Update review

An update on: cardiovascular and respiratory changes during sleep in normal and hypertensive subjects

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1. Introduction

In 1969, Bristow, Honour, Pickering and Sleight \[1\] provided us with one of the very first descriptions of the cardiovascular and respiratory changes occurring during sleep in normal and hypertensive subjects. The study was carried out in 19 subjects, eight with normal and ten with high blood pressure, while one subject was suffering from postural hypotension. The design of the study was rather complex: all subjects had to sleep for three consecutive nights in the laboratory. On night one, systemic arterial pressure was non-invasively determined by an automatically inflated sphygmomanometer. On night two, a continuous electroencephalogram recording was performed, whereas, on night three, continuous recording of brachial intraarterial-pressure was obtained through a small polyethylene cannula that was also used to collect arterial blood without disturbing the patient. An i.v. line was also available for injection of various compounds.

By following the steps of such a protocol they were able (a) to identify the different stages of sleep, (b) to monitor noninvasively arterial blood pressure before, during and after nocturnal sleep, (c) to determine baroreflex sensitivity by quantifying the reflex RR interval lengthening which follows a pharmacologically-induced increase in systolic blood pressure (obtained through i.v. injection of angiotensin II or phenylephrine), (d) to perform repeated measurements of cardiac output by the dye dilution method and (e) to analyse blood gases during sleep and wakefulness.

A number of important results were derived out of these measurements: a description of the changes in intra-arterial blood pressure, cardiac output, arterial blood gases and baroreflex sensitivity that occur between wakefulness and sleep in normal and hypertensive subjects; the significant reduction of total peripheral resistance as a major determinant of nocturnal arterial pressure reduction in the absence of significant changes in cardiac output; the identification of changes in baroreflex sensitivity as well as a resetting of the arterial baroreflex during sleep in hypertensives.

The final conclusion was that “there does not appear to be any qualitative difference between subjects with normal and high blood pressures in their hemodynamic adjustment during sleep except that the latter have an almost five-fold reduction in baroreflex sensitivity both awake and asleep” \[1\].

In the present article, we will briefly discuss some particular features of this pioneering work. We will then report on the further developments that have followed these initial observations up to our times.

2. Hemodynamic changes during sleep

That sleep is characterised by signs of parasympathetic predominance had been shown by the same group of investigators only a few months before, when Smyth et al. \[2\] reported the occurrence of a nocturnal reduction of heart rate and arterial pressure either in the absence of significant changes or in the presence of an increase in baroreflex sensitivity. In the present study \[1\] the same authors found that the degree of fall of pressure was roughly proportional to the waking pressure and that the lowest pressure values were observed during REM sleep.

During sleep, normal subjects did not exhibit any significant change in cardiac output, whereas a small and not significant reduction was observed in hypertensive subjects. The nocturnal reduction in arterial pressure was therefore the result of a decrease in total peripheral resistance, as computed by determining cardiac output and
mean arterial pressure at the same time. Of interest was the observation that in two normal subjects, in whom cardiac output measurements were performed also during REM sleep, a distinct increase could be observed.

The above findings were later confirmed by Kawano et al. [3] and by Casiglia et al. [4] in hypertensive patients. The latter authors reported that the nocturnal reduction in arterial pressure and heart rate was associated with a significant increase in forearm blood flow in normotensive subjects, whereas in hypertensive patients a slight decrease was detectable. Peripheral resistance measured in the legs was greater than in the forearm both during sleep and wakefulness.

3. Heart rate and arterial pressure variability during wakefulness and sleep

By determining arterial blood pressure every 5 min on the first and second night and continuously during the third night, the authors [1] were able to provide important information on arterial pressure and heart rate variability during sleep. Unfortunately, at that time, beat-to-beat variability of cardiovascular parameters was not taken into consideration and the analysis was restricted to averaged individual changes of heart rate and arterial pressure. Heart rate fell during sleep in 14 of the 19 subjects with no significant difference between normotensive and hypertensive subjects. There was also a tendency to faster waking heart rates in the latter group although the degree of nocturnal reduction appeared unrelated with heart rate values observed before sleep. No constant relationship was detectable between the degree of fall in arterial pressure and the degree of bradycardia during sleep.

The clinical and historical relevance of these observations are clearly evident, if we consider the development of ambulatory blood pressure monitoring techniques over the last 20 years and the consistent number of studies which, over the same time period, have specifically addressed the features of 24-h blood pressure variability and assessed its clinical and pathophysiological relevance [5].

Indeed, a time-honoured observation is that blood pressure, although being continuously perturbed by external factors, invariably displays a tendency to come back to a reference level. This fact has since long suggested that attention has to be paid not only to the average blood pressure value but also to the fluctuations of blood pressure around its average level. Such an appraisal appears necessary in order to fully understand how cardiovascular regulation operates and whether a derangement has occurred [5].

Among the various components which characterise 24-h blood pressure and heart rate variability, the attention of most investigators has focused on the blood pressure and heart rate reductions that occur on going from daytime wakefulness to night time sleep. These changes are commonly observed in normal subjects but may be impaired in a number of pathological conditions. The first detailed observations on the large variability that characterises blood pressure and heart rate during 24 h in humans as well as on their marked reductions during night sleep have been obtained only after the same group at Oxford introduced a technique for continuous intra-arterial blood pressure monitoring in ambulant individuals [6,7]. The extensive application of this technique, carried out by only a few experienced groups in the world given its invasiveness and complexity, has provided unequivocal evidence [6–12] that blood pressure continuously and markedly fluctuates under daily life conditions in normal individuals, that heart rate behaves in a similar fashion and that the degree of these fluctuations varies in different clinical conditions. For example, when blood pressure variability was quantified by the standard deviation of its average 24-h value, the degree of blood pressure fluctuations was found to be greater in hypertensive than in normotensive subjects, and in elderly as compared to young individuals [8]. Conversely, when quantified as the standard deviation of their average value, heart rate fluctuations were found to be reduced either in elderly subjects or in diseases such as diabetes mellitus, congestive heart failure, myocardial infarction and, more in general, autonomic failure [12]. When beat-to-beat blood pressure and heart rate values were averaged over 30-min periods, they displayed, both in normotensive and in hypertensive individuals, a significant and parallel reduction during night sleep. This reduction was paralleled by a concomitant reduction of the degree of short-term blood pressure and heart rate variability, as quantified by the standard deviation of half-hour average blood pressure and heart rate values. This observation was taken to indicate that over these time intervals both the heart and peripheral resistance undergo a parallel modulation between day and night by regulatory influences, which are likely to originate within the central nervous system, that act on cardiac and vascular targets in a similar qualitative and quantitative fashion [8,11] (Fig. 1).

4. Blood pressure and heart rate variability: historical and methodological aspects

Although providing a comprehensive description of the signal dispersion around the mean, the standard deviation offers no information on the patterns of rhythmical and non-rhythmical fluctuations that characterise the variability of the signal under study over time. This has led to the development of other methods for the detailed quantification of cardiovascular signal variability, among which spectral analysis is the most popular one. This approach allows the overall variance of a signal to be split into its various frequency components, making use of either the Fast Fourier Transform (FFT) or the autoregressive modelling (AR) method [12–14]. The FFT spectrum is derived
from all data present in the recorded signal, regardless of whether its various frequency components appear as spectral peaks (reflecting regular oscillations) or as more irregular fluctuations, which do not result into clearly identifiable peaks of the spectrum (see below). In contrast, with the AR approach the raw data are used to identify a best fitting model from which the final spectrum, consisting of the direct current (DC) component and a variable number of peaks, is derived. It should be emphasised that these methods yield similar results when FFT is used with some degree of signal smoothing and the AR method is applied with a sufficiently high model order [12–15]. Yet, current use of the FFT and AR approach has led the investigators to proceed in somewhat different directions. With the AR method, attention has been largely focused on spectral components that correspond to regular oscillations at a frequency greater than 0.025 Hz (i.e. relatively fast oscillations with a period shorter than 30 s) and that have been proposed, particularly when expressed in normalised units [13], as indices of autonomic modulation of sinus node and vascular tone. By doing so it has been possible to quantify this modulation either in controlled laboratory conditions, when a stationary signal is employed, or in daily life, when the amplitude and frequency modulations of the above components are quantified by time varying spectral analysis techniques [11,12]. With the FFT method, attention could be directed not only towards fast [15,16] but also to slower components of blood pressure and heart rate variability and indeed the ability of this method to include the whole blood pressure or heart rate recording in a single spectrum has allowed the spectral components to be assessed over a broader range of frequency. This broadband approach [17–19] has led to the important finding that 24-h blood pressure and heart rate spectra are characterised by a $l/f$ trend, i.e. that the amplitude of both fluctuations increases progressively with the reduction in their frequency, which implies that total 24-h blood pressure and heart rate spectral powers depend more on lower than on higher frequency components. The $l/f$ trend of blood pressure and heart rate spectra has also been shown to undergo marked changes following surgical or chemical interference with autonomic cardiovascular influences and to be different in different diseases and conditions [17–20].

Other methods have been proposed to analyse blood pressure and heart rate variability by taking into account the complexity of these signals, their intrinsic non-linearity with the aim of coupling the information obtained from the biological signal with the information derived from physiological or mathematical models. Examples are the approaches that consider the relationship between two or more cardiovascular signals physiologically related to each other. Some of these multivariate models are based on the evaluation of (a) the gain and phase relationship between respiration and either blood pressure or heart rate changes by transfer function analysis [21], (b) the relationship

![Fig. 1. Hour profile of mean arterial pressure (MAP) and heart rate (HR) and of their short-term variabilities (within half hour SD). Data are shown as average half hour values±SD for 89 hypertensive subjects in whom ambulatory blood pressure was monitored intra-arterially for 24 h (Oxford technique) (from Ref. [8] by permission).](image-url)
between specific components of blood pressure and pulse interval fluctuations in the time domain (sequence technique [22–24]) or in the frequency domain [25–27] to obtain a dynamic assessment of ‘spontaneous’ baroreflex sensitivity (see below), and (c) the relationship between blood pressure and pulse interval in a closed-loop fashion by either autoregressive moving average techniques (ARMA models) or, more simply, through Fourier-based transfer function techniques [14,28].

In a number of instances, these approaches have been also employed in the analysis of long-lasting blood pressure or heart rate recordings obtained in ambulant subjects. This approach has allowed us to study autonomic cardiovascular influences out of an artificial laboratory setting and in daily life conditions, and in particular, to focus on neural modulation during wakefulness and sleep without the need of any external intervention as it occurred in Bristow’s experiments [24,26,27].

5. Insights into neural cardiovascular regulation from blood pressure and heart rate variability analysis

Autonomic cardiovascular regulation in humans is usually investigated through the quantification of blood pressure and/or heart rate responses to laboratory testing which interfere in different ways with the central and reflex control of the circulation [29]. However, although providing us with important information on autonomic cardiovascular control in health and disease, this approach is affected by several limitations. In particular, these laboratory methods can hardly be used to investigate the influences involved in the dynamic 24-h autonomic control of the cardiovascular system, and in particular of day and night periods, as testified by the difficulties encountered by Bristow and co-workers in assessing baroreflex sensitivity during sleep [1]. Some of these limitations have been overcome by the analysis of spontaneous fluctuations in cardiovascular signals which appear to offer, in several instances, a deeper insight into normal and deranged mechanisms of autonomic cardiovascular control in a dynamic fashion.

Between-subject differences in blood pressure or heart rate variability can be related to differences in the neural influences responsible for cardiovascular regulation [3,11,13]. These factors include both central and reflex influences, among which the arterial baroreflex plays a fundamental role. Examples of central influences are the hypotension and bradycardia due to the transition from wakefulness to sleep and the pressor and tachycardic responses to physical exercise and to emotional stress [5]. Among the neural influences involved in regulating blood pressure and heart rate fluctuations, evidence is available that the arterial baroreflex exerts an important buffering action on spontaneous blood pressure variability in conscious animals, its inactivation by section of the carotid sinus and aortic nerves being followed by a striking increase in the magnitude of the blood pressure fluctuations [30–32]. An increased variability in blood pressure following anaesthesia or section of the carotid sinus nerves has been reported also in human subjects undergoing neck surgery for a variety of diseases [29]. Finally evidence of the buffering effect of the arterial baroreflex on blood pressure variability has been obtained by demonstrating that, in humans under 24-h intra-arterial blood pressure monitoring, the baroreflex sensitivity as measured by a variety of techniques, is inversely related to the 24-h blood pressure standard deviation [27,33] (Fig. 2).

Evidence is also available that the baroreflex sensitivity enhances heart rate variability. Such evidence comes from observation in sinoaortic denervated animals, that display a reduced degree of heart rate fluctuations compared to intact animals [30,31]. It also comes from the analysis of 24-h blood pressure and heart rate recordings carried out in humans, which has shown that between subjects differences in heart rate variability are related to differences in their baroreflex sensitivity as assessed either by traditional or by more innovative methods [27,33]. Indeed, in any given subject changes in baroreflex sensitivity throughout the 24 h are inversely related to changes in blood pressure variability but directly related to changes in heart rate variability. Thus, the stabilising effect of baroreflex mechanisms on blood pressure may be effected through the ability of baroreceptors to modulate neural cardiac drive in a way that compensates, through changes in cardiac output, the blood pressure changes [34]. The finding that in rats, an atropine-induced reduction in heart rate variability is accompanied by an increase in blood pressure variability [35], further supports this interpretation. However, in other animals and in man [5] the stabilising blood pressure mechanisms appear to be more complex and also involve the influence of baroreflex on vascular resistance as indicated by the fact that blood pressure variability is not increased by reducing heart rate variability by atropine or by abolishing heart rate variations through cardiac pacing [5,36].

The role of autonomic influences in the regulation of blood pressure and heart rate variability, and in particular of their changes between the day and night, has also been addressed by spectral analysis of blood pressure and heart rate variations. A number of studies carried out both in the experimental animals and in humans have shown that heart rate fluctuations at frequencies above 0.15 Hz (i.e. in the high frequency respiration related band) are primarily due to modulation of the sinus node activity by vagal cardiac influences associated with the respiratory cycle although mechanical modulation of sinus rate by atrial stretch seems also to be to some degree involved [12–14,37]. On the other hand, blood pressure fluctuations in the HF range are caused by mechanical effects of respiration and no direct vagal modulation of vasomotor tone appears to be involved [5,14,15,38]. Heart rate fluctuations at frequencies above
0.04 but below 0.15 Hz are mainly mediated by sympathetic influences although parasympathetic ones and, to a lesser extent, non neural influences appear to be also involved [12–14,38–40]. This explains some of the controversies regarding the use of the LF component as an index of sympathetic modulation. When blood pressure is considered, spectral power below 0.15 Hz predominantly reflects fluctuations in vasomotor tone and systemic vascular resistance [12,14,16,39]. At frequencies between 0.025 and 0.04 Hz, this vascular modulation may be dependent on the renin–angiotensin system, endothelial factors, and local influences related to thermoregulation although conclusive evidence that this is the case has never been provided [14]. In contrast, at frequencies between 0.04 and 0.15 Hz the blood pressure fluctuations have repeatedly been interpreted as a marker of sympathetic vasomotor tone [10,11,13,14,39]. When spectral analysis of blood pressure and heart rate changes has been dynamically applied to continuous ambulatory 24-h recordings according to time-varying spectral methods, a significant reduction during the night time of blood pressure powers around 0.1 Hz and a concomitant significant increase in HF heart rate powers has been reported [5,10,13,15,16]. This was done by applying, in a sequential fashion, FFT or AR modelling techniques to 24-h intra-arterial ambulatory blood pressure recordings, after subdividing the signal into consecutive 256 or 512 beat segments and removing those segments containing non-stationarities. In both normotensive and mild essential hypertensive patients, the powers of the abovementioned components underwent marked day and night changes. In particular, a marked reduction at night in the powers of systolic and diastolic blood pressure fluctuations near 0.1 Hz and an increase in HF pulse interval powers were observed. The reduction in power of 0.1 Hz blood pressure spectral component was similarly evident in normotensive and mild hypertensive patients [5,10,15,16], while the nocturnal increase in HF of heart rate or pulse interval was less evident in hypertensive as compared to normotensive individuals. (Fig. 3) The diurnal changes in these spectral components may reflect the reported decrease in sympathetic and increase in parasympathetic activity, which occur during night sleep. These data, in spite of the abovementioned controversy in the interpretation of blood pressure and heart rate spectral components, seem therefore to emphasise the ability of blood pressure spectral powers around 1 Hz to reflect central or reflex-
induced changes in sympathetic modulation of circulation, and the ability of HF heart rate powers to represent a quantitative marker of parasympathetic cardiac modulation.

Quantification of slower blood pressure and heart rate fluctuations (i.e. fluctuations <0.025 Hz) provided by broad-band spectral analysis has recently raised much interest because of the information it may also offer on mechanisms controlling the cardiovascular system over 24 h. An example is the alteration of these fluctuations observed in conscious cats after baroreceptor denervation by section of the sino-aortic nerves [31]. Baroreceptor denervation was responsible for changes in all the spectral components of systolic blood pressure and pulse interval, indicating that baroreflex mechanisms are involved in the genesis not only of the faster (frequencies >0.025 Hz), but also of the slower components of blood pressure and pulse interval variability, i.e. those with periods up to 1.5 h. Interestingly, while after sino-aortic denervation, pulse interval power was reduced at all frequencies, blood pressure power showed much more complex changes. Namely, a significant reduction in the power of spectral components from 0.2 to 0.007 Hz and below 0.0003 Hz; an increase in the power of spectral components from 0.05 to 0.0005 Hz; almost no change in the power of spectral components at the respiratory frequency (around 0.3 Hz). A change in the slope of the f/f trend of blood pressure spectrum was also observed. Thus, baroreflex mechanisms appear to be substantially involved in this phenomenon, although they seem to play a different role on blood pressure fluctuations in relation to the different frequency bands. It has a negligible effect on respiratory blood pressure fluctuations; it buffers blood pressure fluctuations between 0.05 and 0.0005 Hz, but it exerts a pro-oscillatory role on fluctuations around 0.1 Hz and at very low frequencies. This paradoxical pro-oscillatory role of the baroreflex is in agreement with the hypothesis of Wesseling et al. that the spectral peak observed at 0.1 Hz might also be due to a resonance in the baroreflex loop [41–43].

6. Dynamic assessment of baroreflex sensitivity through analysis of blood pressure and heart rate variability

Because the arterial baroreflex is mainly involved in the modulation of both spontaneous blood pressure and heart rate variability, joint analysis of these variability phenomena has been proposed as a way to obtain information on
baroreflex function in daily life [14,34]. This can be achieved both in the time and in the frequency domain. By computer analysis of continuous blood pressure and heart rate recordings in the time domain it is possible [22–24,27] to identify sequences of four or more contiguous heart beats characterised by progressive and linearly related increases in systolic blood pressure and pulse interval (hypertension/bradycardia sequences, +PI/+SBP) or by progressive and linearly related reductions in systolic blood pressure and pulse interval (hypotension/tachycardia sequences, −PI/−SBP). As done with the laboratory technique based on injection of vasoactive drugs, the slope of the regression line between changes in systolic blood pressure and subsequent changes in pulse interval can be taken as an index of the sensitivity of baroreflex control of the heart. It is important to recall that in cats these sequences have been shown to almost completely disappear following surgical baroreceptor denervation, which demonstrates their dependence on the functional integrity of arterial baroreflex [23]. At variance from the results obtained by Bristow et al., baroreflex sensitivity assessed by this ‘spontaneous’ method displays a marked day–night difference, namely, a marked increase from wakefulness to sleep. Moreover, in essential hypertensive patients, the number of 24-h sequences has been found to be markedly reduced whereas the sequence slope has been shown to be markedly lower than in normotensive individuals, with an alteration of its day–night modulation [5,24]. Similar alterations in baroreflex sensitivity have been observed in aged individuals under 24-h intraarterial blood pressure monitoring when compared to controls [27] (Fig. 4).

These observations have extended over a larger database, and in the absence of any external interference with subjects’ autonomic modulation, offer a more detailed quantification of baroreflex heart rate modulation in more physiological conditions than the pioneering observations made by Bristow and co-workers through the i.v. injection of vasoactive drugs during both wakefulness and sleep.

Spontaneous baroreflex sensitivity can be assessed also in the frequency domain by computing the modulus of the cross-spectrum or the squared ratio between blood pressure and heart rate powers in the frequency regions where these powers are coherent, i.e. around 0.1 Hz and at the respiratory frequency [25–27]. As in the case for the sequence slope, this spectral index of baroreflex sensitivity displays a clear-cut 24-h modulation in normotensive individuals, with a marked increase during night sleep, its magnitude and day–night modulation being markedly reduced in hypertensives and elderly individuals with patterns very similar to those seen with the time domain method [26,27,44].

The above observations allow the conclusion that joint computer analysis of blood pressure and pulse interval variability (either in the time or in the frequency domain) provides an innovative and sensitive tool to quantify the sensitivity of the baroreceptor–heart rate reflex and to obtain this quantification also in daily-life conditions [14]. The progress inherent to this approach as compared to the method employed by Bristow and co-workers is substantial because of the avoidance of the limited number of measures, the artificial external stimuli and the abnormal environmental conditions typical of traditional laboratory methods.

Fig. 4. Hour profile of spontaneous baroreflex sensitivity. Data are separately shown as the average slope of hypertension/bradycardia sequences (+/+), hypotension/tachycardia sequences (−/−) and as average alpha coefficient (squared ratio between pulse interval and SBP powers around 0.1 Hz) values for each hour of a 24-h ambulatory intra-arterial recording. Data from eight young and eight elderly subjects are separately shown (from Ref. [27], by permission).
7. Intra-arterial and non-invasive finger blood pressure monitoring in the assessment of autonomic cardiovascular regulation

Proper computer analysis of arterial pressure variability requires beat-to-beat blood pressure signals of good quality, and this has been possible for years only by means of intra-arterial recordings [5,10,45]. Recently, however, the development of continuous finger blood pressure recorders has offered a calibrated non-invasive alternative to the intra-arterial approach. This method [46,47] was shown to provide reliable blood pressure values not only at rest but also during a number of laboratory tests inducing pressor or depressor responses. The analysis of finger pressure recordings offers a reliable quantification of the standard deviation of mean arterial pressure, although this is less so for systolic blood pressure, the variability of which is significantly amplified at the finger level because of pulse wave reflection and distortion. Recent studies [48] have focused on whether this approach is also adequate for more complex time and frequency domain analysis of blood pressure variability. In a group of mild or moderate untreated essential hypertensive patients, spectral analysis by FFT was performed on finger (Finapres TNO) and intra-arterial blood pressure recordings simultaneously obtained for 30 min in a supine resting condition. Spectral powers of blood pressure and pulse interval were integrated over three frequency bands, defined as low frequency (LF, 0.025–0.07 Hz), mid frequency (MF, 0.07–0.14 Hz) and high frequency (HF, 0.14–0.35 Hz). The standard deviations of the average blood pressures of the whole recording period were slightly higher when assessed by finger than by intra-arterial recording, the difference being statistically significant for systolic blood pressure only. The spectral powers of pulse interval were similar for finger and intra-arterial recordings at all frequencies, this being the case also for the spectral powers and mean blood pressure. On the contrary, the spectral powers of systolic blood pressure located in the lower portion of the spectrum (MF and LF powers, and slower fluctuations down to a frequency of 0.001 Hz) were overestimated by analysis of finger blood pressure. In spite of this, the coherence (i.e. a measure of linear relationship in the frequency domain) between intra-arterial and finger blood pressure or pulse interval powers was greater than 0.5 at all frequencies, and was highest at approximately 0.1 Hz (Fig. 5). Based on these data we can conclude that analysis of finger blood pressure recordings should in general be regarded as acceptably accurate in estimating blood pressure variability even on the background of the reported overestimation of systolic blood pressure powers. Moreover, as such an overestimation appears to be relatively constant with time, this noninvasive approach seems particularly suitable to monitor changes in baroreflex sensitivity with time.

Finally, when finger blood pressure recordings were used to non-invasively assess the sensitivity of spontaneous baroreflex control of heart rate through the sequence technique, the quantification of both the number of sequences and their slope so obtained was superimposable to that derived from the analysis of intra-arterial recordings. Similar results were obtained when considering noninvasive and intra-arterial 24-h ambulatory blood pressure tracings simultaneously recorded through a Portapres (the portable version of the Finapres device) [49] and an Oxford system. The Portapres devices, which is equipped

![Fig. 5. Histograms refer to the number of three-beat sequences characterised by progressive increase (+PI/+SBP) or progressive decrease (−PI/−SBP) in pulse interval (Pi) and systolic blood pressure (SBP) (top panel), their mean regression coefficients (mid panel), and variations coefficients of these regression coefficients (bottom panels). Data are shown as means±SE for 14 subjects. Open bars refer to data obtained by analysis of intra-arterial recordings, while hatched bars refer to data obtained by analysis of finger blood pressure recordings by a Finapres device (from Ref. [48], by permission).](image-url)
with two finger cuffs, shifting automatically from one to the other at pre-set time intervals, and with a hydrostatic height correction system, was previously shown to satisfactorily reproduce simultaneous ambulatory intra-arterial blood pressure recordings. The results obtained in 20 subjects by comparing 24-h blood pressure variability data non-invasively obtained with this device with data simultaneously derived from an ambulatory intra-arterial recording have largely confirmed the data obtained in resting conditions. Namely that pulse interval, diastolic and mean blood pressure powers are similar when derived from finger and intra-arterial signals, while systolic blood pressure powers, in particular very low frequency (with periods up to a few hours) and LF powers, are overestimated by analysis of finger blood pressure recordings. Even in these instances, however, such an overestimation is relatively constant with time and does not seem to prevent a reliable tracking of blood pressure changes in different clinical and experimental conditions [50,51].

These data seem thus to support computer analysis of 24-h ambulatory non-invasive finger blood pressure recordings as a new powerful tool to extend our knowledge on the mechanisms involved in dynamical cardiovascular regulation.

8. Baroreflex sensitivity, respiratory activity and sleep stages

One of the most relevant aspects of the paper by Bristow and co-workers al. [1], was the analysis of baroreflex sensitivity in relation to the subject’s clinical condition and to the specific sleep stage. The authors confirmed that a reduction in baroreflex sensitivity characterised hypertensive subjects. The mean waking sensitivity was 14.8±9.2 ms/mmHg in control and 3.0±0.9 ms/mmHg in hypertensive subjects. The lowest value 0.3 ms/mmHg was observed in the patient with postural hypotension. Changes in baroreflex function were also observed ongoing from wakefulness to sleep. These changes consisted of both a change in sensitivity (steeper slope, although only in a minority of subjects) as well as of a resetting (moving the intercept of the regression line between pulse interval and systolic blood pressure to the left on the horizontal axis were SBP values are displayed). Different subjects presented different patterns of change in baroreflex function, although resetting of the reflex was the most common observation. However it was evident that the degree of resetting in the two groups was significantly different being greater in normal than in hypertensive subjects. The main conclusion was that the hemodynamic differences between the two groups were quantitative rather than qualitative indicating that hypertensive subjects differ little from others in their circulatory adjustment to sleep except that they are still hypertensive and their baroreflex sensitivity usually remains reduced. This concept is, in our opinion, of particular importance and has contributed to the present understanding that essential hypertension is characterised by substantial alterations of neural and nonneural mechanisms involved in cardiovascular regulation.

The relationship between the increase in baroreflex sensitivity during sleep and extent of nocturnal reduction in arterial pressure which was initially reported by Bristow et al. was recently reassessed by Vaile et al. [52] who analysed spontaneous baroreflex sensitivity of two groups of hypertensive patients classified as dippers and non-dippers in relation to the amount of nocturnal reduction in arterial pressure. These authors reported that baroreflex sensitivity did not differ significantly between dippers and nondippers and that changes in baroreflex sensitivity were not likely to account for the abnormal pattern of dipping observed in a minority of hypertensive patients. Moreover, changes in baroreflex sensitivity did not seem to contribute to the nocturnal fall of arterial pressure.

A peculiar condition where alterations of the physiological day and night modulation in blood pressure and heart rate as well as in autonomic cardiovascular control can occur in association with alterations in breathing patterns is the obstructive sleep apnoea syndrome (OSAS). This syndrome is increasingly drawing the attention of clinicians and investigators [53–56] because of the evidence provided in the last 10 years that OSAS patients are at a higher risk for systemic diurnal and nocturnal hypertension, nocturnal cardiac arrhythmias, pulmonary hypertension, congestive heart failure, myocardial infarction and stroke [53]. In particular, the higher prevalence of arterial hypertension in OSAS patients (about 50%) has stimulated a number of studies aimed at evaluating the mechanisms responsible for this phenomenon [56]. Among them, a key role seems to be exerted by chemoreflex stimulation, induced by repeated hypoxia, and by the frequent arousals and the resulting sleep fragmentation associated with the apenic episodes, which may all contribute to the enhanced sympathetic activity shown in OSAS patients both during wakefulness and during sleep [57]. Also an impairment of the arterial baroreflex control of circulation may be involved in the genesis of the sympathetic activation typical of OSAS [58]. However, information on baroreflex cardiovascular control in these patients has been until now obtained mostly by means of laboratory stimulations delivered during wakefulness, while scanty information is available on the actual effectiveness of the arterial baroreflex at night in patients with obstructive sleep apnoea. This issue is of crucial importance in the understanding of the mechanisms responsible for the cardiovascular effects of OSAS. At variance from normal subjects, in whom night sleep is characterised by a reduction in blood pressure, heart rate and sympathetic activity and by an increase in baroreflex sensitivity [5,8,10,24], in OSAS patients the reported nocturnal increase in sympathetic activity is often associated with a
blunted reduction in night-time blood pressure and heart rate values [59]. Whether an impaired baroreflex modulation at night, which has been shown in animal studies to predominately influence night-time hemodynamics [60], also contributes to the autonomic and hemodynamic changes observed at night in patients with repeated apneic episodes has never been systematically investigated so far in humans. Only recently, computer analysis of spontaneous fluctuations in blood pressure and heart rate aimed at assessing spontaneous baroreflex sensitivity has been applied to OSAS patients who were found normotensive or borderline hypertensive during wakefulness [61].

Finger blood pressure was monitored beat-by-beat noninvasively (Finapres) at night during polysomnography. Periods of wakefulness and sleep were identified based on EEG recordings. Baroreflex sensitivity was assessed by the sequence technique. In comparison to age-related control subjects, OSAS patients presented during sleep a significant reduction in the number of pooled +RR/+SBP and −RR/−SBP sequences per hour. Moreover, average baroreflex sensitivity during sleep periods was 7.04±0.8 ms/mmHg in OSAS and 10.05±2.1 ms/mmHg in controls. Both the pooled number of sequences and baroreflex sensitivity values of OSAS patients were significantly less than the corresponding night values of control. Of interest was the finding that in OSAS patients, at variance from controls, baroreflex sensitivity during sleep did not show any increase as compared to its values during wakefulness. These data provide evidence that baroreflex sensitivity is depressed in severe OSAS and suggest that in these patients, baroreflex dysfunction and not only chemoreceptor stimulation by hypoxia may be involved in the sympathetic activation which occurs during sleep. Such a dysfunction may contribute to the higher rate of cardiovascular morbidity and mortality reported in these patients.

Thus, the methodology originally proposed by Bristow's and co-workers [1], consisting of nocturnal measurements of blood pressure, heart rate and baroreflex sensitivity as well as of quantification of blood gases concentration, has proven particularly suitable to evaluate autonomic derangement in OSAS patients.

### 9. Changes in blood pressure and heart rate between wakefulness and sleep and cardiovascular prognosis

Bristow and co-workers [1] have provided clear evidence of the occurrence of a blood pressure fall at night both in normotensive and in hypertensive subjects, as later confirmed by studies based on ambulatory blood pressure monitoring techniques [8]. Such a nocturnal blood pressure fall may not occur in all subjects, however. Evidence has been provided [62] that hypertensive subjects in whom the nocturnal blood pressure fall appears to be blunted (non-dipper subjects), may develop a higher degree of target organ damage and/or more frequent cardiovascular events, this being in particular the case for female subjects [63]. The negative prognostic value of a non-dipper condition has not been confirmed, however, by a controlled longitudinal study such as the SAMPLE study [64] in which the difference between daytime and night-time blood pressure was reported to be poorly reproducible (displaying a 40% variability between duplicated ambulatory blood pressure recordings). Moreover, the reduction in left ventricular hypertrophy induced by a one-year anti-hypertensive treatment was significantly related to treatment induced changes in 24 h, daytime or night-time average blood pressure values, but it did not display any significant relation to the blood pressure difference between day and night. The lack of nocturnal blood pressure fall, on the other hand, may have clinical relevance when alterations of the day–night blood pressure profile are reproducible and well detectable. Such alterations may characterise patients in specific pathological conditions, such as Cushing disease, primary or secondary autonomic failure, cardiac or renal transplantation associated with cyclosporine treatment, obstructive sleep apnea syndrome, etc. [5,59].

In conclusions, the original intuition of Bristow and co-workers [1] related to the clinical relevance of a careful and repeated assessment of blood pressure changes between day and night has found and finds support by a growing number of observations in a variety of cardiovascular diseases. The suggestion that the combined assessment of cardiac output, blood pressure, heart rate, baroreflex sensitivity and blood gases concentration during sleep might provide a large body of clinically relevant information, has been widely confirmed by later studies carried out with more sophisticated techniques. Nowadays, a deeper insight into cardiovascular control at night in health and disease might be offered by techniques able to provide a multivariate assessment of the simultaneous changes in blood pressure, heart rate and respiratory activity that occur on going from wakefulness to sleep. This is particularly the case when these techniques may help to quantify, through complex mathematical models of circulation, the features of the reciprocal interactions between blood pressure, heart rate and respiration that physiologically occur in a closed loop condition [14], i.e. in a condition where each of these variables affects the remaining two and is simultaneously affected by them.

### References


