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Author(s):
Wieser, Martin; Gisler, Stefan; Sarabadani Tafreshi, Amirehsan; Ruest, Rafael M.; Buetler, Lilith; Vallery, Heike; Klamroth-Marganska, Verena; Hund-Georgiadis, Margret; Felder, Morena; Schoenberger, Josef L.; Gutknecht, Clemens; Riener, Robert

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ORIGINAL ARTICLE

Cardiovascular control and stabilization via inclination and mobilization during bed rest

Martin Wieser · Stefan Gisler · Amirehsan Sarabadani · Rafael M. Ruest · Lilith Buetler · Heike Vallery · Verena Klamroth-Marganska · Margret Hund-Georgiadis · Morena Felder · Josef L. Schoenberger · Clemens Gutknecht · Robert Riener

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Abstract Cardiovascular deconditioning has long been recognized as a characteristic of the physiological adaptation to long-term bed rest in patients. The process is thought to contribute to orthostatic intolerance and enhance secondary complications in a significant way. Mobilization is a cost-effective and simple method to maintain the cardiovascular parameters (i.e., blood pressure, heart rate) stable, counter orthostatic intolerance and reduce the risk of secondary problems in patients during long-term immobilization. The aim of this project is to control the cardiovascular parameters such as heart rate and blood pressure of bed rest patients via automated leg mobilization and body tilting. In a first step, a nonlinear model predictive control strategy was designed and evaluated on five healthy subjects and 11 bed rest patients. In a next step, a clinically feasible study was conducted on two patients. The mean values differed on average less than 1 bpm from the predetermined heart rate and less than 2.5 mmHg from the desired blood pressure values. These results of the feasibility study are promising, although heterogeneous disease etiologies and individual medication strongly influence the mechanically induced reactions. The long-term goal is an automation of the control of physiological signals and the mobilization of bed rest patients in an early phase of the rehabilitation process. Therefore, this new approach could help to strengthen the cardiovascular system and prevent secondary health problems arising from long-term bed rest.

Keywords Bed rest · Stabilization · Cardiovascular system · Actuated tilt table · Model predictive control

M. Wieser · S. Gisler · A. Sarabadani · R. M. Ruest · L. Buetler · H. Vallery · V. Klamroth-Marganska (✉) · R. Riener
Sensory-Motor Systems Lab, Department of Health Science and Technologies (HEST), Institute of Robotics and Intelligent Systems (IRIS), ETH Zurich, Tannenstrasse 1, 8092 Zurich, Switzerland
e-mail: verena.klamroth@hest.ethz.ch

M. Wieser · A. Sarabadani · V. Klamroth-Marganska · R. Riener
Medical Faculty, Balgrist University Hospital, University of Zurich, Zurich, Switzerland

L. Buetler · J. L. Schoenberger
Center for Neurological Rehabilitation, HELIOS Clinic Zihlschlacht, Zihlschlacht, Switzerland

H. Vallery
BioMechanical Engineering, Delft University of Technology, Delft, The Netherlands

M. Hund-Georgiadis · M. Felder
Department of Neurology, Zuercher Hoehenklinik Wald, Faltigberg-Wald, Switzerland

C. Gutknecht
Maternus Clinic for Rehabilitation, Bad Oeynhausen, Germany

1 Introduction

One major problem with patients suffering from trauma, acute and chronic illnesses is the long-term bed rest during the acute phase and the following rehabilitation process. The cardiovascular and endocrine systems adapt to the immobilization with significant deconditioning. Secondary problems such as orthostatic intolerance, venous thromboembolism, pneumonia, muscle atrophy, osteoporosis and joint contractures arise [15] Therefore, early mobilization of the patient is crucial as it can reduce secondary complications and help to improve the health state.

Increase in orthostatic tolerance is a key for recovery. Orthostatic intolerance is mainly mediated via reduced

blood volume, loss of vascular tone in the extremities and functional alterations in the baroreflex function [12].

The resulting orthostatic hypotension is characterized by an increased pulse rate and a decreased pulse pressure with venous pooling in the legs [11]. During immobility muscle hypotrophy of the gastrocnemius and soleus muscles aggravate the venous pooling because their normal function as "muscle pump" is missing. The resulting venous hemostasis increases the risk of venous thromboembolism and pulmonary emboli [11].

The main therapeutic approaches to circumvent orthostatic hypotension, stabilize the cardiovascular system, permit early mobilization and thus improve health status of long-term bed rest patients in a clinical environment are the use of vasoconstrictor drugs, increase in the blood volume, e.g., through infusions, and the use of compression garments [10]. These methods have side effects and are cost-extensive.

Several research groups tried to find alternative methods and showed that the combination of mobilization, body tilting and foot loading has positive effects on blood circulation and significantly reduces the number of syncopes [9, 21]. Furthermore, a statistically significant acceleration of the rehabilitation process and a significant reduction in time at intensive care were demonstrated [8, 23]. In particular, muscle training can partially reverse the loss of muscle strength that occurs with immobilization, and this positive effect can be further enhanced if resistance is added [15]. Foot loading, e.g., during upright posture, facilitates postural reflexes and supports blood flow through working muscles, venous return and cardiac preload [27]. Still, the only clinically established methods to diminish or prevent deconditioning in the acute as well as the early rehabilitation phase are physical therapies in a nearly vertical aligned bed and medication.

The long-term goal of this project is to stabilize the cardiovascular parameters and improve the organs' microcirculation of bed rest patients during the acute phase and the following rehabilitation process via leg mobilization, body tilting and foot loading. To reach this goal, we use an actuated tilt table to control and stabilize the cardiovascular system of the patients and show the short-term effects (up to 30 min) and feasibility of this approach.

To our knowledge, this is the first system controlling and stabilizing the cardiovascular system of bed rest patients with only mechanical stimuli: body tilting and leg mobilization. Thus, the patients' cardiovascular system can be stabilized in an early phase. Concurrently, the stimuli (movement at the ankle, knee and hip joints, tilting and mechanical loading of the legs) should enhance recovery in terms of the organs' microcirculation, structure (muscle strength) and neurological afferent stimulation. [8, 23] This new approach has the potential to support and stimulate the physiological cardiovascular control.

In this work, we focus on the control design, evaluation with healthy subjects and feasibility tests on bed rest patients in order to present the potential of the new approach.

2 Materials and methods

2.1 Subjects

For the evaluation of the system, five healthy subjects (three female and two male) without history of neurological, psychiatric or cardiovascular disorder, an average age of 26.4 years (range 22–31 years), average weight of 68.6 kg (range 60–90 kg) and average height of 174.2 cm (range 169–180 cm) participated in this study (see Table 1).

Furthermore, 11 bed rest patients (six females and five males) with a history of intracerebral ischemic or hemorrhagic stroke were included in the study (average 1.6 months after the incident; range 1–4 months). Detailed patient characteristics are shown in Table 2.

In a feasibility study, the controller was evaluated with two out of the aforementioned eleven patients after stroke.

Measurements were conducted between July 2010 and April 2011 at ETH Zurich, Switzerland, with healthy subjects and at the Zuercher Hoehenklinik Wald, Switzerland, with patients. The local ethics committee approved the study, and all participants or their legal representatives gave written informed assent. Task and testing procedures were in accordance with institutional guidelines, and the study conformed to the Declaration of Helsinki.

2.2 Actuated tilt table and measurement system

The tilt table Erigo® (Hocoma AG, Volketswil, Switzerland) combines continuously adjustable inclination with an integrated motor-driven stepping function (Fig. 1). The trunk and hip are tightly fixed by a belt system, and the tilt angle α_{tilt} can be adjusted between 0° and 76°. The feet are attached on two separate mobile foot plates. Velcro strips fasten the legs to an end-effector of the tilt table in order to perform reproducible standardized movements. The stepping frequency f_{step} can be continuously adjusted from 0 to 80 steps per minute (max. stepping frequency $f_{\text{step,max}} = 1.33$ Hz) the duration of the extension, and flexion phases are identical and individually adjustable for each subject (adjustable range of motion 0° – 45°). The leg elements move with a 180° phase shift to each other at a constant speed.

Table 1 Data of healthy subjects

Healthy subjects' data					
Subject	Gender	Age	Weight (kg)	Height (cm)	Body mass index
H1	Male	25	90	180	27.8
H2	Male	31	68	179	21.2
H3	Female	28	60	172	20.3
H4	Female	26	63	171	21.5
H5	Female	22	62	169	21.7

BMI body mass index

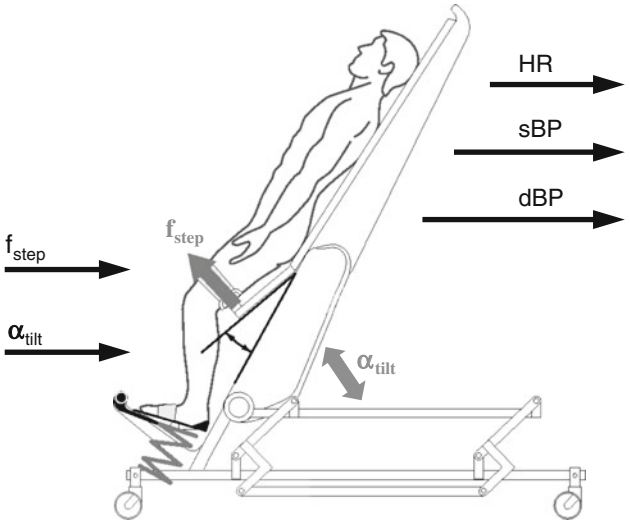

Fig. 1 Measurement setup with the actuated tilt table and the input variables tilt angle α_{tilt} and stepping frequency f_{step}. The physiological output signals are heart rate, HR, systolic and diastolic arterial blood pressure, sBP and dBP, respectively

The continuous blood pressure signal was acquired noninvasively using a CNAP^{TM} Monitor 500 from CNSystems AG, Austria. The blood pressure signals were obtained via a pressure cuff attached to the index and the middle finger. The monitor provided a continuous raw signal that is fed into a g.tec recording system from Guger Technologies, Austria. Data were preprocessed using a second-order Butterworth band-pass filter of 1–30 Hz. By using an adaptive threshold algorithm [5], the systolic blood pressure, sBP, and the diastolic blood pressure, dBP, were extracted by identifying the maxima and minima of the blood pressure signal. The algorithm was only used for peak detection. Thus, to detect the peaks that are related to the dBP, the signal had to be inverted. The peak information was used to get the exact time point in the original signal. To find the BP values, the original signal was scaled. An oscillometric measurement on the upper arm was used to calibrate the continuous BP signal at the beginning of the experiment. Finally, the BP values could be extracted by using the exact time points in the calibrated signal. Based on that beat-to-beat information (dBP value to the next dBP value), time intervals between heartbeats (R–R intervals) were determined in order to calculate the heart rate (HR). Based on that beat-to-beat information (sBP value to the next sBP value), time intervals between heartbeats (R–R intervals) were determined in order to calculate HR.

To filter for oscillations induced by respiration and the cardiovascular system [24], the output biosignals were processed before entering the control loop. A moving average infinite impulse response (IRR) filter of the Direct-Form II was used, which attenuates noise and slightly the short-term natural fluctuations. Window sizes of 30 (group delay of 14.5 s) and 10 (group delay of 4.5 s) with a sampling frequency of 1 Hz were used for HR and BP, respectively.

In the clinical environment, the g.tec recording system was replaced by an Infinity® Delta multivariable patient monitor from Draeger Medical, Germany.

2.3 Model predictive control design

2.3.1 Overview

The cardiovascular system of the human subject is modeled as a nonlinear multi-input multi-output (MIMO) system, with the input vector $\tilde{\boldsymbol{u}}$ containing the tilt angle α_{tilt} and stepping frequency f_{step} that the tilt table imposes on the human, and the output vector $\boldsymbol{y}$ containing the three physiological responses HR, sBP and dBP (Figs. 1, 2). To describe the physiological state of the subject and his corresponding reaction to external stimuli, a physiological model was deployed. The model includes ten internal states and 27 parameters. These internal quantities that keep track of the physiological state of the subject include variables such as HR, venous volume, stroke volume and lung blood volume. Apparently not all of these states can be observed and measured directly and they have to be estimated. To this end, an observer is designed. By adjusting α_{tilt} and f_{step}, the controller aims to keep HR, sBP and dBP close to predefined values and to minimize fluctuations of these physiological signals. The experimenter (when dealing with patients, a physician) defines the vector $\boldsymbol{r}_s$ of desired values for HR, sBP and dBP, which are chosen individually for each subject and described in the section "Experimental

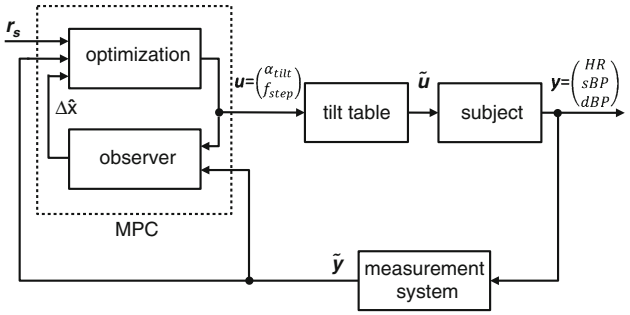

Fig. 2 A model predictive controller sets tilt angle α_{tilt} and stepping frequency f_{step} of the actuated tilt table in order to control heart rate HR, systolic blood pressure sBP and diastolic blood pressure dBP of the human subject. $\Delta\tilde{x}$ is the observer estimation of the deviations of the model's internal states from their true values

protocol". A challenge for the control mechanism is that the states in this physiological system are known to be strongly coupled.

A suitable solution for this type of multivariable control problem is offered by model predictive control (MPC) (Fig. 2) [2]. The key prerequisites for such a MPC design area physiological model that describes the dynamics of the cardiovascular system and can be used to predict future outputs for HR, sBP and dBP, a *measurement system* that provides measured outputs $\tilde{\boldsymbol{y}}$, and an optimization. Since not all the internal states of the physiological model can be measured directly, they need optimization to be estimated using an observer. The observer estimated the deviations of these internal states from their true values and included them in a vector called $\Delta\hat{x}$. The output of the observer, i.e., $\Delta\hat{x}$, is used in the control strategy to correct for the true values of the internal states. This optimization is based on minimizing a cost function, which penalizes control effort and control error. In each time step, the optimization is repeated. A new set of optimal input values for ten future steps of each stimulus is computed. Only the first of ten input terms u for tilting angle and stepping frequency were applied as input to the internal control loops of the tilt table.

The measurement system used to acquire the physiological outputs $\tilde{\boldsymbol{y}}$ (HR, sBP and dBP) is a CNAP Monitor 500, applied in combination with an amplifier (either g.tec from Guger Technologies, Austria, for healthy subjects or Infinity Delta from Draeger Medical, Germany, for patients).

2.3.2 *Physiological model and observer*

A mathematical model of the human cardiovascular system was needed to describe the physiological reactions to verticalization and mobilization. Verticalization leads to an immediate increase in blood volume in the legs and hence decreased venous return. The blood pressure drops and results in baroreflex activation, neural reflexes are instantly activated, and sympathetic action is increased. Accordingly, tilt-table experiments show an increased HR and simultaneously an increased peripheral resistance with an elevated dBP. For sBP, no clear reaction to verticalization has been shown [14, 16, 25, 26, 28, 31]. Less literature is available on the influence of simultaneous mobilization. Some studies show that tilting in combination with mobilization leads to a smaller increase in HR [9, 30] and that the change in blood pressure is significantly higher [9]. In general, passive standing leads to a greater orthostatic challenge than walking [29], and therefore, mobilization stabilizes blood circulation and prevents syncopes during tilting in healthy subjects [9].

To formally model physiological reactions to concurrent tilting and mobilization, we use basic fluid dynamics. The beat-to-beat model (Fig. 3) contains the pivotal elements for simulation of orthostatic reactions, namely a closed hemodynamic system, an internal blood pressure regulation system, the influence of gravity, as well as the reaction to stepping movements.

The first three components, namely the closed hemodynamic system, an internal blood pressure regulation system, and the influence of gravity, were adopted from the physiological model of Akkerman [1]. The model was designed and evaluated originally for tilt table tests only. Additional physiological mechanisms were included to capture the influence of stepping.

In the model, the hemodynamic system is of 8th order and the baroreflex description is of 2nd order. The model is nonlinear and has 10 states, 17 known parameters from literature and 10 unknown parameters. All 10 unknown

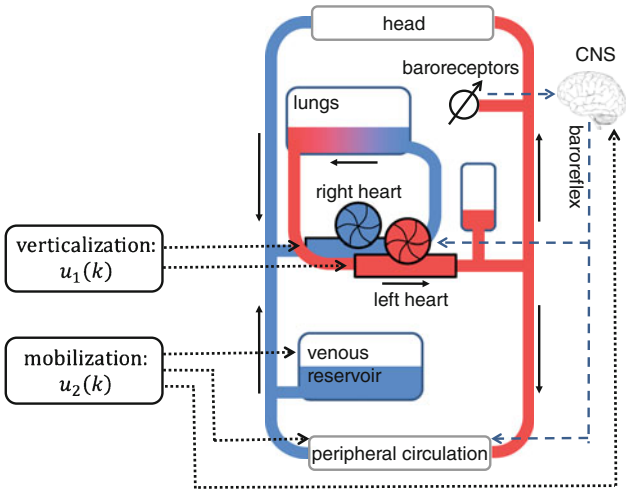

Fig. 3 Cardiovascular model with the inter-connected system of pipes, the reservoirs, the heart as well as the baroreflex system (adopted from Akkermann [1]). The verticalization influences the right and left atrial pressures and the mobilization acts on the venous reservoir, the peripheral circulation as well as the baroreflex system

parameters are individualized for each subject and can be determined during an identification phase. In the identification phase, the individual reactions to verticalization and mobilization of one subject are evaluated, and based on these values, all 10 unknown parameters (Starling mechanism, baroreceptor sensitivity, etc.) can be calculated.

The hemodynamic system can be described as an interconnected system of pipes representing blood vessels. The heart acts as a pump, and the peripheral resistance is modeled via venous and arterial reservoirs. The arteries, veins and the lungs are modeled as compartments with defined volumes and compliances. Constant blood volume is assumed. Thus, fluidic movements through the capillary walls are neglected, but can be modeled indirectly via the reservoirs.

In our model, the essential mechanism underlying blood pressure regulation is the baroreflex. Katona et al. [18] have developed a baroreflex model that is comparable with our model and contains two parts: while one part directly influences HR, the other changes the peripheral resistance.

Gravity acts on each single blood vessel in the cardiovascular system, creating large hydrostatic pressure alterations with change in position. The model of the orthostatic component describes how the tilt angle α_{tilt} of the actuated tilt table influences the cardiovascular system and the physiological states. For simplification reasons, in this model, gravity only influences the right and left cardiac atrial pressures. The change in the height of the heart relative to the supine position is represented by the first input of the model $u_1(k)$, i.e., by the normalized height:

$$u_1(k) = \sin(\alpha_{\text{tilt}}(k)) \tag{1}$$

The variable k denotes the current beat.

Stepping affects the cardiovascular system through different mechanisms: the muscular compression of the venous leg compartments leads to an increase in peripheral resistance and decreases the expandability of the venous vessels, thus decreasing venous compliance. Furthermore, the muscle pump alters the functionality of the baroreflex mechanism by shifting from parasympathetic to sympathetic activity. As stepping is not part of the cardiovascular model of Akkerman, a second input of the model $u_2(k)$ is added as the normalized stepping frequency:

$$u_2(k) = \frac{f_{\text{step}}(k)}{f_{\text{step,max}}}, \tag{2}$$

where $f_{\text{step,max}}$ is 48 spm. As it takes time for the cardiovascular system to adapt to the stepping movements, $u_2(k)$ is fed through a first-order low pass with the constant τ_{step} (for our model: $\tau_{\text{step}} = 40$ heart beats). The influence of stepping in a supine position is very small, because neurological afferent stimulation due to foot loading is missing. Thus, the influence of $u_2(k)$ depends on the first input signal and the normalized height $u_1(k)$. To account for both this dependence and the phase delay, a substitute stepping input $\kappa(k)$ is calculated:

$$\kappa(k+1) = \mathrm{e}^{\frac{-1}{\tau_{\text{step}}}}\kappa(k) + \left(1 - \mathrm{e}^{\frac{-1}{\tau_{\text{step}}}}\right)u_2(k)u_1(k) \tag{3}$$

We assume that this substitute input $\kappa(k)$ affects peripheral resistance R, venous compliance C_{V} and the neural barosignal B in an additive way:

$$\begin{aligned} R(k) &= R + k_{\text{SR}}\kappa(k) \\ C_{\text{V}}(k) &= C_{\text{V}} + k_{\text{SC}}\kappa(k) \\ B(k) &= B - k_{\text{SB}}\kappa(k) \end{aligned} \tag{4}$$

As 9 out of the 10 system states are not measurable, an observer is needed. The type of observer chosen was a Kalman filter. At each time step of the observer ($k_o = 1$ s), the nonlinear cardiovascular model equations are evaluated using the current input $\boldsymbol{u}$ (prediction update) and previous state estimates, followed by a correction that is based on the error between the observed and measured output $\tilde{\boldsymbol{y}}$.

2.3.3 Predictive optimization

For the predictive optimization, the model is linearized around the set point, and the discretization is transformed to a sampling time of 20 s between time steps k_c. At the beginning of the MPC calculation every 20 s, the number of heart beats in the last 20-s time interval must be determined. The prediction horizon is 100 s, and the controller sample time is 20 s, such that the number of prediction steps is $n = 5$. These values for sampling time and prediction horizon are based on pretests. We define the cost function J that reflects the control objective as

$$\begin{aligned} J = \sum_{k_c=1}^{n} &(\boldsymbol{r}_s(k_c) - \boldsymbol{y}(k_c))^T \boldsymbol{Q}(r_s(k_c) - \boldsymbol{y}(k_c)) \\ &+ \Delta\boldsymbol{u}(k_c)^T \boldsymbol{R}\Delta\boldsymbol{u}(k_c) \end{aligned} \tag{5}$$

with the input constraints:

$$\begin{aligned} \Delta\boldsymbol{u}_{\min} \le \Delta\boldsymbol{u} \le \Delta\boldsymbol{u}_{\max} \\ \boldsymbol{u}_{\min} \le \boldsymbol{u} \le \boldsymbol{u}_{\max} \end{aligned} \tag{6}$$

where the first term $(\boldsymbol{r}_s(k_c) - \boldsymbol{y}(k_c))$ is representing the difference between the set point $\boldsymbol{r}_s$ and the actual values $\boldsymbol{y}$. $\boldsymbol{Q}$ is the weighting matrix for the states, penalizing the deviation from the set point. The second part of the equation $\boldsymbol{R}$ is the weighting matrix for control actions, penalizing change $\Delta\boldsymbol{u}$ of the control signal $\boldsymbol{u}$. By minimizing J, the objective is to produce a smooth time course for movement and stepping that brings the subject's physiological states close to the set point.

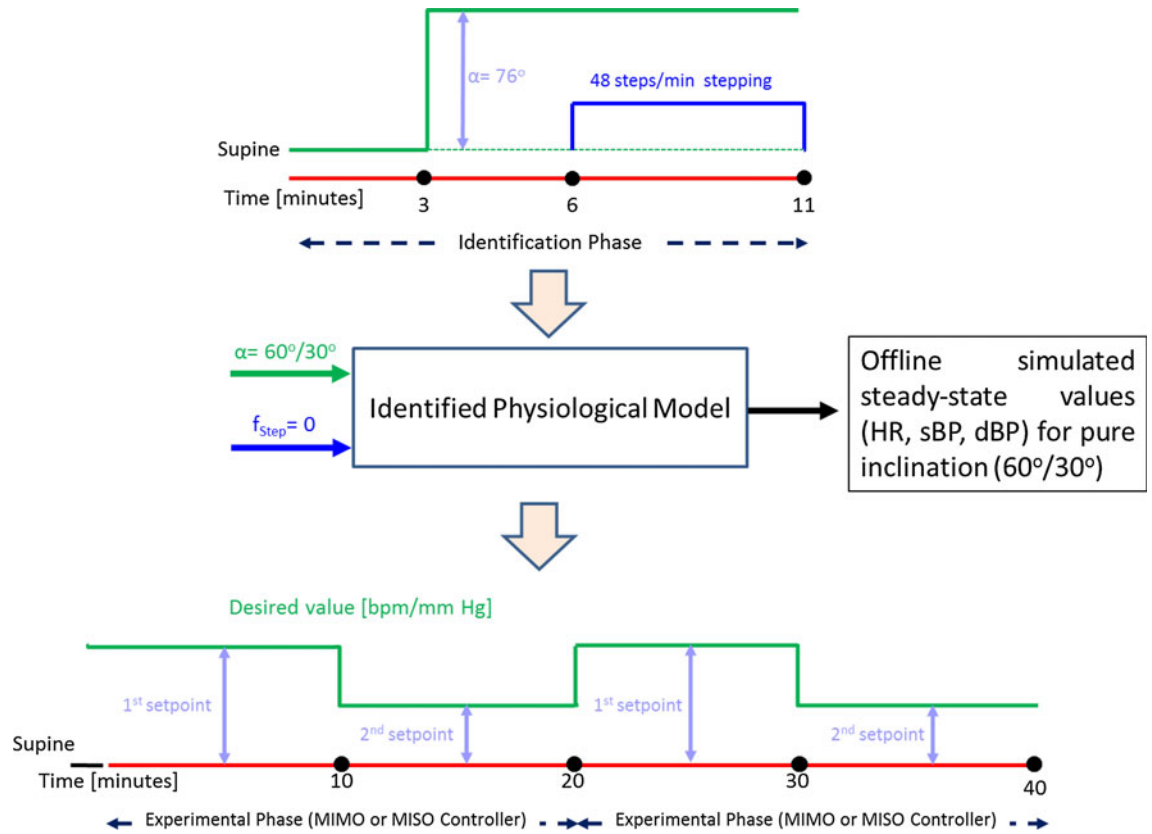

Fig. 4 Experimental protocol

2.4 Experimental protocol

The experimental protocol was divided into two phases: the identification phase of 11 min and the experimental phase of 40 min (Fig. 4).

The identification phase of 11 min was needed in order to identify the physiological values (HR, sBP and dBP) during baseline condition ($\alpha_{\text{tilt}} = 0°$ during the first 3 min) and maximum tilting condition ($\alpha_{\text{tilt}} = 76°$ during the subsequent 3 min). In the following 5 min, the stepping movement was added in order to identify the steady-state values during maximal verticalization and mobilization ($\alpha_{\text{tilt}} = 76°$, $f_{\text{step}} = 48$ spm). A prolonged time phase with stepping (5 min) was chosen to account for the slower dynamics of the cardiovascular system to this assisted gait-like movement of the actuated tilt table compared to verticalization. The steady-state values at supine position are calculated by taking the average of the measured values over the last 2 min before tilting. The steady state for the tilted position is calculated by taking the mean value of minutes 5 and 6. Finally, the steady-state values for the stepping are calculated by taking the mean of minutes 10 and 11.

In the experimental phase of the study, two different controllers were tested for 20 min each. One controller was a multi-input single-output (MISO) system with tilt angle α_{tilt} and stepping frequency f_{step} as input and the controlled HR as output. The other controller was a MIMO system with the same inputs, but sBP and dBP as output. The order of the two controllers was randomized, and the total duration of the control phase was 40 min for each subject. The desired values $\boldsymbol{r}_s$ for HR, sBP and dBP were determined individually by taking the simulated steady-state physiological values (HR, sBP and dBP) for pure inclination (30°, 60°) The determination of the values (30° and 60° set points) was only necessary to demonstrate the feasibility of the method in a clear and standardized way.

Because of legal and safety issues in the hospital, we were not able to use a fully automated system. Although the tilt table Erigo is CE-certified and in use in hospitals, the described software was in the development phase and not certified thus that the system was used in a "human in the loop" manner, meaning that the input signals were determined by the software but given into the system by a human. The input vector $\boldsymbol{u}$ was displayed and manually fed by two experimenters into the actuated tilt table with an approximate delay of 1 s and a precision of 1 deg/0.1 spm. This delay and precision are negligible, considering a controller sampling frequency of 0.05 Hz and slow dynamics of the cardiovascular system to small changes in the input vector $\boldsymbol{u}$. In order to show the feasibility of cardiovascular

Table 2 Overview of all 11 patients: MSO months since onset, the main diagnosis, as well as heart rate- and blood pressure-sensitive medications

No.	Age, sex	MSO	Main diagnosis	Heart rate- and blood pressure-affecting medication
P1	50, Male	1	Intracerebral hemorrhage	ACE-Inhib., Ca+-Antag., beta blocker
P2	80, Female	1	Ischemic brainstem stroke	Diuretics
P3	67, Female	1	Ischemic MCA stroke	Beta blocker
P4	47, Female	1	Ischemic MCA stroke	ACE-Inhib., beta blocker
P5	42, Female	4	Intracerebral hemorrhage	–
P6	46, Male	2	Intracerebral hemorrhage	Ca+-Antag
P7	55, Male	2	Ischemic brainstem stroke	–
P8	89, Female	2	Cerebral microangiopathy	Diuretics, Ca+-Antag
P9	73, Male	1	Intracerebral hemorrhage	Beta blocker
P10	80, Female	2	Intracerebral hemorrhage	ACE-Inhib., Ca+-Antag
P11	73, Male	1	Cerebral microangiopathy	Beta blocker

stabilization with patients, the 60° set point was used to determine the desired values $\boldsymbol{r}_s$. As stabilization of the patients' cardiovascular parameters is the main goal of the study, the control phase with patients was focused only on a single set point during the whole control phase.

3 Results

One patient (out of 11) from the HR analysis and two patients from the blood pressure analysis had to be excluded because of technical problems resulting in a loss of measurement data. During the identification phase, steady-state values for HR, sBP and dBP during tilting and stepping could be detected (steady state for each individual defined as SD $<$ 2 bpm/4 mmHg); the changes in the values of all the individuals are presented in Table 3. The standard deviation within the patient group was high. Nevertheless, all patients showed steady-state values that were higher than in the baseline phase for HR and dBP and lower for sBP. Nine patients reacted with an increase in the steady-state value of the HR (mean 9.0 bpm), seven of the patients reacted with a decrease in the steady-state value of the sBP (mean −5.9 mmHg), and seven patients reacted with an increase in the steady-state value of the dBP (mean 6.6 mmHg).

In the experimental phase with healthy subjects, HR Fig. 5 and sBP together with dBP (Fig. 6) were controlled via the two inputs tilt angle α_{tilt} and stepping frequency f_{step}. Due to high values in the weighting matrix $\boldsymbol{R}$, the controller increased the values for the inclination angle α_{tilt} and the stepping frequency f_{step} rather slowly. Thus, the physiological output signals also changed in a slow and smooth way. After 3–4 min, the desired values according to the first set point (60°) were reached. Because of the anticipative nature of the MPC, the step in the reference signal $\boldsymbol{r}_s$ was detected in advance and included in the optimization procedure. Hence, beginning at minute 8, the "transition phase" from the first set point (60°) to the second set point (30°) had already started. In addition to the set point switch, the controller switches the state-space descriptions from the linearization around the first set point (60°) to the linearization around the second set point (30°), and a drop in the tilt angle α_{tilt} could be seen. Controlling the physiological signals HR, sBP and dBP according to the second set point, 3–4 min were again needed to stabilize these signals around the second set point.

To qualitatively assess control performance, the measured physiological signals were filtered with a second-order Butterworth low-pass filter (cut-off frequency of 0.07 Hz), which allows visual inspection by attenuating the natural fluctuations. The goal of the project is to control the long-term dynamics, e.g., the mean HR, rather than short-term dynamics, i.e., the natural fluctuations, induced by respiration for example. So, to quantitatively assess control performance, the "transition phases" at the beginning and between the set points were excluded, and the mean and standard deviation of the signals were determined during the time periods 4–8 as well as 14–18 min. Mean values represent cardiovascular system long-term dynamics which we aim to control. Standard deviations represent natural short-term fluctuations.

For HR control of one healthy subject (Fig. 5) the average deviation of the desired values of 74.1 (set point 60°) and 64.3 bpm (set point 30°) was −0.61 bpm (SD ±3.1 bpm). The two set points for blood pressure control in Fig. 6 were 128.7 and 124.4 mmHg for sBP as well as 71.8 and 60.3 mmHg for dBP. The average deviation from the desired values was 1.81 mmHg (SD ±3.1 mmHg) for sBP and −0.98 mmHg (SD ±3.2 mmHg) for dBP. The average deviations from the set points in all healthy subjects were −0.73 bpm (SD ± 3.0 bpm) for the HR, 3.45 mmHg (SD ± 2.7 mmHg) for the sBP and −2.14 mmHg (SD ± 2.5 mmHg) for the dBP.

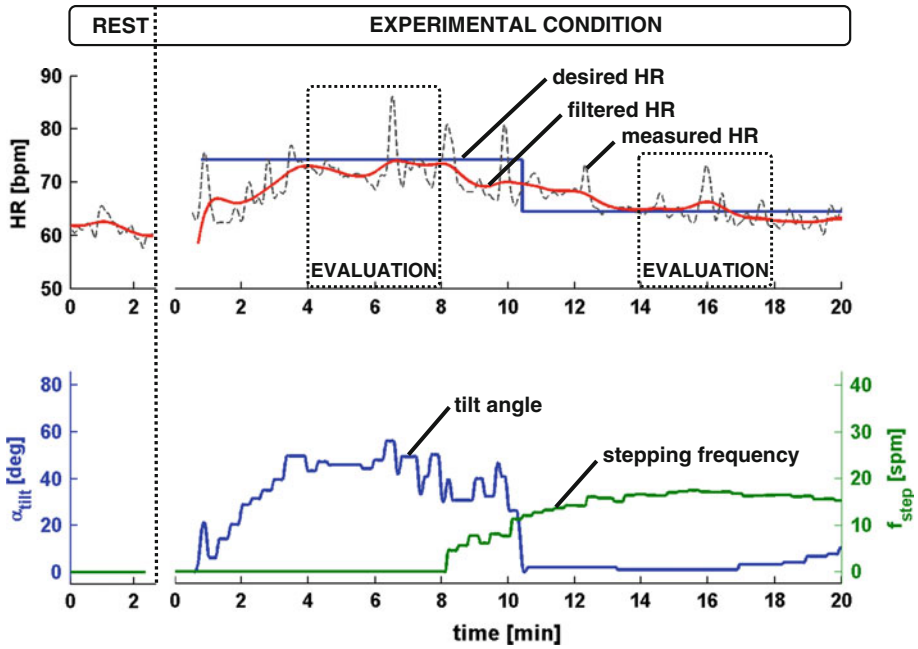

Fig. 5 HR during rest and experimental condition for the healthy subject H1. The two control inputs were tilt angle α_{tilt} and stepping frequency f_{step}. The *dashed*, *gray line* is the measured HR signal, and the *solid*, *red line* is the corresponding filtered HR. For evaluation, only data from the periods 4–8 and 14–18 min were processed (color figure online)

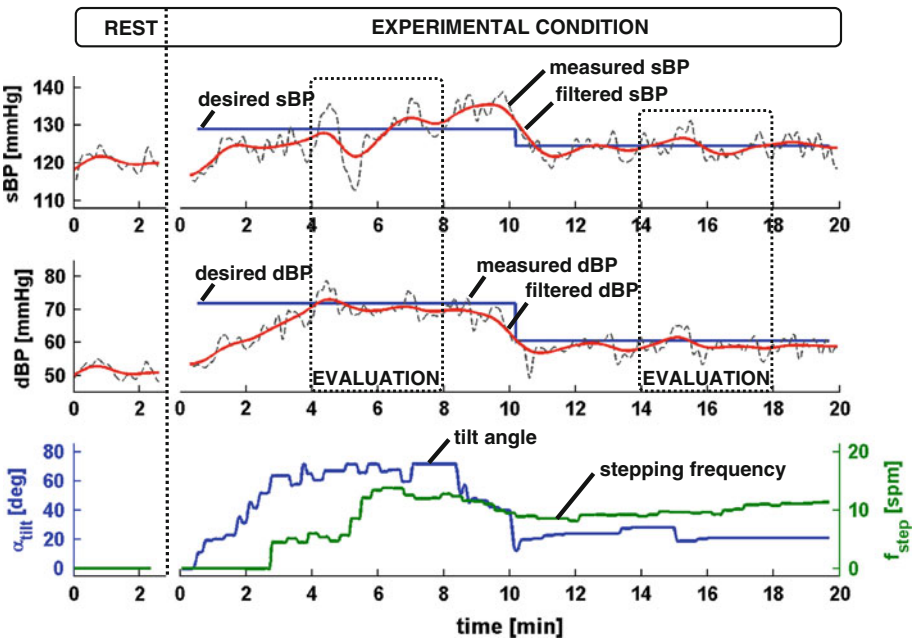

Fig. 6 Blood pressure (sBP and dBP) during rest and experimental condition for the healthy subject H2. The two control inputs were tilt angle α_{tilt} and stepping frequency f_{step}. The *dashed*, *gray lines* are the measured signals, and the *solid*, *red lines* are the corresponding filtered signals. For evaluation, only data from the periods 4–8 and 14–18 min were processed (color figure online)

In the final part of the experiment, the identical controller was evaluated with two bed rest patients. The patient shown in Fig. 7 had a HR of around 90.9 bpm (SD ±0.96 bpm) during the rest condition at the beginning of the experiment. During the experimental phase, the desired HR was 97.7 bpm, which represents the achievement of the desired 60° set point. The mean of the measured HR over the whole control period was 97.4 bpm (SD ±0.68 bpm).

The results of blood pressure control are shown in Fig. 8. The sBP of the bed rest patient was 119.0 mmHg (SD ±0.98 mmHg) and the dBP was 67.8 mmHg (SD ±0.75 mmHg) during rest condition at the beginning of the experiment. During the experimental phase, the desired sBP was set to 110.5 mmHg and the desired dBP to 82.8 mmHg. The measured values in that period settled down to 108.9 mmHg (SD ±3.4 mmHg) and 80.4 mmHg (SD ±2.3 mmHg) for sBP and dBP, respectively.

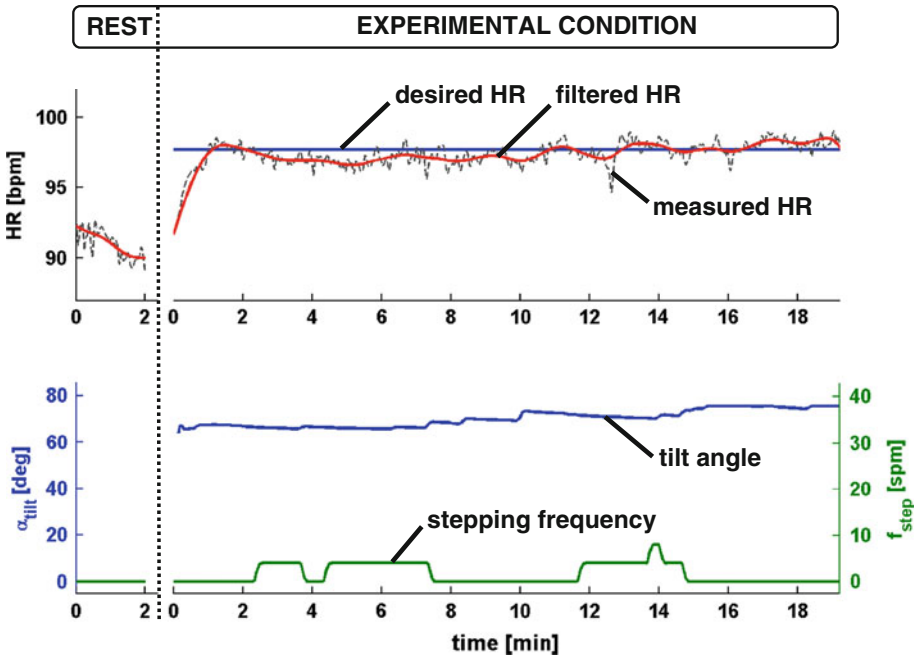

Fig. 7 HR during rest and experimental condition of bed rest patient P11. The two control inputs were tilt angle α_{tilt} and stepping frequency f_{step}. The *dashed*, *gray line* is the measured HR signal, and the *solid*, *red line* is the corresponding filtered one (color figure online)

Table 3 Change in steady-state values for healthy subjects and patients during the identification phase with supine and vertical positions

	Healthy subjects ($n = 5$)		Patients ($n = 11$)	
	Verticalization	Verticalization and mobilization	Verticalization	Verticalization and mobilization
ΔHR (bpm)	10.7 (SD ±1.5)	11.2 (SD ±6.7)	8.1 (SD ±4.3)	5.7 (SD ±3.5)
ΔsBP (mmHg)	9.8 (SD ±1.1)	14.9 (SD ±5.5)	−2.9 (SD ±7.9)	−1.0 (SD ±8.0)
ΔdBP (mmHg)	15.6 (SD ±5.1)	13.9 (SD ±5.8)	4.4 (SD ±5.6)	6.3 (SD ±5.5)

All data refer to the values during the rest condition at the beginning of the experiment

4 Discussion

4.1 Steady-state values

We aim at circumventing the secondary complications of prolonged rest in patients through early mobilization in an actuated tilt table that is controlled by a nonlinear model predictive controller. We evaluated the device on healthy subjects and patients. During the identification phase, steady-state values for HR, sBP and dBP during tilting and stepping could be detected. For healthy subjects, an increase in HR during verticalization is well documented in the literature [4, 6, 14, 16, 22, 25, 26, 28, 31]. Furthermore, the same studies also confirmed a positive change in dBP, whereas the change regarding sBP was found to be increased [4, 6, 22], decreased or not significant [14, 16, 25, 26, 28, 31]. So, our present results of the healthy subjects are in line with basic physiological behavior as described in the literature. In combination with mobilization, blood circulation is stabilized and syncopes can be prevented during tilting in healthy subjects [9]. Unfortunately, the present results show a high standard deviation (Table 3), and it was therefore not possible to draw conclusions regarding mobilization of these subjects.

In hospitalized patients, about 60 % suffer from orthostatic hypotension (OH). The medical causes are manifold and include autonomic neuropathies, hypovolemia, endocrine or cardiovascular causes or drugs [13]. As shown for patients with tetraplegia or neurogenic orthostatic hypotension, HR increases, and sBP and dBP decrease in response to upright standing [7, 10, 17, 20]. The majority of the patients in the present study also reacted with an increased HR and a decreased sBP. Regarding dBP, only two patients showed a decrease, while seven patients showed an increase. Compared to healthy control, the mean of the increased values was three times lower. However, the patients in the present study showed a behavior that is comparable to patients in the literature. As etiologies of the patient groups are different, a direct comparison of the results should be made with caution.

Bed rest patients are generally mobilized during physiotherapy in order to alleviate orthostatic circulatory

dysfunctions. To investigate the benefit of passive leg movements during verticalization via an actuated tilt table, Luther et al. [21] studied occurrence of syncopes, a complication of orthostatic dysfunction, and indicated an increased tolerance to orthostatic stress when tilting was combined with leg mobilization in patients. In the present study, the cardiovascular quantities during verticalization in combination with mobilization showed stabilization of the cardiovascular system.

Steady-state values during the identification phase and reactions to tilting and mobilization differed between healthy subjects and patients. Failure of normal regulatory responses to body tilting is seen in the elderly [13]. Furthermore, antihypertensives are well-known drugs to provoke orthostatic hypotension [19]. Our group of patients was heterogeneous in terms of medication. In particular, during the early phase of rehabilitation, medication was required to stabilize the cardiovascular parameters. Different locations of the brain lesion and other factors can influence the mechanically induced reactions strongly. This could explain why values differed in patients as compared to healthy subjects and why the variability among the patients was quite high. Most of the patients show a clear reaction to tilting and stepping, whereas some patients seem to be insensitive to one of the two inputs (insensitive to tilting: HR of patient P5; insensitive to stepping: dBP of patient P8).

4.2 Experimental phase

Working in real time with raw signals from individual subjects is essential when establishing a control strategy for cardiovascular parameters. As demonstrated via the standard deviations of the steady-state values, the natural short-term variability can be high even without control of the cardiovascular system. For that reason, it was necessary to implement strategies that can cope with the short-term variability. Due to pretests, three issues are implemented to deal with such a high variability: first, the controller sampling frequency was set to only 20 s (0.05 Hz). Second, the controller was only active when the measured value differed more than 10 % of the desired value, and third, the steps of the inclination angle and stepping frequency were rather small because the weighting matrix $\boldsymbol{R}$ contained high values. Thus, the controlled signals changed in a slow and smooth way.

Despite these mechanisms, there was still variability, but during the two experimental phases, it could be shown that the mean values of all five healthy subjects on average differed only by 0.7 bpm from the desired HR, 3.5 mmHg from the desired sBP and 2.1 mmHg from the desired dBP. According to daily clinical practice, a deviation of 3 bpm from a desired HR and 4 mmHg from a desired blood pressure value is in the range of normal variability. Thus, a HR change that is less than 1 bpm is more than satisfactory. The power to control HR in healthy subjects using MPC (MISO control) could be shown. The values for blood pressure showed a higher deviation to their desired values; however, for blood pressure control, two different signals (sBP and dBP) had to be considered at the same time (MIMO control). Compared to the steady-state delta in the identification phase, feasibility of the method could also be shown with the blood pressure signals.

For clinical applications, the control of cardiovascular parameters within a predefined normal range is important for the acute phase as well as the rehabilitation process. In Figs. 6 and 7, the initial condition is shown together with the experimental phase. During this phase, it could be demonstrated that the mean reached values of that patient differed less than 0.5 bpm from the desired HR, 1.6 mmHg from the desired sBP and 2.4 mmHg from the desired dBP.

Therefore, HR control of the two controlled patients is comparable to the results regarding healthy subjects. It was observed that short-term variability (within minutes) is even smaller during the experiments with the patients. One possible explanation could be the medication of the patients. Moreover, short-term variability (also known as heart rate variability—HRV) is a sign of health, and consequently, it is smaller in patients [3].

Furthermore, the blood pressure control was also comparable to the results of healthy subjects. It could be demonstrated that both blood pressure signals (sBP and dBP) could be controlled simultaneously (Figs. 5, 7).

The feasibility study demonstrated the influence of verticalization and mobilization on the cardiovascular system and, in addition, highlighted the possibility of controlling the cardiovascular signals within a predefined range. This new possibility separates the presented approach clearly from well-known bed rest or tilt-table therapies. During a classical therapy, verticalization and leg mobilization are used to stimulate the cardiovascular system via predefined mobilization frequencies and inclination angles. In contrast to that, the presented approach targets the feedback of the cardiovascular reactions and the stabilization of the cardiovascular parameters. So, this approach could also be called a "feedback-related therapy" because it is an approach that is connected and adapted to the change in the cardiovascular parameters itself.

As a vision, this new approach could be used several times per day (e.g., 3 times for 30 min) or even for longer periods (days or weeks without interruption). An "active ICU bed," for example, would support the stabilization of the cardiovascular system during the acute phase as well as enhance the classical goals of the physiotherapy at the same time. Therefore, in the future, maybe, these characteristics will open new opportunities to enhance therapies and shorten rehabilitation phases.

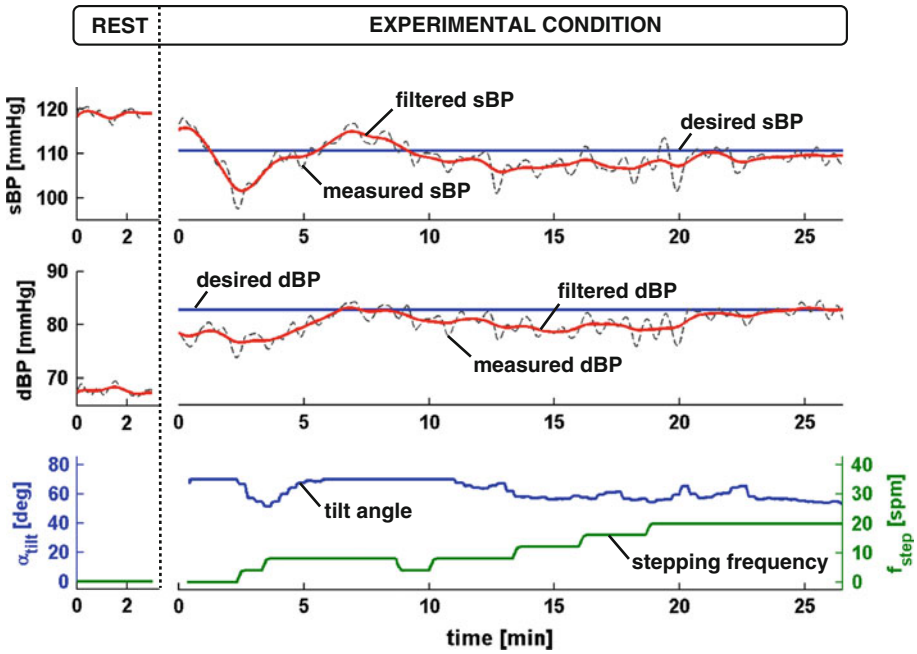

Fig. 8 Blood pressure (sBP and dBP) during rest and experimental condition of bed rest patient P10. The two control inputs were tilt angle α_{tilt} and stepping frequency f_{step}. The *dashed*, *gray lines* are the measured blood pressure signals, and the *solid*, *red lines* are the corresponding filtered ones (color figure online)

4.3 Limitations of the method

The demonstrated control results with patients are promising and demonstrate the feasibility of the method in a clinical environment. Nevertheless, in this study, all desired values for the physiological signals (HR, sBP and dBP) were determined in a standardized, predefined way (30° or 60° set points). These values were chosen arbitrary for the demonstration of feasibility. For clinical applications, physiologically desirable values should be determined by a physician. These values might be based on general norms, guidelines for specific diseases, e.g., after stroke, or patient's state. For safety reasons, we had included a human experimenter in the loop "patient-software- tilt table". Once the method is established, the change in the desired verticalization angle and mobilization speed could be fully automated.

Some of the patients showed a strong reaction, whereas others seem to be rather insensitive to the input signals mobilization and verticalization. The main factors for such a high variability between patients might be the individual differences regarding disease etiology, cerebral lesion location, clinical course and medications. All these factors influence the individual reactions to verticalization and mobilization in a significant way. Beside stepping and tilting, additional important aspects, e.g., psychological factors, might influence the cardiorespiratory system.

The control system is based on a model and the individual responses identified during the identification phase at the beginning of each session. Changes in these assumptions might lead to deviations of the controlled values during the therapy session. This might be of special concern in patients with autonomic nervous system dysfunction and continuous changes in the cardiovascular response. Furthermore, there might be cases where the model does not fit and a control experiment would not be possible. Mobilization of the legs is not appropriate for patients with a lower limb injury. In these patients, the control mechanism must use either a different method for mobilization (e.g., mobilization of the arms or functional electrical stimulation) or verticalization as the only input signal.

4.4 Safety issues

To satisfy safety demands, additional software and hardware changes are required for routine use in clinical settings. The actuated tilt table receives the cardiovascular signals via a medical monitoring system. When the control system is not able to reach the physiological target signals, the monitor's alarm will start.

In the current system, all signals are measured via sensors and wires. If those wires were removed by a wireless system, movement artifacts could be avoided and controller output improved.

5 Conclusions

Mobilization and verticalization are key factors in the conventional physiotherapy of bed rest patients. In a first step, we analyzed the physiological reaction to predefined angles and stepping frequencies in eleven patients on a dynamic tilt table. In a second step, we did a feasibility

study on two patients. We were able to combine the two stimuli mobilization and verticalization and extend their use from physical therapy to direct control and stabilization of the cardiovascular system. The physiological parameters HR, dBP and sBP could be kept within predefined ranges through changing the mechanical parameters (mobilization and verticalization), and this method worked in healthy people as well as in two bed rest patients over a short time period (20 min).

In a next step, we aim to control and stabilize these parameters in combination and over the whole course of immobilization. Thus, we will include more patients in the control experiment and extend the experiment to hours and days. The long-term goal is to prevent the cardiovascular system from deconditioning, thus avoiding orthostatic intolerance and other secondary complications of long-term bed rest. The new method has the potential to enhance the recovery process in the treatment of bed rest patients and reduce the time in intensive care.

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