Functional restitution of cardiac control in heart transplant patients

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Functional restitution of cardiac control in heart transplant patients. Am J Physiol Regulatory Integrative Comp Physiol 282: R900–R908, 2002.—Cardiovascular control is fundamentally altered after heart transplantation (HT) because of surgical denervation of the heart. The main goal of this work was the noninvasive characterization of cardiac rate control mechanisms after HT and the understanding of their nature. We obtained 25 recordings from 13 male HT patients [age = 28–68 yr, time after transplant (TAT) = 0.5–62.5 mo]. The control group included 14 healthy men (age = 28–59 yr). Electrocardiogram, continuous blood pressure (BP), and respiration were recorded for 45 min in the supine position and then during active change of posture (CP) to standing. The signals were analyzed in the time domain [mean and variance of heart rate (HR) and rise time of HR in response to CP] and the frequency domain [low and high frequency (LF and HF)]. Our principal finding was the consistent pattern of evolution of the HR response to standing: from no response, via a slow response (>40 s, TAT > 6 wk), to a fast increase (<20 s, TAT > 24 mo). HR response correlated with TAT (P < 0.001). LF correlated with HR response to CP (P < 0.0001); HF and HR did not. An important finding was the presence of very-high-frequency peaks in the power spectrum of HR and BP fluctuations. Extensive arrhythmias tended to appear at the TAT that corresponds to the transition from slow to fast HR response to CP. Our results indicate a biphasic evolution in cardiac control mechanisms from lack of control to a first-order control loop followed by partial sympathetic reinnervation and, finally, the direct effect of the old sinoatrial node on the pacemaker cell of the new sinoatrial node. There was no indication of vagal reinnervation.

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the evidence supporting vagal reinnervation is indirect. Bernardi et al. (6) examined the changes of HRV in response to atropine. They convincingly concluded that vagal reinnervation is scarce (1 of 79 subjects) after the standard surgical procedure; it is more common in the case of bicaival anastomosis (6 of 10 subjects).

Spectral analysis of instantaneous HR and blood pressure (BP) is widely used to investigate the normal and pathological cardiovascular control system on the basis of the manifestation of autonomic activity in the respective power spectra. Typically, the power spectra of both signals exhibit two distinctive peaks, corresponding to fluctuations at different frequencies. Oscillations at frequencies of \(~0.1\) Hz, usually referred to as low-frequency (LF) peak, are associated with sympathetic and parasympathetic activity, and oscillations at the respiratory frequency, also known as high-frequency (HF) peak, reflect parasympathetic activity. In HT patients, the typical spectral structure of HR and BP has also been observed, contributing to the controversy concerning reinnervation.

Another tool for the investigation of the cardiovascular control system is based on the application of a physiological challenge to the cardiovascular system, such as an active CP from supine to standing position. This maneuver represents a significant provocation to cardiovascular control, demanding the compensation of the drop in blood supply to the brain. It has been shown that CP involves the activation of both branches of the autonomic nervous system (8, 14). Therefore, this simple test has the ability to disclose malfunctions or limitations in the autonomic part of cardiovascular control.

The principal goal of our study is the characterization and identification of the cardiac rate control mechanisms that develop in response to the surgical denervation caused by HT. Elucidation of control in HT patients may have important clinical implications for these patients, as well as for the understanding of normal cardiovascular control and its alteration with disease. The first step in studying mechanisms involved in the cardiovascular regulation is their characterization. Therefore, we utilized an experimental procedure composed of two distinctive phases: a steady-state and a transient phase. The steady-state phase was embodied by supine rest, where oxygen consumption remains fairly constant, while an active CP served as the transient phase. This twofold experimental approach causes the cardiovascular control to function under different physiological conditions. The steady-state conditions permit the use of standard statistical analysis in time and frequency domains, while the transitory phase prohibits the use of simple statistical measures.

The framework of this study provides a phenomenological description of cardiac rate control after cardiac transplantation and its evolution over time. Understanding the phenomenology of cardiovascular control in HT patients sheds light on the issues in question: sympathetic reinnervation, vagal reinnervation, possible compensatory mechanisms, and, essentially, how the intricate control scheme is achieved in the denervated system.

**METHODS**

**Patients and Protocol**

The data were acquired from 13 male HT patients (range 28–68 yr, mean 52 ± 12 yr). All patients received the standard immunosuppressive therapy with cyclosporin, prednisone, and azathioprine. In this group, 25 recordings were performed at various times after transplantation (TAT): 5 patients were recorded once, 6 were recorded twice, and 2 were recorded 4 times at different TAT. The time elapsed since transplant surgery was 0.5–62.5 mo.

All patients were in stable condition with respect to their clinical signs and symptoms. None had any sign of graft rejection before a recording session.

The control group consisted of 14 normal men (range 28–59 yr, mean 41 ± 6 yr). The study was approved by the institutional review committee. All subjects gave their written informed consent. This work fully conforms with the guidelines for research involving animals and human beings of the American Physiological Society. In each recording session, all subjects were monitored continuously in three subsequent positions, including the active transitions between postures: 45 min in the supine position, 5 min during upright standing, and 10 min while sitting. The transitions between postures lasted 10 s. All recordings began after 10 min of supine rest. The transition from standing to sitting was not analyzed.

**Data Acquisition and Preprocessing**

Lead I electrocardiogram (ECG; model MP100, Biopac), continuous BP (Finapres, Ohmeda), and respiration (Respitrace, Ambulatory Monitoring) were monitored noninvasively. The Respitrace has a built-in low-pass filter at 15 Hz, which cannot affect higher harmonics of respiration. All signals were acquired directly to a computer at a sampling rate of 500 Hz.

The respiratory signal was calibrated to tidal volume. The R-R intervals were corrected for arrhythmias, and total trace duration was unchanged. The BP signal was corrected for the self-calibration interruptions to produce a continuous, gap-free signal (27). All signals were low-pass filtered, decimated to 10 Hz, and, only then, subjected to various analysis procedures in time and frequency domains.

**Data Analyses**

**Steady-state analysis: time domain.** The following time domain features of the HR signal were examined, with TAT taken into consideration. 1) Mean HR (HR) during the first 45 min of recording was determined. 2) The HR signal during this 45-min trace was divided into 5-min epochs, and its standard deviation was computed for every epoch. The mean of these standard deviations (STD) was computed, providing a coarse estimate of HRV. This measure is similar to the commonly used SDNN index. 3) Long-term changes in HR during the first 25 min of recording were examined qualitatively.

**Steady-state analysis: spectral analysis.** Before the frequency domain analysis, the HR traces were high-pass filtered using a nonlinear filter by dividing the signal into 50-s epochs and removing the linear trend from each epoch. This filter reduces the effect of the nonstationarity, which tends to
obscure the structure of the HR power spectrum. In eight recordings (obtained from 6 HT patients), the ECG exhibited extensive arrhythmias; therefore, these data were not submitted to spectral analysis.

The following features were examined, with TAT taken into consideration. 1) Power spectra of HR, BP, and respiration were examined qualitatively. 2) LF fluctuations were estimated by integrating the spectra over the 0.02- to 0.15-Hz range. 3) HF fluctuations were estimated by integrating over the respiratory frequency range. This range was determined for each HR trace by inspection of the respiration power spectrum. 4) A normalized value of LF fluctuations was computed as follows: LF/(LF + HF), where LF is LF fluctuation and HF is HF fluctuation. In healthy subjects, this measure is known to reflect the sympathovagal balance. 5) Total power of fluctuations (Total) was calculated by integrating over the 0.02- to 1-Hz range of each power spectrum.

Transient phase: HR response to CP. When considering the transient phase of the experiment, we examined the HR trace qualitatively in the time domain. We focused on the HR response to CP from supine to standing position. A 10-min epoch centered at the CP was considered. The HR signal in this epoch was filtered with a moving median filter with 5-s window width. The moving median filter eliminated the extreme HR values, which result from arrhythmias, while keeping the dynamics of the HR signal intact. As a result, we were able to analyze five recordings that exhibited arrhythmias and were therefore excluded from spectral analysis.

Finally, we measured the time elapsed from the CP until the first maximum in HR ($t_{HR}$). We used the first maximum, inasmuch as HR sometimes decreases and then increases again after the first rise.

In three HT patients, we were unable to analyze the HR response because of severe arrhythmias.

Statistics

Statistical tests are identified in the text where appropriate. Unless otherwise noted, all data are reported as means ± SE. Statistical analysis of LF and HF fluctuations was performed after the logarithm was taken.

RESULTS

Careful examination of the results revealed that the HR response to CP is the key for interpreting all other results. Therefore, the results of the transitional phase of the protocol are reported before those of the steady-state phase, although the latter preceded the former in the time course of the experiment.

Change of Posture

Qualitative examination of the time-dependent HR response to CP disclosed three types of responses (Fig. 1). In group 1 (4 recordings), HR was unaffected (Fig. 1A). Only a slight change in HRV is observed, probably caused by an alteration in the mode of respiration related to CP. In group 2 (10 recordings), the slow HR increase ($t_{HR} > 30$ s) resembles the charging of a capacitor (Fig. 1B); in this group, $t_{HR} = 48–300$ s. In group 3 (8 recordings), the fast HR increase ($t_{HR} \leq 30$ s) was sometimes followed by a slow increase (Fig. 1C) or a decrease (Fig. 1D); in this group, $t_{HR} = 8.6–20$ s. Three recordings were not classified because of severe arrhythmias.

All control subjects exhibited the third behavior, i.e., a fast HR increase. The classification of the HT patients into the three subgroups, according to their HR response to CP, is displayed in Fig. 2 as a function of TAT.

The unchanged HR pattern (group 1) was observed in four recordings (3 patients). Two patients exhibited this HR pattern soon after surgery and exhibited a slow HR increase (group 2) in subsequent recordings.

![Fig. 1. Four typical heart rate (HR) responses to the change in posture (CP) 5 min before and after CP (dashed line) in groups 1 (A), 2 (B), and 3 (C and D). BPM, beats/min; $t_{HR}$, time from CP until the first HR maximum. All normal subjects exhibited the type of HR response shown in C and D.](http://ajpregu.physiology.org/)}
One patient still exhibited the nonresponding HR pattern 3 yr after transplantation. The pattern of slow HR increase (group 2) appeared a few weeks after surgery. A fast HR increase (group 3) first appeared at TAT = 24.5 mo. As TAT progresses, we observe a clear tendency of HT patients to shift from group 1 to group 2 and, eventually, to group 3 (P < 0.001, Kruskal-Wallis test). This tendency was also disclosed on inspection of individual HT patients who were recorded more than once. Moreover, the HR response became faster in subsequent recordings of individual HT patients.

**Steady-State Analysis: Time Domain**

HR was significantly higher in the HT patients (HR_{HT}) than in the control group (HR_N): 85.5 ± 9.3 vs. 72.1 ± 9.8 beats/min (P < 0.0005, unpaired t-test). The HR of all HT subgroups was significantly elevated relative to normal subjects (P < 0.05 for all subgroups). The STD values were much lower in the HT patients (STD_{HT}) than in the control group (STD_N): 1.1 ± 0.8 vs. 4.5 ± 1.1 beats/min (P < 10^{-8}, unpaired t-test). The individual values of HR and STD were correlated neither with TAT nor with the different HT subgroup to which each individual belonged.

An unequivocal pattern of slow gradual reduction in HR was observed in many HT patients during the initial supine rest. This pattern correlated with the HR response to CP. The two typical HR patterns during the first 25 min of supine rest are shown in Fig. 3. All patients of group 1 and nine (of 10) patients of group 2 exhibited this gradual decrease in HR (Fig. 3A). In contrast, only two HT (of 8) patients of group 3 exhibited this HR reduction, while the other six patients and all control subjects did not display such a decrease (Fig. 3B; P < 10^{-7}, Fisher's exact test).

**Arrhythmias**

In seven recordings obtained from five HT patients, we found that a considerable percentage of heartbeats did not originate in the SA node. Those arrhythmias appeared in HT patients whose recordings took place around the TAT corresponding to the transition period from a slow to a fast HR response to CP (group 2 to group 3). Twelve recordings took place at 17 ≤ TAT ≤ 42 mo, and seven of them exhibited such arrhythmias. No significant arrhythmias were found in recordings with TAT < 17 or >42 mo (P < 0.0001, Fisher's exact test). Classification of the HT patients according to the existence of arrhythmias as a function of TAT is shown in Fig. 2. The ECG was classified as arrhythmic when the percentage of arrhythmic beats exceeded 1%. These arrhythmias appeared to be of atrial nature in five recordings. Exact classification of these arrhythmias was difficult, inasmuch as only a single ECG lead was recorded. The arrhythmias appeared in the supine and standing positions. The arrhythmias were not malignant in four patients. However, one patient underwent ablation therapy.

**Steady-State Phase: Frequency Domain**

The typical pattern of HR fluctuations was observed in the recordings of all normal subjects, i.e., the apparent LF and HF peaks. Despite the denervation, a similar spectral pattern was observed in the power spectrum of HR traces of HT patients. However, the power was markedly reduced compared with normal subjects. This typical structure, although reduced in power, existed and persisted in all HT patients, including patients who were recorded only a few weeks after surgery.

The LF component of HRV in the HT patients was closely related to the above-described classification of HR response to CP (one-way ANOVA: \( F(2, 14) = 21.9, P < 10^{-4} \), Spearman rank correlation \( r_s = 0.75, P < 0.002 \)). The LF significantly increased as the HR response to CP became faster (Fig. 4). Moreover, LF fluctuations in all HT subgroups remained strikingly and consistently reduced compared with the control group (for all subgroups, \( P < 10^{-4} \), unpaired t-test). The LF component correlated also with TAT (\( r_s = 0.76, P < 0.001 \)).

The HF component of HRV in HT patients was markedly below normal levels for all TAT values and for all HT subgroups (\( P < 10^{-4} \), unpaired t-test). The power of HF correlated neither with TAT nor with the classification in subgroups. The normalized value LF/
The spectral analysis revealed another intriguing phenomenon: very-high-frequency (VHF) spectral peaks, at frequencies well above the respiratory frequency, were observed in the HR and BP spectra of 9 HT patients (Fig. 5). In several cases, the VHF peaks were even stronger than the HF peak. The VHF peaks did not tend to appear in a specific subgroup \((P > 0.15, \text{ Fisher's exact test})\) or in a specific TAT range \((P > 0.98, \text{ Wilcoxon's rank sum test})\). No significant VHF peaks were found in the respiration signal. No normal subject displayed those VHF peaks.

**DISCUSSION**

This study was designed to achieve two goals: to characterize cardiovascular control in HT patients and, subsequently, to identify the mechanisms behind it. Hence, the protocol of this study was designed to challenge the cardiovascular control in HT patients. A long steady-state period followed by an abrupt transitional phase (CP) induced the recruitment of control mechanisms of the cardiovascular system in HT patients. The results of this experimental protocol, when presented as a function of TAT, reveal the evolution of control mechanisms and their tendency to converge toward normal function. However, the results of this study suggest that even long after transplantation, the almost-normal cardiovascular function exhibited by HT patients is not achieved by restoration of normal reflex mechanisms. Rather, it is achieved by the contribution of several other mechanisms that join the task of controlling cardiovascular function at various stages after transplantation.

**Change of Posture**

The normal HR response to standing (CP) is known to involve a fast increase, peaking \(\sim 10\) s after the CP,

\[
\text{HR}(t) = A \left[ 1 - \exp\left( -\frac{t}{\tau} \right) \right] + B.
\]

where \(A\) is the amplitude of the response, \(B\) is the baseline HR, \(\tau\) is the time constant, and \(t\) is time. In healthy subjects, the fast HR increase is induced by vagal withdrawal, while sympathetic control has a more sluggish effect on HR and plays a secondary role in the first 20 s of the HR response. The roles of both branches of the autonomic nervous system in regulating the HR response to a postural change have been verified with pharmacological interventions (14).

The various types of HR responses to standing exhibited by the HT patients suggest a biphasic evolution in cardiac control mechanisms. The first evolution in cardiac control, from a lack of response to a slow response, occurs several weeks after transplantation. The second change occurs \(\sim 24\) mo after transplantation and involves the transformation of the slow rise in HR to a fast rise.

The lack of HR response in the HT patients of group 1 indicates that the CP does not evoke any reflex control, either neural or hormonal. Interestingly, the seemingly obvious explanation for the lack of HR response, i.e., the surgical denervation, is incomplete. It has been shown that double autonomic blockade does not eliminate the HR response to CP in normal subjects (14). Thus control mechanisms other than neural ones may play a role in HR regulation during a CP. The absence of HR response in patients of group 1 suggests that these HT patients lack all cardiac control reflexes, even the local ones. Another, less likely explanation for the lack of HR responsiveness could be that the SA node experiences some kind of temporary dysfunction, being unable to change its rhythm. However, the remnant HF fluctuations in the HR and the gradual decrease in HR observed during the initial stage of supine rest indicate that the SA node retains its ability to change its rhythm in response to an endogenous stimulus.

The resemblance between the pattern of HR response to CP in patients of group 2 and that of a charging capacitor indicates the presence of a first-order control loop.\(^1\) Sympathetic reinnervation to the

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\(^1\)A first-order control loop is defined as follows: \(HR(t) = A \left[ 1 - \exp\left( -\frac{t}{\tau} \right) \right] + B\).
SA node cannot explain this slow HR response, since this pattern of slow HR increase appeared in recordings performed 6 wk after transplantation. A possible explanation for the slow HR increase is as follows: the initial sudden drop in BP, induced by the CP, activates the baroreceptors, which, in turn, trigger sympathetic activity. The increased sympathetic activity stimulates the adrenal gland and increases the firing rate of the old SA node but has no effect on the SA node of the transplanted heart because of the denervation. The catecholamine spillover from the adrenal gland slowly increases the HR. The rate of HR increase declines as HR (and consequently BP) increases until BP returns to its original values. In parallel, those patients have been shown to develop increased sensitivity to catecholamines (17, 22, 34), thus further increasing the effect of the adrenal gland as a meaningful control mechanism.

The HR response in group 3 patients indicates the presence of a second, faster and more complicated control loop. This mechanism developed around TAT = 24 mo. Whereas the HR response in group 2 can be explained in terms of circulating catecholamines, the response in group 3 is too fast to be ascribed to the adrenal gland (14). Indeed, the steep rise in HR resembles that of healthy, innervated subjects. The resemblance of the HR response in group 3 to the normal HR response raised the conjecture that (partial) sympathetic reinnervation may have occurred in those patients (29). This hypothesis is supported by evidence of partial sympathetic reinnervation found in other studies. However, the fast HR increase (as fast as 8 s) cannot be explained by a sympathetic reinnervation. Indeed, atropine administration in normal subjects causes the HR to increase slowly with CP, peaking after 30 s (14). Therefore, our results in group 3 suggest that a mechanism other than sympathetic reinnervation is responsible for their fast HR increase. The hypothesis of increased sensitivity of cardiac β2-receptors, which may explain the slow HR increase of group 2, cannot justify the speed of the HR response in group 3. From the point of view of the end organ, increased sensitivity of the receptors is equivalent to stronger stimulation. A stronger stimulation triggers a reaction that is stronger in amplitude, yet takes place on the same time scale.

Our explanation for the HR response to CP in those patients is discussed below in view of other results.

**Steady-State Analysis: Time Domain**

Increased HR and reduced HRV in all HT patients have been observed in the past and are explained by the lack of sympathetic and parasympathetic innervation to the SA node (5, 13, 19, 29, 30). In our HT patients, mean HR did not change consistently as a function of TAT or between the groups.

The gradual decrease in HR observed during supine rest in some of the HT patients is closely related to the development of a fast control mechanism. In HT patients who lack a fast HR control (groups 1 and 2), a slow mechanism seems to gradually reduce HR in response to lying down. On the other hand, patients with fast control mechanisms (group 3) and normal subjects did not exhibit such a gradual decrease. This fast control must have induced a fast HR decrease in response to lying down or shortly after assuming a supine position. Our recordings began after 10 min of supine rest, well after this initial fast HR decrease. We therefore observe the gradual HR reduction only in groups 1 and 2. It is important to note that the reduction in HR is a normal response to lying down, as expected considering the reduced activity. The gradual decrease exhibited by patients in groups 1 and 2 discloses the existence of functional HR control mechanisms, albeit very slow ones.

**Steady-State Analysis: Spectral Analysis**

The mere existence of an LF peak and a respiratory peak in HR and BP spectra was first believed to be a sign of reinnervation (15, 33). However, Bernardi et al. (5) proved the existence of a mechanical coupling between respiration and the heart, in addition to the well-known neural one. This coupling is almost negligible in normal subjects, yet it explains the presence of the respiratory peak in the power spectra of HR and BP fluctuations in HT patients (5). An increase in HF fluctuations has been reported (36) in relation to TAT and was attributed to vagal reinnervation. However, in the present study, we did not find any relation between HF and TAT or between the HF and HR response to CP. Our finding, negating such reinnervation, is in accordance with Bernardi et al. (6), in which vagal reinnervation is also denied.

On the other hand, LF fluctuations of HR have been associated with sympathetic reinnervation in several studies (6, 7, 21). In HT patients soon after surgery, where reinnervation is still unlikely, the low-amplitude LF fluctuations in HRV can be explained by a mechanism similar to the one that causes the HF component. The oscillating component of the peripheral resistance probably leads to LF fluctuations in BP, which are then mechanically imposed onto the atrium and the SA node. LF fluctuations thus have a weak, nonneural source apparent soon after transplant, as well as a more dominant neural source, which develops later. In HT patients of group 1, the LF fluctuations are ascribed to the nonneural source; in the other HT patients and in normal subjects, both sources for those fluctuations contribute. In our study, increased LF variability in HRV was clearly associated with an improved HR response to CP. This correlation between LF fluctuations and HR responsiveness is indicative of partial sympathetic reinnervation. The tendency of the normalized HRV parameters [LF/(LF + HF), LF/Total, and HF/Total] to converge toward normal levels with TAT is highly significant. However, this result is difficult to interpret within the framework of this study.

It is important to note that spectral analysis of cardiovascular parameters in HT patients does not yield knowledge regarding their autonomic activity, as op-
posed to the normal system. Rather, it serves as a powerful tool for characterization of the control mechanisms. The dissociation between the spectral information and autonomic activity stems from the dominance of mechanical coupling between HR and respiration and compromised innervation: both challenge the paradigm of HRV and BP variability.

The existence of considerable VHF peaks in the power spectra of HR and BP is remarkable. To our knowledge, this phenomenon, although previously reported (4, 7), has not been thoroughly examined. A detailed analysis of the VHF peaks in this group of patients is presented elsewhere (35). The hypothesis raised in Ref. 35 is that the existence of the VHF peaks is a marker of vagal denervation; it will be described here only briefly. The frequencies of the VHF peaks, which are apparent in the power spectra of HR and BP, seem to occur at multiples of the respiratory frequency and are therefore assumed to be harmonics of the basic respiratory frequency. Spectral analysis of the respiration signal of HT patients did not reveal any significant peaks at frequencies above the respiratory rate. The lack of VHF peaks in the respiration signal rules out linear coupling between respiration and HR or BP as the cause for the VHF peaks in the HR and BP. The VHF peaks are, in this case, essentially different from the harmonics of respiration observed in cases of mechanical ventilation (26). In the latter case, respiration is clearly nonsinusoidal: VHF peaks occur in the respiration signal and are reflected as VHF peaks in the spectra of HR and BP as a result of the mechanical coupling between respiration and HR (26), as does the HF peak (32). It is known that the existence of harmonics of the basic frequency in a control system implies nonlinear coupling in the system (9). Hence, the VHF peaks, assumed to be harmonics of the respiratory rate, must originate from nonlinear coupling between the respiratory system and the heart (35). Indeed, nonlinearities are not uncommon in physiological systems. If the coupling between the respiration and the heart is nonlinear and tends to generate higher harmonics, which we see as VHF peaks, why do we not see those VHF peaks in normal subjects?

We believe that the answer to this question lies in the type of feedback in the control loop. It is known that negative feedback reduces the sensitivity of a system to variations in its parameters: changes in the parameters of the system are not reflected in the output of the system. Specifically, negative feedback reduces the effect of nonlinearities caused by the dependence of the system parameters on the signals and, consequently, reduces higher harmonics in the controlled system (9). This property is one of the reasons for the prevalence of negative-feedback loops in man-made, as well as in natural, control systems. In normal subjects, the fast feedback on HR includes vagal innervation and its related reflexes; normal subjects do not exhibit higher harmonics of the respiratory frequency. The prevalence of VHF peaks in the BP and HR spectra of HT patients of all subgroups is exceptional. This indicates that HT patients lack the fast feedback required to attenuate the harmonics of respiration. It seems that the fast control mechanism developed in some HT patients, capable of generating a fast HR response to CP, is insufficient to linearize the cardiovascular system. The existence of higher harmonics, reflecting the absence of a fast feedback, suggests that vagal innervation is absent and, therefore, cannot account for the fast HR increase in group 3 patients. It is also possible that in normal subjects the VHF peaks in the HR and BP exist but are masked by HF noise of the HRV and BP signal. This assumption is in agreement with our hypothesis concerning the correlation between the VHF peaks and the lack of vagal innervation, since the noise, which presumably masks the VHF peaks in normal subjects and must originate from noisy vagal innervation, is absent in the case of HT patients.

It is important to note that the hypothesis presented here is based on the assumption that the VHF peaks are harmonics of the respiratory frequency. Another, even more exciting possibility is that the VHF peaks are not related to respiration and are caused by a different, unknown mechanism.

Integration of the Results

The HT patients of group 1 have no substantial control over their HR. The main, and perhaps only, cardiovascular control mechanism in those patients is vasomotor control. The transition from group 1 to group 2 is characterized by the emergence of a slow HR increase with CP, indicating the development of a slow, first-order control loop. This transition 6 wk after transplant can be explained by the enhanced sensitivity of cardiac β2-receptors, which has been observed in HT patients (20, 34).

The picture displayed by the HT patients of group 3 is much more complicated. This fast HR response to CP, which is quite similar to the normal HR response, indicates the presence of fast and high-order control mechanisms. In considering the possible mechanisms of response, one must take into account the effect of the partial sympathetic reinnervation, which has occurred in those subjects, as indicated by the relatively elevated LF peak in the HR spectrum. However, the sympathetic system is too slow to account for the fast HR response. On the other hand, vagal reinnervation, which might eventually explain the fast HR increase, has been convincingly shown to be rare by Bernardi et al. (6). This conclusion is also supported by the lack of correlation between the level of HF power and the type of HR response to CP between the level of HF and TAT as well as by the presence of VHF peaks in the spectrum of HR and BP.

We suggest another mechanism for the fast HR response to CP in HT patients. As time after surgery progresses, the suture line between the old and new right atria becomes increasingly conductive. Indeed, conduction over the suture line has been observed in cases of mechanical ventilation (26). In the latter case, respiration is clearly nonsinusoidal: VHF peaks occur in the respiration signal and are reflected as VHF peaks in the spectra of HR and BP as a result of the mechanical coupling between respiration and HR (26), as does the HF peak (32). It is known that the existence of harmonics of the basic frequency in a control system implies nonlinear coupling in the system (9). Hence, the VHF peaks, assumed to be harmonics of the respiratory rate, must originate from nonlinear coupling between the respiratory system and the heart (35). Indeed, nonlinearities are not uncommon in physiological systems. If the coupling between the respiration and the heart is nonlinear and tends to generate higher harmonics, which we see as VHF peaks, why do we not see those VHF peaks in normal subjects?

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The picture displayed by the HT patients of group 3 is much more complicated. This fast HR response to CP, which is quite similar to the normal HR response, indicates the presence of fast and high-order control mechanisms. In considering the possible mechanisms of response, one must take into account the effect of the partial sympathetic reinnervation, which has occurred in those subjects, as indicated by the relatively elevated LF peak in the HR spectrum. However, the sympathetic system is too slow to account for the fast HR response. On the other hand, vagal reinnervation, which might eventually explain the fast HR increase, has been convincingly shown to be rare by Bernardi et al. (6). This conclusion is also supported by the lack of correlation between the level of HF power and the type of HR response to CP between the level of HF and TAT as well as by the presence of VHF peaks in the spectrum of HR and BP.

We suggest another mechanism for the fast HR response to CP in HT patients. As time after surgery progresses, the suture line between the old and new right atria becomes increasingly conductive. Indeed, conduction over the suture line has been observed in cases of mechanical ventilation (26). In the latter case, respiration is clearly nonsinusoidal: VHF peaks occur in the respiration signal and are reflected as VHF peaks in the spectra of HR and BP as a result of the mechanical coupling between respiration and HR (26), as does the HF peak (32). It is known that the existence of harmonics of the basic frequency in a control system implies nonlinear coupling in the system (9). Hence, the VHF peaks, assumed to be harmonics of the respiratory rate, must originate from nonlinear coupling between the respiratory system and the heart (35). Indeed, nonlinearities are not uncommon in physiological systems. If the coupling between the respiration and the heart is nonlinear and tends to generate higher harmonics, which we see as VHF peaks, why do we not see those VHF peaks in normal subjects?

We believe that the answer to this question lies in the type of feedback in the control loop. It is known that negative feedback reduces the sensitivity of a system to variations in its parameters: changes in the parameters of the system are not reflected in the output of the system. Specifically, negative feedback reduces the effect of nonlinearities caused by the dependence of the system parameters on the signals and, consequently, reduces higher harmonics in the controlled system (9). This property is one of the reasons for the prevalence of negative-feedback loops in man-made, as well as in natural, control systems. In normal subjects, the fast feedback on HR includes vagal innervation and its related reflexes; normal subjects do not exhibit higher harmonics of the respiratory frequency. The prevalence of VHF peaks in the BP and HR spectra of HT patients of all subgroups is exceptional. This indicates that HT patients lack the fast feedback required to attenuate the harmonics of respiration. It seems that the fast control mechanism developed in some HT patients, capable of generating a fast HR response to CP, is insufficient to linearize the cardiovascular system. The existence of higher harmonics, reflecting the absence of a fast feedback, suggests that vagal innervation is absent and, therefore, cannot account for the fast HR increase in group 3 patients. It is also possible that in normal subjects the VHF peaks in the HR and BP exist but are masked by HF noise of the HRV and BP signal. This assumption is in agreement with our hypothesis concerning the correlation between the VHF peaks and the lack of vagal innervation, since the noise, which presumably masks the VHF peaks in normal subjects and must originate from noisy vagal innervation, is absent in the case of HT patients.

It is important to note that the hypothesis presented here is based on the assumption that the VHF peaks are harmonics of the respiratory frequency. Another, even more exciting possibility is that the VHF peaks are not related to respiration and are caused by a different, unknown mechanism.
although only a few cases have been reported (23). The electrophysiological test needed to confirm this conduction is performed only when clinical symptoms require medical intervention. Therefore, patients who may exhibit this conduction over the suture line but do not display clinical symptoms might be overlooked. This conjecture is supported by our finding that arrhythmias, mostly of atrial origin, tend to appear in HT patients with TAT that corresponds to the transitional stage between group 2 and group 3 and not in earlier or later TAT. Those arrhythmias, although not malignant, should not be ignored, since they indicate the existence of dynamics in the cardiac conduction system. This alteration in conduction path may lead eventually to conduction of electrical signal between the original and transplanted atria and, consequently, to changes in the effective pacemaker location. It is also possible that, because of improved conductiveness, the original and transplanted atria and, consequently, to eventual to conduction of electrical signal between the old SA node may affect the intrinsic rhythm of the new SA node by “phase-response curve” (PRC) effects, and not by assuming full control of the new SA node by sympathetic reinnervation of the transplanted SA node, namely, by affecting their rate of cell firing, depending on the relative phase within their intrinsic cycle. In the present case, PRC expresses the effect of the transplanted SA node, thereby being the transplanted SA node, namely, by affecting their rate of cell firing, depending on the relative phase within their intrinsic cycle. In the present case, PRC expresses the effect of the transplanted SA node, namely, by affecting their rate of cell firing, depending on the relative phase within their intrinsic cycle.

The combination of a steady state and transition in the experimental protocol and of frequency and time domain approaches in the signal analysis provides a comprehensive phenomenological description of cardiovascular control in HT patients. This description discloses the nature of control mechanisms that evolve after cardiac transplantation. As a function of TAT, we observe a biphasic evolution of cardiac rate control: from lack of HR responsiveness to a slow and simple control mechanism, followed by a transition to a fast control mechanism, which resembles the normal one in terms of response time. The slow control mechanism probably involves sympathetic control mediated by the adrenal gland combined with enhanced sympathetic receptor sensitivity. This is followed gradually by partial sympathetic reinnervation of the transplanted SA node. We hypothesize that the fast control mechanism is a manifestation of conduction-over-the-suture-line effects of the old SA node on the new one, leading to fast HR changes. Our results do not support the incidence of vagal reinnervation.

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REFERENCES


