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Non-invasive evaluation of the conduit function and the buffering function of large arteries in man

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Summary. The purpose of this study was to validate a two-dimensional (2D) echography coupled range-gated Doppler system for the non-invasive measurement of internal diameter, blood flow velocity, and pulse wave velocity of peripheral arteries, such as the common carotid artery (CCA), femoral artery (FA), and brachial artery (BA) in man. The array of the ultrasonic system and the Doppler probe were attached and formed a fixed angle (38° 30′). The artery was firstly visualized using the echographic array probe in order to position the Doppler beam. Then, the range-gated Doppler system was used to measure both internal diameter and blood flow velocity with the sample volume position covering the internal diameter. Using a hydraulic device, there was an obvious correlation between the calculated and the measured velocities ($r = 0{\cdot}98$). Normal values of diameter, blood flow velocity and blood flow were measured in 18 healthy volunteers. The means (± 1 standard deviation) was as follows: diameter, CCA $= 0{\cdot}636 \pm 0{\cdot}027$ cm, FA $= 0{\cdot}843 \pm 0{\cdot}074$ cm, BA $= 0{\cdot}302 \pm 0{\cdot}052$ cm; flow velocity, CCA $= 19{\cdot}5 \pm 2{\cdot}1$ cm s^{-1}, FA $= 11{\cdot}4 \pm 1{\cdot}2$ cm s^{-1}, BA $= 6{\cdot}7 \pm 1{\cdot}0$ cm s^{-1}. Blood flows were as follows: CCA, $370{\cdot}6 \pm 42{\cdot}5$ ml mn^{-1}, FA $387{\cdot}0 \pm 75{\cdot}0$ ml mn^{-1} and BA (wrist occlusion) $29{\cdot}8 \pm 12{\cdot}5$ ml mn^{-1}. The intra-observer reproducibilities for CCA, FA and BA were respectively: for diameter, 4·9%, 4·12% and 14·8%; for velocity, 8·9%, 10·6% and 10·2%. The inter-observer reproducibilities were respectively: for diameter, 5·6%, 5·4% and 11·3% for velocity, 6·5%, 5·7% and 6·3%. Simultaneous determinations of pulse wave velocity from blood flow velocity recording allowed estimations of the distensibility of these arteries. Finally, the coupled echo and range-gated Doppler system permitted non-invasive evaluation of blood flow calculated as the product of the vessel cross-sectional area and measured blood velocity and also of arterial compliance as the ratio of the cross-sectional area and the square of pulse wave velocity. Such estimations of the conduit and buffering functions of peripheral large arteries in man were shown to be more accurate for the common carotid and the femoral arteries than for the brachial artery.

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Introduction

The large arteries have two principal functions (O'Rourke, 1982): the conduit function and the buffering function. The first is defined as the capacity to drain blood flow from the heart to the peripheral vessels and hence to provide oxygen to the tissues. The second is the ability to attenuate the outflow generated by the left ventricle into a smooth flow into the arterioles.

In most instances, only the conduit function has been investigated in man, using either dye-dilution or plethysmographic techniques to measure blood flow. Until recent years, little has been done to evaluate blood flow by direct determination of the cross-sectional area and blood flow velocity of a given large artery. Recently, echographic and Doppler methods have been developed for this purpose but these methods have been applied principally to the measurement of cardiac output and carotid blood flow (Safar *et al.*, 1981; Gisvold & Brubakk, 1982; Goldberg *et al.*, 1982; Reneman *et al.*, 1985, 1986; Van Merode *et al.*, 1989), with little information being obtained for other peripheral large arteries (Lewis *et al.*, 1986). Furthermore, the buffering function of large vessels in association with the conduit function has been poorly investigated. For this purpose, arterial distensibility has been inferred from the non-invasive determination of pulse wave velocity (Bramwell & Hill, 1922). Nevertheless, since distensibility is defined as the per cent increase in volume (dV/V) divided by the change in pressure (dP) in a given large artery (O'Rourke *et al.* 1982), no information on arterial compliance (dV/dP) was obtained. Indeed, concomittant evaluation of arterial volume (V, defined as cross-sectional area of the artery per unit length) is required to evaluate arterial compliance. In recent years, validated methods using echographic and pulsed Doppler systems have been developed in cardiovascular pharmacology to evaluate the cross-sectional area of straight superficial arteries, such as the brachial and the common carotid arteries (Safar *et al.*, 1981; Reneman *et al.*, 1986; Lewis *et al.*, 1986).

The purpose of the present study was to describe and evaluate a new echographic and Doppler device enabling simultaneous evaluation of conduit and buffering functions of different superficial peripheral arteries, such as the common carotid, the brachial and the femoral arteries. Validations of the apparatus are described in both experimental conditions and in healthy volunteers. An application to cardiovascular pharmacology is given, using the converting enzyme inhibitor, Lisinopril (Millar *et al.*, 1982).

Subjects and methods

SUBJECTS

The study was performed in 18 healthy volunteers and six hypertensive patients, all male and aged between 38 and 61 years. Mean ages were respectively 48 ± 6 and

53 ± 8 years (± 1 standard deviation). Mean weights were 75 ± 8 and 78 ± 7 kg and mean heights were 175 ± 7 and 175 ± 6 cm. In the healthy volunteers, blood pressure was consistently below 140 mmHg for systolic pressure and below 90 mmHg for diastolic pressure. Clinical and laboratory investigations consisting of routine blood and urinary measurements, EKG and chest X-rays were constantly within normal limits. In the hypertensive patients, medication was stopped at least 4 weeks before the investigation. All hypertensive patients had sustained essential hypertension with an ambulatory diastolic blood pressure above 95 mmHg and systolic pressure above 160 mmHg measured with a mercury sphygmomanometer. Diastolic blood pressure was assessed on the basis of disappearance of Korotkoff sounds. The investigation was performed after 30 min rest in supine position. Brachial artery haemodynamics were performed under wrist occlusion at suprasystolic pressure. Informed consent was given by the subjects after a detailed description of the procedure. The study was approved by the Ethical Committee of INSERM (Institute National de la Santé et de la Recherche Médicale).

USE OF SYNCHORNIZED 2D ECHOGRAPHY AND RANGE-GATED DOPPLER SYSTEM FOR THE NON-INVASIVE MEASUREMENT OF BLOOD FLOW

In order to measure simultaneously internal vessel diameter and instantaneous blood velocity, a 2D echograph (Phillips SDR 1200) emitting 5 MHz ultrasounds and a 4-MHz pulsed Doppler system (AEM 2-4-8) were coupled. The array of the ultrasonic system and the Doppler probe were attached and formed a fixed angle of 38°30′ with the array of echographic crystals (Fig. 1). The artery was first visualized using the echographic array probe and its internal diameter determined using the built-in caliper (step = 0·25 mm). The axis of the Doppler ultrasonic beam was then displayed on the screen and a brighter segment on this line, representing the range-gated Doppler sample volume, was positioned so that it covered the whole of the arterial internal

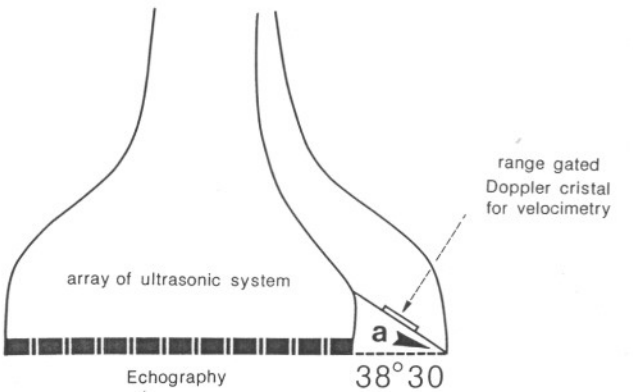

Fig. 1. Schematic representation of the synchronized 2D echography and range-gated Doppler system.

diameter, from its proximal to its distal wall. Indeed, Doppler transducer is alternatively emitter and receiver. Short bursts (0·5 μs) of ultrasound are emitted at a repetition rate of 20 KHz. During an electronic gate, the transducer is switched to receive the reflected signal. Because the electronic gate is opened at an adjustable time after each emission burst, reflected signals are detected only while the gate is opened, i.e. the signals which are detected during a given time interval come from a 'gated' target area (the sample volume) located at a known distance from the transducer. The elapsed time between emission and reception and the duration of the gate opening respectively represents depth and thickness of the sample volume among the beam axis. With a short gate duration (0·5 μs), vessel walls can be localized and internal diameter measured, from which internal cross-sectional area is evaluated with the assumption that the vessel is circular and blood flow calculated according to a cylindric model of the artery. When the gate duration is adjusted so that the sample volume exactly corresponds to the vessel diameter, the recorded Doppler shift output represents the root mean square of all Doppler frequencies along the vessel diameter.

For *hydraulic calibration*, the echo–Doppler system was first tested using a calibrated rolling pump and a rigid plastic tube (Fig. 2) containing a mixture of water

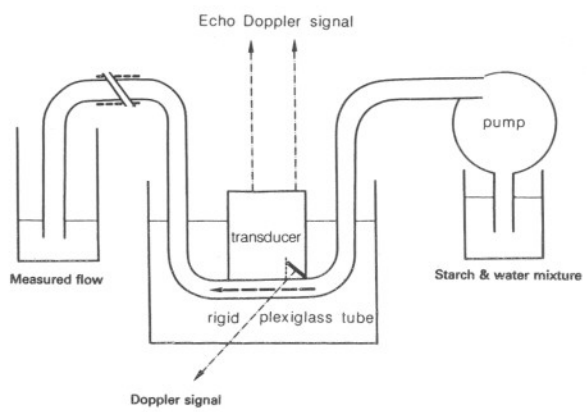

Fig. 2. Schematic representation of the hydraulic calibration.

and starch (4%) maintained at 37°C. The actual mean velocity (cm s^{-1}) of the fluid within the rigid tube was calculated as the flow value (cm^3 s^{-1}) divided by the internal cross-sectional area of the tube (cm^2). Mean Doppler shifts from 0·4 KHz to 1·5 KHz corresponded to real mean velocities ranging from 8 to 40 cm s^{-1}. The regression line of this experimental data set was Doppler shift (Hz) = 0·0435 actual velocity (cm s^{-1}) − 0·031 KHz ($r = 0{\cdot}980$, $P < 0{\cdot}0001$). Applying the classic Doppler formula (Doppler shift = $2 F_e V \cos \phi / c$) where F_2 is the freqency of emitted ultrasounds (4 MHz), V the actual flow velocity, ϕ the angle between the beam axis and the flow axis (38° 30′) and c the propagation velocity of ultrasounds in water at 37°C (1559 m s^{-1}), the measured velocities were calculated from the values of Doppler shift. There was an

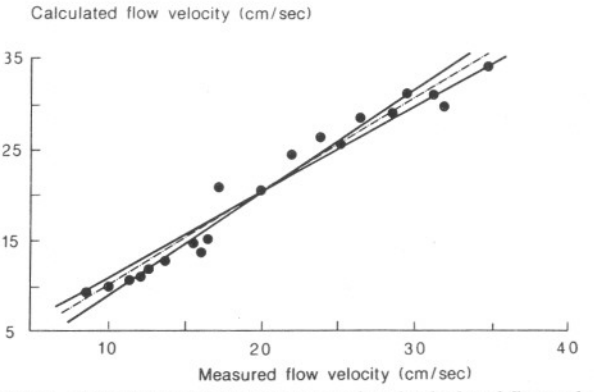

Fig. 3. Hydraulic calibration, (relationship between measured and calculated flow velocity).

obvious linear relationship between the calculated (C) and the measured (M) flow velocities: C (cm s^{-1}) = 1·047 M − 1·06 (r = 0·98, P < 0·001) (Fig. 3).

REPRODUCTIBILITY IN PATIENTS

Intra-observer reproducibility was studied in seven subjects after three consecutive measurements for each subject at intervals of 5 min. It was defined as the difference between the average value and the value corresponding to the largest deviation and expressed as a per cent of the average value. Inter-observer reproducibility was studied in 18 subjects by two independent observers in random order. Reproducibility was defined as the difference between the two observer measurements divided by the measurement done by the first observer. The findings, which are summarized in Table 1, show that inter-observer reproducibility was slightly higher than intra-observer reproducibility, at least for the femoral and the common carotid arteries. For the brachial artery, wide variations were observed.

Table 1. Reproducibility of the Doppler and the echographic measurements

		Diameter: echographic measurement (%)	Diameter: Doppler measurement (%)	Blood flow velocity (%)
Common carotid artery	Intra-observer	1·3	4·9	8·9
	Inter-observer	5·0	5·6	6·5
Femoral artery	Intra-observer	2·8	4·1	10·6
	Inter-observer	5·6	5·4	5·7
Brachial artery	Intra-observer	9·2	14·8	10·2
	Inter-observer	3·2	11·4	6·3

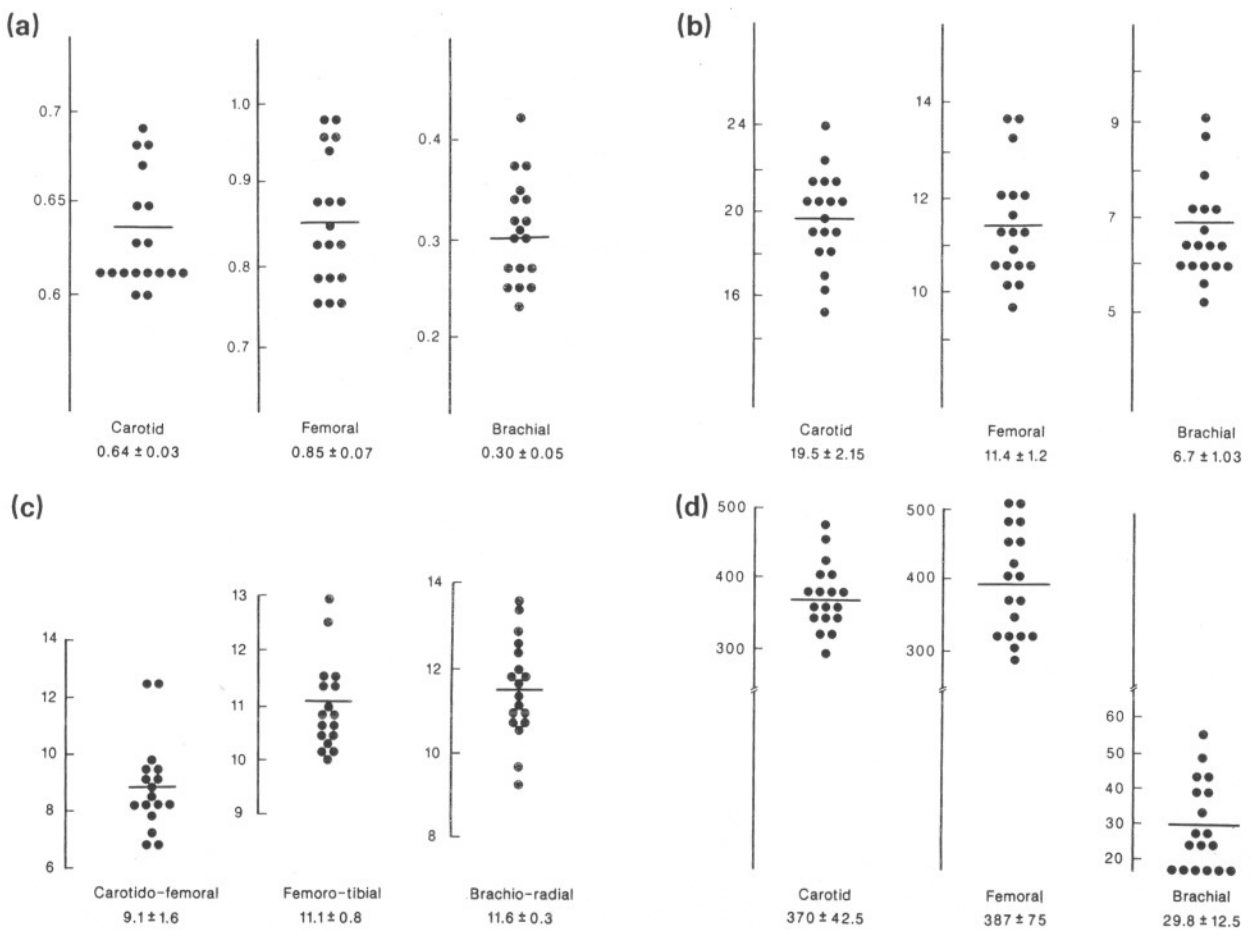

Fig. 4. Healthy volunteers (individual and mean values of parameters). (a) Arterial diameter (Doppler ultrasound cm); (b) blood flow velocity (cm s^{-1}); (c) pulse wave velocity (m s^{-1}); (d) blood flow (ml min^{-1}). Compared with the text mean values have been simplified.

In eight subjects, the haemodynamic measurements using the present apparatus (y) were compared to those measured at the same time by the bidimensional pulsed Doppler system (x) that we validated previously (Safar *et al.*, 1981). Regression equations were $y = 1{\cdot}08x + 0{\cdot}001$ ($r = 0{\cdot}99$) for diameter and $y = 1{\cdot}06\,x - 0{\cdot}39$ ($r = 0{\cdot}99$) for blood flow velocity.

EVALUATION OF PULSE WAVE VELOCITY AND ARTERIAL COMPLIANCE

The elastic properties of the arterial wall, its thickness and the diameter of the vessel are the major determinants of the pulse wave velocity (O'Rourke, 1982). According to the Moens–Korteweg equation, pulse wave velocity (PWV) is defined as:

$$\mathrm{PWV}^2 = Eh/2pr \tag{1}$$

where E = elastic modulus, h = thickness, r = inner diameter and p = blood density. Assuming a thin arterial wall, the elastic modulus may be defined as:

$$E = \mathrm{d}P/\mathrm{d}V/V \tag{2}$$

where, in a given large artery, dP represents the change in pressure and dV/V the per cent change in volume. From equations (1) and (2), arterial compliance (dV/dP per unit length) is thus:

$$\mathrm{d}V/\mathrm{d}P = 3{\cdot}14r^2/p\mathrm{PWV}^2 \tag{3}$$

Thus, arterial compliance may be estimated non-invasively from the determinations of the inner diameter and of PWV.

For PWV determinations, three different Doppler flow recordings were taken simultaneously at the following sites: at the base of the neck over the common carotid artery and in the groin over the right femoral artery; over the right femoral artery in the groin and the right posterior tibial artery; over the brachial artery in the axilla and radial artery at the wrist. Flow was measured with a non-directional Doppler unit (SEGA M842 10 MHz) with hand-held probes (Avolio, 1987). Doppler flow waves were recorded on a Gould tape recorder (M 8188) at high speed (100 or 200 mm s^{-1}). PWV was determined as foot-to-foot wave velocity (O'Rourke, 1982; Avolio, 1987; London *et al.*, 1990). The foot of the flow wave was identified as the point of the commencement of the sharp systolic upstroke. When this point could not be defined precisely, a tangent was drawn to the last part of the preceding flow wave and to the upstroke of the next wave, and the foot wave was taken as the point of intersection of these two lines. The time delay was measured between the feet of the flow waves recorded at these different points, averaged over at least 10 beats and designated as pulse transit time (t). The distance travelled by the pulse was measured over the surface of the body with a tape measurer as the distance between the different

recording sites (D). Arterial PWV was calculated over the three arterial segments as $PWV = D/t$. For the measurements of PWV between the base of the neck and femoral artery, the distance from the suprasternal notch to the carotid location was substracted from the total distance to take into account the pulse travelling in the opposite direction, the PWV being designated as aortic or carotid-femoral PWV. The PWV between femoral and posterior tibial arteries was designated as femoral PWV and that between brachial and radial arteries, brachial PWV. As we have previously shown (London *et al.*, 1990), the individual day-to-day variability was $5{\cdot}3 \pm 3{\cdot}6\%$ for aortic PWV, $5{\cdot}5 \pm 4\%$ for femoral PWV and $7{\cdot}2 \pm 4\%$ for brachial PWV.

ADMINISTRATION OF CONVERTING ENZYME INHIBITOR

In order to evaluate sensitivity of diameter and flow velocity measurements, the haemodynamic study was performed before and 6 h after oral administration of the converting enzyme inhibitor Lisinopril. The dose (10 mg) and the repetition of measurements were adjusted to the pharmacokinetic and pharmacodynamic characteristics of the drug, as previously described (Millar *et al.*, 1982). This investigation was performed only in the six hypertensive patients.

STATISTICAL EVALUATION

Results are presented as mean values ± 1 standard deviation. Correlation and regression coefficients were evaluated using standard techniques. A P-value inferior to 0·05 was considered as significant.

Results

Figure 4 shows the individual and the mean values of haemodynamic parameters in healthy volunteers. Pulse wave velocity was higher in the peripheral ($11{\cdot}1 \pm 0{\cdot}8$ and $11{\cdot}6 \pm 0{\cdot}3$ m s^{-1}) area than in the carotid–femoral area ($9{\cdot}1 \pm 1{\cdot}6$ m s^{-1}). Arterial diameter was $0{\cdot}636 \pm 0{\cdot}027$ cm from the common carotid artery, $0{\cdot}843 \pm 0{\cdot}074$ cm for the femoral artery and $0{\cdot}302 \pm 0{\cdot}052$ for the brachial artery. Blood flow was $370{\cdot}6 \pm 42{\cdot}5$ ml min^{-1} for the carotid artery, 387 ± 75 ml min^{-1} for the femoral artery and $29{\cdot}8 \pm 12{\cdot}5$ ml min^{-1} for the brachial artery (values after wrist occlusion).

Figure 5 shows individual per cent changes of arterial diameter and blood flow velocity produced by Lisinopril. Such variations are shown by comparison with the intra-observer reproducibility of the method. Brachial artery diameter was increased. Flow velocity increased in the carotid and the brachial arteries but decreased in the femoral artery.

Discussion

The present study describes a method for the non-invasive determination of peripheral blood flow. *In vitro* and *in vivo* validations were performed, showing the accuracy of

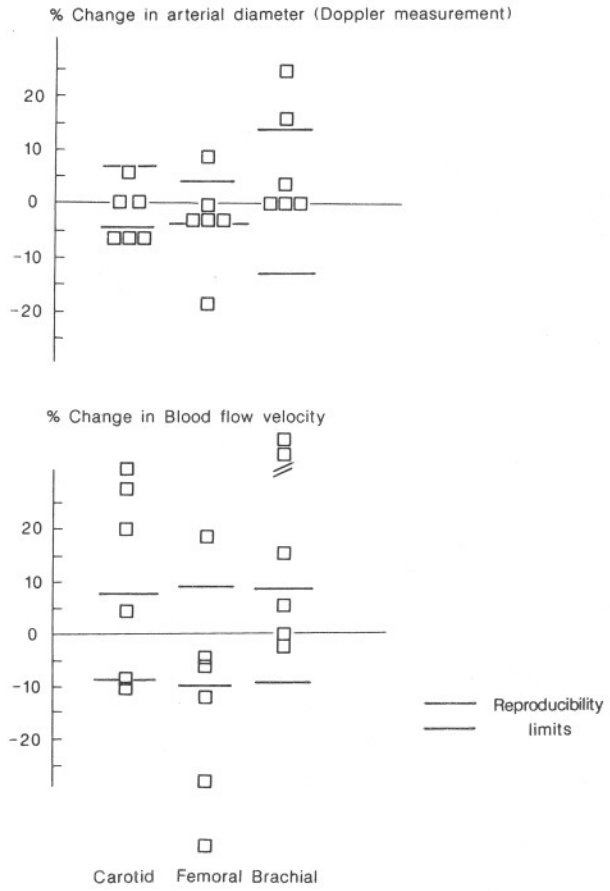

Fig. 5. Effects of Lisinopril (per cent changes in haemodynamic parameters by comparison with the reproducibility limits of the method).

diameter and flow velocity measurements. In particular, a strong correlation was observed when the present method was compared with the bidimensional pulsed Doppler method we have previously described and validated (Safar *et al.*, 1981). Pulsed Doppler flowmetry and plethysmographic methods of the upper limbs have shown to be strongly correlated *in vivo* (Levy *et al.*, 1979, 1981; Safar *et al.*, 1988). Interestingly, the present technique was to be more rapid for the positioning of the transducer in the investigation of three different arteries: the brachial, the common carotid and the femoral arteries.

Whereas the values of common carotid and femoral blood flows are within the limits of those expected from the literature, the normal value of brachial blood flow seemed to be lower (Levy *et al.*, 1979; Safar *et al.*, 1981; Reneman , 1985, 1986; Summer, 1985; Lewis *et al.*, 1986; Asmar *et al.*, 1988; Van Merode *et al.*, 1989). Several explanations

may be proposed for this discrepancy. Firstly, the value of brachial artery diameter was lower than that obtained with the bidimensional pulsed Doppler system we described previously, even when wrist occlusion was used for determinations (Levy *et al.*, 1981; Safar *et al.*, 1981; Laurent *et al.*, 1990). Indeed, with the present device, a 4-MHz transducer was used so that the measurements at the sites of the carotid and the femoral arteries were expected to be better than for the more superficial brachial artery. Secondly, whereas intra-observer variability is expected to be lower than inter-observer variability, this finding was not observed for the diameter measurement of the brachial artery (Table 1), suggesting again that the brachial artery measurements were not reliable. Finally, the results are particularly difficult to interpret since they involve not only the limitations of the method itself but also the spontaneous variability of flow velocity due to rapid changes in vasomotor tone. This is particularly true for the brachial artery (Asmar *et al.*, 1988), because of the richness of the innervation of hand. In order to evaluate such practical problems in cardiovascular pharmacology, haemodynamic parameters were measured before and after administration of the converting enzyme inhibitor Lisinopril. Per cent haemodynamic changes appeared to differ according to the site of measurements, indicating heterogeneous responses in the drug-induced changes in regional blood flow. Nevertheless, it is interesting to note that, at the brachial artery site, changes in diameter and flow velocity were outside the reproducibility limits of the method.

Since the present non-invasive measurement was more accurate for the common carotid and the femoral arteries than for the brachial artery, and since the diameter changes in the former (which are rather elastic arteries) are expected to be minimal by comparison with the latter (which is rather a muscular artery), it should be more advisable to concentrate the haemodynamic measurements on flow velocity alone and not on diameter determination. In our opinion, this statement may be questioned on several grounds. Firstly, the calibre of larger arteries (as the carotid and the femoral arteries) may be influenced actively by pharmacological agents as nitrates or converting enzyme inhibitors (Fig. 5) (Caro *et al.*, 1990; Safar, 1990) and by the mechanism of flow dilatation, as observed experimentally and in humans (Lewis *et al.*, 1986; Pohl *et al.*, 1986; Laurent *et al.*, 1990). Secondly, whereas the diameter of smaller muscular arteries (such as the brachial artery) is very sensitive to vasomotor changes, the diameter in larger elastic arteries is more sensitive to pressure changes, a situation which is important to consider when vasoactive substances are administered. Indeed, any change in the geometry of the peripheral arterial system may influence the level of aortic blood pressure through the mechanism of reflected waves, principally through the change in the site of reflection points and therefore influence the diameter of the thoracic aorta (O'Rourke, 1982). Finally, an estimation of diameter changes permits indirectly an evaluation of the changes in the buffering function of large arteries, as detailed below.

We described in Subjects and Methods that arterial compliance (expressed per unit length) is proportional to the cross-sectional area of the artery and inversely related to

the square of PWV [equation (3)]. Since arterial diameter was measured in the present investigation, the concommittant evaluation of pulse wave velocity gave a clear indication on the visco-elastic properties of the antiviral wall, for instance arterial compliance is expected to be higher in the femoral artery than in the brachial artery. In the case of the carotid–femoral pulse wave velocity, evaluation of arterial compliance is more difficult to obtain since the diameter of the aortic arch was not measured in this investigation. However, with echography, it is possible to measure accurately the diameter of the aortic arch (Isnard *et al.*, 1989). The value approximates to $2{\cdot}54 \pm 0{\cdot}1$ cm in normal subjects, indicating that compliance of the aorta is markedly increased compared with that of the brachial and the femoral arteries.

In conclusion, the present study has shown that, using the combination of echography and Doppler methods, it is possible to evaluate in man both the conduit and the buffering functions of large peripheral arteries such as the common carotid and the femoral arteries, with possible new applications in clinical cardiovascular pharmacology.

Acknowledgments

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