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# Clinical Applications of Arterial Stiffness, Task Force III: Recommendations for User Procedures

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In vivo arterial stiffness is a dynamic property based on vascular function and structure. It is influenced by confounding factors like blood pressure (BP), age, gender, body mass index, heart rate, and treatment. As a consequence, standardization of the measurement conditions is imperative. General and method/device-specific user procedures are discussed.

The subject's conditions should be standardized before starting measurements. These conditions include a minimal resting period of 10 min in a quiet room. It also includes prohibitions on smoking, meals, alcohol, and beverages containing caffeine before measurements. The position of the subject and time of measurements should be standardized. In comparative studies, corrections should be made for confounding factors. Repeated measurements are done preferably by the same investigator, and if available validated with user-independent automated procedures.

As it is not feasible to discuss all methods or devices measuring arterial stiffness in one article, more attention is given to user procedures of commercially available devices, because these devices are of interest for a wider group of investigators. User procedures of methods/devices are discussed according to the nature of arterial stiffness measured: systemic, regional, or local arterial stiffness.

Each section discusses general or method/device-specific user procedures and is followed by recommendations. Each recommendation discussed during the First International Consensus Conference on the Clinical Applications of Arterial Stiffness is quoted with the level of agreement reached during the conference. Also proposals for future research are made. Am J Hypertens 2002;15:445–452


**Key Words:** Arterial stiffness, user procedures, recommendations.

Arterial stiffness is inversely related to arterial distensibility (D). Arterial distensibility and arterial volume (V) are related to arterial compliance (C) by the formula:

$$C = D \times V.$$[1]

Arterial stiffness is determined by vascular function like vascular smooth muscle tone and by the structure of the vessel wall like elastin/collagen content. In addition, arterial stiffness depends on arterial pressure. A higher arterial pressure will increase arterial stiffness.[2] This can be achieved by a higher ventricular ejection, an increased heart rate, a higher vascular resistance, and by early wave reflections.[1,3] As a consequence, in vivo arterial stiffness is not a static but a dynamic property. This means that standardization of measurement conditions is imperative. In addition, apart from the elastic properties obtained at the operating pressure, assessment of elastic properties under isobaric conditions may be important. The general and method/device-specific user procedures are discussed.

## General User Procedures

### Standardization of Subject Conditions

Arterial stiffness is directly or indirectly influenced by all factors influencing blood pressure (BP). Therefore, before starting a measurement, subjects should rest for some time in a quiet room (at room temperature) in an attempt to get

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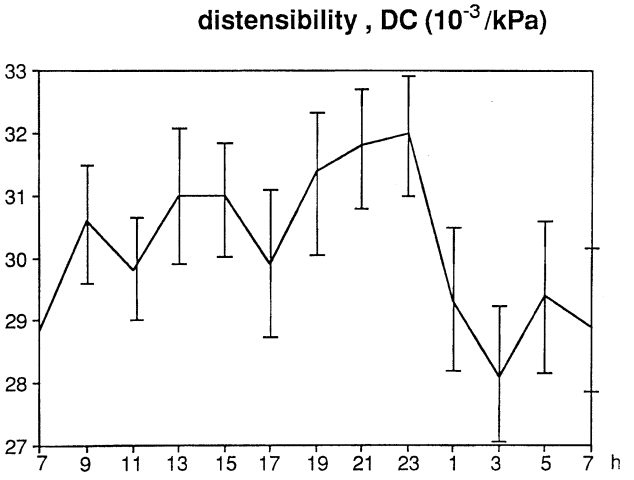


**FIG. 1.** Diurnal variation in arterial distensibility. y-axis, distensibility in $10^{-3}$/kPa; x-axis, time in hours; subjects, 12 healthy young volunteers; standard meals were served at 9 AM, 1 PM, and 7 PM. Subjects stayed in bed from 11 PM until 7 AM. Data are presented as mean ± SEM. DC = distensibility coefficient.

BP, cardiac function, and vasomotor tone as close to basal resting conditions as possible. This basal resting condition is considered the best repeatable in vivo condition. So far no guidelines exist on how long the subject should rest before starting arterial stiffness measurements. This resting period largely differs between investigators from 5 up to 30 min.[4,5] Although no formal studies exist on this issue, most start measurements after subjects are resting for at least 15 min to minimize "noise" due to incomplete basal resting condition.[2,6,7]

For most methods/devices a supine position of the subject is obligatory. With some devices measurements can also be done in sitting position. As BP differs between the sitting and the supine position, it is likely that arterial stiffness will also differ depending on the subject's position. Researchers should mention the position in which measurements have been performed.

Like BP, arterial diameter and stiffness show a diurnal variation, with larger diameter during nighttime.[8,9] As a consequence arterial stiffness tended to increase during sleep (Fig. 1). Therefore, subjects should not sleep during assessments.

After a meal systemic vascular resistance decreases accompanied with an increase in heart rate and cardiac output.[10,11] In a substantial number of subjects and particularly in elderly BP subjects decreases after a meal.[12] All these changes may alter arterial distensibility. These hemodynamic changes last for up to 2 h in the case of a small meal and longer after a large meal.[11] Therefore, for repeated measurements in particular, subject measurements should be performed at the same time of the day, and not within 3 h after a meal. Unless measurements are performed early in the morning, subjects are asked to have a light meal 3 to 4 h before measurements. Subjects should not drink beverages containing caffeine within 3 h before assessments.

Smoking increases arterial stiffness acutely.[7,13] On the other hand, withdrawal of smoking may increase sympathetic tone and thereby increase arterial stiffness. The acute effects of smoking on heart rate last for 75 min, and nicotine tolerance lasts for 1.5 to 2.5 h. Nicotine withdrawal shows a maximum effect at 24 h.[14] Taking into account these data, it is recommended to refrain from smoking for 3 h before assessments.

Like white coat hypertension, it is likely that white coat arterial stiffness may occur. This hypothesis is supported by the fact that (1) in patients with white coat hypertension arterial stiffness was higher[15] and that (2) in subjects with an increased sympathetic tone due to a stress test radial artery compliance was decreased.[16,17] White coat hypertension can be detected with ambulatory devices. Although ambulatory devices for 24-h BP monitoring have been developed, similar validated devices for arterial stiffness do not currently exist. In addition, no self/home measurements are possible for technical or economic reasons. It can be assumed that, like white coat hypertension, white coat arterial stiffness can be limited by repeated consecutive measurements for some time,[18] by performance of measurements by a technical assistant instead of the doctor,[19] or by one or more familiarizing measurements on separate visits.

To minimize short-term influences on arterial stiffness subjects should not speak during measurements and data should be reported as the mean or median of a 10- to 15-sec period to cover at least one respiratory cycle. Another short-term variation in arterial stiffness is induced by spontaneous diameter and distension oscillations with a period ranging from 45 to 70 sec.[20–22] These spontaneous oscillations are assumed more pronounced in muscular than in elastic arteries and were at the radial artery accompanied with a 1.5- to 2-fold change in distensibility.[20] Due to the duration of one oscillation, it often is not practical or feasible to correct for it. This short-term variation in arterial stiffness of predominantly muscular arteries may at least in part explain the lower repeatability of arterial distensibility and compliance measurements in muscular than in elastic arteries.[23]

Finally, arterial stiffness measurements may be disturbed or impossible due to arrhythmia-like extrasystole and atrial fibrillation.

## Standardization of Methodologic Conditions

To limit possible errors in measurements due to temporary changes in subject conditions or due to technical errors, we recommend to perform at least two consecutive measurements. The second should not vary much from the first. If it does, a third measurement is advised. In addition, accepting measurements as valid only when standard deviation of beat-to-beat data is not exceeding 10% of its mean may improve reproducibility.

To limit interobserver variation in measurements, they

**Table 1.** Recommendations on general user procedures for clinical studies: standardize the subject condition

| |
|---|
| Subjects will be at rest for at least 10 min in a quiet room at room temperature. (consensus) |
| Prolong resting period or cancel measurements in conditions where subjects' basal conditions are substantially altered, like when outside temperature is high or immediately after strenuous exercise. (consensus) |
| Subjects have to refrain from smoking, eating, and drinking beverages containing caffeine for at least 3 h before assessments. (consensus) |
| Unless measurements are performed early in the morning, advise a light meal 3 to 4 h before assessments. (large agreement) |
| Subjects should refrain from drinking alcohol 10 h before measurements. (consensus) |
| Subjects may neither speak nor sleep during assessments. (consensus) |
| Investigators should mention in which position measurements have been done (supine, sitting). The supine position is preferred. (large agreement) |
| For repeated measures, subject measurements should be performed at the same time of the day and in the same position. (consensus) |
| Be aware of possible white coat arterial stiffness, and if suspected, perform repeated measurements within one visit or in additional visits to detect it. (consensus) |
| Be aware of possible disturbance of data due to cardiac arrhythmia. (consensus) |

Level of agreement on the recommendations is mentioned within brackets.

are preferably done by one observer, especially for studies with repeated measures. If a valid user-independent procedure exists, it should in general be preferred above user-dependent investigations.

Be aware of the pressure dependence of arterial stiffness. If BP differs between populations being studied, arterial stiffness has to be measured under isobaric conditions.[2,7,24] If this is not possible, corrections should be made using statistical models like analysis of covariance.[6] In comparative studies, data on arterial stiffness should be corrected for most important confounding factors.

Recommendations on general user procedures are formulated in Table 1.

## Method/Device-Specific User Recommendations

Three types of arterial stiffness can be considered: systemic, regional or segmental, and local. As some devices can measure more than one type of arterial stiffness, recommendations on user procedures of a method/device may differ according to the type of arterial stiffness measured. Therefore, method/device-specific recommendations are discussed according to the type of arterial stiffness measured. It is not feasible to discuss user procedures of all available methods. As commercially available devices are of interest of a wider group of investigators, we focus on these devices. Methods and devices discussed and the aspects of arterial stiffness they can assess are shown in Table 2.

### Systemic Arterial Stiffness

Although the ratio of pulse pressure (PP) and stroke volume has been used in the past as a measure of systemic arterial stiffness, this method is considered a very crude approximation. Large agreement was present on avoiding this method for future research. Other methods are debated

**Table 2.** Methods/devices in alphabetical order and the type of arterial stiffness they can assess

| Method/ Device | Systemic | | | | Regional | | | | Local | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Compliance | | Distensibility | | Compliance | | Distensibility | | Compliance | | Distensibility | |
| | OP | IC | OP | IC | OP | IC | OP | IC | OP | IC | OP | IC |
| Applanation tonometry | PCA | | | | | | | | | | | |
| Cine MRI | | | | | | | | | DA | | DA | |
| Complior | | | | | | | PWV | | | | | |
| CR-2000 | PCA | | | | | | | | | | | |
| Nius 02 | | | | | | | | | SA | SA | SA | SA |
| SphygmoCor | PCA | | | | | | PWV | | | | | |
| WTS | | | | | | | PWV | | SA | SA | SA | SA |

OP = at operating pressure; IC = under isobaric conditions; cine MRI = cine magnetic resonance imaging; PCA = pulse contour analysis; PWV = pulse wave velocity; DA = deep arteries like the thoracic and abdominal aorta; SA = superficial arteries like the common carotid, common femoral, brachial and radial artery; WTS = wall track system; CR-2000 = HDI/PulseWave*CR-2000 Research CardioVascular Profiling System.

by Task Force II. They are based on the Windkessel model and make use of pulse contour analysis.[25]

Pulse contour analysis can be performed with different devices like the applanation tonometer[25] and the HDI/PulseWave CR-2000 Research CardioVascular Profiling System (Hypertension Diagnostics Inc, Eagan, MN).[5] The latter device is semiautomated. It makes use of an arterial pressure sensor to provide an arterial pressure waveform at the radial artery, which is calibrated by an oscillometric upper arm BP measurement. The device analyses the pulse contour and aims to calculate total large (C1) and small (C2) artery elasticity index independently. These data are calculated by the device using an algorithm. The pressure sensor is secured within a user-independent holding and positioning device. This latter device allows a technician with a relatively short training to position the sensor on the radial artery and to adjust the position of the sensor to get an optimal pressure wave signal. An optimal pressure wave signal is important as the amplitude of the pressure wave is critical to the analysis. This procedure is facilitated by a dedicated wrist stabilizer. The CR-2000 device automatically collects data over a 30-sec period. Data on repeatability of measurements both at a single visit and on three weekly visits indicate that the compliance measurements are as reproducible as other noninvasive measurements such as heart rate and BP.[5] The intra- and intersession interclass correlations were 73.4% and 58.7% for C1. For C2 these were 83.8% and 72.6%, respectively. Large studies on reproducibility are ongoing.

## Regional or Segmental Arterial Stiffness

Regional arterial stiffness is measured indirectly by measuring pulse wave velocity over the arterial segment. Pulse wave velocity (PWV) is inversely related to arterial distensibility (DC) by the Bramwell-Hill formula:

$$PWV = \sqrt{1/\rho.DC},$$

with $\rho$ representing blood density.[26] Pulse wave velocity can be measured with the Complior (Colson, Paris, France), the Wall Track System (Pie Medical, Maastricht, The Netherlands), the SphygmoCor (PWV Medical Pty Ltd, Sydney, Australia), and by customized devices. All devices can measure PWV in different arterial segments. Pulse wave velocity is calculated by the formula:

$$PWV = \text{distance(m)/transit time (sec)}.$$

The accuracy of the method is expected to be better with a longer distance. Distance is usually measured with a tape measure. Distance can be estimated with acceptable accuracy by direct superficial measurement between the center of the two pressure transducers in case of relatively straight arterial segments like the brachial radial segment. If arterial segments are not straight, measurement of the distance may be a weak point especially if the proximal and distal pulse waves are recorded from two different arterial axis sites, where pulse waves propagate in opposite directions. This is the case for the carotid femoral PWV measurement, an estimate of stiffness of mainly the aortic tract. Some investigators recommend to use (1) the total distance between the carotid and femoral sites of measurement, (2) others subtract the distance from the carotid location to the sternal notch from the total distance, or (3) subtract the distance from the carotid location to the sternal notch from the distance between the sternal notch and the femoral site of measurement.[6,27] All three procedures are approximations being of no importance in intervention studies with repeated measures. However, they can be of great importance in comparing two populations measured with different methods of measuring distance, in pooling data for normal values, or in doing meta-analyses. In addition, abdominal obesity, particularly in men, and large bust in women can make distance measurements inaccurate.[27] This topic is also discussed in detail by Task Force II. An extensive overview of conditions interfering with determination of the traveled distance is given by Asmar.[27] Transit times are measured as the time delay between the feet of the recorded proximal and distal waves.

The Complior is a semiautomated device using pressure transducers. After introduction of the distance in the computer, PWV is calculated automatically as the mean of at least 10 consecutive pressure waveforms.[28]

Whereas the Complior measures the time delay between the two ends of the arterial segment beat to beat, the SphygmoCor and the Wall Track System (WTS) measure the time between the R-wave of the electrocardiogram and the feet of the pressure and distension wave, respectively, at the site of measurement. By measuring consecutively the two ends of the arterial segment under study, the transit time can be calculated and with use of distance PWV is calculated manually. It is likely that simultaneous measurement on the two sites with the Complior is more precise than the consecutive measurement with the two other devices. However, no clinical studies comparing these techniques are available. Measurements take less time with the Complior.

The magnitude of the registered pressure or distension wave is not critical. However, determination of the foot of the wave may be less precise and depends on factors like sampling rate and investigator skills. Apart from the determination of the foot of the wave, devices using pressure sensors do not demand extensive skills and training only takes a short time (few days to weeks). This is also the case for measurement of the PWV with the WTS if the investigator has previous echographic skills. With the Complior 2 there is no need to hold the transducer by hand. The pressure transducers can be fixed over the skin using specific Velcro straps. So far the SphygmoCor has been developed with a hand-held applanation tonometer, but attempts are made to replace this hand-held tonometer by a wristband. Also the Wall Track System can make use of a micromanipulator to fix the ultrasound probe for more user-independent measurements. The devices have been

validated and have shown acceptable reproducibility.[4,28] Repeatability coefficients of PWV of more than 90% have been found with manual methods and with the semiautomated Complior.[27]

## Local Arterial Stiffness

Local arterial stiffness of superficial arteries is measured using echo-tracking techniques. Two major devices have been developed: The NIUS02 and the Wall Track System. At present some researchers also measure local arterial stiffness of deep arteries like the aorta using cine magnetic resonance imaging (MRI).

Local arterial compliance is expressed as compliance coefficient (CC) and is defined as the compliance per unit of length (L), which is the change in cross-sectional area ($\Delta A$) per unit of pressure ($\Delta P$). Likewise local arterial distensibility is expressed as distensibility coefficient (DC), defined as the relative change in cross-sectional area ($\Delta A/A$) of the vessel per unit of pressure. PP is calculated as SBP − DBP. $\Delta P$ during the heart cycle equals PP.

From diameter (d), change in diameter during the heart cycle (distension, $\Delta d$) and $\Delta P$, artery wall properties are calculated using the following equations[6]:

$$DC = (\Delta A/A)/\Delta P = (2\Delta d.d + \Delta d^2)/(\Delta P \cdot d^2)$$

$$CC = (\Delta V/L)/\Delta P = \Delta A/\Delta P = \pi(2d \cdot \Delta d + \Delta d^2)/4\Delta P,$$

where V is arterial volume.

In earlier manuscripts simplified formulas have been used[13]:

$$DC = 2(\Delta d/d)/\Delta P$$

$$CC = \pi d \cdot \Delta d/2\Delta P.$$

These simplified formulas underestimate DC and CC, especially when $\Delta d$ is large compared to d, that is, in young subjects and elastic arteries.

A major source of error with this method may be the accurate assessment of local PP. In the past the Finapress has been used and advocated to measure PP because it has the advantage of measuring beat-to-beat pressure waves simultaneously with distension waves. However, the accuracy of the device remains debated and it was shown that in diabetics and after smoking PP measured with the Finapress at the finger artery differed substantially from PP at the brachial artery measured with the Dinamap.[29] The PP should be measured at the site of the distension measurements. For the assessment of local PP applanation tonometry has been proposed. Applanation tonometry allows noninvasive recording of the arterial pressure waveform and magnitude in both central and peripheral arteries.[30,31] Applanation tonometry requires a stiff or bony structure to flatten but not obstruct the artery wall and a lean skin to avoid cushioning of the pressure pulse. Applanation tonometry is a hand-held procedure at all arterial sites except for the radial artery where a wristband can be used. In general, the signal showing the largest amplitude of the pressure waveform is the most reliable record, but it has been shown that overestimation of the PP is also possible. This technique provides pressure waves, being almost identical to those obtained intra-arterially.[32] In contrast to some investigators,[33] several have found the magnitude of the PP obtained by applanation tonometry unreliable.[34,35] Calibration of the tonometer pressure wave may improve assessment of local PP. Calibration is based on the observation that mean BP is constant throughout the large artery tree and that diastolic pressure does not change substantially.[36] At the reference artery, in general the brachial artery, BP is measured with a validated BP device and PP is calculated as SBP minus DBP. Applanation tonometry is performed at the target and reference artery. From these data, PP at the target artery can be calculated. Applanation tonometry cannot be applied to all subjects and at all arterial sites.[36] In obese subjects applanation tonometry often is inaccurate at a majority of arterial sites. In lean subjects good waveforms can be easily obtained at the radial artery, but in a substantial number of subjects applanation tonometry is not reliable at the femoral artery. In addition, in patients with atherosclerotic plaques or calcified arteries, this method may not be free from any risk. Another technique to assess local PP makes use of a transfer function.[37] Because the use of a universal transfer function appears limited to the upper limb, from radial artery PP only carotid artery and ascending aorta PP can be assessed by this latter technique,[36] which can be performed with the SphygmoCor.

At the common carotid artery ipsilateral vessel wall movements and pressure waveforms are recorded consecutively. At the brachial and femoral arteries, apart from consecutive ipsilateral measurements, simultaneous pressure measurements at the contralateral side are possible. As arterial stiffness at the operating pressure is the result of arterial wall properties and the pressure exerted on the arterial wall, comparison of arterial wall properties has to be done under isobaric conditions. By measuring arterial distension and arterial pressure preferably simultaneously, arterial wall properties under isobaric conditions can be assessed. Some researchers use the Langewouters model to measure isobaric arterial stiffness.[2,7,38,39] Compliance is derived from an arc tangent model fitted by nonlinear regression. This model is based on ex vivo measurements from the aorta.[40] The application of Langewouters model should be restricted to the description of the measured data over the studied pressure range as extrapolation may yield erroneous results.

Another approach measures directly isobaric compliance from the ascending limbs of the distension and pressure waves.[24] Compliance is calculated at a pressure window present in each subject: the larger the window, the higher the accuracy. Therefore, calculation should be done on a window not lower than 10 mm Hg. The pressure and diameter curves are aligned at the foot of each curve and

**Table 3.** Recommendations on user procedures for measuring local arterial stiffness

| |
|---|
| The investigator has to be well-trained. (consensus) |
| Do not use simplified formulas. (consensus) |
| Do not push the artery. (consensus) |
| The use of the Langewouters model versus the measurement of isobaric compliance in a small common pressure window has to be discussed. (large agreement) |
| Pulse pressure should be measured at the site of distension measurements. (consensus) |
| Pulse pressure in the common carotid artery is a valid surrogate for pulse pressure in the ascending aorta. This does not apply to the waveform. (large agreement) |
| In the hands of a large number of investigators pulse pressure data directly obtained from applanation tonometry are not reliable and if so, they should be avoided. (large agreement) |
| Assessment of local pulse pressure using calibrated pressure waves obtained from applanation tonometry appears a valid method. For calibration make use of a validated sphygmomanometer. (consensus) |
| Pulse pressure assessment using calibrated pulse pressures from an individual subject should be compared with those from a universal population-based transfer function. (consensus) |

Level of agreement on the recommendation is mentioned within brackets.

correction is made for differences in phase-characteristics between the echo-tracking and pressure amplifier.

The Nius02 (Asulab, Lausanne, Switzerland) and the Wall Track System (Pie Medical, Maastricht, The Netherlands) allow to assess continuously local arterial distensibility and compliance. The devices measure accurately diastolic diameter (d) and change in diameter during the heart cycle (distension, $\Delta$d).

As the amplitude of the distension wave is critical, investigators have to be well-trained. Most important aspects of the training are the proper positioning of the probe perpendicular to the artery and the placement of the calipers with respect to the lumen wall boundaries. Placement of the calipers on the adventitia results in an overestimation of diameter and underestimation of distension.

The Nius02 is a high precision A-mode echotracking device, which allows continuous measurements at the radial artery. A 10-MHz focused transducer is set perpendicular to the artery with the use of a stereotaxic arm with micrometric screws, and proper positioning is adjusted using the stereo Doppler mode. After switch to A-mode, echoes from both anterior and posterior walls of the artery are visualized and tagged by electronic trackers, allowing recording of the artery internal diameter.[22,41] The processed radiofrequency line is visualized on a computer screen, and the operator selects the peaks corresponding to the interfaces, after which the exact position of each selected peak is determined with the use of an interpolation technique. Finally, radial blood flow velocity is continuously recorded with an 8-MHz Doppler probe (Doptek 2002, Deltex, Chichester, UK). Radial artery flow is calculated from the measurements of velocity and internal diameter. Positioning of the probes and electronic trackers is performed by a well-trained investigator, after which radial parameters are automatically calculated. Intrasession reproducibility of internal diameter and blood flow velocity expressed as coefficients of variation varies from 1.2% $\pm$ 0.4% to 2% $\pm$ 1% and from 6% $\pm$ 1% to 12.6% $\pm$ 1.9%, respectively.

The Wall Track System allows to assess arterial stiffness at different arterial sites and shows acceptable reproducibility.[23] Intersession coefficient of variation of DC and CC at the CCA was 7.1% and 8.5%, respectively. The common femoral artery (CFA) showed the lowest repeatability: a coefficient of variation of 15.2% and 14.2% for DC and CC, respectively. To get an optimal echo image (good resolution and good penetration of ultrasound waves) of the superficial arteries, a 7.5- to 10-MHz transducer is used. For repeated measures it is very important to measure each time at the same place. Sites often measured are the common carotid and femoral arteries 1 to 3 cm proximal to the bifurcation, the brachial artery proximal to the elbow fold. For determination of the latter site, the distance to the medial epicondyl may be helpful. The head in 10-degree anteflection with the head turned 45 degrees to the contralateral side is a good position for CCA measurement. For measurements of the CFA, the lower limb is put in gentle exorotation. In obese subjects a good B-mode visualization of the CFA with a 7.5-MHz transducer may be impossible. In general, right-handed investigators get more repeatable results at the right carotid, brachial, and femoral arteries than at the left arteries and vice versa. Wall track measurements of the brachial and femoral arteries can be measured more user-independent by fixing the arm and lower limb in a groove and by fixing the ultrasound transducer in a robotic arm (micromanipulator). Pressure of the ultrasound transducer on the artery has to be avoided. Pressure on the artery will in general underestimate diameter and overestimate arterial distension.

Cine Magnetic Resonance Imaging has been proposed by some investigators to measure local arterial compliance.[42,43] It could be complementary to the WTS and NIUS02 because cine MRI can measure diameter and distension of deeper arteries like the aorta. However, accuracy of distension measurements should be improved and the problem of noninvasive assessment of local PP of artery has not been resolved yet.

Recommendations on user procedures for measuring local arterial stiffness are formulated in Table 3.

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