Clinical Conference

Ambulatory Blood Pressure Monitoring Use in Hypertension Research and Clinical Practice

Principal Discussans

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In his article on blood pressure measurement by sphygmomanometry published in 1897 in the Gazzetta Medica di Torino,1 Riva Rocci wrote the following: "Blood pressure is acted upon, in a temporary but pronounced fashion, by the state of 'psychic' excitation of the patient. It is enough that the patient is spoken to, that he is invited to read, that he is even looked at suddenly, or that a sudden and even far noise strikes him (e.g., a carriage passing by in the outside street) that his blood pressure raises, and not at all to the same extent in all patients. This emotional reaction may be useful in psychiatry, but in other disciplines these blood pressure rises represent an inconvenience, and it is therefore necessary for the patient to be put in an environment as quiet as possible. Furthermore, because even the application of the instrument causes a temporary blood pressure rise, it is necessary to take not only one but several consecutive blood pressures spaced by 3- or 5-minute intervals until a constant value is measured. This value, however, is not always the minimal value... It should not be necessary to add that it will not be proper to compare data unless obtained in identical conditions or environment, position, time of day, distance from meals, wakefulness, etc. This remark is certainly superfluous for the investigators, but it may be useful to practitioners whose hurry may in this case result in a waste rather than a gain of time."

Thus, knowledge that emotional behaviors can increase blood pressure and that this affects the values taken by the physician goes back to almost the time blood pressure was first measured in an indirect, simple fashion. This is also the case for the current concepts that blood pressure is subjected to pronounced variations, that these variations are different in different subjects, and that for these reasons the prevailing blood pressure of a given individual is not easily reflected by clinical blood pressure values.

However, the increasing interest in blood pressure variability that has occurred in the past 20 years depends on technical progress made in the 1960s, i.e., on the description of methods that allow ambulatory blood pressure to be measured noninvasively or invasively for 24 hours and thus permit day and night blood pressure variations to be observed and quantified.2-4 This article will review the information that has been derived from this progress using data from our group in Milan and will focus on four issues: 1) the effects of emotional behavior on blood pressure and their implications for the diagnosis of hypertension, 2) the mechanisms responsible for the magnitude of 24-hour blood pressure variability, 3) the alterations in blood pressure variability induced by hypertension and aging, and 4) the relevance of this phenomenon for the prognosis of the hypertensive patient and the evaluation of antihypertensive treatment. Discussion of these issues will be followed by a few considerations on some ongoing studies on ambulatory blood pressure monitoring and by an indication of which of the important issues raised by the increasing knowledge in blood pressure variability may receive an answer in the near future.

Behavior and Blood Pressure

Twenty-four-hour intra-arterial and noninvasive blood pressure monitoring in ambulatory conditions has offered a thorough description of the effects of behavior on blood pressure.5 The major contribution has been made with intra-arterial monitoring, because these effects usually have such a dynamic profile as to be only approximately reflected by the limited number of blood pressure values (e.g., one every 15 minutes) obtained by the noninvasive approach. It is thus known that some behaviors (such as eating, drinking, or mental work when performed in the absence of stress) do not affect blood pressure substantially; that nighttime sleep, daytime sleep, and postprandial digestion cause hypotension; and that a variety of other daytime behaviors may raise blood pressure.6 An example is emotion, which can cause a slight blood pressure rise when mild and a pronounced and prolonged pressor response when more marked and long-lasting. This has clinical implications, because sphygmomanometric blood pressure measurements by a physician are emotional for the patient, leading to a blood pressure elevation.7-8 This was shown in 88 hospitalized patients whose blood pressure was checked with sphygmomanometry by an unfamiliar physician while 24-hour or 48-hour ambulatory blood pressure was measured intra-arterially.5-9 In
pressure (MAP) and heart rate (HR) in 88 subjects during a visit by a physician in charge of assessing blood pressure with a sphygmomanometer. In each subject, blood pressure was measured intra-arterially for 24 or 48 hours by the Oxford method. Intra-arterial blood pressure and heart rate values observed during the physician’s visit were compared with those observed 4 minutes before the visit. Data are shown for individual subjects (points) and as average changes for the group as a whole (horizontal bars) (redrawn from Mancia and Parati10 with permission).

86 of the 88 patients, the appearance of the physician caused an increase in the patient’s intra-arterial blood pressure and heart rate, which peaked within 4 minutes. The magnitude of the pressor response was large in some patients and small in others, with a striking between-subject difference (Figure 1). No relation was found between the response and the patient’s age (16–67 years), baseline mean blood pressure (93–167 mm Hg), sex, sex difference from the physician, and pressor or tachycardic responses to laboratory stressors.59 Thus, behavioral dependence of blood pressure is responsible for its overestimation by the traditional blood pressure-assessing procedure. Although reaching hypertensive values in only a subset of individuals (the “white coat” hypertensive patients, see Reference 12), the overestimation is a common phenomenon. It is also a phenomenon that cannot be corrected because of its wide between-subject range and the fact that it cannot be predicted by clinical information and laboratory tests.

The clinical relevance of the white coat phenomenon will be further discussed below. It should be mentioned here, however, that the emotional component of the sphygmomanometric blood pressure measurements can be minimized in various ways. In the patients mentioned above, the blood pressure increase observed at the 10th or 15th minute of the physician’s visit was approximately 50% of the peak response. In addition, when blood pressure was measured in some patients by a nurse, the peak response was less, and at the 10th minute, the blood pressure value was similar to the value before or after the nurse’s visit (Figure 2). Finally, it is known that the pressor response is usually less when blood pressure is self-measured at home14 and absent when automatic or semiautomatic devices are used (Figure 3).13 The pressor response can be attenuated even when blood pressure is measured by a physician, provided the subject is familiar with the procedure because of repeated visits.16–18 Familiarization may not occur in all subjects, however.19 Furthermore, attenuation of the hemodynamically dependent pressor response may take weeks rather than days, because in 16 subjects under intra-arterial ambulatory blood pressure monitoring, four visits by the same physician over a short period of time (2 days) were associated with similar pressor and tachycardic responses.13

**Determinants of Blood Pressure Variability**

Over the 24 hours blood pressure can vary by more than 50 mm Hg. A considerable portion of this variability is due to behavioral influences, presumably through central modulation of autonomic drive to the heart and systemic blood vessels, as further demonstrated by the reduced blood pressure variability that has been shown in subjects with high spinal cord transection.20 But nonbehavioral factors are involved as well, because blood pressure varies even when subjects lie immobile with no apparent changes in activity. By and large, 24-hour blood pressure variations depend largely on central cardiovascular control. This is suggested by data obtained in normotensive and untreated essential hypertensive subjects in whom 24-hour blood pressure was recorded intra-arterially and half-hour average values were calculated from beat-to-beat analysis of the blood pressure tracing. Half-hour average blood pressure values were positively correlated with half-hour average heart rate values (Figure 4). This was not due to the fact that daily life changes in blood pressure are caused by changes in heart rate and cardiac output, because a marked reduction in heart rate variability by atropine did not affect blood pressure variability.22 This probably indicates that factors modulating the heart and blood vessels in a consensual fashion, i.e., exciting or inhibiting both targets together, play a major role in the tendency of blood pressure and heart rate to vary between half hours, the central nervous system being their most likely site of origin.

Other possible factors involved in the determination of blood pressure variability continue to be investigated. At present, the evidence indicates that the circadian blood pressure profile that can be seen in most individuals, i.e., the daytime increase and nighttime fall in blood pressure, is quickly reversed in shift workers at the time they start the night working schedule, excluding an important role of time per se in 24-hour blood pressure variability.23 It also indicates that blood pressure variability depends to some degree on circulatory changes mechanically induced by ventilation, and there are speculations that humoral vasoactive substances, changes in vascular smooth muscle reactivity, and other as yet unknown influences are involved. Finally, the search for factors responsible for blood pressure variability has allowed the clarification of two additional phenomena. First, 24-hour blood pressure is characterized not only by marked and irregular variations but also by rhythmic blood pressure oscillations within the range of 0.02–0.50 Hz (i.e., the so-called low-, mid-, and high-frequency oscillations),24–28 which can be identified...
and quantified by power spectral analysis, taking 256-beat consecutive segments of the ambulatory intra-arterial blood pressure tracing. This suggests that blood pressure variability can be divided into an "irregular" component, originating from the cardiovascular response to environmental stimuli, and several rhythmic fluctuations that are intrinsic to the cardiovascular system. These rhythmic fluctuations are in an early investigational phase, but several interesting features have already emerged. For example, low-, mid-, and

**Figure 2.** Line graphs show rises in intra-arterial systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) during the visit of a physician and nurse in charge of measuring blood pressure with a sphygmomanometer. Data are shown as mean ± SEM changes from control value taken 4 minutes before the visit and refer to 30 subjects under 24-hour intra-arterial blood pressure monitoring. The nurse's visit preceded the physician's visit in 15 subjects and followed it in the remaining 15 (from Mancia et al.13 with permission).

**Figure 3.** Plots show intra-arterial blood pressure and heart rate during the minute immediately preceding beginning of cuff inflation (−1 to 0), the minute immediately after cuff inflation (0 to 1), and the 1-minute control period 5 minutes before cuff inflation. Values measured every 15 seconds are shown. Data refer to hypertensive subjects in whom intrabrachial or radial blood pressure monitoring was performed for several hours in combination with automatic (n=15) or semiautomatic (n=20) noninvasive blood pressure monitoring in the contralateral arm. Automatic and semiautomatic blood pressure readings were obtained every 10 minutes. Data were averaged in each subject and mean ± SEM calculated for the group as a whole (from Parati et al.15 with permission). M, mean arterial pressure; S, systolic; D, diastolic.
high-frequency blood pressure fluctuations tend to account for 20–25% of overall blood pressure variability as quantified by the variance (or standard deviation) of all 24-hour blood pressure values, thereby being smaller than the “irregular” variability component.25 Furthermore, the rhythmic blood pressure oscillations do not have the same amplitude over the 24 hours, and in the mid-frequency range they show a marked systematic reduction during the night, in line with the nighttime reduction of several cardiovascular parameters (Figure 5).25 Finally, we have recently shown27 that over 24 hours blood pressure fluctuates also at frequencies markedly lower than 0.025 Hz and that these “very low”-frequency components contribute to a substantial degree to overall blood pressure variability, as predicted by the 1/f model (according to which, the power of blood pressure fluctuations is inversely proportional to their frequency).28 Interestingly, different components of blood pressure variations may be differently influenced by classic blood pressure control mechanisms. This was shown in unrestrained animals subjected to intra-arterial blood pressure monitoring in which sinoaortic denervation increased overall blood pressure variability29–31 but had a complex effect on specific blood pressure spectral components. That is to say, sinoaortic denervation markedly increased the amplitude of the very low-frequency blood pressure oscillations (Figure 6). The low-frequency oscillations were modestly increased by sinoaortic denervation, whereas the mid-frequency oscillations were reduced and the high-frequency oscillations were not homogeneously altered.31,32

FIGURE 4. Plots show mean arterial pressure and heart rate in 89 ambulant subjects with untreated essential hypertension. Data are shown as mean ± SEM for each half hour. Blood pressure was measured intra-arterially by the Oxford method21 (from Mancia et al21 with permission).

![Mean Arterial Pressure and Heart Rate](image)

FIGURE 5. Plots show low-frequency (LF), mid-frequency (MF), and high-frequency (HF) powers of systolic (SBP) and diastolic (DBP) blood pressures throughout 24 hours. Data refer to mean half-hour powers computed from consecutive segments of 256 beats. Mean ± SEM from 10 patients with untreated mild essential hypertension is shown. Powers are represented as percent of total variance. Note that nighttime (b) mid-frequency powers were significantly less than daytime (a) mid-frequency powers (from Parati et al25 with permission).
The second phenomenon concerns the arterial baroreceptor reflex. In 62 subjects under 24-hour ambulatory intra-arterial blood pressure monitoring, various indexes of blood pressure variability almost always showed an inverse relation with the baroreceptor reflex sensitivity estimated by the bradycardic response to baroreceptor stimulation via an intravenous bolus of phenylephrine or the tachycardic response to baroreceptor deactivation via an intravenous bolus of trinitroglycerin, both responses showing a direct relation with heart rate variability (Figure 7). This was the case also when the baroreceptor reflex sensitivity was estimated by the blood pressure response to the alteration in carotid baroreceptor activity induced by a neck chamber. Most important, the inverse relation between baroreceptor reflex sensitivity and blood pressure variability, a finding confirmed by other studies, was also found within individual subjects in whom hourly blood pressure variability was plotted versus hourly baroreceptor reflex sensitivity estimated by computer analysis of the beat-to-beat relation of the systolic blood pressure and pulse interval values (see below) (Figure 8). It is thus clear that, in line with classic animal data, the arterial baroreceptor reflex limits the blood pressure variations occurring in humans partly via opposite changes in heart rate and cardiac output. The magnitude of these variations in any given individual thus depends on the balance of oscillatory and antioscillatory influences.

Changes in Blood Pressure Variability With Hypertension and Aging

Several studies have reported that in secondary hypertension and in essential hypertension with severe end-organ complications the nocturnal blood pressure fall is reduced or absent. However, in most patients with essential hypertension, the alternation of high daytime and low nighttime blood pressures is preserved. This can be seen in Figure 9, which refers to age-matched normotensive, moderate, and more marked essential hypertensive subjects under 24-hour ambulatory intra-arterial blood pressure monitoring. The circadian blood pressure profile, as well as the circadian heart rate profile, was superimposable in the three groups. The circadian heart rate and blood pressure profiles were also only slightly flattened in old normotensive subjects (n=59; age, 74.5±0.9 years; mean±SEM) compared with young normotensive subjects (n=57; age, 38.2±1.4 years). In the young group, average mean arterial pressure (noninvasive ambulatory monitoring) was 97.1±1.1 mm Hg during the daytime and 85.3±1.1 mm Hg during the nighttime; respective figures for the old group were 93.3±1.0 and 86.5±1.0 mm Hg, the night-related hypotension thus being only slightly reduced. This was also the case for the night-related bradycardia, which amounted to 9.3 and 6.2 beats per minute in the young and old group, respectively (Zito, Parati, Abate, and Mancia, unpublished observations).

Preservation of the circadian blood pressure profile does not mean that hypertension and aging do not affect blood pressure variability. In subjects in whom 24-hour blood pressure was monitored intraarterially and the blood pressure signal was analyzed beat-to-beat, the within-half-hour standard deviation of mean arterial pressure (i.e., the average of all half-hour standard deviations within the recording period) increased progressively from normotensive to borderline, moderate, and more severe essential hypertensive subjects (Figure 10). Furthermore, in old normotensive subjects (see above), the number of blood pressure values differing more than ±20 mm Hg
from the mean daytime or nighttime value was two or three times more frequent than in younger normoten-
sive subjects.21,34,48-50 Thus, hypertension and aging
are associated with an increased degree of short-
lasting blood pressure variations. It may be speculated
that this is accounted for by greater pressor responses
to emotional and other behavioral stimuli due to an
increased central emotional reactivity,10-51 a greater
response of resistance vessels to vasoconstrictor stim-
uli,52-53 or both. It is also possible, however, that
hypertensive and elderly subjects have greater rhyth-
mic oscillations or that the antioscillatory influence of
the arterial baroreceptor reflex is impaired.

This last hypothesis has received experimental sup-
port after development of a technique that allows
arterial baroreceptor reflex sensitivity to be assessed
throughout the 24 hours, avoiding use of vasoactive
drugs and other artificial methods to stimulate and
unload the arterial baroreceptors. The technique con-
ists of scanning the 24-hour intra-arterial blood pres-
sure tracing every 3 msec to identify the large number of
episodes characterized by a progressive increase or
decrease in systolic blood pressure and a linearly related
increase or reduction in pulse interval, respectively. The
baroreceptor reflex nature of these episodes was dem-
onstrated in conscious cats by their striking reduction
after sinoaortic denervation (Figure 11).34 When used
in humans, the following data were obtained55: First, in
any given individual, the sensitivity of the baroreceptor
reflex was strikingly different throughout the day and
night (Figure 12), indicating that the performance of

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\text{BAROREFLEX GAIN AND SBP VARIABILITY}
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\begin{align*}
\text{MAP Standard Deviation (mmHg)} & \quad \text{HR Standard Deviation (b/min)} \\
\text{within half hour SD} & \quad \text{2 hour day SD} \\
\text{among half hour SD} & \quad \text{2 hour night SD}
\end{align*}
\]

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\text{FIGURE 7. Plots show regression lines of mean arterial pressure (MAP) and heart rate (HR) standard deviation (SD) and barore-
ceptor reflex sensitivities measured by the slope of changes in RR interval induced by increasing or reducing systolic blood pressure (SBP) through intravenous boluses of phen-
ylephrine and trinitroglycerin. Only regression lines achieving statistical significance (p<0.05) have been drawn (from Mancia et al33 with permission).}
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\text{FIGURE 8. Line graph shows hourly standard deviation of systolic blood pressure (SD SBP) (filled circles) and barore-
ceptor reflex sensitivity (open circles) in one subject (F.M.). Twenty-four-hour blood pressure was measured intra-arteri-
ally by the Oxford method3 in ambulatory conditions. Barore-
ceptor reflex sensitivity was assessed by the slope of the linear
relation between 1) spontaneously occurring progressive in-
creases in SBP and pulse interval and 2) spontaneously
occurring progressive reductions in SBP and pulse interval.
The two types of sequences pooled amounted to approxi-
mately two thousand over the 24 hours. There was a tendency
for SD and baroreceptor reflex sensitivity to change in opposite
directions (χ² test).}
\]
blood pressure-controlling mechanisms is characterized by marked 24-hour variations. Second, throughout the 24 hours, the baroreceptor reflex sensitivity of essential hypertensive subjects was systematically less than that of normotensive controls. And third, the difference between the two groups was more marked during the night than during the day, because, whereas in normotensive subjects the night was associated with an increased baroreceptor reflex sensitivity, no increase occurred in hypertensive individuals (Figure 13). Similar differences characterized young and elderly normotensive subjects.

**Clinical Use**

Twenty-four-hour intra-arterial blood pressure monitoring can help identification of pheochromocytoma, particularly when the hypertensive crises are too short to allow diagnosis by traditional methods such as sphygmomanometric measurements during the crisis and crisis-related increases in plasma catecholamines. Twenty-four-hour intra-arterial blood pressure monitoring may also exclude a pheochromocytoma by demonstrating little or no increase in blood pressure in the presence of seemingly typical signs and symptoms of this condition.41,36

The main clinical interest of this approach, however, consists in its potential for providing a more precise diagnosis of the blood pressure elevation occurring in a given patient and thus a sharper definition of his or her blood pressure-related risk. This is supported by several observations: First, clinic blood pressure correlates with the incidence of cardiovascular morbidity and
mortality, but, although significant, the correlation coefficient has a relatively low value. Second, clinic blood pressure reflects to only a limited degree 24-hour average blood pressure,58.59 in both untreated and treated hypertension.6 And third, compared with clinic blood pressure, 24-hour or daytime mean blood pressure correlates more closely with the overall end-organ damage of hypertension60.61 and with markers of individual organ damage such as left ventricular hypertrophy62,63 left ventricular systolic and diastolic function,64,65 albuminuria,65 and cerebral ischemia.66 Overall or individual organ damage also bears a direct relation with blood pressures occurring at work,62 with the number of daytime blood pressure peaks,63 with nighttime blood pressure values,67 and with 24-hour blood pressure variability.59 Thus, blood pressure averages and excursions in daily life appear to reflect the consequences of a high blood pressure condition on the cardiovascular system more satisfactorily than clinic blood pressure.

Clinical use of ambulatory blood pressure monitoring is still unsettled, however, and two important caveats should be emphasized. First, with the exception of an uncontrolled follow-up study relating semiautomatic daytime blood pressure with subsequent cardiovascular morbidity and mortality,68 the above-mentioned data on ambulatory blood pressure and end-organ damage refer to cross-sectional observations. Thus, no prospective controlled trial has ever documented that 24-hour average blood pressure, daytime and nighttime blood pressure, daytime blood pressure peaks, or blood pressure variability are prognostically useful or that ambulatory and clinic blood pressure together predict more accurately the chance of an individual developing cardiovascular complications. Second, because of limited sample size, inappropriate selection criteria, and other shortcomings, studies aimed at defining ambulatory blood pressure normalcy have not yet provided conclusive results.69 Thus, lack of prognostic validation and reference values discourages routine diagnosis of hypertension60 by ambulatory blood pressure monitoring. In the authors' opinion, this diagnosis still should be based
mainly on clinic blood pressure, whose prognostic importance has been documented by large-scale epidemiological studies. Ambulatory blood pressure might help to avoid treatment in patients with a high clinic but a clearly low 24-hour or daytime blood pressure mean. However, caution is needed because there is evidence that subjects with white coat hypertension, i.e., with high clinic but low home blood pressure, have metabolic abnormalities and cardiovascular alterations similar to subjects with sustained hypertension, i.e., with high clinic and home blood pressures. Thus, it is still debated whether a temporary blood pressure elevation in the clinic environment is devoid of an increased risk.

Similar caveats apply to the use of ambulatory blood pressure monitoring in the routine assessment of the efficacy of antihypertensive treatment. Ambulatory blood pressure monitoring, however, has become a widely used method for assessing new antihypertensive agents. This is justified by the ability of this approach to precisely determine whether the drug or drug regimen under study provides therapeutic coverage over 24 hours. Furthermore, at variance from clinic blood pressure, intra-arterial and noninvasive ambulatory blood pressures are largely devoid of a placebo effect (Figure 14). This means that 1) the actual blood pressure effect of the active drug is unmasked, increasing the study statistical power, and 2) a placebo group can be avoided, thereby avoiding the related ethical problems. Finally, the 24-hour ambulatory blood pressure mean is more reproducible than clinic blood pressure, the difference reaching two or three times when the mean is computed on 30 or more values (Figure 15). Given the dependence of the number of subjects to recruit on the square of the random blood pressure variations, this implies a striking reduction of the study size. In this context, however, it should be emphasized that the
increased reproducibility of ambulatory blood pressure data is less evident for hourly blood pressure means, regardless of their daytime or nighttime location. In a recent study, our group found that the reproducibility of these means was consistently less than that of the 24-hour mean, the difference often being marked (Figure 16). Thus, when the efficacy of an antihypertensive drug is to be assessed throughout the 24 hours, a too-drastic reduction in the number of patients to be recruited should be avoided, lest there be inadequate power for the analysis of differences in the 24-hour blood pressure profiles.

**Current Studies**

Several basic and clinical problems outlined in the previous sections are currently being investigated. Our group and the Department of Bioengineering at the University of Amsterdam are testing a device that allows finger blood pressure to be monitored beat-to-beat in ambulatory conditions, the monitoring period lasting 24 hours. Comparison with 24-hour intra-arterial blood pressure monitoring has shown that in most instances the device is accurate. It has also shown that, although there is some distortion (e.g., amplification of low-frequency components), the finger pressure signal is suited for power spectrum analysis and arterial baroreceptor reflex testing (Figure 17), indicating that investigation of mechanisms involved in daily cardiovascular regulation may be pursued without resorting to the limiting invasive approach.

We are also investigating the mechanisms responsible for the rhythmic blood pressure oscillations, and, in particular, the possibility that their so-called low-frequency (0.025–0.07 Hz) and mid-frequency (0.07–0.15 Hz) components reflect sympathetic vascular modulation. In conscious normotensive rats subjected to prolonged intra-arterial blood pressure monitoring, chemosympathectomy by 6-hydroxydopamine increased systolic blood pressure variance by 54.2% compared with intact rats. The amplitude of the low-frequency blood pressure oscillations was increased by sympathectomy, and that of the mid-frequency blood pressure oscillations was reduced by approximately 60% (Figure 18). Additional α-blockade did not modify the changes observed with chemosympathectomy alone, leading to the conclusion that the low-frequency blood pressure oscillations...
oscillations are not generated primarily by oscillations in sympathetic firing. On the other hand, the mid-frequency oscillations appear to depend on sympathetic firing. They may also depend to a substantial degree on nonsympathetic mechanisms, their specificity as an index of sympathetic drive therefore being limited.

Finally, we are currently performing 24-hour ambulatory blood pressure monitoring in more than 2,000 individuals of different ages randomly taken from the population of Monza, simultaneously measuring clinic blood pressure, random-zero blood pressure, home blood pressure, and left ventricular mass (echocardiography). These data, and those of a less complex population study under way in Belgium, should define the range of ambulatory blood pressure normalcy, its difference from traditional blood pressure, and its possible relation with the cardiac structure.

Obtaining information on the ambulatory blood pressure relation with the prognosis of hypertension vis-à-vis clinic blood pressure will be more difficult. Clearly, a prospective study based on cardiovascular morbidity and mortality ought to include so many hypertensive subjects as to be difficult. Thus, use of surrogate end points is useful, and some studies are currently examining the ability of ambulatory versus clinic blood pressure to predict the development of left ventricular hypertrophy or the regression of hypertrophy as a result of antihypertensive treatment. Left ventricular hypertrophy may be an appropriate end point because, although there is still no indication that its regression improves prognosis, its presence is related to increased cardiovascular and total death rates.

Questions and Answers

Dr. Gerald F. DiBona (University of Iowa, Iowa City): What accounts for residual power of some 40% after sympathectomy?

Dr. Mancia: I don’t know, but among others, one possibility is rhythmic fluctuations of vascular tone directly generated by periodical smooth muscle contraction. In a more general context, I wish to emphasize that overall blood pressure variance is increased after sympathectomy (possibly because the metabolic vasodilatation accompanying movement cannot be compensated by vasoconstriction in inactive districts, tachycardia, and an increase in cardiac output), suggesting that in the rat the sympathetic nervous system has a prevailing anti-oscillatory role.

Dr. Allyn L. Mark (University of Iowa, Iowa City): You emphasized the variability in white coat hypertension between individuals. Does the magnitude of white coat hypertension relate to baroreceptor reflex sensitivity or the spontaneous rhythmic or nonrhythmic variability of blood pressure?

Dr. Mancia: We have not studied whether the magnitude of the white coat response is related to baroreceptor reflex sensitivity and rhythmic variability of blood pressure. Concerning whether this response relates to overall blood pressure variability, the answer is no. We were not surprised, because blood pressure variability has a nonbehavioral component. Furthermore, pressor reactivity to an emotional stimulus does not reflect reactivity to emotional stimuli of a different nature.

Dr. Allyn L. Mark (University of Iowa, Iowa City): What is the prognostic significance of white coat hypertension?

Dr. Mancia: The issue is not yet settled. On the one hand, epidemiological studies show that occasionally taken blood pressures, i.e., blood pressures inclusive of a white coat component, are predictive of future cardiovascular complications. On the other hand, the Australian trial on treatment of mild hypertension (and other intervention studies) shows that the patients under placebo in whom the initially elevated blood pressure decreased to normal values after a few months (i.e., what we would call white coat hypertensive patients) were a low-risk group. The issue recently has been taken up again by Julius and his associates, who showed, as I briefly recalled above, that white coat hypertensive patients may share to some extent the metabolic and hemodynamic abnormalities of “true” hypertensive patients, rather than being similar to the normotensive subjects. To me, this suggests that it is not at all certain that the marked increase in blood pressure that occurs in a number of subjects during the doctor’s visit is a totally innocent phenomenon.

Dr. Mark W. Chapleau (University of Iowa, Iowa City): You showed, as expected, that baroreceptor reflex sensitivity as determined by changes in heart rate is inversely correlated with blood pressure variability in young subjects. In old subjects, there was no correlation; despite low baroreceptor reflex sensitivity, they still demonstrate decreased pressure variability at night. Is it possible that the elderly rely more on baroreceptor reflex control of vascular resistance? If this is preserved, it may explain the decreased pressure variability at night. Do you have any data on the influence of age on baroreceptor reflex control of sympathetic nerve activity or vascular resistance?

Dr. Mancia: Your question is well posed because we have indeed seen in rats that aging impairs baroreceptor control of heart rate to a much greater extent than baroreceptor control of blood pressure. There is some evidence that this is the case also in humans. We have to consider, however, that the marked reduction in blood pressure and (heart rate) variability induced by sleep is also a centrally originated phenomenon, its occurrence surviving sinoaortic denervation. These central influences governing circulation during sleep may exist in young and old subjects.
Dr. John B. Stokes III (University of Iowa, Iowa City): You indicated that parallel increases and decreases in blood pressure and pulse rate reflect changes in sympathetic outflow. What is the meaning of changes in these parameters in the opposite direction?

Dr. Mancia: I believe that parallel increases and decreases in blood pressure and heart rate reflect central influences, increasing and reducing sympathetic outflow simultaneously to the heart and the peripheral circulation, although other factors capable of consensual cardiac and vascular modulation (such as reflexes from skeletal muscles, sympathetic afferents, epinephrine, and other humoral factors) may play a role. When these parameters are changed in opposite directions, the circulation is under baroreceptor reflex control, as shown by the virtual disappearance of these events after sinoaortic denervation. Note that the time scales of the two phenomena are different: parallel increases and decreases in blood pressure and heart rate can be shown over half-hour periods, whereas opposite blood pressure and heart rate changes last no more than a few beats.

Dr. William J. Lawton (University of Iowa, Iowa City): Most of the data shown involved intra-arterial pressures. Are there any words of caution or differences in extrapolating data from intra-arterial pressures to non-invasive ambulatory blood pressure recording?

Dr. Mancia: Several phenomena documented by intra-arterial monitoring (such as nighttime fall in blood pressure and blood pressure variability, lack of placebo effect, and improved reproducibility) have been seen also with noninvasive automatic monitoring. Caution is mandatory, however, because automatic blood pressure-monitoring devices are somewhat inaccurate when used in ambulatory conditions.6,100,103 Furthermore, with noninvasive monitoring, there is little hope that one will be able to precisely assess blood pressure variability by taking one blood pressure value every 15–20 minutes or so. Nevertheless, any clinical large-scale future of ambulatory blood pressure monitoring is based on the noninvasive approach, which justifies technical research in this area.

Dr. William J. Lawton (University of Iowa, Iowa City): We have seen patients with relatively normal or acceptable office and home blood pressures but elevated ambulatory blood pressure measurements (opposite to the example you showed). Could you comment on this pattern?

Dr. Mancia: We have also come across the pattern you mention, but in our experience this is extremely rare. It is unknown whether having low office and home blood pressures but a high ambulatory blood pressure means an increased risk or represents just a normal variant within the ambulatory blood pressure distribution of the healthy population. This, I believe, might be answered by the Pamela study,90 which collects office, home, and ambulatory blood pressures.

Dr. Annette E. Fitz (University of Iowa, Iowa City): Since nocturnal blood pressure falls in most patients, does including these values in a 24-hour average reduce the differentiating effects of blood pressure averages, or are there periods during the day that would better differentiate groups of hypertensive patients, as, for example, 6 AM to noon or noon to evening?

Dr. Mancia: Your question addresses the crucial issue of whether some blood pressure values within the 24 hours are clinically more important than others. The answer is, I am afraid, that it is not known, although various investigators have described the correlation of organ damage with blood pressure at work, daytime, or nighttime or emphasized (with no clinical evidence) the danger of morning blood pressure rise.102 We need prospective controlled trials to answer these questions.

Dr. Gerald F. DiBona (University of Iowa, Iowa City): Is it true that, although the statistical power is adequate for evaluation of efficacy over a 24-hour period, it is not adequate for evaluation of peak-to-trough efficacy over shorter (i.e., hourly) time periods?

Dr. Mancia: Twenty-four-hour average blood pressure is much more reproducible when taken weeks apart than office blood pressure. Hourly average blood pressures are less reproducible than 24-hour average blood pressure, although on the whole not worse than office blood pressure. This means that studies on antihypertensive drug efficacy can combine an adequate power with a marked reduction in the number of patients only if one takes 24-hour average blood pressure. If one wants to look at the blood pressure-lowering effect hour by hour (and focus in particular on the trough effect), then the number of patients should be adequately increased. The increase should be such as to account for the hourly average value that has shown the worst reproducibility.

Dr. Lawrence G. Hunsicker (University of Iowa, Iowa City): Couldn’t you get around the problem of variability in hour-by-hour determinations of blood pressure by having the same number of patients, but have each patient wear the ambulatory blood pressure monitor for a greater number of days? It seems that what is needed is not more patients, but more blood pressure determinations at each point in each patient.

Dr. Mancia: I couldn’t agree more. The phenomenon is probably due, at least in part, to the fact that means are more reproducible than single values, and one could probably obtain the same advantage by increasing the number of clinical blood pressure values obtained in a given session or the days in which blood pressure is taken. Ambulatory blood pressure, however, has the additional advantage that it allows one to document the antihypertensive effect in conditions similar to those of daily life.

Dr. Sheng Xing Ma (University of Iowa, Iowa City): How long do patients stay in the hospital when they are having 24-hour arterial pressure measured? Is each one the same?

Dr. Mancia: Twenty-four-hour arterial blood pressure is performed in hospitalized patients who are free to move within the hospital area and live the social life of inpatients not confined to bed. Usually, the recording is done after 1 week of hospitalization. Noninvasive ambulatory blood pressure is more commonly done on an outpatient basis, the device being placed in the morning and removed when the subject comes back the following day. We do not make any attempt to rigidly standardize behavior during the recording, but all recordings are made on working days.

Dr. Sheng Xing Ma (University of Iowa, Iowa City): Do you have data related to changes in sympathetic activi-
ties or norepinephrine concentrations and changes in arterial pressure during the 24-hour period.

Dr. Mancia: We do not have data on 24-hour distribution of plasma catecholamines, but this has been shown by other groups. Plasma catecholamines fall during the night and increase during the morning concomitant with the blood pressure and heart rate increase. It appears that the catecholamine increase does not precede but accompanies and follows arousal and resumption of physical activity.

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