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THE METHODOLOGY OF BLOOD PRESSURE RECORDING

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Introduction

Blood pressure is a continuous physiological variable. The heart beats approximately 110,000 times in 24 h and each beat generates a systolic and a diastolic pressure. While directional changes over each 24 h period can be defined (Millar Craig, Bishop & Raftery, 1978), no two beats generate exactly the same pressures; beat-to-beat pressure variation appears to be a random process influenced by an almost infinite number of variables (Goldberg, 1977). Minute to minute variation also appears to be a random process, with changes in physical activity exerting a strong directional influence. Direct comparability is not seen in pressure samples of less than 3 h and even then underlying circadian rhythms have a pronounced influence. It is plainly inconceivable that any random measurement of blood pressure should be representative of any patient's 'blood pressure'; it cannot represent anything more than the blood pressure generated by the heart of that individual under the prevailing conditions (Figure 1).

It is therefore of paramount importance that the clinical pharmacologist who intends to study the effects of drugs on blood pressure in human subjects should define quite precisely the objects of his investigation before choosing a method of measurement. The methodology required to measure the size of a drug effect on the blood pressure response to severe exercise would not necessarily be suitable for determining the size of an effect on blood pressure during deep sleep.

Most studies of blood pressure are concerned with the effects of drugs on relatively high pressures, as defined by arbitrary clinical criteria (Pickering, 1974). The object of therapy in these patients is to reduce the risk of cardiovascular complications, so it would seem logical to use the same measuring methods as those which were used to define the risks. Unfortunately, in these basic studies (Actuarial Society, 1941; Metropolitan Life Insurance Co., 1961; Kannel & Dawber, 1974), the blood pressure measurements were random one-off events, and the methods used were always indirect and never standardized. It is inconceivable that such a crude measurement could be a sensitive indicator of risk and the only factor which makes such figures reliable is the large numbers of subjects involved. No-one could conceive including such large numbers of subjects in a trial examination of a drug without crippling expense. What methods, therefore, should the clinical pharmacologist use and what are the significant parameters of blood pressure that he should extract from his small numbers of patients? Is average pressure more significant than pulse pressure? Is a measure of variation more important than absolute levels? There are, unfortunately, no ready answers to these questions, but they cannot be ignored.

Available methods

Two methodologies of measurement are available to the investigator; direct and indirect. The direct methods are highly-developed, of known and precise accuracy, and yield large quantities of data; the indirect methods are poorly developed, of dubious accuracy, and yield only small quantities of data. Clearly the direct methods are most suitable for scientific studies of blood pressure and yet they are seldom used. The reason for this is their essentially invasive nature; the incredible naivety displayed by generations of clinical cardiologists in interpreting direct pressure measurements made in patients subjected to cardiac catheterization in specialized laboratories full of strange equipment, and medical personnel in full surgical plumage, has led many scientists to doubt the significance of all invasive measurements. The equipment required has restricted measurement to the laboratory, and long-term studies have been hampered by the fear of serious complications. Fortunately, these objections to the direct methods of recording blood pressure have now been largely overcome, but almost all published studies of the effects of drugs on blood pressure have been performed using one or other of the indirect methods of measurements.

Indirect measurement of blood pressure

All indirect methods are firmly based upon the occluding-cuff technique devised by workers such as Hill & Barnard (1897), Riva–Rocci (1896), and Korotkoff (1905), and which has altered very little since their time. In summary, a cuff containing an inflatable rubber bag is wrapped around the arm. The bag is then inflated by means of a one-way hand pump

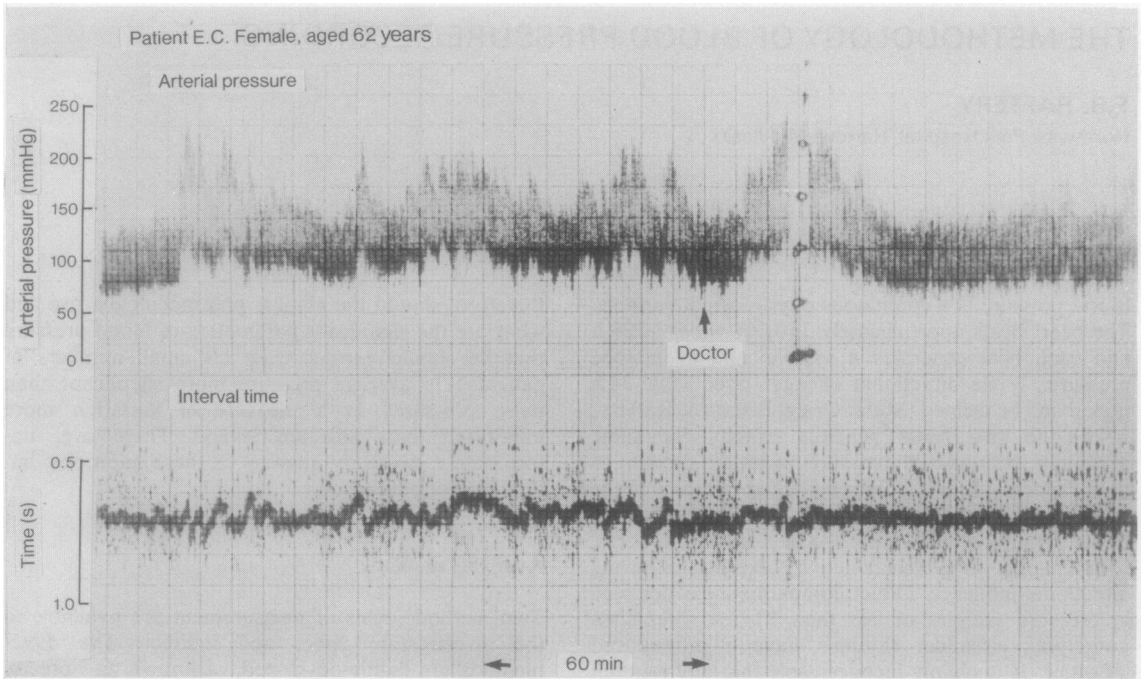

Figure 1 A continuous record of blood pressure. The patient was asleep at the beginning of the record and then woke up and arose from bed. Note the response of blood pressure to the doctor walking towards the bed to calibrate the instrument and then walking away.

until the radial arterial pulse disappears. A valve on the pump is then partially released, and the pressure within the bag allowed to fall. The bag is connected to a mercury-in-glass manometer which expresses the pressure in terms of mm Hg. The pressure corresponding to the first appearance of a pulse in the brachial artery below the cuff (detected by any means) is taken as a measure of the systolic pressure (Figure 2). Korotkoff (1905) detected reappearance of a pulse in the collapsed brachial artery as a succession of sounds accompanying each heart beat and appreciated by means of a stethoscope applied to the artery below the cuff. He defined different kinds of sound appearing as the pressure fell from phase I (initial sound-sharp and of high frequency) to phase IV (disappearance of high frequency leaving only low-frequency noise—'muffling'), and phase V (cessation of noise). Many investigations have been conducted into the genesis of Korotkoff sounds and these were summarized by Burton (1953) as follows:

The walls of the artery below the inflated cuff fall together to form a flat ribbon. As the cuff pressure falls a systolic pulse will eventually succeed in penetrating the length of the cuff, and temporarily distend the artery below. The transverse section of the artery will expand to an ovoid and flow will be highly turbulent, vibrating the tissues around, and then collapsing again (Figure 2). Many comparisons of direct and indirect measurements agree that the first Korotkoff sound (which may be equated with the first appearance of 'flutter' in the collapsed arterial wall, detected by *any* means) is a sensitive indicator of systolic pressure.

As the pressure continues to fall, each successive pulse which penetrates the cuff adds to the volume of blood in the system below, until a point is reached at which the collapsed segment remains distended between beats but flow remains turbulent. In theory the critical opening pressure of the artery has been exceeded in diastole and this must be equal to diastolic blood pressure. The failure to collapse between beats should lead to a loss of highfrequency components with the next systolic expansion—thus there is a clear theoretical link between diastolic pressure and phase IV (muffling). As the cuff pressure continues to fall, a point is reached at which the artery remains fully distended, flow becomes laminar, and the succeeding systolic pulse produces no significant vibration of surrounding tissues; the Korotkoff sounds disappear (phase V). There has been considerable controversy over the years about which of these two points should be taken as diastolic pressure—phase IV or phase V—and even official recommendations have been known to differ (Burton, 1967). Physiological studies

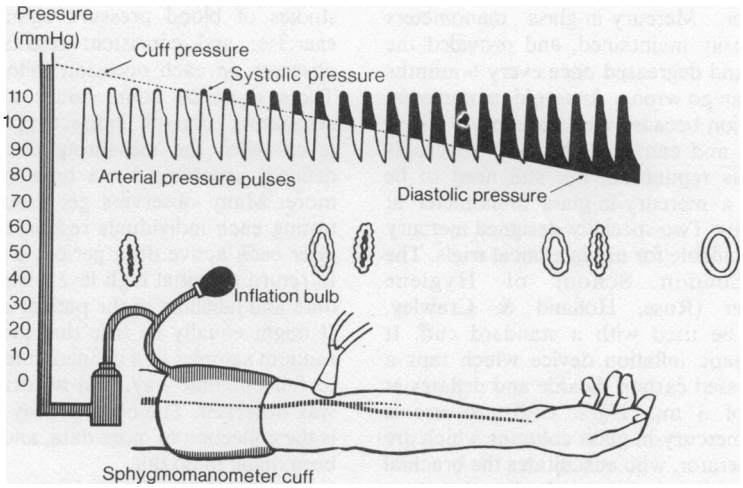

Figure 2 The occluding-cuff method of measuring blood pressure indirectly. Cross-sectional areas of the brachial artery below the cuff during deflation are shown.

comparing direct and indirect pressures have also differed in their conclusions (Raftery & Ward, 1968; Briet & O'Rourke, 1974). These controversies have been enervating and misleading; whatever the results of scientific studies, the difference between phase IV and phase V is usuallly so small as to be of little consequence in the light of the known inaccuracies of the whole technique. It is theoretically correct to take phase IV as *approximating* diastolic pressure, and in practice it is surely best to do so.

The chief reason for saying this is the not infrequent persistence of Korotkoff sounds down to zero cuff pressures. This occurs classically in patients with aortic incompetence and is related to the high cardiac output. It also occurs in other situations of high cardiac output and low peripheral resistance, particularly in pregnant women, where the effects of drugs on blood pressure are of great clinical importance and phase V diastolic readings could be grossly misleading.

Controversies such as phase IV/V/diastolic pressure have drawn attention away from the fact that all correlative studies with direct systolic and diastolic pressures show a wide scatter of results around absolute agreement. It would seem that phase I Korotkoff is a reliable measure of systolic pressure but can be in error by as much as + 18 to −30 mm Hg. (Raftery & Ward, 1968). Phase IV is preferable to phase V for diastolic pressure, on theoretical if not practical grounds, but no matter how diastolic pressure is measured by indirect means, the figure may be in error by similar margins, even when recorded under near-ideal circumstances, for reasons which have yet to be explained. This unreliability of the Korotkoff diastolic pressure probably explains the increased predictive value of systolic over diastolic blood pressure in the Framingham study (Kannel & Dawber, 1974).

There are many other factors which may add to the inaccuracy of an indirect reading. It is now well-established that the bag must be applied snugly over the artery; for adults the cuff must be at least 12 cm wide and for the best results should be 20% wider than the diameter of the arm (Kirkendall, Burton, Epstein & Fries, 1967) with similar and carefully-detailed recommendations for children of all ages. Inaccurate fitting of the cuff has ceased to be an important problem since the introduction of Velcro fittings which enable the cuffs to be applied snugly and accurately without difficulty. Nevertheless obese patients with arms of greater than 20 cm diameter present a problem. There appears to be increasing over-reading of pressure with increasing arm diameter beyond this size, and correcting tables are available (Geddes, Hoff & Badger, 1966) but rarely used. This means that obese persons must often be excluded from clinical trials, despite the fact that high blood pressure is clearly important in the obese.

Other, and incompletely explained physiological quirks, such as the silent interval (Ragan & Bordley, 1941) which sometimes occurs in the Korotkoff sounds during cuff deflation, particularly in the elderly, make for further exclusions and even less confidence in the technique. The rate of cuff deflation is also important, and if it is not accurately standardized can produce marked discrepancies in repeated observations.

The greatest advantage of the occluding cuff technique lies in its familiarity—every medical student and every nurse knows how to use a

sphygmomanometer. Mercury-in-glass manometers are reliable and easily maintained, and provided the system is cleaned and degreased once every 6 months there is little that can go wrong. Anaeroid manometers have a bad reputation because they have levers which require lubrication and can stick. Modern anaeroids do not deserve this reputation, but still need to be calibrated against a mercury-in-glass manometer at six-monthly intervals. Two specially-designed mercury manometers are available for use in clinical trials. The first is the London School of Hygiene sphygmomanometer (Rose, Holland & Crawley, 1964) which can be used with a standard cuff. It includes an automatic inflation device which taps a cylinder of compressed carbon dioxide and deflates at a constant rate of 3 mm Hg/s. Cuff pressure is reflected on three mercury-in-glass columns which are hidden from the operator, who auscultates the brachial artery with the diaphragm of a standard stethoscope. The operator stops the descent of each column by pressing buttons on the front of the instrument when his ears register Korotkoff I, IV and V. The columns have a scale of arbitrary numbers and at the end of each recording the height of mercury in each is read off. The scale is later calibrated against a mercury-in-glass manometer and each number converted to mm Hg. This instrument is an excellent piece of design which completely eliminates the problems of observer bias and digit preference, but it is very bulky and heavy.

The second is the so-called Hawkesley zero-muddling manometer (Wright & Dove, 1970). This looks like a conventional mercury-in-glass instrument and can be used as such. However, it has a wheel which is spun before each measurement to adjust the zero to an unknown level which affects the scale reading in mm Hg. This unknown zero level is determined afterwards, so that the pressure reading can be corrected. Cuff inflation is completely conventional, but the deflation rate can be controlled and regulated by a needle valve. This instrument has the great advantages of simplicity, lightness and portability, and is certainly immune from observer bias; however it is still open to digit preference since the measurer must still correlate his ear and eye to the numbered scale. It would seem that careful servicing is essential to maintain accuracy (Labarth, Hawkins & Remington, 1973), and the instrument is expensive and not readily available from the manufacturing company.

It is generally accepted that either one of these instruments, used by carefully trained observers, is the minimal requirement for studies of drug effects on blood pressure. There are major disadvantages associated with these instruments; they can only be used for one-off readings in carefully defined circumstances and in the setting of a laboratory or outpatient clinic; they are very difficult to use for studies of blood pressure changes during dynamic exercise; and consistent results demand the same observer on each occasion following a rigid routine. There must be some doubt about the validity of comparing one-off indirect pressure measurements (even when the measuring conditions are carefully defined) separated by a time interval of a week or more. Many observers get around this difficulty by testing each individuals response to a placebo period after each active drug period; a failure of the reading to return to initial high levels leads to rejection of the data and labelling of the patient as a 'placebo reactor'. It might equally be true that the readings, which are random samples in a defined time series, just happened to fall out that way, and no drug effect of any kind was observed. The obvious way around this dilemma is the collection of more data, and many attempts have been made to do this.

The simplest way to increase the data-base is to issue each patient in a trial with an instrument which will enable him to measure his own pressures at defined times through each day, and record them on a chart. This method of 'home blood-pressures' has been used by several groups of investigators (Crook & Raftery, 1973; Raftery, 1974; Gordon, Pawsey, O'Halloran, Abbot, Wilson & Silverstone, 1972; Freis, 1954), but always against the background of clinic readings with controlled instruments and with careful patient training and supervision. The averaged pressures from these recordings is more likely to reflect the true average pressure of the individual over a period of time than random clinic recordings, but the accuracy of home recordings must always be under suspicion. The big manufacturers make very satisfactory portable mercury-in-glass manometers which can be used in conjunction with a cheap stethoscope, and cuffs with a built-in stethoscope diaphragm are also available (although not so easy to use as the manufacturers claim).

We have used an anaeroid manometer for this purpose simply because it can be easily used by the patient (Wilkinson & Raftery, 1968).

The objections to home blood pressures are many; the patient must perform isometric exercise to inflate the cuff and this puts up his blood pressure; there is no safeguard against observer bias and digit preference; there is no guarantee that the numbers are not purely fictitious (Raftery, 1974). Nevertheless, the indications are that this method should be tried and there is a real need for a simple and portable design of self-inflating equipment for use in clinical trials.

All the indirect instruments described so far have in common the use of the human ears to detect and interpret vibrations transmitted from the collapsed brachial artery to the surface of the arm as the occluding cuff is deflated. Many instruments have been designed to perform the same task in different ways. They may be classified as follows:

1. *'Sound' detectors*

In these instruments automatic cuff inflation and deflation is linked with a piezo-electric microphone placed over the brachial artery and shielded from extraneous noise. The signal from the microphone is compared with the pressure in the cuff (usually measured by means of small strain gauge) and a display system indicates pressure at Korotkoff I, IV and/or V. The display systems can vary from a chart recording to flashing coloured lights. There are at least fifteen machines of this type on the market, some with manual inflation and some with automatic inflation/deflation systems. Very few published studies are available on the accuracy of these instruments (Irving, Kerr, Ewing & Kirby, 1974; Ramsey, Nicholls & Boyle, 1976), but those available agree that they are less reliable than the basic stethoscope and mercury manometer (Labarth *et al.*, 1973; Hunyor, Flynn & Cochineas, 1978). The microphones are notoriously sensitive to movement and friction of all kinds, are difficult to place accurately (particularly when built into a cuff), and are nothing like as good at detecting phase IV Korotkoff as the human ear. There is no official requirement for these instruments to be properly assessed before their release onto the market and the manufacturers claims are often very misleading (American Heart Association, 1973).

The best of these systems is the Remler M-2000, the prototype of which was developed in the University of California, San Francisco (Kain, Hinman & Sokolow, 1964). This system is portable and has been used by one group of workers for a number of years with considerable success. The most important feature of the system is that it does not attempt to interpret the brachial arterial sounds; it simply records them and all the interpretation is done by an observer listening to the play-back. However it is very expensive and this limits its usefulness in clinical trials.

2. *Wall movement detectors*

Here the Korotkoff sounds have been replaced by detection of initial movement, 'flutter', and finally distension of the arterial wall by means of an echo-sounding device. The commonest method used is ultrasound and the best of these instruments is the Arteriosonde (Roche). This instrument has been carefully evaluated by a number of workers (Gundersen & Ahlgren, 1973) and found to be accurate and reliable, although not all agree that it is superior to the human observer (Hunyor *et al.*, 1978). These instruments are very heavy and exceedingly expensive, which limits the type of study in which they are useful, and as with the 'sound' detectors, placing of the transducer is critical and minor shifts can lead to gross artefact. Another disturbing feature is the production of 'hard' copy. A systematic error in the equipment can be perpetuated and produce readings which look acceptable but may be grossly in error (Hunyor *et al.*, 1978).

Infra-sound is another echo-sounding technique used to detect wall movement, but this technique has been shown to be highly inaccurate and misleading (Edwards, Goldberg, Bannister & Raftery, 1976).

Measurement of blood pressure

The ideal direct method of measuring blood pressure involves the insertion of a miniaturized pressure transducer unit into an artery. Technically this is perfectly feasible, but this type of transducer is very expensive, fragile, difficult to calibrate accurately and liable to clot if left *in situ* for any length of time.

The most commonly used techniques involve placing a cannula in an artery and attaching a pressure-sensitive device to the external end. Cannulae also have a tendency to clot, but provided the system is filled with heparinized saline this is a most unlikely happening. The signal from the transducer can be led directly to amplifiers and an on-line recorder to produce an immediate record of blood pressure and wave form. Alternatively, it can be used to modulate a radio signal and thus be transmitted to a receiver and recorder at some distance from the subject (Irving, Brash, Kerr & Kirby, 1976). Another alternative is to store the signal as a frequency modulation on a miniaturized tape recorder carried by the patient which can be recovered at a later date (Bevan, Honour & Stott, 1966).

Short term records taken in laboratory situations with immediate write-out can be very useful in certain types of investigation, particularly for observing the effects of drugs on well-defined activities such as dynamic or static exercise and the Valsalva manoeuvre. Miniature cannulae which will enable a good and reliable signal to be obtained are freely available (Seldicath Ltd) and small accurate transducers for close application to the ends of cannulae and reliable recording apparatus are available in profusion. Arterial puncture is not as easily performed as venous puncture, but the skills are readily learned and the hazards are not as great as is usually thought. Repeated arterial puncture is an everyday hospital procedure which is seldom associated with serious complications if performed by competent persons.

Long-term studies with direct methods are clearly of greatest interest to clinical pharmacologists and here the problems of complications from indwelling arterial cannulae are of paramount importance. One group of investigators (Irving *et al.*, 1976) has used a closed heparin-filled cannula for periods of 24 h without clotting or embolic complications. Other groups (Bevan *et al.*, 1969; Littler, Honour, Pugsley &

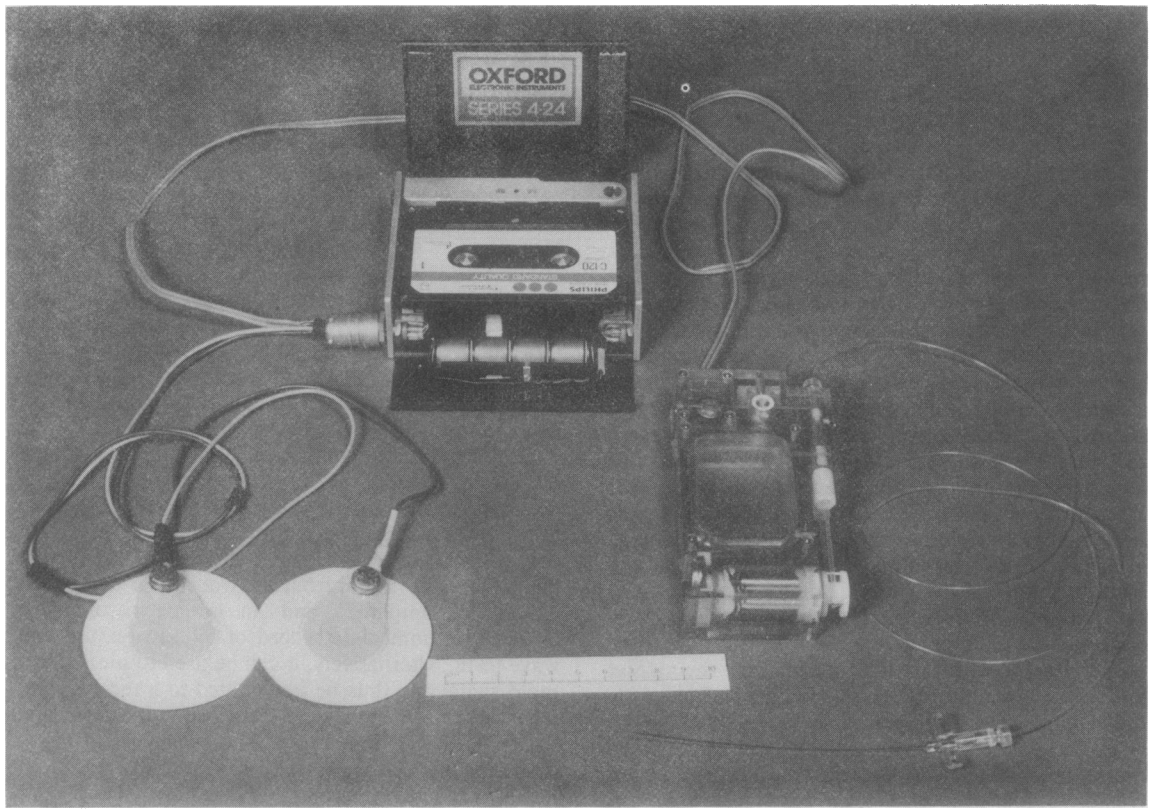

Figure 3 The Oxford ambulatory blood-pressure apparatus. The cannula and perfusion unit are on the right, the tape recorder above and the ECG electrodes on the left.

Sleight, 1975; Goldberg, Raftery & Green, 1976) have used a system with a continuous slow flush of heparinized saline without embolic complications for periods up to 5 consecutive days. The only serious complications so far reported with long-term recording cannulae have been three cases of median nerve palsy which occurred after withdrawal of cannulae from the brachial artery (Littler, 1976). It appeared likely that this was produced by haematoma formation in the enclosed space under the bicipital aponeurosis and no further cases have been reported since the workers concerned recommended puncture above this structure.

Telemetry places severe limitations on the range and usefulness of direct methods in long-term studies. The Oxford system (Bevan *et al.*, 1966) using a miniaturized tape recorder for data storage imposes no such limitations and can be used to obtain continuous records of blood pressure in patients at home and at work and during all sorts of normal physical and mental activities.

The technical and clinical development of this instrument (Figure 3) directed by Professor Sir George Pickering at the Radcliffe Infirmary, Oxford, is an achievement which has enabled full and complete records of blood pressure to be obtained at all times of the day and night without any restraints (emotional or physical), and yet with much greater accuracy than can be achieved with indirect methods (Millar Craig, Hawes & Whittington, 1978).

The cannula is inserted under local anaesthetic into an arm vessel—the brachial artery above the bend of the elbow is used by some and the radial artery at the wrist by others (Murnaghan, 1978). The cannula is attached by plastic tubing strapped to the subject's chest to the perfusion unit (Figure 3). This consists of a chamber containing heparinized saline which is pumped continuously through a needle valve down the tubing and the cannula (0.2 ml/h).

Attached to the top of this chamber is an Akers transducer which receives the pressure wave transmitted by the column of heparinized saline and converts it to an electrical signal. This is transferred to one channel of an Oxford Medilog, a commercially available four-channel miniaturized tape recorder which utilizes commercial tape casettes and runs

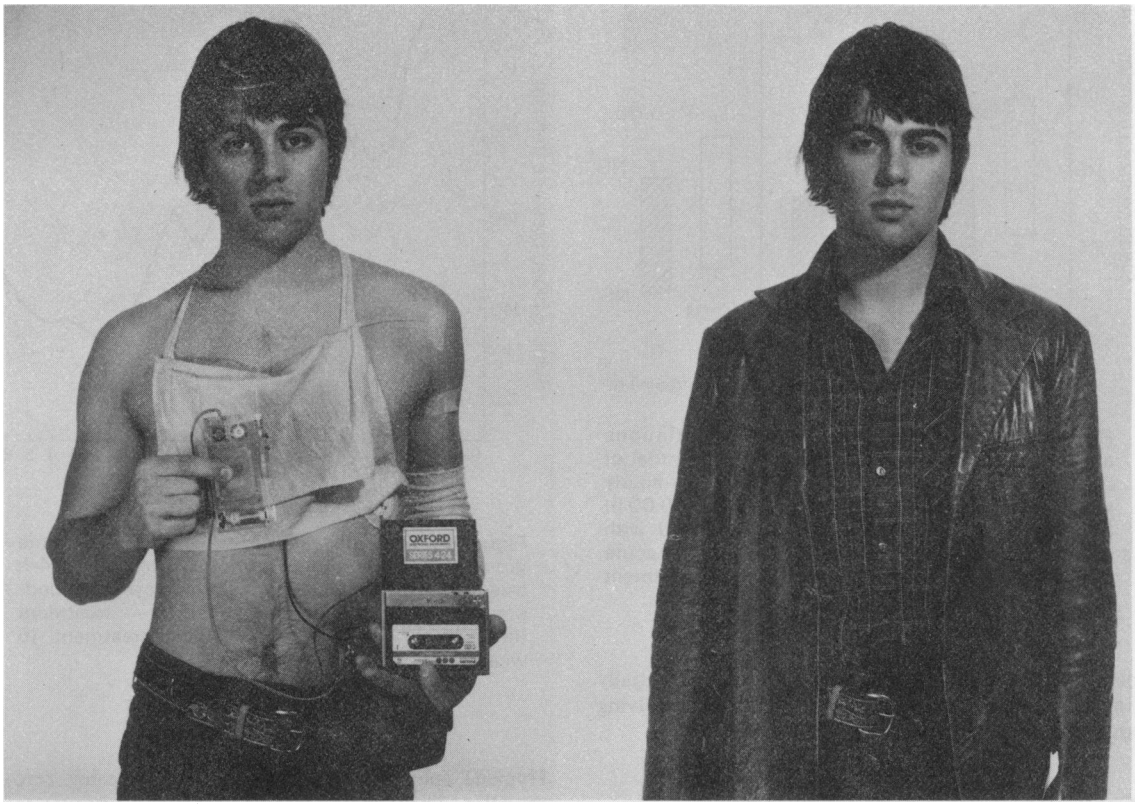

Figure 4 The perfusion unit is packed into a bag suspended over the chest and the tape recorder in a pouch worn around the waist. When the patient is fully dressed, the system is inconspicuous.

slowly for a full 24 h period. Other information such as ECG or EEG can be recorded on the same tape since there are four channels on the recorder. The whole unit is light and highly portable (Figure 4) and the only restrictions on patient activity are twice-daily visits to the laboratory for checking, calibration and re-filling the perfusion chamber. We have been using an improved version of this system for 6 years and have performed long-term studies on 400 patients without serious complications. The studies have been prolonged up to 5 days in five patients but in general it is not necessary to continue for this length of time for most studies. At present, we seldom continue our studies for longer than 48 consecutive hours, and by doing so we find that repeat studies at intervals are quite acceptable to the patients. Several groups of patients have returned for three studies at 8-week intervals and once again this has been accomplished without incident. One embarrassing side-effect of this technique is the quantities of data it produces and the necessity for computer-assisted data handling. It is simple to play back the taped signal and arrive at a 24 h pressure print-out on a physiological recorder, but a computer programme must be used to translate each peak and trough into mm Hg. Three such programmes have been written, and more are being prepared in a number of centres throughout the world. Once this information has been obtained, it is a simple matter to obtain means of pressures over long or short periods and to manipulate them in any fashion (Figure 5). The system is clearly ideal for the study of both acute and chronic effects of drugs on blood pressure and has been used in a number of clinical trials which provide very accurate information on drug effects (West, Sleight & Honour, 1976; Goldberg & Raftery, 1976; Goldberg, Raftery & Wilkinson, 1977). However, the use of a system such as this, while it provides excellent and accurate data (Figure 6) and enables very full observations to be made on all aspects of blood pressure, requires a big investment in equipment and experienced personnel. It is generally agreed that the incidence of complications has been low only because very experienced personnel have been involved in the studies and because meticulous care had been taken by all the groups who use this system. But no matter how good the method and

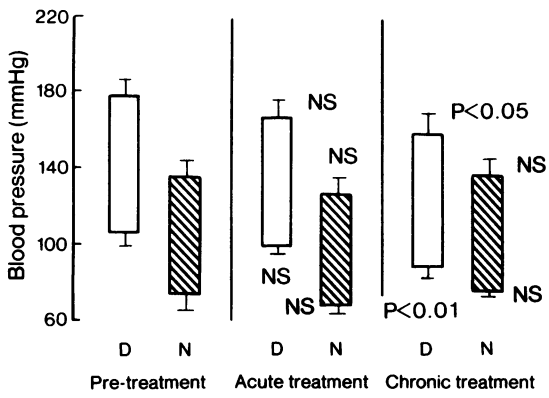

Figure 5 Data computed from continuous ambulatory records from patients ($n=6$) in a trial of once-daily atenolol (100 mg at 09.00 h). Six-hourly mean pressures during the day (D, 12.00–18.00 h) and night (N, 24.00–06.00 h) are compared with records (a) at the start of treatment (b) during acute treatment (first 24 h) and (c) after chronic treatment (6 weeks later).

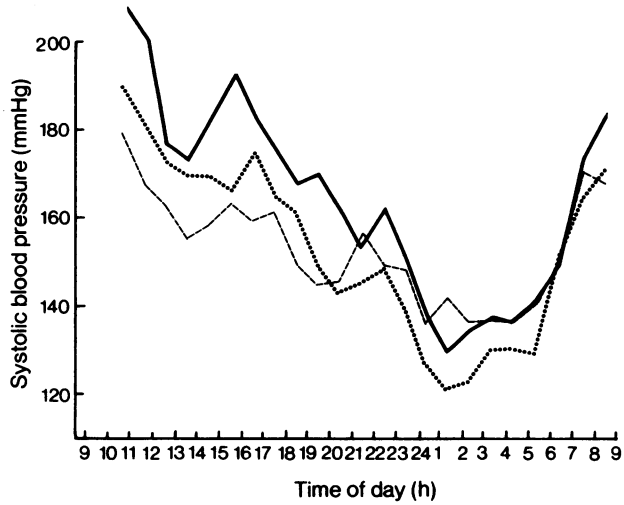

Figure 6 One-hour mean pressures from the same group of patients as in **Figure 5** plotted on a 24-h axis to show the effects of the drug on cyclical blood-pressure variation — pretreatment, · · · treatment (first 24 h), ———— after chronic treatment (6 weeks).

careful the staff involved, it is still potentially hazardous and cannot be used in studies involving anything more than small numbers of patients.

Conclusion

There can be no reasonable doubt that the continuous recording of direct intra-arterial blood pressure by the Oxford system represents the best available method for the clinical pharmacologist. However, its use is strictly limited by the undoubted dangers inherent in long-term arterial puncture, and the necessity for expertise and continuous vigilance to prevent complications. Some method of obtaining the same information non-invasively is urgently required, but no such method has yet been devised and the automatic occluding-cuff devices currently available are not good enough to match the invasive data.

In the meantime, for those who cannot rise to the considerable investment in personnel and equipment required to operate an Oxford system, the best recording method of general use is the occluding-cuff method, used in conjunction with a London School of Hygiene sphygmomanometer or a Hawkesley zero-muddler. These methods give essentially intermittent and low-accuracy data, and it is only logical to expand the information by seeking additional repeated readings. Using subjects to record their own blood pressures with simple, cheap and unsophisticated equipment gives additional information which is probably just as valid as measurements made with more sophisticated (and *much* more expensive) semi-automatic equipment. The profusion of semi-automated machines is best avoided unless the manufacturers can produce hard evidence from reputable independent investigators that their claims are valid. For certain specialized studies (for example, pressure changes during sleep) where a human agency might be impractical, then automatic machines such as the Arteriosonde (Redman, Beilen & Bonnar, 1976) are suitable, provided that the limitations of these instruments are fully realized when making interpretations from the data.

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