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

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

[1]Department of Biomedical Sciences for Health, University of Milan, Milan, Italy
[2]Department of Cardiothoracic, Vascular Anesthesia and Intensive Care, IRCCS Policlinico San Donato, San Donato Milanese, 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 arm was not affected by surgery. Future studies will be aimed to investigate patients during a longer follow-up and to link results to post-surgery adverse outcomes.

1. Introduction

Cardiovascular control can be assessed by the analysis of spontaneous variability of heart period (HP) and systolic arterial pressure (SAP). The linear coupling between variability series is generally assessed as a function of the frequency by the computation of squared coherence (K^2). K^2 function 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]. HP and SAP relation acts in closed loop, being expression of the activity of two different mechanisms: the baroreflex, acting along the direction from SAP to HP and the mechanical feedforward pathway along the opposite direction [3]. K^2 could be considered an unspecific marker since a high value can be found either in case of a strong interaction occurs along both the arms of the closed-loop or when the interaction is strong along only one arm, while the other is inactive. For this reason, more specific methods were proposed by simply switching off one of the two arms of the closed loop at a time, such a way to account for causality without losing decomposition in the frequency domain [4].

Furthermore, cardiovascular control can be impaired by pathology and clinical condition, as it could happen in patients undergoing cardiac surgery and in particular surgical aortic valve replacement (SAVR). A typical evolution after SAVR is that the cardiovascular control of SAVR patients, that it is already impaired before surgery, worsens after the intervention but it could recover during the follow-up [5-8]. Although different methods of analysis have already been exploited to assess cardiovascular control in these patients and modifications of the autonomic function already monitored post-surgery [9,10], a spectral causality approach exploiting casual K^2 [4] has never been applied to describe the evolution of the cardiovascular control recovery after a 3-month follow-up.

Thus, the aim of this work was to evaluate causal and noncausal 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-month follow-up (POST3). At all time points, patients were evaluated at rest in supine position (REST) and during an active standing (STAND) to evoke sympathetic activation and baroreflex unloading.

2. Experimental Protocol and Methods of Analysis

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; SAP = systolic arterial pressure; μ_{HP} = HP mean; σ^2_{HP} = HP variance; 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.

2.1. Experimental Protocol

Fifty-eight patients scheduled for SAVR (age: 65±13 yrs, 39 males) were enrolled at the Department of Cardiothoracic, Vascular Anesthesia and Intensive Care of IRCCS Policlinico San Donato [10]. The study was approved by the ethical review board of the San Raffaele Hospital, Milan, Italy (approval number: 68/int/2018). Written, signed and informed consent was obtained from all subjects. The study was performed in keeping with Helsinki Declaration for studies involving humans. Subjects signed an informed consent before participating. Acquisitions took place in PRE, POST and POST3. Electrocardiogram (ECG) and arterial pressure (AP), noninvasively recorded via a photoplethysmographic device (CNAP Monitor 500, CNSystems, Austria) were sampled at 400 Hz and recorded for 10 minutes with patients at REST and for 10 minutes during STAND. It is still an ongoing study with 58 patients acquired in PRE, 38 in POST and 16 in POST3. From the signals the time series of HP, approximated as the temporal distance between two R-wave peaks on the ECG and SAP, approximated as the maximum of AP within the HP were extracted. Stationary series of 256 consecutive values were extracted in all phases and conditions and were checked and corrected via linear interpolation in case of ectopic beats. From the series, time domain indexes in terms of mean and variance of HP and SAP were extracted and labeled respectively as μ_{HP}, σ^2_{HP}, μ_{SAP}, σ^2_{SAP}.

2.2. Noncausal 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 square modulus of the cross-spectrum between HP and SAP divided by the product of autospectra. K^2 varied with frequency. 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 [4]. K^2 between HP and SAP, $K^2_{HP,SAP}$ was noncausal since $K^2_{SAP,HP}=K^2_{HP,SAP}$. 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) [4]. Analogously, $K^2_{HP\rightarrow SAP}$ 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 within the relative frequency band and were respectively labeled $K^2_{HP,SAP}$(LF), $K^2_{SAP\rightarrow HP}$(LF), $K^2_{HP\rightarrow SAP}$(LF), $K^2_{HP,SAP}$(HF), $K^2_{SAP\rightarrow HP}$(HF) and $K^2_{HP\rightarrow SAP}$(HF) [4].

2.3. Statistical Analysis

Two-way analysis of variance (Holm-Sidak test for multiple comparisons) was used to check differences between experimental conditions (REST and STAND) and phases (PRE, POST and POST3). Analysis was carried out using a commercial statistical software (Sigmaplot 14.5, Systat Software, Inc., Chicago, IL, USA). A $p<0.05$ 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 across acquisition phases and conditions, while σ^2_{SAP} during POST3 at STAND was increased compared to REST and during STAND it was greater in POST3 compared to PRE and POST.

Figure 1 shows the results of noncausal and causal K^2 assessed in LF and HF bands. In POST3 $K^2_{HP,SAP}$(LF) increased during STAND with respect to REST. During

STAND $K^2_{HP,SAP}$(LF) raised in POST3 compared to POST (Fig.1a). Spectral causality analysis explained these increases as the consequence of augmented strength along the baroreflex (Fig.1b) with $K^2_{SAP\rightarrow HP}$(LF) greater during STAND than at REST in POST3 and higher in POST3 than POST and PRE during STAND. $K^2_{HP\rightarrow SAP}$(LF) remained unvaried across phases and conditions (Fig.1c). In the HF band noncausal and causal K^2 analysis was less informative. Indeed, we observed solely a general decrease of $K^2_{HP,SAP}$(HF) during STAND compared to REST (Fig.1d) that it was explained by a tendency of $K^2_{SAP\rightarrow HP}$(HF) to decline in response to the postural challenge (Fig.1e). $K^2_{HP\rightarrow SAP}$(HF) remained unvaried across phases and conditions (Fig.1f).

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 regulation 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) spectral causality analysis allows us to identify 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. However, the vagal withdrawal and sympathetic activation in response to STAND did not cause the expected reduction of HP variance and increase in SAP variance during STAND [12,13] and this conclusion held in both PRE and POST. Furthermore, in both PRE and POST, the expected increase of the $K^2_{HP,SAP}$(LF) in response to STAND was not observed [14], thus indicating that SAVR patients exhibited a depressed autonomic function after intervention [10]. The recovery in POST3 toward a healthier condition [15] was confirmed by the increase of $K^2_{HP,SAP}$(LF) in POST3 during STAND with respect to REST and during STAND in POST3 compared to POST.

When decomposed along the two arms of the closed loop cardiovascular regulation, the behavior of $K^2_{HP,SAP}$(LF) during POST3 was mirrored by the changes of $K^2_{SAP\rightarrow HP}$(LF). This finding suggests that the baroreflex arm fully explains the link between HP and SAP in POST3 and strongly supports the notion that the improvement of cardiovascular regulation 3 months after surgery is the consequence of baroreflex function amelioration. Remarkably, similar increases of the strength of the causal link from SAP to HP in response to postural stressor were detected in healthy subjects using different causality tools [13,16]. On the contrary, $K^2_{HP\rightarrow SAP}$(LF) resulted unchanged between groups and conditions, thus indicating that the mechanical feedforward pathway was not affected by SAVR and by the postural challenge.

We confirmed the lack of response to STAND during PRE, thus stressing the limited preoperative autonomic responsiveness to stressors in this population [8,10]. In addition, we stress that the increase of $K^2_{SAP\rightarrow HP}$(LF) during STAND was not visible in PRE, thus suggesting that surgery plays a role on the post-operative improvement of cardiovascular control that becomes manifested after a period of 3 months.

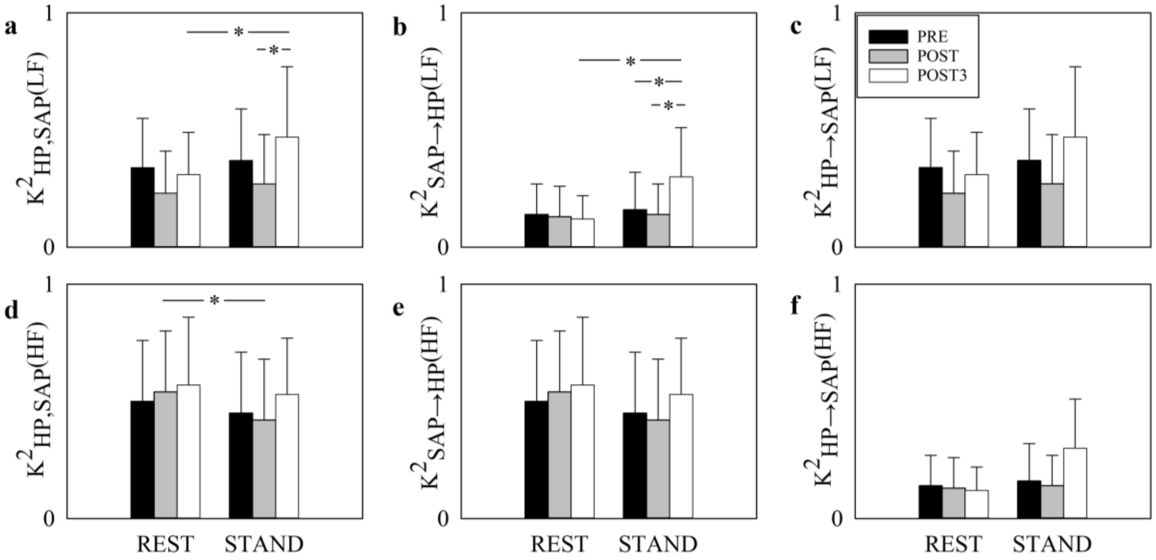

Figure 1. The grouped bar-graphs show: $K^2_{HP,SAP}$(LF) (a), $K^2_{SAP\rightarrow HP}$(LF) (b), $K^2_{HP\rightarrow SAP}$(LF) (c), $K^2_{HP,SAP}$(HF) (d), $K^2_{SAP\rightarrow HP}$(HF) (e) and $K^2_{HP\rightarrow SAP}$(HF) (f) as a function of the experimental condition (i.e. REST and STAND). Data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

5. Conclusions

This work exploits a spectral causality approach to assess cardiovascular control in patients undergoing SAVR evaluated during STAND in PRE, POST and POST3. Results show that, as expected, cardiovascular control is reduced during POST and is recovered after a 3-month follow-up. Spectral causality approach allowed us to reveal that this recovery is more related to the amelioration of 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 relevance of performing a spectral causality analysis to monitor the progression of the cardiovascular control recovery after SAVR. Future studies should be focused on increasing the size of the population, performing a longer follow-up and link cardiovascular markers to the occurrence of post-surgery adverse events. For a methodological standpoint future works should account for the possible presence of confounding factors, such as respiration that might mix up causal relation [16], using conditional spectral causality tools that have the possibility to condition out disturbing factors [17,18]. Modifications of different markers of baroreflex function, such as latency, should be monitored as well [19].

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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