Adv Exp Med Biol - Advances in Internal Medicine (2017) 2: 3–19
DOI 10.1007/5584_2016_83

Published online: 9 October 2016

Understanding Blood Pressure Variation and Variability: Biological Importance and Clinical Significance

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Abstract

Variability is a normative property of blood pressure necessary for survival which likely contributes to morbidity and mortality through allostatic load. Because of its allostatic and adaptive properties blood pressure responses to peculiar situations like the visit to the clinic can lead to the misdiagnosis of hypertension. Cuff methods of blood pressure measurement can also create blood pressure variation when there really is none. There are also physiological differences between populations related to their evolutionary history that likely further affect the extent of population differences in 24-h blood pressure variability. Quantifying the sources and extent of blood pressure variability can be done using natural experimental models and through the evaluation of ecological momentary data. It is very likely that the results of population studies of blood pressure variability and morbidity and mortality risk are inconclusive because the parameters used to assess blood pressure variability do not reflect the actual nature of blood pressure allostasis.

Keywords

Blood pressure variability • Allostasis • Allostatic load

1 Introduction

In 1988, Peter Sterling and Joseph Eyre (1988) introduced the physiological concept of allostasis, which literally means "stability through change" to describe the behavior of dynamic physiological functions. The idea is that variation in physiological parameters occurs as a means of adaptation, so that there is a nexus between external conditions and the body's ability to meet the demands imposed by them which is all regulated by the brain. Thus, there is no "dynamic steady state" or setpoint in these functions meaning that they do not maintain homeostasis, but rather there is a multitude of stable states that occur as responses to

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continuously changing environmental demands. In introducing this concept, Sterling and Eyre used blood pressure as an exemplar, because of its inherent variability. In fact, variation is what gives blood pressure its adaptive value (James 1991, 2013), and is perhaps its single most important normative property, since without it human beings would not survive (James 2013).

The inherent variability in blood pressure was first recognized by Stephen Hales in his pioneering experiments in the horse that were reported in 1733, in which he endeavored to evaluate the nature of the arterial pulse using a cannula inserted into the crural artery (O'Rourke 1990; Pickering 1991). The oscillations he observed in the blood pulses where such that he concluded that any instantaneous measure of the blood pressure would never be exactly the same over the lifetime of the animal (Parati et al. 1992). Through the nineteenth century anecdotal evidence regarding blood pressure variation in humans accumulated, and in 1897 Riva-Rocci in his description of sphygmomanometry reported that the actual procedure of making a blood pressure measurement could induce an increase in pressure so large as to affect the process of obtaining valid data (Parati et al. 1992). Seen from the perspective of allostasis, what this observation meant is that the mere occluding of the artery is enough of a stressor to initiate a physiological response which will change blood pressure.

Nikolai Korotkoff, a field surgeon during the Russo-Japanese war discovered the auscultatory technique of blood pressure measurement using the sphygommanometric method of Riva-Rocci and a stethoscope, reporting on the sounds that bear his name to the Imperial Military Medical Academy in St. Petersburg, Russia in 1905 (Paskalev et al. 2005). Since the sounds could be coupled to the cuff pressure registered on the mercury column of the sphygmomanometer, numeric values could be assigned to both the blood pulse maxima and minima (systole and diastole) based upon the appearance and disappearance of sound. With this important insight, blood pressure level, as well as variation over time could be quantified.

Through the first half of the twentieth century, a variety of observations regarding blood pressure variation using auscultatory and intra-arterial techniques both outside and inside the clinic were made. First, numerous laboratory studies demonstrated that typically occurring variation in physiological habitus and the environment such as postural change, respiration, exercise, and external temperature all profoundly affected the variability of blood pressure (e.g. James 1991; Pickering 1991; Rowell 1986). There were also studies indicating that there was substantial variability in "resting blood pressure" by venue and over time. One of particular note was the report by Ayman and Goldshine (1940) who trained hypertensive patients or their family members in how to take blood pressures at home. They found that these measurements differed from clinic measurements by as much as 70/36 mmHg, a difference which persisted over 6 months. Other studies around that time suggested that the emotional or psychological state of the person could affect the reliability of resting ausculted blood pressure measurements (e.g. Levy et al. 1944; Rogers and Palmer 1944), and there were also data to suggest that variation in a person's pressure could be influenced by the familiarity between the patient and the person taking the pressure (Shapiro et al. 1954) as well as the gender of the person taking the pressure (Comstock 1957). During this time, the variation in resting blood pressure in and out of the office that was related to the patient's response to the procedure or circumstances (which from an allostatic perspective is an adaptive adjustment to the perceived stressfulness of the situation) was seen medically as something that confounded accurate clinical assessment and thus needed to be minimalized.

In the 1960s there was an increasing number of studies examining blood pressure variability outside the laboratory and clinic. These studies emerged with the technical development of the Remler® ambulatory blood pressure recorder which required that subjects manually inflate the cuff (see Hinman et al. 1962; Kain et al. 1964; Sokolow et al. 1966), and with the

development of intra-arterial devices that measured pressure continuously (Richardson et al. 1964). A classic study by Bevan et al. (1969) employing an intra-arterial device provided data that showed just how variable blood pressure could be over the course of a typical day. This case study and others like it unambiguously showed that blood pressure levels were tied directly to what someone was feeling and doing as well as the circumstances. These data clearly indicated that blood pressure did not maintain a homeostatic "steady state" but rather allostatically changed to meet the demands of the circumstance.

As ambulatory blood pressure monitoring technology improved from the 1970' through the 2000s, the effects of various typical behaviors on blood pressures were evaluated, first using intra-arterial devices and later using automatic ambulatory blood pressure monitors that employed either auscultatory or oscillometric technology (James 2013; Pickering 1991). These studies, often undertaken by non-medical researchers, were designed to quantify the amount of intraindividual blood pressure variation over the course of a day associated with psychological, sociological, and environmental sources using data from larger scale population samples. Their purpose was to evaluate how the things that people do, think and experience as part of their lifestyle relate to the development of sustained high blood pressure and subsequent cardiovascular pathology (James 2013). The upshot of the results of these studies is that the extent of out of office blood pressure variation and its relation to pathology may not only be determined by both the mix and psychological appraisal of the activities and relationships that are experienced by a subject during the course of a day, but also by the duration and frequency of the experience of these factors over a lifetime (James 2007, 2013).

Over the past decade, there has been interest in evaluating the morbidity and mortality risk of circadian, diurnal or nocturnal blood pressure variation and the question has been raised as to whether variability should be treated (Asayama et al. 2015; Flores 2013; Palatini et al. 2014; Parati et al. 2015). The purpose of this brief overview is to critically examine blood pressure variability and variation both within and outside the office, separating its adaptive function from possible pathology using the perspective of the allostasis paradigm.

2 Are There Multiple Intrinsic Biological Rhythms That Contribute to Blood Pressure Variability?

From an allostatic perspective, all the measurable variation in blood pressure is related to beat-to-beat changes in the actions of the heart which in turn, are triggered by the actions of the brain (Sterling 2004). There are factors that acutely (very short time frame) influence the pulse wave of blood as it is ejected from the heart, such as respiration (Pickering 1991). Other than the acute metabolically interactive processes that are related to the maintenance of life (e.g. the need for tissue oxygen exchange and the release of carbon dioxide and other metabolic byproducts through exhaling), all other blood pressure variation occurs to adapt people to their circumstance, largely through the effects of numerous humoral and hormonal inputs that are regulated by the brain's response to external and internal stimuli (Sterling 2004).

Circadian blood pressure variation, most notably that related to the biobehavioral changes from waking to sleep reflect adaptive responses to habitual activity and postural variation associated with everyday life processes and sleep (James 2013; James et al. 2015). Other potential rhythms such as seasonal variation (Parati et al. 1992; Pickering 1991) likely arise from beat to beat adjustments to ambient temperature (transitions from heat to cold) and the various seasonal behavioral and social changes that are tied to culturally relevant seasonal traditions (James 1991, 2013; James and Baker 1995; James et al. 1990b).

Since blood pressure change is an adaptive process, changes in seated clinic auscultatory blood pressures over longer time frames such as monthly or yearly, must reflect either (1) changed social or psychological conditions experienced

by the patient that are influencing the patients perceptions of the circumstance in the clinic; (2) changes in the underlying cardiovascular structure so that the system that is generating the pressure is itself changed or changing; or (3) perhaps both (Gerin and James 2010; Jhalani et al. 2005; Kleinert et al. 1984; Pickering 1991).

There is also a difference in evaluating blood pressure variability from invasive beat-to-beat assessments (based on continuous intraarterial or plethysmographic measurements) and non-invasive techniques, where a cuff occlusion method is employed and systolic and diastolic pressures are determined over a 20–30 s time frame using the appearance and disappearance of audible sound, high frequency signal components, or by examining a reflective waveform generated inside the blood pressure cuff (Pickering and Blank 1995) (see Fig. 1). In evaluating beat to beat pulse tracings, the diastolic (nadir) and systolic (zenith) pressures of the pulse are directly connected and influence one another whereas auscultatory or oscillometric systolic and diastolic pressures are estimates not tied to a particular pulse. Beat-to beat systolic and diastolic measurements will change in tandem with externally driven stimuli, however, the time it takes for the bladder-cuff assembly to deflate and re-establish blood flow is long enough to miss the effects of hormonal inputs as they happen, so that the factors affecting systolic pressure may be different than those affecting diastolic pressure (Blank et al. 1995). This difference will give a false impression of the amplitude of the blood pulse, possibly creating variation where there really is none. This variation is an artifact of the measurement technique.

In addition to the time frame issue that affects the variation of pulse pressure, added variability

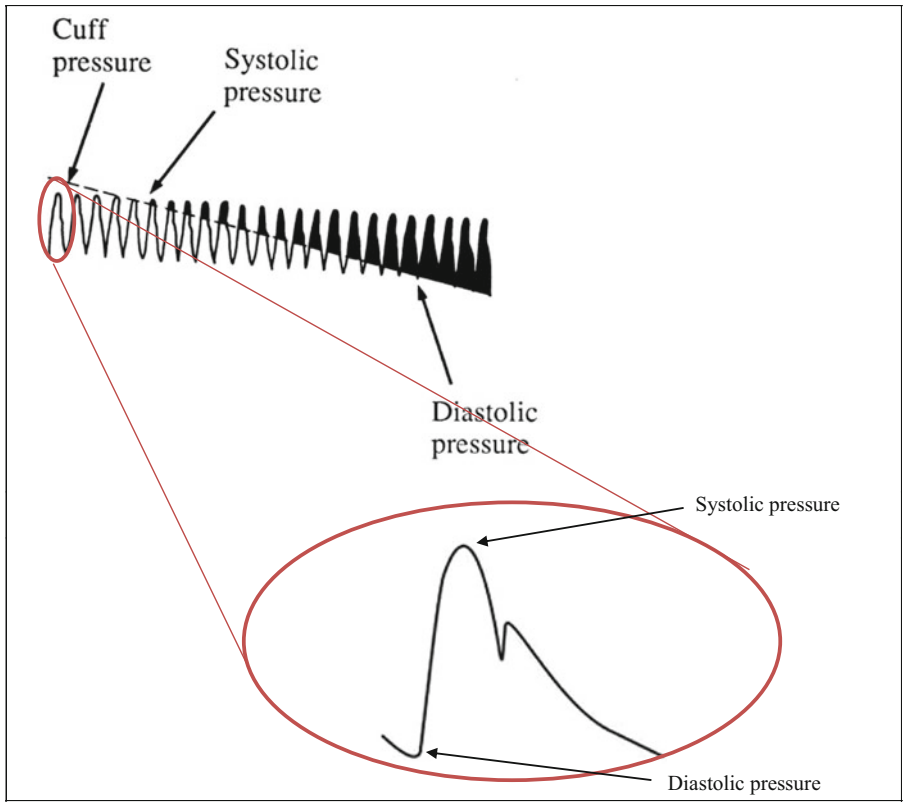

Fig. 1 Differences between the recorded systolic and diastolic pressures from intraarterial or plethysmographic measurements (depicted in the *circular insert*) and a cuff measured pressure where systolic and diastolic pressure are tied to the Korotkoff phase I and phase V sounds

can be created using cuff-based measurement methods by simply changing the position of the cuff relative to the heart when cuff deflation occurs (Pickering 1991; James et al. 2015). For example, blood pressure during sleep can appear to be quite variable, but that variation may be due to simple factors such as changes in sleep position, so that depending upon whether the pressure is taken while a subject is on their left or right side, or on their back or stomach, it can appear to change by 15 mmHg or more (James et al. 2015). Cuff position could also increase waking pressure variation during an ambulatory monitoring as well, also depending upon the position of the arm during cuff deflation (Pickering 1991).

So, are there different types of blood pressure variability that need to be considered clinically? It seems unlikely, because if blood pressure change is adaptive, meaning it changes to meet the circumstance, then all blood pressure variability must be beat-to-beat and what gives the impression of shorter and longer term variation patterns is the general patterning of life experiences, momentary reactions, and the intermittency of clinic or ambulatory measurements.

3 White Coat Hypertension, Masked Hypertension and the Life Experience of Visiting the Clinic

Seen from the perspective of the patient, going to the doctor is an event! The environment of the clinic, office, or hospital is uniquely different from every other place that the patient goes. Allostatically, a blood pressure taken during the event (being in the clinic) will reflect the patient's adaptive response to it. As Riva-Rocci noted (see above), arterial occlusion is enough of a stimulus to initiate an increase in blood pressure, but because the taking of a blood pressure is also an entirely unique social interaction involving a physician, nurse, or other medical professional and the patient, there will also be effects related to the perceptions of the patient connected to that interaction. Even if the pressure is taken by an automatic device with no one present, that situation still requires an adaptive response from the patient. When the blood pressure response to this peculiar environment exceeds the average response to all other daily environments, the patient is said to exhibit a white coat effect, but if that effect leads to ausculted blood pressure measurements that exceed 140/90 (hypertension Rubicon) the patient is diagnosed with white coat hypertension. Whether blood pressure responds with an acute heightened response in the clinic may largely depend on prior patient experiences with the setting and prior relationships with the people within it.

That a blood pressure measurement can be profoundly influenced by the perceptions of the patient was dramatically demonstrated by Mancia and colleagues (1987) in their classic study in which blood pressure readings were continuously taken intra-arterially on one arm while a nurse or physician took an ausculted blood pressure from the other. The intra-arterial measurements showed that relative to the pressure prior to the ausculted measurement interaction with the physician, there was an increase of some 23/18 mmHg when the physician took the ausculted pressure. Further, the increase in pressure by the physician was about twice the effect seen when a nurse took the pressure.

What did the patient perceive that lead to the increase in pressure? A more recent study by Jhalani et al. (2005) provides some answers. They examined the acute effects of anxiety and expectancy on clinic measured pressures and found that when assessed as a specific office related effect, anxiety had a substantial influence on increasing pressure in the office. In their study, they measured anxiety before, during, and after blood pressure was measured. They also showed that there is an effect related to the patients' expectations about what their blood pressure measurement will be. Their findings suggest that prior experience can trigger anxiety regarding this peculiar environment and the relationships within it, so that the blood pressure response is elevated. These psychological factors will lead to a diagnosis of hypertension if the ausculted numbers exceed 140/90.

Masked hypertension is defined by the precise opposite effect seen with white coat hypertension. Specifically in these patients, adaptation to the peculiar clinical environment requires less of a response than an average of the responses to all other events outside the clinic. Rather than being made anxious, they may be calmed by the setting and interpersonal interactions. Interestingly, masked hypertension is seen not so much a relaxed adaptation as it is an absence of high risk behaviors which elevate pressure outside the clinic such as alcohol consumption, smoking, or contraceptive use (see Longo et al. 2005 for example).

Studies have been done which have evaluated the morbidity and mortality risk associated with the diagnosed conditions of white coat and masked hypertension which are defined from the average blood pressure in the clinic and the average blood pressure response to all other conditions during the day (e.g. everything not in the clinic). Pierdomenico and Cuccurullo (2011) did a metaanalysis comparing the risk for cardiac and cerebral events among patients who were diagnosed as normotensive, white coat hypertensive, masked hypertensive and essential hypertensive based on the out of clinic-inside clinic blood pressure difference and found that white coat and normotensive patients had similar risk as did the masked hypertensives and essential hypertensives. This kind of finding suggests that inside clinic-outside clinic variation may not be important to cardiovascular health, and that in fact, the determination of who really has hypertension should be made from average pressure experienced across many different situations and not from the peculiar setting of the clinic or office.

4 Ambulatory Blood Pressure Variability as a Risk Factor

Given that blood pressure is a response to ambient conditions, it would stand to reason that an evaluation of the relationship between its circadian variation and morbidity or mortality would necessarily involve assessing the appropriateness of the pressure responses to the various external and internal conditions that drive the continuous changes (see Zanstra and Johnston 2011 for example). However, virtually every study that examines blood pressure variation as a risk factor for cardiac or cerebral events ignores the dynamic interplay between blood pressure and the specific environmental demands an individual confronts during daily life. Instead, studies of blood pressure variation and vascular risk focus on the event predictability of some measure of the statistical dispersion or cumulative differences of the sample of blood pressures taken with a non-invasive ambulatory blood pressure monitor over the course of one 24-h period (a day) or the average waking-sleep blood pressure transitions (either "dipping"-the difference between average waking pressure and average sleep pressure, or the "morning surge"-the difference between various pressures prior to and just after morning awakening), (see for example Asayama et al. 2015; Hansen et al. 2010; Palatini et al. 2014; Parati et al. 2015; Taylor et al. 2015). These measures are examined only with regard to a possible linear relationship; that is, the studies only address the question of whether risk is related to being too low or too high on the various parameter scales. The inconsistent results from these studies, where some suggest variability is an important risk factor and others find little or no effect has spurred a controversy as to whether blood pressure variation should be a target for treatment (e.g. Asayama et al. 2015). Before this type of issue can be addressed, it is useful to examine what each indicator of the variability, or variation in these risk related studies is measuring. Are the indexes and parameters that are employed in these studies suitable and meaningful indicators of blood pressure variability?

Standard deviations (SD) or coefficients of variation (CV) are measures of the dispersion around a mean of a variable that is normally distributed. These are calculated from presumably random samples of a population of measurements. However, if the distribution of the overall population is not normal and the sampling is unrepresentative and small, these measures will be biased, inaccurate, and uninformative (Cochran 1977). Given that 100,000 or

more systolic and diastolic pressures are generated over a 24-h period, and non-invasive ambulatory monitors sample perhaps 50 of those (5/100ths of 1 % of all those generated) which vary with time and conditions in a systematic way (pressures change to adapt the person to continuously changing circumstances) what is the value of the SD or CV of that sample in predicting risk? Parati et al. (1992) some 25 years ago noted that these kinds of measures don't tell you anything about how single values, as collected, are distributed around the mean. Do the pressures spread out or is there perhaps a bimodal shape? Many odd distributions could provide the same calculated SD or CV. These measures do not provide any information about the pattern and extent of individual pressure responses, and because as noted above, what needs to be evaluated in an assessment of how variability affects pathology is the appropriateness of the variation, they really are unsuitable variability indicators for examining morbidity and mortality risk.

Furthermore, the SD and CV as indicators of 24-h blood pressure variation are poorly reproducible over 24-h (see for example, James et al. 1990a; and the review by Asayama et al. 2015). In our study, we compared 24-h variability in normotensive and hypertensive patients over 2 weeks. Figure 3 shows the timing and spacing of each measurement on each day for both groups of subjects. Note how different the days are. This disparity is actually typical when comparing daily non-invasive ambulatory monitoring data. What we found is that people did different things on different days, and while there were enough pressures to provide a reasonably stable average over time, the varying mix of conditions and times when pressures were taken, were poorly matched day to day. This mismatch profoundly affected the distribution of the pressures around the mean, rendering the distributionally tied measures of variation (SD, CV) irreproducible (James et al. 1990a).

The "average real variability" (ARV24) has also been used as an indicator of blood pressure variability and is defined as the mean of the absolute differences of consecutive non-invasive ambulatory measurements. The effects of this parameter on the predictability of events are small or inconclusive (e.g. Asayama et al. 2015; Hansen et al. 2010). Bearing in mind that each of the sequential blood pressures taken by non-invasive ambulatory monitors are a response to the ambient condition in which they are taken, the ARV24 can go up or down depending upon what the person confronts and is doing during the day. What this quantity really represents is a summary score of the differences between peak blood pressure responses to some indeterminate number of sequential unknown stressors. Ultimately, the magnitude of this parameter depends solely upon the variability of the environments experienced and the behavior/emotional responses of the patient (James 1991, 2013). Thus, a patient who is monitored on a day where they are inactive, remain at home and are emotionally stable will have low ARV24, whereas one that performs multiple varying tasks, transitions through many daily microenvironments (goes to work, out to dinner, etc.) and experiences an array of emotions will have a high ARV24. Since the blood pressure changes are adaptive and are a normative response to the tribulations of everyday life, it is not clear from the studies that have used this parameter why high (or low) values of ARV24 would be indicative of pathology or health.

The other variation measures used in risk studies are "dipping" and the "morning surge." These are measures of blood pressure change between the state of waking and the state of sleep. Conceptually, dipping refers to the blood pressure transition from waking to sleep, whereas the morning surge refers to the transition from sleep to waking. Operationally, there is no consistent definition for either measure across studies, although with dipping, a Rubicon of 10 % decline, particularly for systolic pressure seems to be the popular demarcation line for normalcy and pathology, although there is no definitive reason why this value is the clinically relevant cut-point (Asayama et al. 2015; Flores 2013; Taylor et al. 2015). Again, seeing blood pressure as an adaptive response, the waking average that is used to determine dipping is based on a mean of values that are tied to the conditions experienced on the day of study. So depending upon

whether a person had a difficult day or an easy day, the waking average could be higher or lower. There are ample data showing that excessive psychological stress during the day can also carry over and increase sleep pressure (see James et al. 1989 for example), so non-dipping may occur on a given night simply because it was a stressful waking day. Another problem with the concept of dipping is that it assumes that all people experience just the two distinctive periods (waking and sleep) over the day, so that "waking" and "sleep" happen during the day and night. This presumption is demonstrably false as there are plentiful data showing that waking-sleep patterns can change with age and that this affects the circadian patterns of adaptive blood pressure responses in ways that confound the determination of dippers and non-dippers (see Ice et al. 2003). Likewise, whatever pressure(s) chosen to define the post- awakening point and the low pre-awakening point in defining the morning surge are also adaptive responses to the conditions when they are measured, so that its relative magnitude may be related to any number of factors affecting both sets of measurements. And, as previously noted, there are also other issues with "sleep" pressures taken by a cuff occlusion method that have to do with the position of the cuff relative to the heart that will influence the level and variability of "sleep" blood pressures (James et al. 2015).

It is not surprising that waking-sleep transition measures are often found to have poor reproducibility as well as differential effects in different populations (Asayama et al. 2015; Taylor et al. 2015). Patterns of behavior, stress, and sleep quality vary from day to day, and all these are factors that may be influenced by the cultural background and occupation of the patient (James 2007). While there may be theoretical reasons to believe that the variability in blood pressure associated with wakefulness and sleep ought to have health implications, the operationalization of the concepts using non-invasive ambulatory measurements are inadequate because they don't embrace the adaptive nature of blood pressure which makes it impossible to define what normative transitions ought to be. Without a clear definition of normalcy, there is no way to coherently use these measures for treatment purposes (Flores 2013).

So, after evaluating the nature of the parameters that have been employed to assess the morbidity and mortality risk of blood pressure variability in large international and community based populations, it appears that none of them are meaningful indicators of what is or is not appropriate variability, and therefore can't really address the question of whether blood pressure variability ought to be treated.

5 Ambulatory Blood Pressure Variation: How Do You Measure It?

To understand why blood pressure varies during the day, you need to have information regarding the ambient conditions when measurements are made. If blood pressure is responding to these conditions during everyday life, you need to be able to show that as they change, so does blood pressure.

Several means have been used to classify the conditions of ambulatory blood pressure measurements. While direct observation of subjects wearing the monitor has been used (e.g. Ice et al. 2003), for most studies of blood pressure variation, subjects have self-reported the ambient conditions of each blood pressure measurement in a diary, which have taken on a variety of forms, from pencil and paper to hand held computers as has been discussed (see James 2007, 2013). Most behavioral studies of blood pressure variation have not been conducted with a focus toward allostasis, or even understanding cardiovascular adaptation. Rather, studies have simply defined the sources of diurnal blood pressure variation, or evaluated whether people with specific characteristics differ in their responses to similar lifestyle related stimuli (Gerin and James 2010; James 2013).

Studies designed to evaluate what affects blood pressure variation and by how much have generally taken two forms. As has been noted (James 2007, 2013), the first approach is one where each blood pressure measurement is assessed with regard to simultaneously recorded

circumstances reported in a diary (often called ecological momentary data) using inferential statistical models (see for example Brondolo et al. 1999; Gump et al. 2001; James et al. 1986; Kamarck et al. 2002; Kamarck et al. 1998; Schwartz et al. 1994). In this analysis, the sources of blood pressure variation are separated based on the reported diary entries (such as the posture of the subject, the location of the subject, etc.). The proportion of variation associated with each is quantified, as is the number of mmHg the alternative levels of each (such as posture-standing, sitting, reclining) contribute to either increasing or decreasing the values of individual blood pressure measurements. In evaluating blood pressure variation this way, the choice of diary reporting alternatives is critical. The potential sources of variation chosen to have reported in the diary and how they get recorded will dictate how the variation in blood pressure gets analyzed (James 2007, 2013). Analysis of ecological momentary blood pressure data has been undertaken using raw (e.g. Brondolo et al. 1999; Kamarck et al. 2003; Schwartz et al. 1994) and standardized e.g. (Brown et al. 1998; Ice et al. 2003; James et al. 1986) data. The estimated effect sizes from different studies using these approaches vary considerably, due in part to the fact that there is no consensus as to what ought to be the standard value against which sources of variation should be measured, but also because of the demographic and cultural diversity of the groups studied (James 2007, 2013).

The second form employs what might be termed a "natural experiment" which has been discussed at length elsewhere (see James 1991, 2007, 2013). However in brief, natural experiments are studies in which there are a priori design elements that define predictable dynamically changing behaviors or situations that occur during a typical day (James 2013). This kind of study is done by anthropologists and human population biologists, and it is an approach that has its roots in psychological and psychophysiological paradigms in which blood pressure reactivity to various stressful tasks are evaluated in the laboratory, (see for example, Pickering and Gerin 1990; Linden et al. 2003; Kamarck et al. 2003). In these laboratory experiments, a baseline condition is established and then the subject undertakes a series of predefined tasks that will elicit a response. The difference between the baseline measurements and those during the tasks define the magnitude of blood pressure reactivity (James 2013). Because they are conducted in a laboratory, there are controls in the experiment such that specific effects can be isolated, measurements can be taken in a systematic way, and all the participants experience the same protocol. Control groups can also be included in the experiment. Moving this experimental paradigm to a "natural" setting (e.g. into real life and outside the laboratory) requires modification because no true baseline can be established. But, a "natural experiment" can be designed where blood pressure changes can be evaluated as people move from situation to situation (such as their work and home situations) during the course of their everyday lives. For example, a person who lives in a suburb and commutes to an urban workplace every day likely has a structured, urban work environment where economic related activities occur, where social interactions take place with non-relative co-workers, and where a specific occupational hierarchy dictates the nature of social relationships (James 2013). The characteristics of this situation diverge sharply with that of the suburban home, where domestic tasks and leisure activity happen in a social context where interactions are with relatives and neighbors (James 2013). The variation in blood pressure required to adapt to these relatively predictable situations can be assessed by comparing the average blood pressure while in them with that during overnight sleep, or more specifically, while the person is quietly recumbent in a dark room acting as a pseudo-baseline.

In assessing blood pressure variability, it is important to realize that the blood pressure distributional parameters that come from an array of measurements will be related since they are determined from a single vascular system that has specific structural and functional properties. That is, the mean and variance of the population of pressures measured over the course of 24-h on the same person will be related. This is called

heteroscadasticity and it is well known (Pickering 1991). Thus, people with lower 24 h average blood pressure will tend to have a narrower range of blood pressures diurnally than those with higher average pressures. Pickering (1991) has noted that this heteroscadasticity is probably related to underlying arterial structural differences such as stiffness and/or other functional factors such as differences in vasoactive hormone receptor density or sensitivity (see for example, van Berge-Landry and James (2008).

Over the past 30 years numerous studies have been conducted that have identified various psychological, social and behavioral parameters that are associated with increased ambulatory blood pressure variation. These effects have been summarized in a number of reviews (see for example, Gerin and James 2010; James 2007, 2013; Zanstra and Johnston 2011). In brief, mood variation, postural variation, situational variation, and activity variation all contribute significantly to diurnal blood pressure variation. These effects are further modified by seasonal (temperature) effects, dietary effects (e.g. sodium intake), alcohol consumption, smoking, specific social interactions (such as with spouses) and among employed people, the appraisal of job strain (Gerin and James 2010; James 2013; Zanstra and Johnston 2011). Any given effect can be small, but a blood pressure measurement is a response to all that are relevant when the measurement occurs, so that the impact of each of the factors is additive and can lead to substantial circadian blood pressure variation. An example of how this variation is additive is shown in Fig. 2.

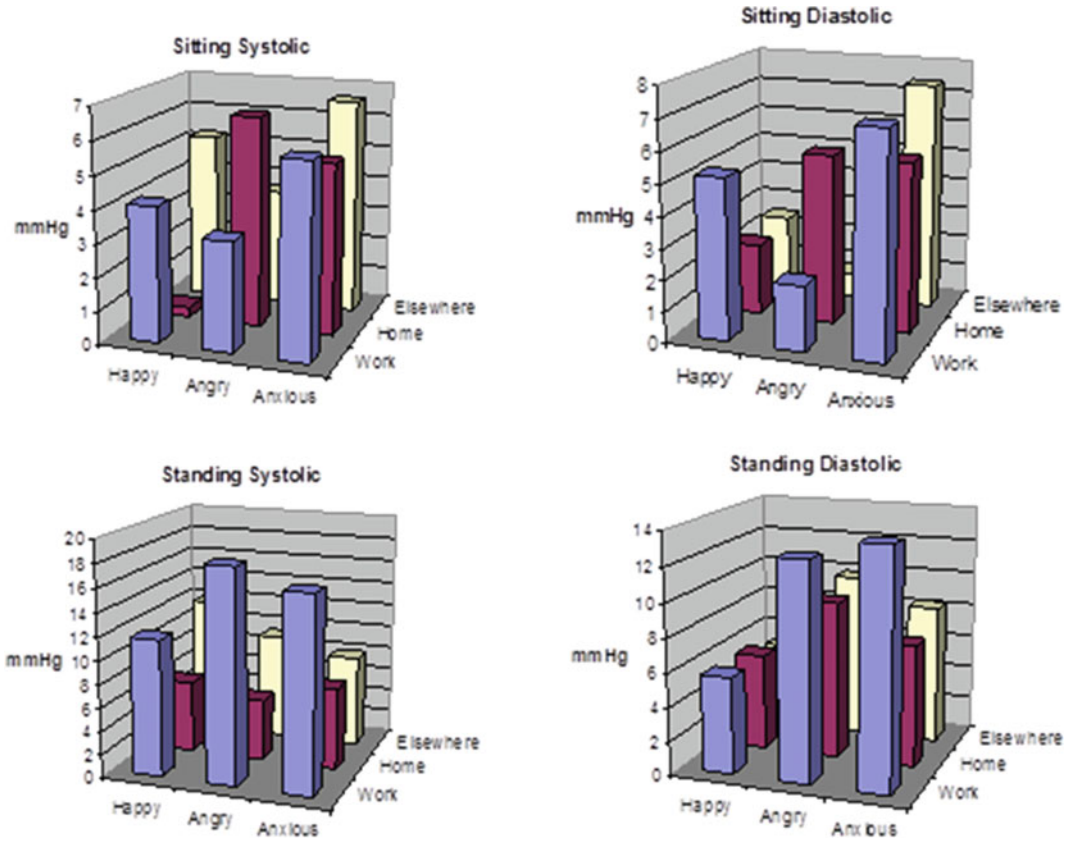

Fig. 2 The amount of diurnal blood pressure variation associated with variation in posture (sitting, standing), situation (work, home, and elsewhere) and reported emotional state (happy, angry, anxious) on daily blood pressure (Data from James et al. 1988). The variation is defined as mmHg from the 24-h mean, and is based on the assumption that the measure of dispersion around the 24-h mean (standard deviation) is 10 (Modified from James 2013)

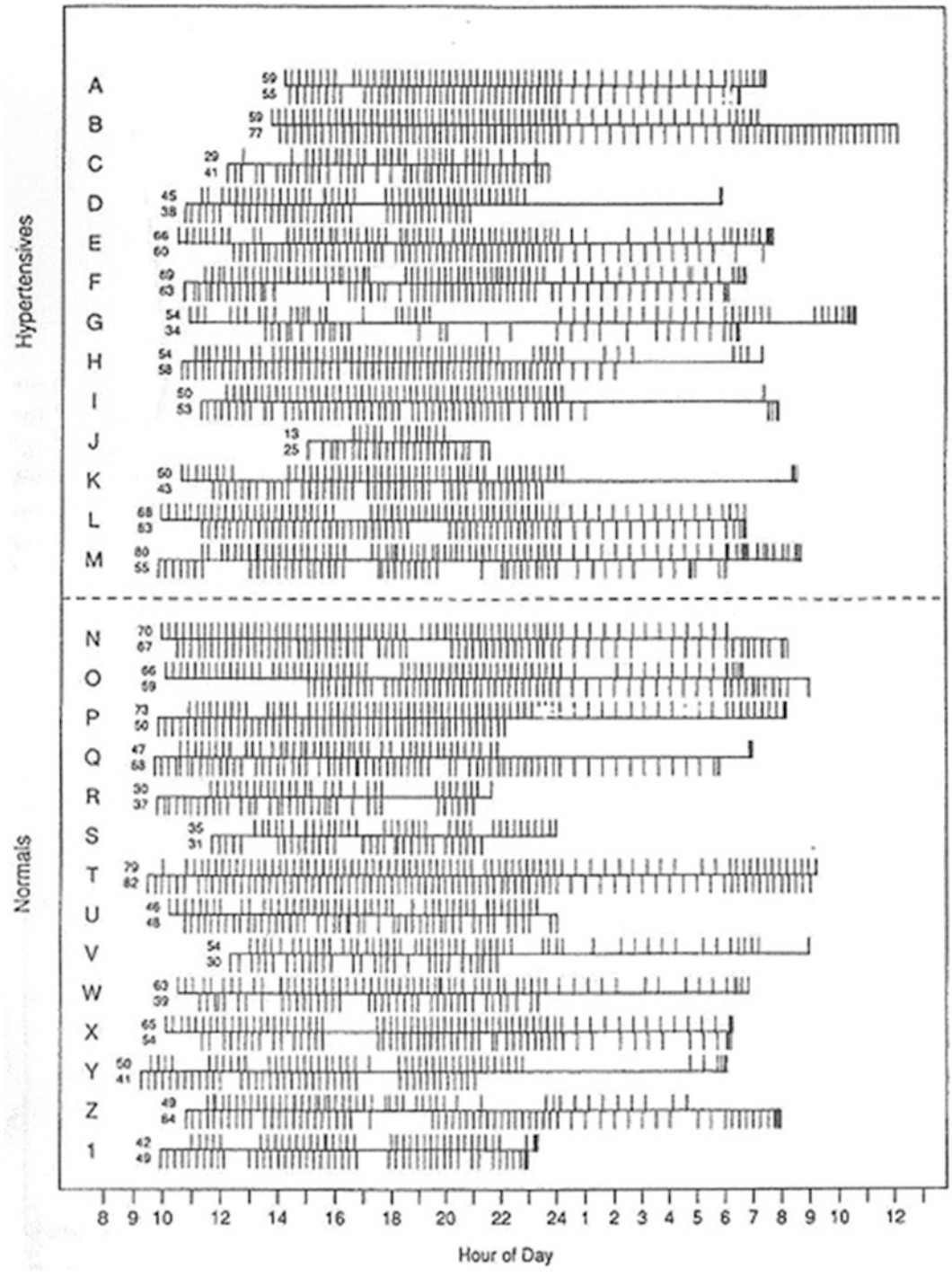

Fig. 3 The pattern of blood pressure measurements taken 2 weeks apart, in normotensive and hypertensive patients using a non-invasive ambulatory blood pressure monitor. Note the different numbers of pressures taken each time and the differences in the time spread between pressures. Test-retest correlations between the systolic/diastolic SDs were 0.18 and 0 .22 respectively (Modified from James et al. 1990a)

In the example, note that the size of the estimated blood pressure adjustments associated with the mix of ecological momentary factors varies considerably. A closer examination of the effects shows that they are more or less additive with regard to blood pressure variation. Each set of factor alternatives defines a momentary state typically experienced by a person. From the figure it is easy to see that the allostatic change in blood pressure from one state to another can be substantial. Because a change in habitus from sitting to standing, or a mood change from happy to angry could happen almost instantly, it is clear that the process of allostasis, as reflected in blood pressure variation, is also instantaneous.

6 The Effects of Human Evolution on Blood Pressure Variation

As has been previously discussed (James 1991, 2010, 2013; James and Baker 1995), there has been physiological evolution in our species, some of which has been driven by climate and diet, so that there are various population or ethnic group physiological differences that can affect how an individual's blood pressure varies (James and Baker 1995; Young et al. 2005; James 2010, 2013). The influences of these genetic differences are the result of natural selection and are reflected in populational variation in blood pressure responses to environmental stressors such as prolonged cold temperature and dietary salt.

Current evolutionary evidence suggests that all modern human populations are descended from tropical "heat adapted" ancestors in Africa, somewhere between 100,000 and 200,000 years ago (Smith 2010), and it is also true that modern sub-Saharan African populations retain that heat adapted physiology, or more precisely a physiology adapted to a mostly hot, wet environment (Hanna and Brown 1979; James 2010, 2013; Young et al. 2005). However, many present day populations currently live in and have survived in temperate and freezing climates for millennia. When cold or freezing conditions are experienced in the unprotected human, there is a sympathetically driven constriction of peripheral arteries, particularly in the hands and feet that is designed to conserve body heat, which, if left unchecked, will lead to significant tissue damage in theses appendages (e.g. frostbite) (James and Baker 1995). To combat the tissue damage, ancestral human populations who migrated out of Africa over the past 100,000 years or so to ecosystems characterized by temperate and cold climates evolved a peripheral cold induced vasodilatory (CIVD) response through natural selection (Steegmann 1975). CIVD is a periodic release of the arterial constriction which suffuses the cold peripheral tissues with blood, rewarming them so that they are protected from frostbite for a time (James and Baker 1995). However, what this also means is that populations who did not migrate to these colder ecosystems (those remaining in Africa) did not develop this form of cold adaptation since such a response was unnecessary in tropical climates (James and Baker 1995). Numerous studies have found that African-American populations (whose migration to colder climate environments is very recent evolutionarily) show a generally more intense vasoconstrictive response to peripheral cold stress, with either inadequate or no CIVD (James and Baker 1995; Steegmann 1975). The increased cold pressor response among African-Americans is most often noted in studies of hand emersion in freezing water, however, research has also shown that cold to the face also elicits the accentuated pressor response among African-Americans (Anderson et al. 1988; Treiber et al. 1990) and that African-Americans may further exhibit heightened myocardial and vasoconstrictive reactivity during passive exposure to ambient temperatures from 8 to 10 °C (Kelsey et al. 2000). What these findings mean is that the typical outside exposure of the face during the cold of winter is probably sufficient to elicit the enhanced pressor and vasoconstrictive responses among African-Americans.

Why this is significant from the perspective of blood pressure variation is that the sympathetically driven peripheral vasoconstriction that is

induced by cold stress increases blood pressure (Pickering and Gerin 1990). It is thus possible that African Americans living in the temperate and freezing climates of North America or Europe experience chronic cold stress through the winter months, potentially experiencing more chronic vasoconstriction due the their enhanced cold pressor response and inadequate CIVD which in turn will increase the overall variability of their circadian pressure relative to other population groups (James 2013; James and Baker 1995). This possibility is supported by studies which suggest that sympathetic hormone receptors among African-Americans may be more sensitive than those of European-Americans (Mills et al. 1995), and that the diurnal variation in blood pressure of African-Americans is more accentuated than that of European-Americans in relation to diurnal changes in catecholamines (Van Berge-Landry et al. 2008).

There are also two salient aspects of heat adapted physiology, or more precisely a physiology adapted to the mostly hot, wet environment in which *Homo sapiens* evolved: the ability to (1) profusely sweat and (2) retain salt (sodium). The latter is important because salt availability is limited in tropical ecosystems (James 2010; James and Baker 1995; Young et al. 2005). A geographic cline from the equator to the poles of "heat adapted" allelic variants from 5 functional genetic sites that affect salt retention and blood vessel tone has been reported by Young et al. (2005). Specifically, in their study, DNA samples from 53 geographically dispersed populations from the equator to the poles suggest that native populations living within 10° of the equator (hot, salt poor environments) have an average 74 % "heat adapted" allelic variants, while populations within 10° of the arctic (cold, salt rich environments) have only 43 % "heat adapted" variants. Based on this distribution, the authors hypothesized that the frequency of "heat adapted" alleles declined as our African ancestors colonized ecosystems that were cooler and salt rich and then rose again among groups that migrated from those areas back to more salt poor tropical climates (Young et al. 2005; James 2010, 2013). They further argued that since the "heat adapted" alleles facilitate salt retention and excessive dietary salt intake can contribute to the development of hypertension, populations with an increased numbers of "heat adapted" alleles are more susceptible to hypertension, particularly if they have migrated in more recent times to cooler salt rich ecosystems or who have had salt substantially increased in their diets (Young et al. 2005). It has been suggested that these genetic findings may partially explain the higher prevalence of hypertension and cardiovascular morbidity in African-American populations, at least as it may relate to variation of salt in the diet (James 2010, 2013). What this also means, however, is that blood pressure variation related to salt intake may be different depending upon the evolutionary history of the population being evaluated.

To summarize, evolutionarily developed differences in peripheral cold responses and salt and fluid retention likely affect allostatic blood pressure responses. However, in a broader context, what these studies suggest is that the extent to which blood pressure may vary, or move to presumptively adaptive states in response to challenges may depend upon how natural selection has shaped an individual's physiology. That is, the same set of conditions may lead to completely different blood pressure responses due to the fact that their physiologies differ as a consequence of natural selective processes that occurred in their ancestral populations. These underlying physiological differences should thus be considered when evaluating allostatic blood pressure variation in studies that examine ethnically diverse groups.

7 Rethinking Blood Pressure Variability and Morbidity and Mortality Risk

In a more recent discussion, Sterling (2004) contrasted the basis of allostasis with that of homeostasis, which defines physiological processes in terms of maintaining a stable internal environment. That is, in the homeostatic

paradigm, the purpose of physiological regulation is to restrict internal parameters to specific "setpoints" so that substantial variation or deviation from that value is seen as pathology, indicating some mechanism is "broken" and needs correcting. In many ways, the current medical evaluation of blood pressure in this manner dramatically affects how blood pressure variability and morbidity/mortality risk studies are carried out. Essentially, studies are designed to assess the impact of too much or too little variability, so that if the amount is extreme, it must mean that that there is underlying pathology in the pressure maintenance feedback loops. I think it is not an unreasonable observation these studies have not provided the kind of results that would be clinically helpful. In fact, some researchers have concluded from the results that blood pressure variability is simply not an important clinical issue (see Asayama et al. 2015).

However, if blood pressure is treated as something that is normatively variable as would be the case in the allostasis paradigm, then the relationship between blood variability and pathology takes on a completely different dimension. In 1998, McEwen (1998) introduced the term "allostatic load" to describe the long term pathological effects of systems that undergo allostasis, or adaptation through change. "Allostatic load" can be defined as the wear and tear that the body experiences due to repeated cycles of allostasis as well as the inefficient turning on or shutting off of the regulatory responses. Morbidity and mortality can ensue from the effects of four types of allostatic load. The first type is the "repeated hits" to the system that result from long term normative continuous changes from minimal to maximal values. The second type is a lack of adaptation or habituation, where an accentuated initial response to acute stressors that should attenuate over time does not. The third type would emerge from prolonged accentuated responses where a maximal response is attained but then never attenuates after the stressor is removed and the fourth type would result from an inadequate response to stressors where substantial changes would be the appropriate adaptation, but instead there is minimal response. While these types are described as separate possibilities, any or all types of allostatic load might contribute to physiological decline of an individual's cardiovascular system over time. Thus, following the principles of allostatic load, the variability of blood pressure that would contribute to morbidity and mortality is an intrinsic inevitable property of the cardiovascular system, but inappropriate variability in the form of lack of habituation, and prolonged excessive or prolonged inadequate responses to typical daily conditions and stressors could accelerate the pathological process. Thus, variability might not be something that you would treat, but it would be a marker indicating there is something else wrong. Appropriate variability to daily life events could be defined from studies of the sources of variability (see above). What one might then look for clinically is change in the extent of variability associated with events over time, and if there is change, find out what caused the change and if possible, treat it.

8 Conclusions

Variability is a normative property of blood pressure necessary for survival which likely contributes to morbidity and mortality through allostatic load. Because of its allostatic and adaptive properties blood pressure responses to peculiar situations like a visit to the clinic can lead to the misdiagnosis of hypertension. Cuff methods of blood pressure measurement can also create blood pressure variation when none exists. There are also physiological differences between populations related to their evolutionary history that likely further affect the extent of population differences in 24-h blood pressure variability. Quantifying the sources and extent of blood pressure variability can be done using natural experimental models and through the evaluation of ecological momentary data. Finally it is very likely that the results of population studies of blood pressure variability and morbidity and mortality risk are inconclusive because the parameters used to assess blood pressure

variability do not reflect the actual nature of blood pressure allostasis.

References

Anderson NB, Lane LD, Muranaka M, Williams RB Jr, Houseworth SJ (1988) Racial differences in blood pressure and forearm vascular responses to the cold face stimulus. Psychosom Med 50:57–63

Asayama K, Fang-Fei W, Hara A, Hansen TW, Li Y, Staessen JA (2015) Prognosis in relation to blood pressure variability; con side of the argument. Hypertension 65:1170–1179. doi:10.1161/HYPERTENSIONAHA.115.04808

Ayman D, Goldshine AD (1940) Blood pressure determinations by patients with essential hypertension: the difference between clinic and home readings before treatment. Am J Med Sci 200:465–474

Bevan AT, Honor AJ, Stott FH (1969) Direct arterial pressure recording in unrestricted man. Clin Sci 36:329–344

Blank SG, Mann SJ, James GD, West JE, Pickering TG (1995) Isolated elevation of diastolic blood pressure: real or artifact? Hypertension 26:383–389

Brondolo E, Karlin W, Alexander K, Bubrow A, Schwartz J (1999) Workday communication and ambulatory blood pressure: implications for the reactivity hypothesis. Psychophysiology 36:86–94

Brown DE, James GD, Nordloh L (1998) Comparison of factors affecting daily variation of blood pressure in Filipino-American and Caucasian nurses in Hawaii. Am J Phys Anthropol 106:373–383

Cochran WG (1977) Sampling techniques. Wiley, New York

Comstock GW (1957) An epidemiological study of blood pressure levels in a biracial community in the southern United States. Am J Hyg 65:271–315

Flores JS (2013) Blood pressure variability: a novel and important risk factor. Can J Cardiol 29:557–563

Gerin W, James GD (2010) Psychosocial determinants of hypertension: laboratory and field models. Blood Press Monit 15:93–99

Gump BB, Polk DE, Kamarck TW, Shiffman S (2001) Partner interactions are associated with reduced blood pressure in the natural environment: ambulatory blood pressure monitoring evidence from a healthy, multiethnic adult sample. Psychosom Med 63:423–433

Hanna JM, Brown DA (1979) Human heat tolerance: biological and cultural adaptations. Yearb Phys Anthropol 22:163–186

Hansen TW, Thijs L, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K et al (2010) Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. Hypertension 55:1049–1057

Hinman AT, Engel BT, Bickford AF (1962) Portable blood pressure recorder: accuracy and preliminary use in evaluating intra-daily variation in pressure. Am Heart J 63:663–668

Ice GH, James GD, Crews DE (2003) Blood pressure variation in the institutionalized elderly. Coll Antropol 27:47–55

James GD (1991) Blood pressure response to the daily stressors of urban environments: methodology, basic concepts, and significance. Yearb Phys Anthropol 34:189–210

James GD (2007) Evaluation of journals, diaries, and indexes of worksite and environmental stress. In: White WH (ed) Clinical hypertension and vascular disease: blood pressure monitoring in cardiovascular medicine and therapeutics, 2nd edn. The Humana Press, Totowa, pp 39–58

James GD (2010) Climate-related morphological variation and physiological adaptations in Homo Sapiens. In: Larsen CS (ed) A companion to biological anthropology. Wiley-Blackwell, Malden, pp 153–166

James GD (2013) Ambulatory blood pressure variation: allostasis and adaptation. Auton Neurosci Basic Clin 177:87–94

James GD, Baker PT (1995) Human population biology and blood pressure: evolutionary and ecological considerations and interpretations of population studies. In: Laragh JH, Brenner BM (eds) Hypertension: pathophysiology, diagnosis and management. Raven Press, Ltd, New York, pp 115–126

James GD, Yee LS, Harshfield GA, Blank S, Pickering TG (1986) The influence of happiness, anger and anxiety on the blood pressure of borderline hypertensives. Psychosom Med 48:502–508

James GD, Yee LS, Harshfield GA, Pickering TG (1988) Sex differences in factors affecting the daily variation of blood pressure. Soc Sci Med 26:1019–1023

James GD, Cates EM, Pickering TG, Laragh JH (1989) Parity and perceived job stress elevate blood pressure in young normotensive working women. Am J Hypertens 2:637–639

James GD, Yee LS, Pickering TG (1990a) Winter-summer differences in the effects of emotion, posture, and place of measurement on blood pressure. Soc Sci Med 31:1213–1217

James GD, Pickering TG, Schlussel YR, Clark LA, Denby L, Pregibon D (1990b) Measures of reproducibility of blood pressure variability measured by noninvasive ambulatory blood pressure monitors. J Ambul Monit 3(2):139–147

James GD, Bovbjerg DH, Hill LA (2015) Daily environmental differences in blood pressure and heart rate variability in healthy premenopausal women. Am J Hum Biol 27:136–138. doi:10.1002/ajhb.22609

Jhalani J, Goyala T, Clemow L, Schwartz JE, Pickering TG, Gerin W (2005) Anxiety and outcome expectations predict the white-coat effect. Blood Press Monit 10:317–319

Kain HK, Hinman AT, Sokolow M (1964) Arterial blood pressure measurements with a portable recorder in hypertensive patients: variability and correlation with 'casual' pressure. Circulation 30:882–892

Kamarck TW, Schiffman SM, Smithline L, Goodie JL, Paty JA, Gnys M, Jong JY (1998) Effects of task strain, social conflict, on ambulatory cardiovascular activity: life consequences of recurring stress in a multiethnic adult sample. Health Psychol 17:17–29

Kamarck TW, Janicki DL, Shiffman S, Polk DE, Muldoon MF, Liebenauer LL, Schwartz JE (2002) Psychosocial demands and ambulatory blood pressure: a field assessment approach. Physiol Behav 77:699–704

Kamarck TW, Schwartz JE, Janiki DL, Schiffman S, Raynor DA (2003) Correspondence between laboratory and ambulatory measures of cardiovascular reactivity: a multilevel modeling approach. Psychophysiology 40:675–683

Kelsey RM, Alpert BS, Patterson SM, Barnard M (2000) Racial differences in hemodynamic responses to environmental thermal stress among adolescents. Circulation 101:2284–2289

Kleinert HD, Harshfield GA, Pickering TG, Devereux RB, Sullivan PA, Marion RM et al (1984) What is the value of home blood pressure measurement in patients with mild hypertension? Hypertension 6:574–578

Levy RL, Hillman CC, Stroud WD, White PD (1944) Transient hypertension: Its significance in terms of later development of sustained hypertension and cardiovascular-renal disease. J Am Med Assoc 126:829–833

Linden W, Gerin W, Davidson K (2003) Cardiovascular reactivity: status quo and a research agenda for the new millennium. Psychosom Med 65:5–8

Longo D, Dorigatti F, Palatini P (2005) Masked hypertension in adults. Blood Press Monit 10:307–310

Mancia G, Parati G, Pomidossi G, Grassi G, Casadei R, Zanchetti A (1987) Alerting reaction and rise in pressure during management by physician and nurse. Hypertension 9:209–215

McEwen BS (1998) Protective and damaging effects of stress mediators. N Engl J Med 338:171–179

Mills PJ, Dimsdale JE, Ziegler MG, Nelesen RA (1995) Racial differences in epinephrine and beta 2-adrenergic receptors. Hypertension 25:88–91

O'Rourke MF (1990) What is blood pressure? Am J Hypertens 3:803–810

Palatini P, Reboldi G, Beilin LJ, Casiglia E, Eguchi K, Imai Y et al (2014) Added predictive value of nighttime blood pressure variability for cardiovascular events and mortality: the Ambulatory Blood Pressure International Study. Hypertension 64:487–493. doi:10.1161/HYPERTENSIONAHA.114.03694

Parati G, Mutti E, Omboni S, Mancia G (1992) How to deal with blood pressure variability. In: Brunner H, Waeber B (eds) Ambulatory blood pressure recording. Raven Press, Ltd, New York, pp 71–99

Parati G, Ochoa JE, Lombardi C, Bilo G (2015) Blood pressure variability: assessment, predictive value, and potential as a therapeutic target. Curr Hypertens Rep 17:23. doi:10.1007/s11906-015-0537-1

Paskalev D, Kircheva A, Krivoshiev S (2005) A centenary of auscultatory blood pressure measurement: a tribute to Nikolai Korotkoff. Kidney Blood Press Res 2:259–263. doi:10.1159/000090084

Pickering TG (1991) Ambulatory monitoring and blood pressure variability. Science Press, London

Pickering TG, Blank SG (1995) Blood pressure measurement and ambulatory pressure monitoring: evaluation of available equipment. In: Laragh JH, Brenner BM (eds) Hypertension: pathophysiology. diagnosis and management, 2nd edn. Raven Press, Ltd., New York, pp 1939–1952

Pickering TG, Gerin W (1990) Cardiovascular reactivity in the laboratory and the role of behavioral factors in hypertension: a critical review. Ann Behav Med 12:3–16

Pierdomenico SD, Cuccurullo F (2011) Prognostic value of white-coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated subjects: an updated meta-analysis. Am J Hypertens 24:52–58

Richardson DW, Honour AJ, Fenton GW, Stott FH, Pickering GW (1964) Variation in pressure throughout the day and night. Clin Sci 26:445–460

Rogers WF, Palmer RS (1944) Transient hypertension as a military risk: its relation to essential hypertension. N Engl J Med 230:39–42

Rowell LB (1986) Human circulation: regulation during physical stress. Oxford University Press, New York

Schwartz JE, Warren K, Pickering TG (1994) Mood, location and physical position as predictors of ambulatory blood pressure and heart rate: application of a multilevel random effects model. Ann Behav Med 16:210–220

Shapiro A, Meyers T, Reier MF, Ferris EB (1954) Comparison of blood pressure response to Veriloid and to the doctor. Psychosom Med 16:478–488

Smith FH (2010) Species, populations, and assimilation in later human evolution. In: Larsen CS (ed) A companion to biological anthropology. Wiley-Blackwell, Malden, pp 357–378

Sokolow M, Werdegar D, Kain HK, Hinman AT (1966) Relationship between level of blood pressure measured casually and by portable recorders and severity of complications in essential hypertension. Circulation 34:279–298

Steegmann AG (1975) Human adaptation to cold. In: Damon A (ed) Physiological anthropology. Oxford University Press, New York, pp 130–166

Sterling P (2004) Principles of allostasis: optimal design, predictive regulation, pathophysiology, and rational therapeutics. In: Schulkin J (ed) Allostasis, homeostasis, and the costs of physiological adaptation. Cambridge University Press, Cambridge, pp 17–64

Sterling P, Eyer J (1988) Allostasis: a new paradigm to explain arousal pathology. In: Fisher S, Reason J (eds) Handbook of life stress. Wiley, New York, pp 629–649

Taylor KS, Heneghan CJ, Stevens RJ, Adams EC, Nunan D, Ward A (2015) Heterogeneity of prognostic studies of 24-hour blood pressure variability:

systematic review and meta-analysis. PLoS ONE 10 (5), e0126375. doi:10.1371/journal.pone.0126375

Treiber FA, Musante L, Braden D, Arensman F, Strong WB, Levy M, Leverett S (1990) Racial differences in hemodynamic responses to the cold face stimulus in children and adults. Psychosom Med 52:286–296

Van Berge-Landry HM, Bovbjerg DH, James GD (2008) The relationship between waking-sleep blood pressure and catecholamine changes in African American and European American women. Blood Press Monit 13:257–262

Young JH, Chang YC, Kim JD, Chretien J, Levine MA, Ruff CB, Wang N, Chakravarti A (2005) Differential susceptibility to hypertension is due to selection during the out-of-Africa expansion. PLoS Genet 1(6), e82

Zanstra YJ, Johnston DW (2011) Cardiovascular reactivity in real life settings: measurement, mechanisms and meaning. Biol Psychol 86:98–105