# Model for the assessment of heart period and arterial pressure variability interactions and of respiration influences

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**Abstract**—*A model which assesses the closed-loop interaction between heart period (HP) and arterial pressure (AP) variabilities and the influence of respiration on both is applied to evaluate the sources of low frequency (LF ~ 0·1 Hz) and high frequency (HF, respiratory rate ~0·25 Hz) in conscious dogs (n = 18) and humans (n = 5). A resonance of AP closed-loop regulation is found to amplify LF oscillations. In dogs, the resonance gain increases slightly during baroreceptor unloading (mild hypotension obtained with nitroglycerine (NTG) i.v. infusion, n = 8) and coronary artery occlusion ((CAO), n = 6), and it is abolished by ganglionic transmission blockade ((ARF), Arfonad i.v. infusion, n = 3). In humans, this gain is considerably increased by passive tilt. Different, possibly central, sources of LF oscillations are also evaluated, finding a strong rhythmic modulation of HP during CAO. At HF, a direct respiratory arrhythmia is dominant in dogs at control, while it is considerably reduced during CAO. On the contrary, in humans, a strong influence of respiration on AP is shown which induces a reflex respiratory arrhythmia. An index of the gain of baroreceptive response, $\alpha_{cl}$, was decreased by NTG and CAO, and virtually abolished by chronic arterial baroreceptive denervation (TABD, n = 4) and ARF.*

**Keywords**—*Arterial pressure variability, Autonomic nervous system, Baroreceptive mechanisms, Cardiovascular control, Closed-loop identification, Heart rate variability, Mayer waves, Respiratory arrhythmia*

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## 1 Introduction

SPECTRAL ANALYSIS of heart rate (or equivalently of heart period (HP)) variability (SAYERS, 1973), and of other cardiovascular signals (mainly arterial pressure (AP)) has revealed the presence of spectral peaks which carry information about the sympatho/vagal interaction, which governs autonomic cardiovascular control (AKSELROD *et al.*, 1981; POMERANZ *et al.*, 1985; PAGANI *et al.*, 1984; 1986; LOMBARDIA *et al.*, 1987).

Following the definitions by Pagani *et al.* (PAGANI *et al.* 1986), we are mainly interested in the measurement of two spectral components:

(*a*) at low frequency (LF), i.e. a spontaneous oscillation around 0·1 Hz related to AP Mayer waves (MAYER, 1876.).
(*b*) at high frequency (HF) triggered by respiration, usually around 0·25 Hz, depending on breathing rate.

The generation mechanisms of LF oscillations, the way in which respiration induces HF variability and the involvement of AP/HP interactions are not well established (KOEPCHEN, 1984). In some physiological studies (GUYTON and HARRIS, 1951) and most modelling works, LF waves are explained as the result of a self-oscillation (HYNDMAN, *et al.*, 1974; HOSOMI and HAYASHIDA, 1984; KITNEY *et al.*, 1985; MADWED *et al.*, 1989) or of a resonance of short-term AP regulation. On the contrary, neuro-physiological studies suggest the presence of LF modulations at a central level (PREISS and POLOSA, 1974; KOEPCHEN *et al.*, 1975).

Respiration is either considered a source of AP variability inducing a reflex respiratory sinus arrhythmia (DE BOER *et*

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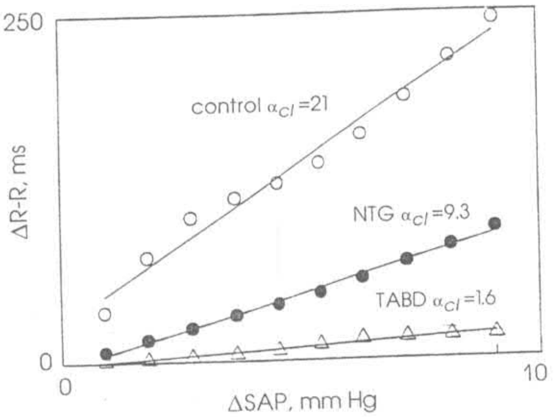

**Fig. 3** *Evaluation of baroreceptive mechanisms by means of* $\alpha_{cl}$ *in three different conditions; conscious dog in the control state (open circles), NTG infusion (closed circles), TABD (open triangles); considering, for example, the control condition, the response of the isolated* $H_{ts}$ *block versus an input ramp of s (open circles) increases almost proportionally; therefore, it is possible to draw the relevant regression line with a good correlation; its slope value is the index* $\alpha_{cl}$ *expressed in ms mm* $Hg^{-1}$; *note the decrease of* $\alpha_{cl}$ *during the unloading of baroreceptors (NTG, closed circles) and its drastic reduction after chronic baroreceptive denervation (TABD, open triangles)*

unloading) and baroreceptive denervation (TABD, baroreceptive response virtually removed). Note the accuracy of the linear fitting and the sensitivity of the $\alpha_{cl}$ index.

### 2.3 *Mechanical effects* $h_{st}(1)$

The mechanical block $H_{st}$ closing the *s-t-s* loop was shown to admit (BASELLI *et al.*, 1987; 1988*b*), for our purposes, the very simple structure of a single beat delay with $H_{st}(z) = h_{st}(1)z^{-1}$. The mechanical index $h_{st}(1)$ embeds two opposite effects:

(*a*) positive stroke–volume effect: i.e. prolonging the HP, an augmented ventricular filling causes a higher pulse pressure in the oncoming wave.
(*b*) negative run-off effect; i.e. a longer diastole decreases arterial filling, thus lowering AP.

Therefore, the sign of $h_{st}(1)$ indicates which effect is prevalent in influencing the next SAP value.

### 2.4 *AP regulation, s-s loop* $G_{ss}(LF)$, $h_{ss}(1)$

The short-term AP reflex regulation is described by the *s-s* loop formed by block $H_{ss}(z) = h_{ss}(1)z^{-1} + \cdots + h_{ss}(n)z^{-n}$. Amplifying or damping effects of this loop are better evaluated plotting its closed-loop gain $G_{ss}(z) = 1/(1 - H_{ss}(z))$. This is an all-pole filter, which is well suited to detecting the presence of resonances described by dominant poles. It was experimentally found that $G_{ss}$ has an amplifying peak in correspondence to the LF variability component, whereas contribution of the HP/SAP interaction is negligible (BASELLI *et al.*, 1988*b*). Therefore, as shown in Fig. 4, the peak value at LF, $G_{ss}(LF)$, is retained as an index of the contribution of AP regulation to the genesis of LF oscillations.

The first parameter of $H_{ss}$, $h_{ss}(1)$ deserves separate consideration, as it basically represents the propagation of SAP changes from one beat onto the next pressure wave. This can be explained by the time constant determined by the arterial tree compliances and resistances, as classically described by windkessel models. This purely passive and mechanical effect should be reflected by $h_{ss}(1)$ values smaller than 1 (i.e. an SAP change is only partially retained in the next beat); otherwise, a superposition of fast neural modulations can be argued.

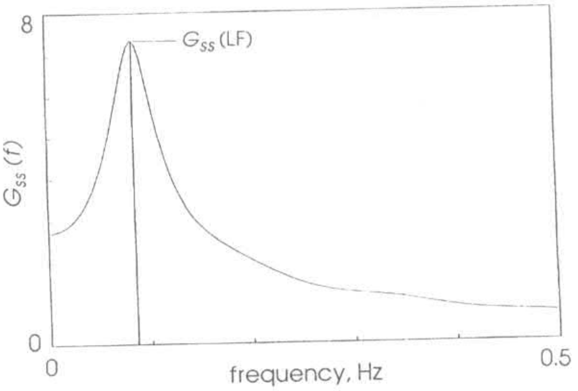

**Fig. 4** *Example (dog in the control state) of the measurement of* $G_{ss}(LF)$. $G_{ss}(f)$ *represents the closed-loop gain function of AP regulation s-s (loop); hence, the peak value of the LF resonance is measured*

### 2.5 *Respiratory effects* $log\,(\Theta_t)$, $log\,(\Theta_s)$

Two possible pathways transmitting respiration effects either on HP or SAP are evaluated estimating $R_t$ and $R_s$ blocks, respectively. Respiration itself is modelled with an autoregressive filter $M_r$, fed by the white noise $\{w_r\}$ with variance $\lambda_r^2$. The contribution of respiration to HP variability is easily obtained after the model identification, considering the squared modulus of the overall transfer function from $w_r$ to $t$ times $\lambda_r^2$, i.e. the partial spectrum of HP variability due to respiration:

$$S_{t/r}(f) = |[(1 - H_{ss})R_t + H_{ts}R_s]M_r/[1 - H_{ss} - H_{st}H_{ts}]|^2\lambda_r^2$$

Clearly, the effects of the two pathways (though not additive in power) are lumped into $S_{t/r}(f)$. Therefore, it is easy to simulate the absence of one of them by constraining to zero either $R_s$ or $R_t$ and obtaining the modified partial spectra $S_{t/r}(f\,|\,R_t, R_s = 0)$ and $S_{t/r}(f\,|\,R_t = 0, R_s)$, as shown in Fig. 5. (upper and lower panels, respectively). The index $\Theta_t$, is obtained as the ratio of the respective HF band powers:

$$\Theta_t = P_{t/r}(HF\,|\,R_t, R_s = 0)/P_{t/r}(HF\,|\,R_t = 0, R_s)$$

Roughly speaking, $\Theta_t$ represents the importance of $R_t$ versus that of $R_s$ in determining the HF component of HP, i.e. the amount of direct respiratory arrhythmia over that of reflex respiratory arrhythmia. In a similar way

$$\Theta_s = P_{s/r}(HF\,|\,R_t, R_s = 0)/P_{s/r}(HF\,|\,R_t = 0, R_s)$$

evaluates the HF component in SAP and represents the effects on SAP of respiratory arrhythmia over SAP changes directly induced by respiration; again, the importance of $R_t$ over that of $R_s$. As a result, both $\log(\Theta_t)$ and $\log(\Theta_s)$, when positive indicate that respiration affects the sinus node more directly than the vessels; the opposite situation when negative.

### 2.6 *Residual signals and detection of different LF sources;* $P_{ut}(LF)$, $P_{us}(LF)$

Inputs $\{u_t\}$ and $\{u_s\}$ are not directly measured signals but can be obtained as residuals of HP and SAP variability, respectively, after the subtraction of closed-loop interactions and respiration effects. They contain contributions external to the considered regulation loops, which are likely to reflect a central modulation of the sinus node, in $u_t$, and a centrally driven or spontaneous vasomotor activity, in $u_s$.

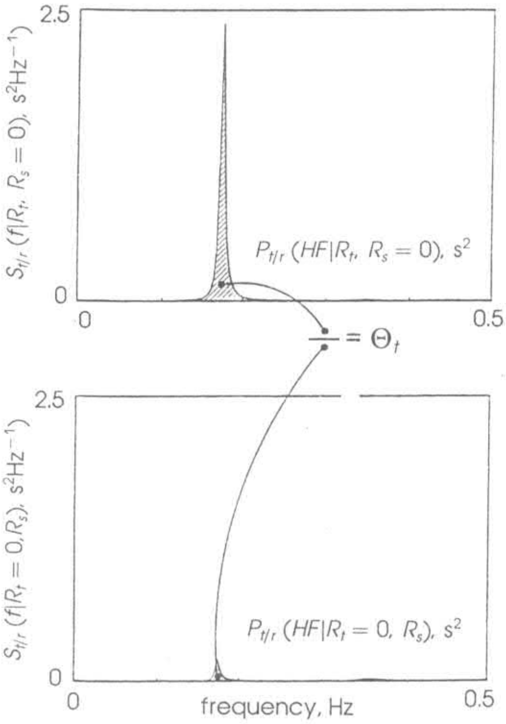

**Fig. 5** *Definition of index $\Theta_t$, i.e. importance of pathway $R_t$ over that of $R_s$ or, in other words, comparison of direct and reflex respiratory arrhythmia; upper panel: direct respiratory influences are evaluated computing the partial spectrum of HP variability due to respiration modified constraining to zero $R_s$, $S_{t|r}(f|R_t, R_s = 0)$; the relevant HF power $P_{t|r}(HF|R_t, R_s = 0)$ is obtained; lower panel: symmetric evaluation of reflex respiratory arrhythmia, obtained constraining to zero $R_t$, and computing $P_{t|r}(HF|R_t = 0, R_s)$; $\Theta_t$ is obtained as ratio of the two measurements; in this case (dog in the control-state) direct respiratory arrhythmia is prevalent and a positive log ($\Theta_t$) value is obtained*

Their spectral content is modelled by the AR filters $M_t$ and $M_s$, respectively, enabling description of central or other oscillators through the poles of these filters and also the quantification (through AR spectral decomposition) of the power of oscillations before amplifying or damping effect of the considered loops.

In this regard, it is extremely important to quantify the possible presence of residual LF components, which may reveal a generation mechanism of these rhythms at levels higher then AP control. For example, Fig. 6 displays a spectrum of $u_t$, $S_{ut}(f)$, with a residual peak at LF, which is experienced during coronary artery occlusion (CAO), indicating an LF modulation of the sinus node independent of the HP/SAP interaction and AP regulation.

The LF component power, $P_{ut}(LF)$, is normalised by the total HP variability power, var $[t]$, to quantify its relative weight. In a similar way, LF components in $u_s$ are normalised by the SAP variability power, yielding the index $P_{us}(LF)$/var $[s]$. After the extraction of the residual spectral features, only random prediction errors are left, i.e. the white noises $\{w_t\}$ and $\{w_s\}$ with variances $\lambda_t^2$ and $\lambda_s^2$, respectively.

## 3 Experimental protocol

### 3.1 *Experimental studies*

The experiments analysed in this paper are part of a larger experimental protocol carried out on chronically instrumented conscious dogs at the Centro di Richerche Cardiovascolari, CNR, Centro Cardiologico Fondazione Monzino, Milan, in order to assess the spectral components of HP and AP variabilities as markers of the dynamic sympathovagal balance (Rimoldi *et al.*, 1990). A total of 18 dogs was considered in this study.

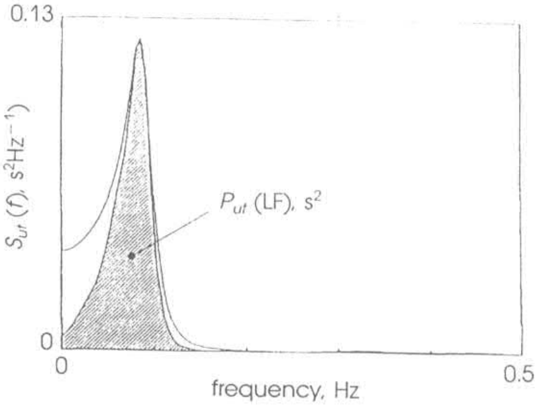

**Fig. 6** *Computation of $P_{ut}(LF)$; an example of the result relevant to a conscious dog during CAO, a situation in which it is possible that central LF oscillations modulate the HP variability; note the remarkable LF peak in the spectrum of input $u_t$, $S_{ut}(f)$; $u_t$ represents the residual variability of HP and is not explained by the interactions considered; its spectral content is AR modelled and decomposed, detecting and measuring possible LF components*

A group of dogs ($n = 12$) was chronically instrumented and analysed after complete recovery in the control condition and during pharmacological studies: nitroglycerine (NTG) infusion ($n = 8$) and Trimetaphan (Arfonad, ARF) infusion ($n = 3$). NTG infusion causes a moderate decrease of AP, and hence a sympathetic response due to baroreceptive unloading. ARF infusion produces a complete ganglionic blockade and excludes virtually all control circuits.

A sub-group ($n = 4$) subsequently underwent chronical total arterial baroreceptive denervation (TABD) and was analysed after a suitable recovery period. This condition offers the opportunity of studying the short-term HP response to AP changes with the baroreceptive mechanisms almost completely eliminated.

A separate group ($n = 6$) of dogs underwent chronical instrumentation and surgical intervention for the implantation of an hydraulic occluder on the coronary artery, in order to cause ischaemia in a limited zone of the myocardium, when activated. Data collection was performed after complete recovery during a control period and during a brief (2 min) period of coronary artery occlusion (CAO), sufficiently long to analyse HP and AP variabilities, but sufficiently short to avoid pain reactions. This was a situation of reflex sympathetic activation, but with a virtual absence of AP changes.

NTG and CAO offer the opportunity of observing the arousal of LF oscillations (which are very small in the control state of dogs) due to two different mechanisms of sympathetic excitation. Chronic TABD represents selective deactivation of baroreceptive mechanisms, whereas ARF represents complete deactivation of autonomic control. See work by Rimoldi *et al.* (Rimoldi *et al.*, 1990) for more detailed information on the experimental protocol.

### 3.2 *Human studies*

Clinical data were part of a larger study carried out at Patalogia Medica, Ospedale L. Sacco, Universitá di Milano (Furlan *et al.*, 1990) on patients with suspected hypertension. A limited set of subjects ($n = 5$) diagnosed as having mild hypertension, is considered here. Data were analysed considering periods of rest and of tilt (passive orthostatism), during which a non-invasive recording of respiratory movements and an ECG recording were added to an invasive AP measurement, permitting the present analysis. Tilt is a classical manoeuvre enhancing sympathetic modulation of the sinus node and vascular bed; it causes a remarkable increase in the LF component, which in humans is larger than HF, even at rest.

### 3.3 *Data analysis*

Recordings of ECG, AP and respiratory movements were A/D converted on a DEC PDP-11/24 minicomputer (300 Hz sampling frequency, 12-bit precision). Further processing was carried out on a DEC VAX-750 minicomputer.

The QRS complexes in the ECG were automatically recognised using a derivative-threshold algorithm, and the R-peak position was fixed with a minimum jitter by parabolic interpolation, in order to provide a precise measurement of the HP as R-R interval duration. The AP wave was analysed by detecting the diastolic (DAP) and systolic (SAP) AP values (BASELLI *et al.*, 1986). Respiratory excursions were sampled in correspondence to the R peak (CERUTTI *et al.*, 1988). Mean values were computed and subtracted from each discrete series. The variances (total power) of HP and SAP, var $[t]$ and var $[s]$, were also computed.

SAP and HP were separately processed by parametric AP spectral analysis and automatically decomposed into spectral components, thus obtaining the central frequency and the power, which is expressed in absolute or in normalised units (dividing by the total power minus the power of components below 0·03 Hz) (PAGANI *et al.*, 1986), for both LF and HF components.

The beat-by-beat variability series relevant to SAP $\{s(i)\}$, HP $\{t(i)\}$ and the respiration $\{r(i)\}$ were used to estimate the model parameters and compute the indexes defined above. The protocol also included the calculation of cross-spectra, spectra (total or partial) and transfer functions yielded by the model identification.

### 3.4 *Statistics*

Data are presented as mean values ±SE. A student's $t$-test for paired observations was used to test the significance of the differences between control conditions and the various situations in animal experiments, and the difference between rest and tilt in human studies. The same test was used to verify the significance of deviations of indexes from constant values as zero or one. A $p$ value $<0{\cdot}05$ was considered significant.

Goodness of fit indexes are computed in order to evaluate to what extent the model is able to describe the power of the signals, in a way similar to the familiar squared linear correlation index. Thus the indexes $\rho_s^2 = \{\text{var}\ [s] - \lambda_s^2\}/\text{var}\ [s]$, $\rho_t^2 = \{\text{var}\ [t] - \lambda_t^2\}/\text{var}\ [t]$, $\rho_r^2 = \{\text{var}\ [r] - \lambda_r^2\}/\text{var}\ [r]$ for $s$, $t$ and $r$ are computed, respectively.

## 4 Experimental results

Results concerning the goodness of fit obtained by the model in the various experimental conditions are summarised in Table 1. At least 70 per cent of HP variability power and even more of SAP variability was explained by the model. The remaining part of the power is contained in the white random signals $w_t$ and $w_s$, respectively, which describe unpredictable events exciting the system, in addition to features not accounted for by the model. Slightly lower values were found for respiration, according to the more deterministic pattern of this signal poorly modelled by the AR black box $M_r$.

*Table 1 Goodness of fit indexes for SAP variability $\rho_s$, HP variability $\rho_t$ and respiration $\rho_r$; values (mean ±SE) are given for (a) animal experiments and (b) human studies*

| index | $\rho_s$ | $\rho_t$ | $\rho_r$ |
|---|---|---|---|
| (*a*) | | | |
| control<br>$n = 18$ | 0·93<br>±0·013 | 0·72<br>±0·028 | 0·69<br>±0·045 |
| NTG<br>$n = 8$ | 0·87<br>±0·024 | 0·78<br>±0·042 | 0·64<br>±0·049 |
| CAO<br>$n = 6$ | 0·94<br>±0·008 | 0·83<br>±0·026 | 0·90<br>±0·035 |
| TABD<br>$n = 4$ | 0·96<br>±0·014 | 0·83<br>±0·055 | 0·70<br>±0·090 |
| ARF<br>$n = 3$ | 0·76<br>±0·075 | 0·72<br>±0·121 | 0·72<br>±0·150 |
| (*b*) | | | |
| rest<br>$n = 5$ | 0·75<br>±0·027 | 0·80<br>±0·063 | 0·66<br>±0·071 |
| tilt<br>$n = 5$ | 0·84<br>±0·030 | 0·86<br>±0·015 | 0·63<br>±0·063 |

Statistical results relevant to the investigated indexes in the various experimental conditions are summarised in Table 2. Significance is indicated for differences from basal (control in dogs, rest in humans) conditions; deviations from zero, for all parameters except $G_{ss}(LF)$ to indicate either a significant homogeneity in sign (for log $(\Theta_t)$, log $(\Theta_s)$, $h_{st}(1)$ and $h_{ss}(1)$) or significant presence of power (for $P_{ut}(LF)$/var $[t]$ and $P_{us}(LF)$/var $[s]$); and deviations from one, for $G_{ss}(LF)$ (significant amplification, when higher) and $h_{ss}(1)$ (not purely passive effect, when higher). Overall results are also illustrated, in each experimental condition, in Fig. 7, sketching the model with the following features:

(i) pathways resulting in effects of minor importance are dotted or even omitted.

(ii) sources of LF rhythms are displayed as oscillators plotted inside the $s$-$s$ loop (to indicate a loop resonance) and/or in the inputs, and the HF source is identified with respiration.

(iii) the sign of $h_{st}(1)$ is indicated, together with changes in $\alpha_{cl}$ and $h_{ss}(1)$.

Results relevant to spectral features of variabilities, together with the statistics of mean HP, SAP and diastolic AP (DAP), are briefly referred to, in order to establish a framework for modelling results; reference is made to RIMOLDI *et al.*, (1990) and to FURLAN *et al.*, (1990) for discussion of this topic in conscious dogs and humans, respectively.

Conscious dogs in the control state (HP = 0·78 ± 0·04, SAP = 127·7 ± 5·4, DAP = 74·3 ± 2·0) are characterised by a largely dominant HF component in both HP and SAP variability. As illustrated in Fig. 7*a*, respiratory influences were recognised by the model as impinging directly on the sinus node. As indicated by log $(\Theta_t)$, the importance of $R_t$ was clearly higher (about 10 times comparing powers conveyed to HP variability) than that of $R_s$, which was almost completely masked by the dominant respiratory arrhythmia. A resonance amplifying LF oscillations was recognised in the $s$-$s$ loop, and no other LF source was detected.

Although the major part of variability was led by HP, the closed-loop method was able to disentangle the existing

*Table 2 Values (mean ±SE) of the various indexes of the model; (a) animal experiments: control, nitroglycerine infusion (NTG), coronary artery occlusion (CAO), total arterial baroreceptive denervation (TABD), ganglionic blockade (ARF); (b) human studies; rest and passive tilt stimulation*

| index<br>dimension | $G_{ss}(LF)$<br>no | $P_{ut}(LF)/\mathrm{var}[t]$<br>no | $P_{us}(LF)/\mathrm{var}[s]$<br>no | $\log_{10}(\Theta_t)$<br>no | $\log_{10}(\Theta_s)$<br>no | $\alpha_{cl}$<br>ms mm Hg$^{-1}$ | $h_{ss}(1)$<br>no | $h_{st}(1)$<br>mm Hg s$_{-1}$ |
|---|---|---|---|---|---|---|---|---|
| (*a*) | | | | | | | | |
| control<br>$n = 18$ | 3·5‡<br>±0·36 | 0·047†<br>±0·020 | 0·005<br>±0·003 | 0·94†<br>±0·06 | 0·27<br>±0·14 | 13·8†<br>±2·24 | 0·79†, ‡<br>±0·08 | −21·2†<br>±2·1 |
| NTG<br>$n = 8$ | 4·2‡<br>±1·00 | 0·058<br>±0·035 | 0·185<br>±0·173 | 1·19†<br>±0·28 | −0·03<br>±0·30 | 4·5†<br>±1·00* | 0·62†<br>±0·270 | 18·2<br>±24·7 |
| CAO<br>$n = 6$ | 5·0‡<br>±0·76 | 0·532†<br>±0·198* | 0·028<br>±0·018 | 0·36<br>±0·14* | −0·29†<br>±0·08* | 6·4†<br>±1·13* | 1·19†<br>±0·15* | −20·8†<br>±5·6 |
| TABD<br>$n = 4$ | 2·2<br>±1·16 | 0·017<br>±0·015 | 0·825<br>±0·714 | 1·28†<br>±0·16 | 0·27<br>±0·12 | 1·1<br>±0·35* | 1·12<br>±0·56 | 2·6<br>±36·3 |
| ARF<br>$n = 3$ | 0·8<br>±0·16* | 0·045<br>±0·037 | 1·43<br>±0·55 | 0·34<br>±0·30 | −1·08<br>±0·39* | 1·2<br>±0·50* | −0·57<br>±0·32* | 10·4<br>±29·7 |
| (*b*) | | | | | | | | |
| rest<br>$n = 5$ | 4·2‡<br>±0·38 | 0·0001<br>±0·001 | 0·025<br>±0·018 | 0·42†<br>±0·12 | −1·98†<br>±0·16 | 4·0†<br>±0·61 | 0·81†<br>±0·10 | −24·8†<br>±3·9 |
| tilt<br>$n = 5$ | 10·4‡<br>±2·4* | 0·00005<br>±0·00003 | 0·011<br>±0·006 | 0·57†<br>±0·10 | −2·76†<br>±0·16* | 3·5‡<br>±0·53 | 1·45†, ‡<br>±0·20* | −13·9†<br>±4·1 |

* significant difference ($p < 0{\cdot}05$) from basal condition
† significant deviation from zero ($G_{ss}(LF)$ excluded)
‡ significant deviation from one ($G_{ss}(LF)$ and $h_{ss}(1)$ only)

feedbacks and measure the response of baroreceptive mechanisms, finding fairly high values of $\alpha_{cl}$. Negative effects of HP on SAP ($h_{st}(1) < 1$) and normal mechanical ($0 < h_{ss}(1) < 1$) propagation of SAP changes were found.

Under NTG infusion, the moderate decrease in blood pressure (SAP = 105·7 ± 3·8, DAP = 68·1 ± 3) causes a slight tachycardia (HP = 0·51 ± 0·04), revealing the reflex sympathetic activation. The spectral pattern is characterised by a marked decrease of HF component in both variabilities and an increase of LF. The interpretation furnished by the model, sketched in Fig. 7*b*, was a reduction of the respiratory influences carried by the $R_t$ pathway enabling the detection of the effect of $R_s$ pathway on SAP as revealed by log $(\Theta_s)$.

The gain of the *s-s* loop resonance was only slightly augmented, no other LF oscillators were detected, but a general increase in broadband inputs in LF range contributed to excite the LF resonance of the *s-s* loop. The baroreceptive unloading was revealed by the marked decrease in $\alpha_{cl}$. The mechanical effect described by $h_{st}(1)$ had a different sign from subject to subject, as at times the positive stroke–volume effect (masked at control) was prevalent on the negative run-off effect; the compliance effect ($h_{ss}(1)$) was not altered.

Transient and limited myocardial ischaemia caused by CAO is marked by a limited change in mean cardiovascular parameters (HP = 0·5 ± 0·07, SAP = 107·6 ± 5·1, DAP = 76·2 ± 3), whereas the marked sympathetic response is accompanied by a remarkable reduction in respiratory arrhythmia and increase in LF oscillations. The model (see Fig. 7*c*) described the drop in HF by an inhibition of the effect of pathway $R_t$ on both HP and SAP variability (decrease in log $(\Theta_t)$ and log $(\Theta_s)$, respectively.

LF arousal was ascribed to the appearance of a clear LF component in $u_t$ (Fig. 6). About 50 per cent of total power ($P_{ut}(LF)$/var $[t] = 0{\cdot}532$) *was explained by residual LF components impinging on the sinus node and possibly generated at central level (as depicted by the LF generator in Fig. 7c)*. A slight increase in *s-s* loop LF resonance contributed to amplify this phenomenon at AP level. The increase of $h_{ss}(1)$ to values above 1 indicated a not purely passive nature of fast pressure/pressure feedbacks. The mechanical effect of HP was not altered, in keeping with the moderate change in cardiovascular parameters; whereas the decrease in the baroreceptive response of HP reflected the sympathetic activation and the consequent vagal inhibition.

In dogs with baroreceptor afferents chronically removed (TABD, HP = 0·62 ± 0·07; SAP = 172·7 ± 8·1, DAP = 112·4 ± 10), pressure regulation is altered as indicated by the high mean values and slow trends affecting the very low frequencies of SAP spectrum; HP spectrum is concentrated at HF. The key finding was the strong reduction in $\alpha_{cl}$, as expected from an index of baroreceptive response (Fig. 7*d*). Another major issue is that the importance of the $R_t$ pathway in determining respiratory arrhythmia (high log $(\Theta_t)$) was unchanged after this selective deactivation of baroreceptive feedbacks, further supporting the negligible presence of a reflex respiratory arrhythmia in conscious dogs, as recognised in the control condition. The pressure control index $G_{ss}(LF)$, together with mechanical indexes, appeared to be altered in relation to the AP misregulation.

After ganglionic blockade by ARF intrusion in intact dogs, HP is shortened and AP drastically reduced (HP = 0·50 ± 0·04, SAP = 64·2 ± 4·1, DAP = 31·8 ± 3); HP variability is virtually absent, and AP variability, albeit strongly decreased, displays a detectable HF component. As shown in Fig. 7*e*, a virtual opening of the control loops was detected ($\alpha_{cl}$ close to 0, $G_{ss}$ close to 1). Influences on the sinus node are also blocked, and direct (probably mechanical) respiratory effects on SAP (high negative log $(\Theta_s)$ value) were recognised.

Human subjects in basal condition (rest, HP = 0·80 ± 0·02, SAP = 145·2 ± 15·1, DAP = 78·6 ± 9·6) display the usual spectral pattern in humans characterised by a remarkable LF component, about three times larger than the HF component. As shown in Fig. 7*f*, the model considered these LF oscillations as enhanced by an LF *s-s* loop resonance (amplification by a factor $G_{ss}(LF) = 4{\cdot}2$ means an 18-fold multiplication in power of the inputs to the loop). This phenomenon was greatly enhanced by passive orthostatism (tilt, HP = 0·68 ± 0·03, SAP = 150 ± 10·8, DAP = 90·4 ± 11·6). The increased LF component was explained by an augmented $G_{ss}(LF)$ value (10·4, i.e.

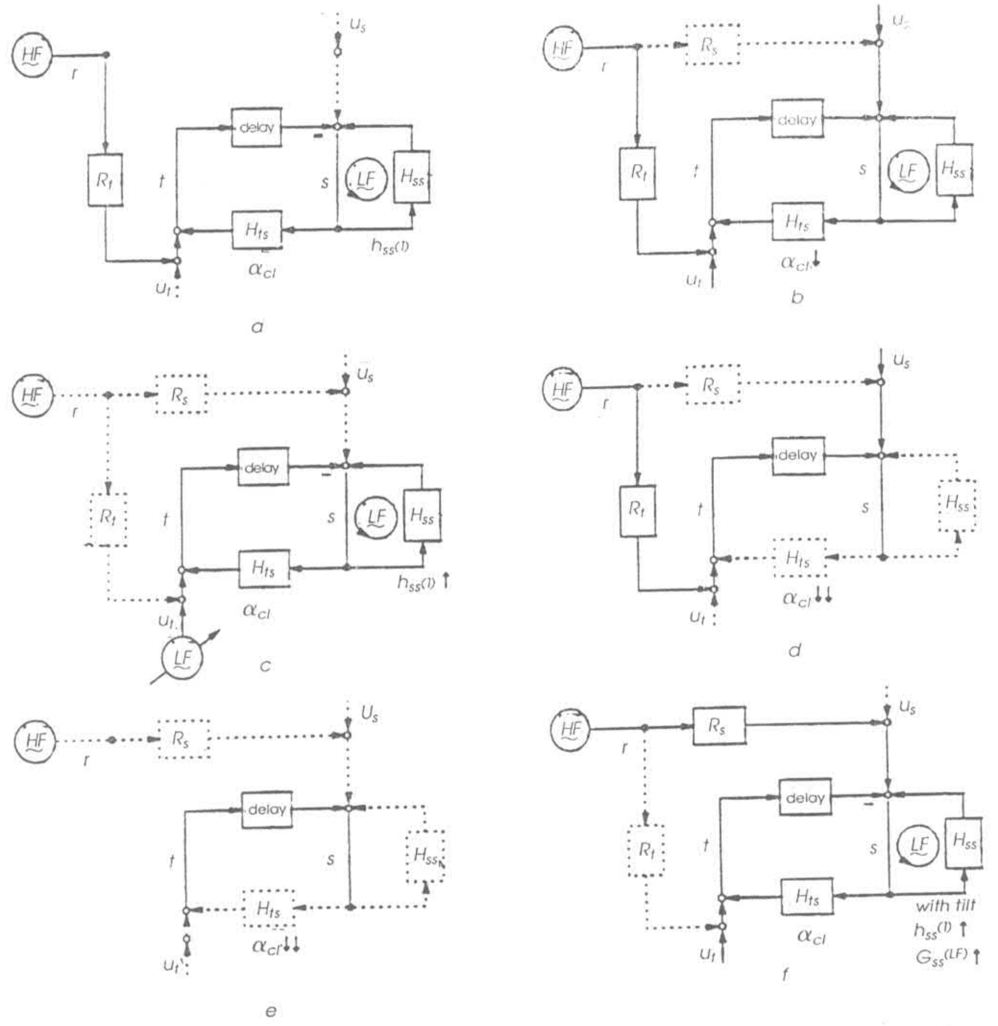

**Fig. 7** *Pictorial representation of the model identification results in various experimental conditions; (a) conscious dog in the control state; high direct respiratory arrhythmia, small LF due to AP regulation, high baroreceptive response, negative mechanical effect; (b) conscious dog during baroreceptive unloading (NTG infusion): decreased direct respiratory arrhythmia and baroreceptive response, altered mechanical effect; (c) conscious dog during coronary artery occlusion (CAO): appearance of a possibly central source of LF oscillations modulating the sinus node (input oscillator on t), decreased direct repiratory arrhythmia and baroreceptive response, fast SAP/SAP feedbacks ($h_{ss}(1)$), mechanical effect of HP on SAP not altered; (d) conscious dog with chronic baroreceptive denervation (TABD): virtually removed baroreceptive response, intact direct respiratory arrhythmia; (e) ganglionic blockade (ARF infusion) in intact dogs: abolished baroreceptive response, AP regulation and respiratory arrhythmia; (f) human subjects at rest and during tilt: large LF oscillations mainly related to AP regulation resonance, increased by a further activation of this mechanism during tilt, effect of respiration prevalently elicited on AP, presence of reflex respiratory arrhythmia, direct respiratory arrhythmia further decreased by tilt, negative HP/SAP effect, fast SAP-to-SAP effect augmented during tilt*

more than 100-fold multiplication in power of any LF disturbance) in relation to the vascular nature of the stimulus. Index $h_{ss}(1)$ increased during tilt above the purely mechanical passive range. HP-SAP interaction was characterised by a negative mechanical effect and by a baroreceptive response, which was moderate possibly in relation to the mild hypertension of the subjects. In an opposite way to dogs, respiration appeared to affect the HF variability of SAP more directly (Fig. 7*f*). The contribution of direct respiratory arrhythmia was even more reduced with tilt; again a reduction of sinus node modulation corresponding to a vagal withdrawal.

## 5 Discussion

### 5.1 *LF generation mechanisms*

One of the main results of the present study is that both vascular modulation mechanisms regulating the AP level and different (possibly central) oscillation sources can be involved in the generation of LF spectral peaks in the variability signals.

The vascular mechanism is recognised as one of the main contributions to LFs, in keeping with the pioneering work of Hyndman *et al.* (HYNDMAN *et al.*, 1974) and subsequent studies (DE BOER *et al.*, 1987; MADWED *et al.*, 1989). In dogs, this feature is evident, despite the very small percentage of LF components in the control state; it is slightly enhanced during a mild hypotensive manoeuvre as NTG infusion and a pure sympathetic stimulus as CAO. Ganglionic blockade, however, excludes the regulation mechanisms and virtually removes the resonance. In humans the contribution of LF vascular resonance to variability is already remarkable at rest and furthermore is dramatically enhanced by tilt. These elements together indicate that a closed-loop interaction between the vascular bed and its neural modulation does enhance LF oscillations.

Nevertheless, the hypothesis of independent LF sources must also be considered, in accordance with the perspective of several neurophysiological studies (PREISS and POLOSA, 1974; KOEPCHEN *et al.*, 1975), supported by direct measurements of neural efferent activity. By means of the present indirect method, a residual LF variability peak (i.e. external to the control loops considered by the model) is evidenced in dogs during CAO, appearing as a direct LF modulation of HP variability. This phenomenon appears as a cardio-cardiac sympathetic reflex modulation elicited amplifying or unmasking an LF source existing at higher (possible central) levels, the effects of which impinge directly on the sinus node. Mechanical effects convey this narrow-band LF input to AP regulation, which, by resonating, contributes to amplifying and synchronising it at a similar (but not necessarily equal) frequency of AP variability.

Returning to the vascular mechanism of LF generation, it should be remarked that it is described by the present model as a resonance rather than a spontaneous oscillator. Therefore, even broad band inputs (with no peak or specific component at LF) may contribute to the peak of power at LF, because AP regulation resonance is able to synchronise them. Spurious components of an irregular respiration are a possible source of broadband power in the LF range and require further investigation in their effects on vascular modulation of AP variability.

### 5.2 *Fast SAP-to-SAP feedbacks*

A positive attenuated, $(0 < h_{ss}(1) < 1)$ propagation of SAP perturbations from one beat to the next is found in basal conditions, and can be mainly related to the arterial compliances and to the time constant of diastolic run-off, which tend to maintain pressure levels with a windkessel-like behaviour. Concerning short-term variability, this feature has the effect of decreasing the stability of the AP control loop (BURATTINI *et al.*, 1987), enhancing the effect of the delays in the AP regulation, which most likely account for the existence and frequency of the control loop resonance (HYNDMAN *et al.*, 1974).

In the condition of sympathetic stimulation (CAO and tilt), values slightly above unity were found, suggesting the additional presence of neurally mediated positive feedbacks (MALLIANI *et al.*, 1986).

### 5.3 *Respiratory variability pathways*

Another main finding is that respiratory activity can directly modulate both AP levels and HP duration, being the two contributions to HF variability evident at various degrees in the different experimental conditions.

In the conscious dog in the control state, the respiratory rhythm is directed mainly on the sinus node. The almost non-existent changes in the genesis of respiratory arrhythmia produced by arterial baroreceptor denervation provide further support to a negligible contribution of reflex respiration influences on HP in the intact animal. Furthermore, the marked reduction of the importance of the sinus node modulation during the sympathetic activation produced by CAO is additional, albeit indirect, evidence that the neural HF modulation of HP occurs mostly through the vagi.

A different basal behaviour is displayed in humans, as a dominant influence of respiration on AP is experienced (this is probably related to a strong modulation of ventricular filling, but this model has no element to disentangle the various possible influences on the vascular bed). Therefore, respiratory arrhythmia in humans is due to a reflex modulation of the sinus node in response to AP variability, together with a moderate direct modulation.

In this regard, we suggest that modelling methods assessing the sympatho/vagal drive of the sinus node, by means of the overall transfer function from respiration to heart rate variability (SAUL *et al.*, 1989), should compensate the LF amplification effect of vascular regulation, particularly when applied in humans.

### 5.4 *Closed-loop evaluation of baroreceptive mechanisms*

Index $\alpha_{cl}$, as a measure of the gain of block $H_{ts}$ from SAP-to-HP variability, appears to describe well the changes that are known to occur in the overall gain of baroreceptive response of HP under various experimental conditions. Indeed, $\alpha_{cl}$ is reduced in dogs both during NTG infusion and CAO, manoeuvres which both increase sympathetic activity (SAGAWA *et al.*, 1983; GNECCHI-RUSCONE *et al.*, 1987). More importantly, the low value of this index observed during Arfonad infusion, which blocks ganglionic transmission, as well as in animals deprived of baroreceptor influences, indicates that $\alpha_{cl}$ seems to constitute a reliable index of such mechanisms, when intact.

In conclusion, the proposed closed-loop analysis appears to be well suited to disentangling the feed-forward and feedback pathways contributing to the HP-AP interaction. Indeed, this is verified in the presence of various origins of variability, i.e. it is independent of which of two variabilities is leading the other one. This is not the case with simplified open-loop methods which require bands with a predominant AP drive to be selected; e.g. both HF and LF in humans, and only LF (not HF) in dogs in the control state (but with a negligible fraction of variability), and no band in dogs during CAO.

### 5.5 *HP variability effect on SAP*

As far as short-term variability is concerned, it is found that HP duration changes are negatively reflected on the next SAP value; in fact, the augmented diastolic run-off due to a longer HP is only partially compensated by an increased pulse pressure. This gives to the AP-HP-AP loop the characteristics of a mild negative feedback.

The mechanical effects of HP on AP are not altered by sympathetic stimuli such as CAO and tilt, but changes are evident when the pressure level is altered even moderately as during NTG infusion; possibly as a consequence of the different elastic load (PAGANI *et al.*, 1979) or the augmented effect of HP changes on stroke volume.

## 6 Conclusions

These results confirm that different mechanisms are involved in the generation of the variability rhythms which have been extensively studied as markers of the sympatho-vagal interaction controlling the cardiovascular function. Therefore, the application of methods of multi-channel signal analysis and closed-loop identification, such as that described here, can extract more information than can be obtained by the usual techniques of single-channel spectral analysis of variability signals. This information can be assessed by means of selected indexes, which can be automatically obtained through the described model, and which can be useful both for a deeper comprehension of the physiology of cardiovascular control and for clinical applications.

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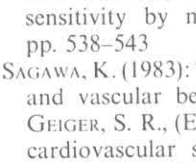

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