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Interaction of 0.1-Hz Oscillations in Heart Rate Variability and Distal Blood Flow Variability

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Abstract—Biophysical features of 0.1-Hz oscillations of heart rate variability (HRV) and distal blood flow (DBF) variability were compared in healthy subjects and patients after acute myocardial infarction (MI). Patients with acute MI (72 men and 53 women; 125 in total) and healthy subjects (23 men and 10 women; 33 in total) aged 30–38 and 20–46 years, respectively, participated in the study. The patients were involved in the study for a year after acute MI. The delay in coupling 0.1-Hz oscillations of HRV and DBF variability was estimated. In healthy subjects, the delay in the heart ⟶ DBF coupling proved to be less than the delay in the DBF ⟶ heart coupling. Acute MI results mainly in disruption of the heart ⟶ DBF coupling, which is partially restored by the end of the first year after acute MI, though it remains lower than in healthy subjects. The DBF ⟶ heart coupling is rapidly restored to the level of healthy subjects within three weeks after acute MI.

Keywords: 0.1-Hz oscillations, heart rate variability, distal blood flow

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Heart rate variability (HRV), as well as blood pressure and distal blood flow (DBF) variabilities, is known to be expressed in periodical oscillations at a frequency of about 0.1 Hz [1–6]. Autonomic regulation of the cardiovascular system was studied using various methods of mathematical simulation [7–9]; in particular, 0.1-Hz oscillations of both HRV and blood pressure were found to be due to the functional features of the baroreflex control of systemic blood pressure (the lag time is ~2.1 s, and the feedback delay is ~2,6 s [10]).

There is objective evidence of the functional autonomy of 0.1-Hz oscillations of HRV and DBF variability [11]. In healthy subjects, 0.1-Hz oscillations are mostly synchronized [12]. In patients with myocardial infarction (MI), the level of synchronization of low-frequency oscillations of HRV and DBF variability is reduced, though it is improved later to a certain extent [12, 13]. We have previously reported [13] that the level of synchronization of 0.1-Hz oscillations in patients with acute MI is a sign of important prognostic value.

However, the data on the interaction of 0.1-Hz oscillations of HRV and of DBF variability are not available so far. Since coupling the regulatory mechanisms underlying 0.1-Hz oscillations is normally observed [12], one can assume that one oscillatory process prevails over the other; i.e., the driving process determines the adjustment of the driven one.

The heart–DBF coupling at the level of 0.1-Hz oscillations can be described using biophysical parameters, such as the delay time and dominant direction of coupling.

We studied the biophysical parameters of coupling 0.1-Hz oscillations of HR and DBF variability in healthy subjects and patients with acute MI.

METHODS

A prospective observational study enrolled 125 patients with acute MI (72 men and 53 women aged from 30 to 83 years) who were treated in the clinic of the Saratov Research Institute of Cardiology. The patients gave their informed written consent to participate in our study. The table shows the characteristics of medical histories of the patients with MI, as well as the main clinical data.

The control group consisted of 33 apparently healthy subjects (23 men and 10 women) aged from 20 to 46 years.

After hospitalization, all patients with acute MI were treated in accordance with the current guidelines for the treatment of acute coronary syndrome. The groups of drugs used for treatment can be also seen in the table.

The patients involved in our study were under prospective examination for a year. The checkpoints of the study (time after the acute MI) were two to five days,

Clinical history characteristics of patients with acute myocardial infarction (MI) in the group studied ($n = 125$)

Indices	Units	Values
Sex	% women	42% of women
Age	Years	65 (57; 74)
Anamnesis data		
Ischemic heart disease, stenocardia	%	79.2%
A history of acute MI	%	47.2%
Time after MI	years ago	3 (1; 8)
Chronic heart failure	%	36.8%
Arterial hypertension (AH)	%	62.4%
AH duration	years	10 (5; 20)
A history of stroke	%	7.2%
Peripheral arterial disease	%	1.6%
Chronic renal failure	%	3.2%
Type 2 diabetes mellitus	%	8.8%
Chronic obstructive pulmonary disease	%	11.2%
Smoking	%	22.6%
Data of physical examination		
Acute coronary syndrome with *ST* elevation	%	64.0%
Abnormal *Q* wave on ECG	%	63.2%
Acute heart failure, *Killip* 2–4	%	9.6%
Hospital mortality	%	1.6%
Complicated acute myocardial infarction	%	12.0%
Systolic blood pressure at admission	mmHg	140 (120; 160)
Diastolic blood pressure on admission	mmHg	85 (80; 90)
Body mass index	kg/m^2	27.7 (24.8; 29.3)
Laboratory data		
Cholesterol total	mg/dl	189 (166; 218)
Triglycerides	mg/dl	99 (86; 130)
Blood creatinine	mg/dl	0.79 (0.76; 0.82)
Left ventricle ejection fraction	%	50 (46; 57)
Therapy after hospitalization with acute MI (key indices)		
Thrombolysis	%	32.0%
Anticoagulants	%	96.8%
Antiaggregants	%	100%
β-adrenoblockers	%	84.0%
Inhibitors of angiotensin-converting enzyme	%	91.9%
Calcium antagonists	%	6.5%
Diuretics	%	43.5%
Cardiac glycosides	%	2.4%
Statins	%	7.3%

Note: The data are presented as median and quartile range, *Me* (25%; 75%).

three weeks, six months, and one year. At these checkpoints, we determined the delay of coupling between 0.1-Hz oscillations of HR and DBF variability.

Autonomic regulation of the cardiovascular system was studied using a synchronous recording of an electrocardiogram (ECG) and photoplethysmogram (PPG), as well as mechanical recordings of breathing in the recumbent position. Each recording lasted for 10 min. The recordings were made against the background of arbitrary breathing in all the subjects. In the group of patients that had had MI, the recordings were performed in the period from 1 p.m. to 3 p.m. in all the aforementioned checkpoints during a year after MI.

The ECG, PPG, and breathing were recorded using an EEGA-21/26 Entsefalan-131-03 electroencephalograph model 10 (Medikom-MTD, Russia) with a set of standard sensors. Signals were recorded at a frequency of 250 Hz and a resolution of 12 bit. PPG was recorded using a pulsoxymetric sensor (in transmitted light) on the distal phalanx of the index finger. Breathing was recorded to control respiration spontaneity, the lack of forced inspiration or breath-holding to exclude random effects of respiration on the cardiovascular system. Thus, all studies were conducted under relatively standard conditions of spontaneous breathing. In further analyses, we used EEG and PPG recordings containing no noises, extrasystoles, significant linear trends, or transitional processes. The sequence of *RR* intervals was isolated from the electrocardiogram to plot an equidistant heartbeat time series with a sampling rate of 5 Hz using approximation by cubic splines. Rhythms of about 0.1-Hz were identified in the heartbeat time series and PPG by means of the band-pass filtering within a range of 0.05–0.15 Hz frequencies. The delay in the coupling of 0.1-Hz oscillations of HR and DBF variations was evaluated from the ensemble-averaged recordings of the impact force (*Gy*) from one to another element of the system by means of modeling phase dynamics; in particular, different directions of coupling (heart $\longrightarrow$ DBF and DBF $\longrightarrow$ heart) were studied.

Since the recordings are discrete time series, it is convenient to consider the difference form of the equations:

$$\varphi_{1,2}(t+\tau) - \varphi_{1,2}(t) = F(\varphi_{1,2}(t), \varphi_{2,1}(t), \mathbf{a}_{1,2}) + \varepsilon_{1,2}(t)$$

where $\varphi_1(t)$ and $\varphi_2(t)$ are signal phases, τ is a final time interval, $\varepsilon_{1,2}(t)$ are noises with a zero mean, and F is a trigonometric polynomial of the form

$$F(\varphi_1, \varphi_2, \mathbf{a}_k) = \frac{\alpha_0^{(k)}}{\sqrt{2}} + \sum(\alpha^{(k)}\cos(\varphi_1 + \varphi_2) + \beta^{(k)}\sin(\varphi_1 + \varphi_2)),$$
$$k = 1.2,$$

where $\mathbf{a}_k \equiv (\alpha_0^{(k)}, \{\alpha^{(k)}\}, \{\beta^{(k)}\})$ are the vectors of coefficients; the impact forces themselves were calculated as follows:

$$Gy_{1,2} = \frac{1}{2\pi^2}\int_0^{2\pi}\int_0^{2\pi}(\partial F(\varphi_{1,2}, \varphi_{2,1}, \mathbf{a}_{1,2})/\partial\varphi_{2,1})^2 \times d\varphi_1 d\varphi_2.$$

The maximum of *Gy* versus the lag time curve is indicative of a delay in coupling the oscillations studied and the maximum position makes it possible to determine the magnitude of a delay. Statistical significance of the delay estimates was determined as follows. Under the hypothesis that the random values α_k and β_k are not connected, they are independent and similarly distributed according to the normal law with a zero mean and a variance $\sigma^2_{\alpha_k}$. Hence, the value $\chi^2_{j\to k} = (\alpha_k^2 + \beta_k^2)/\sigma^2_{\alpha_k}$ is distributed according to the χ^2 law with two degrees of freedom. The distribution function of this value $\Phi_2(x)$ is tabulated. Suppose that $\hat{\chi}^2_{2,1-p}$ is a number such that $\Phi_2(\hat{\chi}^2_{2,1-p}) = 1-p$; i.e., $1-p$ is a quantile of the distribution. If $\chi^2_{j\to k} > \chi^2_{2,1-p}$, then we can disprove the hypothesis of the absence of association at the p level of significance. The lower the p, the more reliable this conclusion is. The general value $p = 0.05$ is assumed to show a sufficiently high reliability. The value $\sigma^2_{\alpha_k}$ is unknown; however, we can use the estimate

$$\hat{\sigma}^2_{\alpha_k} = \frac{2\hat{\sigma}^2_{\varepsilon_k}}{N}\left(1 + 2\sum_{l=1}^{\tau/\Delta t}\left(1 - \frac{l}{\tau/\Delta t}\right)\cos\left(\frac{(\hat{\omega}_k + \hat{\omega}_j)}{\tau/\Delta t}\right) \times \exp\left(-\frac{l(2\hat{\sigma}^2_{\varepsilon_k} + 2\hat{\sigma}^2_{\varepsilon_j})}{2\tau/\Delta t}\right)\right),$$

instead, where the noise variance $\hat{\sigma}^2_{\varepsilon_k} = \min_{\omega_k, \alpha_k, \beta_k} S(\omega_k, \alpha_k, \beta_k)$. Thus, the level of significance that allows us to infer a conclusion about the $j \to k$ association is estimated as $p_{j\to k} = \Phi_2(\hat{\chi}^2_{2,1-p})$. The formula for estimating $\sigma^2_{\alpha_k}$ was obtained under the assumption that the function of noise autocorrelation ε_k declines linearly within the interval $[0, \tau]$. If the *Gy* maximum, together with the 95% confidence interval, assumes positive values on the graphs, the estimate of the delay time is significant at the level 0.05.

RESULTS

A delay in coupling 0.1-Hz oscillations of HRV and DBF variability was estimated in the control subjects and patients with MI. Figure 1 shows the results obtained.

During the first week of acute MI, the skatter of *Gy* values was rather wide, and, in the case of an impact of 0.1-Hz HRV oscillations on DBF variability (heart ⟶ DBF), the results proved to be nonsignificant. In subsequent periods of observation (three weeks, six months, and one year after MI), the results were significant, and the maxima appeared on the curves of *Gy* versus the lag time of the heart ⟶ DBF coupling. In particular, there was no clear-cut maximum against the background of general increase in the *Gy* parameters on the third day after acute MI, whereas by the sixth month, a significant maximum appeared on the graph, which was indicative of a delay of 2.5–4.5 s on the effect of 0.1-Hz oscillations in DBF variability on the same oscillations in HRV. By the end of the first year after acute MI, a delay in the heart ⟶ DBF coupling declined to 1.5–2.5 s (Fig. 1).

Analysis of 0.1-Hz oscillations in DBF ⟶ heart coupling during the first week after acute MI revealed no significant maxima on the curve *Gy* versus lag time. However, at the subsequent checkpoints (three weeks, six months, and one year after acute MI), there was a steady maximum of a delay for 1.5–2.5 s in this coupling.

Analysis of the recordings obtained in healthy subjects revealed, in the heart ⟶ DBF coupling, a distinctive maximum corresponding to a delay of about 1 s, which is somewhat lower than the value obtained in patients with MI by the end of the first year. In the DBF ⟶ heart coupling, there was a maximum corresponding to a delay of 2–2.5 s, which is consistent with the parameters obtained in patients by the end of the first year.

Figure 2 shows changes in the delay time obtained for the ensemble in each period of observation by calculation of the index of phase synchronization of the test delay time:

$$\rho(\Delta) = \sqrt{\langle \sin(\phi_1(t-\Delta) - \phi_2(t))\rangle^2 + \langle \cos(\phi_1(t-\Delta) - \phi_2(t))\rangle^2},$$

where Δ is the test delay time. It can be seen in the figure that the average delay values and the scatter of estimates are similar to those determined for observation periods 2–4. The average delay values are about 2 s, which is consistent with the results obtained by simulating the phase dynamics of periods 2–4, and they are somewhat higher than the values obtained in healthy subjects. The delay values are positive, which corresponds to the predominant direction of the effect, heart ⟶ DBF.

DISCUSSION

The results of this study concern a debatable issue of the blood circulation physiology, namely, the nature of 0.1-Hz oscillation of DBF. Some authors believe that 0.1-Hz oscillations are of myogenic origin [14–16] rather than a result of autonomic neurogenic influence. Another version of the origin of 0.1-Hz oscillations of DBF assumes the neurogenic nature of these oscillations [2–4, 17].

When studying the biophysical features of 0.1-Hz oscillations in the variabilities of HR and DBF, we have found that, in healthy subjects, the heart ⟶ DBP coupling has a higher operation speed than the DBF ⟶ heart coupling, which testifies to the predomination of 0.1-Hz oscillations in HRV. Of interest is the short delay (about 1 s) in the phasic coupling of 0.1-Hz oscillations in the heart ⟶ DBF direction in healthy subjects aged from 20 to 46 years.

In patients with acute MI, coupling between 0.1-Hz oscillations in HRV and DBF variability is disturbed mostly for the heart ⟶ DBF direction. Restoration of coupling in this direction occurs gradually and reaches the maximum by the end of the first year after acute MI, but the delay (1.5–2.5 s) fails to attain the level of healthy subjects (~1 s). Conversely, the DBF ⟶ heart coupling is restored to the initial level comparable with the level of healthy subjects (1.5–2.5 s) within three weeks after acute MI.

We have found that, under certain conditions, 0.1-Hz oscillations in DBF prevail over oscillations in HRV, and the phase of the last signal depends on the phase of the first signal with a certain delay time. This phenomenon characteristic of patients with MI (about 25% of the entire patient group) raises the question of the physiological mechanism of phase coupling of 0.1-Hz oscillations. This coupling with a short delay time (1.5–2.5 s) that prevails in the direction DBF ⟶ heart cannot be explained by the inverse mechanical effect of myogenic DBF oscillations on autonomic heart control. Hypothetically, this phenomenon can be explained by the influence of the autonomic nervous system.

In general, our results are consistent with the data on the dependence of the 0.1-Hz oscillation phase in blood microcirculation (the brain microcirculation was studied) on the same parameter in blood pressure (as determined by finger plethysmography) with a certain delay time (2–2.5 s) [18]. Note that, in fact, the authors of [18] also studied coupling of 0.1-Hz oscillations in PPG

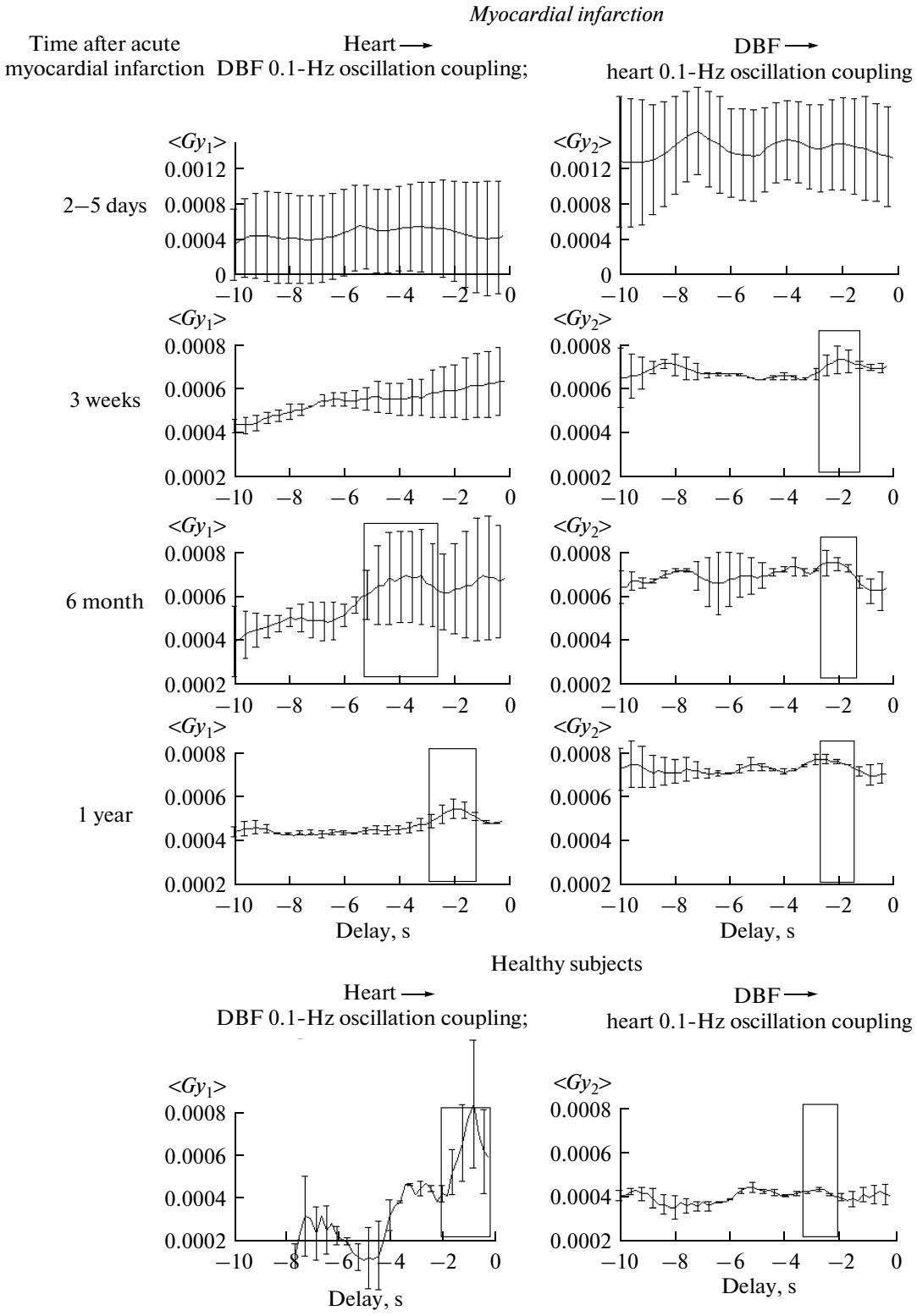

Fig. 1. Ensemble-averaged recordings of the impact force (*Gy*) from some to other 0.1-Hz oscillations (in HRV or DBF variability as dependent on the delay in coupling). The results were obtained by simulating the phase dynamics in healthy subjects and in patients with coronary heart disease at different checkpoints after MI. Rectangles indicate the expected maxima corresponding to the delay position in coupling between the systems.

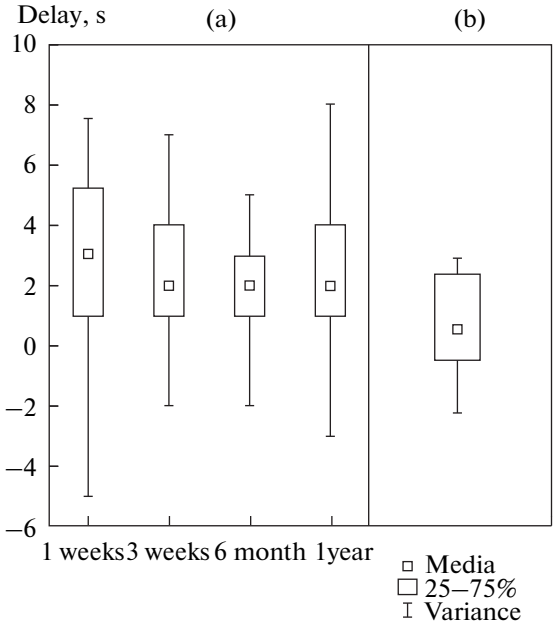

Fig. 2. Distribution of the delay time in various periods as calculated from the index of phase synchronization. (a) Patients with coronary heart disease; (b) healthy subjects. *X* axis, time after myocardial infarction.

and in the distal blood flow of the brain. This phase coupling between 0.1-Hz oscillations in blood flow of different regions of circulation, which is interpreted by the authors as the influence of phase dynamics of blood pressure at a frequency of 0.1 Hz on the phase dynamics of brain circulation, is extremely debatable.

We believe that phase coupling of 0.1-Hz oscillations in HRV and DBF variability form the basis for the phenomenon of phase synchronization of these oscillations [11–13], including the dynamics of synchronization of 0.1-Hz oscillations in patients during the first year after MI.

Normally, 0.1-Hz oscillations are known to be almost always synchronized [11–12]. However, in healthy subjects, 0.1-Hz oscillations in DBF are not a result of mechanical transmission of similar oscillations in HRV and blood pressure because of the 1-s delay in the phase coupling of these oscillations in the heart ⟶ DBF direction and because of the functional independence of 0.1-Hz oscillations during the phase–frequency capture by the external signal [11].

It can be suggested that the disturbed baroreflex 0.1-Hz-regulation of the heart is the biophysical mechanism responsible for disruption of coupling in the heart ⟶ DBF direction in patients with acute MI, though autonomic heart control retains sensitivity to the incoming influence of 0.1-Hz oscillations in DBF. However, physiological reasons for the heart ⟶ DBF failures of this kind remain unclear.

The neurogenic nature of 0.1-Hz oscillations in DBF is likely to be the most suitable explanation for the above phenomena; however, as noted above, this theory has both supporters and opponents; so the issue requires further investigation.

CONCLUSIONS

In phase interaction of 0.1-Hz oscillation in HRV and DBF variability, the heart ⟶ DBF coupling normally prevails with a delay time of about 1 s, whereas the delay in DBF ⟶ heart coupling is 1.5–2.5 s.

During the acute period of MI, interactions at the level heart ⟶ DBF are disrupted, and this primarily concerns to the coupling of 0.1-Hz oscillations from heart to DBF. Restoration of the DBF ⟶ heart coupling to the initial level occurs during the first months after acute MI, whereas restoration the heart ⟶ DBF coupling takes place gradually during the first year, and this parameter fails to reach the level characteristic of healthy subjects. In some patients (about 25%) with acute MI, 0.1-Hz oscillations of DBF variability prevail in the heart ⟶ DBF coupling.

The physiological mechanisms of the phase interactions between 0.1-Hz oscillations in HRV and DBF variability should be additionally studied.

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