A network physiology approach to cardiovascular, cardiorespiratory and cerebrovascular dynamic interactions

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Introduction

Control mechanisms are responsible for the homeostasis of physiological variables in humans

The health of the entire organism depends on the correct functioning of regulatory reflexes

The intricated nature of these regulations requires a multivariate dynamic approach capable to describe the directionality of the interactions and to account for disturbances that might mix up causal relationships

Aim

To propose a methodological framework for studying physiological control mechanisms fully under the perspective of network physiology

The framework will be made practical over cardiovascular, cardiorespiratory and cerebrovascular regulations

Outline

1) Possibilities offered by a network physiology approach designed to assess physiological control mechanisms

2) Examples of physiological regulations: the cases of cardiovascular, cardiorespiratory and cerebrovascular controls

3) A network physiology approach based on Wiener-Granger causality analysis

4) Experimental protocols and acquired variability series

5) Results relevant to the application of the network physiology approach to cardiovascular, cardiorespiratory and cerebrovascular data

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Possibilities offered by a network physiology perspective

The possibilities offered by a network physiology approach designed to assess physiological control mechanisms are mainly grounded on

i) disentangling closed loop relationships

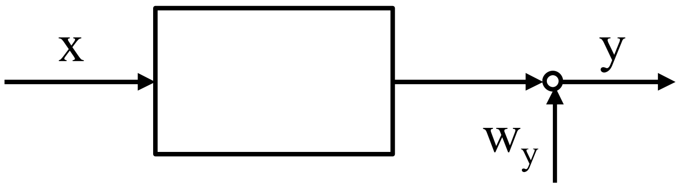
ii) accommodating multivariate recordings and accounting for exogenous colored disturbances

iii) classifying the type of influence according to its effect on a physiological function

Disentangling closed loop relationships

traditional
approach

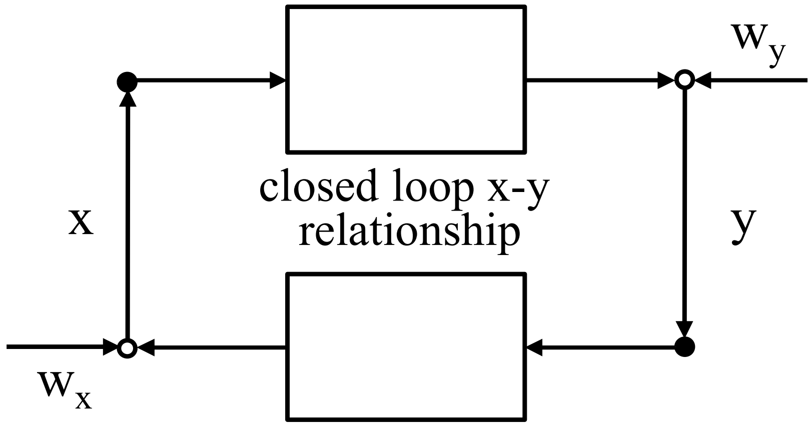
feedforward pathway



feedforward
relationship
from x to y

network
physiology
approach

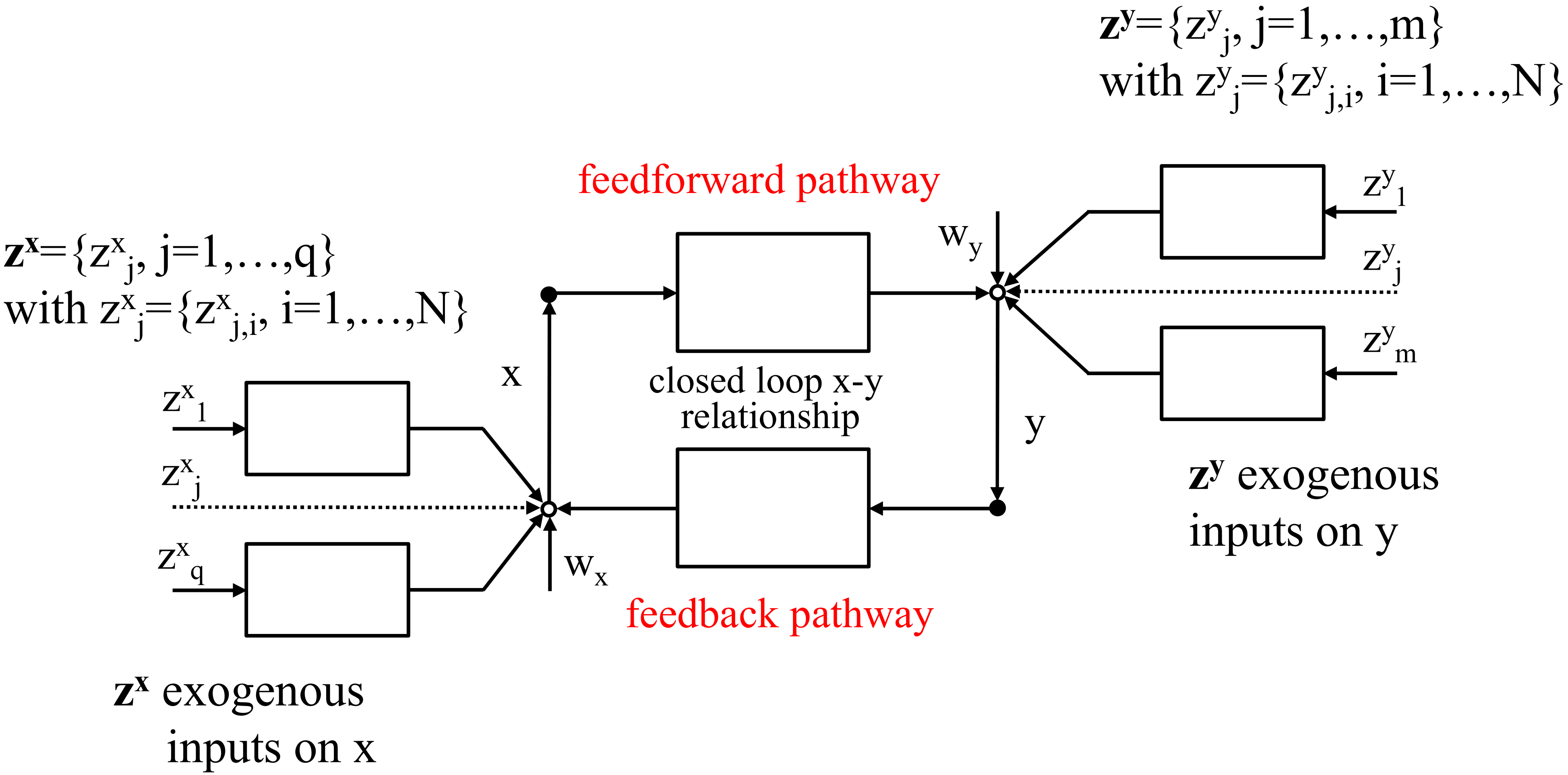
feedforward pathway



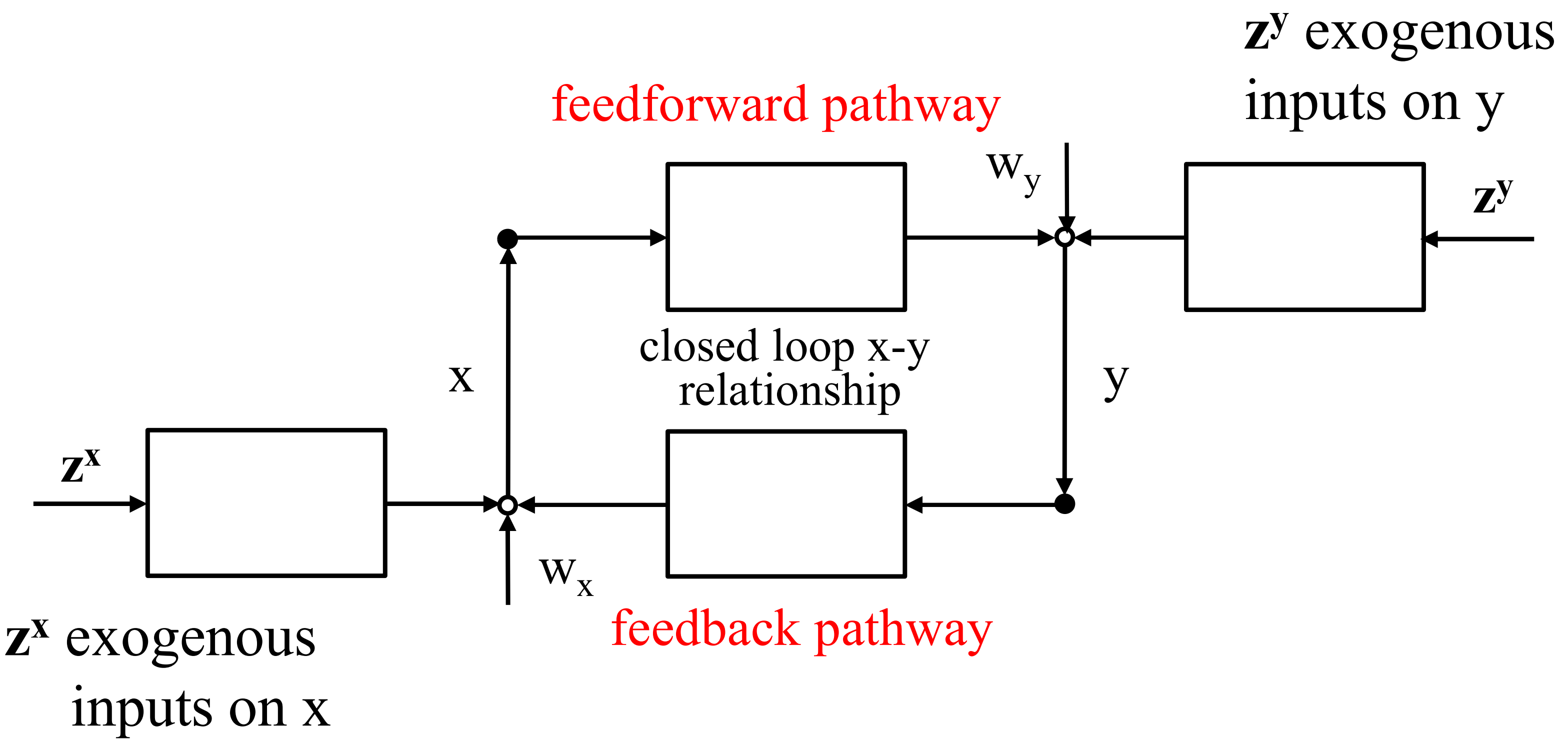
feedback pathway

closed loop
x-y relationship

Accommodating multivariate recordings and accounting for exogenous colored inputs



Classifying the type of influence according to its effect on a physiological function



z^x can be classified as confounder/suppressor of $y \longrightarrow x$
z^y can be classified as confounder/suppressor of $x \longrightarrow y$

z^x is confounder/suppressor of $y \longrightarrow x$ if the knowledge of z^x reduces/enhances the strength of the causal relationship from y to x

z^y is confounder/suppressor of $x \longrightarrow y$ if the knowledge of z^y reduces/enhances the strength of the causal relationship from x to y

D.P. MacKinnon et al, Prev Sci, 1, 173-180, 2000

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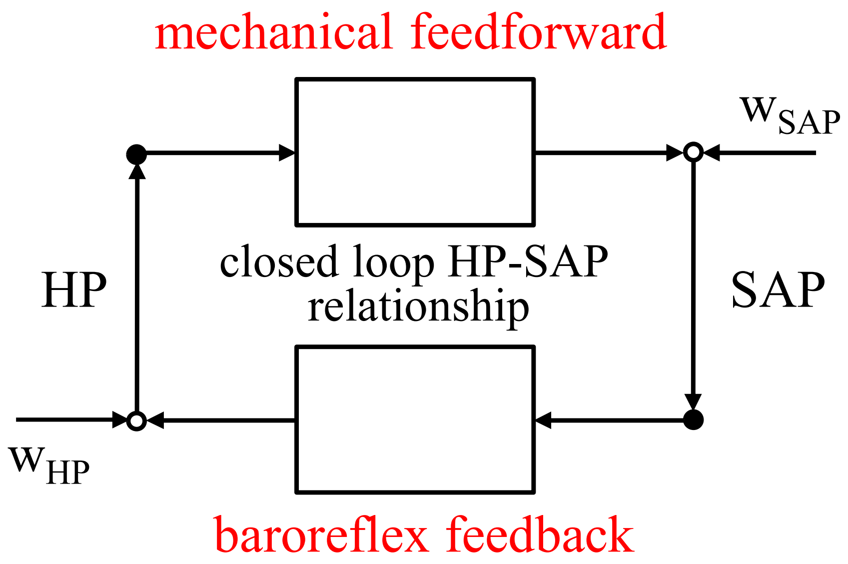
Cardiovascular control loop

Cardiovascular control loop accounts for the dynamical interactions between heart period (HP) and arterial pressure (AP) values, both systolic (SAP) and diastolic (DAP)



baroreflex feedback

$$SAP_i \uparrow \longrightarrow HP_i \uparrow$$

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

mechanical feedforward

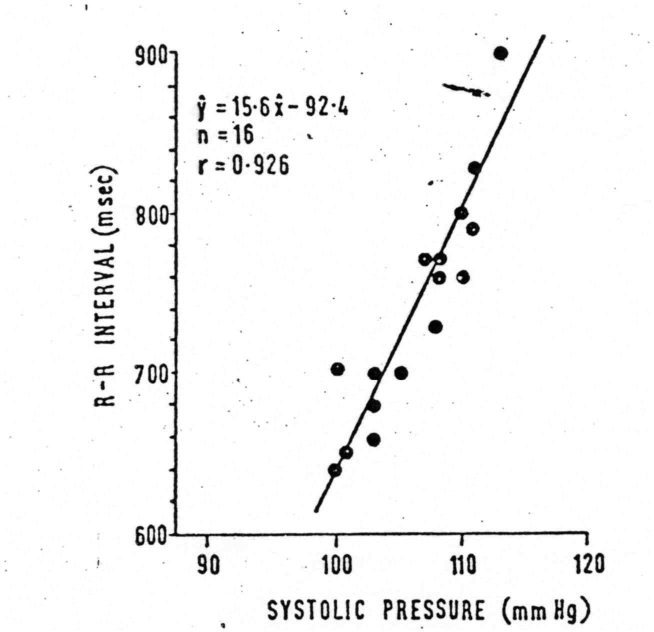
$$HP_i \uparrow \longrightarrow DAP_i \downarrow \begin{cases} \nearrow SAP_{i+1} \downarrow & \text{Windkessel effect} \\ \searrow SAP_{i+1} \uparrow & \text{Frank-Starling effect} \end{cases}$$

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

Probing the pathways from SAP to HP and vice versa

baroreflex feedback

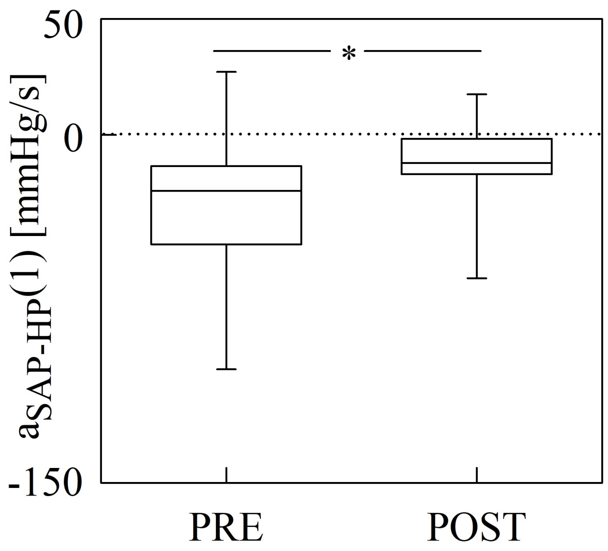
SAP⟶HP



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

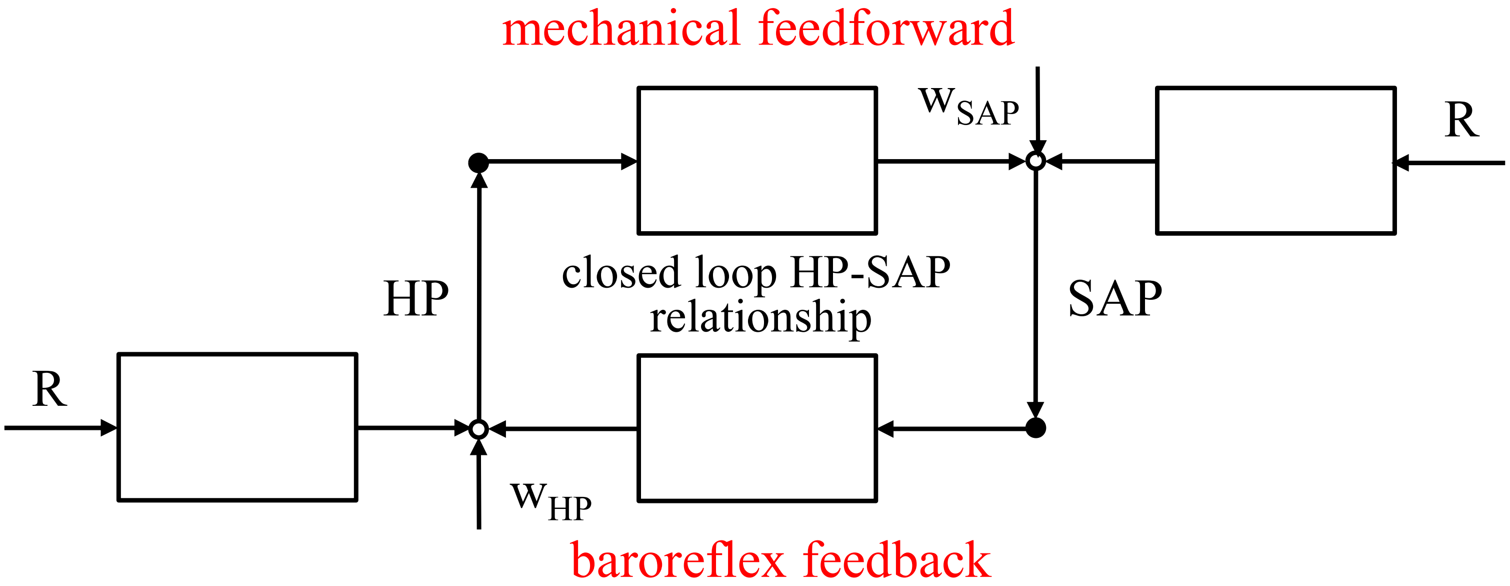
mechanical feedforward

HP⟶SAP



A. Porta et al, J Appl Physiol, 115, 1032-1042, 2013

Respiratory activity influences cardiovascular control loop



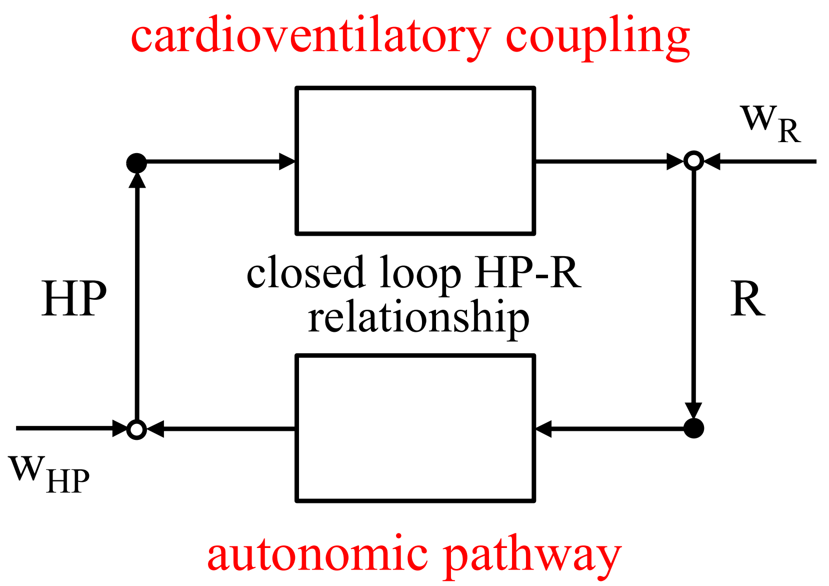
R ⟶ HP: respiratory centers gate autonomic outflow modulating the activity of the sinus node

R ⟶ SAP: respiration induces variations of intrathoracic pressure driving changes of venous return and stroke volume

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

Cardiorespiratory control loop

Cardiorespiratory control loop accounts for the dynamical interactions between HP and respiration (R)



autonomic pathway

respiratory centers ⟶ autonomic outflow ⟶ HP

D.L. Eckberg, J Physiol, 548, 339-352, 2003

cardioventilatory coupling

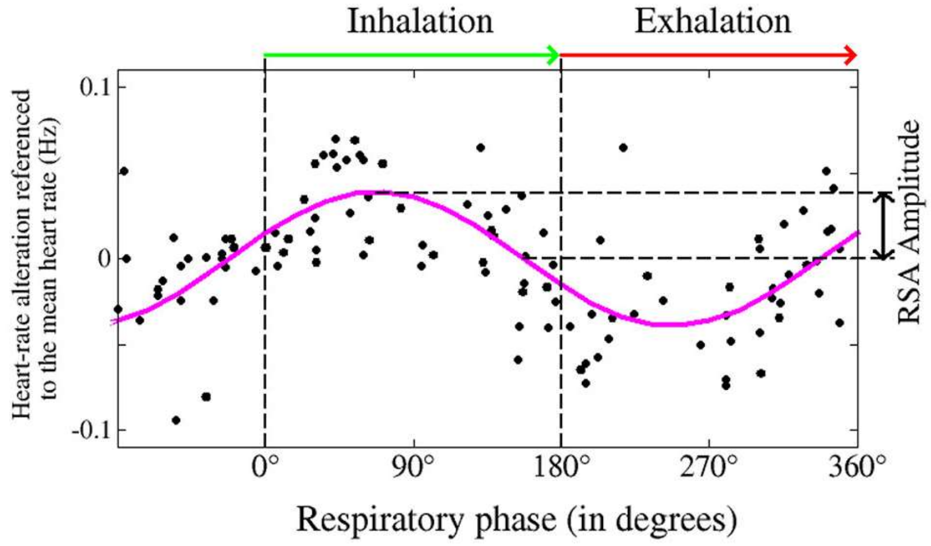
the latency between the cardiac beat just preceding the inspiratory onset and the inspiratory onset is constant

D.C. Galletly and P.D. Larsen, Br J Anaesth, 79, 35-40, 1997

Probing the pathways from R to HP and vice versa

autonomic pathway

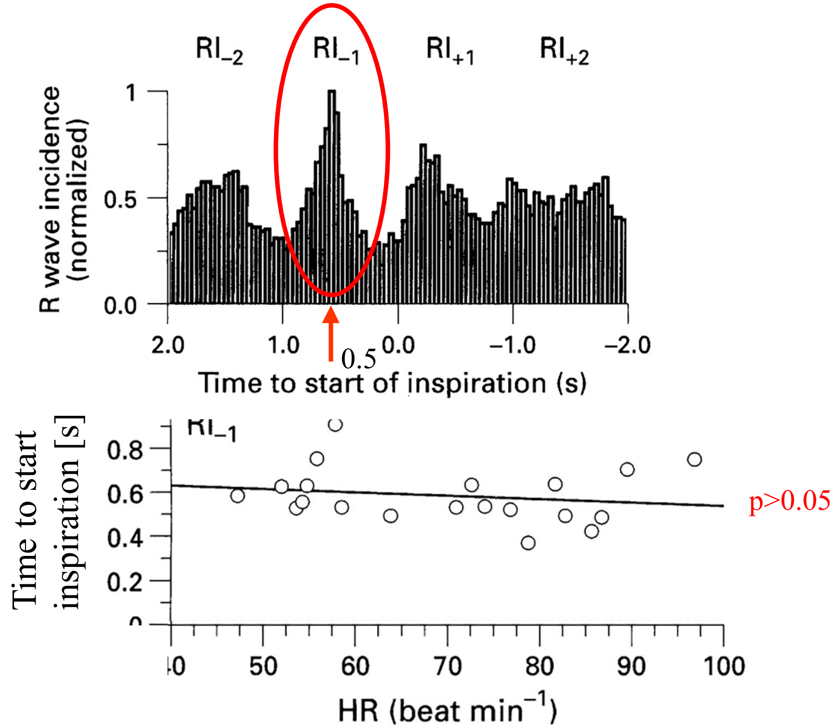
R⟶HP



T. Penzel et al, Front Physiol, 7, 460, 2016

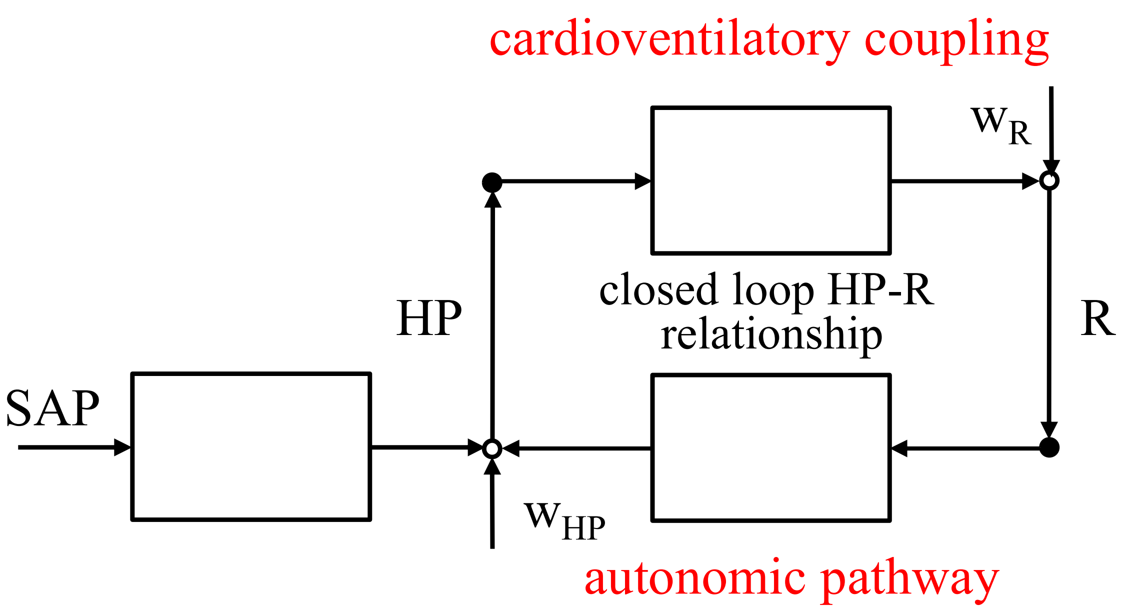
cardioventilatory coupling

HP⟶R



D.C. Galletly and P.D. Larsen, Br J Anaesth, 79, 35-40, 1997

Arterial pressure variations influence cardiorespiratory control loop

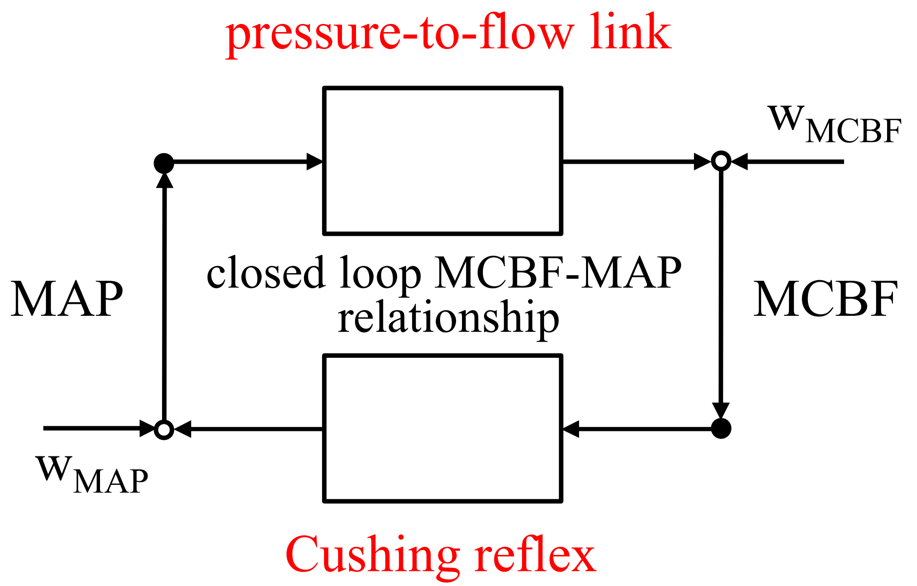


SAP ⟶ HP: direct influences of arterial pressure changes on HP mediated by the activation of the baroreflex

R.M. Abreu et al, Front Physiol, 11, 134, 2020

Cerebrovascular control loop

Cerebrovascular control loop accounts for the dynamical interactions between mean AP (MAP) and mean cerebral blood flow (MCBF)



pressure-to-flow link

MAP⟶MCBF is the result of fundamental laws of fluid dynamics

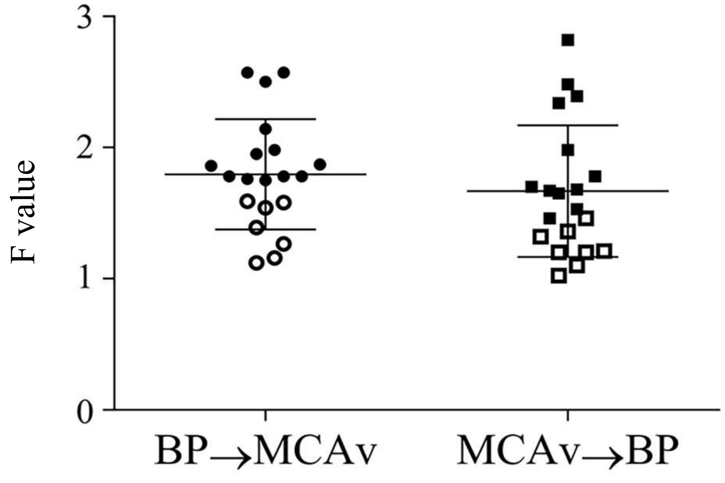
Y.C. Tzeng et al, J Appl Physiol, 117, 1037-1048, 2014

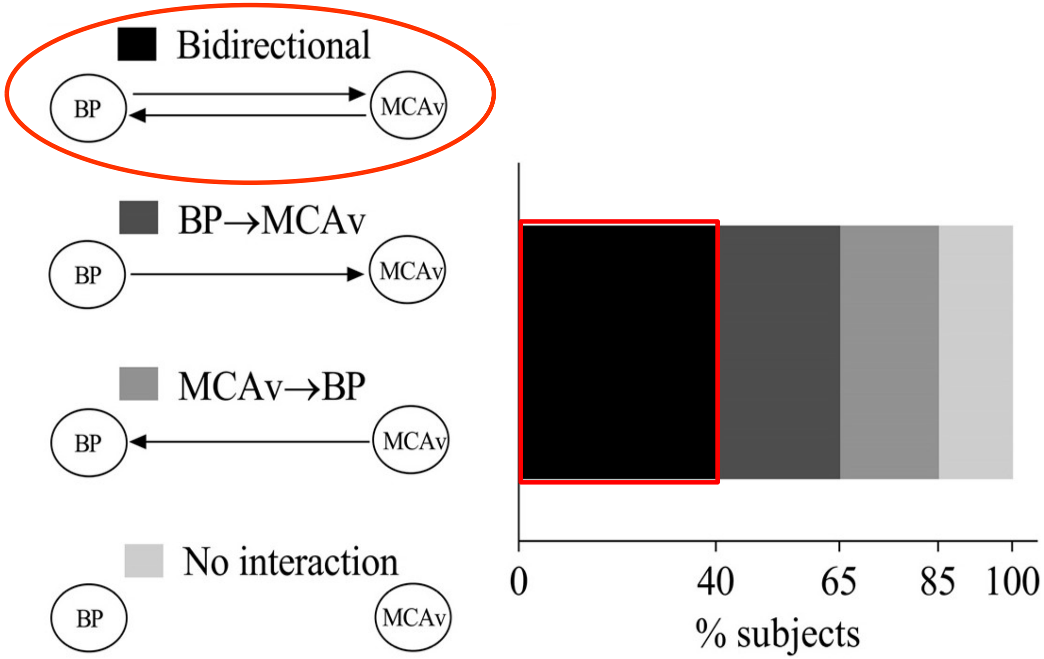
Cushing reflex

MCBF↓ ⟶ sympathetic activity↑ ⟶ MAP↑

H. Cushing, Amer J Med Sci, 124, 375-400, 1902

Probing the pathways from MAP to MCBF and vice versa





S. Saleem et al, Am J Physiol, 315: R484–R495, 2018

pressure-to-flow link

MAP⟶MCBF

Cushing reflex

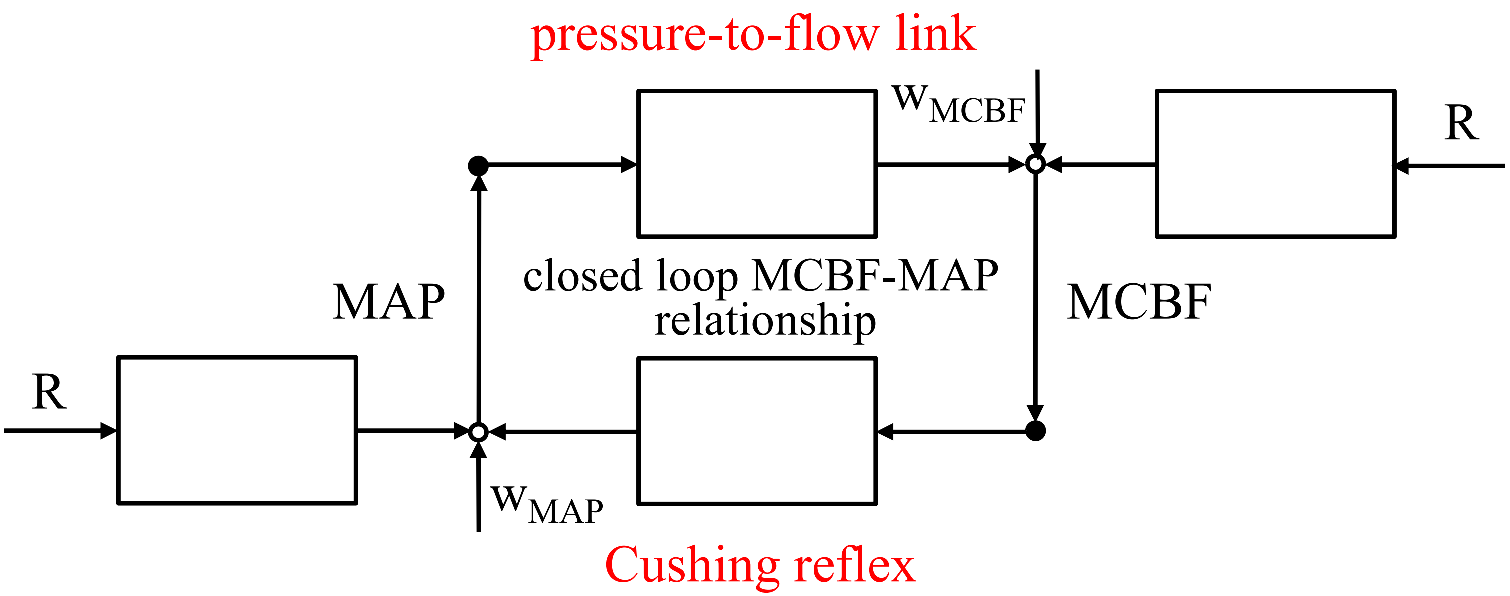
MCBF⟶MAP

⇨

in healthy humans at supine resting

MAP↔MCBF

Respiratory activity influences cerebrovascular control loop



R ⟶ MAP: respiration induces variations of intrathoracic pressure driving modifications of venous return and stroke volume

R ⟶ MCBF: respiration induces movements of cerebrospinal fluid and, in turn, changes of intracranial pressure

A. Porta et al, IEEE Trans Biomed Eng, 69, 2065-2076, 2022

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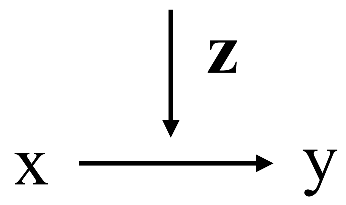
Generalities about Wiener-Granger causality



Given an effect series $y=\{y_i, i=1, \ldots, N\}$, a cause series $x=\{x_i, i=1, \ldots, N\}$ and a set of m exogenous influences $\mathbf{z}=\{z_1, \ldots, z_j, \ldots, z_m\}$ with $z_j=\{z_{j,i}, i=1, \ldots, N\}$,

$$\mathbf{y}_i^- = (y_{i-1}, \ldots, y_{i-p})$$
$$\mathbf{x}_i^- = (x_{i-1}, \ldots, x_{i-p}) \text{ and}$$
$$\mathbf{z}_i^- =\{\mathbf{z}_{1,i}^-, \ldots, \mathbf{z}_{j,i}^-, \ldots, \mathbf{z}_{m,i}^-\} \text{ with } \mathbf{z}_{j,i}^- = (z_{j,i-1}, \ldots, z_{j,i-p})$$

are the vectors formed by p past values of the effect, p past values of the cause and the set of vectors collecting p past values of the m exogenous signals with $j=1, \ldots, m$

Wiener-Granger causality approach

Defined the full universe of knowledge as $\Omega=\{x,y,\mathbf{z}\}$ the dynamics of y can be described in Ω as

$$y_i^{\Omega} = f^{\Omega}(\mathbf{y}_i^{-}, \mathbf{x}_i^{-}, \mathbf{z}_i^{-}) + w_i^{\Omega}$$

where $f^{\Omega}(\cdot)$ is an appropriate function identified in Ω

Analogously, defined the restricted universe of knowledge as $\Omega\backslash\{x\}=\{y,\mathbf{z}\}$, the dynamics of y can be described in $\Omega\backslash\{x\}$ as

$$y_i^{\Omega\backslash\{x\}} = f^{\Omega\backslash\{x\}}(\mathbf{y}_i^{-}, \mathbf{z}_i^{-}) + w_i^{\Omega\backslash\{x\}}$$

where $f^{\Omega\backslash\{x\}}(\cdot)$ is an appropriate function identified in $\Omega\backslash\{x\}$

Wiener-Granger causality approach

Fitting procedures lead to the estimation of $f^{\Omega}(\cdot)$ in Ω, thus providing a prediction of y_i in Ω as

$$\hat{y}_i^{\Omega} = \hat{f}^{\Omega}(\mathbf{y}_i^-, \mathbf{x}_i^-, \mathbf{z}_i^-)$$

and to the estimation of $f^{\Omega\backslash\{x\}}(\cdot)$ in $\Omega\backslash\{x\}$, thus providing a prediction of y_i in $\Omega\backslash\{x\}$ as

$$\hat{y}_i^{\Omega\backslash\{x\}} = \hat{f}^{\Omega\backslash\{x\}}(\mathbf{y}_i^-, \mathbf{z}_i^-)$$

Wiener-Granger predictability improvement

Given y and the prediction of y, $\hat{y}$, the mean square prediction error λ^2 of y can be calculated in Ω and $\Omega\backslash\{x\}$ as

$$\lambda^2_{\Omega} = \frac{1}{N}\sum_{i=1}^{N}(y_i - \hat{y}_i^{\Omega})^2 \quad \text{and} \quad \lambda^2_{\Omega\backslash\{x\}} = \frac{1}{N}\sum_{i=1}^{N}(y_i - \hat{y}_i^{\Omega\backslash\{x\}})^2$$

The causal predictability (CP) from x to y given **z** is computed as the difference between λ^2 in $\Omega\backslash\{x\}$ and that in Ω,

$$CP_{x \rightarrow y|\mathbf{z}} = \lambda^2_{\Omega\backslash\{x\}} - \lambda^2_{\Omega}$$

$CP_{x \rightarrow y|\mathbf{z}}$ is taken as a measure of the strength of the causal link from x to y above and beyond the contribution of past values of y and **z**

C.W.J. Granger, J Econ Dyn Control, 2, 329-352, 1980

Different metrics to assess Wiener-Granger predictability improvement

$CP_{x \rightarrow y|\mathbf{z}}$ can be computed according to several metrics

$$CP_{x \rightarrow y|\mathbf{z}} = \lambda^2_{\Omega\backslash\{x\}} - \lambda^2_{\Omega}$$

unnormalized CP

$$NCP_{x \rightarrow y|\mathbf{z}} = \frac{\lambda^2_{\Omega\backslash\{x\}} - \lambda^2_{\Omega}}{\lambda^2_{\Omega\backslash\{x\}}}$$

normalized CP

$$\log CP_{x \rightarrow y|\mathbf{z}} = \log \frac{\lambda^2_{\Omega\backslash\{x\}}}{\lambda^2_{\Omega}}$$

log CP ratio

A. Porta et al, Physiol Meas, 37, 276-290, 2016

Wiener-Granger causality approach without considering z

Defined the full universe of knowledge as $\Omega=\{x,y,\mathbf{z}\}$ the dynamics of y can be described in $\Omega\backslash\{\mathbf{z}\}$ as

$$y_i = f^{\Omega\backslash\{\mathbf{z}\}}(\mathbf{y}_i^-, \mathbf{x}_i^-) + w_i^{\Omega\backslash\{\mathbf{z}\}}$$

where $f^{\Omega\backslash\{\mathbf{z}\}}(\cdot)$ is an appropriate function identified in $\Omega\backslash\{\mathbf{z}\}$

Analogously, defined the restricted universe of knowledge as $\Omega\backslash\{x,\mathbf{z}\}=\{y\}$, the dynamics of y can be described in $\Omega\backslash\{x,\mathbf{z}\}$ as

$$y_i = f^{\Omega\backslash\{x,\mathbf{z}\}}(\mathbf{y}_i^-) + w_i^{\Omega\backslash\{x,\mathbf{z}\}}$$

where $f^{\Omega\backslash\{x,\mathbf{z}\}}(\cdot)$ is an appropriate function identified in $\Omega\backslash\{x,\mathbf{z}\}$

Wiener-Granger causality approach without considering z

Fitting procedures lead to the estimation of $f^{\Omega\backslash\{\mathbf{z}\}}(\cdot)$ in $\Omega\backslash\{\mathbf{z}\}$, thus providing a prediction of y_i in $\Omega\backslash\{\mathbf{z}\}$ as

$$\hat{y}_i^{\Omega\backslash\{\mathbf{z}\}} = \hat{f}^{\Omega\backslash\{\mathbf{z}\}}(\mathbf{y}_i^-, \mathbf{x}_i^-)$$

and the estimation of $f^{\Omega\backslash\{x,\mathbf{z}\}}(\cdot)$ in $\Omega\backslash\{x,\mathbf{z}\}$, thus providing a prediction of y_i in $\Omega\backslash\{x,\mathbf{z}\}$ as

$$\hat{y}_i^{\Omega\backslash\{x,\mathbf{z}\}} = \hat{f}^{\Omega\backslash\{x,\mathbf{z}\}}(\mathbf{y}_i^-)$$

Wiener-Granger predictability improvement without considering z

Given y and the prediction of y, $\hat{y}$, the mean square prediction error λ^2 of y can be calculated in $\Omega\backslash\{\mathbf{z}\}$ and $\Omega\backslash\{x,\mathbf{z}\}$ as

$$\lambda^2_{\Omega\{\mathbf{z}\}} = \frac{1}{N}\sum_{i=1}^{N}(y_i - \hat{y}_i^{\Omega\backslash\{\mathbf{z}\}})^2 \quad \text{and} \quad \lambda^2_{\Omega\backslash\{x,\mathbf{z}\}} = \frac{1}{N}\sum_{i=1}^{N}(y_i - \hat{y}_i^{\Omega\backslash\{x,\mathbf{z}\}})^2$$

The CP from x to y is computed as the difference between λ^2 in $\Omega\backslash\{x,\mathbf{z}\}$ and that in $\Omega\backslash\{\mathbf{z}\}$

$$CP_{x\rightarrow y} = \lambda^2_{\Omega\backslash\{x,\mathbf{z}\}} - \lambda^2_{\Omega\backslash\{\mathbf{z}\}}$$

$CP_{x\rightarrow y}$ is taken as a measure of the strength of the causal link from x to y above and beyond the contribution of past values of y

C.W.J. Granger, J Econ Dyn Control, 2, 329-352, 1980

Different metrics to assess Wiener-Granger predictability improvement without considering z

$CP_{x \rightarrow y}$ can be computed according to several metrics

$$CP_{x \rightarrow y} = \lambda^2_{\Omega \backslash \{x,\mathbf{z}\}} - \lambda^2_{\Omega \backslash \{\mathbf{z}\}}$$

unnormalized CP

$$NCP_{x \rightarrow y} = \frac{\lambda^2_{\Omega \backslash \{x,\mathbf{z}\}} - \lambda^2_{\Omega \backslash \{\mathbf{z}\}}}{\lambda^2_{\Omega \backslash \{x,\mathbf{z}\}}}$$

normalized CP

$$\log CP_{x \rightarrow y} = \log \frac{\lambda^2_{\Omega \backslash \{x,\mathbf{z}\}}}{\lambda^2_{\Omega \backslash \{\mathbf{z}\}}}$$

log CP ratio

A. Porta et al, Physiol Meas, 37, 276-290, 2016

Confounder/suppressor (C/S) test

According to the definition of C/S, **z** is a confounder of the causal link from x to y if

$$CP_{x \to y|\mathbf{z}} < CP_{x \to y} \quad \Rightarrow \quad CP_{x \to y|\mathbf{z}} - CP_{x \to y} < 0$$

meaning that the introduction of **z** reduces the strength of the causal relationship from x to y

Conversely, **z** is a suppressor if

$$CP_{x \to y|\mathbf{z}} > CP_{x \to y} \quad \Rightarrow \quad CP_{x \to y|\mathbf{z}} - CP_{x \to y} > 0$$

because the introduction of **z** enhances the strength of the causal relationship from x to y

C/S test and redundancy/synergy balance

Since it can be proven that

$$CP_{x \rightarrow y} - CP_{x \rightarrow y|\mathbf{z}}$$

is the balance between redundancy and synergy of x and **z** in contributing to y, the C/S test is equivalent to check the sign of the balance between redundancy and synergy of x and **z** in contributing to y

When CP is computed via unnormalized CP, the balance between redundancy and synergy is the interactive predictability (IP)

$$CP_{x \rightarrow y} - CP_{x \rightarrow y|\mathbf{z}} = IP(Y;X,\mathbf{Z})$$

When CP is computed via log CP ratio, the balance between redundancy and synergy is the interactive transfer entropy (ITE)

$$CP_{x \rightarrow y} - CP_{x \rightarrow y|\mathbf{z}} = ITE(Y;X,\mathbf{Z})$$

A. Porta et al, IEEE Trans Biomed Eng, 69, 2065-2076, 2022

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Experimental protocols

1) Graded head-up tilt in healthy humans

2) Head-up tilt in subjects prone to develop orthostatic syncope

3) Propofol-based general anesthesia in patients scheduled for coronary artery bypass grafting

Graded head-up tilt protocol

19 nonsmoking healthy humans (age: 21-48, median=30, 8 men)

We recorded electrocardiogram (ECG) from lead II, noninvasive finger AP via Finometer MIDI (Finapres Medical Systems, The Netherlands) and R via thoracic belt (Marazza, Monza, Italy) at 300 Hz during graded head-up tilt (T)

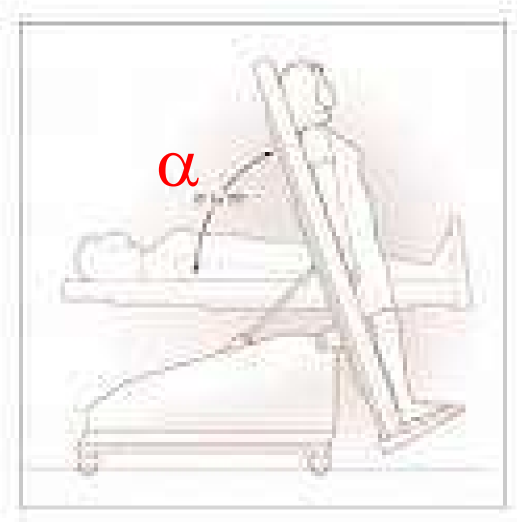


Table angle α was randomly chosen within the set {15,30,45,60,75,90}

Each T session lasts 10 minutes was always preceded by a session (7 minutes) at rest in supine position (REST) and followed by a recovery period (5 minutes). Each subject performed all T sessions (i.e. T15, T30, T45, T60, T75, T90)

Syncope protocol

13 subjects who never experienced postural syncope (noSYNC, age: 27±8 yrs, 5 males) and 13 subjects prone to develop postural syncope (SYNC, at least three episodes in the last year, age: 28±9 yrs, 5 males)

We acquired ECG (lead II), noninvasive finger AP (Portapres, Finapres Medical Systems, Amsterdam, The Netherlands), R via thoracic belt (Marazza, Monza, Italy) and cerebral blood flow (CBF) velocity via a transcranial Doppler device (Multi-Dop T, 2MHz, Compumedics, DWL, San Juan Capistrano, CA, USA) from the left or right middle cerebral artery at 1000 Hz

Signals were recorded at REST and during T60 prolonged for 30 minutes

REST always preceded HUT. Analyses were carried out in the first 10 minutes well before developing presyncope signs. While all SYNCs developed syncope before ending session, none of noSYNCs did

Propofol-based general anesthesia protocol

17 patients (age: 64±8, yrs, 17 males) scheduled for coronary artery bypass grafting

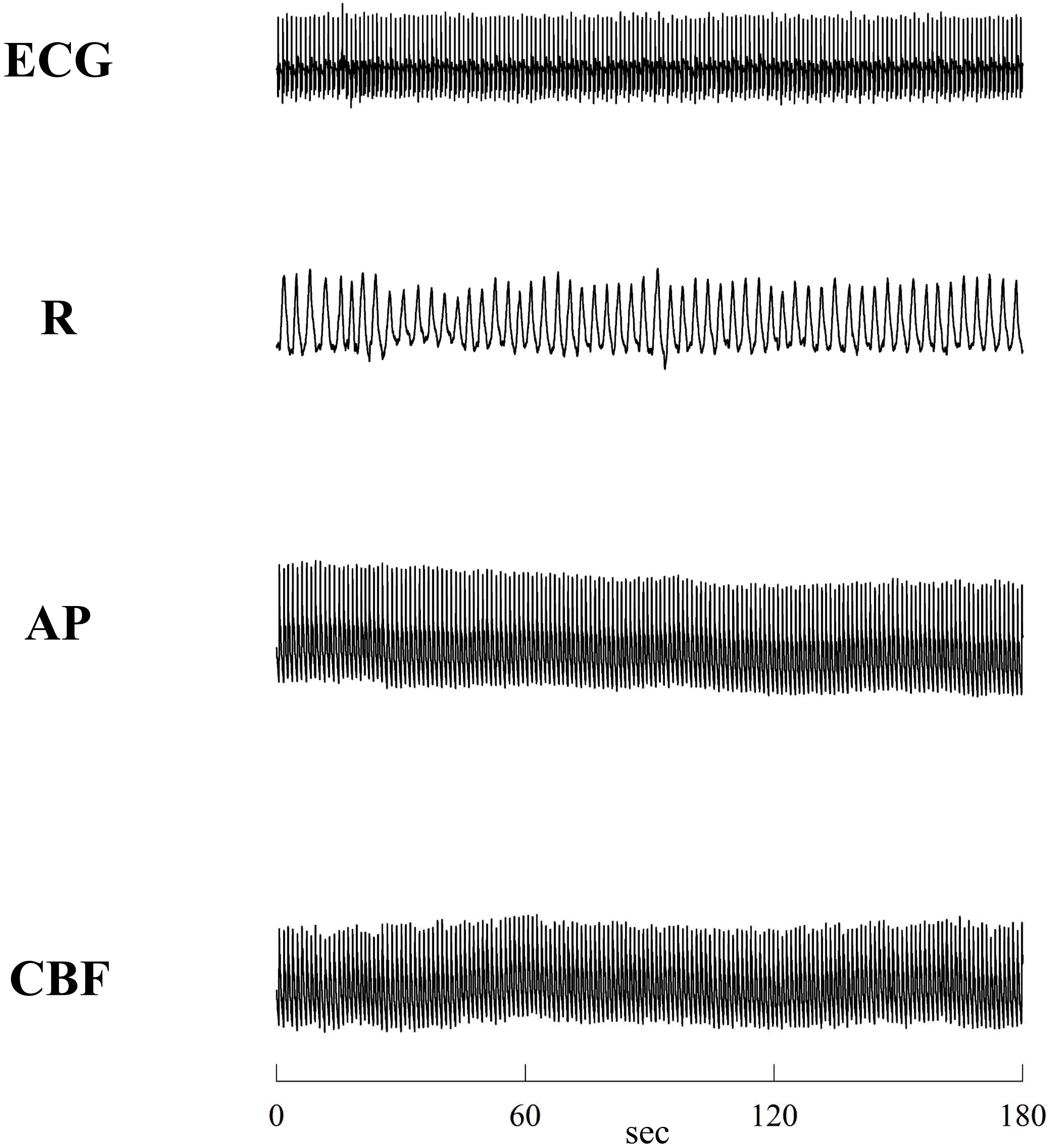
We recorded ECG (lead II), invasive AP from the radial artery and CBF velocity via a transcranial Doppler device (Multi-Dop T, 2MHz, Compumedics, DWL, San Juan Capistrano, CA, USA) from the left or right middle cerebral artery at 1000 Hz. R was derived from ECG.

Anesthesia was induced and maintained with propofol. Remifentanil was utilized as analgesic agent. Acquisition sessions lasted 10 minutes

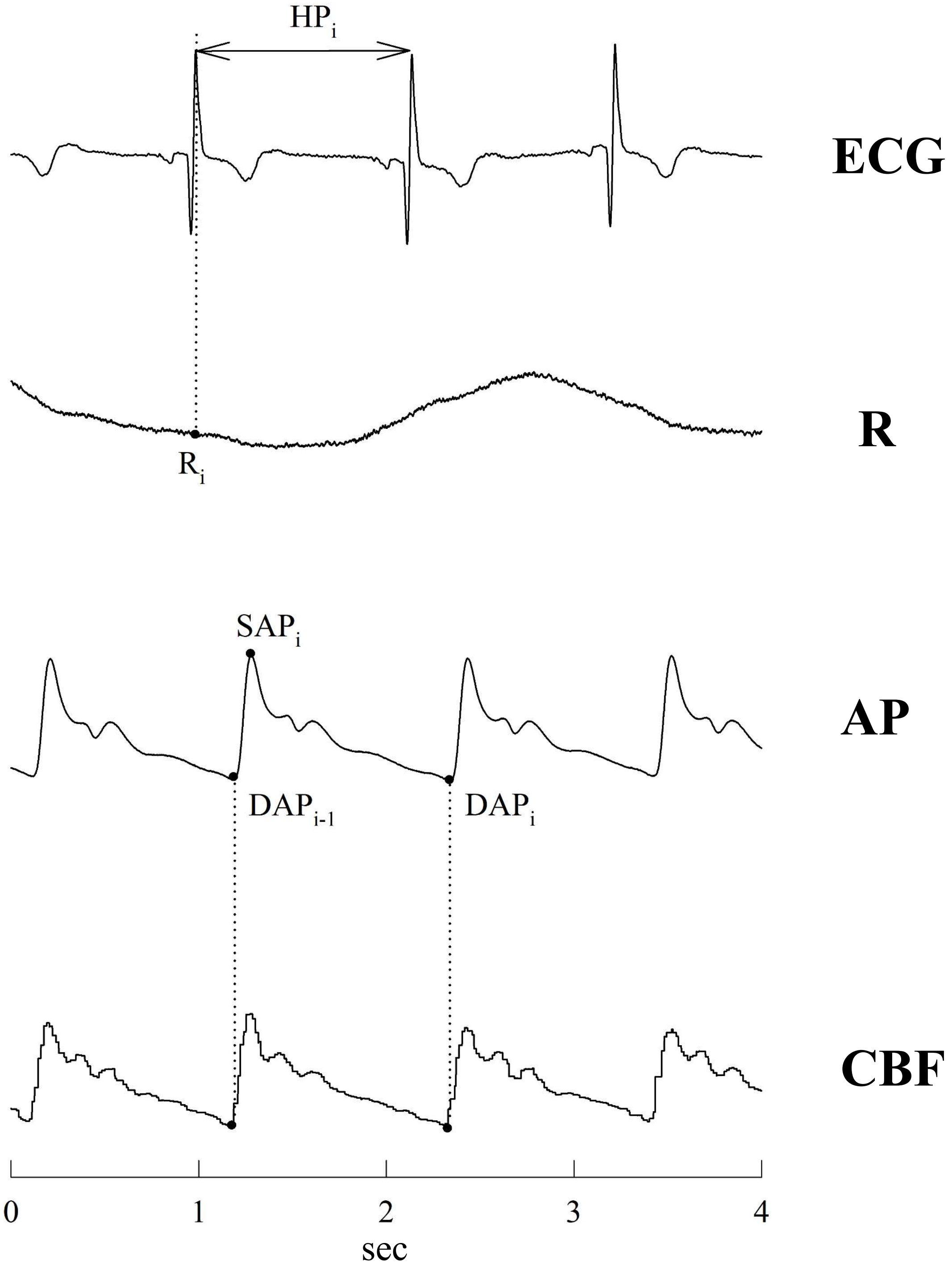
PRE: before the induction of general anesthesia and after standard premedications including administration of atropine (0.5 mg) and fentanyl (100 μg), during spontaneous breathing

POST: after intubation of the trachea, during propofol anesthesia, before opening the chest, during mechanical ventilation at 12-16 breaths/minute

Acquired signals



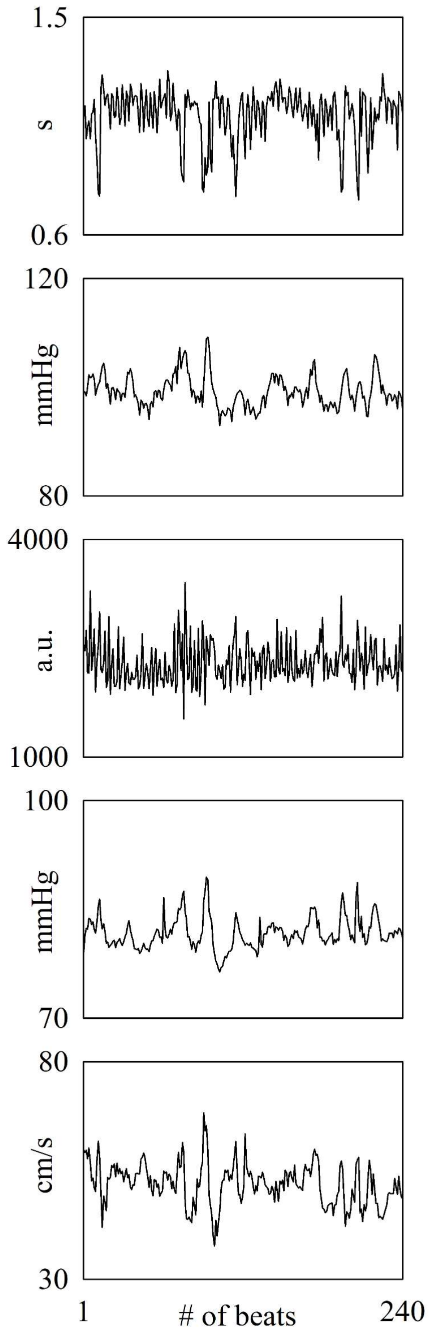
Conventions of measurement



$$MAP_i = \frac{\int_{t_{DAP_{i-1}}}^{t_{DAP_i}} AP(t)\cdot dt}{HP_i}$$

$$MCBF_i = \frac{\int_{t_{DAP_{i-1}}}^{t_{DAP_i}} CBF(t)\cdot dt}{HP_i}$$

Beat-to-beat series



$HP=\{HP_i, i=1,\ldots,N\}$

$SAP=\{SAP_i, i=1,\ldots,N\}$

$R=\{R_i, i=1,\ldots,N\}$

$MAP=\{MAP_i, i=1,\ldots,N\}$

$MCBF=\{MCBF_i, i=1,\ldots,N\}$

with $N=250$

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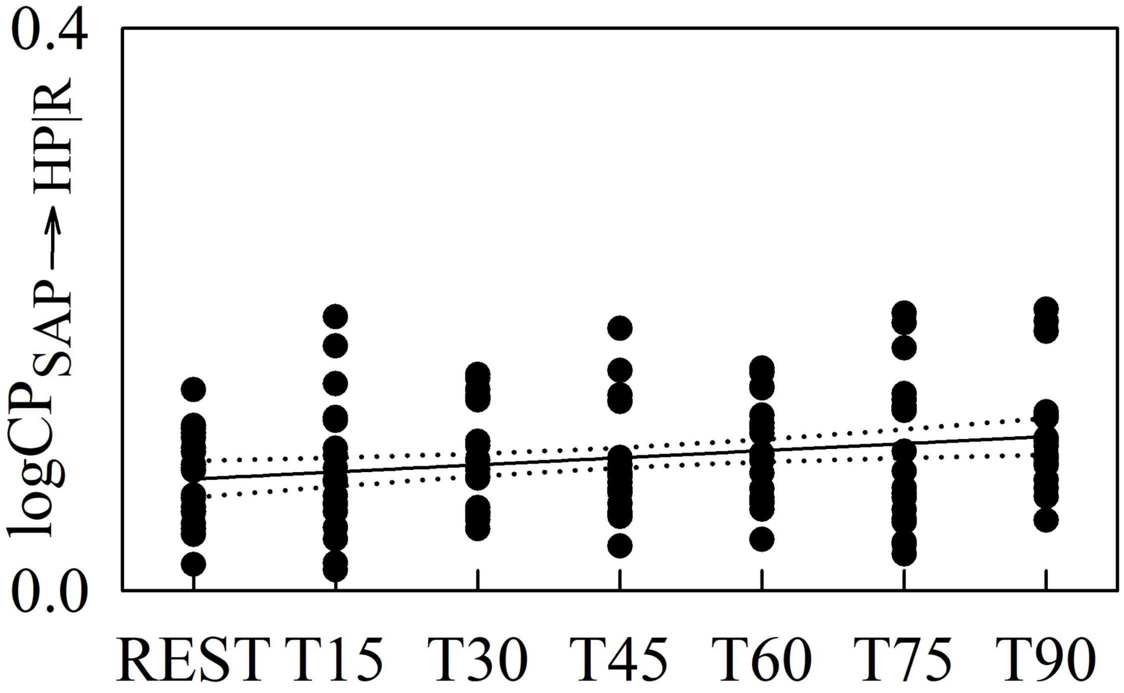
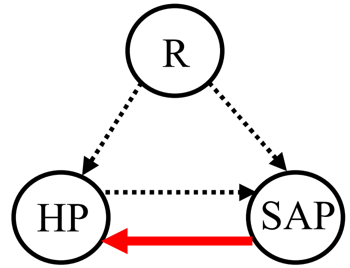
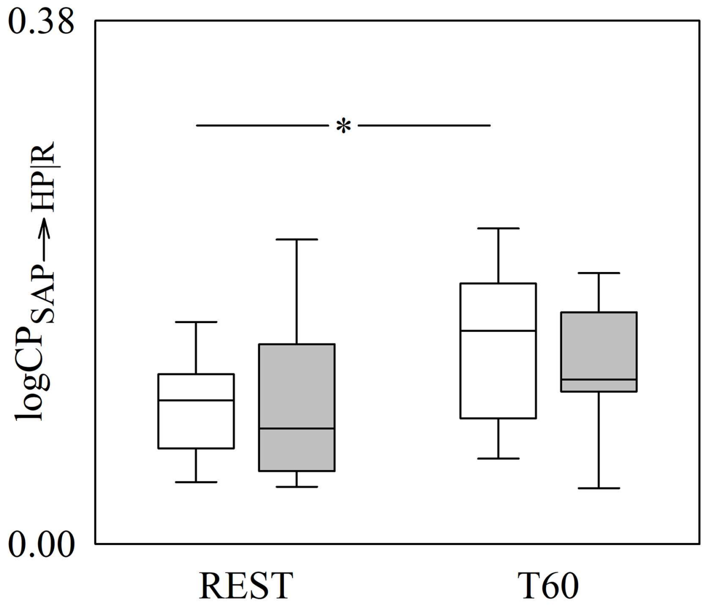
Cardiovascular interactions accounting for R during graded head-up tilt

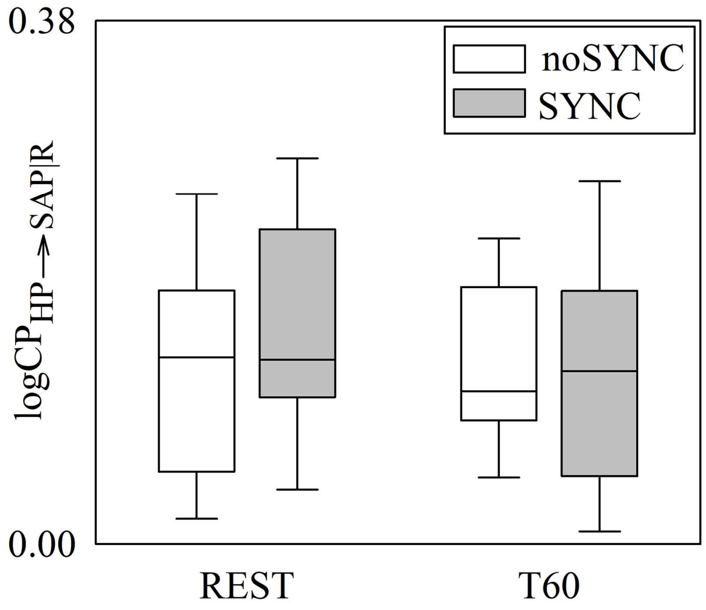




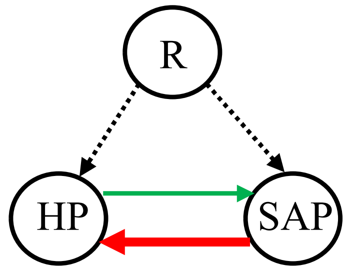
A. Porta et al, PLoS ONE, 10, e0132851, 2015

Cardiovascular interactions accounting for R in SYNC and noSYNC individuals

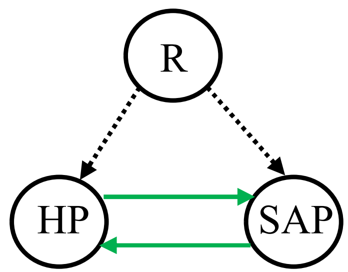




noSYNC during T60

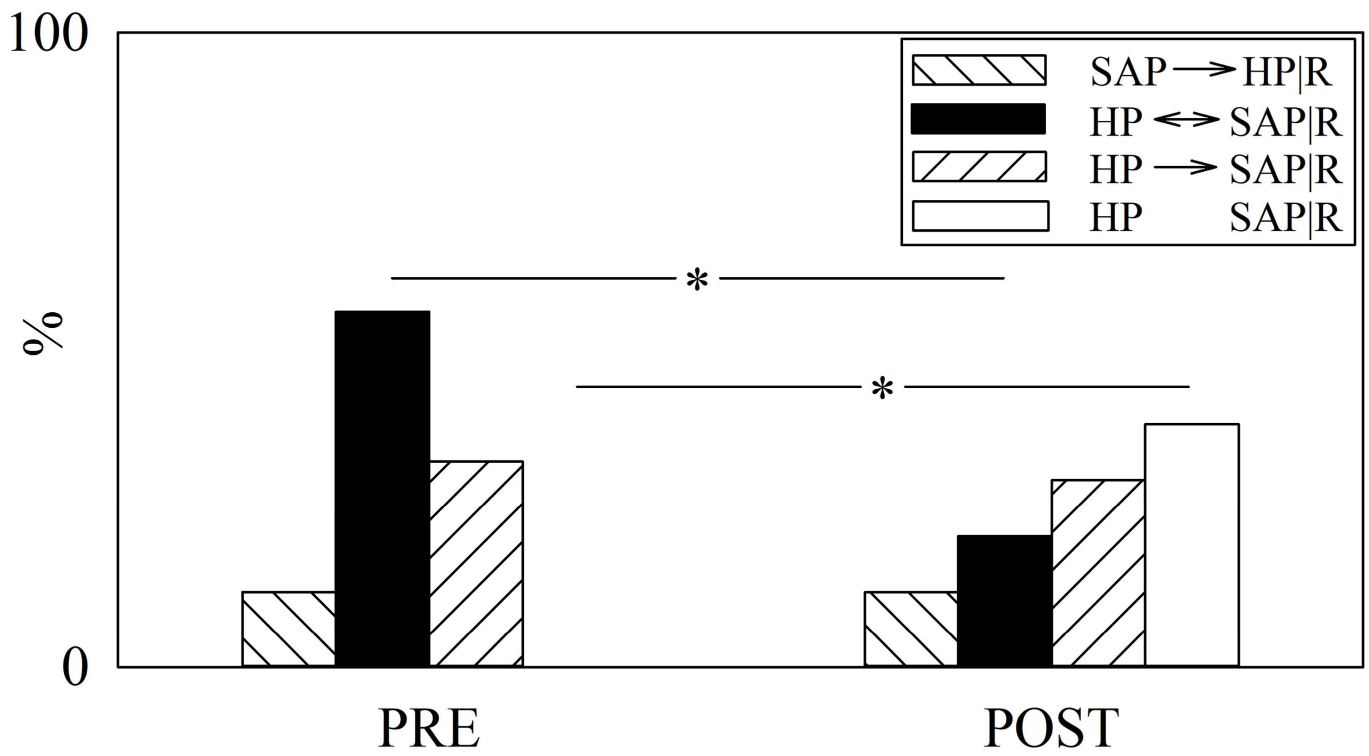


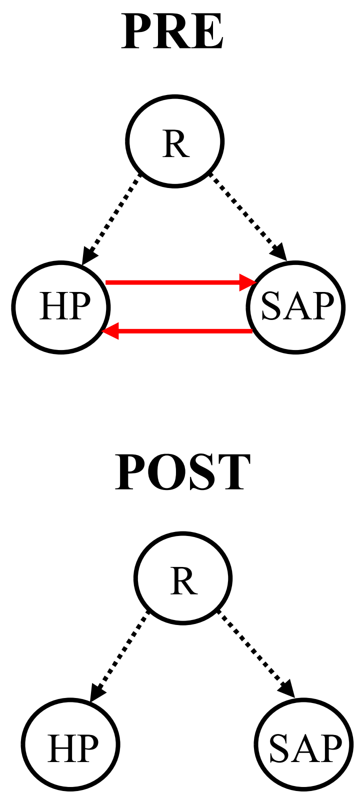
SYNC during T60



V. Bari et al, Physiol Meas, 38, 976-991, 2017

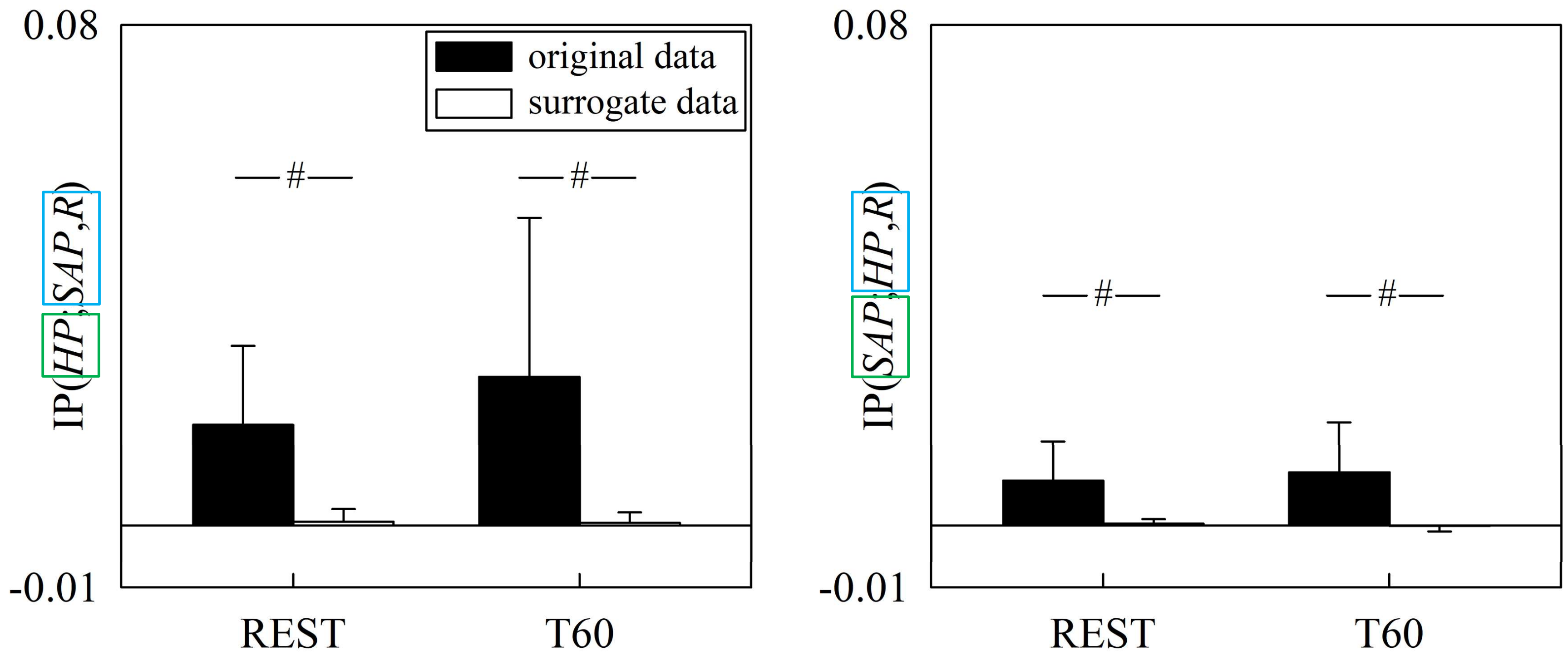
Cardiovascular interactions accounting for R during general anesthesia with propofol





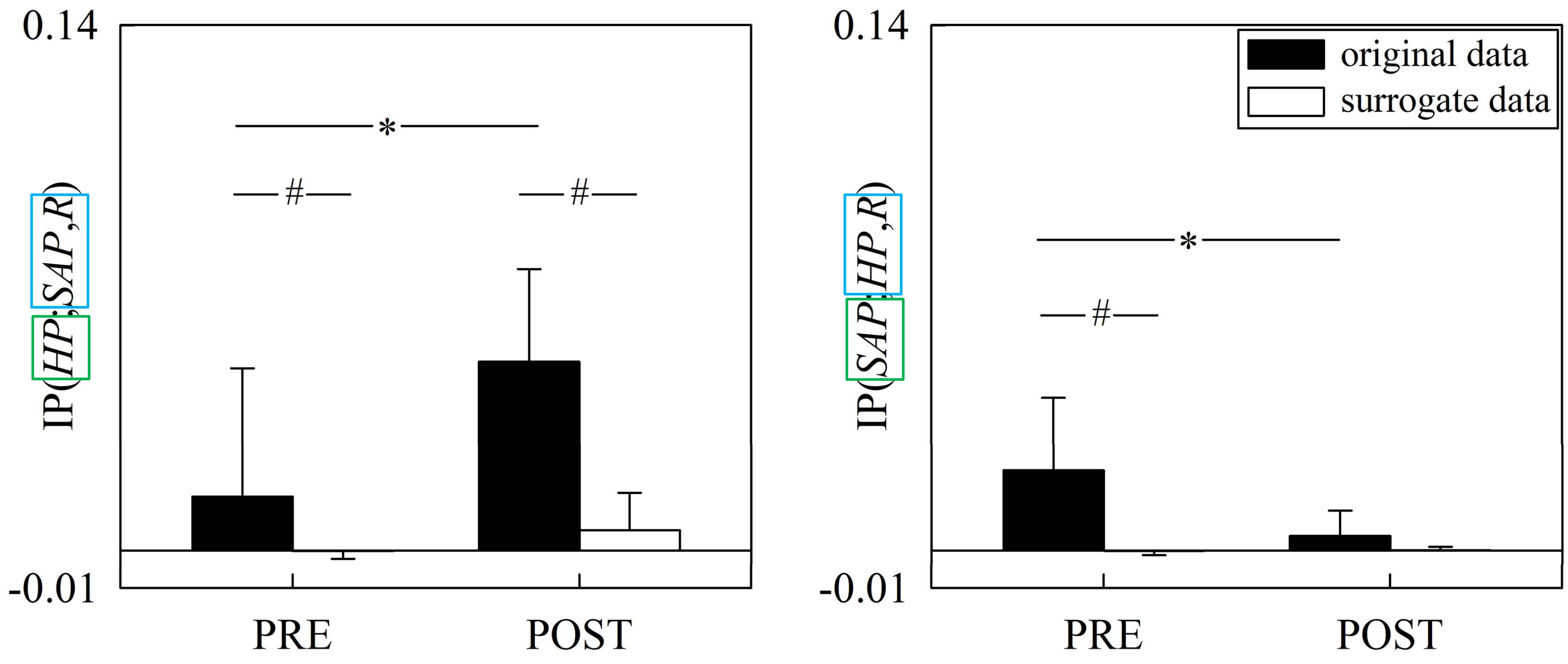
A. Porta et al, J Appl Physiol, 115, 1032-1042, 2013

R is a confounder of the cardiovascular interactions in healthy subjects



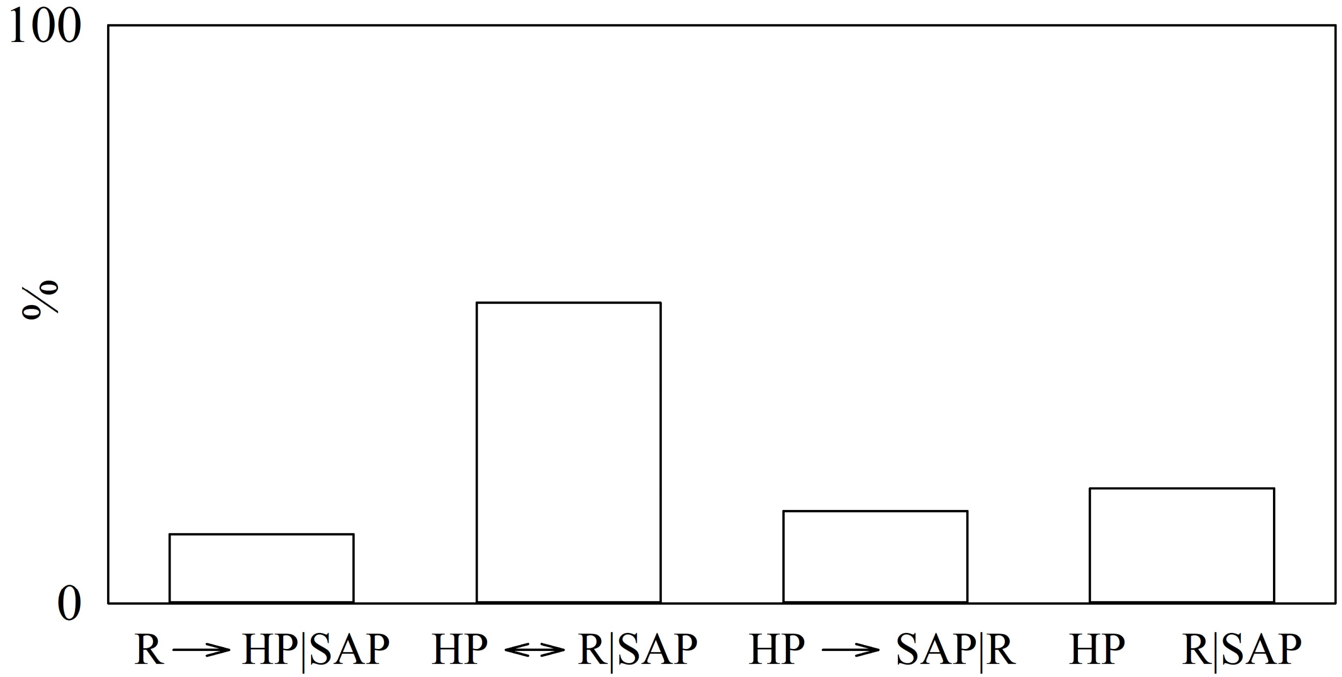
A. Porta et al, IEEE Trans Biomed Eng, 69, 2065-2076, 2022

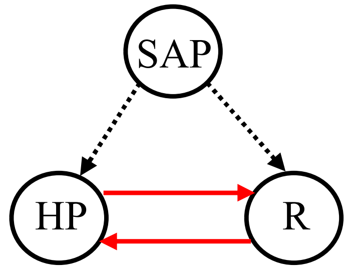
R is a confounder of the cardiovascular interactions during general anesthesia with propofol



A. Porta et al, IEEE Trans Biomed Eng, 69, 2065-2076, 2022

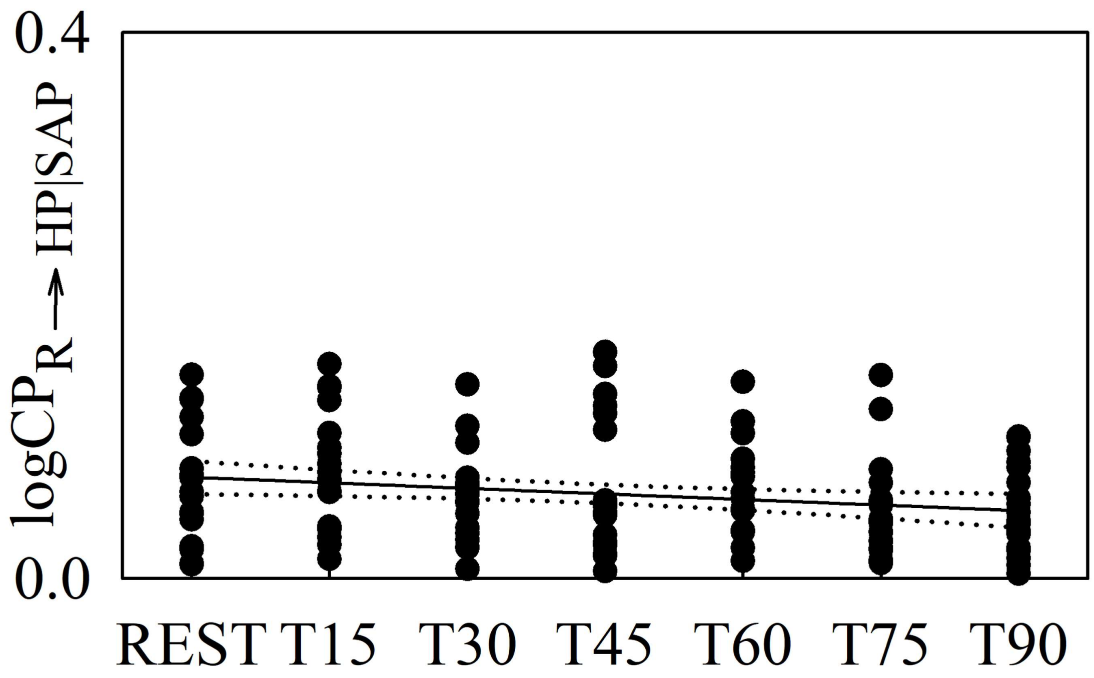
Cardiorespiratory interactions accounting for SAP influences in healthy subjects

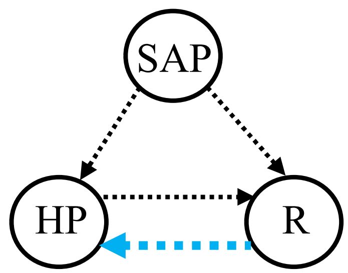




A. Porta et al, Phil Trans R Soc A, 371, 20120161, 2013

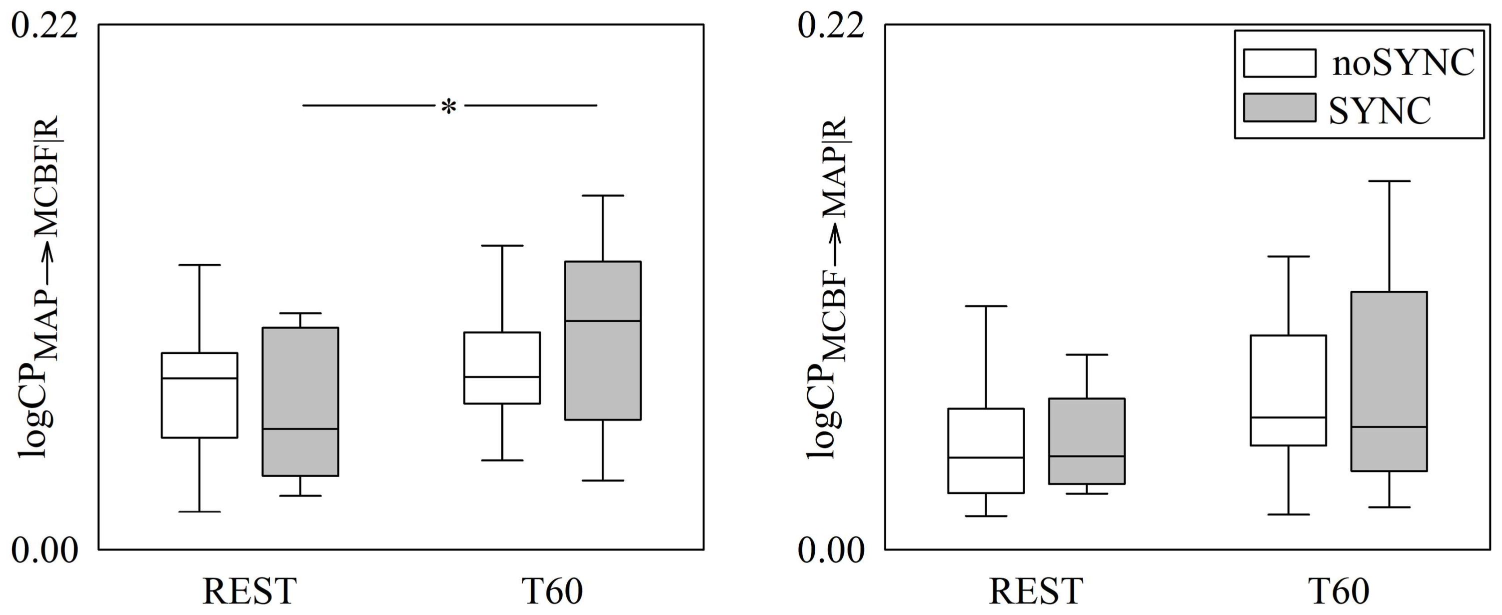
Cardiorespiratory interactions accounting for SAP during graded head-up tilt

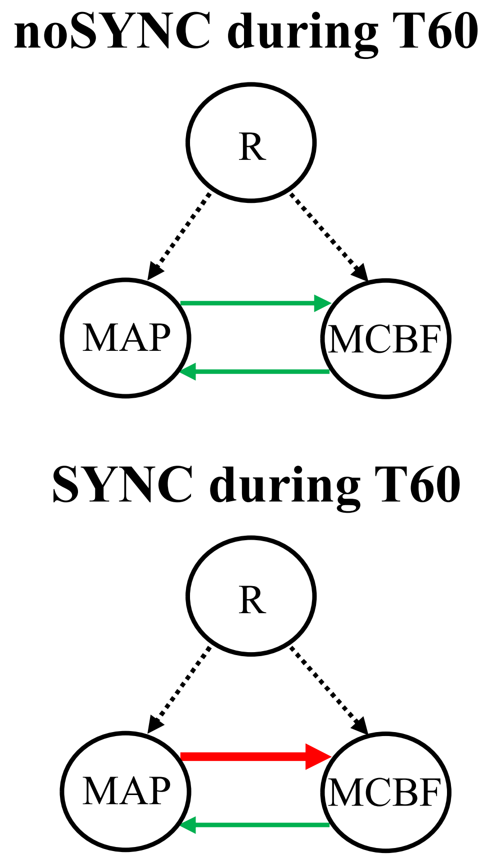




A. Porta et al, PLoS ONE, 10, e0132851, 2015

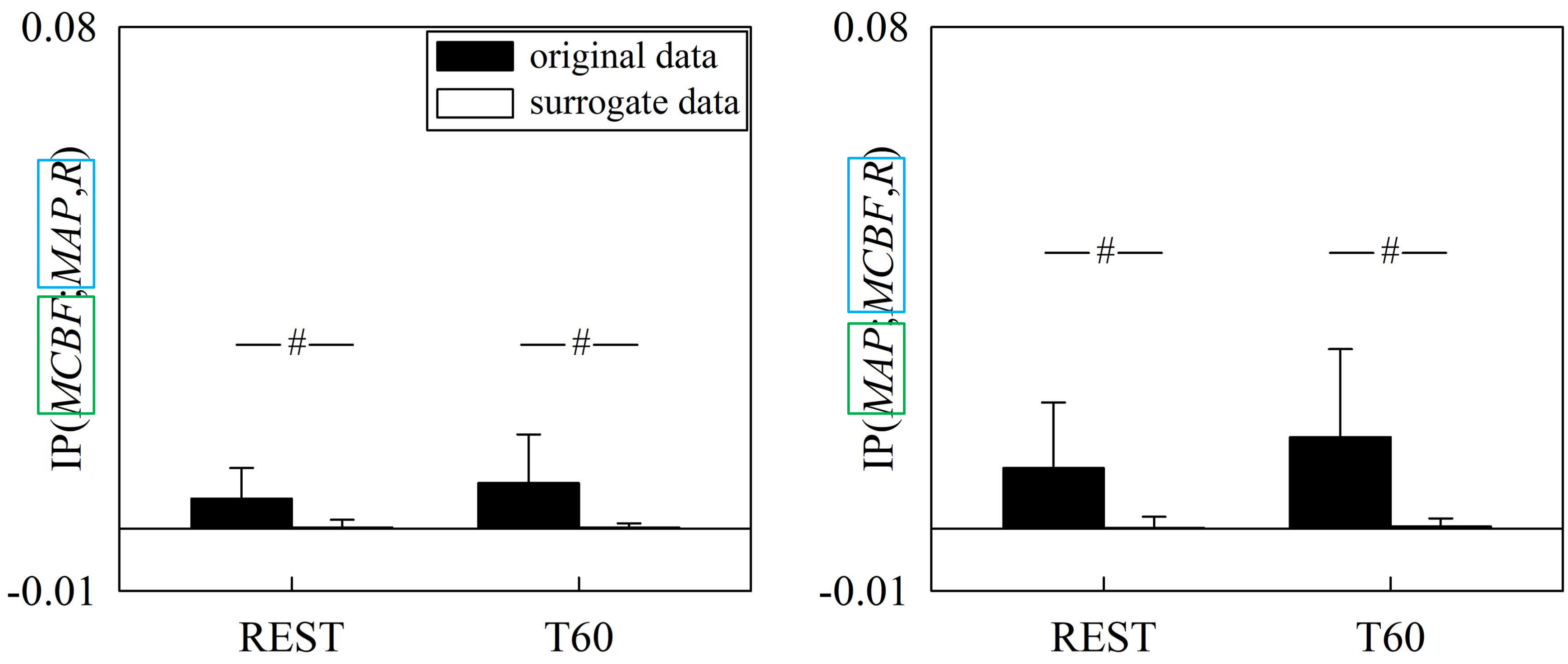
Cerebrovascular interactions accounting for R in SYNC and noSYNC individuals





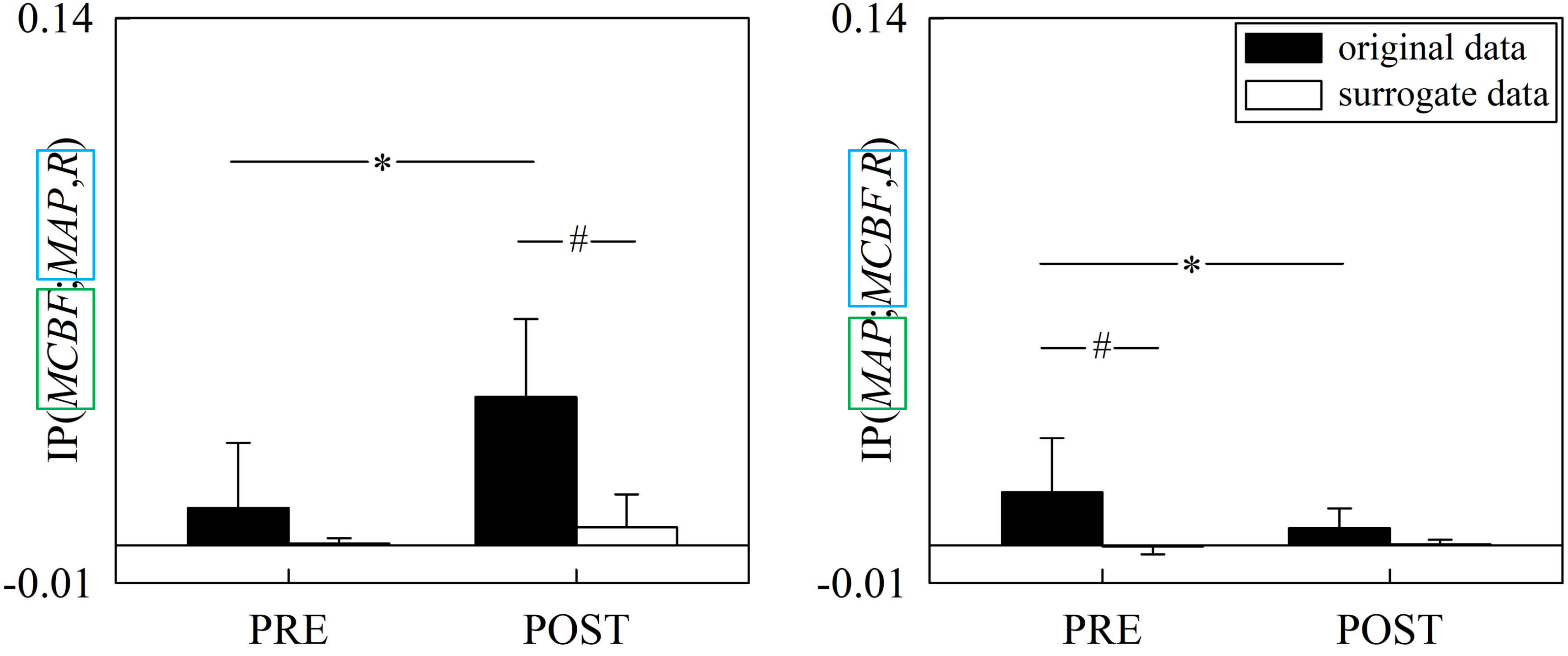
V. Bari et al, Physiol Meas, 38, 976-991, 2017

R is a confounder of the cerebrovascular interactions in healthy subjects



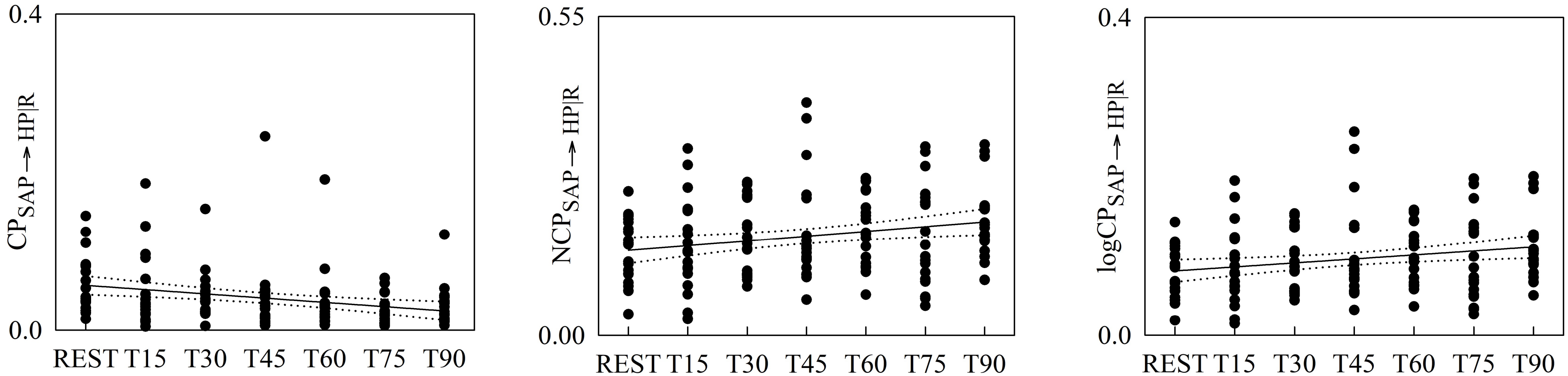
A. Porta et al, IEEE Trans Biomed Eng, 69, 2065-2076, 2022

R is a confounder of the cerebrovascular interactions during general anesthesia with propofol



A. Porta et al, IEEE Trans Biomed Eng, 69, 2065-2076, 2022

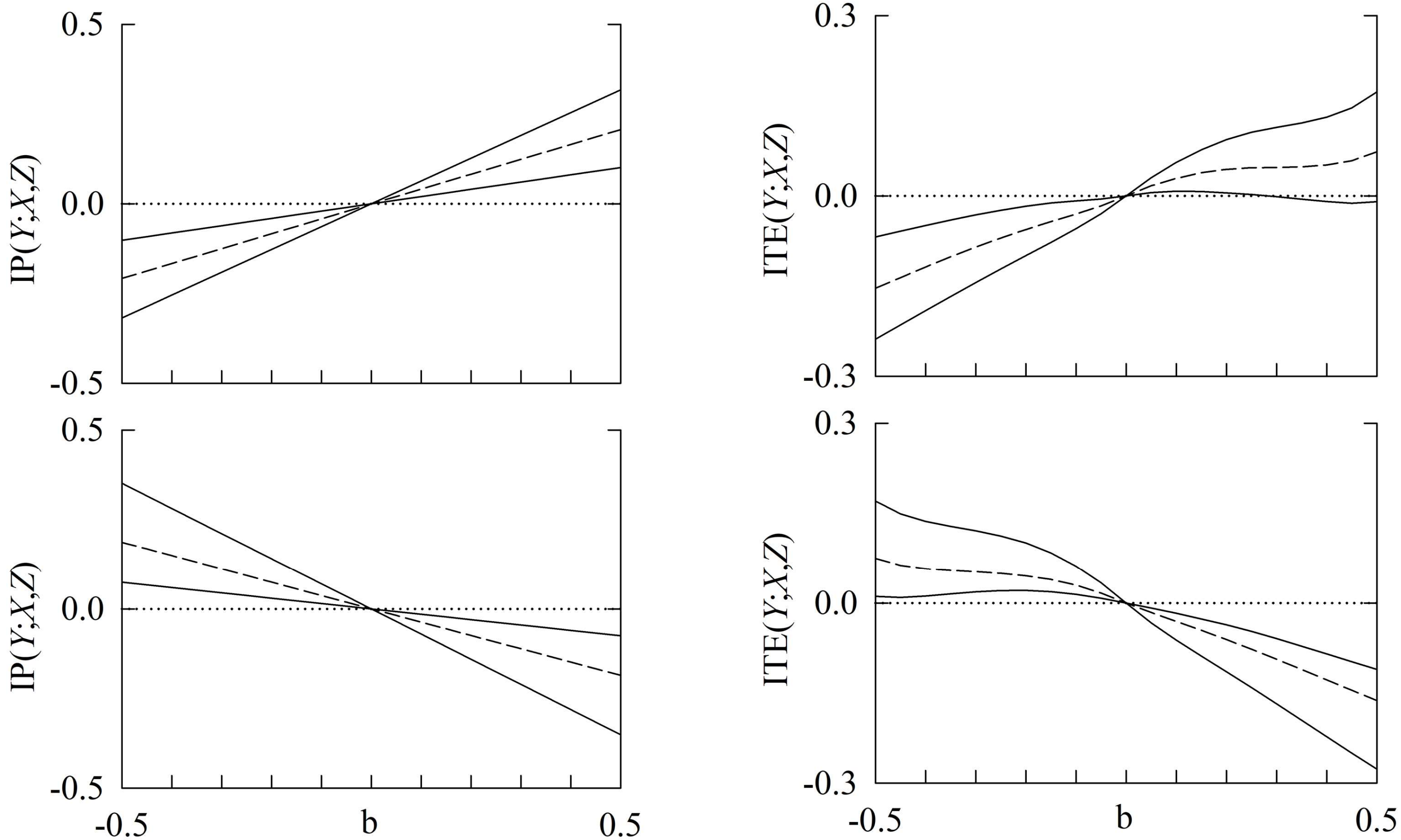
Results of the network physiology approach might depend on CP metric



A. Porta et al, Physiol Meas, 37, 276-290, 2016

Unnormalized CP is biased by the reduction of complexity of the target signal

Results of C/S test might depend on synergy/redundancy balance metric



A. Porta et al, IEEE Trans Biomed Eng, 69, 2065-2076, 2022

ITE might suggest an excess of synergy compared to IP due to the nonlinear characteristic of the logarithm function

Conclusions

A network physiology approach to the assessment of physiological control mechanisms was proposed and applied to cardiovascular, cardiorespiratory and cerebrovascular data

The framework appears to be particularly powerful in describing closed loop interactions, accommodating multivariate recordings, accounting for colored exogenous inputs and classifying the type of disturbance according to its effect on the causal relationship

Results stress the ability of the framework to derive information that can be hardly obtained from more traditional input-output techniques such as cross-spectral analysis