# Afferent Somatosensory Information as a Possible Cause of Cardiac-Locomotor Coupling?

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## Abstract

*Cardiac-Locomotor Coupling (CLC), referring to the 1:1 synchronization of Heart Rate (HR) by locomotion, has not been satisfactorily explained as yet. Recent neuroanatomical research has shown that ergoreceptors have projections to the nucleus tractus solitarii, a brainstem structure where baroreceptor afferents also terminate. We have attempted to induce and demonstrate fictive CLC in 15 healthy young men in supine posture. Somatosensory ergoreceptor stimulation achieved by Transcutaneous Electrical Nerve Stimulation (TENS) at the feet at 1:2 HR/TENS ratio. The synchrogram tool was used to quantify synchronization, which was significant though weak in two separate sessions (3.1+/-0.1%, p<0.02 and 1.8+/-0.1%, p<0.04). These figures contain high level of Occasional Coincidence of Frequencies (OCF) effect, emphasizing the caution required in any study aimed at quantifying synchronization. Future protocol will include 1:1 ratio in standing posture.*

## 1. Introduction

Cardiac-Locomotion Coupling (CLC) is a generally recognized phenomenon of which the mechanism has not yet been identified. Locomotion (step rate) tends to synchronize the Heart Rate (HR) to cause CLC in a 1:1 entrainment ratio in humans during walking or running[1-3] and cycling[1,4]. Experiments with rhythmic hopping and rope jumping have not been successful in showing CLC[5]. This suggests a requirement for alternating left and right instead of simultaneous locomotion. In addition, hopping and jumping should involve increased sympathetic activity, compared to simple walking or running, which may reduce CLC.

Kirby and Donville [4,5] reviewed and proposed 5 reasons why a state of CLC could be preferable: 1) maximizing flow of oxygenated blood to the exercising musculature; 2) minimizing cardiac afterload; 3) enhancing venous return; 4) enhancing expulsion of blood from the heart by a mechanical visceral piston effect; 5) optimising all-body energy consumption. These hypotheses have all been experimentally addressed without convincing results. The first three explanations were estimated to be unlikely due to the gentle variation in the phase lag between cardiac and locomotion cycles[2,4]. If these mechanisms play a major role in the evolvement of CLC, then we would expect a specific phase between the HR and locomotion. The visceral piston hypothesis was negated by cycling[4] and jumping[5], and the energy consumption hypothesis an ergometry study[4].

The sixth hypothesis reviewed is that CLC is induced by neural interactions among central pattern generators, affected by afferents from the cardiovascular and locomotor systems[6-8]. For that hypothesis, Kirby gave no reason why such interaction would be efficient or attractive for the organism. Experiments with fictive locomotion, induced by electrical stimulation of the mesencephalic locomotor region in decerebrated cats, have demonstrated that this tends to synchronize respiration and heart rate[9]. This would make the centrally generated motor rhythm a candidate synchronizing mechanism. The fact that smooth exercise (bicycle ergometer), not involving vertical movements also has a synchronizing effect[4] would comply with the centrally generated motor rhythm hypothesis. According to [2], it is possible to infer that some neural circuit arising from sensory inputs during walking influences cardiac rhythm. In addition, it has generally been accepted that the thin sensory fibers classified into group III and IV can be stimulated by pressure and pain and by certain metabolic substances produced by muscular contractions, and that this stimulation causes increased cardiorespiratory responses. How exactly the motor rhythms reach the heart is difficult to say (possibly by modulations in the sympathetic and parasympathetic outflow).

The fact that CLC is such a strong phenomenon, while until now the underlying mechanism could not be identified, made us further pursue the 'neural hypothesis', by applying fictive locomotion-associated neural electrical stimulation to the feet. We have investigated the effect of the rhythmic sensory afferent neural traffic from the moving muscles and from the skin of the stepping or pedalling feet. This rhythmic neural

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information travels to the central nervous system, on its way passing the brain stem, where the respiratory and vasomotor centers are located, thus affecting cardio-respiratory control. The likelihood of this hypothesis can be tested by rhythmic peripheral electrical nerve stimulation, which generates rhythmic sensations without movement and without activity of the motor cortex. The relationship between HR and autonomic activity is widely investigated[10]. Our hypothesis is that vagal and sympathetic activity may be affected by sensory stimulation and therefore under certain conditions, the stimulation may be coupled with the HR. Bipolar 2/s Transcutaneous Electrical Nerve Stimulation (TENS) bursts applied to the feet apparently have an autonomic training effect, such as increased baroreflex sensitivity[11]. This suggests, that the sensory information from the periphery is important and may have central effects. In the following, we thus investigate if there are signs of synchronization of the heart by 2/s burst TENS stimulation.

## 2. Materials and methods

### 2.1. Subjects and data acquisition

Fifteen healthy male subjects, age (mean±std) 25.9±3.7 years were recorded in a previous study on improvement of baroreflex sensitivity by sensory stimulation to the feet. The full protocol is described in ref. [11] and will be described briefly. ECG (leads I, II and V3) was recorded at 500Hz, HR was (mean±std) 66±9bpm. Recordings took place in three days of measurements, A, B and C. Day B was one day after day A, and day C was several weeks apart. Subjects were in supine rest for 30min followed by 60min with sensory stimulation applied to the feet in days A and B and "sham stimulation" in day C (control session).

Electrode pairs for bipolar stimulation of both feet were attached. The lateral stimulation electrodes covered the two main branches of the peroneal nerve (N. fibularis superficialis). At adequate stimulation intensities, A-alpha and A-beta sensory fibers are excited, which gives rise to distinct sensations, while motor fibers are still not excited. The sensory fibers that run under the electrode convey information from major areas of the dorsal part of the foot. The medial stimulation electrodes were positioned above branches of the tibial nerve (N. tibialis) that innervate the heel and the plantar part of the foot. At adequate stimulation intensities, the sensory fibers are excited, while motor fibers are not or nearly not. Both lateral and medial electrodes induce sensations that can be described as touching, stroking, or scratching of the dorsal and plantar part of the foot.

TENS bursts had a period of 0.42 to 0.46sec for producing an approximated 1:2 HR/TENS ratio. Each burst lasted 80ms and contained 9 pulses of 150μs width and 10ms interval. The TENS unit (Kit 866, Magenta Electronics LTD, Burton-on-Trent, Staffs., UK) was modified to make bursts parameters adjustable and balance the leads to produce total current of zero. Sham stimulation was achieved by introducing 10-megaohm resistances in the electrode circuits. This made electrostimulation too weak to provoke any sensation. The subjects were told that they received potentially effective subthreshold stimulation.

QRS complexes were detected from the lead II trace using a threshold and manual correction method followed by a squared interpolation to refine R-waves timing estimation. TENS signal time vector in sessions A and B were extracted from the ECG channel. This was possible due to the distinct parameters of the pulsed TENS signal.

### 2.2. The synchrogram

Our approach for quantifying synchronization between R waves and TENS time series was to enhance a previously developed algorithm for the visualization of phase coupling: the synchrogram[3,12,13]. We have modified this algorithm into a quantitative measurement of synchronization among any two time series for any rational ratio m:n[13]. The method was applied for the time series pairs from each subject and compared with two sets of surrogated data. a) Data obtained by using synthetic computer generated TENS signals and b) Data obtained by switching R-wave and TENS time series between different recording sessions of each subject.

Synchronization is expressed as a region along the time axis, in which two rhythms are related with a simple rational number (m:n). The synchrogram is based on inserting two time series, calculating the relative phase for a set of m:n values and finding the synchronized regions with a running window and a stability threshold procedure. The results are given by a set of location and duration values of the synchronization regions, for each m:n ratio. These results should then be further processed for statistical characterization. The relative phase $\phi$ between the slow rate (HR) and the fast rate (TENS) is calculated for each fast rate data point. Then, the relative phase is folded according to the m:n values in question within a normalized $2\pi$ phase axis to obtain the folded relative phase $\psi$. An example of 1:2 synchrogram and the detection procedure is displayed in Fig. 1.

Detection of synchronized regions was performed by applying a running window along $\psi$, and measuring the deviation width $\delta$ along time. Unwrapped phase is used to avoid phase discontinuities. Window size was 10 seconds, with a detection threshold of 0.5rad (approximately 10% of $2\pi$). A point was considered to be synchronized when the deviation range of the exceeding points in the window was less than the defined threshold. Finally, all points inside the detected window were regarded synchronized along with the first point. The set

of durations and locations of all synchronized regions in a recording were statistically analyzed. Total time of synchronization in percentage units was calculated and used as the main estimate for synchronization.

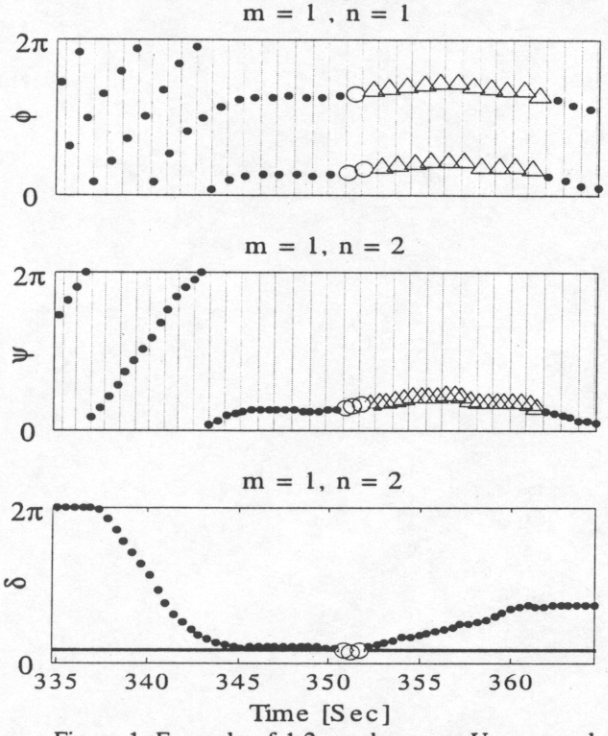


Figure 1. Example of 1:2 synchrogram. Upper panel $\phi$ is the original relative phase between the slow rate (HR) and fast rate (TENS). Vertical lines mark the R wave events. The two horizontal trends describe a region with 1:2 synchronization. Middle panel $\psi$ is the folded relative phase with m:n ratio of 1:2. The two horizontal trends were folded to one. Lower panel $\delta$ is the running window width calculation. Horizontal line is the detection threshold. Circles in all panels denote the detected pulses and triangles in the upper panels denote the complementary pulses included in the detected windows. All vertical units are in radians.

Synchronization between two rhythms might occur randomly by occasional coincidence of non-stable frequencies or as in our case, a TENS rate which is 100 times more stable than the HR (0.5% and 50% drifts respectively along 60min recording). Two surrogate techniques were used to quantify OCF. The first technique was session cross-over control where data sets were switched between different sessions of the same subject. E.g. use the TENS trigger vector of session A, with the R-wave vector of session B of the same subject (combination AB). The level of synchronization was compared to the true AA combination for testing the presence of OCF, expecting a significant higher levels at AA to ensure true synchronization phenomenon. The second surrogate technique used a pre-defined synthetic TENS trigger vector and use it with the true HR vector. Again, this will quantify the OCF level to be compared with the true synchronization levels measured.

## 3. Results

ECG and TENS signal quality limited our analysis to 12 out of the 15 subjects. Total synchronization level was measured for each session and subject with 1:2 HR/TENS ratio using the first surrogating technique. The mean+/-std synchronization level $<p_t>$ was evaluated for all subjects for combinations AA with its surrogates: AB, and AC, as well as for combination BB with surrogates: BA and BC (Table 1). Clearly, the true synchronization levels in AA and BB were significantly higher than their OCF levels by 52-54% and 75-114% respectively ($p<0.02$ and $p<0.04$, Wilcoxon Signed Rank Test) based on the optimal m:n levels (details below).

Table 1. True and OCF synchronization levels

| Combination | AA | AB | AC |
|---|---|---|---|
| $<p_t>$ m:n [%] | 3.14 | 2.04 | 2.07 |
| $<p_t>$ 1:2 [%] | 2.80 | 1.91 | 1.90 |
| Combination | BB | BA | BC |
| $<p_t>$ m:n [%] | 1.78 | 1.02 | 0.83 |
| $<p_t>$ 1:2 [%] | 1.62 | 0.83 | 0.83 |

Estimation error is 0.08% ; N=12
std among subjects is 4.3-5.6% for A and 1.8-2.4% for B

By using error propagation analysis, we obtain an estimate for the individual error $E\{<p_t>\}=0.08\%$. This estimation error is negligible comparing to the large std. Also, subject 3 contributed 57% and 36% of the total synchronization level of all subjects in sessions A and B respectively. This subject showed high synchronization of 19.8% and 7.0% in sessions A and B. However, the results remained significance when excluding this subject from the analysis (not shown).

The tolerance of HR and TENS rate would suggest an optimal synchronization for a different m:n ratio for each subject and session. Therefore, a set of m:n values examined and the maximal synchronization level was chosen to be the representative level for each session and subject. This will give rise to slightly higher levels than the simplified 1:2 case (Table 1). Taking all m:n combinations with integers below 10 that will give ratios within the HR/TENS rate range, left us with the set: {2:3,5:8,3:5,4:7,5:9,1:2,4:9,3:7,2:5,3:8,1:3,3:10}.

On the second surrogate technique, a set of fixed period TENS signals and the true R-wave vectors were used to evaluate synchronization level for 1:2 ratio (Table 2). The OCF levels varied in the range of 0.33-4.36%. Some values were high comparing to the true values 2.8% and 1.6% (Table 1).

Table 2. OCF levels for synthetic TENS rates

| TENS [sec] | 0.40 | 0.42 | 0.44 | 0.46 | 0.48 | 0.50 |
|---|---|---|---|---|---|---|
| $<p_t>_A$ [%] | 0.36 | 0.83 | 1.82 | **4.30** | **4.45** | 1.87 |
| $<p_t>_B$ [%] | 1.00 | 1.64 | 2.72 | **3.05** | 2.41 | 1.73 |
| $<p_t>_C$ [%] | 0.83 | **3.49** | 2.10 | **3.34** | **4.09** | **3.10** |

Estimation error is 0.08% ; N=12
Values higher than 2.8% are in bold (Table 1, 1:2 ratio for AA).
std among subjects was in the range 0.7-9.1% (mean 3.9%)

## 4. Discussion

Using the session cross-over control, a significant synchronization levels were obtained for AA and BB comparing to their surrogates. However, the absolute levels are low (3.14% and 1.78%) and contained high levels of OCF. In addition, using the synthetic surrogate control method we obtained higher levels (up to 4.36%) of synchronization for the surrogate data comparing to the true data. This finding emphasizes the caution required when interpreting weak synchronization levels, and the need to enhance the synchronization levels in future studies. According to the definition of Kirby[5], coupling phenomena should meet three criteria. First, the incidence of identified synchronization ratios should significantly exceed a control level. Second, there should be some consistency (within and among subjects) of the ratios identified. Third, there should be a consistent and extended phase relationship (again, within and among subjects) between the two rhythms. Our results met partly the first two criteria and failed to meet the third.

Two protocol limitations may perhaps reduce the optimal synchronization level achievable with our method. First, CLC has been reported for heart rates of 120bpm or higher, during locomotion activity at a similar rate[1-4]. The TENS in our protocol was at the appropriate rate to simulate locomotion (130 to 143bpm), though it was approximately twice the mean HR at supine rest. Our study was thus performed around a 2:1 ratio between TENS and HR instead of 1:1. A second aspect could be the stimulation pattern. Our experiment involved simultaneous stimulation to both feet while most of the evidences for CLC were observed for alternating locomotion patterns (walking, running or cycling)[1-4]. To be noted, no evidence for CLC was found during simultaneous locomotion pattern (hopping and rope skipping)[5]. In order to enhance the induced CLC effect, future protocol will include 1:1 ratio in standing position, and alternating feet stimulation.

In this study, we have attempted to simulate CLC by inducing sensory stimulation to the feet (using TENS). We have obtained significant levels of synchronization though its baseline is very weak and may be obscured by the OCF effect. Our results indicate that OCF should be considered with great caution in any study aimed to quantify synchronization. HR changes induced by sensory stimulation may provide access to non-invasive therapy procedures, such as improvement of fitness with "fictive" training in disabled patients[11]. Above all, the goal of understanding the origin and possible contribution of the CLC phenomenon is yet to be achieved.

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