HEART TRANSPLANTATION – SPECTRAL AND BISPECTRAL ANALYSIS

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Abstract- **Heart transplantation offers a unique view into an unusual cardiovascular system, with a denervated heart. We investigate noninvasively the compensatory cardiovascular control mechanisms, which develop following transplant.**
ECG, continuous blood pressure and respiration are recorded in supine position and during transition to standing, and analyzed in time and frequency domains. 25 recordings were obtained from 13 male HT patients at time after transplant (TAT) ranging 0.5-65 months.
We observed an interesting evolution with TAT in heart rate response to active standing: from no response, via a slow response, to a fast increase. Another important finding was the existence of very high frequency (VHF) peaks in the power spectra of HR and BP fluctuations, in 8 recordings. Analysis using bicoherence indicates that some of those peaks are harmonics of respiration, while others originate from an unknown source.
Our results indicate that with TAT, compensatory cardiovascular mechanisms develop in a biphasic process towards seemingly normal control. We found evidence for the direct effect of the old SA node on the transplanted one, yet no indication of vagal reinnervation. The presence of VHF peaks, unrelated to respiration, suggests the existence of a yet unknown control mechanism, which may be masked in normal subjects.
Keywords – **Bispectrum, Polyspectra, Heart Rate Variability, Spectral Analysis, Cardiac Transplantation**

I. INTRODUCTION

Heart transplant (**HT**), in addition to evidence of personal fortitude and medical proficiency, presents an intriguing and unique model of cardiovascular control. During the surgical procedure, the newly transplanted and old atria are sutured together. The new SA node, which sets the heart rate (**HR**), is fully denervated. The old SA node is still innervated but the electrical signal originating from it cannot cross the suture line. Therefore, the absence of the neural limbs for HR regulation leaves the heart with only its hormonal control. It has been shown, that a process of sympathetic reinnervation takes place after transplantation and some sympathetic reinnervation is evident several months following surgery [1]. Vasomotor control (neural and hormonal) is unaffected by the surgery, yet it undergoes modifications due to the pressor effect of immunosuppressive therapy. It is important to note that in HT patients, the effect of cardiac denervation can be studied under otherwise healthy physiological conditions. In contrast, typical studies of the denervated heart involve drastic pharmacological or surgical interventions, which either cannot be performed in humans or dramatically alter the physiology of the cardiovascular system (**CVS**).

The principal aim of this study is to characterize the cardiovascular control mechanisms in HT patients and the evolution of those mechanisms over time following transplant. Understanding the CVS control in HT patients may elucidate the evolution of compensatory mechanisms and their nature. In addition, the surgical denervation may unveil yet unknown aspects of the control mechanisms in the healthy CVS.

Spectral analysis of HR and blood pressure (BP) is widely used to investigate the CVS system, due to the manifestation of autonomic control in power spectra. In the case of HT patients, such analysis provides valuable characterization of the HR and BP in terms of linear correlations. In previous work [2], we have found that in several HT patients the power spectrum of HRV exhibits very high frequency (**VHF**) peaks, at frequencies well above the respiratory frequency. We hypothesized that those atypical peaks indicate nonlinearities in the CVS and related them to lack of vagal reinnervation. In the present study, we use methods adopted from the Higher Order Statistics approach. This approach provides tools of statistical analysis of nonlinearities in signals, and for the understanding of the statistical relations between different peaks in the power spectrum. Such information is not available from typical spectral analysis.

II. METHODOLOGY

The recordings were obtained from 13 male HT patients (age: 28-68, mean=52±12 years). All patients received immunosuppressive therapy [3]. In this group, 25 recordings were performed at Times-After-Transplant (**TAT**) in the range 0.5-65 months: 5 subjects were recorded once, 6 subjects were recorded twice and two subject were recorded 4 times, at different TAT. None of the subjects had any signs of graft rejection prior to any recording session. The control group consisted of 14 normal male subjects (age 28-59, mean=41±6 years).

The subjects were monitored continuously in 3 different postures: 45 min in supine position, 5 min during upright standing and 10 min while sitting. The transitions between postures were metronome paced, and lasted 10 sec. The recordings began following 10 min of supine rest. Lead I ECG (Biopac), continuous BP (Finapres-Ohmeda) and respiration (Respitrace) were acquired directly to a computer at a rate of 500 Hz.

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Abstract

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Following very accurate R-wave detection, all signals were low-pass filtered, decimated to 10 Hz, and only then, subjected to various analysis procedures in time and frequency domains.

The following time domain features of the HR signal were examined:

- Mean HR during first 45 min - $\langle HR \rangle$
- For each HR trace (divided into 5 min subtraces) an average $\langle STD \rangle$ was computed, providing a coarse estimate of HRV.
- Long-term changes in HR during the first 25 min were examined qualitatively.

Before performing a frequency domain analysis, the HR trace was high pass filtered using a nonlinear filter, by dividing the signal into 50 sec epochs and removing the linear trend from each epoch. This filter reduced the effect of the non-stationarity, which tended to obscure the structure of HRV spectrum. Such a filter is rarely required in normal subjects, in whom HRV is much higher and hence less susceptible to be affected by non-stationarity. Several HT subjects experienced extensive arrhythmias; their data was therefore not submitted to spectral analysis. Qualitative and quantitative features were examined, taking TAT into consideration:

- Pattern of power spectra of HR, BP and respiration.
- Low frequency fluctuations (LF), obtained by integrating the spectra over the 0.02-0.15 Hz range.
- High frequency fluctuations (HF), obtained by integrating over the respiratory frequency range.
- LF/(LF+HF), reflecting sympathovagal balance.

The bispectrum and bicoherence can be assessed in several ways, either from the cumulants or directly from the Fourier transform of the signal. The definition of bispectrum of a signal $x(t)$ is [4]:

$$C(\omega_1,\omega_2) = \sum_{t_1=-\infty}^{\infty} \sum_{t_2=-\infty}^{\infty} c(t_1,t_2) \exp\left(-i(\omega_1 t_1 + \omega_2 t_2)\right) \quad (1)$$

where $c(t_1,t_2)$ is the 3rd order cumulant. An unbiased and consistent estimator of $C(\omega_1,\omega_2)$ can be derived from the Fourier transform of $x(t)$, denoted by $X(\omega)$, in a way similar to the Welch Periodogram. The signal $x(t)$ is divided into M (overlapping or nonoverlapping) sections and the Fourier transform $X_k(\omega)$ of every section k is computed (eventually multiplied by a window)

$$\hat{C}(\omega_1,\omega_2) = \tfrac{1}{M} \sum_{k=1}^{M} X_k(\omega_1) X_k(\omega_2) X_k^*(\omega_1+\omega_2) \quad (2)$$

Let us consider, as an example, a case were the power spectrum exhibits peaks at the angular frequencies ω_1, ω_2 and $\omega_1+\omega_2$ with amplitude A. The components in the sum in (2) have approximately the same magnitude:

$$\left| X_k(\omega_1) X_k(\omega_2) X_k^*(\omega_1+\omega_2) \right| \approx A^3, \quad \forall k \quad (3)$$

However, the phase of those components depends on the properties of the signal. If the peak at $\omega_1+\omega_2$ is unrelated to the other two, e.g. it is not the result of a nonlinearity, then the variation in the phase will reduce the sum to zero. Conversely, a constant phase difference between the oscillations will cause the sum to assume a value of A^3. Similarly to the coherence index, we use the bicoherence, which is a normalized version of the bispectrum:

$$B(\omega_1,\omega_2) = \frac{\hat{C}(\omega_1,\omega_2)}{\left| \hat{S}(\omega_1)\hat{S}(\omega_2)\hat{S}(\omega_1+\omega_2) \right|^{1/2}} \quad (4)$$

were $\hat{S}(\omega)$ is the estimate of the power spectrum of $x(t)$. $B(\omega_1,\omega_2)$ is an estimator of the statistical cross-correlation between the 3 oscillations. Therefore, $B(\omega_1,\omega_2) \approx 1$ indicates that the 3 spectral peaks at ω_1, ω_2 and $\omega_1+\omega_2$ are related, whereas low values of $B(\omega_1,\omega_2)$ indicate that the 3 peaks are statistically independent. The bicoherence of all recordings, which exhibited the VHF peaks in the power spectra of HR or BP, was computed and the interaction between the peaks was examined.

In addition, the HR trace was examined qualitatively, focusing on the HR response to CP from supine to standing position. A 10 min epoch centered at the CP, was considered.

III. Results

Response to Change in Posture - The analysis performed in this study spans the characterization of the CVS in HT patients over several dimensions. We found that the key for an integrative understanding of all the results lies in the HR response to CP. The HT patients exhibited 3 kinds of responses, as shown in Fig. 1:

Group #1: HR unaffected (Fig. 1A). Only a change in HRV is observable (4 recordings).

Group #2: Slow HR increase (Fig. 1B), resembles the charging of a capacitor (10 recordings).

Group #3: Fast HR increase (Fig. 1C), sometimes followed by a slow decrease or increase (8 recordings).

Three HT recordings were not classified due to the occurrence of severe arrhythmias. All control subjects exhibited the third behavior, i.e. a fast HR increase. We display the classification of HT subjects into the 3 subgroups as a function of TAT in Fig. 2.

Statistical properties of HR - Statistical properties of the HR were significantly different between the HT and control subjects. The $\langle HR \rangle$ was higher in the HT group, whereas the $\langle STD \rangle$ was much lower (see [5] for details). There was no correlation between $\langle HR \rangle$ and $\langle STD \rangle$ with TAT, nor with the HR response to CP.

Long-term HR decrease in Supine Rest - Several recordings exhibited an atypical gradual HR decrease during the first 25 min of supine rest [3]. This slow HR reduction was observed in 13 (out of 14) recordings of groups 1 and 2, thus at early TAT. In contrast, 2 (out of 8) recordings of group 3 and none the control group exhibited this decrease.

Existence of Arrhythmias - As mentioned, several recordings exhibited arrhythmias. The severity of the arrhythmias ranged from several ectopic beats dispersed

over the 60 min of recording, to extensive arrhythmias that prevented all analyses. All the arrhythmia-containing recordings were obtained at the intermediate TAT, namely in the range 17-42 months. HT patients, who experienced arrhythmias in one of their recordings, did not exhibit arrhythmias in earlier recordings with TAT<17. The arrhythmias appeared to be mostly of atrial nature. However, exact classification of these arrhythmias was difficult since only one ECG lead was used.

Spectral and Bispectral analysis - Both BP and HR signals resulted in the typical LF and HF peaks (see Fig. 3), although the HT patients exhibited much lower spectra. This structure existed for all HT subjects. The LF peak increased on average as the HR response to CP became faster (see Fig. 4). Yet, the LF peak remained significantly lower than in the control group even for group 3. The HF component of HRV was markedly below normal values for all HT patients (p<0.0001, unpaired t-test). The power of HF peak correlated neither with TAT, nor with the classification to groups. However, the ratio LF/(LF+HF), which was well below normal values for group1, increased in group 2 and assumed normal valued in group 3.

The spectral analysis in HT patients revealed an intriguing phenomenon: spectral peaks at frequencies well above the respiratory frequency. Those VHF peaks were apparent in the spectrum of HR as well as BP. The VHF peaks were found in 8 recordings. Examination of the bicoherence of those HR traces revealed two sets of VHF peaks. The peaks of the first set were plain harmonics (second or higher) of the respiratory frequency, i.e. a peak at $B(\omega_{resp},\omega_{resp})$. The second set were peaks in the spectra of HR and BP, which were unrelated to the respiratory frequency. Three recordings exhibited the first set of peaks, 4 recordings exhibited both the first and second sets, and one recording exhibited only the second set. There was no significant correlation between the incidence of VHF peaks and the HR response to CP or TAT.

A power spectrum of HR with VHF peaks is shown in Fig. 5 with the corresponding bicoherence for an HT patient with TAT=19 months. The spectral peaks are labeled by numbers and the bicoherence peaks are labeled by Greek letters. Peak 1 is the LF peak, peak 2: HF peak, peak 3: second harmonic of peak 2 (indicated by α), peak 4: unrelated to peaks 1-3 (lack of peaks between α and γ), peak 5: coupling of peak 2 and 4 (indicated by β), peak 6: second harmonic of peak 4 (indicated by γ). This specific example displayed additional peaks at even higher frequencies (omitted here).

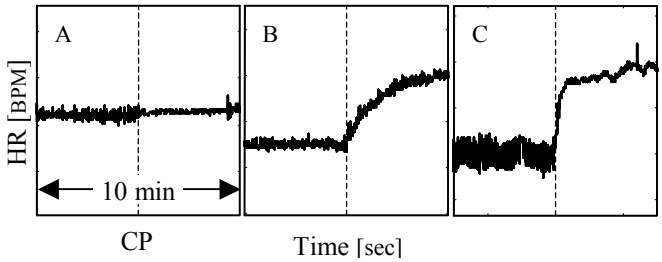

Fig. 1: Classification of the HT subjects into the 3 groups according to their HR response to CP, plotted vs. TAT.

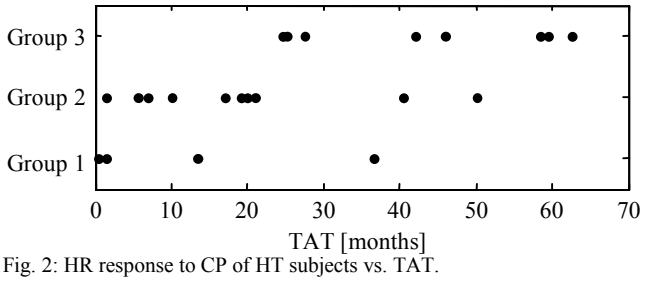

Fig. 2: HR response to CP of HT subjects vs. TAT.

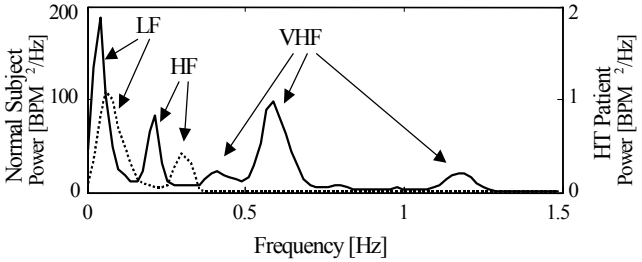

Fig. 3: HR spectra of a normal subject (dotted) and HT patient (solid). Note the 2 order-of-magnitude difference in the ordinate, and the presence of VHF peaks in the spectrum of the HT patient.

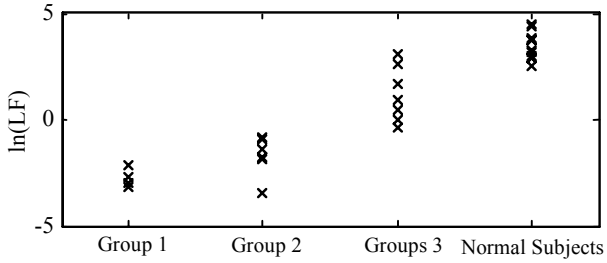

Fig. 4: Log of the LF component of HRV, according to the HR response to CP. Note the increase in LF as function of subgroup number.

IV. Discussion

The experimental procedure of this study was designed to cause the CVS control system in HT patients to disclose its function and regulation. The combination of time and frequency analyses and the combination of steady-state (supine rest) and transitional (CP) conditions provided abundant information about the functioning of the denervated CVS and its compensatory control mechanisms. We found that several descriptive CVS parameters converged over time towards normal values. Yet, all along, the CVS of HT patients remains strikingly different from the normal one.

A remarkable example of the convergence of CVS parameters towards normal behavior is the HR response to CP. The 3 types of responses and their correlation with TAT suggest that the evolution of compensatory mechanisms is biphasic. Immediately after surgery, the denervation, which explains the reduced HRV and increased HR, seems to govern the CVS control. At this stage, vasomotor control probably compensates for the lack of neural control over the heart. Then, several weeks after surgery, a simple first order control mechanism evolves. This mechanism, which probably includes the baroreceptors and the adrenal gland, may be responsible for the charging-capacitor-like HR

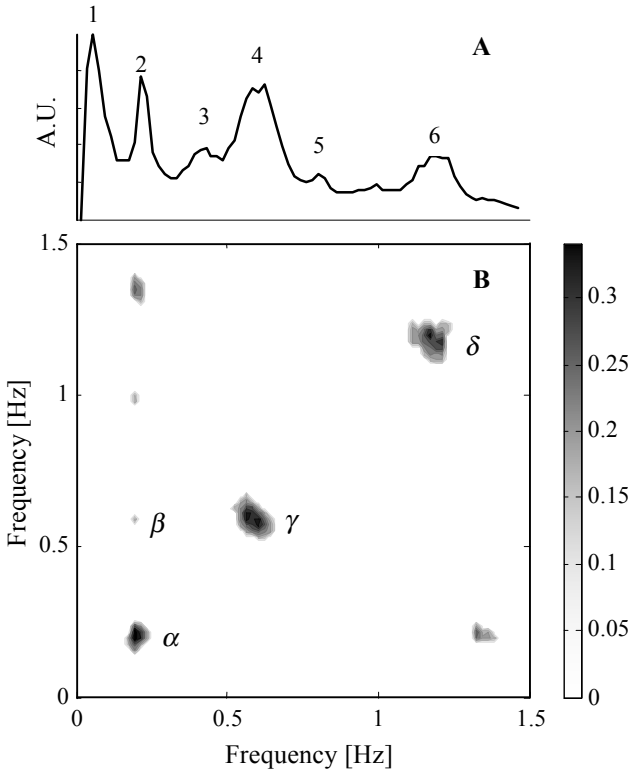

Fig. 5: HRV Power spectrum (A) and the corresponding bicoherence (B), displayed as gray scales, of an HT patient. The spectral peaks are marked by numbers and the bispectral peaks are marked by Greek letters.

increase. Later, after about 24 months, a fast, higher order control mechanism evolves, which enables HR to increase on a brief time scale, similar to normal subjects. In normal subjects, the fast HR increase is known to be mediated by vagal withdrawal [6]. Yet, vagal reinnervation is known to be scarce in HT patients [7]. Indeed, vagal reinnervation would have been reflected by a decrease in mean HR and an increase in the HF component of HRV. Neither phenomena was observed. Another phenomenon confirms the absence of vagal reinnervation: the existence of VHF peaks in the power spectra of HRV and BP [2]. Vagal innervation serves as a negative feedback in the CVS, thus linearizing its inherent nonlinearities and consequently diminishes harmonics of the respiratory frequency. Hence, the existence of higher harmonics of respiration suggests the lack of such feedback, namely, vagal reinnervation. Other mechanisms must thus be responsible for the fast HR increase. Partial sympathetic reinnervation is known to occur several months after transplantation [1]. Sympathetic reinnervation was convincingly associated with increased LF fluctuations, as also observed here. However, sympathetic activity is unable to cause such a fast HR response [6]. Thus, we are left with a puzzle: what mechanism causes the fast HR increase?

Although a positive answer to this question cannot be provided in this study, we suggest a possible mechanism. The old SA node is still innervated, and therefore increases its rate in response to the CP. If the electrical signal could cross, even weakly, through the suture line, it might cause the new SA node to also increase its rate. Indeed, atrioatrial conduction has been observed in several cases. The occurrences of arrhythmias at the same TAT at which the fast control mechanism emerges, as well their atrial origin, suggest that alterations in the atrial electrical conduction system occurs, supporting this hypothesis.

Another question, which still lacks an explanation, is the origin of the second set of VHF peaks (non harmonics). Those peaks seem independent of the respiratory frequency suggesting that they are caused by another mechanism. This obscure mechanism is probably revealed in HT patients as a result of the denervation, but may actually exist in normal subjects too. It is important to note that those peaks were observed in both HR and BP spectra, therefore excluding aliasing as the cause of the VHF peaks.

V. Conclusion

The combination of an extensive analysis and a straightforward noninvasive experimental procedure provided a rich description of CVS functioning after heart transplantation. Our results indicate the development of a simple control loop soon after surgery, followed by partial sympathetic reinnervation and the emergence of a fast control mechanism around 2 years after surgery. Although not proving it yet, the results comply with the hypothesis of conduction over the suture line as the fast control mechanism. In addition, the existence of VHF peaks opens a completely new field of exploration into the CVS control. The nature of the VHF peaks must still be verified by other methods of analysis and by investigation of additional data.

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