Hemodynamic Interventions for Inducing Blood Pressure Variation in Laboratory Settings

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Introduction

Arterial blood pressure (BP) parameters are key hemodynamic indices often used for screening and diagnosis of various pathophysiological conditions. Brachial artery BP measurement using a bladder-type pressure cuff and sphygmomanometer (auscultatory or oscillometric technique) is a routine part of clinical assessments. Over the past few years, the interest in methods that allow non-invasive, cuffless evaluation of BP parameters has increased to overcome the fundamental limitations of cuff-based techniques [1]. Cuffless techniques rely on exploring the relationship between BP and BP-dependent non-invasively measurable physiological parameters. Such theoretical or heuristic mathematical models generally require subject- and/or population-specific calibration procedure to quantitatively convert the acquired physiological parameters into pressure. Pulse transit time estimates, arterial vessel characteristics, and various hemodynamic indices are typically utilized to implement cuffless BP evaluation techniques [2]; these parameters are subject specific. Hence, a calibration curve and/or BP prediction model that is tailored to each subject would be optimal for accurate measurement [3]. Further, these calibration curves/models would have to be updated at regular intervals for accurate and reliable BP evaluation [2].

In order to develop subject-specific calibration curves or data-driven prediction models, the desired input physiological parameters should be recorded over a wide range of BP values from the subject. For this, resting BP level should alter via suitable BP perturbing interventions. Calibration curves or prediction models obtained through data recorded from a single intervention may not be effective for accurate BP evaluation [2]. Subject-specific data obtained from multiple interventions that perturb BP through different physiologic mechanisms could potentially provide reliable prediction models. Hemodynamic interventions such as drug-induced methods, anesthesia induction, and intensive care unit (ICU) therapies are typically followed to produce major BP changes over a wide physiological range [4]. However, these approaches are technically demanding, highly invasive, require well-trained physicians with clinical and/or research experience, and limited to hospitalized subjects. Therefore, subject-specific calibration curve/model construction and recalibration via invasive interventions cannot be adopted to realize cuffless BP techniques for wearable devices and routine screening applications. Practically feasible non-invasive interventions are needed to perturb BP parameters during the design, validation and recalibration phases of cuffless BP devices.

In this work, we evaluated the variation in brachial BP parameters during multiple hemodynamic interventions that change the BP level through different physiological mechanisms. Five non-invasive interventions namely; (i) cold pressor test, (ii) treadmill-running exercise, (iii) mental arithmetic, (iv) leg-raise test, and (v) sustained handgrip test were preferred for the validation study. These BP perturbing interventions could be safely performed in laboratory/non-specialist settings without the assistance from a physician or a trained investigator. Further, they could mimic various daily life activities such as experiencing cold weather conditions, brisk walk or performing strenuous exercise, stressful situations et cetera. An *in-vivo* study was conducted on randomly recruited normotensive subjects in order to characterize the BP altering strategies of aforesaid interventions. Measurement protocol of the performed study, BP perturbing procedure, recommended experimental conditions, *in-vivo* study results and observations are discussed in the following sections.

Materials and Methods

Subject Selection

Fifteen normotensive subjects ranged in age from 22 to 34 years comprising of males and females (body mass index = 22 – 29 kg/m^2) were recruited for the present *in-vivo* study. The study objectives and measurement protocol were explained to each participant and their written informed consent was obtained. This study conforms to the principles outlined in the Declaration of Helsinki. Before data collection, participants were requested to relax for 5 – 10 min to reduce their anxiety and to bring the BP parameters and heartrate to the normal level.

Study Protocol

The *in-vivo* validation study was designed by including five hemodynamic interventions listed in tab .1. Systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP) and heartrate were repeatedly measured from the brachial artery under (i) physically relaxed condition, (ii) during an intervention, and (iii) post-intervention recovery period. Measurements were performed using a clinical grade automatic BP monitor (SunTech® 247™ – SunTech Medical Inc. NC, USA; resolution = 1 mmHg) with a bladder-type pressure cuff. During the study, resting BP

Table 1: Hemodynamic Interventions for Altering BP Parameters

Intervention	Protocol	Observations and comments
Cold pressor test 	Immerse both the hands into an ice water container for 2 – 4 min. Maintain the ice water temperature between 3 – 5°C.	• Minimum 2 min intervention required for moderate perturbation in BP • Trivial body movement/motion artifacts • Sensitive towards individual pain threshold and pain tolerance
Treadmill-running exercise 	Run on a treadmill for 7 – 10 min. Start with a low speed of 3 km/h, and increase the speed at a steady rate (maximum up to 10 km/h).	• Significant variation in SBP and heartrate • Maintain heartrate < 85% of (220 – Age) • Prone to body movement/motion artifacts during the intervention period • High breathing artifacts during post-intervention recovery period
Mental arithmetic 	Perform serial subtraction of a two-digit number from a four-digit number quickly and repetitively for 4 – 5 min.	• Recreation of real-life stressful situation • Trivial body movement/motion artifacts • Variations in BP may not be observed when the participant is an experienced public speaker or intellectually sound in mathematics
Leg-raise test 	By adopting the supine posture, raise and hold one leg without any support, for 2 – 3 min.	• Moderate variation in BP parameters and heartrate • Post-test BP recovery time < 1 min • Minimal body movement/motion artifacts • Not recommend in patients with sciatica
Sustained handgrip test 	Hold and clench handles of the spring-type handgrip in both the hands by putting in maximum effort for a sustained time until fatigued.	• Substantial variation in BP parameters and heartrate • Minimal body movement/motion artifacts • Strength deficit of the muscles associated with variation BP level

and heartrate (baseline values) of each subject were measured for 2 – 3 min. After the baseline measurement, the participants underwent a BP perturbing intervention task (protocols are summarized in the tab. 1), followed by a recovery phase, in which they rested until BP and heartrate returned to the baseline value or remained in steady level. It was preferred to conduct only one intervention task per day for an individual subject. This helped to investigate the physiological response and cardiovascular reactivity of each intervention independently.

Results and Discussion

Intervention Characteristic Curve for BP Variation

For each subject, the recorded brachial SBP, DBP, MAP, and heartrate were analyzed and compared in order to characterize the BP altering strategies of preferred interventions. The average time interval between two consecutive BP measurement was approximately 42 s, which is the time taken by the BP monitor to inflate, deflate, and report the measured values. The obtained discrete readings of each BP parameter was interpolated onto their successive readings to produce continuous curves showing the locus of instantaneous variation in BP parameters. This interpolation allowed characterization of BP variation due to an external intervention.

Fig. 1 depicts typical intervention characteristic curve illustrating variation in BP level during the course of study, under increasing BP conditions. This projected curve was obtained by generalizing data recorded during the present study over all the subjects. However, an intervention characteristic curve for each BP parameter is subject-specific. As shown in fig. 1, the fiducial parameters of BP intervention characteristic curve were defined with re-

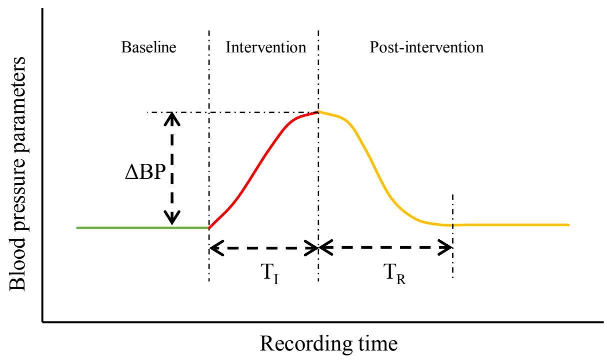

Figure 1: Typical BP intervention characteristic curve

spect to initial baseline and post-intervention measurements. The total time taken to perform an intervention task as per the protocol (tab. 1) is denoted as the intervention period (T_I). The post-intervention recovery period (T_R) is defined as the time taken to regain initial baseline values or a steady BP level after finishing an intervention task. The maximum increment yielded in the BP level from its baseline value is expressed as an absolute change (ΔBP), this quantitative metric for SBP, DBP and MAP are ΔP_S, ΔP_D, and ΔP_M respectively. Similarly, the maximum variation in heartrate (with respect to baseline heartrate) during the intervention task is denoted as ΔHR.

The proposed fiducial parameters were evaluated separately for all five interventions to investigate their individual effect. Representative characteristic curves (obtained from a subject with age = 17 years and body mass index = 24 kg/m^2) demonstrating the variations in BP parameters and heartrate during all five interventions has been presented in fig. 2. It may be noted that the treadmill-running exercise is subject to significant body movement and motion artifacts. As a consequence, measurements recorded while performing the treadmill-running task were not reliable, and hence those data points were removed from its characteristic curves.

Hemodynamic Variation due to External Intervention

All five interventions included in this study are known to increase BP parameters, however, the induced variations and post-intervention recovery are caused by the different physiological phenomenon. The proposed fiducial parameters defining hemodynamic variations due to external interventions have been summarized in fig. 3 using box-and-whisker diagrams pooled over all the subjects. The absolute values of T_I were limited by pre-defined study protocol as per the nature of interventions, however, the absolute T_R values depended on physiological response and cardiovascular reactivity to an intervention task. Absolute T_R for each BP parameter was comparable (< 5% variation), and hence an average T_R has been depicted in fig. 3. Due to elaborated T_I and severity of the treadmill-running task, its mean T_R was higher (4.2 min) than the corresponding metrics offered by other intervention tasks. Both the leg-raise and sustained handgrip tests (means of T_R = 0.6 min and 0.9 min respectively) yielded rapid post-intervention recovery from the elevated BP level.

It may be observed from the box-and-whisker diagrams that the cold pressor test yielded a moderate increment in all BP parameters (mean values of ΔP_S = 22.5 mmHg, ΔP_D = 16.7 mmHg and ΔP_M = 18 mmHg). These BP variations are mediated by a sudden increase in the peripheral vascular resistance due to vasoconstriction, the underlying mechanism being the autonomic neural pathways acting via sympathetic nervous system [5]. Cardiac output and heartrate typically increase during aerobic exercise like running on a treadmill, which leads to a significant increment in SBP (mean values of ΔP_S = 37.6 mmHg and ΔHR = 67.2 bpm) with a moderate variation in DBP level (mean ΔP_D = 14.4 mmHg) during the post-exercise recovery period. However, in physical tasks such as sustained handgrip test, the static contraction of muscles against fixed mechanical spring load causes a marked increase in all the BP parameters with a relatively small heartrate variability [6]. The presented study also demonstrated substantial variation in the BP parameters (means values of ΔP_S = 28.5 mmHg, ΔP_D = 26.7 mmHg and ΔP_M = 26.5 mmHg) with a mean heartrate increment of 17.6 bpm during the sustained handgrip test.

Consistent with the physiological theory, a moderate increment in SBP, DBP, and MAP was observed during the

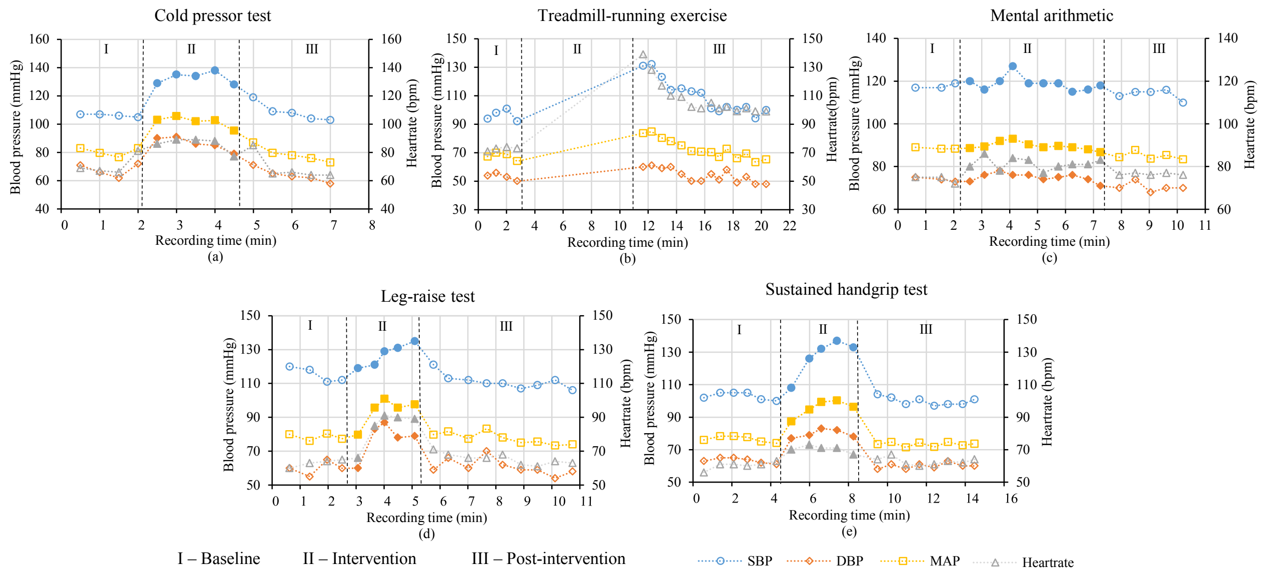

Figure 2: Subject-specific intervention characteristic curves obtained from a particular subject, illustrating the variation in SBP, DBP, MAP and heartrate during (a) cold pressor test, (b) treadmill-running exercise, (c) mental arithmetic, (d) leg-raise test, and (e) sustained handgrip test

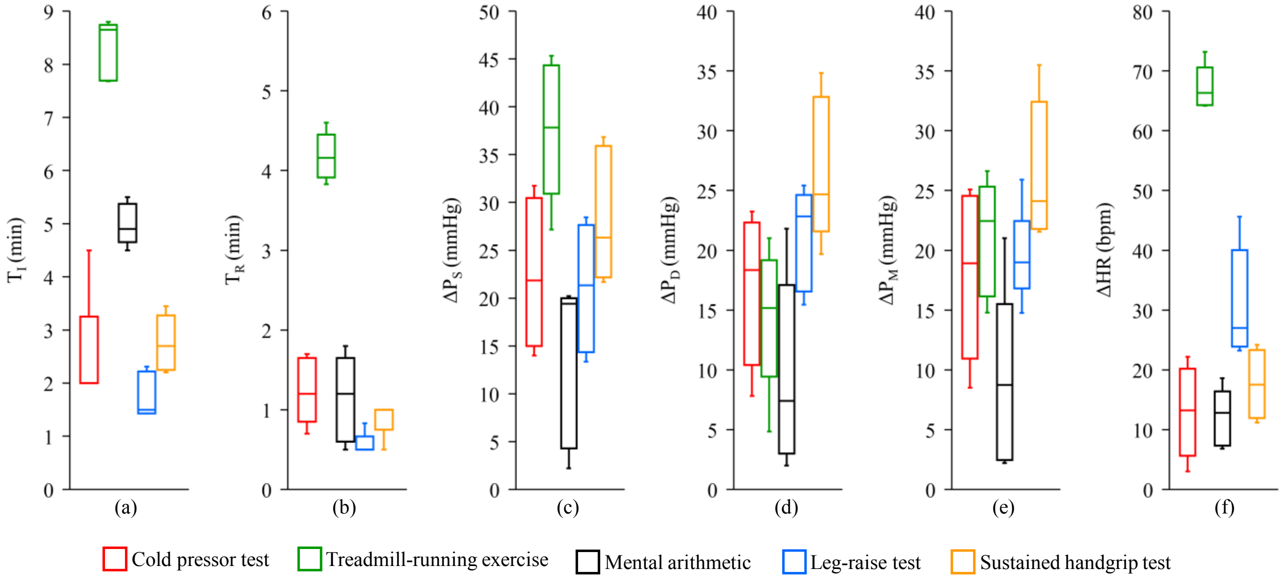

Figure 3: Box-and-whisker plots illustrating the measured fiducial parameters (a) T_I, (b) T_R, (c) ΔP_S, (d) ΔP_D, (e) ΔP_M, and (f) ΔHR pooled over all the subjects

active leg-raise test (mean values of ΔP_S = 21.1 mmHg, ΔP_D = 21 mmHg and ΔP_M = 19.5 mmHg). These variations are induced when a subject is performing a voluntary leg-raise the lowered perfusion pressure to the sustained contracting leg muscles is being compensated with an increase in cardiac output and BP, acting via the central pressor response [7]. Hemodynamic variations observed during the mental arithmetic test were idiosyncratic and prone to psychological reactions. Short-term changes in BP parameters were observed for the recruited subjects during the mental arithmetic test due to increase in sympathetic activity and dumping of baroreflex. Mean values of ΔP_S, ΔP_D, and ΔP_M obtained from the mental arithmetic test were 13.6 mmHg, 9.5 mmHg and 8.9 mmHg respectively. Heartrate variations were also not prominent (mean ΔHR = 12 bpm) during the mental arithmetic test in the recruited normotensive subjects.

Conclusions

This study demonstrated five hemodynamic interventions that perturb resting BP level in a safe and controlled manner. During the study, the BP parameters were found to vary at different levels in accordance with the physiological response, which mimics daily life activities of an individual. For each subject, brachial SBP, DBP, MAP, and heartrate were measured from three phases: baseline, during the intervention and post-intervention recovery period. BP altering strategies of the preferred interventions were evaluated using the proposed BP intervention characteristic curve and fiducial parameters. The treadmill-running exercise found to induce significant variations in SBP and heartrate. However, the measurements were susceptible to motion and breathing artifacts. A moderate variation in all BP parameters was observed during the cold pressor test, where no physical movements were involved. Therefore, the cold pressor test may be a recommendable method for acquiring physiological signals under varying BP conditions with minimum error due to motion and breathing artifacts. Further validation study in a large population is in progress, in which BP and BP-dependent physiological parameters are recorded in a beat-by-beat manner during multiple interventions. Data recorded from such extensive studies can be used for developing BP prediction models through data-driven methods such as machine learning. Such models can be potentially used in wearable devices and cuffless 24-hour ambulatory BP monitors.

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