Phase-dependent heartbeat modulation by muscle contractions during dynamic handgrip in humans

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Niizeki, Kyuichi, and Yoshimi Miyamoto. Phase-dependent heartbeat modulation by muscle contractions during dynamic handgrip in humans. Am. J. Physiol. 276 (Heart Circ. Physiol. 45): H1331–H1338, 1999.—The influence of cardiac phase on the response of the cardiac pacemaker to dynamic hand contraction in eight healthy young men was studied to determine whether heart rate response to muscle contraction varied as a function of timing within the cardiac cycle. Changes in R-R interval (RRI) in response to muscle contraction were measured at various cardiac phases during heartbeat-synchronized handgrip at a rate of one contraction per two heartbeats. To extract the direct effect of the muscle contraction on the RRI, spontaneous slow variations and respiratory sinus arrhythmia were removed from the total RRI fluctuations in the frequency domain. Cross-correlograms between the extracted RRI fluctuations and muscle contraction showed that the coupling was strong when the muscle contraction occurred at the middle phase of the cardiac cycle. Muscle contraction at the systolic phase of the cardiac cycle had a tendency to produce a phase advance (shortening of RRI), whereas muscle contraction at the middle phase or later had a tendency to produce a phase delay (prolongation of RRI). The results showed the presence of a neuronal circuit that modulates the cardiac pacemaker activity depending on the timing of muscle contraction in the cardiac cycle.

heartbeat fluctuations; cross-correlogram; respiratory sinus arrhythmia; synchronization

HEARTBEAT IS INFLUENCED by a number of physiological mechanisms, including central interaction and afferent inputs from various receptors, such as arterial baroreceptors, chemoreceptors, and pulmonary stretch receptors (20). Spectral analysis of beat-to-beat fluctuations of heartbeat has shown specific peaks in the spectrum (1, 20). The peak corresponding to the preferential frequency of respiratory rhythm is known as respiratory sinus arrhythmia (RSA). RSA is the main component of short-term fluctuations of heartbeats and is thought to occur as a result of phasic autonomic input to the sinoatrial node. It has been demonstrated that the amplitude and latency of heart rate change depend on when the stimulus occurs within the cardiac cycle. For instance, RSA has been shown to be modulated by the timing of respiratory events in the cardiac cycle (11, 14), and the magnitude of the vagal response depends on the timing of baroreceptor stimuli within the respiratory and cardiac cycles (5, 23).

Recent studies have demonstrated that heartbeat is also modulated by muscle contraction rhythm (16, 17). During cycling in humans, muscle contraction affected the magnitude of RSA depending on the respiratory phase (16). Furthermore, temporal phase-locked synchronizations between heart rate fluctuations and locomotor cycle have been found during treadmill walking and running (13, 17, 18). Such locomotor-related modulation of heartbeat appears to be a manifestation of coordination between cardiac and locomotor rhythms. We hypothesize that there might be an intrinsic property in the cardiac pacemaker or some neuronal circuits that coordinates with the muscle contraction rhythm. Furthermore, we propose that muscle contraction occurring at different times in the cardiac cycle will induce different changes in heartbeat timing and that this could cause phase-dependent coupling between cardiac and muscle contraction rhythms.

The phase relationship between muscle contraction and cardiac responsiveness has not been characterized. Thus the purpose of this study is to determine how cardiac rhythm interacts with muscle contraction rhythm. We use handgrip to investigate the response of heartbeat fluctuation to muscle contraction timing within cardiac cycles. Handgrip was chosen because it engages only a small and local muscle group, and it is therefore easy to determine the relative phase relationship between cardiac cycle and muscle activity. Cross-correlation between heartbeat fluctuation and muscle contraction is estimated when the muscle contraction rhythm is in phase with the cardiac cycle. Our results suggest that the muscle contraction timing influenced not only the magnitude of modulation but also the direction of response of the heartbeat.

METHODS

Subjects. Eight healthy men [mean age 22.0 (range 21–24) yr] with no history of cardiopulmonary diseases volunteered for the study. Each subject gave informed consent after a verbal explanation of the experimental procedures was given.

Experimental procedures and measurements. Studies were conducted in a quiet room with temperature maintained at 23–25°C. Subjects were in the sitting position and were instructed to relax. Before the data collection, subjects performed a maximal voluntary contraction (MVC) test using a hand dynamometer (model Dm-100N, Yagami). The dynamic hand contractions consisted of right-handed repetitive squeezing of a handgrip device developed for this study; the load of the device was set to 10% MVC of each subject. When muscle contraction rhythm is slower and is overlapped with respiratory rhythm, it becomes impossible to discriminate the muscle contraction-induced fluctuation from total heartbeat variations. Therefore, the handgrip rate was chosen to be one contraction per two heartbeats to solely assess the influence
of muscle contraction. The subjects handgripped according to computer-generated buzzer signals. The buzzer signals were generated after an adaptive preset delay following the upstroke of the QRS complex of the electrocardiograph (ECG). The delay between the QRS complex onset and the beginning of the sound was changed stepwise to scan several cardiac phases. To minimize anticipatory effects, the subjects were not aware of the change in buzzer signal timing. The subjects were instructed to relax as soon as possible after each handgrip contraction to prevent the extension of muscle activity over two heartbeats. For a given experimental day, three to four trials of handgrip were performed. Each trial included a 1-min rest followed by 9 min of handgrip and 1 min of recovery, with a rest period of ≥15 min between each trial. The subject was given a 1-min warm-up period, after which four kinds of cardiac phase were scoured in one trial, each lasting 2 min. During data collection the subjects were allowed to breathe voluntarily. We also conducted a sham study in which the auditory cues were given at various cardiac phases in the absence of contractions.

Data collection. The R-R interval (RRI) was measured continuously from a surface ECG by using standard bipolar leads. The skin was abraded with polish gel (SkinPure, Nihon Kohden) and cleaned with alcohol to reduce skin electrode impedance. The ECG signal was amplified and filtered (10–300 Hz) to distinguish the R waves of the QRS complex and was digitized with a sampling frequency of 1 kHz by a personal computer-based system (80486 CPU) equipped with a 12-bit analog-to-digital converter (model AD12-16A, Contec). The time at which the R waves occurred was measured and stored directly on a personal computer. Systolic blood pressure (SBP) data were also measured using a volume-compensation finger cuff (Ohmeda 2300, Finapres) and cleaned with alcohol to reduce skin electrode impedance. The ECG signal was amplified, full-wave rectified, and smoothed to ensure equally spaced RRI. In addition, linear baseline trends in the data were eliminated by linear regression. Then, a fast-Fourier transform (FFT) was applied to yield the power spectral density (PSD) of the fluctuation in RRI (Fig. 2A, top, thick line). The FFT was also performed on the integrated EMG and respiratory signals digitized at 10 Hz (Fig. 2A, top, thin and dashed lines). The dominant frequencies of muscle contraction and respiratory rhythms were determined from the periodgrams. After the PSDs of the muscle contraction and respiratory rhythms were estimated, slower variations of RRI and RSA were removed by application of a rectangular window filter in the frequency domain. The filter was applied to the frequency range from zero to the low corner frequency of muscle contraction, at which the muscle contraction PSD decreased to baseline level. The corner frequency was determined by visual inspection of the muscle contraction rhythm PSD. In Fig. 2A, top, the corner frequency was determined at 0.45 Hz. Care was taken to ensure that the muscle contraction frequency showing peak PSD did not overlap the fundamental or harmonic frequencies of respiration. The data were not evaluated when the dominant frequency of muscle contraction was an integer ratio of the respiratory frequency. An inverse Fourier transform was then applied to yield the heartbeat fluctuation associated with muscle contraction. The corresponding RRI values before and after filtering are depicted in Fig. 2A, middle, together with the integrated EMG signals. Low-

Fig. 1. Definition of variables $t_s$ and $T_R$. ECG, electrocardiogram; EMG, electromyogram; $\int$EMG, integrated EMG.

Data analysis. The cardiac phase of muscle contraction ($\phi_m$) was defined as follows (Fig. 1). A computer program reset the timer to zero whenever the QRS complex crossed a preset trigger level, and the distance between the onset of the QRS complex of the ECG and the onset of the EMG firing ($t_s$) was then measured with a resolution of 1 ms (12). The stimulus phase $\phi_s$ was calculated with respect to the heart period ($T_R$) of the same beat, i.e., $\phi_s = t_s/T_R$. We analyzed how the RRI was modulated depending on the muscle contraction timing within a cardiac cycle ($\phi_m$). To do this, we calculated a cross-correlogram (CCG) between the muscle contraction-induced heartbeat fluctuation and the integrated EMG. Heart period fluctuation provoked by a brief muscle contraction was superimposed on the RSA and any remaining variations such as low-frequency components of the 10-s period rhythm. By applying a rectangular window filter in the frequency domain, we subtracted these fluctuations from the total heartbeat variations to extract the direct effect of the muscle contraction. First, unequal RRI were aligned sequentially and interpolated at 10 Hz with use of Lagrange interpolation to ensure equally spaced RRI. In addition, linear baseline trends in the data were eliminated by linear regression. Then, a fast-Fourier transform (FFT) was applied to yield the power spectral density (PSD) of the fluctuation in RRI (Fig. 2A, top, thick line). The FFT was also performed on the integrated EMG and respiratory signals digitized at 10 Hz (Fig. 2A, top, thin and dashed lines). The dominant frequencies of muscle contraction and respiratory rhythms were determined from the periodgrams. After the PSDs of the muscle contraction and respiratory rhythms were estimated, slower variations of RRI and RSA were removed by application of a rectangular window filter in the frequency domain. The filter was applied to the frequency range from zero to the low corner frequency of muscle contraction, at which the muscle contraction PSD decreased to baseline level. The corner frequency was determined by visual inspection of the muscle contraction rhythm PSD. In Fig. 2A, top, the corner frequency was determined at 0.45 Hz. Care was taken to ensure that the muscle contraction frequency showing peak PSD did not overlap the fundamental or harmonic frequencies of respiration. The data were not evaluated when the dominant frequency of muscle contraction was an integer ratio of the respiratory frequency. An inverse Fourier transform was then applied to yield the heartbeat fluctuation associated with muscle contraction. The corresponding RRI values before and after filtering are depicted in Fig. 2A, middle, together with the integrated EMG signals. Low-
frequency RRI oscillations were completely removed after filtering.

To quantitate the amount of RRI variation in relation to muscle contraction, cross-correlation analysis was performed on the extracted muscle contraction-induced RRI and integrated EMG. The peak amplitude of the CCG was used to evaluate the strength of concordance between the two rhythms. The CCG was calculated for a relatively short lag time (5 s) compared with the entire data set to keep the bias error as small as possible. Under this condition, the predicted bias error would be 5% (5 s/102.4 s). Phase shift of the CCG was defined as the difference between the time showing the peak of the CCG and the zero lag time (Fig. 2A, bottom). The phase shifts were measured at each CCG peak, and the average was taken. The averaged phase shift was normalized using the mean period of the CCG and is referred to as the "normalized \( \phi_d \)."

The influence of the muscle contraction cardiac phase on maximum CCG (CCG_{max}) and \( \phi_d \) was evaluated. Because \( \phi_d \) is periodic (i.e., \( \phi_d = 0 \) corresponds to \( \phi_d = 1.0 \)), the following second-order Fourier series regression curves were applied to the relationships between CCG_{max} and \( \phi_d \), and \( \phi_d \) and \( \phi_d \):

\[
y(\phi_d) = \sum_{k=1}^{2} [a_k \sin (2\pi k x) + b_k \cos (2\pi k x)]
\]

where \( y \) denotes CCG_{max} or \( \phi_d \) and \( x \) denotes \( \phi_d \). Constants \( a_k \) and \( b_k \) were determined to minimize the squared error between \( y(\phi_d) \) and the respective experimental values.

For the statistical analysis, significance was defined as \( P < 0.05 \).

**RESULTS**

The mean values of the RRI and SBP at rest and during handgrip are shown in Table 1, together with the mean frequencies for respiration and muscle contraction. For each subject, the RRI during handgrip...
was only slightly lower than that at rest. Similarly, mean SBP during handgrip increased only slightly compared with that at rest. RRI and SBP values during handgrip did not significantly correlate with \( \phi_S \). The mean respiratory frequencies during handgrip were lower than those during muscle contraction in all subjects and were not related to subharmonic values of the muscle contraction frequency. It was important that the respiratory frequency did not overlap the muscle contraction frequency; otherwise, the muscle contraction-induced fluctuation could not be extracted quantitatively because of RSA effects.

Figure 3 shows typical trial results of subject HO, which include a \( \phi_S \) trace, time series of RRI and SBP, extracted muscle contraction-induced RRI in each of the four cardiac phases (I, II, III, and IV), and the CCG between the RRI fluctuation due to muscle contraction and the integrated EMG signals. After 1 min of rest the subject performed handgrip at a random cardiac phase for a warm-up period of 1 min. Heartbeat-synchronized handgrip commenced 2 min after the experiment began. During cardiac phase I (120–240 s) the mean \( \phi_S \) was 0.82; it shifted to 0.05 during phase II (240–360 s), 0.58 during phase III (360–480 s), and 0.29 during phase IV (480–600 s). In this case the mean muscle contraction frequency and respiration frequency were 0.51 and 0.30 Hz, respectively. Figure 3C shows the original RRI (thin lines) and its extracted component (thick lines) related to the muscle contractions for each cardiac phase. An increase in the RRI fluctuation due to muscle contraction can be seen in phases II and IV. Figure 3D shows the CCGs between the extracted RRI fluctuation and the integrated EMG signals. A clear CCG oscillation can be seen in each cardiac phase, indicating that the fluctuation of RRI correlated with the muscle contraction. The peak of the CCG increased in amplitude in phases III and IV (midrange of \( \phi_S \)). The sham study confirmed that CCG max in the absence of contraction was negligible (i.e., 0.096 ± 0.022 SD), as shown in Fig. 2B, bottom. Therefore, the extracted components from the observed RRI fluctuation are considered to be caused by muscle contraction, not by the effects of auditory cues.

Figure 4 shows the influence of muscle contraction timing within the cardiac cycle of the cardiac-muscle contraction coupling (CCG max) in each subject. The thick lines show the Fourier regression curve fitted to the experimental data, and the horizontal dashed lines show the CCG max level obtained in the sham experiment for each subject. Although slight variations in the magnitude of CCG max can be seen among the subjects, in general, CCG max increased in magnitude around the middle of \( \phi_S \). The shape of the CCG max-\( \phi_S \) relationship in five of eight subjects (HO, HS, NT, MI, and KT) was similar, but that of the remaining three subjects (YY, HU, and IK) showed a different pattern.

Figure 5 shows the influence of muscle contraction timing within the cardiac cycle on the phase shift (normalized \( \phi_S \)) for all eight subjects. \( \phi_S < 0.5 \) indicates a phase delay in the RRI response, which means the muscle contraction induces a prolongation of RRI. On the other hand, \( \phi_S > 0.5 \) indicates a phase advance, which means the muscle contraction induces a shortening of RRI. The muscle contraction elicits a phase advance or phase delay of the cardiac rhythm. These phase shifts vary with the \( \phi_S \) at which the muscle contraction is initiated. For example, the muscle contraction originated early in the cardiac cycle at \( \phi_S \sim 0.3 \) produced a relative shortening in the RRI (phase advance) in subject HO. When the muscle contraction originated in the later phase of the cardiac cycle, however, a relative prolongation in the RRI was induced (phase delay). However, a variation in the responses among the subjects was also seen.

**DISCUSSION**

The primary finding of this study is that the timing of the muscle contraction within the cardiac cycle influences the correlation of muscle-cardiac interaction. Muscle contraction originating around the middle phase of two successive heartbeats is associated with an increase in the CCG, indicating an enhancement of the fluctuations related to muscle contraction. Muscle contraction originating at a heartbeat decreased the amplitude of the CCG. This result suggests that cardiac rhythm coordinates with muscle contraction rhythm dependent on the muscle contraction timing.

In the present study, evidence supporting the existence of phase-dependent heartbeat modulation due to muscle contraction was obtained using cross-correlation analysis. Cardiac responses to muscle contraction...
were extracted indirectly from spontaneous RRI fluctuations by using a window filter applied in the frequency domain. This was done so that respiratory interaction did not interfere with the quantitative evaluation of phase dependency of the cardiac pacemaker due to muscle contraction. With use of a CCG, RRI fluctuation due to muscle contraction can be quantified, because only fluctuations common to muscle contraction and heartbeat contribute to an increase in the peak of the CCG. The peak amplitude of the CCG depends on the amount of fluctuation of the frequency common to muscle contraction and heartbeat fluctuation. Inasmuch as muscle contraction frequencies were usually higher than respiratory frequencies and were not coincident with the harmonics of respiratory rhythm (Table 1), the responses shown in Figs. 4 and 5 are not a result of respiratory modulation of heartbeat. Rather, the responses shown in Figs. 4 and 5 are considered to be averaged over all respiratory phases. The phase dependency was also not a consequence of psychological influence from auditory cues, since the amplitude of the CCG between the RRI fluctuation and the buzzer signal in the absence of muscle contraction is indeed negligible compared with the CCG in the presence of muscle contraction (Fig. 2B, bottom).

In most of the subjects, muscle contraction-induced fluctuation (CCG\textsubscript{max}) was greatest in the midrange of \( f_s \), whereas it decreased immediately after a heartbeat. In other words, the influence of muscle contraction-induced fluctuation appears to be related to the phase of the cardiac cycle. Phase advance had a tendency to occur in the early to middle cardiac phases, implying that muscle contraction occurring around the systolic phase of the cardiac cycle provokes a shortening of RRI.
We predicted that the phasic afferent originating from contracting muscles might act as a periodic external input to the cardiac pacemaker, and synchronization could occur depending on the phase-response characteristics (6). According to the theoretical analysis of Pavlidis (19), the synchronization can occur in phase-advanced regions, where the slope of the phase-response curve is greater than $-2$ and less than $0$. The midrange of $\phi_s$ (regions of phase advance with a negative slope of the $\phi_a$-$\phi_s$ relationship) appears to fit this criterion.

Little is known about the mechanism(s) for phase dependency between cardiac rhythm and muscle contraction rhythm. The rapid change in RRI fluctuation due to muscle contraction suggests that phase dependency is mediated through the neuronal origin, perhaps through the parasympathetic nervous system, since the sympathetic nervous system cannot respond as quickly to the muscle contraction frequency (2), and cardiac responses to sympathetic stimulation are phase independent (24). Reflex effects on the parasympathetic nervous system have been shown to play a major role in causing phase-dependent modulation of heartbeat. For example, amplitude and latency of heart rate change after electrical vagal stimulation depend on the timing of the stimulus within the cardiac cycle (14, 25).

Fig. 4. Influence of muscle contraction timing within RRI on cardiac-muscle contraction coupling (CCG$_{max}$) in all subjects. Solid lines, 2nd-order Fourier regression lines fitted to data by least-squares method. Dashed lines, CCG$_{max}$ levels obtained in sham experiment for each subject.

Fig. 5. Influence of muscle contraction timing within RRI on phase shift ($\phi_d$) in all subjects. Solid lines, 2nd-order Fourier regression lines fitted to data by least-squares method. Top: schematic illustration of $\phi_d$ between muscle contraction (thick lines) and RRI fluctuation (dotted lines).
magnitude of RSA has also been shown to vary the timing of the onset of respiration relative to heartbeat (10, 25). The above evidence leads us to suspect that sensory drive associated with muscle contraction may cause the inhibition of cardiac efferent vagal activity. Afferent fibers, classified as group III, are stimulated by dynamic exercise, as has been shown in animal experiments (22). Furthermore, reflex of afferent fibers affects the autonomic nervous system (15, 22). Such a mechanism could operate in the modulation of coupling between cardiac and muscle contraction rhythm. However, whether this is only a potential mechanism for producing phase dependency is unknown. Several researchers have suggested that the phase sensitivity results from some intrinsic property in the cardiac cell and/or tissue. The response to brief electronic stimuli in isolated cardiac tissue or cells showed a phase resetting during some phases (8, 10, 25). Frantz et al. (7) demonstrated in isolated whole hearts that volume loading to the ventricle can induce ventricular excitation, which finally entrains the intrinsic electrical heart rhythm. Contracting muscle could affect the rate of ventricular filling through muscle pump action and, therefore, may alter the duration of the cardiac cycle. Thus the phase-dependent property may involve an intrinsic characteristic of the heart as well as interactions of afferent signals arising from stimulation of mechano- and chemosensitive receptors in contracting muscles.

The amplitude of CCG_max and the profiles of normalized \( \phi_0 \) against \( \phi_s \) differ among the subjects. This may be due to the difference between the relative length of RRI and the duration of muscle contraction among the subjects. \( \phi_s \) was defined as the time lag between the onset of the QRS complex of the ECG and that of the muscle contraction, normalized by the RRI of the same heartbeat. Although the subjects attempted to perform impulsive muscle contraction in the shortest possible time, if the duration of muscle contraction was comparable to RRI, \( \phi_s \) would be less precise. In this case, the response of the cardiac pacemaker is considered to be smoothed or averaged over the duration of the muscle contraction. Furthermore, the duration of diastole increases as the period of the cardiac cycle increases, whereas the duration of systole remains constant (9). Hence, when the RRI is shortened, the systolic phase shifts to a larger \( \phi_s \). This effect would change the response profile of phase dependency. An alternative explanation is that the response of the cardiac pacemaker may vary depending on the frequency of muscle contraction. Previous studies have shown that the magnitude of RSA decreases with respiratory frequency (4), indicating that the transduction gain from input (respiration) to output (RRI) through efferent vagal activity decreases with increasing perturbed stimulation frequency. If cardiac efferent vagal activity is involved in the muscle contraction-related modulation of heart rate, an increase in the muscle contraction frequency is expected to cause a reduction in the magnitude of modulation.

Spectral analysis requires a stationary phase relationship between cardiac and muscle contraction rhythm. However, this requires the muscle contraction frequency to be an integer ratio of heart rate. As shown in Table 1, spontaneous respiratory frequency was ~0.3 Hz, meaning that the muscle contraction frequency overlaps the RSA and low-frequency component of fluctuations if the ratio of heartbeat to muscle contraction is >3:1. To avoid this, the ratio was chosen to be 2:1. Because the magnitude of the response is considered to depend on the strength and rate of muscle contraction, studies increasing the intensity (>10% MVC) and rate (e.g., 1:1 ratio) may yield different phase relationships between heartbeat response and muscle activity. If the modulation of heartbeat by muscle contraction is mediated through reduction of cardiac vagal activity, the magnitude of modulation is expected to decline when the intensity or rate is increased, because increased mean heart rate results in a decrease in parasympathetic activity (22). This is a subject of future study.

In summary, phase-dependent heartbeat modulation due to muscle contraction was demonstrated during dynamic handgrip. The effects of muscle contraction timing within the cardiac cycle on heartbeat fluctuations were characterized using CCG. On the basis of the present results, muscle contraction appears to provide a phasic input for cardiac rhythm, which may be a coordinating factor preventing the period of muscle contractions from overriding the systolic phase of the cardiac cycle. Whether similar situations can be extrapolated to other natural locomotor activities such as walking, running, and cycling in humans is uncertain.

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