Editorial

New Technological and Clinical Trends in Blood Pressure Theranostics: Is it Time to Consider a Spatio-Temporal Approach?

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Abstract: Blood pressure (BP) is traditionally assessed, for centuries, at the brachial artery by cuff-based sphygmomanometric techniques. Technological and methodological innovations as well as emerging new findings from clinical studies and trials now provoke a re-consideration of traditional strategies for BP management. The existing knowledge regarding the occurring changes of BP over time (temporal variability) and the evident differences of BP levels between central and peripheral arteries (spatial variability) now pilots the progress in current therapeutic and diagnostic ("theranostic") concepts and practices in hypertension. This special issue of Current Pharmaceutical Design covers current and intriguing topics regarding the technological, physiological, diagnostic, therapeutic and prognostic aspects of "spatio-temporal" assessment of BP variations. Moreover an in-depth analysis of other topics such as antihypertensive drugs metabolism and polypharmacy at the elderly are included.

Keywords: Central blood pressure, pulse pressure amplification, blood pressure variability, ABPM, chronotherapy, hypertension, circadian rhythm.

Blood pressure (BP) is traditionally assessed, for centuries, at the brachial artery by cuff-based sphygmomanometric techniques. Pharmaceutical, industrial and clinical strategies have been focused on brachial BP measurements; mostly on systolic and diastolic BP and less often on mean BP and pulse pressure. Single measurements of these parameters at clinic or office are most commonly used for the assessment of arterial BP levels. However, there is emerging evidence supporting that:

- Blood pressure varies along the arterial tree. Thus, BP (and particularly systolic) at arteries close to target organs (e.g. aorta-heart, renal artery-kidney, carotid artery - brain) differs from the BP at the brachial artery.
- Blood pressure varies in time (during the day, weeks, year or even between visits to medical centers or office).
- Central and peripheral BP does not have always the same response to pharmaceutical or non-pharmaceutical interventions.
- There is a chronotropic pharmaceutical effect on BP levels.
- Spatial (along the arterial tree) and temporal BP variability have an additional independent prognostic value beyond and above single brachial BP measurements.

Based on the fact that: a) aortic BP is more relevant than brachial pressure in respect to cardiac function and b) BP values as a function of time are more relevant than a single measurement of BP under specific conditions, it is expected that pharmaceutical interventions, management of hypertension and prediction of BP-related risk could be further optimized. This might be achieved if therapeutic and diagnostic (theranostic) strategies would take into account the above spatiotemporal BP dynamics.

The present issue of Current Pharmaceutical Design covers current and intriguing topics regarding the technological, diagnostic, therapeutic and prognostic aspects of spatio-temporal assessment of BP. An in-depth analysis and discussion of antihypertensive drugs metabolism and polypharmacy at the elderly are also included.

At first, a thorough historical overview and analysis of the most important developments in BP measurement is presented by Karamanou *et al.* [1], revealing the technological and methodological evolution in the understanding and diagnosis of high BP. Tsoucalas *et al.* present the historical milestones in anti-hypertensive drug treatment highlighting the various concepts in the therapy of hypertension through centuries [2].

A methodological and technological breakthrough in the assessment of BP has been introduced the last few decades by the development of new methods and devices for the non-invasive estimation of central BP. Current methods and technologies for central BP assessment are thoroughly described and discussed in a state-of-the-art article by Millaseau and Agnoletti [3].

Although the clinical relevance of brachial BP measurement for cardiovascular (CV) risk stratification is nowadays widely accepted, brachial BP values may lead to inaccurate risk stratification which could be overcome by use of the more relevant central (i.e. aortic) BP values. An update of current evidence supporting the additive value of central hemodynamics in risk assessment strategies beyond and above brachial BP is provided by Yannoutsos *et al.* [4].

Reduction strategies of BP, aiming to decrease CV risk, are currently based on office assessment of brachial artery BP. Emerging evidence now suggests that central pressures may predict better CV diseases than brachial BP. Moreover, brachial and central BP may respond differently to certain antihypertensive drugs with a potential different effect on patients' outcome. Rinaldi *et al.* present and discuss previous and current studies showing that central hemodynamics have an additive value for risk reduction strategies over and above brachial blood pressure [5].

Differences in BP measurements between arms can be observed in routine clinical practice. Various studies have associated inter-arm differences with vascular disease and increased CV morbidity and mortality. The methodological and clinical implications of difference in BP measurements between arms are thoroughly discussed by Clark C.E. [6].

Blood pressure variability (BPV) is considered nowadays a novel risk factor for CV disease with a great body of clinical evidence supporting that short-term and long-term BPV is a significant and independent predictor of target organ damage, CV events and mortality. As a result the attenuation of excessive fluctuations of systolic and diastolic BP has been suggested as an additional therapeutic target. Höcht *et al*. provide an update of published preclinical and clinical studies which have focused in the assessment of drug effects or other interventions on the different types of BPV and their contribution in the prevention of CV events [7].

Timing of anti-hypertensive drug administration by taking into account the circadian BP rhythm, has been investigated by several studies up to now. Schillaci *et al.*, conducted a systematic review of the available evidence, showing that bedtime dosing of antihypertensive medication reduces nocturnal BP and increases day-night BP fall more than standard morning dosing [8]. A further insight in the bedtime hypertension chronotherapy is provided by Smolensky *et al.* [9].

At the elderly polypharmacy is a critical phenomenon that determines quality of life and CV mortality. Franchini *et al.* present a very interesting approach for analyzing co-morbidity data derived from social networks.

The discovery and development of new drugs is a high-risk enterprise that requires significant investments in capital, time and scientific expertise. The study of xenobiotic metabolism is a major part of the research and development of drugs with a substantial contribution in antihypertensive therapy as well. The state-of-the-art review by Zisaki *et al.* [10], provides detailed metabolic profiles of the major clusters of antihypertensive agents, including their metabolites and their metabolizing enzymes, and it also presents specific information concerning the computational methodologies that have been used to predict the metabolic profile of various antihypertensive drugs.

Despite the development and availability of effective antihypertensive drugs, increased arterial BP levels are poorly controlled worldwide. Partially, this may be due either to poor patients' compliance to their physicians' recommendations or to the traditional strategies for BP measurement or monitoring. Advancement in BP reduction has been introduced by telemonitoring of BP levels. Mc Kinstry *et al.* [11], present and discuss the existing evidence from several randomized controlled trials which have shown that telemonitoring of BP (patients can communicate home BP measures to healthcare providers) is associated with statistically and clinically significant reductions in blood pressure.

The rapid progress in biomedical engineering has transformed modern medicine. Existing knowledge and available technologies may lead to major improvements in the management of hypertensive patients. This could be achieved by implementing into clinical practice an integrated, spatio-temporal approach (as illustrated at figure 1) for the diagnosis and therapy of increased BP levels.

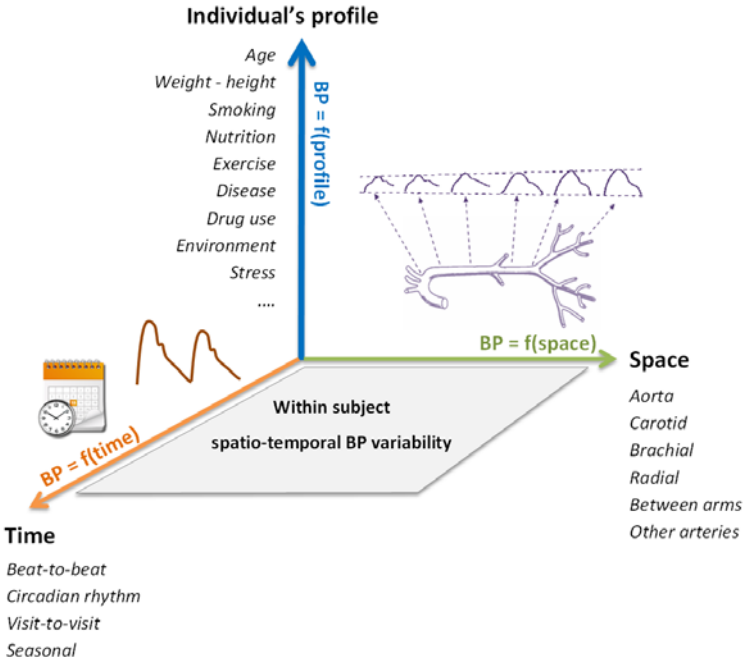

Figure 1. Different dimensions of within-subject blood pressure variability. BP value for each subject is a function (f) of subject's current status-profile, time of measurement and arterial site of measurement.

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