the polynomial that describes the relation along the opposite arm of the closed-loop (i.e. from HP to SAP). Vice versa, $K^2_{HP\rightarrow SAP}$ was obtained switching off the polynomial describing the relation from SAP to HP [4]. $K^2_{HP,SAP}$, $K^2_{SAP\rightarrow HP,}$ $K^2_{HP\rightarrow SAP}$ were assessed in LF and HF band by sampling them at their maximum in the relative frequency band and were respectively labeled $K^2_{HP\text{-}SAP,LF}$, $K^2_{SAP\rightarrow HP,LF,}$ $K^2_{HP\rightarrow SAP,LF}$, $K^2_{HP\text{-},SAP,HF}$, $K^2_{SAP\rightarrow HP,HF}$ and $K^2_{HP\rightarrow SAP,HF}$ [4].

2.3. Statistical analysis

Two-way analysis of variance, with Holm-Sidak test for multiple comparisons, was used to check differences between experimental conditions (REST and STAND) and phases (PRE, POST and POST3) using a commercial statistical software (Sigmaplot 14.5, Systat Software, Inc., Chicago, IL, USA). A p<0.05 with appropriate *post hoc* correction was always deemed as significant.

3. Results

Table 1 shows time domain markers as derived from HP and SAP time series. μ_{HP} was reduced during STAND in all three conditions and, during POST, was also lower than PRE and POST3 at both REST and STAND. σ^2_{HP} in POST at REST was decreased with respect to PRE. μ_{SAP} was unchanged among acquisition phases and conditions while σ^2_{SAP} during POST3 at STAND was increased with respect to either REST, PRE and POST.

Figure 1 shows results relative to non-causal and causal K^2 assessed in LF and HF bands. K^2_{LF} in POST3 was increased in STAND with respect to REST and with respect to POST. A similar circumstance was reflected along the baroreflex, regarding $K^2_{SAP\rightarrow HP,LF}$ that in POST3

during STAND was larger than REST but also than PRE and POST. Non causal K^2_{HF} during POST was reduced in STAND with respect to REST. Finally, $K^2_{SAP\rightarrow HP,HF}$ was unchanged among phases and conditions, as well as $K^2_{HP\rightarrow SAP,LF}$ and $K^2_{HP\rightarrow SAP,HF}$.

4. Discussion

The main findings of this work can be summarized as follows: i) cardiovascular control was confirmed to be impaired after surgery in patients undergoing SAVR; ii) cardiovascular control is improved after a 3-months follow-up; iii) the improvement of cardiovascular control is due to the baroreflex arm of the closed-loop HP-SAP regulation; iv) a causal analysis allows to identifies differences along the two arms of the closed-loop cardiovascular regulation.

Patients undergoing SAVR responded to STAND with the expected reduction of μ_{HP} at all three time points. Anyway, the vagal withdrawal and sympathetic activation expected was not reflected in a reduction of HP variance and increase in SAP variance during STAND that was not observed in either PRE and POST [12, 13]. Furthermore, at REST, cardiovascular control resulted reduced during POST, as observable by a lower variability of HP with respect to PRE and also by a lower K^2 in HF band in POST at REST with respect to PRE, indicating that SAVR patients have a depressed autonomic function after intervention [10].

Interestingly, K^2 in LF band was increased in POST3 in STAND with respect to REST and with respect to POST. When decomposed along the two arms of the closed-loop cardiovascular regulation, the same behavior was observed along the baroreflex arm, i.e. on the direction from SAP to HP where $K^2_{SAP\rightarrow HP,LF}$ was increased in POST3 at STAND with respect to REST and to both PRE and POST. That would mean that, at POST3, the coupling between HP and SAP would be increased in STAND, as due to a possible recovery of cardiovascular control at the follow-up. This finding would be in line with previous works showing an increased coupling along the baroreflex during head-up tilt in healthy subjects [14, 15] but not in conditions depressing autonomic function as general anesthesia [16] and pathology [13]. On the contrary, $K^2_{HP\rightarrow SAP,LF}$ resulted unchanged between groups and conditions, indicating that the mechanical feedforward pathway was not affected by SAVR and by the postural challenge.

Findings suggest that cardiovascular control would be depressed already before surgery and even worsened after surgery, since we observed a lack of reaction to STAND during PRE and POST and a reduction of parasympathetic variability in POST. Nevertheless, after a 3-months follow-up, cardiovascular control showed a recovery, confirming previous studies [8] and suggesting an improvement in autonomic function that could have a reflection on the long-term outcome of the patients.

5. Conclusions

This work exploits a causal frequency domain approach to assess cardiovascular control in patients undergoing SAVR evaluated during an active standing test before surgery (PRE), within one week after surgery (POST) and after a 3-months follow-up (POST3). Results show that, as expected, cardiovascular control is reduced

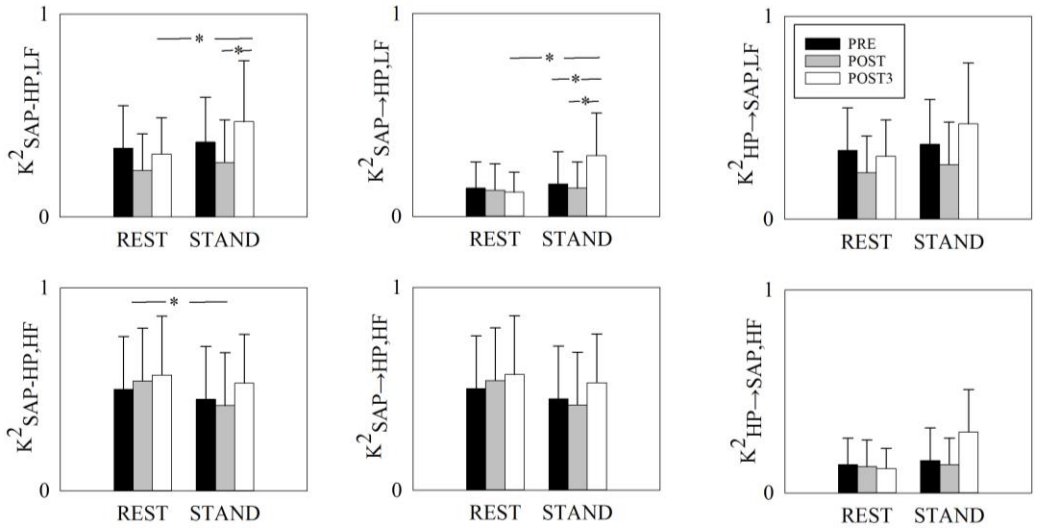

Figure 1. The grouped bar-graphs show: a) $K^2_{HP\text{-}SAP,LF}$, b) $K^2_{SAP\rightarrow HP,LF}$, c) $K^2_{HP\rightarrow SAP,\,LF}$, d) $K^2_{HP\text{-},SAP,HF}$, e) $K^2_{SAP\rightarrow HP,\,,HF}$ and f) $K^2_{HP\rightarrow SAP,HF}$ as a function of the experimental phase (PRE, black bars, POST, grey bars, POST3, white bars) and conditions (REST and STAND). The symbol * indicates $p<0.05$ between conditions or phases.

during POST and is recovered after a 3-months follow-up. Furthermore, causal K^2 approach allowed to reveal that this increase is more related to the baroreflex arm of the closed-loop HP-SAP regulation while along the mechanical feedforward arm the parameters remained unchanged. Results are promising and highlight the need of performing a causal analysis to assess cardiovascular control in patients undergoing SAVR. However, future studies will be needed to acquire a larger number of patients during follow-up and to perform a longer follow-up and link cardiovascular markers to the occurrence of post-surgery adverse events.

Acknowledgements

The study was supported by the Italian Ministry of Health Grant RF-2016-02361069 to A. Porta.

References

[1] V. Bari, E. Vaini, V. Pistuddi, A. Fantinato, B. Cairo, B. De Maria, L. A. Dalla Vecchia, M. Ranucci and A. Porta, "Comparison of Causal and Non-causal Strategies for the Assessment of Baroreflex Sensitivity in Predicting Acute Kidney Dysfunction After Coronary Artery Bypass Grafting," *Front. Physiol.*, vol. 10, pp. 1319, Oct 18, 2019.

[2] R. W. de Boer, J. M. Karemaker and J. Strackee, "Relationships between short-term blood-pressure fluctuations and heart-rate variability in resting subjects. I: A spectral analysis approach," *Med. Biol. Eng. Comput.*, vol. 23, *(4)*, pp. 352-358, Jul, 1985.

[3] A. Porta, V. Bari, T. Bassani, A. Marchi, V. Pistuddi and M. Ranucci, "Model-based causal closed-loop approach to the estimate of baroreflex sensitivity during propofol anesthesia in patients undergoing coronary artery bypass graft," *J. Appl. Physiol.*, vol. 115, *(7)*, pp. 1032-1042, 2013.

[4] A. Porta, R. Furlan, O. Rimoldi, M. Pagani, A. Malliani and P. van de Borne, "Quantifying the strength of the linear causal coupling in closed loop interacting cardiovascular variability signals," *Biol. Cybern.*, vol. 86, *(3)*, pp. 241-251, Mar, 2002.

[5] R. Bauernschmitt, H. Malberg, N. Wessel, G. Brockmann, S. M. Wildhirt, B. Kopp, J. Kurths, G. Bretthauer and R. Lange, "Autonomic control in patients experiencing atrial fibrillation after cardiac surgery," *Pacing Clin. Electrophysiol.*, vol. 30, *(1)*, pp. 77-84, Jan, 2007.

[6] L. Compostella, N. Russo, C. Compostella, T. Setzu, A. D'Onofrio, G. Isabella, G. Tarantini, S. Iliceto, G. Gerosa and F. Bellotto, "Impact of type of intervention for aortic valve replacement on heart rate variability," *Int. J. Cardiol.*, vol. 197, pp. 11-15, Oct 15, 2015.

[7] V. Bari, M. Ranucci, B. De Maria, B. Cairo, V. Pistuddi and A. Porta, "Model-based directional analysis of cardiovascular variability identifies patients developing atrial fibrillation after coronary artery bypass grafting," *International Journal of Cardiology*, 2018.

[8] S. Demirel, V. Akkaya, H. Oflaz, T. Tükek and O. Erk, "Heart rate variability after coronary artery bypass graft surgery: a prospective 3-year follow-up study," *Ann. Noninvasive Electrocardiol.*, vol. 7, *(3)*, pp. 247-250, 2002.

[9] A. Porta, F. Gelpi, V. Bari, B. Cairo, B. De Maria, C. M. Panzetti, N. Cornara, E. G. Bertoldo, V. Fiolo, E. Callus, C. De Vincentiis, M. Volpe, R. Molfetta, V. Pistuddi and M. Ranucci, "Monitoring the Evolution of Asynchrony between Mean Arterial Pressure and Mean Cerebral Blood Flow via Cross-Entropy Methods," *Entropy*, vol. 24, *(1)*, 2022.

[10] A. Porta, A. Fantinato, V. Bari, F. Gelpi, B. Cairo, B. De Maria, E. G. Bertoldo, V. Fiolo, E. Callus, C. De Vincentiis, M. Volpe, R. Molfetta and M. Ranucci, "Evaluation of the impact of surgical aortic valve replacement on short-term cardiovascular and cerebrovascular controls through spontaneous variability analysis," *PLoS One*, vol. 15, *(12)*, pp. e0243869, Dec 10, 2020.

[11] G. Baselli, A. Porta, O. Rimoldi, M. Pagani and S. Cerutti, "Spectral decomposition in multichannel recordings based on multivariate parametric identification," *IEEE Trans. Biomed. Eng.*, vol. 44, *(11)*, pp. 1092-1101, Nov, 1997.

[12] A. Porta, E. Tobaldini, S. Guzzetti, R. Furlan, N. Montano and T. Gnecchi-Ruscone, "Assessment of cardiac autonomic modulation during graded head-up tilt by symbolic analysis of heart rate variability," *Am. J. Physiol. Heart Circ. Physiol.*, vol. 293, *(1)*, pp. 702, Jul, 2007.

[13] V. Bari, B. De Maria, C. E. Mazzucco, G. Rossato, D. Tonon, G. Nollo, L. Faes and A. Porta, "Cerebrovascular and cardiovascular variability interactions investigated through conditional joint transfer entropy in subjects prone to postural syncope," *Physiol. Meas.*, vol. 38, *(5)*, pp. 976-991, 2017.

[14] V. Bari, B. De Maria, C. E. Mazzucco, G. Rossato, D. Tonon, G. Nollo, L. Faes and A. Porta, "Cerebrovascular and cardiovascular variability interactions investigated through conditional joint transfer entropy in subjects prone to postural syncope," *Physiol. Meas.*, vol. 38, *(5)*, pp. 976-991, May, 2017.

[15] L. Faes, G. Nollo and A. Porta, "Mechanisms of causal interaction between short-term RR interval and systolic arterial pressure oscillations during orthostatic challenge," *J. Appl. Physiol.*, vol. 114, *(12)*, pp. 1657-1667, 2013.

[16] V. Bari, A. Fantinato, E. Vaini, F. Gelpi, B. Cairo, B. De Maria, V. Pistuddi, M. Ranucci and A. Porta, "Impact of propofol general anesthesia on cardiovascular and cerebrovascular closed loop variability interactions," *Biomedical Signal Processing and Control*, vol. 68, 2021.

Address for correspondence:
Dr Vlasta Bari, PhD
Department of Biomedical Sciences for Health, University of Milan
IRCCS Policlinico San Donato
Via Morandi 30, 20097 San Donato Milanese, Milan, Italy
email: vlasta.bari@grupposandonato.it