Disentangling cardiovascular control mechanisms via multivariate modeling techniques: the “spontaneous” baroreflex

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Focus

Baroreflex is one of the most important regulatory mechanisms and the evaluation of its sensitivity is physiologically and clinically relevant

Baroreflex sensitivity was found helpful in identifying subjects at risk for life-threatening arrhythmias

Baroreflex Sensitivity and Heart Rate Variability in the Identification of Patients at Risk for Life-Threatening Arrhythmias

Implications for Clinical Trials

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Background—The need for accurate risk stratification is heightened by the expanding indications for the implantable cardioverter defibrillator. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) focused interest on patients with both depressed left ventricular ejection fraction (LVEF) and the presence of nonsustained ventricular tachycardia (NSVT). Meanwhile, the prospective study Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) demonstrated that markers of reduced vagal activity, such as depressed baroreflex sensitivity (BRS) and heart rate variability (HRV), are strong predictors of cardiac mortality after myocardial infarction.

Methods and Results—We analyzed 1071 ATRAMI patients after myocardial infarction who had data on LVEF, 24-hour ECG recording, and BRS. During follow-up (21±8 months), 43 patients experienced cardiac death, 5 patients had episodes of sustained VT, and 30 patients experienced sudden death and/or sustained VT. NSVT, depressed BRS, or HRV were all significantly and independently associated with increased mortality. The combination of all 3 risk factors increased the risk of death by 22×. Among patients with LVEF<35%, despite the absence of NSVT, depressed BRS predicted higher mortality (18% versus 4.6%, $P=0.01$). This is a clinically important finding because this group constitutes 25% of all patients with depressed LVEF. For both cardiac and arrhythmic mortality, the sensitivity of low BRS was higher than that of NSVT and HRV.

Conclusions—BRS and HRV contribute importantly and additionally to risk stratification. Particularly when LVEF is depressed, the analysis of BRS identifies a large number of patients at high risk for cardiac and arrhythmic mortality who might benefit from implantable cardioverter defibrillator therapy without disproportionately increasing the number of false-positives. **(*Circulation.* 2001;103:2072-2077.)**

Key Words: nervous system, autonomic ■ baroreceptors ■ heart rate ■ myocardial infarction ■ arrhythmia

M.T. La Rovere, Circulation, 103:2072-2077, 2001

Baroreflex sensitivity was found helpful in predicting total cardiac mortality after myocardial infarction

ARTICLES

Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction

Maria Teresa La Rovere, J Thomas Bigger Jr, Frank I Marcus, Andrea Mortara, Peter J Schwartz, for the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators

Summary

Background Experimental evidence suggests that autonomic markers such as heart-rate variability and baroreflex sensitivity (BRS) may contribute to post-infarction risk stratification. There are clinical data to support this concept for heart-rate variability. The main objective of the ATRAMI study was to provide prospective data on the additional and independent prognostic value for cardiac mortality of heart-rate variability and BRS in patients after myocardial infarction in whom left-ventricular ejection fraction (LVEF) and ventricular arrhythmias were known.

Methods This multicentre international prospective study enrolled 1284 patients with a recent (<28 days) myocardial infarction. 24 h Holter recording was done to quantify heart-rate variability (measured as standard deviation of normal to normal RR intervals [SDNN]) and ventricular arrhythmias. BRS was calculated from measurement of the rate-pressure response to intravenous phenylephrine.

has significant prognostic value independently of LVEF and of ventricular arrhythmias and that it significantly adds to the prognostic value of heart-rate variability.

Lancet 1998; **351:** 478–84

See Commentary page

Introduction

Several clinical and laboratory findings have been identified to aid in risk assessment for survivors of acute myocardial infarction. Left-ventricular dysfunction and the presence of frequent ventricular premature complexes (VPC) each roughly doubles the risk of death.[1,2]

The autonomic nervous system has been extensively implicated in the triggering of sudden death,[3–5] and experimental evidence indicates that alterations in autonomic balance, characterised by reduced vagal activity and thus resulting in relative sympathetic dominance, might help identify individuals after myocardial infarction who are at high risk of life-

M.T. La Rovere, Lancet, 351:478-484, 1998

Introduction

The classical assessment of baroreflex sensitivity is based on the administration of a vasoactive drug and on the observation of the evoked heart period changes

Several non invasive methods based on the exploitation of the spontaneous arterial pressure and heart period variabilities have been proposed

Unfortunately, these methods assessing the “spontaneous” baroreflex provide indexes that may be weakly correlated each other and even in disagreement with the baroreflex sensitivity derived from the “invasive” procedure

Aims

To propose a multivariate approach for the assessment of “spontaneous” baroreflex

To interpret the disagreement among baroreflex sensitivity estimates based on differences among the models underlying each technique

Outline

1) Modeling the baroreflex

2) Method for invasive estimation of the baroreflex sensitivity and its implicit underlying model

3) Traditional methods for the non invasive estimation of the baroreflex sensitivity and their implicit underlying models

4) Model-based methods for the non invasive estimation of the baroreflex sensitivity

5) Comparing invasive and non invasive baroreflex sensitivity estimates (between-class comparison)

6) Comparing non invasive baroreflex sensitivity estimates (within-class comparison)

7) Interpreting the disagreement between baroreflex sensitivity estimates

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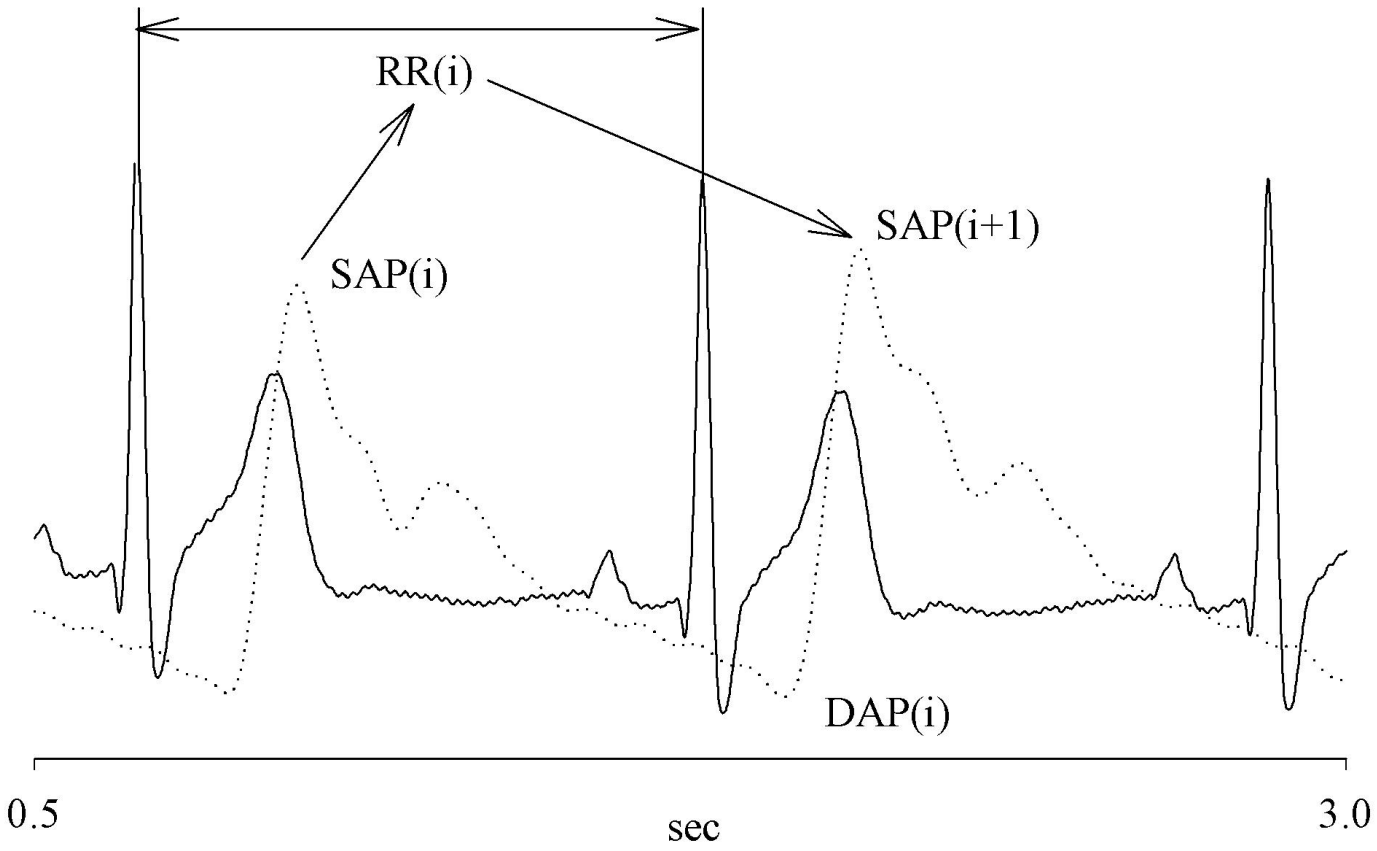
Operative definition of baroreflex

Baroreflex is a cardiovascular closed loop control mechanism that adjusts heart period (HP) to compensate for arterial pressure (AP) changes

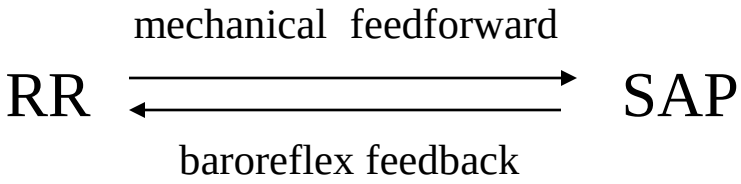
HP-AP interactions ⟹ HP-SAP interactions

Beat-to-beat SAP and RR measures

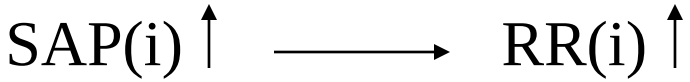


SAP(i) ⟶ RR(i) but not viceversa

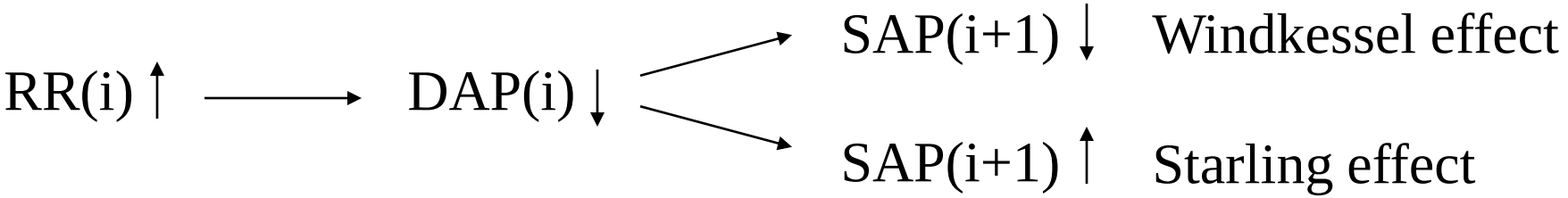
Towards a definition of a RR-SAP bivariate model



baroreflex feedback



mechanical feedforward



Towards a definition of a RR-SAP bivariate model

$RR(i) = f(RR_m, SAP_n) + u_{RR}(i)$ baroreflex feedback

$SAP(i) = g(SAP_p, RR_q) + u_{SAP}(i)$ mechanical feedforward

with

$RR_m = |RR(i-1) \dots RR(i-m)|$ 1xm

$SAP_n = |SAP(i-k_{RR\text{-}SAP}) \dots SAP(i-k_{RR\text{-}SAP}-n+1)|$ 1xn

$SAP_p = |SAP(i-1) \dots SAP(i-p)|$ 1xp

$RR_q = |RR(i-k_{SAP\text{-}RR}) \dots SAP(i-k_{SAP\text{-}RR}-q+1)|$ 1xq

and

$f(\cdot,\cdot)$ and $g(\cdot,\cdot)$ two functions (even non linear)

u_{RR} and u_{SAP} two noises (even correlated) but additive and independent of RR and SAP series respectively

Bivariate linear model of RR-SAP interactions

When considering small changes around the mean

$$rr(i) = RR(i) - \mu_{RR}$$
$$sap(i) = SAP(i) - \mu_{SAP}$$

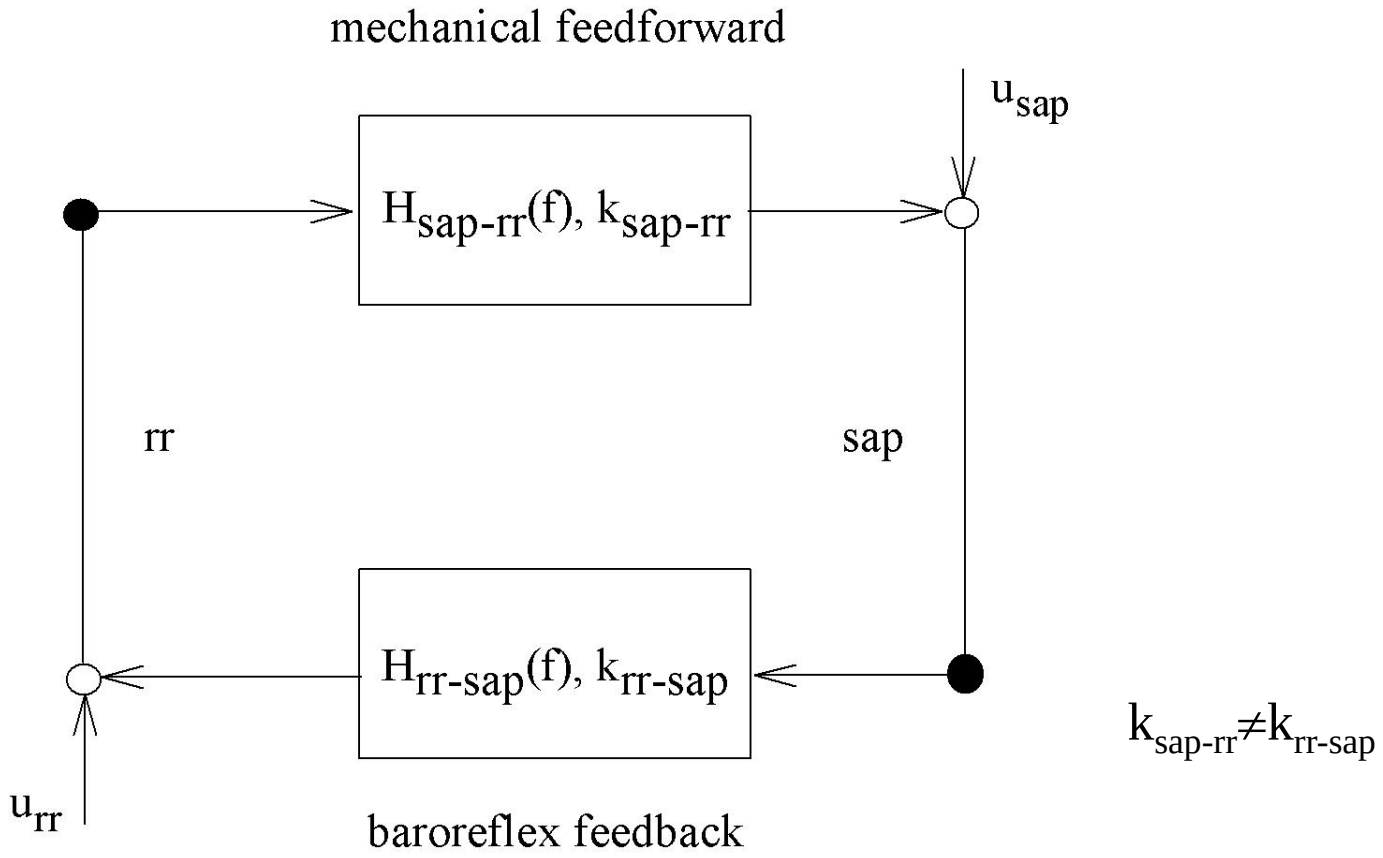
the bivariate model becomes linear

$$rr(i) = f(rr_m, sap_n) + u_{rr}(i) \qquad \text{baroreflex feedback}$$
$$sap(i) = g(sap_p, rr_q) + u_{sap}(i) \qquad \text{mechanical feedforward}$$

with

$f(\cdot,\cdot)$ and $g(\cdot,\cdot)$ linear combinations of past rr and sap values weighted by constant coefficients

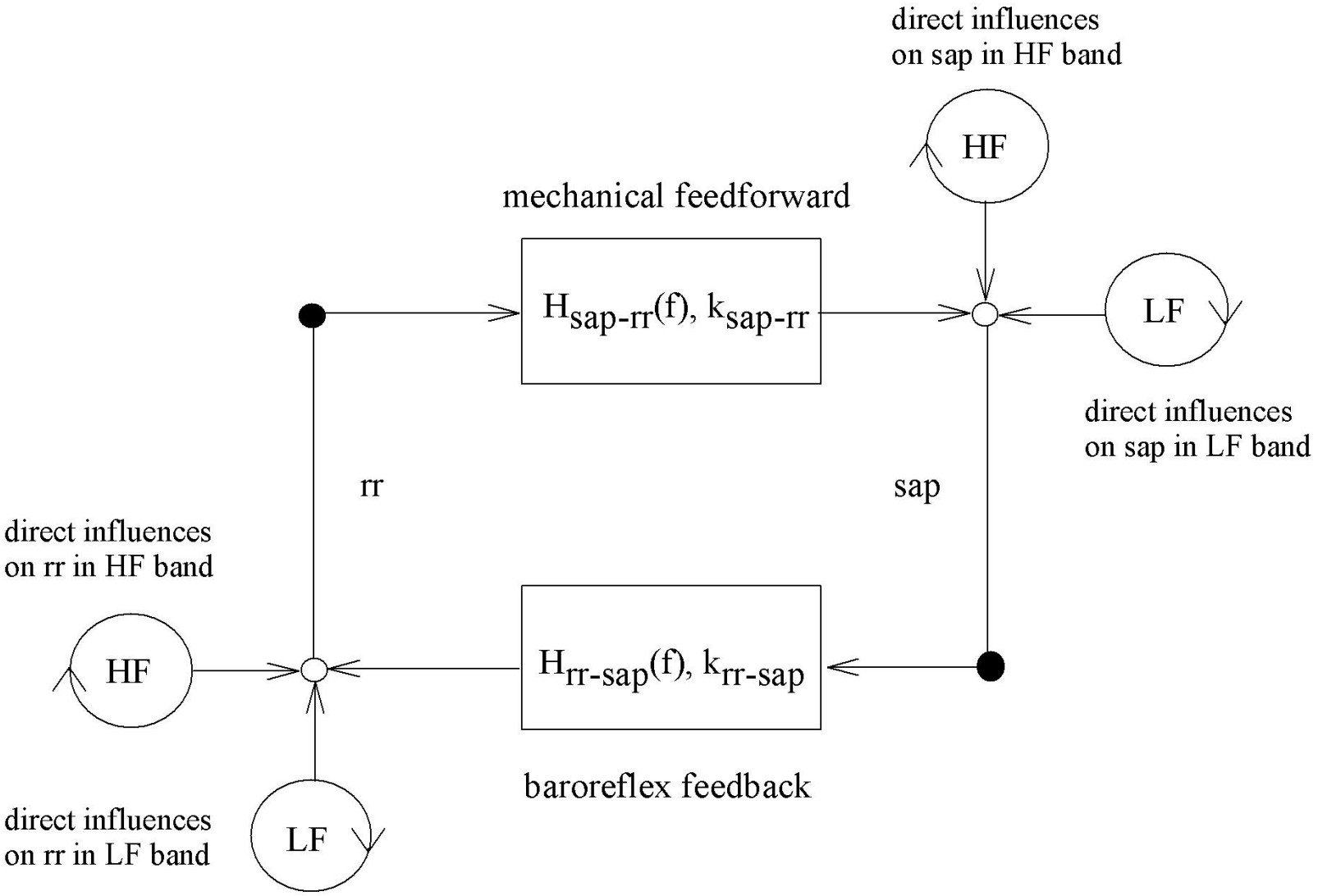
Block diagram of the bivariate linear closed loop model of the baroreflex regulation



$H_{sap\text{-}rr}(f)$, $k_{sap\text{-}rr}$: transfer function and delay of the feedforward arm

$H_{rr\text{-}sap}(f)$, $k_{rr\text{-}sap}$: transfer function and delay of the feedback arm

Towards a better definition of the inputs to the closed loop model of the baroreflex regulation



Linear closed loop model of the baroreflex regulation and of the respiratory influences

When considering small changes of respiration R around the mean

$$r(i) = R(i) - \mu_R$$

the bivariate linear model can be modified to account for respiration

$$rr(i) = f(rr_m, sap_n, r_r) + u_{rr}(i) \quad \text{baroreflex feedback}$$

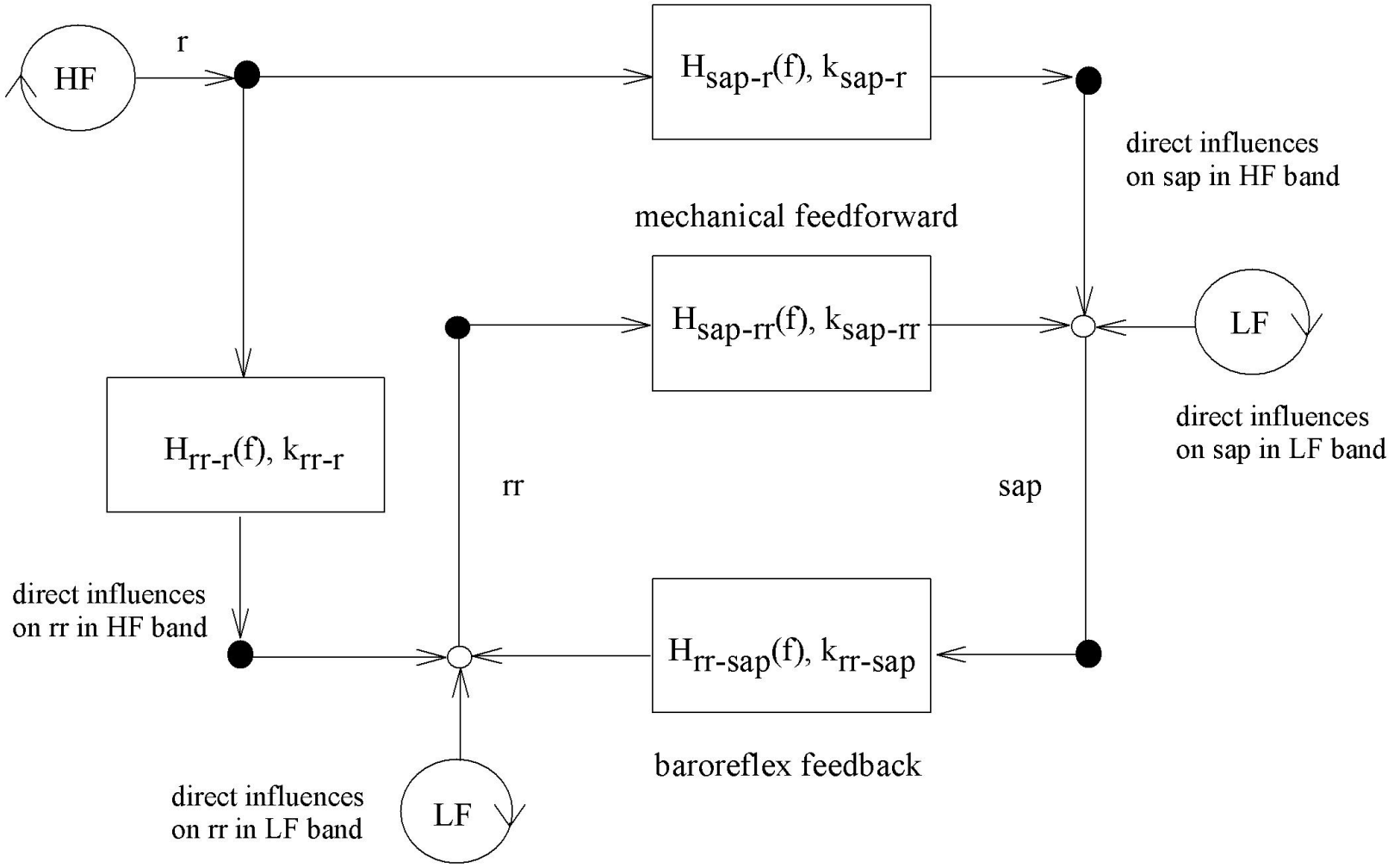
$$sap(i) = g(sap_p, rr_q, r_s) + u_{sap}(i) \quad \text{mechanical feedforward}$$

with

$f(\cdot,\cdot)$ and $g(\cdot,\cdot)$ linear combinations of past rr, sap and r values weighted by constant coefficients

Hypothesis: R exogenous input (i.e. R → RR and R → SAP but not viceversa)

Minimal linear model of the baroreflex regulation



$H_{sap-r}(f)$, k_{sap-r}: transfer function and delay from r to sap

$H_{rr-r}(f)$, k_{rr-r}: transfer function and delay from r to rr

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Invasive estimation of the baroreflex sensitivity

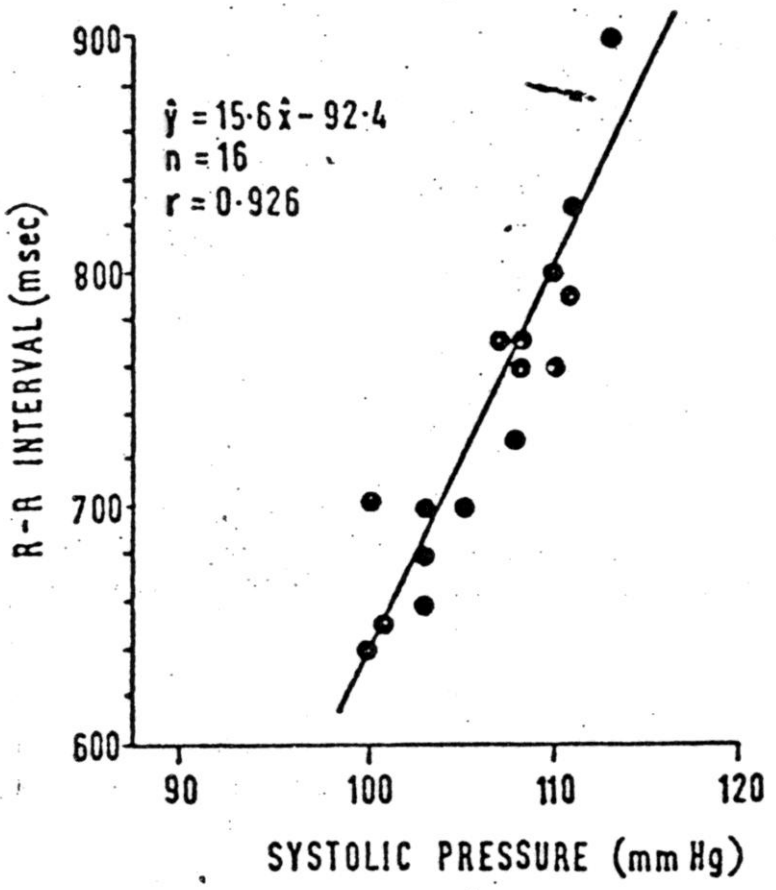
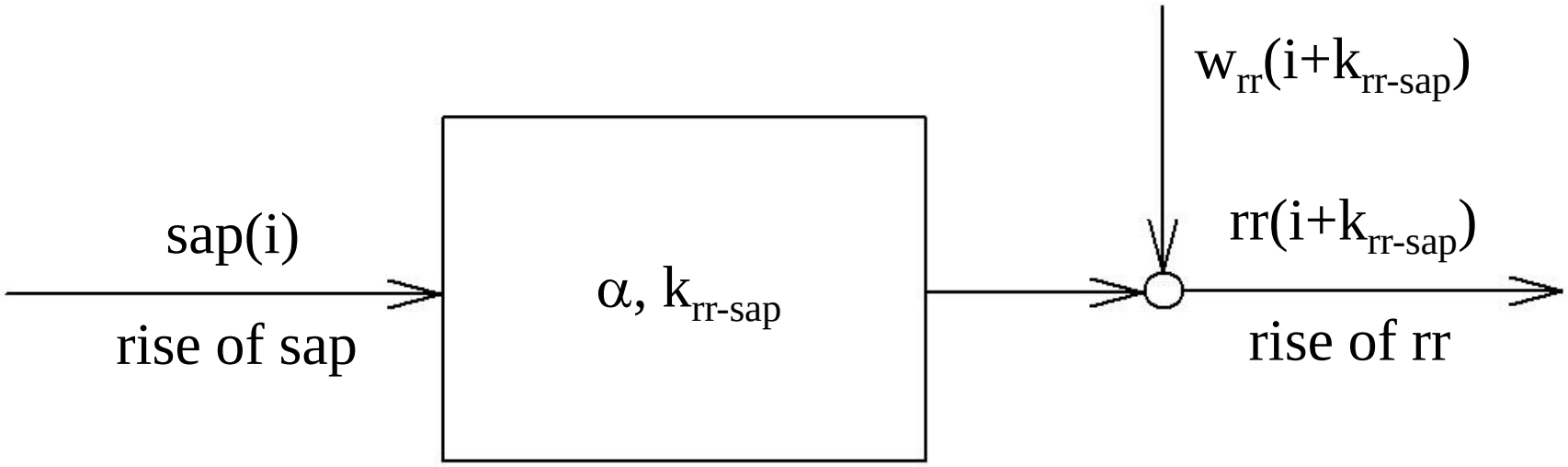


FIGURE 1

Subject N5. Response to 1.5 μg angiotensin in stage 4 sleep. This is the plot of the pressures designated in Table 1.

H.S. Smyth et al, Circulation Res, 24:109-121,1969

Mathematical model underlying the invasive estimation of the baroreflex sensitivity



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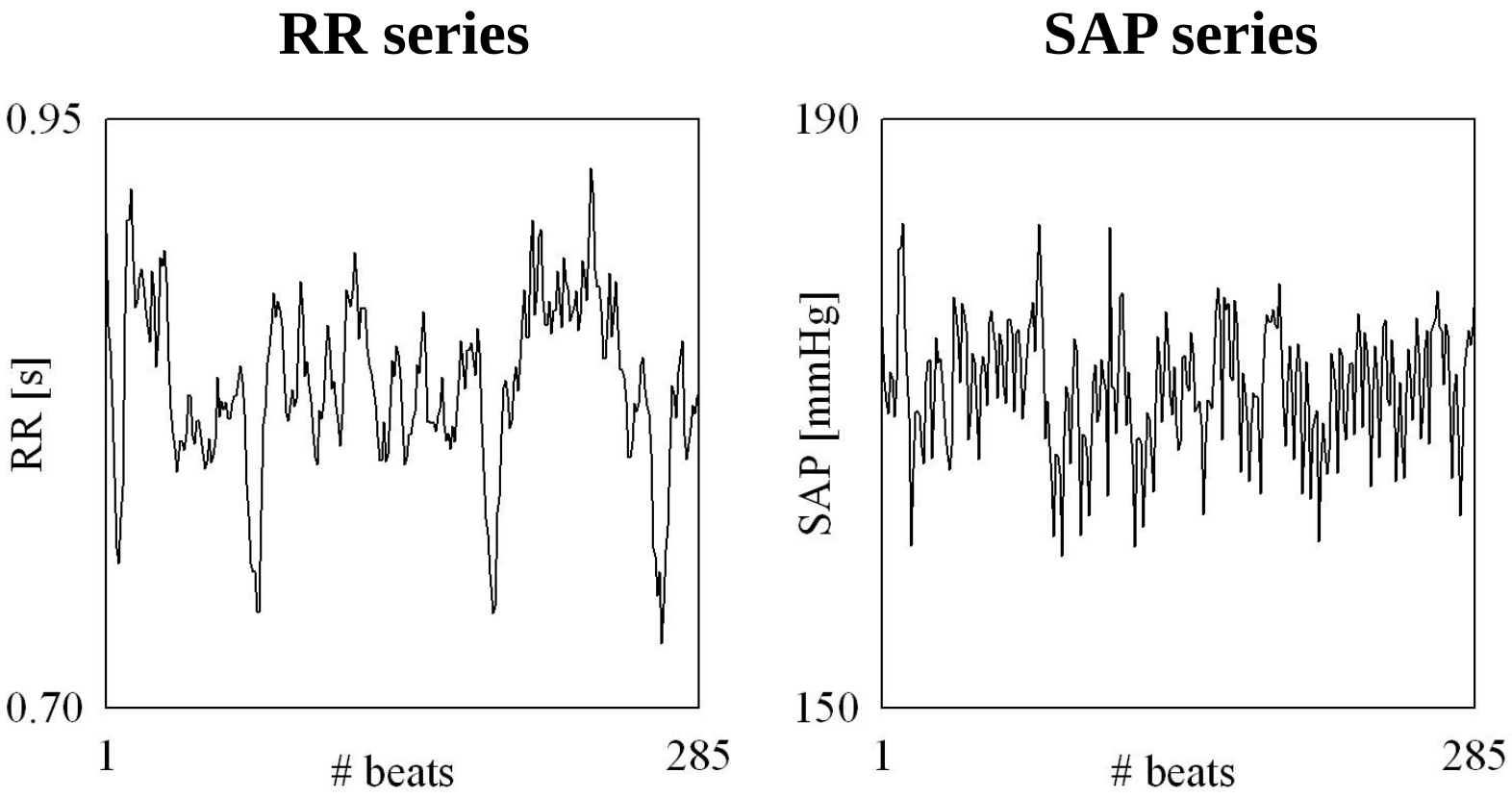
Spontaneous RR and SAP beat-to-beat variabilities in a mild hypertensive patient at rest



Traditional methods for the evaluation of the baroreflex gain based on spontaneous RR and SAP variabilities

1) baroreflex sequence analysis

G. Bertinieri et al, J Hypertens, 3:S79-S81, 1985

2) α index

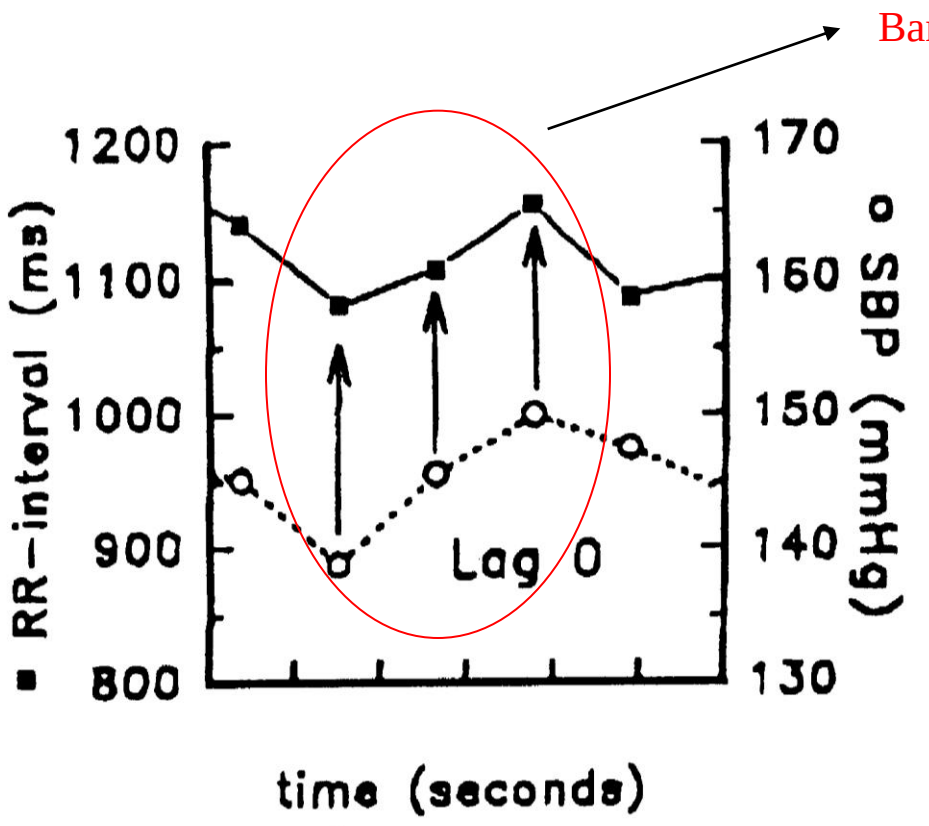
M. Pagani et al, Hypertension, 12:600-610, 1988

3) transfer function analysis

H.W.J. Robbe et al, Hypertension, 10:538-543, 1987

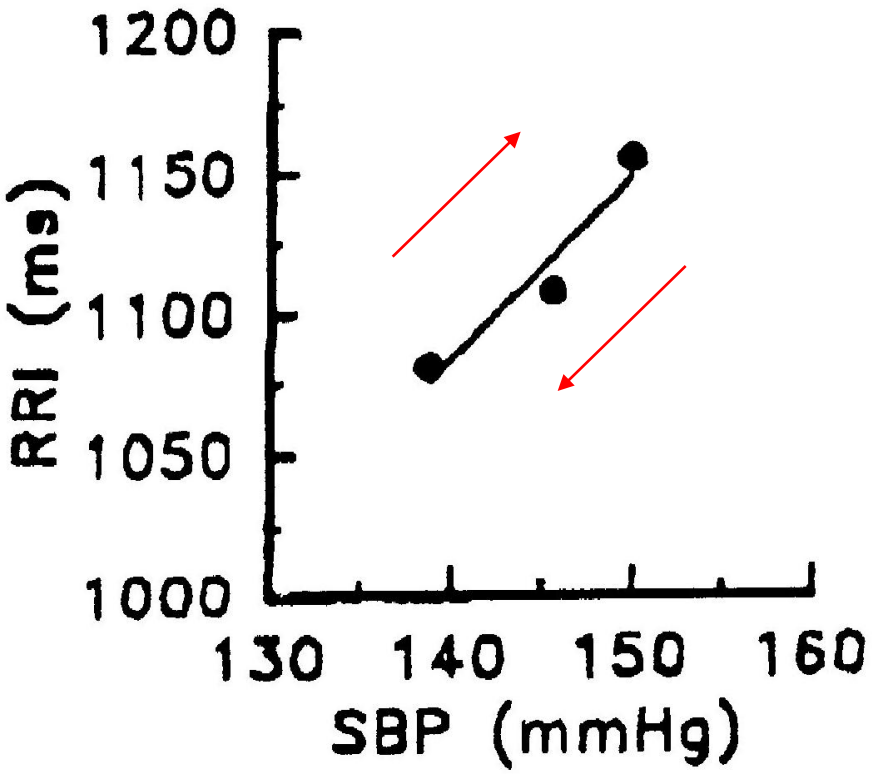
Baroreflex sequence analysis

Baroreflex sequence analysis searches for RR-SAP sequences characterized by at least two contemporaneous increases (or decreases) of both RR and SAP



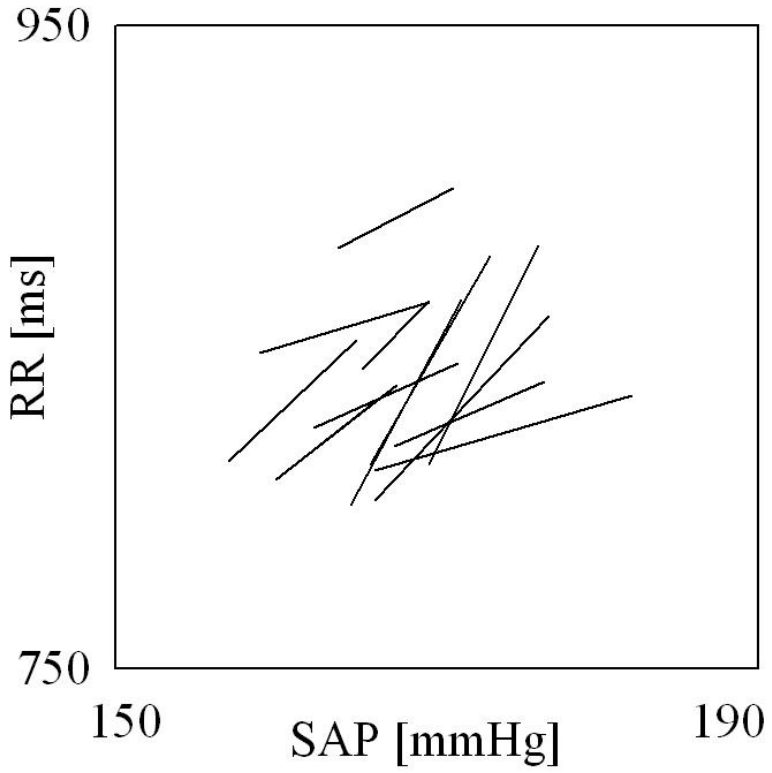
A.P. Blaber et al, Am J Physiol 268, H1682-H1687, 1995

Representation of a baroreflex sequence in the (RR,SAP) plane



A.P. Blaber et al, Am J Physiol 268, H1682-H1687, 1995

Baroreflex sequence analysis



number of consecutive RR and SAP increases (or decreases) = 3

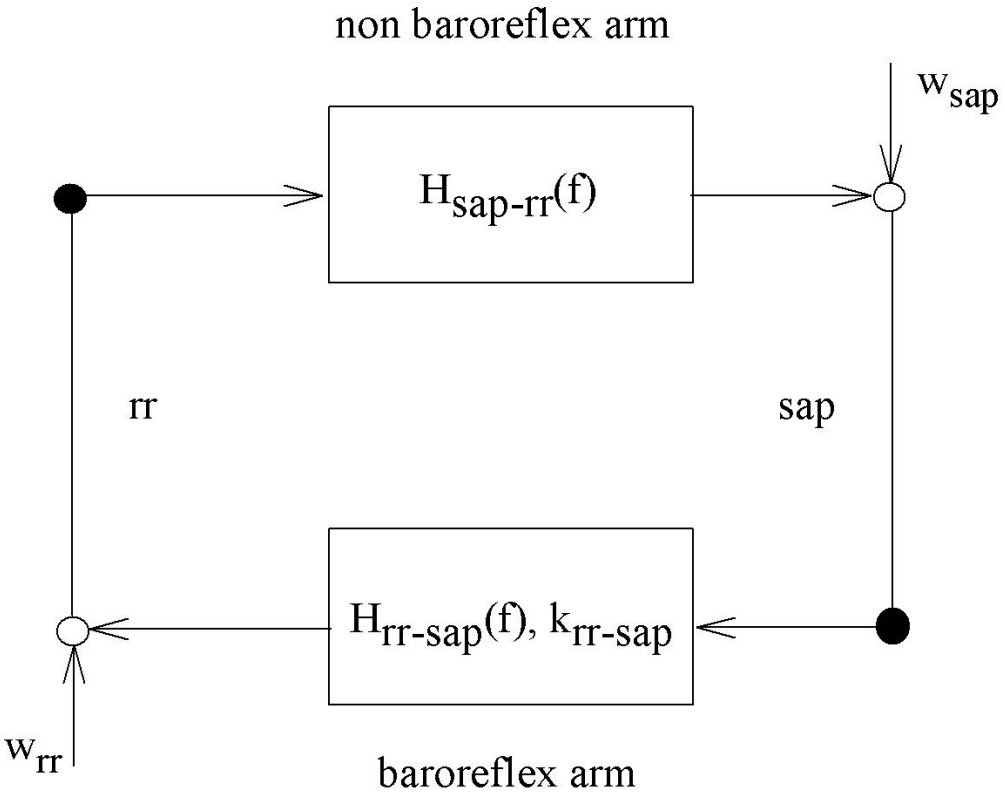
$|\Delta RR| \geq 5$ ms

$|\Delta SAP| \geq 1$ mmHg

$r \geq 0.85$

delay of $H_{rr\text{-}sap}$, $k_{rr\text{-}sap}$, is assigned (here $k_{rr\text{-}sap}=0$)

Mathematical model underlying baroreflex sequence analysis

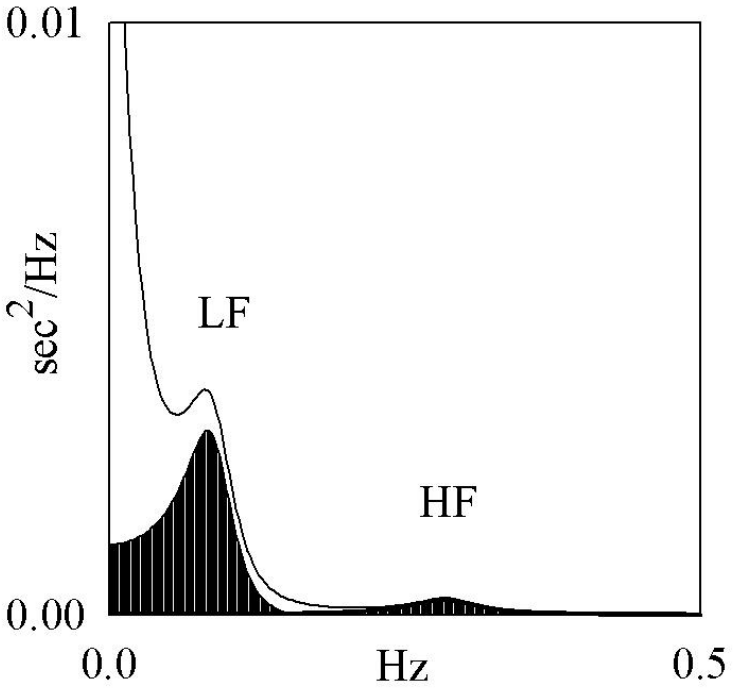


Baroreflex sequence method, by subdividing sequences in baroreflex and non baroreflex, actually imposes a causal, closed loop, model

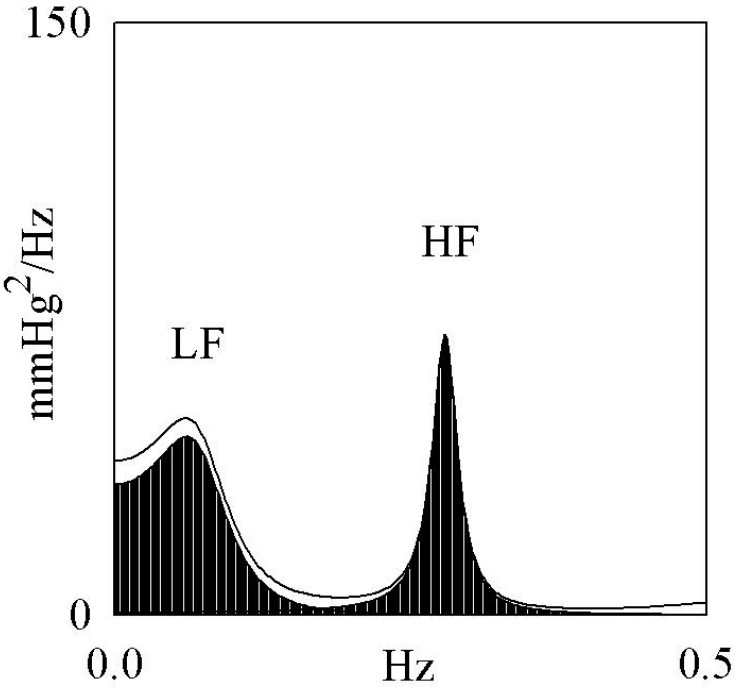
However, since the blocks $H_{rr\text{-}sap}$ and $H_{sap\text{-}rr}$ are without memory over past values, only simultaneous interactions are disentangled (fast actions)

α index

PSD RR



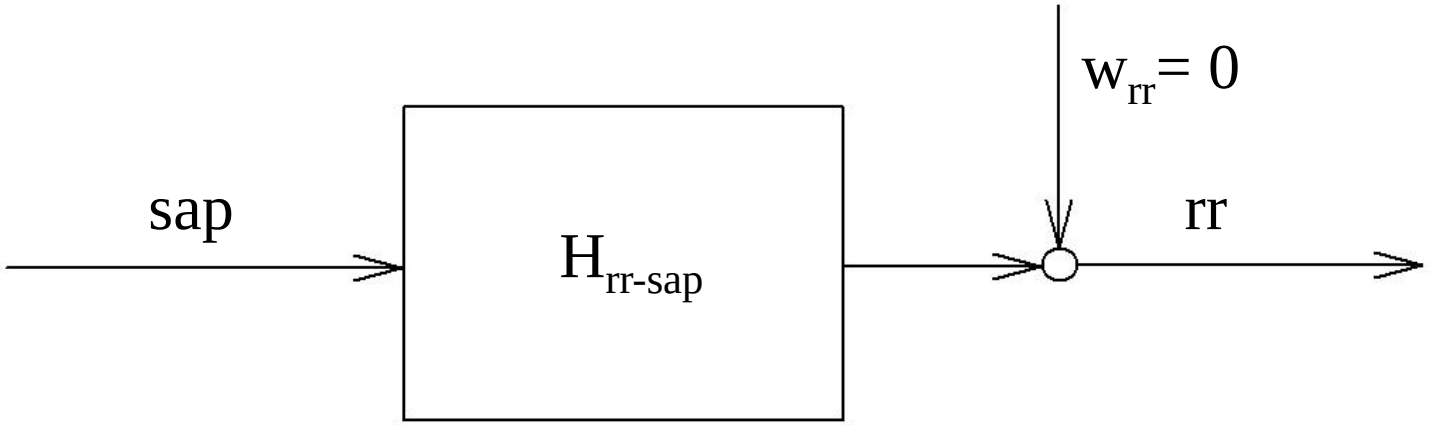
PSD SAP



$$\alpha_{PS}(LF) = \sqrt{\frac{P_{rr}(LF)}{P_{sap}(LF)}}$$

$$\alpha_{PS}(HF) = \sqrt{\frac{P_{rr}(HF)}{P_{sap}(HF)}}$$

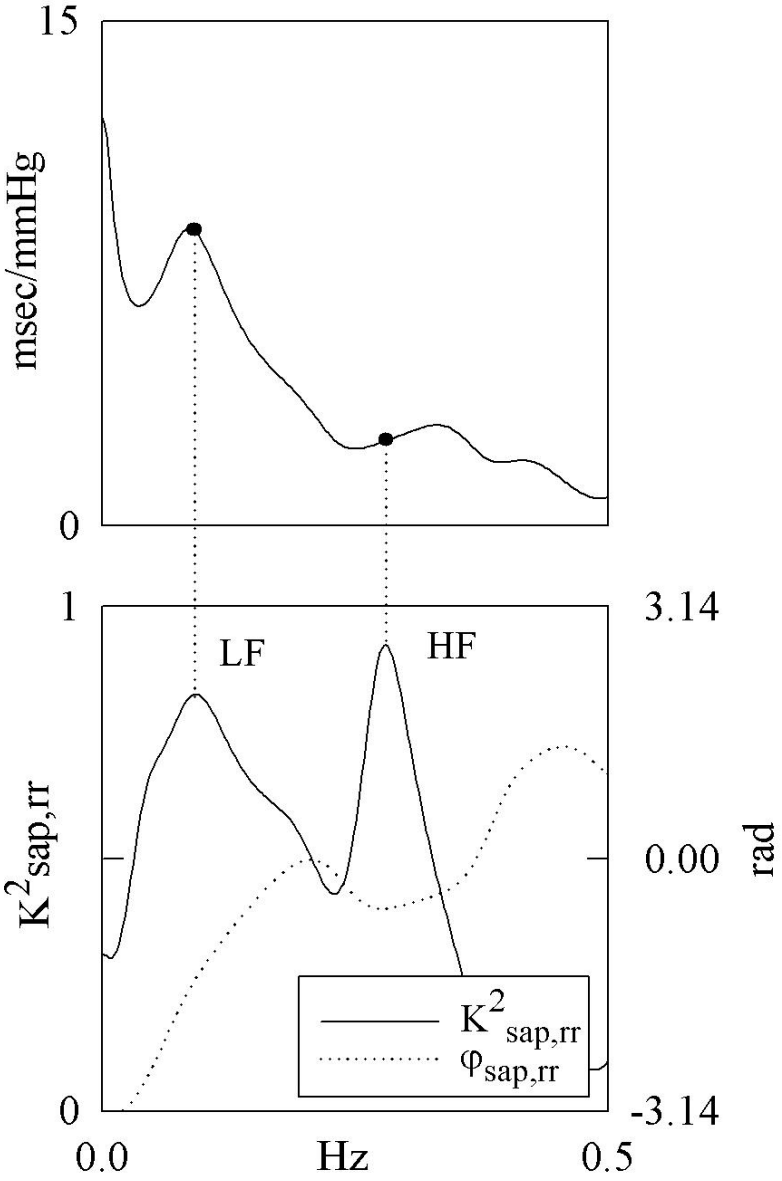
Mathematical model underlying α index estimation



Hypotheses

1) RR and SAP series interact in open loop
2) SAP and RR series are correlated
3) RR interval lags behind SAP
4) w_{rr}=0 in LF and HF bands

Transfer function estimation based on cross-spectral analysis



α is calculated as

$$\alpha_{CS}(LF) = |H_{rr\text{-}sap}(LF)| = \frac{|C_{rr\text{-}sap}(LF)|}{S_{sap}(LF)}$$

$$\alpha_{CS}(HF) = |H_{rr\text{-}sap}(HF)| = \frac{|C_{rr\text{-}sap}(HF)|}{S_{sap}(HF)}$$

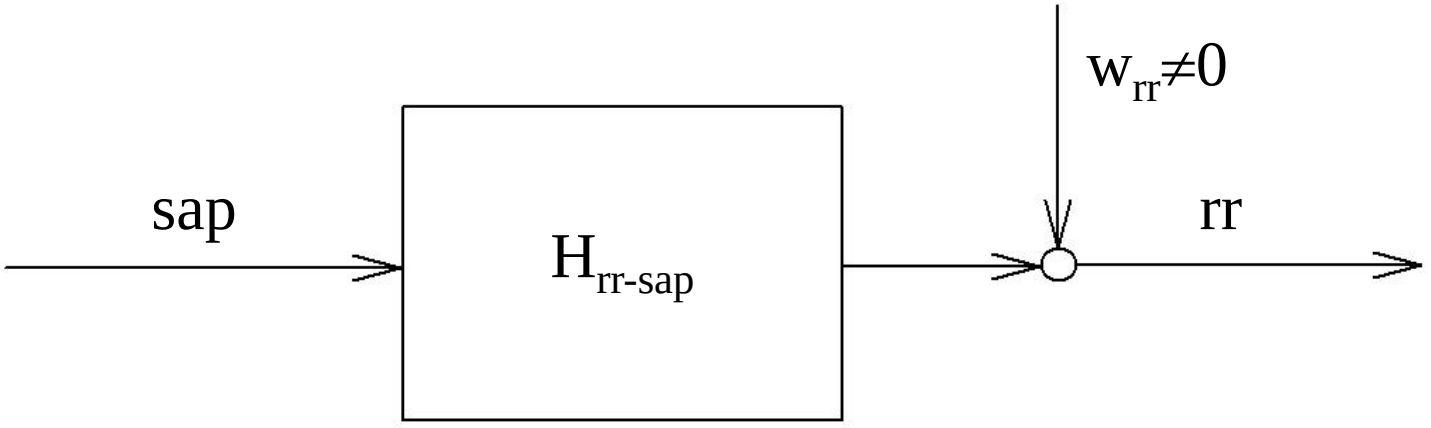
or as the average of the gain over LF or HF bands

H.W.J. Robbe et al, Hypertension, 10, 538-543, 1987

or from the impulse response of $H_{rr\text{-}sap}(f)$

R.B. Panerai et al, Am J Physiol, 272, H1866-H1875, 1997

Mathematical model underlying transfer function estimation based on cross-spectral approach



Hypotheses

1) RR and SAP series interact in open loop
2) RR and SAP are correlated (tested with $K^2_{rr,sap}$)
3) RR interval lags behind SAP (tested with $C_{rr,sap}$ phase)
4) w_{rr} uncorrelated to sap

Limitations of the traditional non invasive estimates of the baroreflex sensitivity

1) Causality (i.e. RR interval lags behind SAP) is an hypothesis (not tested by the methods)

2) Rough or absent modeling of the closed loop relationship between RR and SAP series

3) Rough modeling of inputs capable to drive RR interval variability independently of SAP (e.g. respiration)

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Model-based methods for the evaluation of the baroreflex gain from spontaneous RR and SAP variabilities

1) Open loop bivariate causal models

   A. Porta et al, Am J Physiol, 279, H2558-H2567, 2000
   G. Nollo et al, Am J Physiol, 280, H1830-1839, 2001

2) Open loop bivariate causal models accounting for respiration

   D.J. Patton et al, Am J Physiol, 39, H1240-H1249, 1996
   A. Porta et al, Am J Physiol, 279, H2558-H2567, 2000

3) Closed loop bivariate causal models

   R. Barbieri et al, Ann Noninv Electrocard, 3, 264-77, 1996
   R. Barbieri et al, IEEE Eng Med Biol Mag, 20, 33-42, 2001

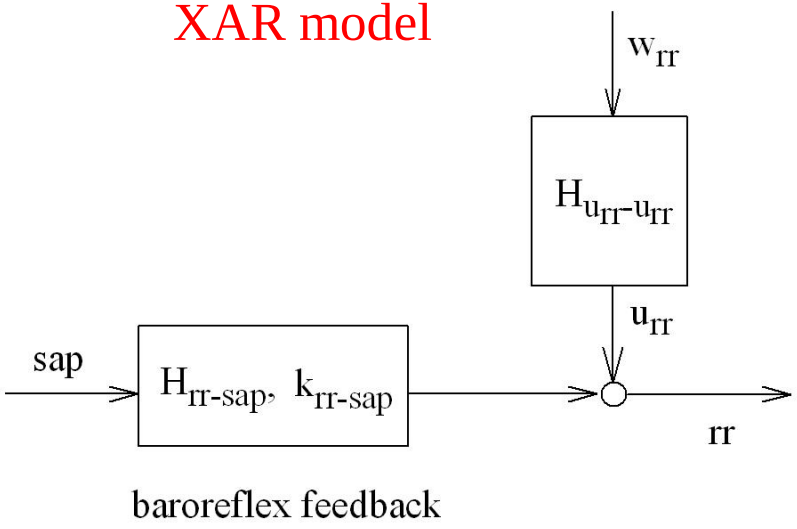
4) Closed loop bivariate causal models accounting for respiration

   G. Baselli et al, IEEE Trans Biomed Eng, 35, 1033-1046, 1988
   G. Baselli et al, Med Biomed Eng Comput, 32, 143-152, 1994

Two examples of causal open loop models

Exogenous (X) model with autoregressive (AR) noise

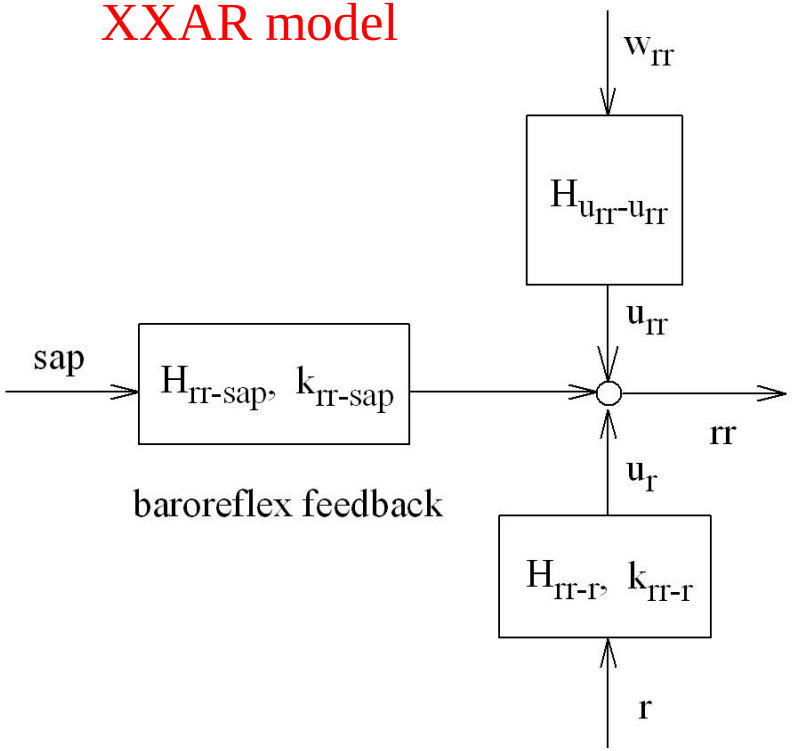
XAR model



A. Porta et al, Am J Physiol, 279: H2558-H2567, 2000

Double exogenous (XX) model with autoregressive (AR) noise

XXAR model

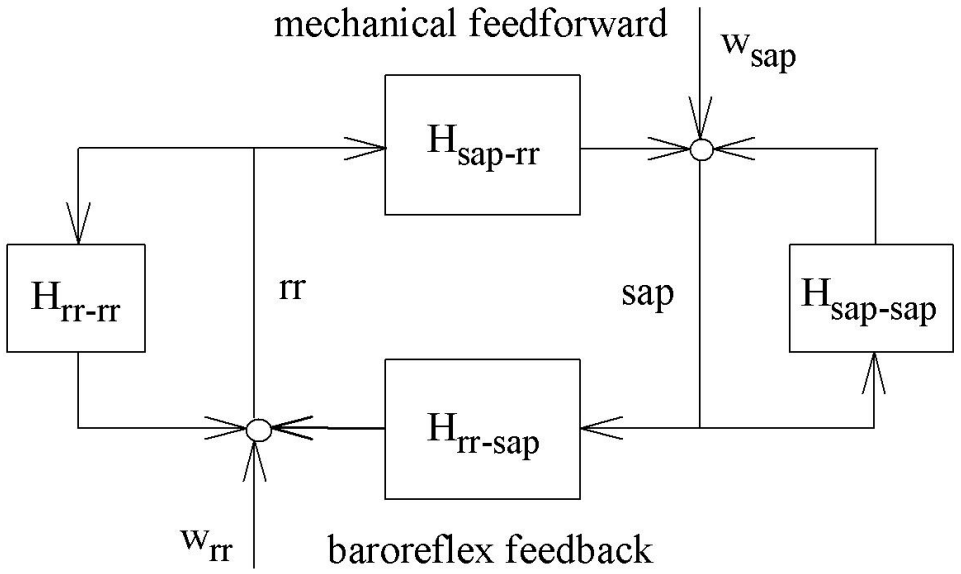


A. Porta et al, Am J Physiol, 279: H2558-H2567, 2000

Two examples of causal closed loop models

Bivariate autoregressive (AR2) model

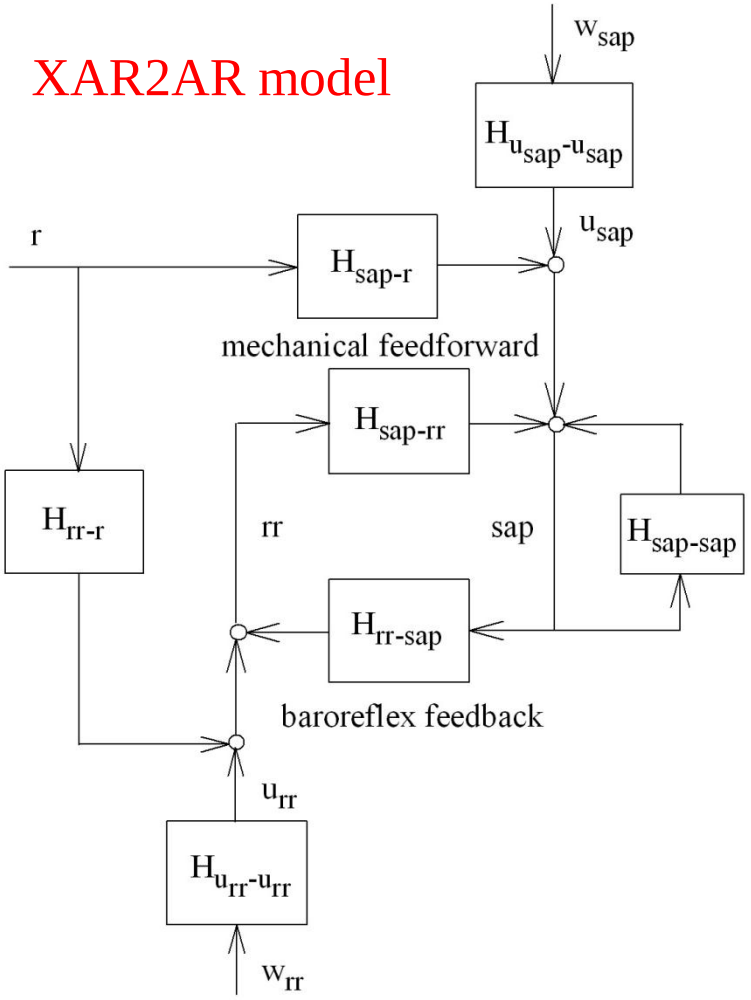
AR2 model



A. Porta et al, Biol Cybern, 86, 241-251, 2002

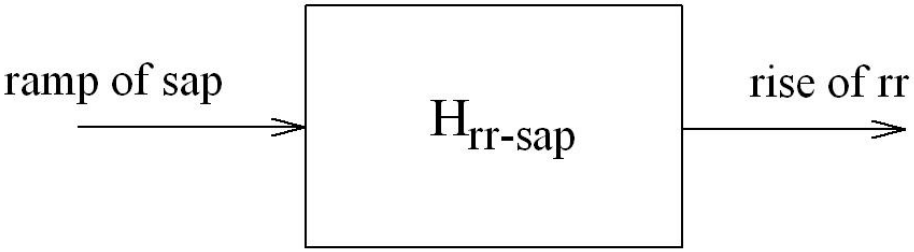
Bivariate autoregressive (AR2) model with exogenous (X) input and autoregressive (AR) noises

XAR2AR model

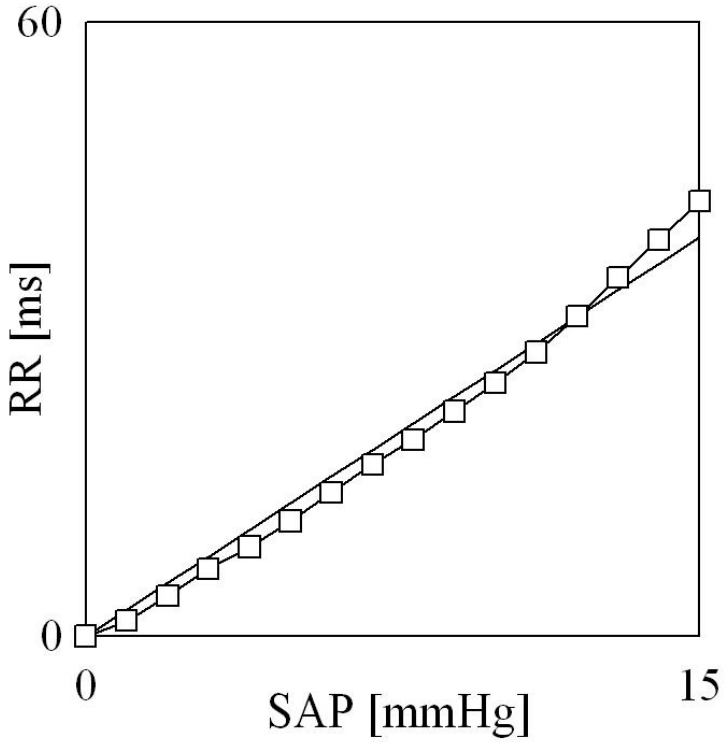


G. Baselli et al, IEEE Trans Biomed Eng, 35, 1033-46, 1988

Estimation of the baroreflex sensitivity from causal models



baroreflex feedback



Baroreflex sensitivity indexes derived from a mild hypertensive patient at rest

Invasive baroreflex sensitivity

α=3 ms/mmHg

Traditional "spontaneous" baroreflex sensitivity

α_{SEQ}=5.4 ms/mmHg

α_{PS}(LF)=8.7 ms/mmHg α_{PS}(HF)=3.1 ms/mmHg

α_{CS}(LF)=7.8 ms/mmHg α_{CS}(HF)=2.5 ms/mmHg

Model-based "spontaneous" baroreflex sensitivity

α_{XAR}=2.5 ms/mmHg α_{AR2}=2.3 ms/mmHg

α_{XXAR}=1.9 ms/mmHg α_{XAR2AR}=1.3 ms/mmHg

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Linear regression analysis between the baroreflex gains estimated by invasive (α) and by non invasive methods (α_{SEQ} and α_{CS}(LF)) in normotensive subjects and borderline hypertensive patients

	r (vs α)	p
α_{SEQ}	0.5	<0.001
α_{CS}(LF)	0.48	<0.001

Modified from L.L. Watkins et al, Hypertension 28, 238-243, 1996

Baroreflex gains estimated by invasive (α) and by non invasive methods (α_{SEQ} and α_{CS}(LF)) in normotensive subjects and borderline hypertensive patients

	Normotensive	Borderline hypertensive	p (normotensive vs hypertensive)
α	19.6±9.1	12.8±5.4	<0.05
α_{SEQ}	15.7±6.6	11.0±5.5	<0.05
α_{CS}(LF)	10.1±5.1	6.2±2.5	<0.01

Values are expressed as mean±standard deviation.

Modified from L.L. Watkins et al, Hypertension 28: 238-243, 1996

Linear regression analysis between the baroreflex gains estimated by invasive (α) and by non invasive methods (α_{SEQ}, α_{PS}(LF), α_{PS}(HF), α_{CS}(LF), α_{CS}(HF), α_{ARXAR}(LF) and α_{ARXAR}(HF)) in patients less than two weeks after myocardial infarction

	r (vs α)	p
α_{SEQ}	0.80	<0.001
α_{PS}(LF)	0.49	0.036
α_{PS}(HF)	0.66	<0.001
α_{CS}(LF)	0.65	<0.001
α_{CS}(HF)	0.57	0.002
α_{ARXAR}(LF)	0.63	<0.001
α_{ARXAR}(HF)	0.68	<0.001

Modified from G. Nollo et al, Am J Physiol 280, H1830-H1839, 2001

Baroreflex gains estimated by invasive (α) and by non invasive methods (α_{SEQ}, α_{PS}(LF), α_{PS}(HF), α_{CS}(LF), α_{CS}(HF), α_{ARXAR}(LF) and α_{ARXAR}(HF)) in patients less than two weeks after myocardial infarction

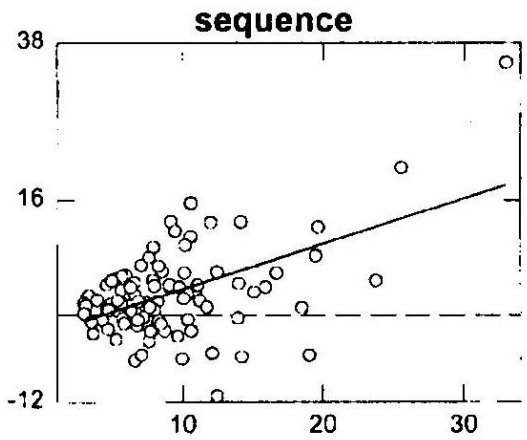
	ms/mmHg	p (vs α)
α	6.43±4.73	
α_{SEQ}	12.56±7.06	<0.001
α_{PS}(LF)	12.54±8.35	0.003
α_{PS}(HF)	11.73±6.85	<0.001
α_{CS}(LF)	8.30±6.51	n.s.
α_{CS}(HF)	9.58±6.42	0.01
α_{ARXAR}(LF)	4.38±3.54	0.024
α_{ARXAR}(HF)	6.34±4.10	n.s.

Values are expressed as mean±standard deviation.
$p<0.05$ was considered significant

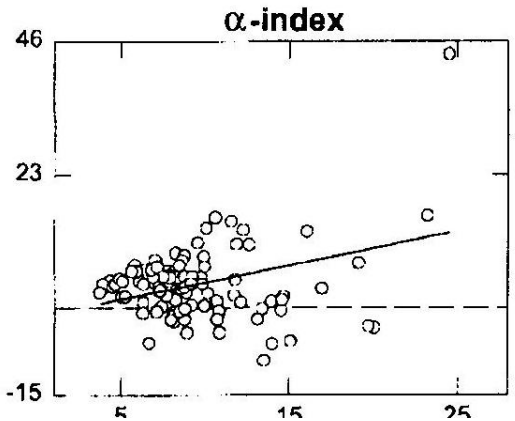
Modified from G. Nollo et al, Am J Physiol 280, H1830-H1839, 2001

Bland-Altman plots between α and α_{SEQ}, α_{PS}, α_{CS}, α_{CS}(LF), α_{IR} in a population including 30% of individuals with established coronary artery disease

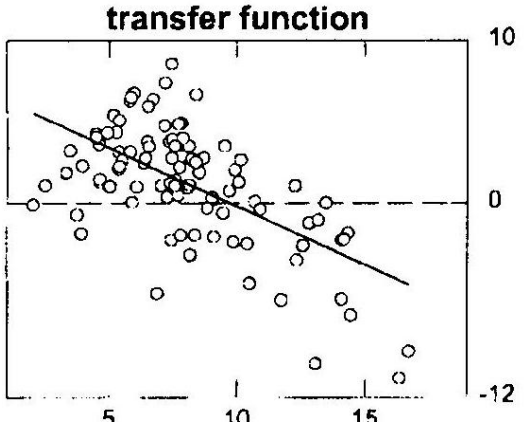
α_{SEQ}



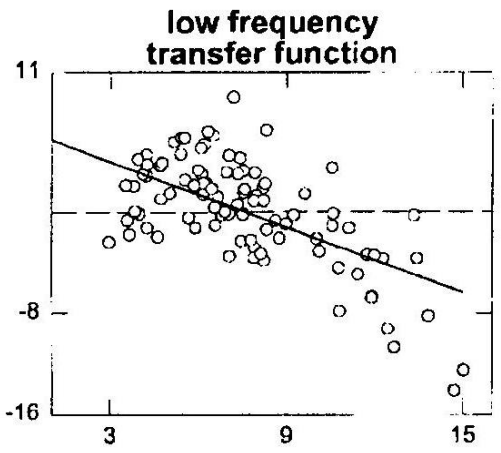
α_{PS} (from 0.05 to 0.3 Hz)



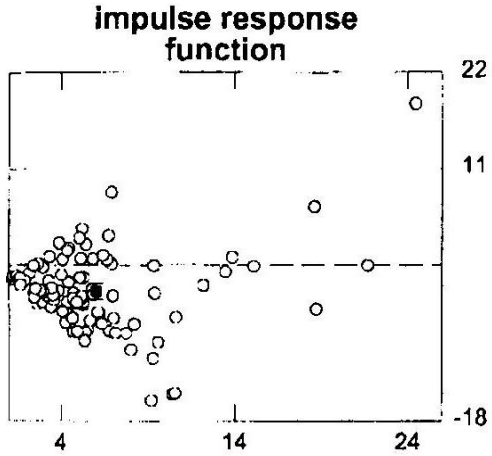
α_{CS} (from 0.05 to 0.3 Hz)



α_{CS}(LF)



α_{IR}



R.D. Lipman et al, Hypertension, 42, 481-487, 2003

Correlations between α and α_{SEQ}, α_{PS}, α_{CS}, α_{CS}(LF), α_{IR} in individuals within the lowest tertile of α

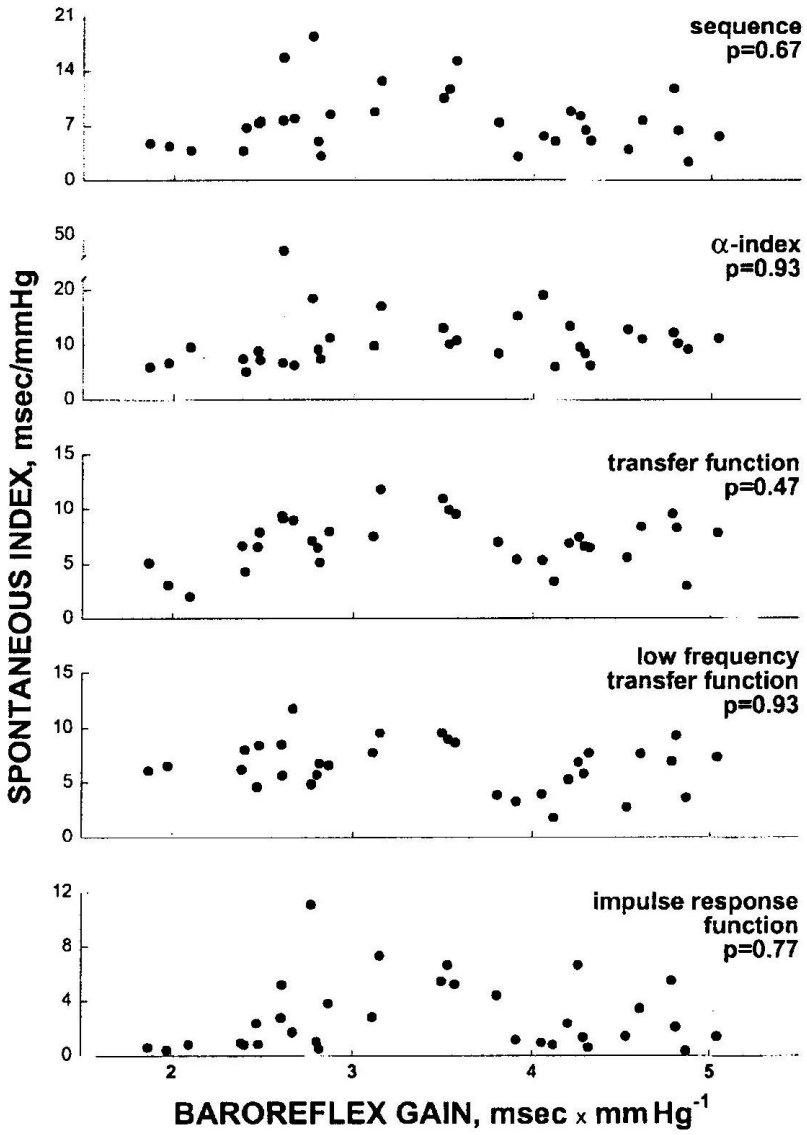
α_{SEQ}

α_{PS}

α_{CS}

α_{CS}(LF)

α_{IR}



α_{PS} was assessed from 0.05 to 0.3 Hz

α_{CS} was assessed from 0.05 to 0.3 Hz

R.D. Lipman et al, Hypertension, 42, 481-487, 2003

Comparing invasive and non invasive baroreflex sensitivity estimates (between-class comparison)

Bad news

1) Correlation between invasive and non invasive baroreflex sensitivity estimates depends on population

2) Correlation may be weak or even absent (especially when the baroreflex sensitivity is low)

3) A significant correlation may coexist with constant and/or proportional biases

Good news

1) Both invasive and non invasive indexes can detect the impairment of the baroreflex function

Outline

1) Modeling the baroreflex

2) Method for invasive estimation of the baroreflex sensitivity and its implicit underlying model

3) Traditional methods for the non invasive estimation of the baroreflex sensitivity and their implicit underlying models

4) Model-based methods for the non invasive estimation of the baroreflex sensitivity

5) Comparing invasive and non invasive baroreflex sensitivity estimates (between-class comparison)

6) Comparing non invasive baroreflex sensitivity estimates (within-class comparison)

7) Interpreting the disagreement between baroreflex sensitivity estimates

Baroreflex gains estimated by traditional non invasive methods (α_{SEQ}, α_{PS}(LF), α_{PS}(HF), α_{CS}(LF) and α_{CS}(HF)) and by a causal parametric model (α_{XXAR}) in conscious dogs

	C	NT	CAO	TABD
α_{SEQ}	40.6±24.0 [b]	17.6±8.7[a,b]	15.7±7.3[a,b]	8.3±3.0[a,b]
α_{PS}(LF)	20.7±9.7	4.4±2	13.1±5.4	-
α_{PS}(HF)	45.3±21.9 [b]	14.7±7.3[a,b]	17.1±6.4[a,b]	6.9±4.1[a,b]
α_{CS}(LF)	19.3±8.9	3.9±2.4	12.2±5.7	-
α_{CS}(HF)	46.4±23.6 [b]	14.4±7.7[a,b]	15.1±6.9[a,b]	8.8±3.4[a,b]
α_{XXAR}	14.7±7.2	3.6±2.7[a]	8.3±10.6[c]	1.0±1.2[a]

Values are expressed as mean±standard deviation. C, control; NT, nitroglicerine infusion; CAO, coronary artery occlusion; TABD, total arterial baroreceptor denervation. [a] $p<0.05$ NT, CAO,TABD vs C, [b] $p<0.05$ α_{BS}, α_{PS}(HF), α_{CS}(HF) vs α_{XXAR}, [c] $p<0.05$ α_{XXAR} vs α_{PS}(LF), α_{CS}(LF)

Modified from A. Porta et al, Am J Physiol, 279, H2558-H2567, 2000

Correlation analysis between various non invasive methods in healthy subjects at rest

$\alpha_{PS}(LF)$ $\alpha_{PS}(HF)$ α_{SEQ}

Table 3. *Matrix of ICC between procedures of estimates of BRS in supine position*

		LF	HF	WG	SEQ	SEQ (PI & MBP)	SEQ (HR & MBP)	TRS	X-AR
HF	a	0.77							
	s	0.88							
	n	21							
WG	a	0.08	0.11						
	s	0.13	0.27						
	n	21	21						
α_{SEQ} SEQ	a	0.77	0.91	0.14					
	s	0.84	0.97	0.31					
	n	21	21	21					
SEQ (PI & MBP)	a	0.47	0.63	0.04	0.49				
	s	0.73	0.70	0.16	0.65				
	n	21	21	21	21				
SEQ (HR & MBP)	a	0.05	0.03	0.07	0.03	0.03			
	s	0.50	0.51	0.26	0.50	0.83			
	n	21	21	21	21	21			
TRS	a	0.91	0.82	0.16	0.83	0.53	0.05		
	s	0.92	0.92	0.28	0.87	0.81	0.61		
	n	21	21	21	21	21	21		
α_{XAR} X-AR	a	0.09	0.008	0.22	0.03	0.04	0.09	0.06	
	s	0.14	0.02	0.22	0.08	0.17	0.36	0.11	
	n	21	21	21	21	21	21	21	
Z	a	0.53	0.24	0.03	0.26	0.18	0.11	0.43	−0.14
	s	0.87	0.65	0.03	0.57	0.73	0.47	0.79	−0.18
	n	10	10	10	10	10	10	10	10

a, intraclass correlation coefficient (ICC) calculated with absolute values; s, ICC calculated with standardized variables, *n*, number of couples of points; WG, weighted gain.

D. Laude et al, Am J Physiol, 286, R226-R231, 2004

Comparison between non invasive baroreflex sensitivity estimates during graded bicycle exercise

BRS	REST	EXE1	EXE2	EXE3	REC
α_{BS}	13.6±6.2	6.0±2.7 *†	4.6±2.0 *†	3.5±1.2 *†	12.0±5.9
$\alpha_{FT(LF)}$	22.3±19.5	13.0±7.5	3.5±1.1 *	3.5±2.5 *	11.0±12.2 ‡
$\alpha_{FT(HF)}$	30.6±19.4	11.2±6.4 *	3.7±2.3 *†	2.6±1.9 *†	14.3±10.3 ‡
$\alpha_{AR(LF)}$	16.7±9.9	7.4±4.5 *†	5.0±3.0 *†	2.9±2.6 *†	15.2±11.2
$\alpha_{AR(HF)}$	19.1±11.2	5.5±3.7 *†	4.3±3.4 *†	3.3±3.4 *†	15.8±12.4
$\alpha_{CS(LF)}$	14.2±10.5	7.9±3.8	3.7±1.8 *†	2.2±1.2 *†	11.6±7.9
$\alpha_{CS(HF)}$	16.4±7.8	7.4±5.1 *†	4.1±2.8 *†	3.1±2.6 *†	15.2±11.0
α_{XAR}	7.6±6.7	3.0±3.5 *	0.9±1.1 *	0.5±0.6 *	4.2±4.1
α_{XXAR}	6.0±7.0	2.8±3.7	0.9±0.7 *	0.6±0.6 *	3.1±3.7

Values are expressed in ms/mmHg as mean±SD. The symbols * and † indicate a significant difference between EXE1, EXE2, EXE3 and REST or REC respectively, and the symbol ‡ indicates a significant difference between REST and REC.

F. Vallais et al, Physiol Meas, 30, 201-213, 2009

Correlation between non invasive baroreflex sensitivity estimates during graded bicycle exercise

REST

BRS	α_{BS}	$\alpha_{FT(LF)}$	$\alpha_{FT(HF)}$	$\alpha_{AR(LF)}$	$\alpha_{AR(HF)}$	$\alpha_{CS(LF)}$	$\alpha_{CS(HF)}$	α_{XAR}	α_{XXAR}
α_{BS}		0.29	0.73*	0.40	0.92*	0.40	0.82*	0.37	0.23
$\alpha_{FT(LF)}$			0.70*	0.90*	0.45	0.96*	0.57*	0.88*	0.77*
$\alpha_{FT(HF)}$				0.76*	0.85*	0.74*	0.79*	0.60*	0.44
$\alpha_{AR(LF)}$					0.54*	0.96*	0.62*	0.72*	0.60*
$\alpha_{AR(HF)}$						0.55	0.94*	0.45	0.28
$\alpha_{CS(LF)}$							0.69*	0.81*	0.69*
$\alpha_{CS(HF)}$								0.56	0.41
α_{XAR}									0.96*
α_{XXAR}									

EXE

BRS	α_{BS}	$\alpha_{FT(LF)}$	$\alpha_{FT(HF)}$	$\alpha_{AR(LF)}$	$\alpha_{AR(HF)}$	$\alpha_{CS(LF)}$	$\alpha_{CS(HF)}$	α_{XAR}	α_{XXAR}
α_{BS}		0.62*	0.72*	0.63*	0.84*	0.71*	0.81*	0.58*	0.64*
$\alpha_{FT(LF)}$			0.73*	0.57*	0.46*	0.83*	0.65*	0.61*	0.55*
$\alpha_{FT(HF)}$				0.40*	0.67*	0.69*	0.73*	0.46*	0.40*
$\alpha_{AR(LF)}$					0.51*	0.80*	0.61*	0.68*	0.71*
$\alpha_{AR(HF)}$						0.68*	0.77*	0.35*	0.32*
$\alpha_{CS(LF)}$							0.81*	0.84*	0.76*
$\alpha_{CS(HF)}$								0.75*	0.70*
α_{XAR}									0.94*
α_{XXAR}									

REC

BRS	α_{BS}	$\alpha_{FT(LF)}$	$\alpha_{FT(HF)}$	$\alpha_{AR(LF)}$	$\alpha_{AR(HF)}$	$\alpha_{CS(LF)}$	$\alpha_{CS(HF)}$	α_{XAR}	α_{XXAR}
α_{BS}		0.68*	0.87*	0.69*	0.85*	0.76*	0.84*	0.46	0.19
$\alpha_{FT(LF)}$			0.77*	0.75*	0.77*	0.94*	0.74*	0.41	0.12
$\alpha_{FT(HF)}$				0.80*	0.98*	0.74*	0.98*	0.41	-0.06
$\alpha_{AR(LF)}$					0.77*	0.65*	0.87*	0.23	-0.27
$\alpha_{AR(HF)}$						0.72*	0.97*	0.45	0.01
$\alpha_{CS(LF)}$							0.69*	0.39	0.15
$\alpha_{CS(HF)}$								0.39	-0.12
α_{XAR}									0.62*
α_{XXAR}									

The symbol * indicates a significant correlation with $p<0.05$.

F. Vallais et al, Physiol Meas, 30, 201-213, 2009

Comparing non invasive baroreflex sensitivity estimates (within-class comparison)

Bad news

1) Non invasive methods provide different estimates of the baroreflex gain

2) Some of the non invasive estimates are not correlated with others

3) Correlation might depend on the experimental condition

Good news

1) All non invasive indexes can detect unloading or impairment of baroreflex

Outline

1) Modeling the baroreflex

2) Method for invasive estimation of the baroreflex sensitivity and its implicit underlying model

3) Traditional methods for the non invasive estimation of the baroreflex sensitivity and their implicit underlying models

4) Model-based methods for the non invasive estimation of the baroreflex sensitivity

5) Comparing invasive and non invasive baroreflex sensitivity estimates (between-class comparison)

6) Comparing non invasive baroreflex sensitivity estimates (within-class comparison)

7) Interpreting the disagreement between baroreflex sensitivity estimates

Toward a possible explanation of the differences between invasive and non invasive baroreflex estimates

Physiology underlying pharmacologically forced RR interval response

Open loop along baroreflex

Physiology underlying spontaneous variability

Closed loop interactions perturbed by noises in LF and HF bands

Matching physiology with methods for baroreflex sensitivity estimation

Physiology underlying pharmacologically forced RR interval response

Open loop along baroreflex

Physiology underlying spontaneous variability

Closed loop interactions perturbed by noises in LF and HF bands

Model underlying the method for invasive estimate of baroreflex sensitivity

Open loop along baroreflex

Model underlying the methods for non invasive estimate of baroreflex sensitivity

Various models depending on the approach

Toward a possible explanation of the differences among non invasive baroreflex estimates

Differences among non invasive baroreflex estimates might be the effect of the different model underlying each technique

Indeed, non invasive methods differ in the ability of accounting for three factors

1) causality or directionality in the SAP-RR dynamical interactions

2) respiratory inputs perturbing SAP-RR interactions

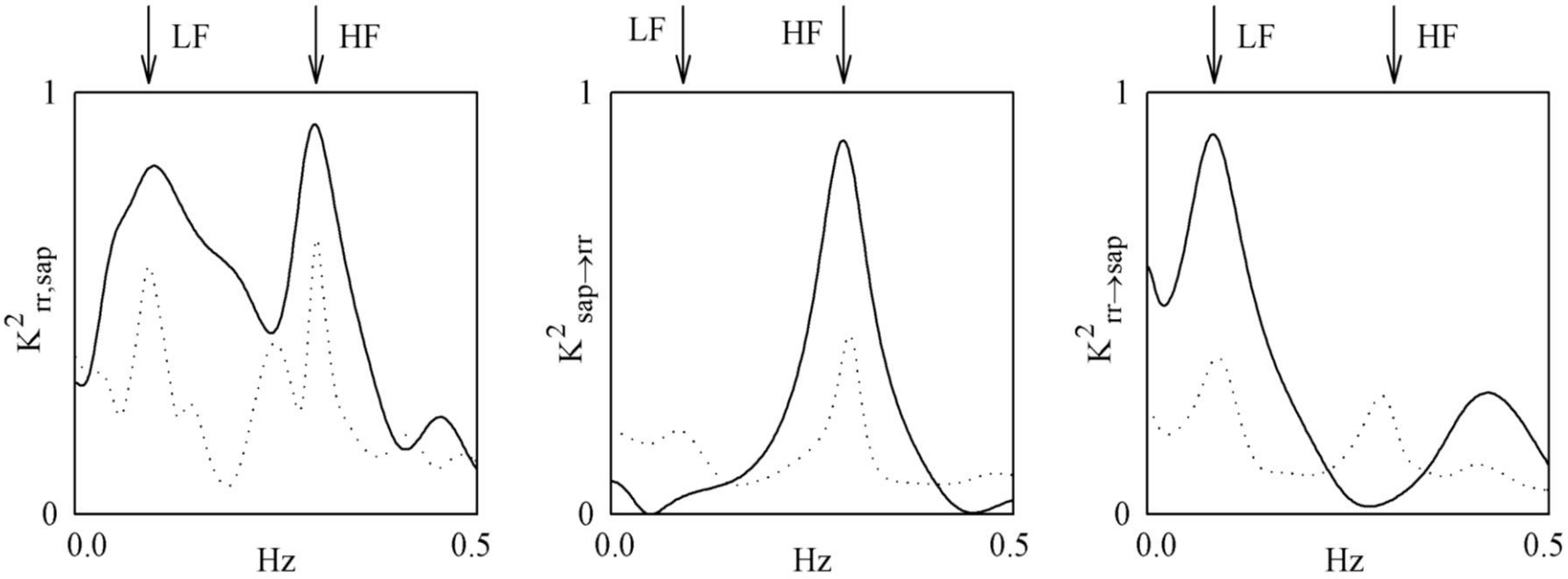
3) regulatory inputs in the LF band independent of baroreflex

Causality (or directionality) in the SAP-RR dynamical interactions

baroreflex feedback

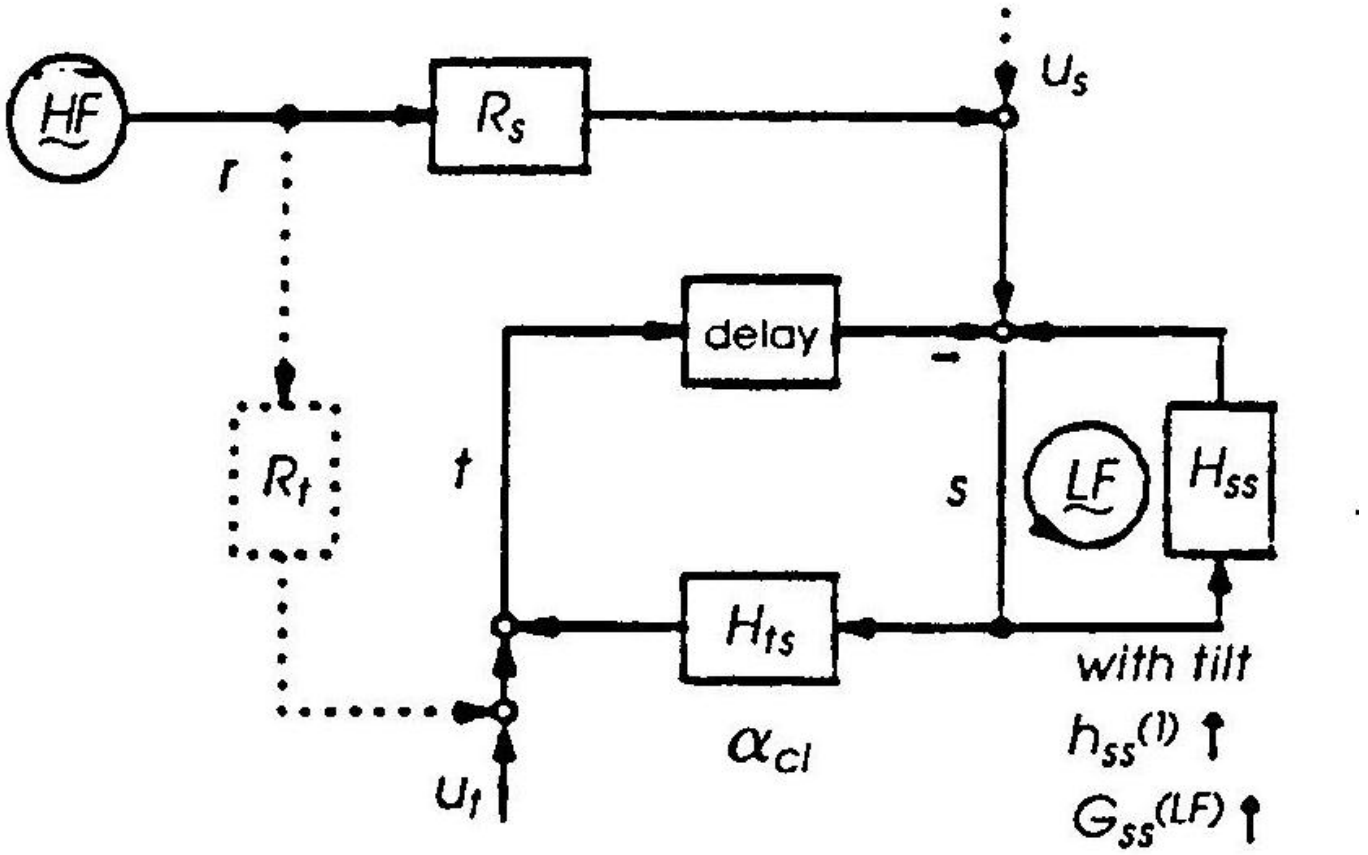
mechanical feedforward

$K^2_{rr,sap}$ $K^2_{sap \rightarrow rr}$ $K^2_{rr \rightarrow sap}$



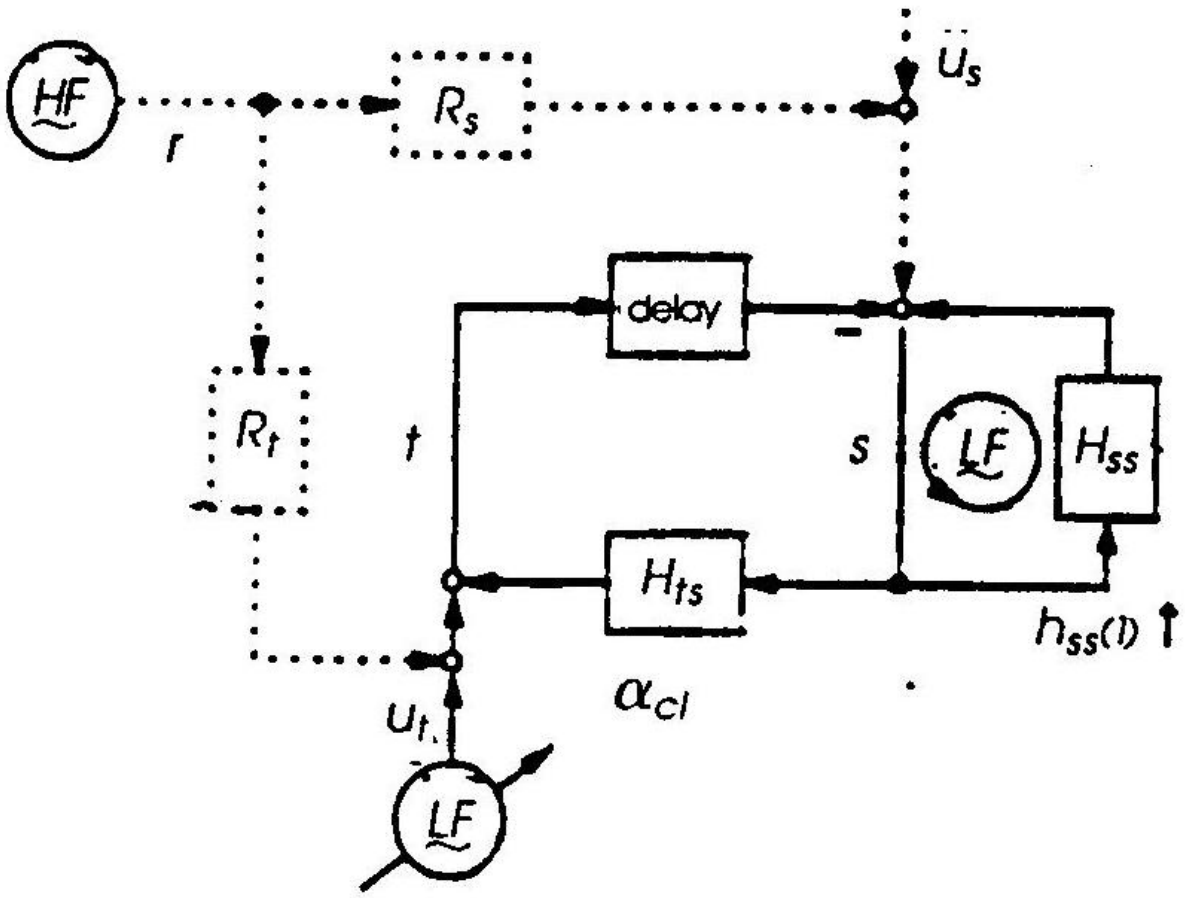
A. Porta et al, Biol Cybern, 86, 241-251, 2002

Effects of respiration on SAP-RR interactions



G. Baselli et al, Med Biomed Eng Comput, 32, 143-152, 1994

Effects of regulatory inputs in the LF band independent of baroreflex



G. Baselli et al, Med Biomed Eng Comput, 32, 143-152, 1994

Conclusions

Poor matching of the non invasive techniques with physiology may be responsible for the disagreement between invasive and non invasive estimates

Different abilities of the non invasive techniques in taking into account causality (or directionality) in the SAP-RR interactions and inputs capable to change heart period independently of SAP both in LF and HF bands might be responsible for the disagreement among non invasive techniques

Among non invasive techniques those based on closed loop models should be better explored on large sets of data as they can guarantee a better matching with physiology