Evidence of unbalanced regulatory mechanism of heart rate and systolic pressure after acute myocardial infarction

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Received 10 October 2001; accepted in final form 1 May 2002

Nollo, Giandomenico, Luca Faes, Alberto Porta, Barbara Pellegrini, Flavia Ravelli, Maurizio Del Greco, Marcello Disertori, and Renzo Antolini. Evidence of unbalanced regulatory mechanism of heart rate and systolic pressure after acute myocardial infarction. Am J Physiol Heart Circ Physiol 283: H1200–H1207, 2002. First published May 16, 2002; 10.1152/ajpheart.00882.2001.—The interactions between systolic arterial pressure (SAP) and R-R interval (RR) fluctuations after acute myocardial infarction (AMI) were investigated by measures of synchronization separating the feedback from the feedforward control and capturing both linear and nonlinear contributions. The causal synchronization, evaluating the ability of RR to predict SAP (χSF) or vice versa (χFS), and the global synchronization (χ) were estimated at rest and after head-up tilt in 35 post-AMI patients, 20 young and 12 old. Significance and nonlinearity of the coupling were assessed by surrogate data analysis. Tilting increased the number of young subjects in which RR-SAP link was significant (from 17 to 19) and linear (from 11 to 18). In AMI, both significance and linearity of the coupling were low at rest (26 significant and 24 nonlinear) and further reduced after tilt (17 significant and 16 nonlinear). Old subjects showed a partial recovery of linearity after tilt (rest: 1 linear of 7 significant; tilt: 5 linear of 8 significant). In young subjects, the causal synchronization indexes were balanced and increased from rest (χFS = 0.072 ± 0.037 and χSF = 0.054 ± 0.028) to tilt (χFS = 0.125 ± 0.071 and χSF = 0.108 ± 0.053). On the contrary, in old subjects and AMI patients, the feedforward was prevalent to the feedback coupling at rest (old: χFS = 0.041 ± 0.023 and χSF = 0.069 ± 0.042; AMI: χFS = 0.050 ± 0.030 and χSF = 0.089 ± 0.053). Tilting blunted the unbalance in old subjects (χFS = 0.065 ± 0.052 and χSF = 0.069 ± 0.044) but not in AMI patients (χFS = 0.040 ± 0.019 and χSF = 0.060 ± 0.040). Thus, after AMI, nonlinear mechanisms are elicited in RR-SAP interactions. Furthermore, the neural regulation of the cardiovascular system resulted in imbalance as a consequence of impaired feedback and enhanced feedforward control mechanisms.

causal analysis; nonlinear coupling; synchronization; baroreflex regulation

The neural regulation of circulation is accomplished by the central control and the peripheral reflex mechanisms, which continuously interact in modulating the dynamics of heart rate and arterial blood pressure. A major role in the maintenance of a dynamic form of “homeostasis” is played by the arterial baroreflex (24). However, in humans, feedforward mechanisms of cardiovascular regulation operating through mechanically coupled changes in systolic arterial pressure (SAP) and R-R interval (RR) have been suggested (1, 27). Furthermore, it has been demonstrated that age and acute myocardial infarction (AMI) can strongly damage the cardiovascular performance by affecting the capability of the system to accomplish the beat-to-beat regulation of the heart rate (3, 5, 6, 13). Thus for describing the complex regulatory mechanisms appropriate causal models able to disentangle the causal verses of the RR-SAP regulation have been proposed (2, 18).

On the other side, the awareness of the complex interactions among hemodynamic, electrophysiological, and humoral variables makes inappropriate the assumption of pure linear dynamics in the genesis of cardiovascular fluctuations and of their interactions. The most common tools used for analyzing the variability of the cardiovascular signals fail in detecting couplings between rhythmicities occurring at different frequencies, suggesting the introduction of statistics able to characterize nonlinearity in time series (9). While several authors have provided evidence that nonlinear dynamics are present in the heart rate variability (8, 12, 26), recognizing also a role for predicting cardiac death after AMI (7), nonlinear approaches to the study of RR-SAP coupling have not been followed yet. Recently, cross-conditional entropy (CCE) measures were proposed for evaluating the coupling between short time variability series in biological systems (23).

The aim of this study was to investigate the changes occurring after AMI in the synchronization between the spontaneous variabilities of the cardiac cycle length and the arterial pressure by disentangling the causal verses of their mutual relationship and without imposing any linear assumption. This approach made

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it possible to evaluate separately the feedback and feedforward regulation of RR and SAP and to verify the existence of nonlinear mechanisms originating the cardiovascular interactions.

METHODS

Study populations. The study included 35 post-AMI patients (58.5 ± 10.2 yr), examined 10 ± 3 days after AMI and two control groups of healthy subjects: 20 young (25.0 ± 2.6 yr) and 12 old (63.1 ± 8.3 yr).

Post-AMI patients were part of larger database collected for a GISSI-3 arrhythmia substudy from February 1992 to July 1993 (16). According to the general study protocol, when present (8 patients), ß-blocker therapy was discontinued two half-lives before the recording session to avoid any interference with the autonomic and cardiovascular systems. Eligible patients presented sinus rhythm and were not taking antiarrhythmic drugs.

All control subjects were normotensive and free from any known disease based on anamnesis and physical examination at the time of the study.

Experimental protocol and measurements. Cardiovascular signals were recorded in the electrophysiology laboratory in the morning, in comparably comfortable and quiet ambiance conditions with subjects in sinus rhythm and breathing spontaneously. After a period of 15 min allowed for subject stabilization, electrocardiograms and arterial pressure signals were recorded for 10 min in a supine rest position, followed by 10 min of passive 60° head-up tilt. Arterial blood pressure was recorded at finger level by a photoplethysmographic Finapres device (Ohmeda 2300; Englewood, CO). All signals were digitized with a 1-kHz sampling rate.

RR and SAP values were automatically measured on digitized electrocardiogram and arterial blood pressure signal. The series were then cleaned up from artifacts, windowed to 300 points, and detrended by a high-pass filter to fulfill stationarity criteria (17). The normalized tachogram (t) and systogram (s) series were eventually obtained by subtracting the mean values and dividing by the SD.

Causal nonlinear analysis of RR-SAP coupling. Starting from the systogram series of N samples, s = [s(i), i = 1, . . . , N]. N − L + 1 patterns sL(i) of length L were extracted as [s(i), s(i − 1), . . . , s(i − L + 1)], and their Shannon entropy (SE) was estimated. By measuring the dispersion of the patterns in the L-dimensional space, SE evaluates the amount of information carried by s given its partition in L-length patterns. To consider the information lead from the systogram to the tachogram, single samples of the series t = [t(i), i = 1, . . . , N] were jointed to the patterns of s obtaining the mixed pattern [t(i), sL(i)] (23). An example with L = 3 is reported in Fig. 1. The CCE was then calculated as a function of L as the difference between the SE of the mixed patterns and the SE of the patterns of s. As shown in Fig. 2A, CCE quantifies the amount of information carried by the tachogram that cannot be derived from the systogram, i.e., the unpredictability of t(i) starting from sL(i). To prevent the poor estimation of SE due to the limited number of samples available for the cardiovascular signals, in this study the corrected CCE introduced by Porta et al. (23) was utilized. By normalizing (by the division by the SE of t) and complementing to unity the corrected CCE values, a measure of the predictability of the tachogram when L-length patterns of the systogram are observed, the synchronization function, was...
obtained (see Fig. 2B). The maximum over \( L \) of the synchronization function, quantifying the maximum amount of information of \( t \) explained by \( s \), was taken as the causal synchronization index \( \chi_{st} \). In an analogous way, the predictability of the systolic pressure starting from the cardiac period \( \chi_{ts} \) was evaluated by inverting the role of the series \( s \) and \( t \). The higher of \( \chi_{st} \) and \( \chi_{ts} \) was eventually assumed as the global synchronization \( \chi \), indicating the maximum amount of information exchanged by the two series. Because the \( i \)th cardiac period cannot influence the \( i \)th SAP value, the series \( s \) was one beat delayed before evaluating \( \chi_{ts} \) (17). We make reference to Ref. 23 for the methodological details and simulations.

**Surrogate data analysis.** The method of surrogate data (19, 28) was applied to test 1) the significance and 2) the nonlinearity of the coupling between RR and SAP variability series. For this purpose, two types of surrogate data were generated according to the null hypothesis of 1) uncorrelated and 2) linearly correlated series. In the first case, the original RR and SAP series were Fourier transformed, and their Fourier phases were substituted with independent random numbers. After inverse Fourier transform was performed, two surrogate series (type I surrogates) having the same frequency distribution and power spectra as the original pair of signals, but completely uncoupled, were derived. The second type of surrogate data (type II surrogates) preserved not only the individual RR and SAP spectra but also the magnitude of their cross-spectrum. This was obtained by adding the same random number to the Fourier phases of the two series. In this way, the linear coupling was maintained, whereas nonlinear interactions were destroyed (19).

Fifteen independent pairs of type I and type II surrogate series were derived from each pair of original RR and SAP series. The synchronization index \( \chi \) was then computed on the original and on the set of surrogate series, and finding a statistical difference led to rejection of the null hypothesis and thus to detection of the presence of the searched property.

**Statistical analysis.** An ANOVA test was used to assess the significance of the comparison between all indexes across the three groups (unpaired data). The differences between \( \chi_{ts} \) and \( \chi_{st} \) within groups were checked by Student’s \( t \)-test (paired data) and were considered statistically significant at \( P < 0.05 \).

The significance and the nonlinearity of RR-SAP coupling were verified by the hypothesis testing included in the method of surrogate data. The null hypothesis was rejected when the synchronization of the original series was higher than the critical value of the \( \chi \) distribution evaluated on the surrogate pairs. The critical \( \chi \)-value was obtained, under the hypothesis of normal distribution, assuming a \( P \) value of 0.05.

A chi-squared test for a \( 2 \times 2 \) contingency table was performed to assess the statistical difference of the significance and of the nonlinearity of RR-SAP coupling between pairs of groups.

**RESULTS**

Table 1 reports the baseline characteristics of the variability series measured in rest and tilt conditions on patients belonging to the three populations. During head-up tilt, all groups showed a significant decrease of the cycle length along with a decrease of the total RR variability in old subjects and AMI patients. In AMI patients, the tilt test determined significant variations of the mean and SD of the systolic pressure. An increase in variability of SAP series was also observed in young subjects.

**Global coupling.** At rest, the \( \chi \) resulted equal to 0.079 ± 0.037 in young subjects, 0.070 ± 0.042 in old subjects, and 0.092 ± 0.053 in AMI patients. The three values were not statistically different (ANOVA, \( P > 0.05 \)). Figure 3 shows how the tilt testing pointed out a differentiated response of \( \chi \) for the three populations. Indeed, after tilt, the synchronization was markedly increased in young subjects (\( \chi = 0.139 \pm 0.068 \)) and was not significantly changed in old subjects (\( \chi = 0.080 \pm 0.048 \)), whereas AMI patients showed a significant decrease (\( \chi = 0.062 \pm 0.039 \)). The index increased in 16 of 20 young subjects (80%) and decreased in 28 of 35 AMI patients (80%). As a result, the amount of coupling measured by the synchronization index after the tilt maneuver was higher for young than for old subjects (\( P < 0.05 \)) and AMI (\( P < 0.005 \)) patients. The analysis of significance of \( \chi \) performed by type I surrogate data, supported these results. Indeed, moving from rest to tilt, the number of subjects showing uncoupling (solid circles in Fig. 3 and first row of Table 2) resulted slightly decreased in young subjects, substantially unchanged in old subjects, and markedly increased in AMI patients. As expected, the average value of the synchronization index evaluated on type I surrogate series was independent of groups and experimental conditions.

The presence of nonlinear features underlying the interactions between RR and SAP was investigated by the means of type II surrogate data analysis on subjects for which the synchronization \( \chi \) resulted significantly larger than zero. Table 2 and Fig. 4 evidence the number of subjects showing nonlinear coupling for the three populations in both rest and tilt conditions. At rest, this number was lower for young (6 of 17 cases) than for old subjects (6 of 7 cases, \( P = 0.07 \)) and AMI (24 of 26 cases, \( P < 0.001 \)) patients. After tilt, the coupling resulted highly linear in young subjects (1 nonlinear of 19 significant) and remained highly nonlinear in post-AMI patients (16 nonlinear of 17 signif-
lower where the coupling was detected as nonlinear. AMI subjects showed the lowest values of $\chi$ calculated on type II surrogates.

**Causal coupling.** The results of the causal synchronization analysis are summarized in Table 3 and Fig. 5. In young subjects, the two causal synchronization indexes $\chi_{st}$ and $\chi_{ts}$ measured a comparable coupling level either in the supine or orthostatic positions. As shown for $\chi$, the causal indexes also augmented after the tilt maneuver. In old subjects, $\chi_{st}$ was significantly higher than $\chi_{ts}$ at rest, but this difference was not maintained during tilt. No significant changes were observed between the two indexes moving from supine to standing position. In AMI patients, a marked unbalance between the causal synchronization indexes was observed at rest and preserved during tilt. Both $\chi_{ts}$ and $\chi_{st}$ were reduced by the tilt maneuver.

As reported in Table 3, at rest $\chi_{ts}$ was reduced in old subjects and AMI patients compared with young subjects. During tilt, this index resulted lower in AMI patients than in old and young subjects and lower in old than in young subjects. At rest, $\chi_{st}$ was significantly increased for AMI with respect to young subjects and after tilt was lower in old subjects and AMI patients than in young subjects.

**DISCUSSION**

This work points out that the study of the complex cardiovascular regulation in impaired conditions can be improved by considering the causal dependencies between cardiac cycle length and systolic pressure and without a priori assuming the linearity of their coupling. In particular, the use of CCE allows us to incorporate both linear and nonlinear contributions into a quantitative measure of RR-SAP coupling. Moreover, the introduction of causality leads to the simultaneous and separate evaluation of feedback and feedforward mechanisms, quantifying their relative contribution to the overall cardiovascular regulation.

**Nonlinearity in RR-SAP dynamic interaction.** The presence of significant coupling was verified by generating a set of pairs of surrogate series (type I surrogates) in which any link was totally destroyed by randomizing the phase spectra of original RR and SAP series and then looking for statistical differences in the synchronization index. Nonlinear mechanisms in the RR-SAP link were then assessed with the same methodology by generating a new set of pairs of surrogate series (type II surrogates) in which the linear coupling was maintained and nonlinear coupling canceled by conserving phase differences between RR and SAP randomized phase spectra. Analysis of type I surrogates assessed at $\sim 0.03$ the synchronization level of completely uncoupled series, whereas the $\chi$ value for type II surrogates resulted dependent on the nature of RR-SAP interactions. Indeed, after type II surrogate generation, the synchronization level was unchanged for linearly coupled series and was blunted when nonlinearities significantly affected the coupling. Moreover, when nonlinearity is detected, the synchroniza-
tion gap between original and surrogate series may provide information about the extent of linear versus nonlinear components of the coupling. Thus the fact that in AMI patients the synchronization of type II surrogates resulted very low, approaching the uncoupling level, indicates the predominance of nonlinear features with respect to linear ones in determining the coupling between cardiac period and arterial pressure fluctuations. Although in resting conditions the average coupling strength was not significantly different among the three groups, the presence of nonlinear dynamics in RR-SAP interactions was found much more in post-AMI patients than in young subjects. Differences across groups became more evident after sympathetic stimulation as synchronization increased in the young group, was substantially unchanged in the old group, and was decreased in AMI group. In physiological conditions, tilting is supposed to reduce the complexity of RR and SAP, entraining all the operating mechanisms in the low-frequency band (15, 22) and increasing the number of correlated sequences between the two series (11). In our study, this tilt-induced simplification of the coupling was documented in young subjects by the increase of the synchronization index and of the number of patients showing pure linear RR-SAP interactions. This feature was partially verified also in old subjects that after tilt showed a prevalence of linear interactions between RR and SAP fluctuations. Differently, in AMI patients, the synchronization index was reduced after tilt, the number of subjects showing uncoupled RR and SAP dynamics was doubled, and where the coupling was significant its nature resulted nonlinear in all but one.

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<th>Table 2. Summary of surrogate data analysis</th>
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Values of the global synchronization index (x) are means over the specific numbers of subjects.

![Figure 4](http://ajpheart.physiology.org/) Results of surrogate data analysis for testing the significance and the presence of nonlinearity in the coupling between heart rate and systolic pressure. Bar graphs show the partition of the 3 populations in subjects exhibiting nonlinear coupling (solid area of bars) and pure linear coupling (open area of bars) obtained by type II surrogate data analysis during rest (A) and after tilt maneuver (B). The height of the bars represents the total number (N) of subjects for which R-R interval and systolic arterial pressure series resulted as significantly coupled after type I surrogate data analysis. *P < 0.01 and **P < 0.001 vs. AMI patients (chi-squared test).

Table 3. Nonlinear causal synchronization between systolic pressure and cardiac cycle length variability series

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<td>Rest</td>
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<td>Tilt</td>
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<td>x_{t/s}</td>
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<td>0.105 ± 0.053</td>
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<td>0.125 ± 0.071</td>
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<td>Significance</td>
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Values are means ± SD. x_{s/t}, causal synchronization from tachogram to systogram; x_{t/s}, causal synchronization from systogram to tachogram. *P < 0.05 vs. AMI patients; †P < 0.05 and ‡P < 0.005 vs. young subjects.
Unbalanced RR-SAP regulation. As demonstrated by young subjects, in physiological conditions the coupling strength evaluated on the two regulatory pathways is substantially balanced and preserved also after the sympathetic activation. In old subjects, our results showed an unbalanced RR-SAP regulation with increased feedforward and a decreased feedback mechanism, thus confirming a recent study pursued by linear cross-spectral analysis (21). This unbalancing was more marked in patients 2 wk after the infarction, mostly due to an increase of coupling on the feedforward regulatory pathway. Previous studies based on the analysis of the concurrent changes in RR and SAP demonstrated a dependence of the balancing between feedforward and feedback mechanisms on the efficiency of the neural control (11, 20). In our study, the increased extent of coupling on the feedforward arm could be explained by considering the passive behavior of the vascular bed due to the arterial stiffening induced by age and disease, which favors the mechanical matching between the left ventricle and the vasculature.

By the passive assumption of the orthostatic position, the imbalance was reduced in old subjects through a partial recovery of the coupling on the baroreflex path, whereas it was kept in AMI patients. It has been suggested that the alterations in the sympathovagal balance at the sinus node present at rest after AMI prevent its further modifications after the tilt maneuver (13). In the same way, tilt seems able to neither improve the synchronization in both arms of the RR-SAP regulatory mechanism, as happens in young subjects, nor to recover the balancing between the two causal regulations, as happens in old subjects.

The results of previous (11, 18, 27) and present investigations assess the importance of separately investigate the two arms of the regulatory loop, indicating a possible differentiate capability of one cardiovascular variable to affect the other. The increased strength of coupling on the nonbaroreflex path found in the present study for AMI patients supports the concept that feedforward mechanisms play a dominant role in the control of circulation in impaired pathologic conditions. As the nonbaroreflex coupling does not merely reflect a mechanical matching but can be mediated by the autonomic nervous system (11), the measure of the balancing between feedback and feedforward mechanisms could provide a new perspective for evaluating the neural regulation of the cardiovascular function.

Impairment of heart rate regulation. In basal conditions, the synchronization causal index indicated in old subjects and post-AMI patients a reduction in the ability of the systolic pressure changes to drive heart rate variability. This finding agrees with others demonstrating a decrease of baroreflex sensitivity with age and coronary disease (6, 10). However, in the regulation of the heart rate, two opposite feedback mechanisms, the vagally mediated arterial baroreflex (negative feedback) and the excitatory sympathetic efferent discharge (positive feedback), are involved (14). The causal synchronization index $\chi_{k/a}$, accounting for both...
these mechanisms, cannot be strictly related to the baroreflex gain. Hence, in post-AMI patients, the reduced vagal activity could be counterbalanced by the enhanced sympathetic activity, thus explaining the comparable values found in patients and healthy age-matched control groups.

Again, the continuous interaction between excitatory and inhibitory feedback mechanisms should be considered to explain the different effects of the tilt maneuver on the causal measure of coupling across the three groups. Whereas it has been demonstrated that the baroreflex gain is reduced when subjects change from a lying to standing position (4, 25), in young subjects we found a consistent increase of coupling. Thus it seems that in physiological conditions the tilt-induced increase in sympathetic activity overwhelms the vagal deactivation and determines the observed growth of $\chi^{1/2}$. On the other hand, the smoothed response of old subjects to the assumption of the orthostatic position, documented by a lower shortening of RR length, was reflected also by the poor increase of the synchronization measure. Finally, the decrease of this index observed in AMI patients can be attributed to the inability of these patients to respond to tilt-induced changes in cardiac output by further sympathetic activation (13). Therefore, the reduction of causal synchronization after tilt demonstrated in AMI patients an impairment of mechanisms regulating heart rate with a depressed negative feedback and a not-responding overloaded positive feedback. This uncoupling could also contribute to the lack of the cardiac output documented by the lowering of SAP during standing position.

Potential limitations. According to the study protocol, cardiovascular signals of the AMI group were recorded at predischarge time on patients in pharmacological washout. Because of this constraint, only patients able to support without appreciable risk the duration of mechanisms regulating heart rate with a depressed negative feedback and a not-responding overloaded positive feedback. This uncoupling could also contribute to the lack of the cardiac output documented by the lowering of SAP during standing position.

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In summary, our study emphasizes the importance of considering nonlinearity and causality for investigating on the interactions between spontaneous fluctuations of the cardiovascular parameters in nonphysiological conditions. Indeed, whereas in healthy young subjects the coupling between heart rate and arterial pressure occurs mainly through linear interactions, in old subjects and post-AMI patients the presence of nonlinear mechanisms was found to play an important role. Furthermore, differently from physiological conditions, 2 wk after AMI the baroreflex feedback regulation seems to be deeply damaged as its capability to respond to sympathetic stimulation was denied, whereas the strength of feedforward regulation was markedly enforced. This finding supports the concept that a balance between the two arms of the regulatory mechanism is essential to achieve the most adequate regulation of cardiovascular system.

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AJP-Heart Circ Physiol • VOL 283 • SEPTEMBER 2002 • www.ajpheart.org


