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Closed-loop identification of hemodynamic control systems

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CLOSED-LOOP IDENTIFICATION OF HEMODYNAMIC CONTROL SYSTEMS

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by

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May 1983

Signature of Author _____

May 23, 1983

Accepted by _____

Prof. Franz B. Tuteur

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Abstract

The dynamic interactions between heart rate and blood pressure are studied, under normal physiological conditions, using new methods to extract information from noisy feedback-control systems. Given only measurements of spontaneously fluctuating heart rate and blood pressure and no interventions, the effect of spontaneous changes in blood pressure on heart rate (which are mediated primarily by the arterial baroreflexes) are separated from the effect of spontaneous changes in heart rate on blood pressure (which are mediated primarily by the mechanical properties of the left ventricle and the arterial system). Finite impulse response and rational transfer function models for the arterial baroreflex and for the combined mechanical properties of the left ventricle and arterial tree are identified in closed-loop in the conscious dog during normal sinus rhythm and in the anesthetized dog during electrically-induced atrial fibrillation. In normal sinus rhythm, an impulse response model for the baroreflex is identified which has a negative gain and a dominant time constant of approximately one second. Heart rate fluctuations during normal sinus rhythm, however, are not sufficiently rich at frequencies less than 0.5 hertz to identify a similar impulse response describing the effect of perturbations in heart rate on blood pressure. Nevertheless, electrically-induced atrial fibrillation enriches the variability of heart rate and blood pressure below 0.5 hertz such that causal, rational transfer functions may be identified in closed-loop in each of the two directions between heart rate and blood pressure. During atrial fibrillation the linear effects of fluctuations in heart rate on blood pressure are identified as a system with a positive gain, a corner frequency of approximately 0.1 hertz, and a time constant of approximately 1.6 seconds. This system may provide a minimally-invasive estimate of the combined properties of the input impedance of the aorta and the mechanical properties of the left ventricle. The effect of fluctuations in blood pressure on ventricular rate in atrial fibrillation is identified as a system with a negative gain, a corner frequency of approximately .25 to .3 hertz, and a time constant of approximately 0.6 seconds. This result is consistent with the impulse response model identified for the baroreflex during normal sinus rhythm and suggests that the arterial baroreflex modulates AV nodal conduction during atrial fibrillation for blood pressure changes that are slower than about 0.3 hertz. These investigations suggest that the mutual effects of two fluctuating hemodynamic variables on each other may be separately identified if appropriate closed-loop, stochastic identification methods are employed. These methods require no experimental interventions, and thus may provide new noninvasive methods to study hemodynamic control systems, with simple measurements of fluctuating hemodynamic variables, in a variety of clinical settings.

Table of Contents

List of Figures

Chapter 1

INTRODUCTION

Heart rate, blood pressure, and respiration have long been known to fluctuate on a beat-to-beat and breath-to-breath basis [3]. In 1733, Stephen Hales documented this variability in hemodynamic parameters with the first quantitative measurements of arterial blood pressure [41, 3]. He noted a correlation between interbeat interval, blood pressure, and the respiratory cycle [41, 3]. Figure 1-1 illustrates this beat-to-beat variability (from top to bottom) in recordings of atrial electrogram, breathing movement, and arterial pressure in a healthy conscious dog. This correlation of interbeat interval with the respiratory cycle is often considered a sign of health. It may be absent in congestive heart failure or absent in fetal distress during labor. The correlation of blood pressure with the respiratory cycle, when there is a marked decrease in arterial pressure with each breath, is known as pulsus paradoxus and has long been recognized as an important clinical sign which may indicate cardiac tamponade.

In addition to the periodic fluctuations of instantaneous heart rate and arterial blood pressure that correlate with the respiratory cycle, there are well known periodic fluctuations that are slower than respiration. They were first documented in arterial blood pressure soon after the introduction of the recording manometer in the mid 19th century by L. Traube [84], E. Hering [42], E. Cion [19], and S. Mayer [61] (see Figures 1-2 and 1-3). They were documented later in heart rate by

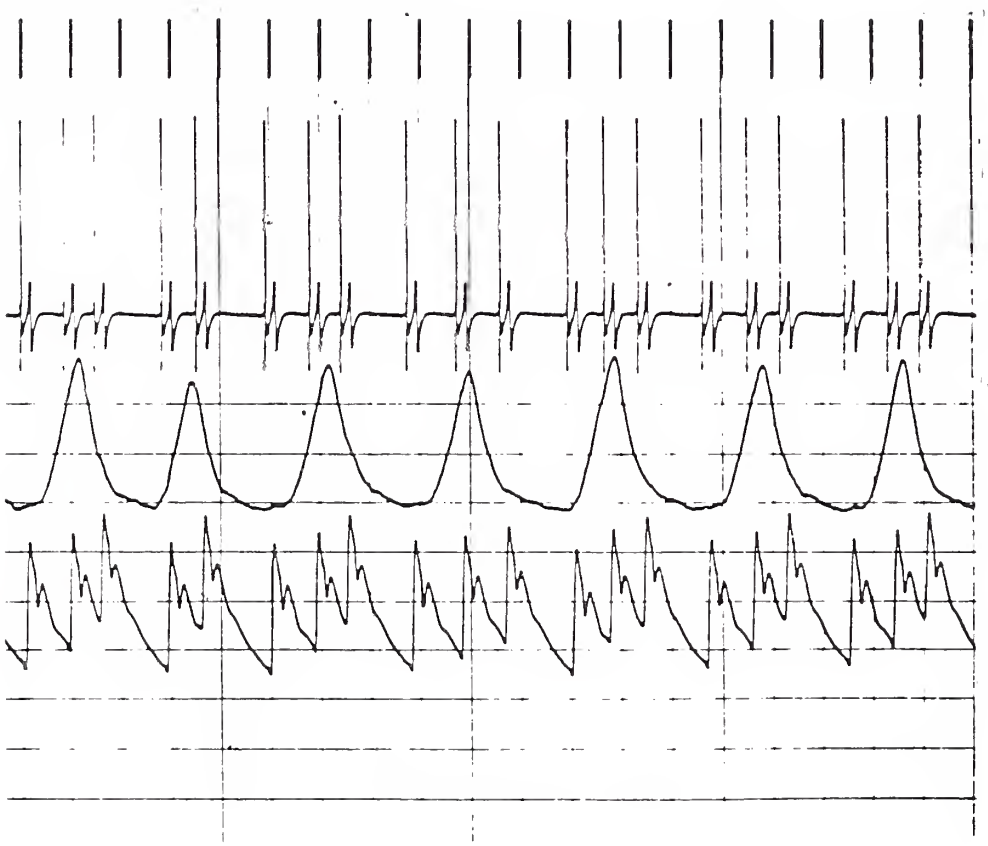

Figure 1-1: Periodic Fluctuations in Atrial Electrogram (top), Respiration (middle), and Systemic Arterial Blood Pressure (bottom) in a conscious, healthy dog.

Frederick in 1882 [27] and Fleisch in 1932 [26] (see Figure 1-4), in systemic venous pressure by Golwitzer in 1929 [34] and also in arterial blood flow by Golenhofen in 1957 [33] and Kenner in 1972 [53].

Fluctuations in individual hemodynamic parameters have since been studied extensively by many investigators [3, 50, 67, 75, 45, 54, 71] and a number of theories exist to explain their origin, yet there have been few efforts to mathematically characterize interactions between two or more fluctuating cardiovascular signals. Since heart rate and blood

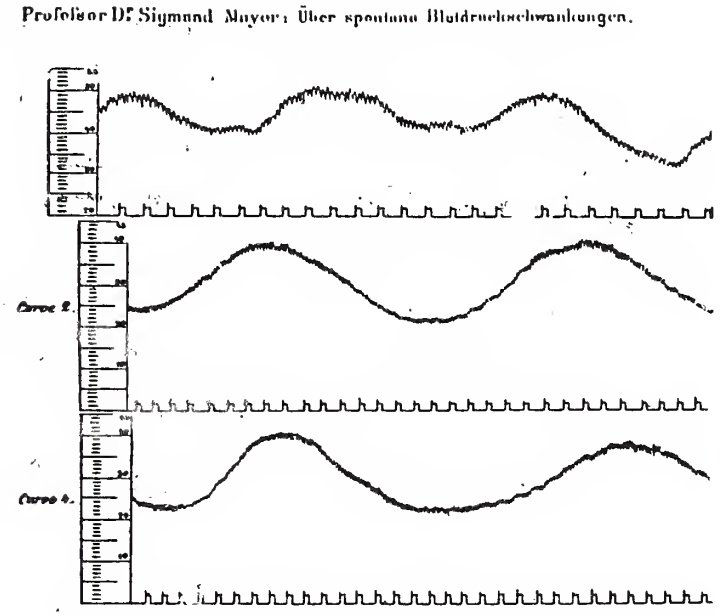

Figure 1-2: Mayer Waves in Arterial Blood Pressure [61]

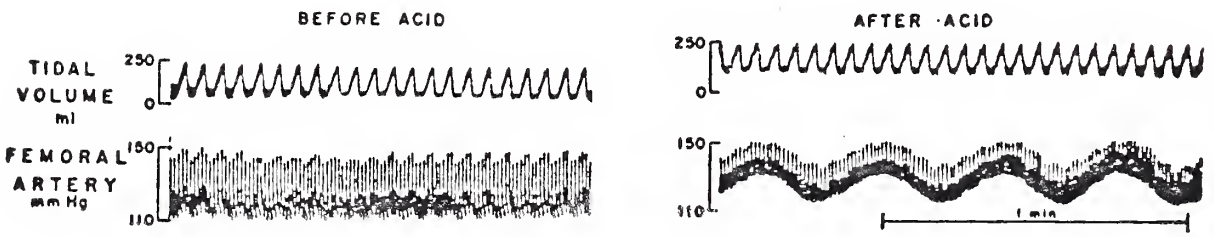

FIG. 2. Appearance of Mayer waves following iv administration of 0.3 M HCl.

Figure 1-3: Mayer Waves Induced by Acidosis [24]

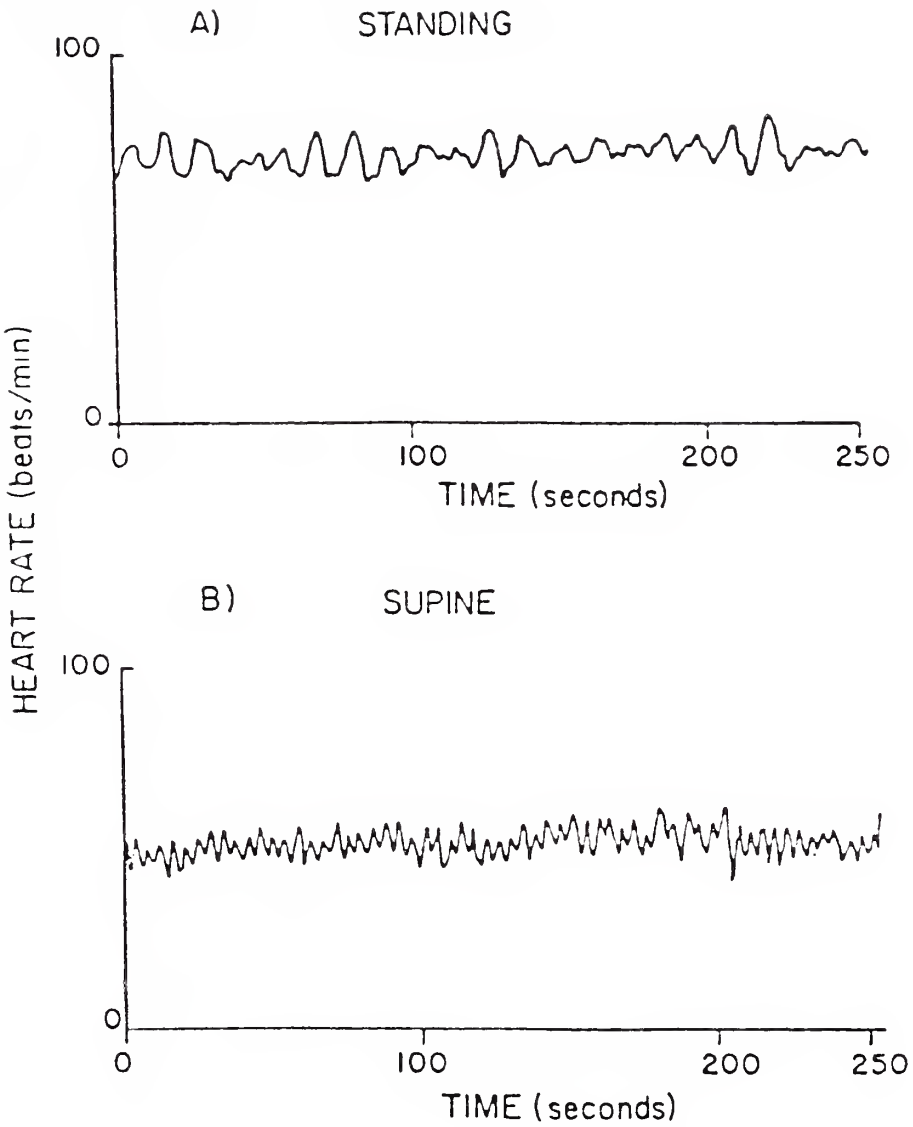

Figure 1-4: Slow Waves in Heart Rate Induced by Standing (a), (compare with sitting (b)) [67]

pressure both spontaneously exhibit similar fluctuations and therefore continuously perturb the mechanisms that act to control them, characterization of interactions between these two fluctuating signals may reveal information about the hemodynamic mechanisms that regulate them under normal physiological conditions.

This study attempts to characterize interactions between fluctuations in heart rate and blood pressure during normal sinus rhythm and during electrically-induced atrial fibrillation.

Since the mechanisms by which perturbations in heart rate affect blood pressure (i.e. ventricular and arterial mechanics) are physically distinct from the control reflexes by which perturbations in blood pressure modulate heart rate (i.e. arterial baroreceptors), we must employ methods that will be able to separate the directional effects between these two variables. Such methods are those that are required to identify the parameters of a system that is operating in closed-loop (i.e. with feedback control). These methods are reviewed in [40] and also in a longer version of this thesis submitted as a doctoral thesis in electrical engineering [52]. Methods based on Fourier spectra, as used, for example, in [94, 64, 25] to study interactions between heart rate, blood pressure, and respiration, are inherently limited in their ability to separate directional interactions, for they violate a fundamental condition for the identifiability of a closed-loop system. By identifying transfer functions directly in the frequency domain, they confuse the effects of future and the past events. We will use time-domain methods to identify strictly-causal, parametric models that inherently avoid confusion about the direction of time and therefore prevent confusion about directional effects between signals.

This thesis will examine the feasibility and limitations of employing closed-loop identification[1] to study how heart rate and blood pressure interact as they fluctuate spontaneously under normal physiological conditions. Advantages of these methods are that they

1. rely on minimally-invasive measurements of heart rate and blood pressure,
2. require no exogenous test signals to excite the control systems under study since they rely on small, spontaneous hemodynamic perturbations,
3. do not require the interruption of any feedback paths, and yet they are able to estimate the behavior of the system as if there were no feedback.

Disadvantages are that

1. only partial information may be obtained about a control reflex if it is only partially stimulated by spontaneous physiological perturbations,
2. some conditions for the identifiability of closed-loop systems have to be assumed and are not checkable.

These methods have been used successfully in industrial and aerospace applications [65, 63, 20] but rarely in medicine [83]. Thus, in an effort to both demonstrate their applicability to medical problems and to outline their limitations, this study will attempt to separately identify, during both normal sinus rhythm and atrial fibrillation, linear, discrete-time, models for

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[1]Systems identification may be defined as follows. Given a physical system and a class of models for that system, identification is the process by which a particular model within that class is chosen such that it best describes the physical system with respect to a criterion. Identification is performed in closed-loop when the open-loop characteristics of a system are estimated using measurements that were obtained while the system was operating in closed-loop.

1. the effect of fluctuations in heart rate on blood pressure, which may contain information about both ventricular and arterial dynamics, and

2. the effect of fluctuations in blood pressure on heart rate, which may contain information about the arterial baroreflex.

Chapter 2

METHODS

2.1 Experiments

Recordings of electrocardiogram (ECG), arterial blood pressure, central venous pressure, and respiration in conscious, unanesthetized dogs, with chronically implanted arterial and venous catheters and atrial epicardial electrodes, were recorded continuously on FM magnetic tape while the dog rested quietly. Stationary segments of steady-state data at least 5 minutes long were recorded at the beginning of each experiment and during the administration of one or more of the following drugs: propranolol (a beta-sympathetic blocker), glycopyrrolate (a peripheral parasympathetic blocker), phentolamine (an alpha-sympathetic blocker), and angiotensin converting enzyme inhibitor (a blocker of the renin-angiotensin system). Experiments were also performed with atrial pacing. Only the baseline data with no interventions will be discussed in this preliminary report.

Additional experiments were performed[2] with anesthetized dogs, where atrial fibrillation was induced by electrical stimulation of the right atrium via epicardial electrodes. Electrocardiogram, femoral arterial pressure, and breathing movement by inductive plethysmography were recorded continuously on FM tape for episodes of at least five minutes.

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[2]by Ronald D. Berger

2.2 Data Preprocessing

Stationary, steady-state epochs of data (i. e. electrocardiogram, breathing movement, and arterial blood pressure) at least 5 minutes in length were sampled by an analogue-to-digital converter. The electrocardiogram was sampled at 360 hertz while arterial blood pressure and breathing movement were sampled at 4 hertz after passing through a four-pole anti-aliasing analogue filter. The electrocardiogram was analyzed by a pattern recognition routine implemented on a microprocessor which detects the time of occurrence of each R-wave [76]. A sequence of R-R intervals resulted. Four estimates of instantaneous heart rate per second were obtained by counting the number of heart beats within a 1/2 second window that is shifted over the sequence of R-R intervals. This sequence of instantaneous heart rate values, sampled at 4 hertz, was aligned in time with the band-limited measurements of arterial blood pressure and respiration which also were sampled at 4 hertz.

2.3 Numerical Methods

2.3.1 Autospectra and Coherence

The autospectra for instantaneous heart rate, arterial blood pressure, and respiration were estimated using a windowed periodogram method. Epochs of stationary data sampled at 4 hertz for 256 seconds were used to compute the spectra and coherences in the frequency band 0.02 to 2.0 hertz. Regions in this frequency band where the coherence between heart rate and blood pressure is high are the regions where the following estimates of transfer functions will be most reliable.

2.3.2 Closed-loop Identification

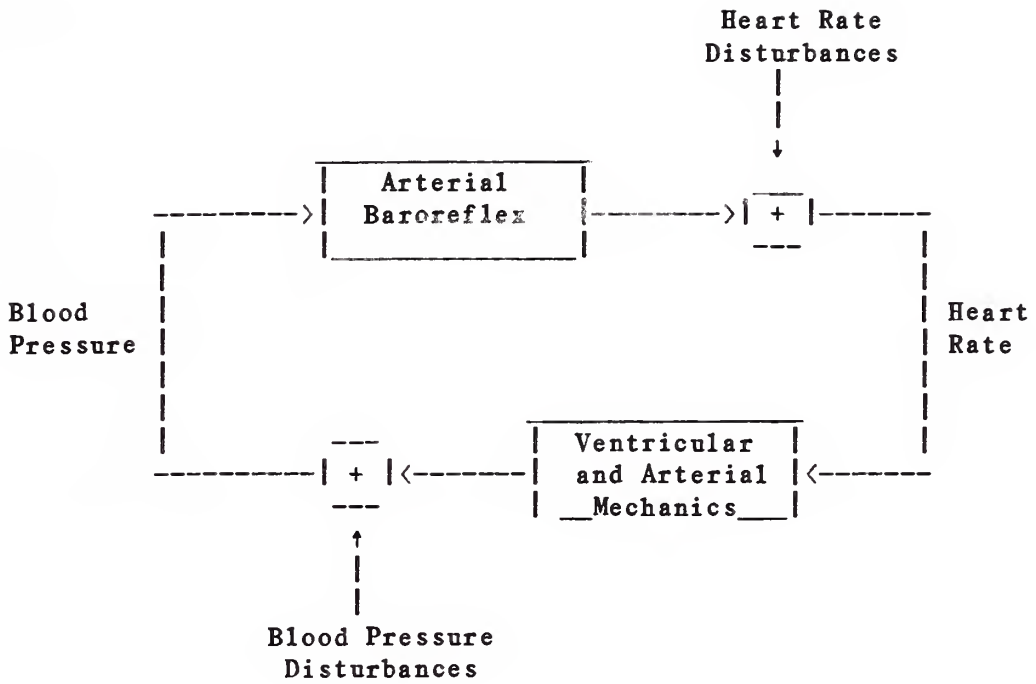

Figure 2-1: Symmetric Closed-Loop Model

Given measurements of spontaneously fluctuating heart rate and blood pressure, a symmetric closed-loop model, figure 2-1, in which the feedforward path represents the arterial baroreceptor reflex and the feedback path represents the mechanical properties of the left ventricle and the arterial tree was identified using five minute epochs of stationary data during normal sinus rhythm and during atrial fibrillation. The direct method of closed-loop identification [40, 52] was implemented using a prediction error algorithm to estimate the

parameters in the following coupled, linear[3], autoregressive-moving average models with exogenous known inputs and unknown colored noise, i.e. ARMAX(p,q,r) models of the following form:

$$A_1(z)\ Y(z) = B_1(z)\ X(z) + \frac{W_1(z)}{C_1(z)}$$

$$A_2(z)\ X(z) = B_2(z)\ Y(z) + \frac{W_2(z)}{C_2(z)}$$

where Y =(instantaneous heart rate - mean heart rate) and X =(arterial blood pressure - mean blood pressure). $A_1(z)$, $B_1(z)$, $C_1(z)$ and $A_2(z)$, $B_2(z)$, $C_2(z)$ are polynomials in z^{-1} of orders p_1, q_1, r_1 and p_2, q_2, r_2 respectively (i.e. $A_1(z) = \sum_{i=0}^{p_1} a_1(i)z^{-i}$) with $a_1(0)= a_2(0)= c_1(0)= c_2(0)=1$ and $b_1(0)= b_2(0)=0$. $W_1(z)$ and $W_2(z)$ are independent zero-mean white noise processes. Distinct feedforward and feedback transfer functions, B_1/A_1, and B_2/A_2, are directly identifiable from closed-loop data if

- the inputs to each path are independent of present and future values of the output disturbances in each path, and
- the output disturbances in each path are independent of each other.

These conditions are assumed by the above closed-loop model. Each path is identified separately from closed-loop data using a recursive generalized least squares estimator. The recursive estimator employs a UDU^t factorization of the parameter error covariance. The model orders

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[3]Since blood pressure and heart rate fluctuate only by small amounts about their steady state mean values, it may not be unreasonable to assume that the systems that respond to and generate these fluctuations operate within linear regimes in the neighborhood of an equilibrium point.

are estimated using a modified AIC information criterion derived in [52].

Two classes of models were identified

1. discrete-time, finite impulse response models, $B(z^{-i})$ for $i=1,2,\ldots,q$, corresponding to ARMAX(1,q,r) equations with all autoregressive coefficients set to zero except for a(0)=1. In this case for an impulse input (i.e. $x_i=1$ for i=0 and zero otherwise) the output, y_i, is the impulse response and equals the moving average coefficients, $y_i = b_i$.

2. discrete-time, rational transfer function models, $B(z^{-i})/A(z^{-j})$ for $i=1,2,\ldots,q$ and $j=0,1,\ldots,p$, corresponding to ARMAX(p,q,r) equations with p+1 nonzero autoregressive coefficients and q nonzero moving average coefficients. The roots of $A(z^{-i})$ are estimates of the poles and the roots of $B(z^{-i})$ are estimates of the zeros of the transfer function.

Chapter 3

CLOSED-LOOP IDENTIFICATION RESULTS

3.1 Normal Sinus Rhythm

Figure 3-1 shows typical time series and spectra for instantaneous heart rate, arterial blood pressure, and respiration that have been low-pass filtered such that they only contain frequencies below 2 hertz. Note that the spectra for heart rate and blood pressure primarily contain power in a narrow frequency band near the mean breathing rate, .35 hertz, in this example. In figure 3-2 the coherence between heart rate and blood pressure is highest between approximately 0.1 to 0.7 hertz. This is the frequency region where there is a high correlation between heart rate and blood pressure fluctuations. It is the best region in which to attempt to identify dynamic relationships between heart rate and blood pressure.

Spontaneously fluctuating heart rate and arterial blood pressure were used to identify a finite impulse response model for the arterial baroreflex in closed-loop in the conscious dog during normal sinus rhythm. Figure 3-3 shows the mean impulse response for the effect of small, spontaneous changes in blood pressure on heart rate. It was computed from 6 experiments in 4 dogs. Each impulse response was scaled such that the absolute value of the its minimum point was normalized to unity. This impulse response has a negative gain and a first-order time constant of approximately one second, suggesting that a step increase in

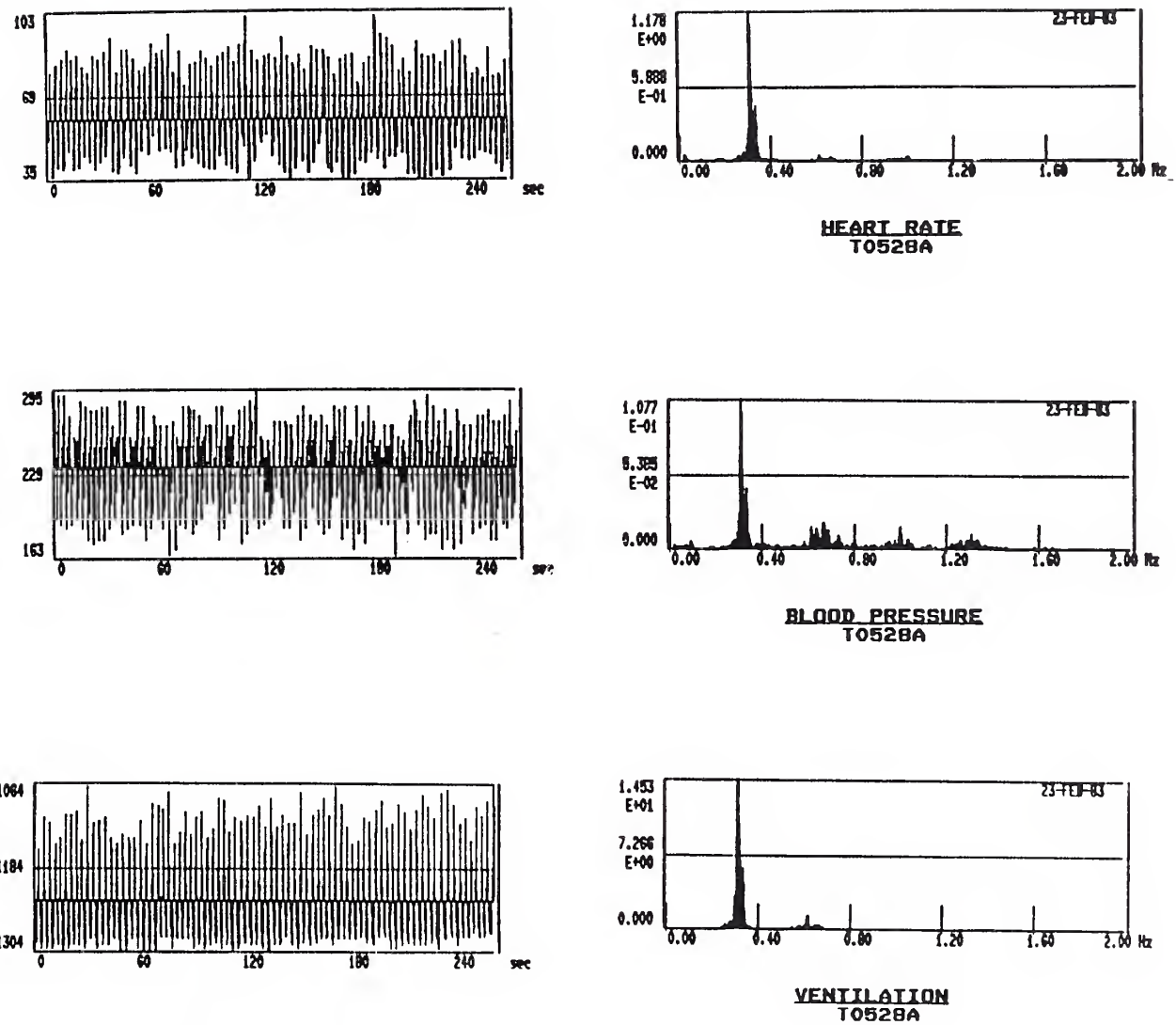

Figure 3-1: Typical Time Series and Spectra for Heart Rate (top), Blood Pressure (middle), and Respiration (bottom) During Normal Sinus Rhythm

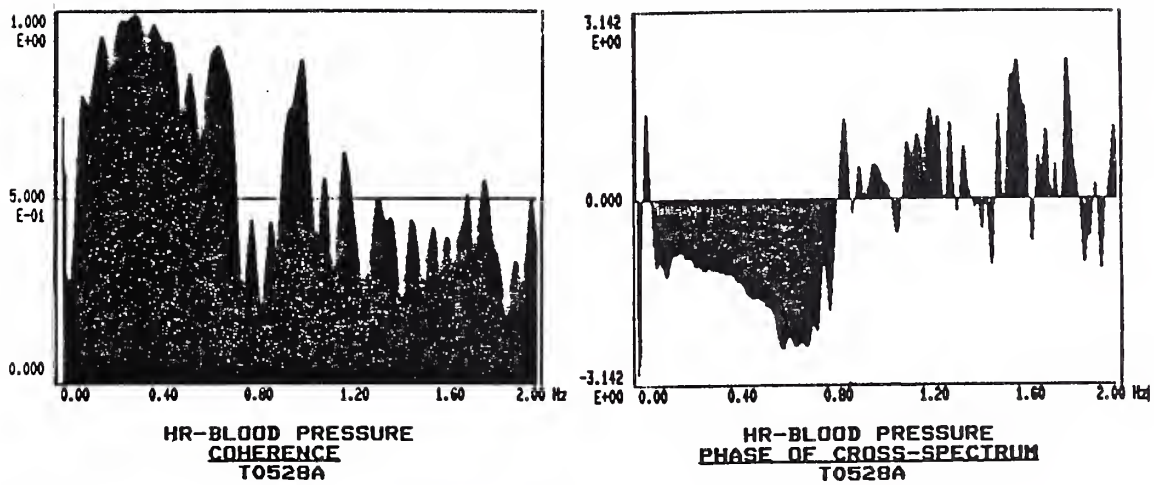

Figure 3-2: Typical Coherence and Phase between Heart Rate and Blood Pressure During Normal Sinus Rhythm

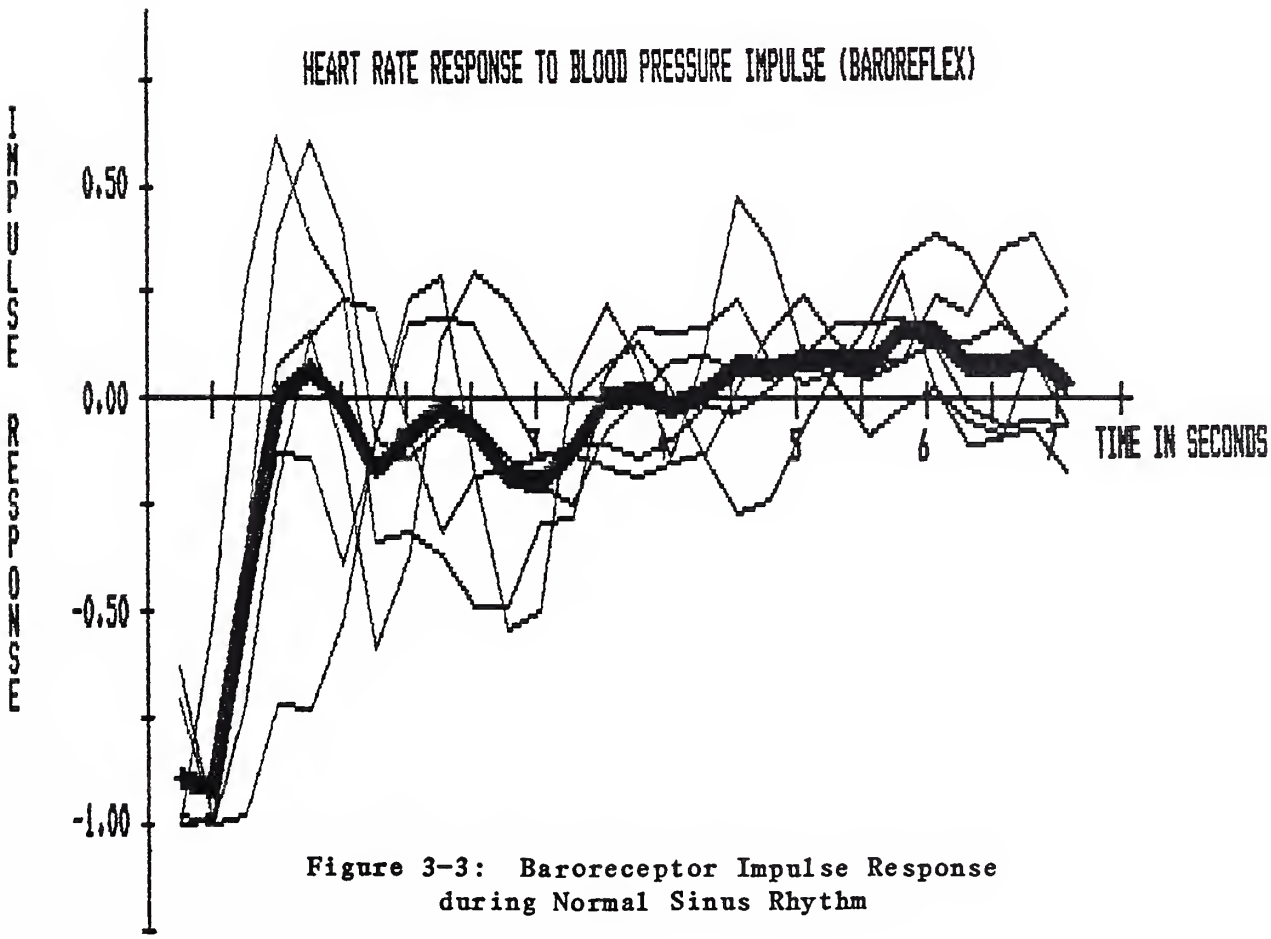

Figure 3-3: Baroreceptor Impulse Response during Normal Sinus Rhythm

blood pressure results in a bradycardia that exponentially approaches a lower mean heart rate with a time constant of one second. This result is consistent with the response of the arterial baroreflexes and will be discussed in section 4.1. The absolute gain of this response was not estimated in these experiments but may be computed subsequently using the blood pressure calibration signals that were recorded with each experiment.

During normal sinus rhythm, heart rate variability is not sufficiently rich[4] for frequencies less than 0.5 hertz to identify a similar relationship between heart rate fluctuations and blood pressure. Figures 3-4 and 3-5 display estimates of two different functions that characterize the effect of fluctuations in heart rate on blood pressure. They are the finite impulse response and transfer function, respectively. However, in this example, the energy of heart rate and blood pressure fluctuations is concentrated in a narrow frequency band (see figure 3-1), and thus little information may be obtained from these estimates. In figure 3-4 the impulse response demonstrates little more than a spurious oscillation about zero which may mask any information that might underlie it. Similarly the transfer function in figure 3-5 shows spurious peaks. These spurious peaks correspond to the spurious oscillations in the impulse response. They are artifacts that may occur when the heart rate signal's spectrum is close to zero in regions where the blood pressure

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[4]Sufficiently rich is a technical term which refers to a signal that has energy that is significantly greater than zero in the frequency band in which the system identification is being performed (see [52]).

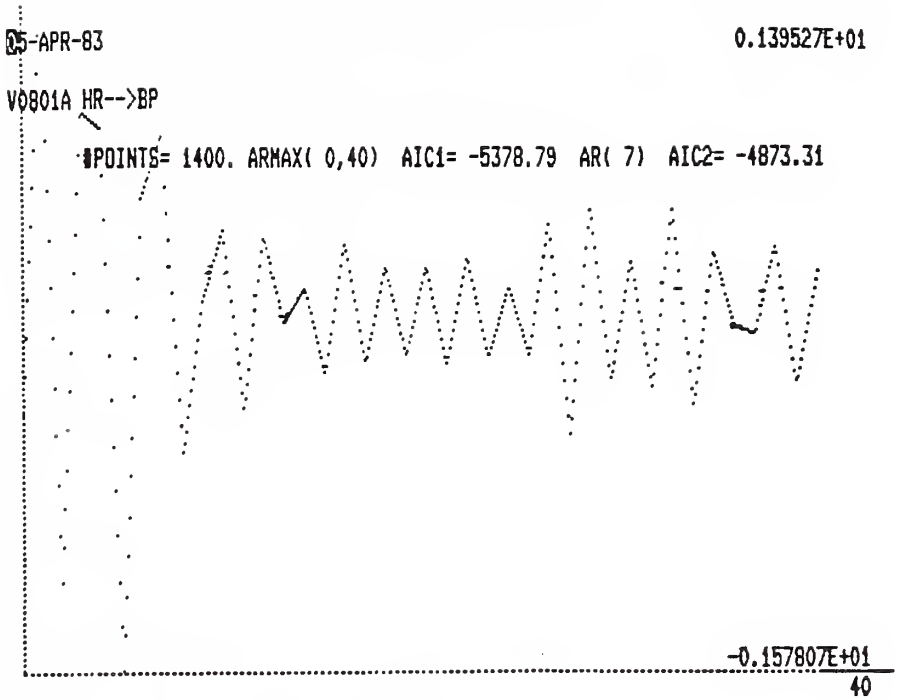

Figure 3-4: Impulse Response for the Effect of Fluctuations in Heart Rate on Blood Pressure During Normal Sinus Rhythm

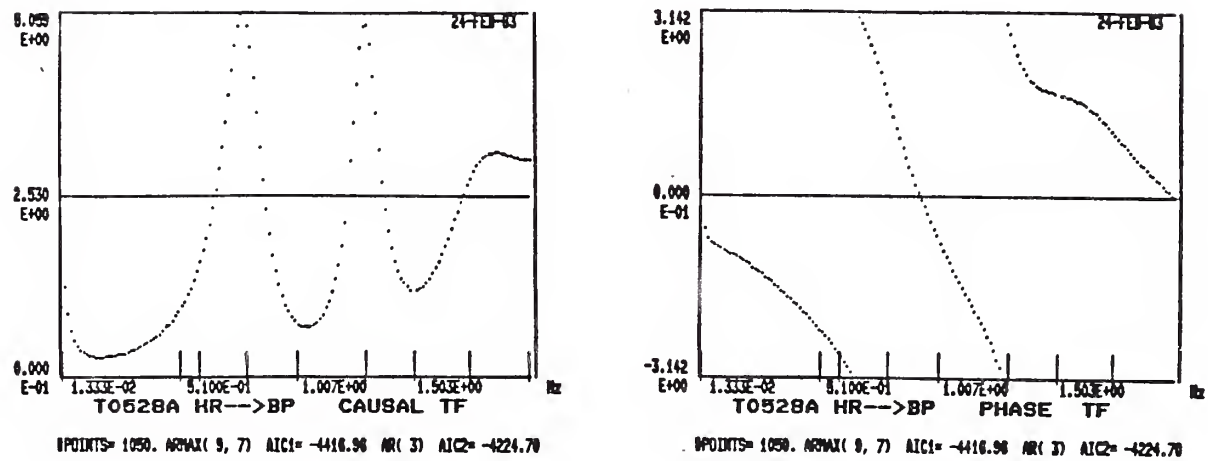

Figure 3-5: Transfer Function for the Effect of Fluctuations in Heart Rate on Blood Pressure During Normal Sinus Rhythm

signal's spectrum has peaks. This may occur when heart rate fluctuates only over a very limited frequency band and when the blood pressure signal has not been adequately prefiltered to remove its frequency-modulated components.[5] It may be possible to circumvent this problem during normal sinus rhythm by limiting the identification to a narrow frequency band and appropriately prefiltering both heart rate and blood pressure.[6] Another way to circumvent this problem is to enrich the fluctuations of heart rate such that they contain energy over a broader frequency band as occurs during atrial fibrillation.

Thus, during normal sinus rhythm, it was possible to identify an impulse response describing the effect of small, spontaneous changes in blood pressure on heart rate. However, it was not possible, with this set of data, to estimate a nonzero relationship in the opposite direction, i.e. relating small, spontaneous changes in heart rate to changes in blood pressure.

3.2 Atrial Fibrillation

Electrically-induced atrial fibrillation in the anesthetized dog enriches the variability of heart rate and blood pressure below 0.5 hertz such that causal, rational transfer functions may be identified in

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[5]The spectra of modulated cardiovascular signals are discussed in detail in [52].

[6]See [52] for a more complete discussion of partial identification with suboptimally rich signals.

closed-loop in each of the two directions between heart rate and blood pressure. Compare the spectra of heart rate and blood pressure during atrial fibrillation, figure 3-6, to those during normal sinus rhythm, figure 3-1. Note that during atrial fibrillation the signals have a broader bandwidth and tend to have more energy at frequencies below 0.5 hertz. Note also that the coherence between heart rate and blood pressure during atrial fibrillation is highest in this frequency band, figure 3-7.

During atrial fibrillation a transfer function is identified for the linear effects of slow fluctuations in heart rate on blood pressure (see figure 3-8). Estimates are quite similar for several experiments in two dogs, see figure 3-8. The frequency response of this transfer function rolls off rapidly with a corner frequency at approximately 0.1 hertz. This corner frequency corresponds to a time constant of approximately 1.6 seconds. The phase begins at zero in most examples and is consistent with a positive gain.[7] This transfer function may describe combined properties of the input impedance of the aorta and the mechanical properties of the left ventricle. It will be discussed in section 4.2.

During atrial fibrillation a transfer function is also identified

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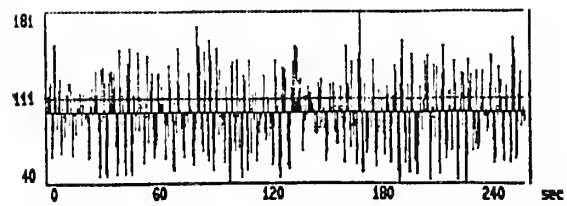
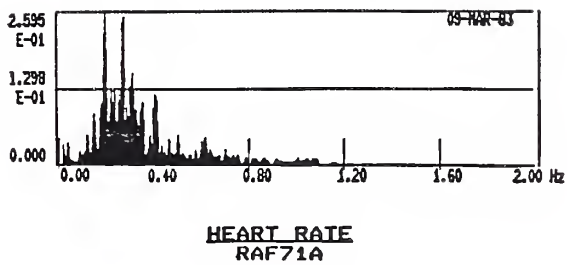
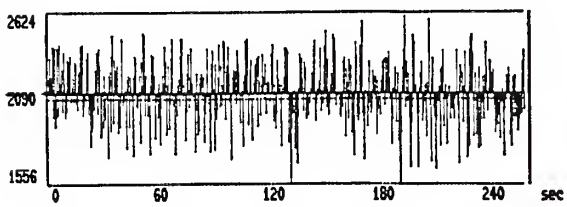
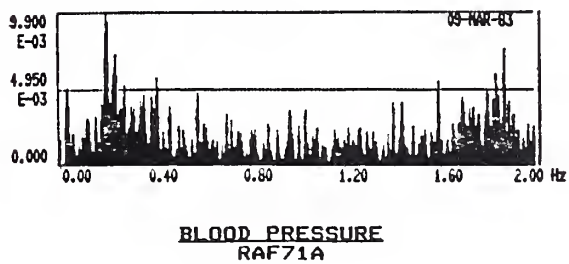
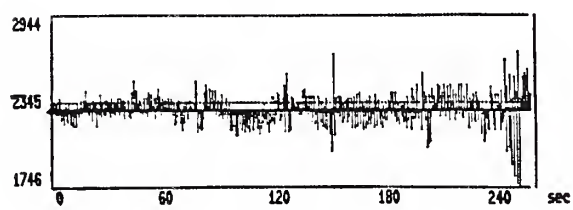
[7]Note that we have only examined these transfer functions for frequencies up to 0.5 hertz even though the ARMAX estimates actually compute them up to 2 hertz. Figure 3-10 demonstrates that there is a large artifact near 2 hertz that is due to the different filters used to preprocess heart rate and blood pressure. This artifact virtually precludes accurate estimates of finite impulse response models directly because in the time domain this artifact appears as a large oscillation that masks the low frequency effect that is visible in the frequency domain below 0.5 hertz.











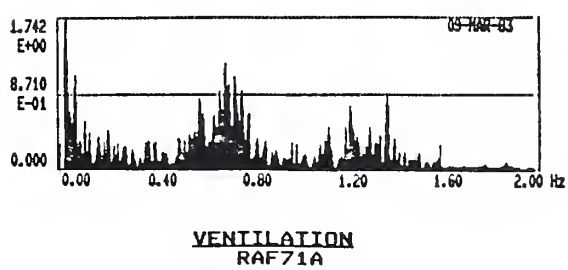


Figure 3-6: Typical Time Series and Spectra for Heart Rate (top), Blood Pressure (middle), and Respiration (bottom) During Atrial Fibrillation

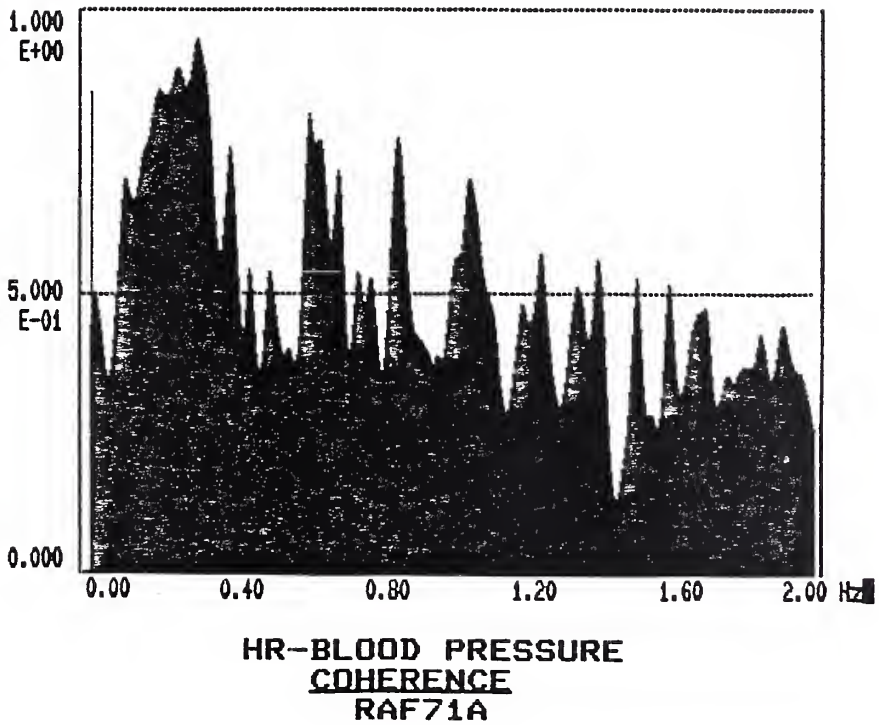


Figure 3-7: Coherence between Heart Rate and Blood Pressure During Atrial Fibrillation

which characterizes the effect of small, spontaneous changes in blood pressure on ventricular rate. Estimates again are quite similar for several experiments in two dogs, see figure 3-9. This transfer function rolls off at a higher frequency than the transfer function for the effect of heart rate on blood pressure. It has a corner frequency of about 0.25 to 0.3 hertz which corresponds to a time constant of about 0.6 seconds, figure 3-9. It's phase, in most examples, begins at π suggesting that the gain has a negative sign, figure 3-9. Both the negative gain and the time constant of approximately 0.6 seconds are consistent with the

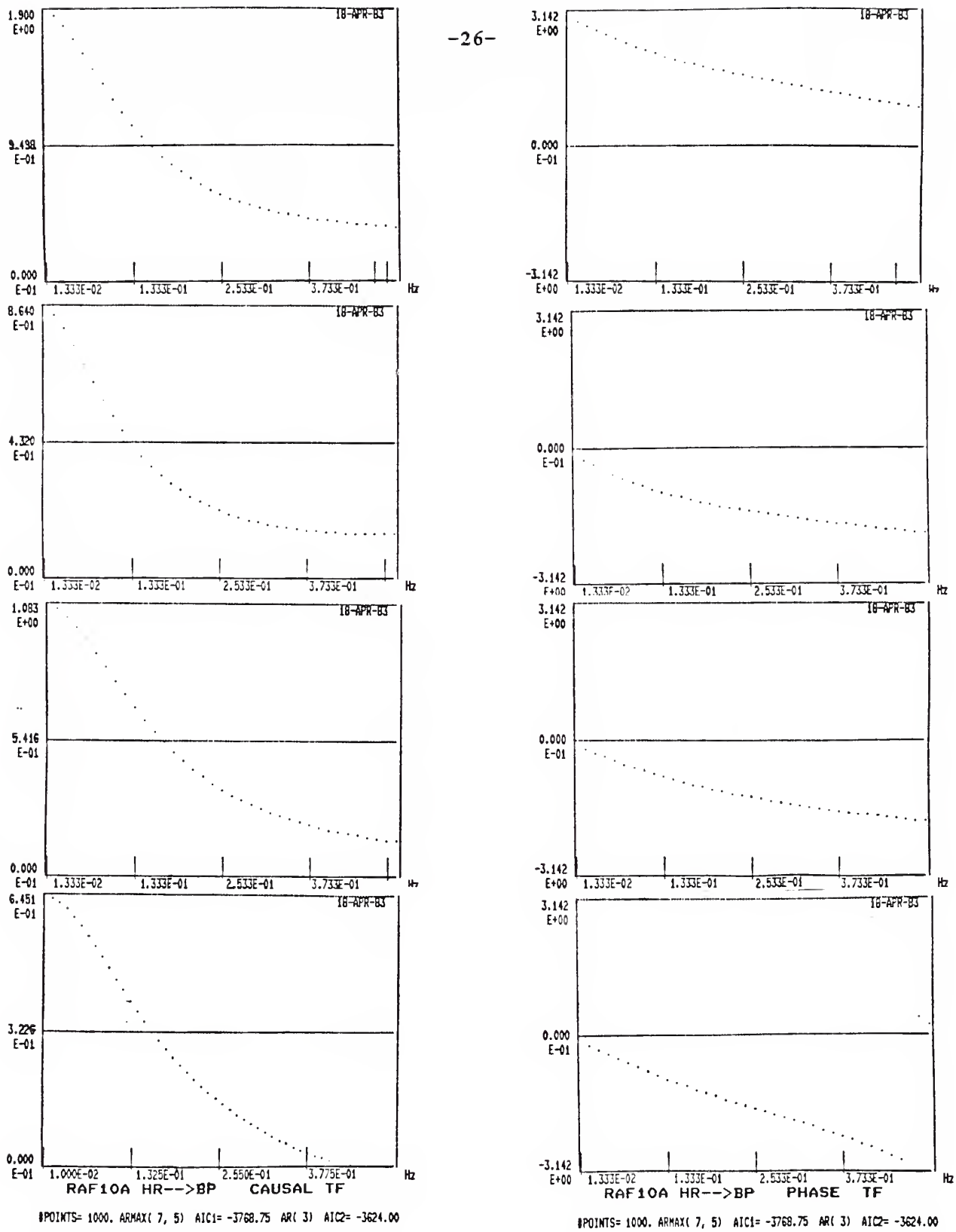
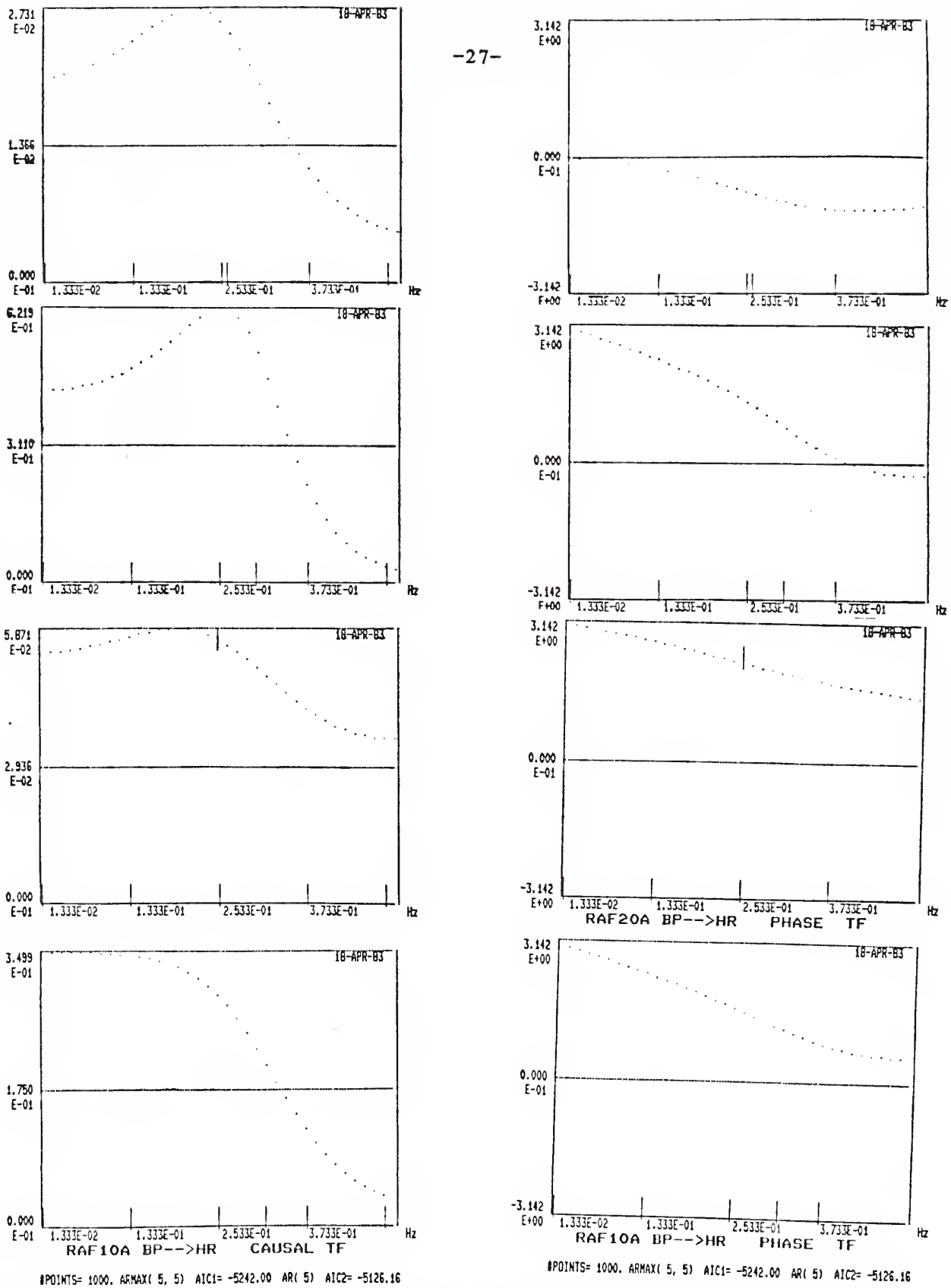


Figure 3-8: Transfer Function Estimates (amplitude and phase) for the Effect of Fluctuations in Heart Rate on Blood Pressure During Atrial Fibrillation



#POINTS= 1000. ARMAX(5, 5) AIC1= -5242.00 AR(5) AIC2= -5126.16

#POINTS= 1000. ARMAX(5, 5) AIC1= -5242.00 AR(5) AIC2= -5126.16

Figure 3-9: Transfer Function Estimates (amplitude and phase) for the Effect of Fluctuations in Blood Pressure on Ventricular Rate During Atrial Fibrillation

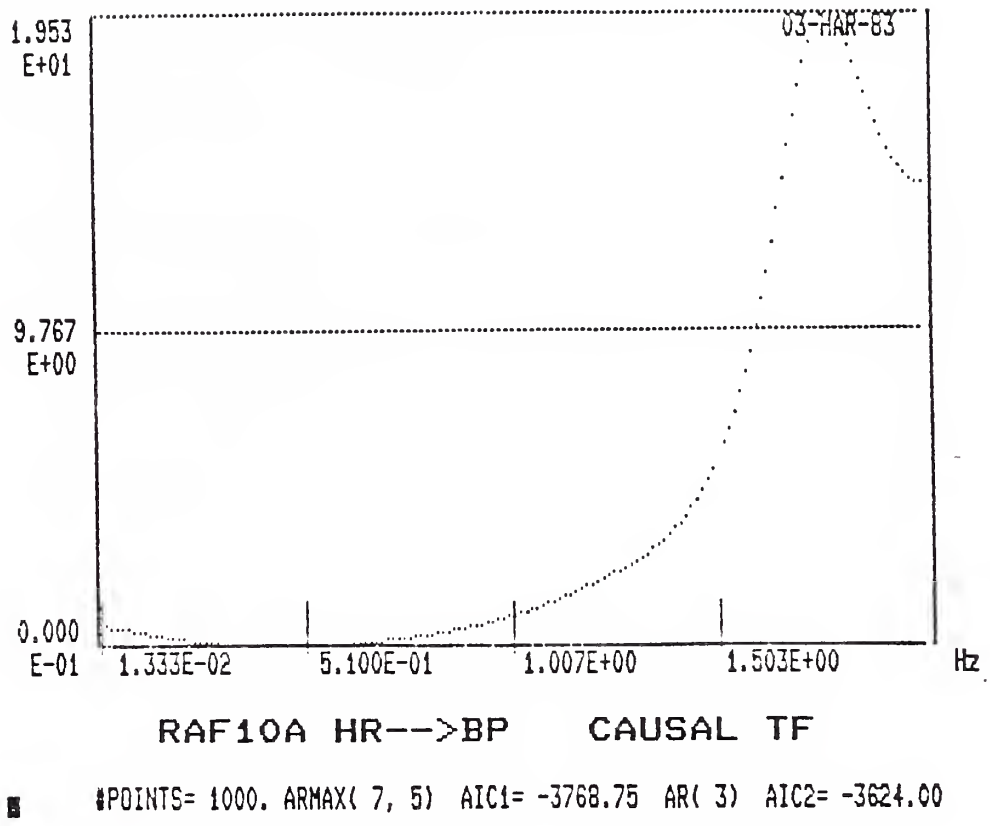


Figure 3-10: Transfer Function for the Effect of Fluctuations in Heart Rate on Blood Pressure During Atrial Fibrillation up to 2 Hertz

negative gain and time constant of approximately one second identified in section 3.1 for the baroreceptor impulse response during normal sinus rhythm. It suggests that the arterial baroreflex may modulate atrio-ventricular conduction during atrial fibrillation.

Thus estimates for the dynamic effects of small changes in blood pressure on heart rate have been identified during normal sinus rhythm and during atrial fibrillation. In addition, estimates in the reverse direction, i.e. for the dynamic effects of small changes in heart rate on

blood pressure, have been identified during atrial fibrillation but not during normal sinus rhythm. The significance of these results will be discussed in the following chapter.

3.3 Summary of Results

1. Finite impulse response models relating fluctuations in blood pressure to heart rate are identified during normal sinus rhythm. They are consistent with the response of a first-order linear system with a negative gain and a time constant of approximately one second. This result may describe the arterial baroreceptor reflex.

2. During normal sinus rhythm, heart rate variability is not sufficiently rich below 0.5 hertz to identify the effect of perturbations of heart rate on blood pressure.

3. Atrial fibrillation enriches the spectrum of heart rate and blood pressure below 0.5 hertz and allows the identification of a transfer function relating the effect of perturbations of heart rate on blood pressure. This transfer function has a positive gain and a corner frequency of approximately 0.1 hertz. This result is similar to estimates of arterial input impedance obtained in open-loop by Ringo et. al. [69], but may, in addition, contain information about the mechanical properties of the left ventricle.

4. During atrial fibrillation a transfer function is identified for the effect of blood pressure perturbations on heart rate. It has a negative gain, a corner frequency at approximately .25 to .30 hertz, and a time constant of approximately 0.6 seconds. This result is consistent with the finite impulse response model obtained for the arterial baroreflex during normal sinus rhythm.

Chapter 4

DISCUSSION

4.1 The Effect of Small Changes in Blood Pressure on Heart Rate

The time course of the effect of small changes in systemic arterial blood pressure on instantaneous heart rate have been quantified. During both normal sinus rhythm and during atrial fibrillation an increase in blood pressure results in a decrease in heart rate with a characteristic time course. The dominate component of this time course is exponential with a time constant of approximately one second. This may represent the time course of the combined vagal and sympathetic effects of the arterial baroreflexes on heart rate. To a first approximation, this result is consistent with the time course by which changes in vagal firing affect heart rate. Changes in vagal firing have been shown to affect heart rate with a time constant on the order of one second, whereas changes in sympathetic activity usually take on the order of several seconds to affect heart rate [73, 81, 48, 49, 88, 89]. The estimated time constant of approximately one second suggests that, in our young healthy dogs, baroreflex control of heart rate is dominated by the vagus, suggesting a relatively high level of parasympathetic tone. A time constant on the order of several seconds might suggest that sympathetic control of heart rate predominated, such as would be expected in congestive heart failure.

The frequency response estimates for the effect of small changes in blood pressure on ventricular rate during atrial fibrillation suggest

that fluctuations in blood pressure up to approximately 0.3 hertz are able to modulate ventricular rate. This result also is consistent with a predominance of parasympathetic, rather than sympathetic, modulation of ventricular rate since autonomic-blocking studies of heart rate variability suggest that the sympathetic nervous system is not able to modulate heart rate at frequencies much faster than 0.1 hertz, whereas the parasympathetic system may [3, 67, 50].

The absolute gain of the arterial baroreflex was not estimated in this initial study, however the sign of the gain was reproducibly estimated as negative. This would be expected since, for an increase in blood pressure, the arterial baroreflex results in a decrease in heart rate. Estimates of the absolute gain may easily be obtained from this data by calibrating the blood pressure signals with calibration data that is stored on the recordings of each experiment. An estimate of the baroreflex gain that could be obtained in closed-loop from simple measures of heart rate and blood pressure, might be of great clinical interest in the study of hypertension and congestive heart failure, two conditions where there is evidence that baroreflex sensitivity is reduced [22, 39, 66, 43]. The gain of the effect of fluctuations in blood pressure on heart rate may also be used as a quantitative estimate of parasympathetic and/or sympathetic control of heart rate in situations where one or the other is known to predominate.

4.2 The Effect of Small Changes in Heart Rate on Blood Pressure

During normal sinus rhythm we were not able to estimate a nonzero time course for the effect of small changes in instantaneous heart rate on systemic arterial blood pressure. The reason for this is that the fluctuations in heart rate during normal sinus rhythm were not sufficiently rich over a broad enough frequency band to result in detectable changes in blood pressure. Thus an important concept in systems identification has been illustrated; in simple terms, one can not obtain information about how a system responds to inputs if sufficient inputs are not applied to excite the system. Our methods require no exogenous inputs, but they will only work if adequate spontaneous inputs, i.e. fluctuations, are available.

Ringo et. al. [69] point out that important cardiovascular control actions occur in the arterial input impedance spectrum at frequencies lower than about 0.5 hertz and that some type of low frequency enhancement is ordinarily needed to observe this region of the impedance spectrum. He notes that Kenner [53] used low frequency oscillations in flow to estimate renal artery input impedance. Taylor [82] and Rubenstein [74] used pseudorandom excitation to estimate frequency dependent cardiovascular parameters. Ringo et. al. computed arterial input impedance from the effect of arterial flow on arterial pressure. He enriched the low-frequency fluctuations of arterial flow by frequency modulating heart rate with a pacemaker. His measurements were obtained in open-loop because changes in blood pressure could not in turn affect heart rate since the heart rate was controlled by a frequency-modulated

pacemaker. We, however, enriched the low-frequency fluctuations of heart rate by inducing atrial fibrillation which results in a pseudorandom distribution of RR intervals. Our estimates differ from those of Ringo et. al. in that we estimated the frequency-dependent effects of heart rate on blood pressure rather than the frequency-dependent effects of flow on blood pressure, and thus our results should represent the combined mechanical properties of, not only the arterial system, but also the left ventricle.

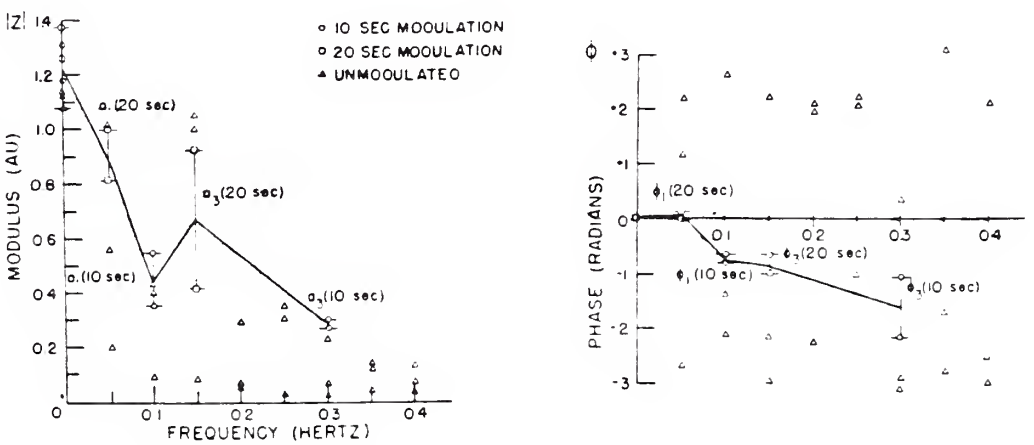


Fig. 9. The magnitude and phase of the low-frequency arterial input impedance calculated from the transformed flow and pressure data. The solid line is drawn through those data points computed from the first and third harmonics of the 10 and 20 s modulated data. The error bars indicate the range of values associated with different modulation indexes. These results are contrasted with the impedance values computed from the unmodulated flow and pressure data which exhibit large amounts of scatter for multiple data sets.

Figure 4-1: Magnitude and Phase of Arterial Input Impedance from Ringo et. al. [69]

The estimate of arterial input impedance obtained by Ringo et. al. is shown in Figure 4-1. It is, to a first approximation, consistent with the estimates obtained for the lumped mechanical properties of the left ventricle and the aorta shown in Figure 3-8. Thus, during atrial

fibrillation, we were able to estimate a nonzero transfer function relating small changes in heart rate to changes in blood pressure. This transfer function may provide an approximate estimate of aortic input impedance, and perhaps, may also be used to study the mechanical properties of the left ventricle in patients with atrial fibrillation.

All of the above results are preliminary, and further experiments are needed reproduce and validate them. Nevertheless, they are exciting because they were obtained without any interventions except those required to record blood pressure and heart rate.

In summary, these investigations suggest that the mutual effects of two fluctuating hemodynamic variables on each other may be separately identified under certain circumstances[8] if appropriate closed-loop identification methods are employed. They suggest that information about hemodynamic control systems may be extracted from the dynamic interactions of spontaneously fluctuating hemodynamic variables. Closed-loop identification of interactions between fluctuating cardiovascular variables thus may provide new noninvasive methods to study hemodynamic control systems in a variety of clinical settings.

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[8]See [52] for a technical discussion of the precise conditions required to identify a feedback-control system in closed-loop.

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