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Quantitative analysis of externally-induced patterns and natural oscillations in the human cardiovascular response: Implications for development of a biofeedback system

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ABSTRACT

Immobilization and prolonged bed rest can result in secondary complications that threaten survival chances of patients. Early mobilization can be achieved with a robotic tilt table that allows modulation of the external stimuli body inclination, passive robotic leg exercise, and functional electrical stimulation. However, due to the prevalence of cardiovascular instability in the patients, it may not be safe. A closed-loop biofeedback system with the external stimuli as inputs to control three relevant cardiovascular variables (i.e., heart rate, and systolic and diastolic blood pressures as outputs) would allow safe and early mobilization. To evaluate the feasibility of developing such a biofeedback system, we conducted a series of open-loop experiments with ten healthy subjects. Steady-state changes in the cardiovascular variables that were induced by the inputs (i.e., induced biosignal differences) were defined as gains of the system. Natural oscillations during these steady-state changes were considered as noise. We analyzed these features to test (1) whether the externally-induced changes are differentiable from natural oscillations and (2) whether the gains of the system are clinically relevant (i.e., >2.5 beats/min for heart rate, and >5 mmHg for systolic and diastolic blood pressures). To this end, we compared signal differences (i.e., induced changes in the biosignals; the gains of the system) with noise (i.e., natural oscillations) from a statistical perspective. Results showed that (1) only the changes induced by body inclination were differentiable from natural oscillations, and (2) only change of the body inclination produced reliable clinically relevant changes, and this only held for heart rate and diastolic blood pressure but not systolic blood pressure. We conclude that it is feasible to utilize body inclination for the development of a biofeedback system to control either heart rate or diastolic blood pressure. However, such a system where only two of the three relevant cardiovascular variables can be controlled, and these not simultaneously, would have limited clinical value.

1. Introduction

Patients after medical events such as stroke or spinal cord injury are often bed-ridden for a prolonged period. This extended bed rest is associated with secondary medical complications such as muscle atrophy, cardiovascular deconditioning, and negative neural adaptations [1]. These secondary adverse effects can even lead to life-threatening conditions [2]. Very early mobilization cannot only prevent such harmful complications but also promote recovery and potentially reduce patient time in bed [3]. Provision of a safe and very early mobilization, however, requires keeping the patient's cardiovascular variables within medically tolerable ranges [4,5].

Therefore, we pursue a new rehabilitation strategy. The goal is to develop an intelligent rehabilitation bed based on the Erigo tilt table (Hocoma AG, Switzerland), that can mobilize the patients in an early phase (like after incident) using different external stimuli [5]. We aim to use these external stimuli in a closed-loop manner to control the three cardiovascular variables heart rate (HR), and systolic and diastolic blood pressures (sBP, dBP) simultaneously

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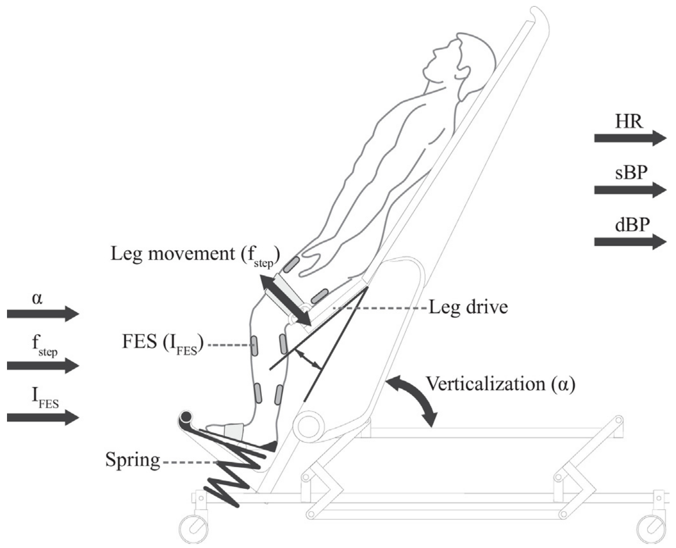

Fig. 1. Erigo tilt table together with the inputs and outputs of the system (The Erigo tilt table, picture adapted with permission from Hocoma AG, Switzerland.): Verticalization is provided by changing the inclination angle of the tilt table α. Passive robotic leg exercise is provided through a leg drive with an adjustable speed f_{step}. The table is further enhanced with electrical stimulation module which enables providing electrical stimulation to the leg muscles with adjustable parameters (here, current I_{FES}) during robotic leg exercise. The outputs – HR, sBP, and dBP – are measured in a continuous manner.

within ranges safe for the patient [5–7]. For this purpose, we have considered three input stimuli (see Fig. 1): (1) inclination angle of the tilt table, (2) frequency of passive leg exercise (stepping), and (3) intensity of functional electrical stimulation (FES) provided to the leg muscles during the passive stepping.

In our previous works [5–8] we focused on designing the closed-loop controller. In particular, to enhance the controller design [8], we considered identification of simple models describing the relationship between the inputs and the induced changes in HR, sBP, and dBP responses. To this end, we conducted a series of open-loop experiments and measured HR, sBP, and dBP of ten healthy subjects under four different study protocols. Based on the identified models, potential challenges for designing an individual-specific closed-loop control system were identified and discussed [8]. The current work aims to answer a more fundamental question: Is developing a biofeedback system based on the considered external stimuli feasible?

In the current work, we pursued finding the answer to this question from a general rather than an individual-specific perspective.

To assess the feasibility of developing the cardiovascular biofeedback system, we considered two perspectives: first, how the output patterns (i.e., system gains; induced steady-state changes in HR, sBP, and dBP in response to the input stimuli) are differentiable from natural oscillations (i.e., natural HR, sBP, and dBP variability). This was important as the inability to differentiate steady-state changes from natural oscillations, i.e., the poor signal-to-noise ratio can be a challenge for system identification [9] and controller design [10]. Second, we measured whether the output patterns reach clinically meaningful levels and the inclusion of corresponding inputs in the loop is practically beneficial.

2. Materials and methods

2.1. Robotic tilt table and measurement equipment

The Erigo (Hocoma AG, Switzerland) is a robotic tilt table designed for very early rehabilitation [11]. The tilt table inclination angle can be continuously adjusted between 0 and 75°, where the maximum effective angle during our experiments was measured to be 71° [8]. The table also has a passive exercise mechanism which can provide automated passive stepping-like exercise with a frequency of 0–80 steps per minute. Moreover, it is equipped with an FES module which can electrically stimulate the leg muscles during the passive exercise and potentially, enhance the training effect (see Fig. 1).

We used a CNAP® monitor 500 (CNSystems Medizintechnik AG, Austria) to measure the raw blood pressure (BP) signal (100 Hz). To measure the BP, the monitor utilizes a double-finger and an arm cuff and it requires an initial 2 min calibration period. We calibrated the monitor every time before running an experiment. Moreover, to ensure an accurate measurement, we used a sling to keep the arm and hand at the heart level during the experiments [8]. The maxima and minima of the raw BP signal were detected online to calculate sBP and dBP biosignals, respectively. HR was calculated based on the HR period computed from the time intervals between dBP values [8]. For complete description of data collection, and study protocols see [8].

2.2. Participants and study protocols

Ten healthy male subjects (mean age: 25.1 ± 2.6 years (standard deviation); mean weight: 81.0 ± 7.2 Kg; mean height: 181.2 ± 6.97 cm; mean body mass index (BMI): 24.8 ± 2.9 [kg/m^2]) provided written informed consent and participated in the study (ClinicalTrials.gov registration identifier NCT02268266). The participants went through four study protocols (see Fig. 2a–d), while we measured their cardiovascular responses – HR, sBP, and dBP – to four different input types (for complete details see [8]): (1) inclination angle α of the tilt table (Inclination); (2) stepping without FES (Stepping), where the (passive) stepping frequency f_{step} was modulated; (3) stepping with FES (Stepping+FES), where FES with constant intensity was applied to the leg muscles during passive stepping; (4) change in FES intensity (FES Amplitude), where the FES current amplitude I_{FES} was modulated during passive stepping.

For each subject, we conducted the experimental protocols generally on one day. Although the order of the protocols was not randomized, the time gaps between them were sufficiently long that they were considered independent [8].

For the study protocols involving FES, the minimum, and maximum FES amplitude were defined as minimum applicable current intensity I resulting to visible contraction I_{MIN}, and maximum tolerable intensity I_{MAX} by the subject. These values were between 7 and 30 mA and they were identified for each subject for each muscle group (i.e., Mm. quadriceps femoris, tibialis anterior, biceps femoris, and gastrocnemius) using a similar procedure to the one used in [12]. For the stimulation, each muscle group was stimulated differently according to its I_{MIN} and I_{MAX}, however, one common intensity level was considered for all the muscle groups. For example, the stimulation with I_{MIN} or $0.8I_{\mathrm{MAX}}$ (see Fig. 2-d) meant stimulation of all the muscle groups with their already identified I_{MIN} or 80% of their already identified I_{MAX}. Although the FES amplitude input intensity was defined with two levels of I_{MIN} and I_{MAX}, for the subjects' safety maximum up to 80% of I_{MAX} in the protocols was applied (see Fig. 2-d). In all experiments, FES frequency was 40 Hz and its pulse width 300 μs.

The study protocols were as follows [8]: (1) Study protocol 1 (see Fig. 2-a) examined the responses to the input stimulus "change in inclination angle". After 5 min rest in supine, the subject was tilted to $\alpha = 71°$ (i.e., maximum effective angle), later went back to supine position, and again tilted to another tilt angle ($\alpha = 40°$), which was followed by a rest period in supine. It was conducted in two variations; the first variation was carried out with the first square-wave signal going to $\alpha = 71°$ of tilt (see Fig. 2-a) and second