Comments on How to Perform Valid Ultrasound Measurements of Carotid Artery Intima-Media Thickness and Lumen Diameter

*John Wikstrand**

Wallenberg Laboratory for Cardiovascular Research, Gothenburg University, Sweden

Abstract

The joint experience from many research laboratories around the world shows that high quality 2-D ultrasound images may be recorded from the common carotid artery and the carotid artery bulb. In most cases, the image from the carotid artery shows a typical double-line pattern similar in appearance from the near and far wall of the artery. In spite of the similarity of the near and far wall images the thickness of the intima-media complex can only be measured in a valid way in the far wall position. This is because it is only in the far wall that the intima-media complex is defined by leading edges from echoes of interest. In vitro experiments and measurements of arterial wall segment thicknesses obtained by histology and by vascular ultrasound also confirm that only far wall intima-media thickness, in contrast to near wall thickness, may be accurately measured. The anatomical location of a biological structure is always defined by a leading edge of an echo, and the thickness of a structure as the distance between the leading edges of two different echoes.

If lumen diameter is measured in the carotid artery, this measurement should be carried out according to the leading edge principle. If changes in common carotid lumen diameter are observed in prospective studies, analyses of common carotid artery cross-sectional area may help in interpreting the results.

In measurements of intima-media thickness it would seem advisable to focus on far wall common carotid artery and carotid artery bulb recordings. Our advice would be to define a composite mean of 10 mm sections from the far wall common carotid and far wall carotid artery bulb intima-media thickness as the primary outcome variable.

We conclude that main outcome variables in ultrasound studies of atherosclerosis should be from the far wall. It would seem advisable to focus on far wall common carotid artery and carotid artery bulb intima-media thickness. It is likely that including near wall measurements and measurements from the internal carotid artery will decrease measurement precision and lead to increases in sample size in scientific studies; or even dilute positive results in an otherwise well designed study.

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Correspondence:
John Wikstrand, Wallenberg Laboratory for Cardiovascular Research, Gothenburg University, Sweden, Tel: + 46 706 081818;
E-mail: john.wikstrand@gmail.com

Introduction

B-mode ultrasound is a valuable non-invasive, sensitive and reproducible technique for measurement of far wall carotid artery Intima-Media Thickness (abbreviated as IMT in many reports) and lumen diameter, and for identifying and quantifying atherosclerotic burden and cardiovascular risk [1,2]. The application of the technique ranges from determining prevalence of atherosclerosis in large-scale epidemiological studies, research on the Aetiology and Pathophysiology of early atherosclerotic development, and also for investigating preventive measures in randomized clinical trials.

However, a review on the topic did not correctly illustrate how lumen diameter should be measured [3], and measurements of near wall IMT thickness, performed by some research groups, cannot be done in a valid way. This review will comment on some methodological aspects regarding ultrasound measurement of carotid artery intima-media thickness and lumen diameter, and also comment on the limitations of the technique.

The arterial wall contains three distinct separate layers intima, media and adventitia (Figure 1). Atherosclerosis is a disease affecting the intima leading to intimal thickening, but there is no method available at present, which can measure only intima thickness *in vivo*. However, intima-media thickness may be measured with ultrasound and an increase in intima-media thickness
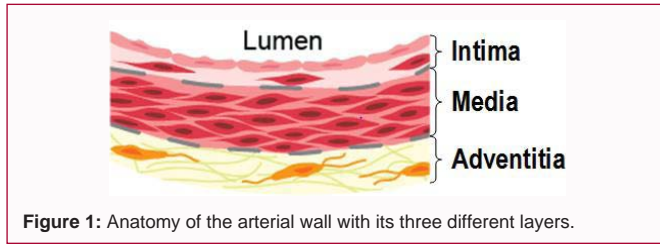
Figure 1: Anatomy of the arterial wall with its three different layers.

Figure 2: Ultrasound recording from a carotid artery showing the typical double-line pattern from both the near and far wall of the artery. The arrow indicates the transition from common carotid artery to carotid artery bulb.
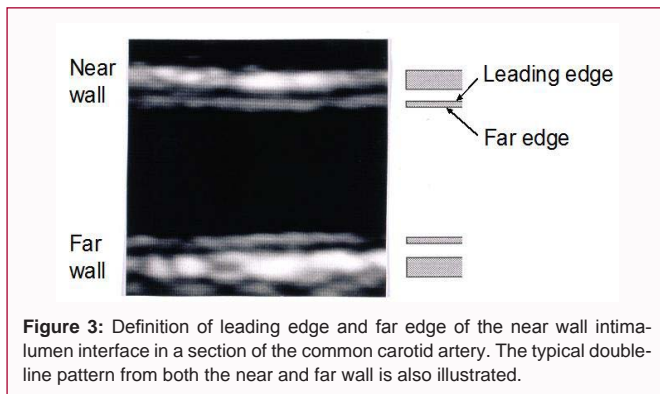

Figure 3: Definition of leading edge and far edge of the near wall intima-lumen interface in a section of the common carotid artery. The typical double-line pattern from both the near and far wall is also illustrated.

in atherosclerotic prone areas is used as an indicator of intimal thickening. The first limitation is thus that we measure a surrogate variable for intimal thickening, that is intima-media thickness. This may underestimate intimal thickening since media thickness may decrease in connection with intimal thickening during atherosclerosis development. In rare cases a primary increase in media thickness may also occur, which can increase intima-media thickness. This may lead to an overestimation of intima thickness when intima-media thickness is used as a surrogate variable for intimal thickening.

Figure 2 shows an ultrasound recording from a carotid artery illustrating the typical double-line pattern from both the near and the far wall of a carotid artery. Figure 3 shows the definition of leading and far edge of the near wall intima-lumen interface echo in a section of the common carotid artery. The typical double-line pattern from both the near and far wall is also clearly illustrated in this figure.

Theoretical Considerations-Visibility of Below-Resolution Structures

Small structures, the dimensions of which are far beyond the resolution limits of the equipment, can be detected and produce a clearly visible ultrasound echo [1,2]. The explanation for this phenomenon is that each tissue interface, no matter what size,

produces an echo if there is sufficient difference in structure, i.e. in acoustic impedance between two structures (i.e. the very thin interface between two fluids such as oil and water will produce a clear echo that is much thicker than the interface itself, which is infinitely thin). Thus, the thickness of an echo defining an interface is not related to the thickness of the actual structure of interest (for further comments, see below). The anatomical delineation of a biological structure is always defined by a leading edge, i.e. the upper demarcation line of an echo (Figure 3).

In vitro Experiments

A B-mode two-dimensional image from the carotid artery may be described as containing seven echo zones: three from the near wall, three from the far wall, and an echo free zone in between (Figure 2 and 3) [1,2]. When inspecting the three echo zones from the near and far walls, respectively, and comparing it with a picture of the anatomy of the arterial wall (Figure 1) one may be deluded into believing that this similarity implies that the three echo zones anatomically correspond to intima, media and adventitia, and that the echo free space in the middle corresponded to lumen of the artery. This was actually also argued to be the case when the technique was new [4]. However, keeping the fundamental principles of the ultrasound method in mind (summarized above), this cannot be the case. Our group decided to perform a couple of *in-vitro* experiments to prove our case.

The *in vitro* experiments were designed to illustrate two things of fundamental importance when interpreting the ultrasound image of an artery:

1. The thickness of the echo created by the interface between the liquid (blood) in the lumen and the intima of the vessel wall has no anatomical relationship to the thickness of the intima itself; and

2. The transition between the vessel wall and the vessel lumen in the near wall is defined by the leading edge of the echo from the lumen-intima interface, not by the far edge of this echo.

Thus the thickness of the echo created by the interface between the intima and the liquid (blood) in the lumen in the near wall has no anatomical relationship to the thickness of the intima.

Summary of experiments performed

The *in vitro* experiments were performed on human arteries removed at autopsy [1,2].

Experiment 1: Trepanation experiment. The vessel was cut open longitudinally and mounted, slightly stretched, with pins on a rectangular rubber sheet. Now, with a corneal trepanation instrument intima and part of the media was removed at various depths (Figure 4). The vessel was then placed in a bath with buffer solution. The ultrasound transducer was mounted in a fixture in the bath at a distance of about 10 mm above the vessel specimen. The intimal surface faced the transducer. The results clearly illustrates that a sharp demarcation echo still can be recorded between the buffer solution and the blood vessel even after the trepanation procedure has removed the intima. The echo was there irrespective of the depth of the trepanation into the media (the echo looked the same even if the intima was removed). The conclusion is that we cannot measure the thickness of the intima by measuring the thickness of the echo created by the difference in acoustic impedance between liquid (blood or buffer solution) and the intima.
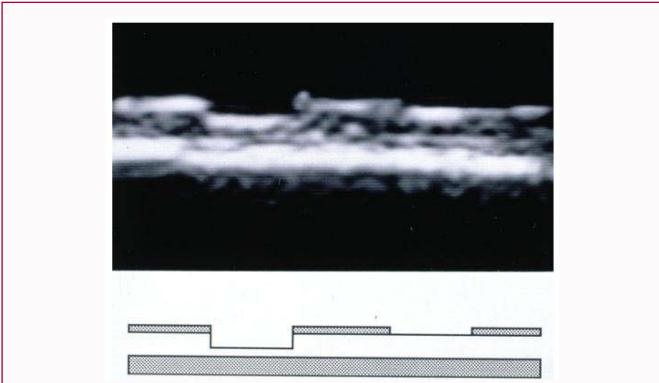
Figure 4: Illustration of ultrasound image in which the intima and part of the media were removed at various depths using a corneal trepanation instrument (see text for comments).
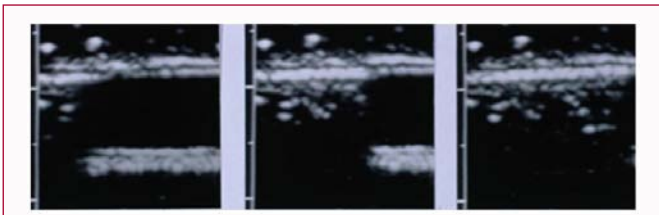

Figure 5: Illustration of an ultrasound image in which an air bubble was introduced between the vessel wall and the liquid solution in the vessel wall lumen. The image shows (from left to right) how the leading edge of the near wall intima/lumen interface echo coincides with the leading edge of the echo from the vessel wall/ air bubble echo when the air bubble moves to the right. Note the increasing size of the echo shadow created by the air bubble when the bubble extends to the right.

Experiment 2: Using an air bubble: In the second experiment, part of an intact carotid artery was mounted in the bath with buffer solution. The transducer was mounted as before at a distance of 10 mm above the near wall of the vessel. The artery was closed at one end, while the other end was connected to a syringe filled with buffer solution and some air. Using the syringe, an air bubble was now slowly created above the buffer solution and in direct contact with the near wall intima.

The results showed, as expected, that a sharp, high contrast echo was created by the intima/air interface (Figure 5). The most important observation, of course, was that the leading edge of the near wall intima/air bubble interface echo corresponded to the leading edge of the near wall intima/buffer interface echo. When the air bubble extends along the vessel wall the near wall "intima" echo disappears completely, it is so to say swallowed by the echo from the air bubble. The results of this experiment clearly illustrates that the near wall/ lumen transition is defined by the leading edge of this echo line 2 in (Figure 6), not by the far edge line 3 in (Figure 6) [4].

As a reaction to the *in vitro* experiments performed by our group [1,2], Gene Bond's group at Bowman Gray School of Medicine in Winston-Salem decided to re-evaluate *in vitro* measurements of arterial wall segment thickness obtained by histology and by ultrasound recordings [4]. Wong et al. interpreted the similarity of the echo picture with anatomy to indicate that the thicknesses of the echoes (Figure 3) corresponded to the thicknesses of intima, media and adventitia, respectively (Figure 1). They therefore embarked on trying to correlate the thickness of single echoes by measuring on leading and far edges of the different echoes [4]. They concluded,
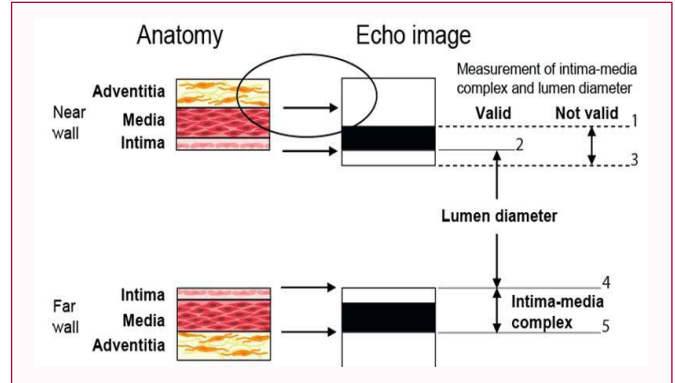

Figure 6: Illustration of the anatomical correlates to echoes that may be recorded from a carotid artery. Observe that all valid measurements are performed on leading edges of the different echoes; that a thickness of an echo has no correlate to a thickness of an anatomical structure, and that the thickness of an anatomical entity is always defined by the distance between the leading edges of two different echoes. The figure also illustrates that the near wall adventitia-media interface cannot be identified in the ultrasound image (encircled, see text for comments). Valid measurements may be done of the far wall intima-media thickness, but not of the near wall intima-media thickness. Lumen diameter may be measured in a valid way. 1= far edge of near wall adventitia echo; 2= leading edge of echo from near wall intima-lumen interface; 3= far edge of echo from near wall intima-lumen interface; 4= leading edge of echo from far wall lumen-intima interface; 5= leading edge of echo from far wall media-adventitia interface.

however, that their experiments showed that it was not possible to accurately measure single layers in the arterial wall with ultrasound, nor was it possible to accurately measure the intima-media thickness in the near wall. Their experiments corroborated our findings that only far wall intima-media thickness could be accurately measured.

Near Wall Adventitia-Media Interface and Near Wall Intima-Media Thickness

The following important question arises: Is it possible to identify the leading edge of an echo from the interface between adventitia and media in the near wall? If this echo cannot be identified in the image, near wall intima-media thickness can of course not be measured.

The first prerequisite for being able to define the adventitia-media interface of the near wall is that the thickness of the echoes produced by the lower part of the adventitia is not overlapping a possible echo produced by the adventitia-media interface. The adventitia, in contrast to the media, is normally quite echogenic with bright echoes produced also by the adventitia tissue adjacent to the adventitia-media interface. Therefore, any possible echo from the adventitia-media interface is lost in the echo produced by the lower parts of the adventitia (Figure 6, see encircled part). This is the reason for that valid measurements of near wall intima-media thickness cannot be done. This problem cannot be overcome by making the reading on the far edge of the adventitia echo, since by definition the location of this echo is always clearly below the true location of the adventitia-media transition (and thus lead to an underestimation of the near wall intima-media thickness, Figure 6, see encircled part). Furthermore, the location of the far edge of the adventitia echo is dependent on several factors which are not possible to standardize or control for, such as gain-setting (the echo will be thicker the higher the gain), and individual composition of adventitia tissue, which means that the underestimation will vary from case to case.

Near Wall Intima-Lumen Interface

The near wall intima-lumen interface is defined by the leading

edge of the second echo from the near wall (Figure 3 and 6; marked with 2 in Figure 6), which in images from the common carotid artery is well defined in most cases. This echo is well defined since normally the media has a low echogenic structure and therefore does not produce any echoes disturbing the mostly highly echogenic intima-lumen interface. Defining and delineating the intima-lumen interface in the near wall should be done on the leading edge of this second echo. Unfortunately groups dealing with measurement of what incorrectly is defined as near wall "intima-media thickness" rarely measure on the leading edge of this echo (although always well defined if the echo exists at all), but on the far edge of this echo, which is against fundamental principles for ultrasound delineation of anatomical structures. One might speculate that this is a futile way of trying to compensate for not being able to define the leading edge of the adventitia-media echo of the near wall (and measure on the far edge of the adventitia echo instead), but only has the effect of increasing the measurement error. In addition, in this case the measurement error will vary from case to case because also the thickness of the intima-lumen echo is dependent on several factors that are not possible to standardize or control for, such as gain-setting and individual composition of the intima.

Ultrasound recordings of near wall images are not redundant, however. On the contrary, this segment of the wall should be clearly visualized. This will guarantee that the vessel is being imaged in an optimal way, i.e. presenting an ultrasound image with the largest (true) diameter; and thus a guarantee that the far wall intima-media thickness will be correctly measured (90 degree angle between ultrasound array and arterial wall). A poorly visualized near wall may indicate a non-optimal imaging view. Furthermore, the leading edge of the near wall intima-lumen interface is used when measuring lumen diameter (Figure 6).

Measurements of Lumen Diameter

In measurement of lumen diameter of the common carotid artery, this should to be done from the leading edge of the near wall intima-lumen echo to the leading edge of the echo from the far wall lumen-intima interface (distance between echoes marked 2 and 4 in Figure 6). The two leading edges defining lumen diameter of the common carotid artery can be easily recorded in most cases. From Lumen Diameter (LD) and far wall common carotid Intima-Media Thickness (IMT) the cross-sectional common carotid intima-media area (A) may be calculated as $(A)=\pi(0.5\ LD+IMT)^2 - \pi(0.5\ LD)^2$ [2]. This is a useful variable to calculate when interpreting changes in intima-media thickness if changes in lumen diameter have also been recorded in a prospective study. This is because changes in intima-media thickness over time could be just secondary to changes in lumen diameter and not to atherosclerotic changes per se. A change in lumen diameter will automatically lead to a secondary (functional) change in intima-media thickness (compare with inflating a balloon).

There is one good example in the literature when changes in intima-media thickness were misinterpreted because of this phenomenon [5]. In this study an increase in intima-media thickness was recorded after institution of treatment with a diuretic (but not on a calcium antagonist), which was erroneously interpreted to indicate a progression of atherosclerosis on the diuretic. However, calculations showed that the cross-sectional intima-media area was unchanged, and that the increase in intima-media thickness was secondary to the decrease in lumen diameter probably caused by the diuretic treatment (not observed on the calcium antagonist).

Far Wall Intima-Media Thickness

The leading edge echo from the lumen-intima interface and from the media-adventitia interface of the far wall can be recorded for the common carotid artery and carotid artery bulb in the majority of cases, thus enabling valid measurements of far wall intima-media thickness (distance between echoes marked 4 and 5 in Figure 6).

However, present experience from several groups indicates that it is difficult to achieve reliable high quality measurements of intima-media thickness of the internal carotid artery in prospective studies. This is probably due to anatomical reasons, it is hard getting the ultrasound transducer in a good recording position for the curved internal carotid artery located deeply high up on the neck below the cheek (especially so in overweight people). Furberg et al. reported that less than 50% of the internal near wall intima-media complex could be visualized on duplicate baseline scans, and less than 70% from far wall scans [5,6]. Our recommendation is to refrain from trying to measure the intima-media complex from the internal carotid artery, it is likely that including these in scientific studies will decrease measurement precision and lead to increases in sample size; or even dilute positive results in an otherwise well designed study, especially so if near wall measurements are also included.

Axial Resolution

The theoretical axial resolution of a 7-MHz transducer is approximatively 0.3 mm [7]. This means that if the intima-media complex is thinner than 0.3 mm, the leading edges of the two echo interfaces from far wall intima and adventitia respectively cannot be separated and measurement of the intima-media complex is not possible (Figure 7) upper panel. If, however the intima-media complex is thicker than 0.3 mm two separate echoes may be recorded, and intima-media thickness measured (Figure 7) lower panel.

Reading

A computerized analyzing system for measurement of intima-media thickness and lumen diameter in carotid and femoral arteries has been developed by our group in collaboration with Chalmers University of Technology [7,8]. The system, used also by many other research groups in this field both in Europe and also in the US, includes automatic detection of echo interfaces (10 mm long sections of the artery, see below), and also includes optional interactive modification
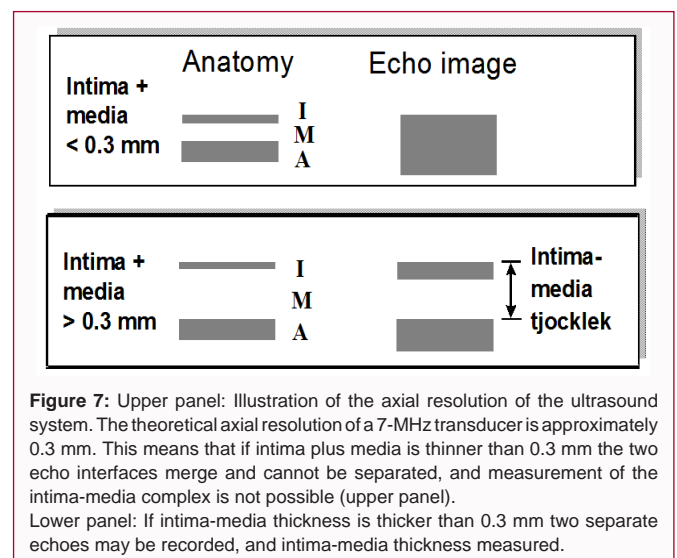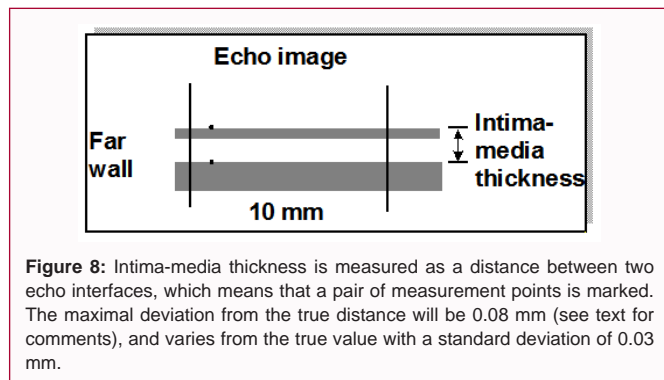

Figure 7: Upper panel: Illustration of the axial resolution of the ultrasound system. The theoretical axial resolution of a 7-MHz transducer is approximately 0.3 mm. This means that if intima plus media is thinner than 0.3 mm the two echo interfaces merge and cannot be separated, and measurement of the intima-media complex is not possible (upper panel).

Lower panel: If intima-media thickness is thicker than 0.3 mm two separate echoes may be recorded, and intima-media thickness measured.

Figure 8: Intima-media thickness is measured as a distance between two echo interfaces, which means that a pair of measurement points is marked. The maximal deviation from the true distance will be 0.08 mm (see text for comments), and varies from the true value with a standard deviation of 0.03 mm.

of the delineated echo interfaces to be done by the technician performing the readings. The advantages of such a system are that it greatly increases the speed of measurements, and also reduce the variability between readers [7,8]. Furthermore, such a system reduces the problem with drift over time in prospective studies.

Comment on Measurement Precision of Intima-Media Thickness

Reports from ultrasound studies often give results with 2 or 3 decimals of an mm, and the question arises, can we measure with such precision? Yes, we can (provided measurements have been performed on leading edges of echoes).

One image point (pixel) in the digitized ultrasound image (7-MHz transducer) is approximately 0.08 mm (may vary somewhat from equipment to equipment). In each single measurement point, the maximal deviation from the true value will be maximum half a pixel, that is 0.04 mm. However, intima-media thickness is measured as a distance between two echo interfaces, which means that a pair of measurement points is marked. The maximal deviation from the true distance will therefore be 0.08 mm, and varies from the true value with a standard deviation of 0.03 mm (Figure 8) [2,7,8].

Measurements along a 10 mm section of the artery in the digitized image means approximately 125 measurement points (10/0.08=125). Assume (arbitrarily) that at least ten of these are independent. This means that in measurement of one image, the measurement error over a 10 mm section will be $0.03/\sqrt{10} \approx 0.009$ mm (10 independent pairs of measurement points); and for just one maximum value in the section $0.03/\sqrt{1} \approx 0.03$ mm (1 pair of measurement points). These calculations are applicable for one individual. The precision increases when more than one image from an arterial segment is recorded and a mean value is calculated (measurement error for left and right with two 10 mm sections images from each side give a mean of four images and a precision of $0.03/\sqrt{40} \approx 0.005$ mm). If a composite of common carotid and carotid bulb (mean) is used based on duplicate scans from each 10 mm section from both right and left side (8 scans in total) the precision is $0.03/\sqrt{80} \approx 0.003$ mm. When a mean value from a group of subjects is calculated the precision increases further.

Observe that the precision is much higher from a 10 mm section (with 125 pairs of measurement points) of an artery compared to just one point (i.e. one single maximum value from just one pair of measurement points). The coefficient of variation is also lower for the former compared to the latter [2,6]. It might be advisable to present both mean values, and also max value measurements in scientific reports.

Our advice would be to define a composite mean of 10 mm sections from far wall common carotid and carotid artery bulb intima-media thickness as the primary variable of interest. In order to reduce variability in recordings and measurements of intima-media thickness and lumen diameter due to phase in the cardiac cycle we recommend recording of images in end-diastole via ECG-triggering (top of R-wave is easy to use) [2,7].

Conclusion

The joint experience from many research laboratories around the world shows that high quality 2-D ultrasound images may be recorded from the common carotid artery and the carotid artery bulb. In most cases, the image from the carotid artery shows a typical double-line pattern similar in appearance from the near and far wall of the artery. In spite of the similarity of the near and far wall images the thickness of the intima-media complex can only be measured in a valid way in the far wall position. This is because it is only in the far wall that the intima-media complex is defined by leading edges from echoes of interest. *In vitro* experiments and measurements of arterial wall segment thicknesses obtained by histology and by vascular ultrasound also confirm that only far wall intima-media thickness, in contrast to near wall thickness, may be accurately measured. The anatomical location of a biological structure is always defined by a leading edge of an echo, and the thickness of a structure as the distance between the leading edges of two different echoes.

It has been claimed that near wall measurements are reliable because there is a relatively good correlation between far wall intima-media thickness and "near wall intima-media thickness" in cross-sectional studies. However in prospective studies it is the very small changes in intima-media thickness over time (delta values) that are in the focus. No data has yet been published from prospective ultrasound studies illustrating a good correlation between delta values (baseline minus follow-up) from measurements of near wall "intima-media thickness" changes *vs.* far wall intima-media thickness changes during follow-up.

If lumen diameter is measured in the carotid artery, this measurement should be carried out according to the leading edge principle. If changes in common carotid lumen diameter are observed in prospective studies, analyses of common carotid artery cross-sectional area may help in interpreting the results.

Present experience from several groups indicates that it is difficult to achieve reliable high quality measurements of intima-media thickness of the internal carotid artery in prospective studies. In measurements of intima-media thickness it would seem advisable therefore to focus on far wall common carotid artery and carotid artery bulb recordings. Better precision and probably smaller sample sizes can be achieved by measuring on 10 mm sections of the artery sections of interest than just single max values. Our advice would be to define a composite mean of 10 mm sections from the far wall common carotid and far wall carotid artery bulb intima-media thickness as the primary outcome variable.

We conclude that main outcome variables in ultrasound studies of atherosclerosis should be from the far wall. It would seem advisable to focus on far wall common carotid artery and carotid artery bulb intima-media thickness. It is likely that including near wall measurements and measurements from the internal carotid artery will decrease measurement precision and lead to increases in sample size in scientific studies; or even dilute positive results in an otherwise well designed study.

Acknowledgement

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