Multi-Site Pulse Transit Times, Beat-to-Beat Blood Pressure, and Isovolumic Contraction Time at Rest and Under Stressors

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***Abstract*—This study investigates the beat-to-beat relationships among Pulse Transit Times (PTTs) and Pulse Arrival Times (PATs) concomitantly measured from the heart to finger, ear and forehead vascular districts, and their links with continuous finger blood pressure and isovolumic contraction time (IVCT). These aspects were explored in 22 young volunteers at rest and during cold pressure test (CPT, thermal stress), handgrip (HG, isometric exercise) and cyclo-ergometer pedalling (CYC, dynamic exercise). The starting point of the PTT measures was detected by the seismocardiogram. Results indicate that PTTs measured at the ear, forehead and finger districts are uncorrelated each other at rest, and during CPT and HG. The stressors produced district-dependent changes in the PTT variability. Only the dynamic exercise was able to induce significant changes with respect to rest in the PTTs mean values (-40%, -36% and -17%, respectively for PTT_{ear}, PTT_{fore}, PTT_{finger}), and synchronize their modulations. Similar trends were observed in the PATs. IVCT decreased during the application of stressors with a minimum at CYC (-25%) reflecting an augmented heart contractility. The increase in blood pressure (BP) at CPT was greater than that at CYC (137 vs. 128 mmHg), but the correlations between beat-to-beat transit times and BP were maximal at CYC (PAT showed a higher correlation than PTT; correlations were greater for systolic than for diastolic BP). This suggests that pulse transit times do not always depend directly on the beat-to-beat BP values but, under specific conditions, on other factors and mechanisms that concomitantly also influence BP.**

***Index Terms*—Heart contractility, local hemodynamics, pulse arrival time, pulse wave velocity, seismocardiography, total peripheral resistance, vascular control.**

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I. Introduction

OVER the years there has been a rising quest for wearable systems able to monitor cardiovascular performance in daily life (e.g., to check safety and health at work), clinics and rehabilitation. Among the parameters that can be provided by these devices, one of the most interesting for its potentialities and simplicity in the measure is the Pulse Transit Time (PTT), i.e., the time that the arterial pulse takes to travel between two arterial sites. From its measure the Pulse Wave Velocity (PWV) may also be derived as PWV = d/PTT, where d is the distance between the two sites. PTT has a rich informative content. It is related to blood pressure (BP) and to the anatomical and functional characteristics of the arterial wall in the path between the two measurement sites. They include vascular stiffness and arterial peripheral resistance, the latter depending on the lumen of the small muscular arteries and arterioles.

To date, PTT has been extensively exploited for non-invasive estimation of the stiffness of the elastic arteries, usually by measuring the timing of the pulse at carotid and femoral arteries and computing the corresponding PWV [1]. It has been shown that an increased PWV between these arteries reflects an augmented arterial stiffness, which is a major independent predictor of cardiovascular risk [2], [3].

Additional interest in the PTT refers to the attempt to use it for the cuffless BP estimation. Since the late 1970s [4], [5] many research laboratories have been focusing on this topic because, should the goal be reached, it would lead to a significant simplification in the BP assessment and application to wearable devices. The topic of cuffless BP measurement has been previously examined in extensive reviews, e.g., [6], [7]. In this area PTT is commonly measured from the heart to the finger and the measure should theoretically start from the opening of the aortic valve and end at the arrival of the pressure pulse at the finger. While the arrival of the pulse at the distal site may be easily obtained, e.g., by a tonometer or a photoplethysmograph, the proximal measure is more complex. Indeed, in a clinical environment the opening of the aortic valve is usually detected by ultrasound techniques, but out of the laboratory this assessment is difficult to be obtained by wearable devices. Thus the starting point for measurement of transit time is often simplified by considering the occurrence of the R peak in the ECG as a surrogate of the aortic valve opening. The obtained measure is called Pulse Arrival Time (PAT) and

includes the real PTT plus an extra time corresponding to the delay from the R peak and the opening of the aortic valve. Since the closure of the mitral valve occurs in proximity of the R peak in normal subjects [8], this extra time approximates the Isovolumic Contraction Time (IVCT). This is the time period in which the left ventricle contracts while both mitral and aortic valves are closed and the blood inside the ventricular cavity is pressurized without any change in the ventricular volume. IVCT is associated with cardiac contractility (generally, the lower its value, the greater the contractility), is variable over time, and its modulation depends on factors and control mechanisms in part different from those influencing PTT [9]. This means that the simplification in measuring PAT is paid with a lower accuracy in the estimation of the real pulse transit time.

Different equations have been proposed to model the PTT-BP relationship [6], [7]. In all instances, some initial calibration is needed to adapt the parameters of the equations to each individual. The essential hypothesis underlying this approach is that in each subject the relation between PTT and BP remains quite stable over time, thus making only one or few initial calibrations sufficient for an accurate continuous BP monitoring over prolonged periods of time. The goodness of the BP estimate obtained by this technique has been widely investigated both in laboratory steady-state conditions and under mental and physical stress [9]–[11] leading to controversial results [12]. The critical factor in the identification of a proper model to estimate BP from the PTT measurement is the continuous modulation of the arterial tone and peripheral resistance exerted by humoral factors and neural mechanisms, including baroreflex and central autonomic drives [13]. This modulation can modify the PTT-BP relation in seconds, making any calibration valid for a short period only [7]. In addition, the location and modality of detection of peripheral pulses can have a significant influence on the consistency of the calibration obtained with passive or active interventions to alter BP [14].

Both the above applications make use of PTT (or PAT) to selectively study a single factor (the arterial stiffness and BP, respectively) among the many others that influence the transit time, and specific actions are needed to exclude interferences from the remaining off-target factors. Indeed, in the stiffness estimation, BP should be also assessed to properly interpret the PWV measure, and in the cuffless BP estimation calibrations are required to remove the interferences of the vascular factors.

However, there might be value also in studying the PTT *per-se*. In fact, a marked increase of major factors influencing PTT (arterial stiffness, blood pressure, vasoconstriction of conduit arteries or peripheral arterioles) represents a potentially deleterious prognostic sign associated with increased cardiovascular risk [3], [4], and all lead to a PTT reduction (and increased PWV). Thus, it could be conceived that, whatever is the cause, an abnormal drop in PTT could *per-se* represent an alert for underlying cardiovascular changes affecting the subject's health. This hypothesis yet remains to be clinically tested, but if validated, would encourage the use of PTT as a risk marker in the remote monitoring of cardiac patients at home within the frame of telemedicine and telerehabilitation programs.

As for the cuffless BP estimation, in most research studies PTT and PAT are commonly measured from the heart to the fingertip. Ear and forehead have also been proposed for the distal measure, particularly if obtained by wearable devices. However, transit time data collected at various sites may be not equivalent because individual vascular districts are characterized by specific hemodynamic controls, influencing local vessel characteristics and blood distributions [15]. In addition the proportion of elastic vs. muscular arteries and arterioles in the path from the heart to the distal measurement site play a role in the measured PTT and PAT dynamics. Indeed, whilst propagation times through large arteries depend mainly on the intrinsic elastic properties of the arterial wall, propagation times in small peripheral vessels are affected by changes in caliber and wall thickness resulting from the modulation of smooth muscle tone [16], [17].

Actually, knowledge of the differences in the informative content and dynamics of the transit time detected at each vascular district may be relevant not only for the interpretation of the collected data, but also in relation to methodological aspects, including the proper selection of the measurement district, and the appropriate definition of experimental procedures.

In literature, most studies investigating PTT or PAT from the heart to finger, ear and forehead considered the transit times separately for each distal site, either considering BP [18]–[21] or not [22]–[26]. However, the identification of differences in the PTT features would be highly facilitated by a concomitant PTT measure at the three sites. At present, to the best of our knowledge only one study considered transit times simultaneously measured at the three target sites [27]. The article focused on the presentation of a new measurement device, and differences among the PATs simultaneously measured at the three districts in resting supine subjects were proposed as an example of the system performance. Thus, at present most aspects of the physiological interaction among transit times in those areas are still virtually unexplored.

Aim of this pilot study was to obtain further insight on this issue. In particular, we examined the beat-to-beat mutual relationships among PTTs/PATs concomitantly recorded at ear, forehead, and finger, and their correlations with continuous blood pressure. These aspects were considered in stationary and non-stationary conditions: at rest and under the action of three stressors known to elicit specific vascular and cardiac responses in terms of changes in BP, heart rate (HR), sympathetic activity, peripheral resistance and cardiac output, i.e., the cold pressure test (thermal stress), the handgrip (isometric exercise) and the cyclo-ergometer pedalling (dynamic exercise). The IVCT dynamics at rest and under stress were also explored.

II. Methods

A. The SeisMote System and the Seismocardiogram

Apart from continuous BP, all signals used in this study have been collected by a custom device developed in our laboratory, the SeisMote system. Details have been previously provided [28]. In summary, the system consists of a wireless network of multiple (up to 12) sensorized nodes, each having the size of a coin and weight of 6 grams (Fig. 1).

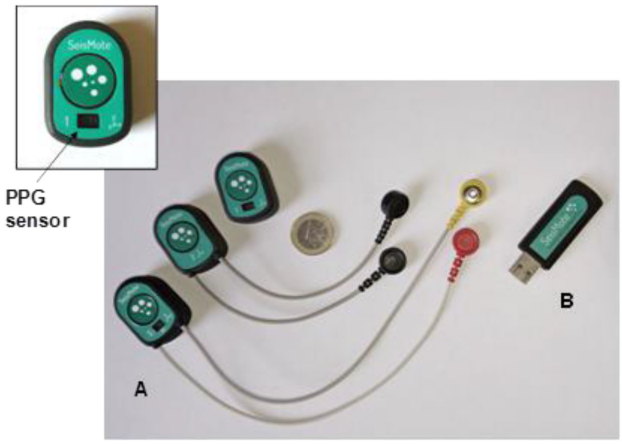

Fig. 1. The SeisMote system. (A) Nodes for the measure of different combinations of signals; from left to right: ECG-PPG-ACC-ROT, ECG-ACC-ROT, ACC-GYR-ROT. (B) USB hub of the network. Inset: position of the PPG sensor in the node. See text for abbreviations.

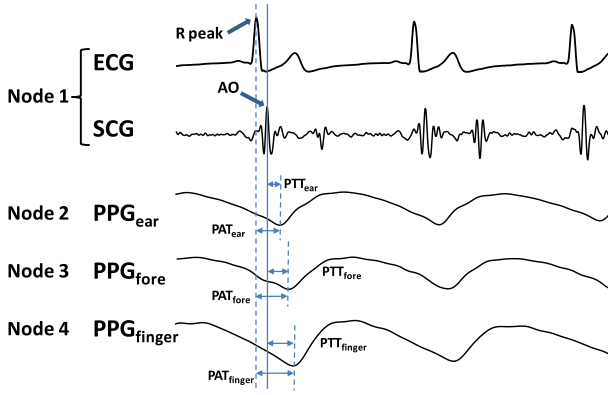

Fig. 2. Example of the collected signals with indication of the AO fiducial point in the seismocardiogram and definition of PTTs and PATs.

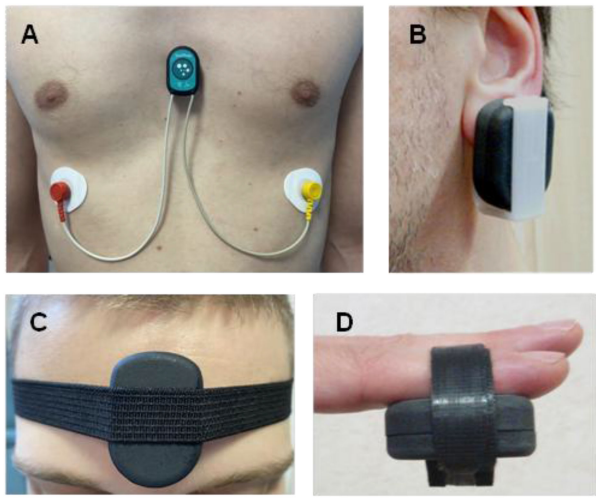

Fig. 3. Positioning of the sensorized nodes for the experiment. On the sternum for ECG and SCG measurement (A), and on earlobe (B), forehead (C) and fingertip (D) for the measure of the three local PPGs.

Each node detects 3D accelerations (ACCs), 3D rotations (ROTs, by a gyroscope), and, in variable combinations also electrocardiogram (ECG) and/or photopletysmogram (PPG). All signals are sampled at 200 Hz with 16-bit resolution. In total, the network can simultaneously measure up to 36 signals with an inter-node time shift ∼200 µs. Each node transmits in real time the stream of data produced by its internal sensors to the hub of the network, consisting of a USB dongle connected to the computer. An ad-hoc program synchronizes data coming from all nodes and creates a unique data stream for visualization, storage, and analysis.

When a node of the SeisMote system is positioned on the sternum, the internal accelerometer detects the seismocardiogram (SCG) namely the thorax micro-accelerations produced by the beating heart. SCG is a three-dimensional signal with an amplitude in the order of few milli-gs, where g is the gravity acceleration (9.8 m/s^2). In spite of its 3D nature, only the dorso-ventral component of acceleration (corresponding to the z-axis in our accelerometers) is usually considered in literature for the SCG measure, and in this study, we conform with this conventional approach.

The signal waveform is characterized by several displacements and one of them, usually termed AO peak, corresponds to the opening of the aortic valve (see Fig. 2). This correspondence was previously demonstrated by comparisons with simultaneous ultrasound images [8], [29], [30]. In this study the AO fiducial point has been used for the PTT measure as indicated below.

B. Data Collection Protocol

Twenty-two young healthy volunteers were recruited for the study (10M, 12F, age: 24-35 yrs). The study was approved by the local Ethical committee (protocol 8_14/10/2020) and the subjects gave their informed written consent to their participation.

In each subject ECG, SCG and three PPGs were measured by 4 nodes of the SeisMote system. As shown in Fig. 3, one node was placed by a double-adhesive tape on the sternum for detection and measurement of ECG and SCG. Ag-Cl pre-gelled electrodes were used for the ECG detection. For measurement of PTT the remaining three nodes, including the PPG sensor, were respectively placed on the left ear lobe (the node was fastened by a clip), in the middle of the forehead (fastened by an elastic band), and on the left forefinger (fastened by a small strap). The infrared LEDs were used for the PPG measures to penetrate deeper in the tissues, as suggested in [6]. Continuous finger blood pressure was concomitantly measured by the Finometer device using the vascular unloading technique (Finapres Medical Systems BV, Enschede, The Netherlands); the system micro-cuff was placed on the middle finger of the left hand.

After instrumentation, the subject was asked to relax on a chair for 5 minutes, and subsequently carried out a 7-step experimental protocol according to the following sequence:

1. Rest (REST): 5-min sitting.
2. 2. Cold pressure test (CPT): 2-min right hand immersion into a bowl filled with water at 3-5°C.
3. Recovery1: 5-min sitting rest just after CPT.

4. Handgrip (HG): 3-min handgrip contraction at 30% of the Maximal Voluntary Contraction (measured in advance before instrumentation).
5. Recovery2: 5-min sitting rest just after HG.
6. Cycling (CYC): 5-min pedalling on a recumbent cycloergometer with a 75W workload.
7. Recovery3: 5-min sitting rest just after CYC.

SeisMote and Finometer data were collected in four separate recordings: (i) at REST, (ii) during CPT and Recovery1, (iii) during HG and Recovery2, (iv) during CYC and Recovery3. Before each recording the Finometer was calibrated with a cuff BP brachial measure, then the automatic adjustment of the signal (Physiocal) was activated and maintained till the signal quality was scored "great" by the system. After this, the Physiocal was turned off to avoid interruptions in the BP signal, and the data recording was activated in both devices. To maintain synchronization with the SeisMote data, the finger wearing the Finometer micro-cuff consecutively tapped for 6 times on the sensorized node on the sternum so to create concomitant spikes on the Finometer and Seismote signals. Tapping was done at the beginning and at the end of each recording.

C. Data Processing

All signals (continuous BP, ECG, PPGs, z-axis acceleration) were synchronized and band-pass filtered to remove possible noise components and baseline wanderings. Filtered signals were then segmented into individual heart beats. Each beat was defined as a data window starting 150 ms before the relevant R peak in the ECG signal and ending 150 ms before the next R peak. From every heart beat the following information was obtained: in the BP signal, the systolic (S) and diastolic (D) BP values, defined as the maximal and minimal values of the pressure waveform; in ECG and z-axes acceleration, the occurrence time of R peak and AO fiducial point, respectively. The resolution of the above timings was further improved from the original 5 ms (signals are sampled at 200Hz) to 1 ms by signal interpolation and resampling [31]. The Nyquist–Shannon sampling theorem guarantees that this was possible because all signals are bandlimited to 50 Hz as maximum and sampled at 200 Hz, thus the interpolation can accurately reconstruct the signal and allow the time locations of the points of interest at a higher resolution.

From PPG, we considered the foot of each pulse. The estimation of this fiducial point was based on a two-step procedure. In the first step the PPG was low-pass filtered by a centered 5-point moving average filter and the minimum of the filtered PPG waveform was identified. Subsequently we considered a window of 13 filtered points centered around the minimum. Data inside the window have been fitted by a second-order polynomial regression line which was then re-sampled at 1kHz as also suggested in [6]. The minimum of this line was taken as the PPG foot timing.

1) Derived Parameters: From the above variables additional parameters were derived on a beat-to-beat basis.

HR was calculated as the reciprocal of the time interval between consecutive R peaks of the ECG multiplied by 60.

The three pulse transit times were measured as the time delay from the opening of the aortic valve (indicated by the occurrence of the AO fiducial point in the SCG) and the arrival of the foot of the pressure pulse at the ear, $\mathrm{PTT_{ear}}$, forehead, $\mathrm{PTT_{fore}}$, and finger, $\mathrm{PTT_{finger}}$ (Fig. 3). From here on when we refer to a transit time "measured *at a given district"*, it will be a shortened form of "measured *from the heart to a given district"*.

In each subject, the distances from the suprasternal notch to finger, earlobe and forehead were measured and pulse velocities ($\mathrm{PWV_{ear}}$, $\mathrm{PWV_{fore}}$, $\mathrm{PWV_{finger}}$) were estimated from the corresponding PTT values. The length of the path to the fingertip was measured positioning a flexible tape ruler along the internal part of the arm, the path to the earlobe by following the mid lateral line of the neck, and the path to the forehead extending the earlobe measure along the mid lateral line of the head till the eyebrows and then horizontally till the mid-forehead. The group minimal and maximal measures for each path were: Heart-Fingertip 80-102 cm, Heart-Earlobe 26-38 cm, Heart-Forehead 44-57 cm.

We also computed the $\mathrm{PAT_{ear}}$, $\mathrm{PAT_{fore}}$, $\mathrm{PAT_{finger}}$ by considering the time of occurrence of the R peak instead of the AO fiducial point as starting point for the transit time estimation. For each beat the IVCT value was the difference $\mathrm{PAT_{finger}}$ - $\mathrm{PTT_{finger}}$.

2) Signal Analysis: In this study we analyzed data collected at REST, and during the acute application of the stressors, namely at CPT, HG and CYC.

From data collected during the recovery phases, we only verified that at the end of recovery from CPT and HG, all variables returned to their baseline value. This was done to exclude the possibility that the measures taken during any given stressor were affected by residuals of previous efforts. The analysis of recovery data will be carried out in subsequent studies.

In each subject the mean value was computed for each variable and condition. Correlation among SBP, DBP, PTTs and PATs variables was also quantified by the Pearson's coefficient. Before estimation of the coefficients, the visual inspection of the scattergram of each pair of variables revealed no evidence of nonlinear trends.

Variability was quantified by the SD1 and SD2 parameters derived from the Poincaré plot (a scattergram in which each sample of a variable is plotted against the subsequent sample), and by the SD1/SD2 ratio [32]. SD1 is the standard deviation of the points measured along the axis perpendicular to the identity line of the plot; this index quantifies the variability of consecutive values (in this context usually termed "short-term" variability; in our case it corresponds to the instantaneous beat-to-beat variability). SD1 is equivalent to the Root Mean Square of Successive Differences, RMSSD, scaled by the $\sqrt{2}$ factor, and is thus calculated as

$$\begin{aligned} \boldsymbol{SD1} &= \frac{1}{\sqrt{2}}\ \boldsymbol{RMSSD} \\ &= \frac{1}{\sqrt{2}} \sqrt{\frac{1}{\boldsymbol{N}-1} \sum \left(\boldsymbol{x_{n+1}} - \boldsymbol{x_n}\right)^2} \end{aligned} \tag{1}$$

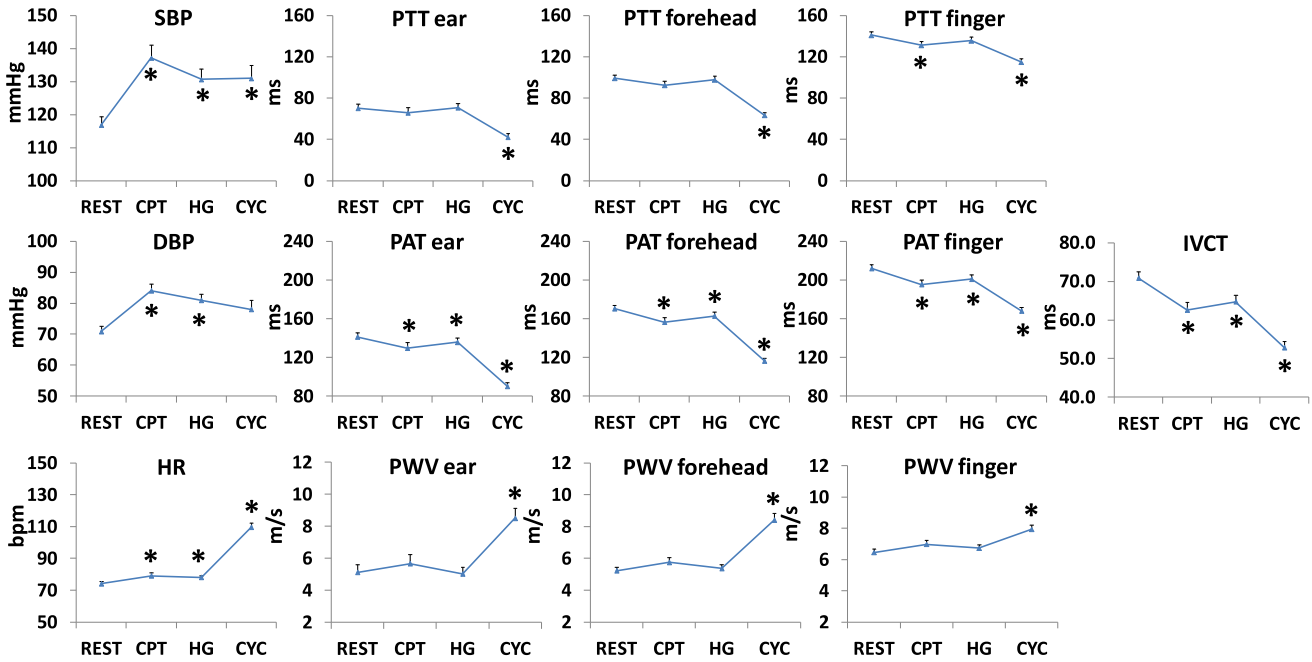

Fig. 4. Group mean values of all variables at REST, CPT, HG and CYC. $*$=p$<$0.05. The error bars represent the standard error of the estimates.

where $\boldsymbol{x}_n$ is the value of the generic variable at the beat $\boldsymbol{n}$ and $\boldsymbol{N}$ is the total number of beats.

SD2 is the standard deviation of the points measured along the identity line; it provides a quantification of all the remaining components of the dataset variability ("long-term" variability) and is calculated as

$$\boldsymbol{SD2} = \sqrt{2\boldsymbol{SD}^2 - \boldsymbol{SD1}^2} \tag{2}$$

where $\boldsymbol{SD}$ is the standard deviation of the variable.

In the HR analysis the short term component of variability, here quantified by SD1, is traditionally associated with respiration and the vagal drive to the heart, while SD2, includes the HR fluctuations with periods from 6 seconds to 25 seconds reported to be linked with the sympathetic activity [33]. In this framework the SD1/SD2 ratio quantifies the prevalence of the vagal-driven fluctuations over the other components of the HR variability [34]. Obviously this physiological interpretation of the Poincaré indices is only valid for HR. When these parameters are estimated from other variables different interpretations may apply. For the transit times the short-term variability (SD1) is still reported to be influenced by respiration through the mechanical influence of the intrathoracic pressure changes caused by breathing on the thoracic vessels [35], [36], while it may be conceived that SD2 reflects a less specific interplay among the long-term modulations of the PTT determinants.

3) Statistics: The statistical significance of changes in variables from REST vs. each stressor condition was evaluated by the ANOVA for multiple measures followed by a Student t-test with the Bonferroni correction for repeated comparisons. Before the statistical evaluation, the normality of each distribution was checked and data were log-transformed when appropriate. Differences were considered significant with p$<$0.05.

III. Results

In this study 28442 heart beats have been analysed.

A. Means

The average value of all variables in each condition are shown in Fig. 4.

SBP means increased during all stressors with respect to REST, the maximal values occurring at CPT. DBP rose at CPT and HG but not at CYC. HR slightly increased at CPT and HG and, to a greater degree at CYC. An opposite pattern was observed for IVCT in which all stressors produced a significant shortening with respect to REST, with the maximal drop at CYC.

All PTTs and PATs markedly dropped at CYC. Milder decreases were observed for the three PATs also at CPT and HG.

Given the inverse relation with PTT, the PWVs measured at the three districts showed maximal increments at CYC.

A detailed quantification of the above changes in transit times, velocities and IVCT is shown in Fig. 5. It is worth noting that at CYC the $\mathrm{PTT_{ear}}$ and $\mathrm{PTT_{fore}}$ pronounced drops (from 70 to 42 ms, and from 99 to 63 ms, respectively) led to wide swings in the $\mathrm{PWV_{ear}}$ and $\mathrm{PWV_{fore}}$, from 5.1 to 8.5 m/s (+67%) and from 5.2 to 8.4 m/s (+62%) respectively. In the same condition the $\mathrm{PTT_{finger}}$ reduction was less marked (from 141 to 115 ms) corresponding to a much lower change in the $\mathrm{PWV_{finger}}$, from 6.5 to 7.9 m/s (+22%).

B. Correlations

The correlation coefficients between SBP and DBP vs. PTTs and PATs are shown in Fig. 6. It appears that the links between variables are limited at CPT and HG, while strengthened at

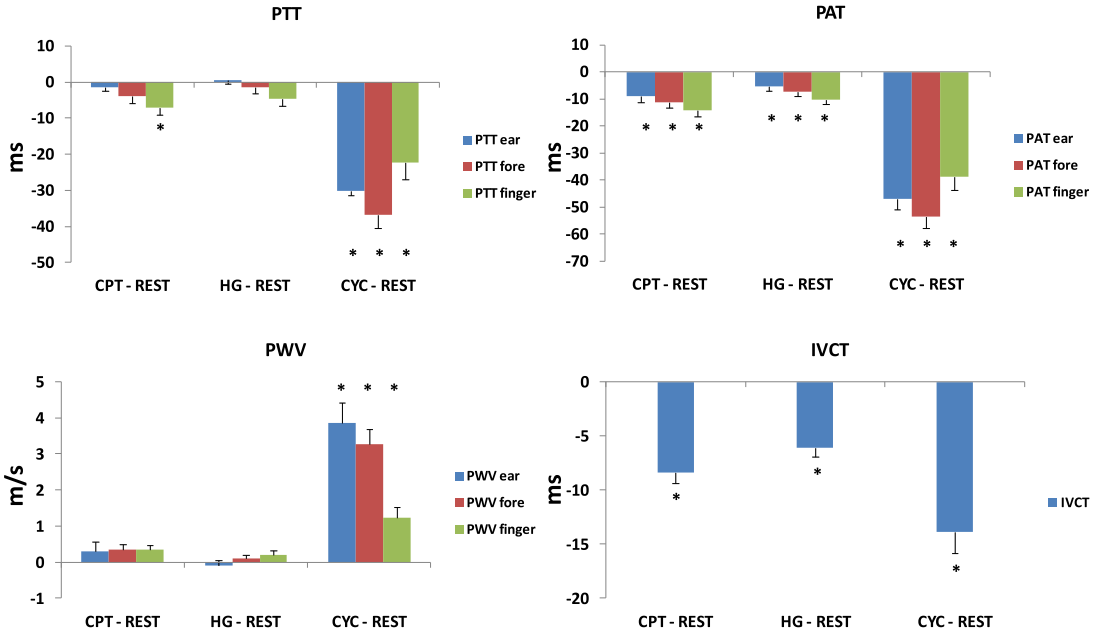

Fig. 5. Quantification of the PTTs, PATs, PWVs and IVCT changes from REST to CPT, HG and CYC. $*$=p$<$0.05. The error bars represent the standard error of the estimates.

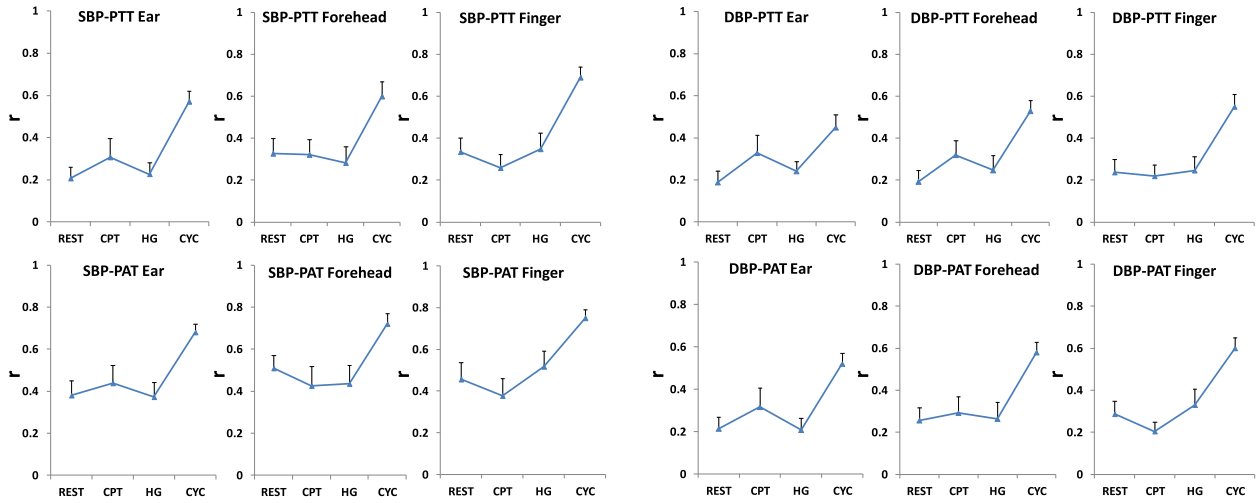

Fig. 6. Group correlations among SBP and DBP vs. PTTs and PATs. The error bars represent the standard error of the estimates.

CYC. In this case the maximal correlation was between SBP and PAT_{finger} (r = 0.76).

As illustrated in Fig. 7 (upper panel), correlations among PTTs are quite low at REST, CPT and HG (ranging from 0.37 to 0.48). All of them rose at CYC (PTT_{ear}-PTT_{finger} 0.77, PTT_{fore}-PTT_{finger} 0.81, PTT_{ear}-PTT_{fore} 0.83). Correlation coefficients between corresponding PTT-PAT pairs were always greater than 0.83 in every condition (Fig. 7, lower panel).

C. Variability

The SD1 and SD2 indexes and the SD1/SD2 ratios for all variables are reported in Fig. 8.

1) Short-Term Variability - SD1: At CPT the short-term variability increased for DBP, HR and PAT at the forehead and finger districts.

At HG DBP increased while the other variables remained close to the rest values.

At CYC short term variability increased for DBP and PWV at all districts, while it dropped for HR (where a lowering in the short term variability is expected because of the known reduction in the vagal activity under physical exercise), PAT_{ear} and PAT_{fore}.

2) Long-Term Variability - SD2: At CPT the long-term variability increased for SBP, DBP, HR and PTT_{ear}.

At HG SD2 significantly rose for DBP and PTT_{fore}.

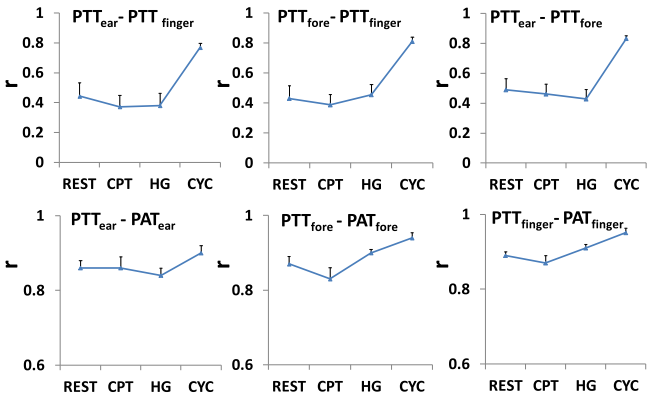

Fig. 7. Group correlations among PTTs and between PTTs vs. PATs. The error bars represent the standard error of the estimates.

At CYC it was observed the maximal increase in the long-term variability for SBP, HR, all transit times and pulse velocities. DBP rose but less markedly than under the other stressors.

3) SD1/SD2 Ratio: As a general statement, it appears that in pulse transit times, pulse wave velocities, and IVCT, the short-term components of variability provides a contribution to the overall variability that at REST, CPT and HG is much greater than that observed for BP and HR.

At CPT the balance between variability components remained quite stable for most variables with a slight reduction for the PTT_{ear}.

At HG the ratio decreased for DBP, HR and IVCT.

At CYC the ratio remained quite stable for DBP and IVCT, and significantly decreased for any other variable.

IV. Discussion

In this study we investigated the beat-to-beat dynamics of transit times simultaneously measured at the finger, earlobe and forehead districts and their relationship with continuous BP and IVCT. We also explored how these parameters changed from rest to non-stationary conditions elicited by three stressors which are known to induce modifications in the factors influencing the pulse transit times. The PTT measures started from the instantaneous opening of the aortic valve as detected by the seismocardiogram.

In the next subsections we will comment on the juxtaposition of our results with the physiological mechanisms known to be elicited by each stressor.

A. Rest vs. Stressors

1) Rest: In line with current knowledge, we observed that at rest the PTT mean values were progressively greater moving from ear, to forehead and then finger sites. These values were less than proportional to the distance of each distal measurement district from the heart, thus leading to PWVs progressively increasing from 5.1 m/s at the ear to 6.5 m/s at the finger. In addition to this known framework, we observed that in stationary condition the PTT short-term variability (as quantified by the SD1 index) was similar for the 3 PTTs, irrespective of the measurement site. The long-term variability estimated by the SD2 index was still comparable for PTT_{ear} and PTT_{fore}, with only a minimal increase for the PTT_{finger}. However, in spite of these substantial similarities, at rest the average correlations among PTTs were extremely low, with a wide dispersion of individual values.

Little correlation was also found between PTTs and beat-to-beat SBP or DBP values. An example of desynchronization between PTT and SBP fluctuations at rest is illustrated in Fig. 9. In this instance it is apparent that the occurrence of a significant SBP deviation does not correspond to any noticeable deflection in the PTTs trends. The presence of a concomitant change in HR, likely of baroreflex origin, excludes the hypothesis of a possible artifactual nature of the pressure peak.

It is known that PTT and BP are both under the influence of common factors (e.g.,TPR and CO), but it should be considered that 1) their respective sensitivity to these factors is likely to be different, and 2) the PTT we measured at each site is also influenced by possible spontaneous and stressor-induced vasomodulations occurring locally and along the arterial path from the heart. This means that a given modulation of each of these factors may have dissimilar effects on PTTs and BP.

In this perspective it might be conceived that at rest spontaneous changes of TPR and CO around their respective operating-points are minimal, still sufficient to modify BP but not always enough to influence PTT (maybe because of a prevailing influence of local vasomotion), thus leading to a poor correlation between the variables.

2) Cold Pressure Test: It has been reported that the thermal stress induced by this test selectively increases the sympathetic outflow to the vessels, with consequent raises in SBP, DBP, total peripheral resistance, and vasoconstriction of the main muscular arteries and arterioles. The sympathetic effect on the heart was found to be limited thus leading to small changes, if any, in HR and cardiac output (CO) [37]–[40].

In agreement with the above findings, when our subjects immersed their hand in the cold water, SBP and DBP markedly rose with respect to REST, reaching their highest values in the whole experiment while HR only slightly increased. We also observed a 11% reduction in the IVCT, indicating an augmented heart contractility.

In this physiological context no change was observed for PTT_{ear} and PTT_{fore} mean values. On the contrary, a reduction was observed for the PTT_{finger}, thus supporting previous indications of a major influence of the vasoconstriction induced by CPT on the finger than on the face vascular areas [25], [41], [42]. During CPT, the fastest components of variability increased in DBP and HR.

As mentioned in the Methods section, SD1 in the HR and in the transit times reflects the respiratory activity, thus the observed elevation of this variability component in the cardiac rhythm and in the PAT at the forehead and finger districts is compatible with a reported increase in the tidal volume during CPT [43]. Indeed, most of the subjects of our study reported to have increased the depth of breathing during CPT to relieve the discomfort of the thermal stress.

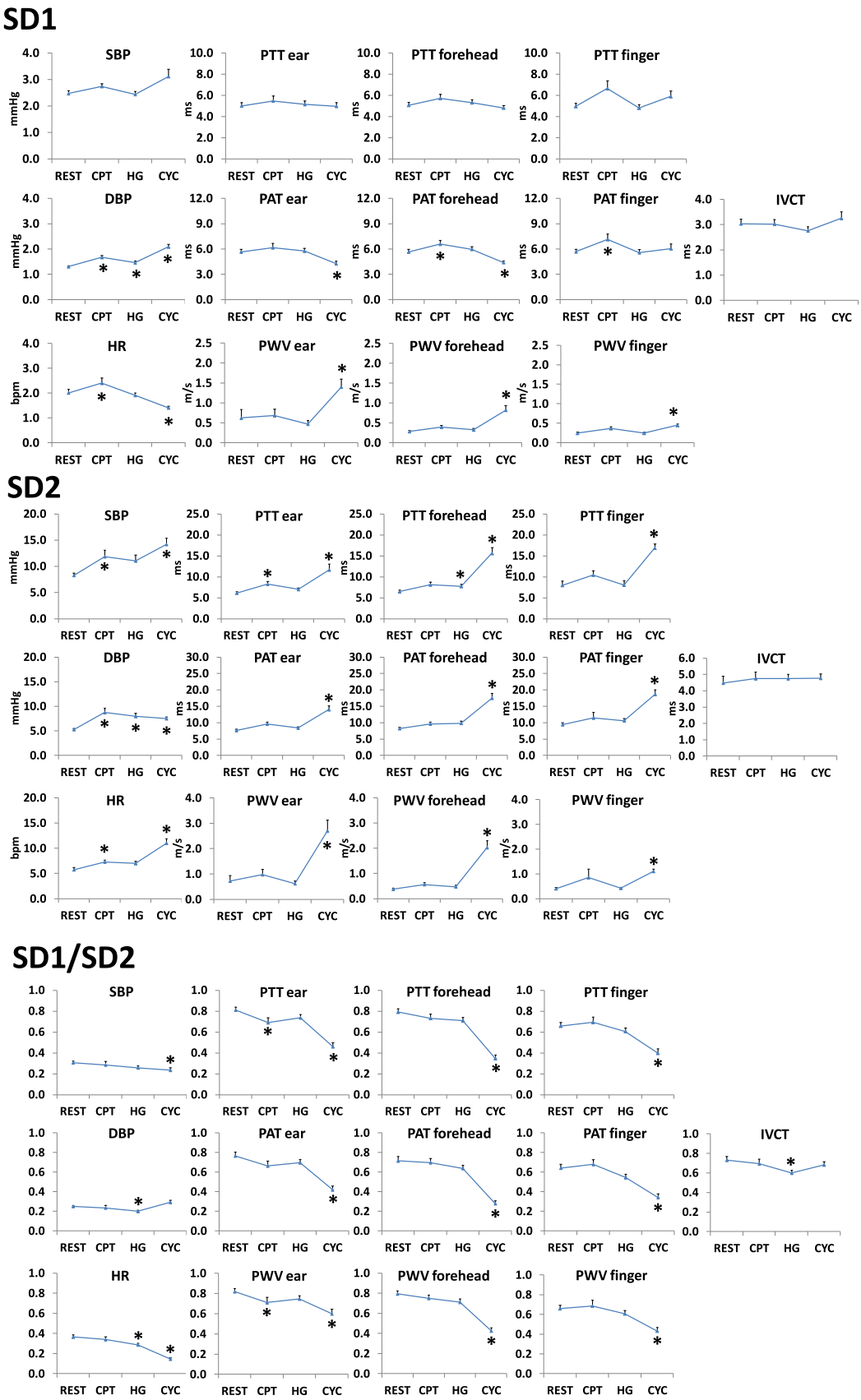

Fig. 8. Beat-to-beat variability. Top panel: SD1; Mid Panel: SD2; Lower Panel: SD1/SD2. $*$=$p<0.05$. The error bars represent the standard error of the estimates.

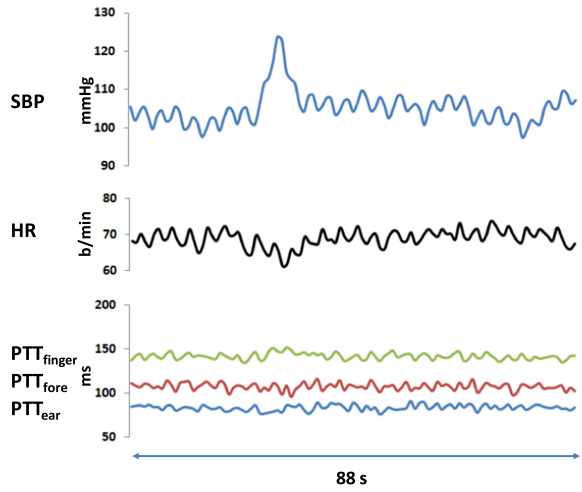

Fig. 9. Example of an SBP change at rest not corresponding to concomitant PTT displacements.

Correlations among the transit times remained low. Limited correlations were also observed between transit times vs. SBP and DBP, in spite of the above mentioned occurrence of maximal absolute values of the BP variables.

3) Handgrip: It is known that the isometric exercise leads to an increment in the vasoconstrictor sympathetic nerve activity with a rise in SBP, DBP, HR, and peripheral vascular resistance [10], [37], [44]–[46]. Our data are consistent with the above findings in that we observed increases for SBP, DBP and HR with respect to REST.

Conflicting findings are available on the effects of isometric exercise on the stroke volume (SV), with some studies reporting SV drops [47], [48], and other reporting SV augmentations [49], [50]. In our study we observed an increase in the heart contractility as reflected by a diminished IVCT, thus suggesting a SV rise.

Again, also at HG all correlations among transit times and between transit times and BP variables were characterized by reduced r values.

4) Cycling: The third stressor we considered was dynamic exercise. It differs from the previous two stressors because is characterized by a substantial metabolic demand requiring a major increase in the blood flow and significant changes in the blood distribution within the vascular bed. During exercise oxygen and nutrient consumption is high, increasing with the intensity of physical effort, and an augmented blood flow to the working muscles is needed. This is obtained by a marked raise in CO, and a diversion of a large part of the circulating blood to the districts involved in the exercise. Blood redistribution is obtained by a vasodilation of the districts supplying the active muscles and a concomitant vasoconstriction of all the remaining vascular areas [49]–[51]. The net result of this strategy is a reduction in TPR and a moderate increase of SBP (the expected drastic increase in this variable caused by the CO raise is largely mitigated by the reduction in TPR). On this premise we may assume that the local arterial resistance of ear, forehead, and hand districts, being not involved in the exercise, was augmented at CYC.

In line with the above indications, we observed an increase in SBP, although less marked than at CPT, no change in DBP and a marked upward swing of HR. The IVCT further dropped, reflecting an additional increase in myocardial contractility, needed to provide the required blood supply.

Concerning the transit times, our study indicates that at variance from what was observed at CPT and HG, CYC produced significant drops in all PTTs and PATs mean values measured at the three districts. These reductions led to an increase in the respective PWVs, with the magnitude of the rise that was maximal at the ear and minimal at finger.

During dynamic exercise, the short-term variability dropped significantly in HR, as expected because of the vagal withdrawal associated with exercise. For IVCT and all PTTs SD1 was unchanged with respect to REST, with slight reductions for PAT_{ear} and PAT_{fore}. The long-term variability increased for all variables apart from IVCT. The SD1/SD2 ratio decreased in most variables, including HR, in which the reduction of this index further proves the reduction of the vagal activity during dynamic exercise [34].

The PTT drops at CYC are likely to be caused by the vasoconstriction needed for the blood flow diversion to the legs, possibly stronger than that produced by the other stressors, or/and by a possible residual increase in the blood flow also reaching the finger and face districts thus augmenting the wall tension of the local arteries. Current evidence does not allow entering in deeper detail on this issue. Indeed, during dynamic exercise CO and vascular resistance are controlled by a complex interplay of humoral and neural mechanisms activated by central commands, baroreflex, metaboreflexes, mechanoreflexes, and discordant findings are available on the magnitude of their effects on the districts not directly involved in the exercise [52].

We observed that dynamic exercise also synchronized the PTTs fluctuations at the three sites, maybe indicating that the control strategy exerted by the above mechanisms is similar in the vascular districts we considered in our study.

Moreover, at variance from the other stressors, CYC resulted in significant correlations between SBP and transit times with strength progressively increasing from the ear to the finger sites; SBP was more correlated with PATs than with PTTs. Lower correlations were found between DBP and transit times.

B. Differences Among Stressors

According to literature, all stressors considered in our study are expected to lead to changes of at least one factor influencing the transit times (sympathetic activity, peripheral resistance, cardiac output). Notwithstanding this, with respect to REST most of the PTT changes in terms of absolute values, synchronization, and link with BP, only occurred at CYC. An exception was the observed (and expected) reduction in the PTT_{finger} at CPT possibly caused by a known vasoconstriction of the muscular arteries induced by the thermal stress. However, this change was also minimal with respect to the much greater drop of the same variable at CYC.

This means that at CPT and HG the magnitude of the changes in the above factors was not in general sufficient to markedly influence PTTs.

CPT was the condition which produced the highest BP values and low PTT-BP correlations. Conversely, consistent PTT-BP

correlations were only observed at CYC, where SBP increased but not as much as at CPT, and DBP neither changed from REST. These facts suggest that PTTs are not always directly influenced by the beat-to-beat blood pressure values. The occurrence of events such as that illustrated in Fig. 9, in which an SBP change is not mirrored by a PTT modulation, further supports this reasoning.

Our data rather suggest that the correlation between transit times and BP does not invariably reflect a cause-effect link, but rather, in specific conditions (at CYC in our study) the action of underlying physiological mechanisms and factors which *simultaneously act upon* PTTs and BP creating their reciprocal synchronization.

C. Differences in the PTTs Measured at the Three Vascular Sites

As detailed in the above comments it appears that:

- The three PTTs are characterized by an independent behavior (low among-PTTs correlation) at rest, during CPT and HG. A synchronization was only observed during the dynamic exercise.
- At CPT, the thermal stress only induced a mild reduction in the average value of $\mathrm{PTT_{finger}}$. CYC resulted in marked drops in all PTTs, with the magnitude of changes maximal for $\mathrm{PTT_{fore}}$ and minimal for the $\mathrm{PTT_{finger}}$.
- Regarding the PTTs dynamics, while at rest, the short- and long-term components of the PTT variability measured at the three districts are quite similar, CYC induced district-specific modifications. Indeed, the magnitude in the increase in the long-term variability of PTTs during exercise was progressively greater from the ear to the finger district. The same progression between districts was observed in the value of the correlation between PTTs and SBP at CYC.

D. PTT vs. PAT

The respective PAT and PTT pairs measured at each site were highly correlated in all conditions (see lower panels of Fig. 7). This means that in our subjects the IVCT variability does not (or only minimally) mask the PTT dynamics included into the PAT. On the contrary in all instances the correlations between PATs and BP were higher than those between PTTs and SBP indicating that, at least in young healthy subjects, IVCT favors the link between transit times and blood pressure.

E. DBP and IVCT

At CYC PTTs and PATs correlations vs. DBP were always lower than those involving SBP.

As expected, the IVCT mean value decreased during the application of the stressors, indicating an increased contractility which reached the maximal value at CYC. No major changes were observed in the IVCT variability among conditions.

F. Limitations and Perspectives

Our study has a descriptive nature and our aim was to obtain a quantitative picture of the phenomena being investigated. In Discussion we juxtaposed the known physiological effects of stressors with our data, but refrained to enter in physiological speculations too far away from our evidence. Deeper physiological interpretations may derive from specific investigations based on a different experimental design including a selective laboratory activation of each factor involved in the PTT and BP control.

Moreover, this pilot study is based on data collected on a limited sample of young healthy subjects. It cannot be excluded that part of the results, particularly those referring to the response to stressors might not be entirely translated to different classes of age where the physiological response to thermal stress and exercise may be different. Further studies based on a larger population including subjects with a wider range of ages are deemed necessary to generalize our findings.

V. Conclusion

From our results the following conclusions may be drawn.

First, our data indicates that the PTTs fluctuations measured at the ear, forehead and finger districts are independent of each other at rest, and during CPT and HG. The stressors produced district-dependent changes in the PTT variability.

Moreover, the dynamic exercise was the only stressor able to induce significant changes with respect to REST in the mean values of the PTTs and synchronize their modulations (as reflected by the high correlations among PTTs observed at CYC).

Finally, we observed that SBP increased more in CPT than in CYC, but the dynamic exercise was the condition in which beat-to-beat PTTs and SBP values were maximally correlated. This suggests that transit times do not always depends directly on the beat-to-beat BP values but rather, in some conditions, such as the dynamic exercise, on other factors and mechanisms that concomitantly also influence BP.

Referring to the possible use of transit times for the cuffless BP measure, our data indicate that in young healthy subjects the maximal beat-to-beat correlation between PTT and BP is observed at the finger site using the SBP-PAT pair. However we also observed that the level of this correlation largely varies in different conditions, thus suggesting that further investigations might be required to verify the robustness of this BP measurement approach in daily life.

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