THE SIXTH EUROPEAN SYMPOSIUM ON ULTRASOUND CONTRAST IMAGING

The sixth European Symposium on Ultrasound Contrast Imaging

to be held in Rotterdam, The Netherlands

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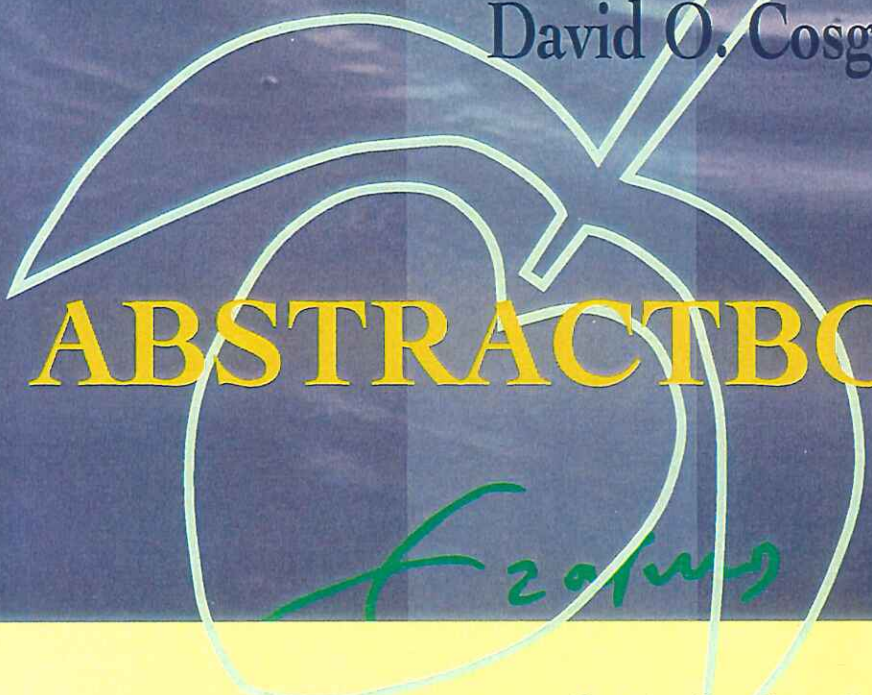
ABSTRACTBOOK



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POTENTIAL CLINICAL APPLICATIONS OF REAL-TIME MYOCARDIAL PERFUSION IMAGING.

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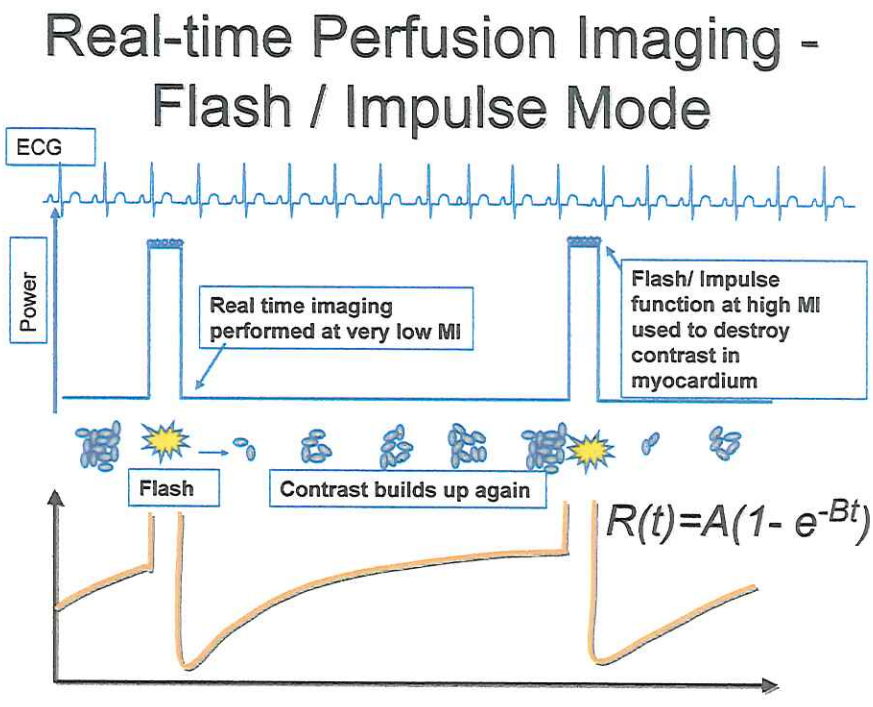
Intermittent imaging has been conventionally used for evaluating myocardial perfusion with ultrasound contrast agents. This is because the contrast microspheres are usually destroyed by conventional ultrasound intensities and time needs to be allowed for the contrast to re-perfuse into the scan plane. Intermittent imaging can be technically difficult to use and does not facilitate simultaneous evaluation of wall motion. Real-time perfusion imaging requires use of significantly lower ultrasound output power (approx 0.1MI) to reduce contrast destruction to negligible levels. When low output power is utilised, the contrast to tissue sensitivity ratio needs to be increased significantly to facilitate detection of myocardial perfusion. A number of techniques to achieve this are available and they include Power Pulse Inversion (ATL), Power Modulation (Agilent) and Coherent Imaging (Acuson).

Clearly, one of the major advantages of real-time imaging techniques are that they allow evaluation of the scan plane, wall motion and perfusion simultaneously. Studies are technically simpler to perform in real-time because it is easier to maintain the desired scan-plane and this scan plane can be modified as required to avoid artefacts such as lateral wall drop-out.

The ability to simultaneously evaluate wall motion and perfusion has potential applications during stress echo studies, where the incremental benefit of obtaining perfusion information as well as wall motion/thickening will be self evident in the evaluation of reversible ischaemia and viability.

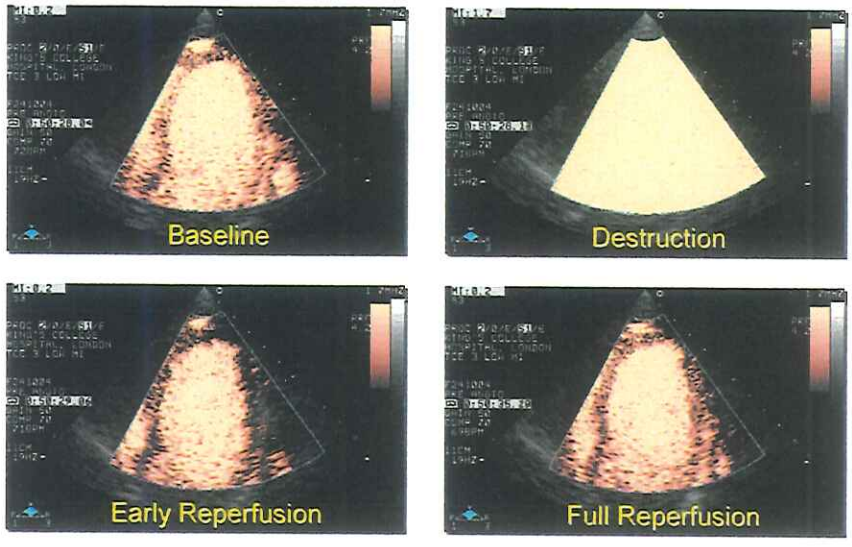
In viability studies alone, the demonstration of myocardial contrast in hypokinetic or akinetic segments implies microvascular integrity and could be taken as a marker of tissue viability.

Acute coronary syndromes could be readily assessed by real-time perfusion techniques. Either to demonstrate resting hypoperfusion, or reflow/no-reflow following thrombolysis or primary PTCA. This may be particularly important in the clinical setting of TIMI 3 flow with no evidence of microvascular reperfusion.



Real-time perfusion techniques have the potential to allow quantification of myocardial blood flow. This could in theory be achieved by destroying the contrast using several high intensity imaging frames (flash/impulse) and then monitoring the rate of reperfusion into individual myocardial segments. The slope of the reperfusion curve (B) is proportional to flow velocity and the plateau level (A) is proportional to blood volume. Both of these values can be combined in the formula illustrated above to estimate blood flow R(t). This technique contains a number of assumptions which may limit its use to evaluating relative changes in blood flow (following an intervention or stress) rather than measuring absolute values. Examples of apical 4 chamber perfusion images taken before, during and after flash destruction are shown below.

Power Modulation Imaging with "Flash" Destruction



In summary, real-time myocardial perfusion imaging is a relatively new technique, which has the potential to be easier to apply than intermittent imaging. In addition, it has a number of exciting potential clinical applications, all of which are currently undergoing clinical evaluation.

RECENT ADVANCES IN REAL-TIME MYOCARDIAL PERFUSION IMAGING

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Display of transmural gradient

Complete transmural perfusion defects are rare, more often perfusion is more impaired in the subendocardial than in the subepicardial layers. Until now, display of subendocardial perfusion abnormalities was difficult in patients using intravenous myocardial contrast echocardiography. With low power real-time perfusion imaging we have been able to display fixed and inducible subendocardial perfusion deficits. The transmural perfusion gradient has to be taken into account for positioning of the ROIs, when quantitative analysis is performed using the contrast replenishment curves.

Quantitative analysis: need for parametric imaging

"Flash-replenishment" curves have been shown to provide quantitative information on myocardial perfusion. However, with available equipment the data acquisition, calculation of the replenishment curves and the display of the results is cumbersome. The "flash-replenishment" technique is certainly not doable in a clinical setting. Parametric imaging seems to be the solution for this problem. Using this technique corresponding frames of consecutive cardiac cycles are aligned and replenishment curves automatically and simultaneously are calculated in multiple ROIs. The parameters of the fitting curves are displayed using a colour map. This way easily understandable images are generated allowing delineation of areas with different replenishment kinetics.

Perspective for establishing real-time perfusion imaging as a clinical tool for evaluation of inducible myocardial ischemia

For the time being only preliminary studies are available for echocardiographic perfusion imaging which therefore may be used as a supplement rather than a substitute of an established stress echo protocol for assessment of LV motion. With the current knowledge of MCE it is reasonable to introduce MCE in several levels:

Prerequisite Sufficient experience with contrast applications for LVO (handling of the agents and ultrasound system)

Level 1	Assessment of LV wall motion (contrast enhanced)
	+ myocardial contrast (qualitative) using bolus injections of contrast
Level 2	Assessment of LV wall motion (contrast enhanced)
	+ myocardial contrast (qualitative) using infusions of contrast
Level 3	Assessment of LV wall motion (contrast enhanced)
	+ myocardial contrast (qualitative and quantitative) using infusions of contrast

QUANTIFICATION OF MYOCARDIAL BLOOD FLOW WITH POWER MODULATION REAL-TIME MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY IN DOGS

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It was previously shown in animal models that myocardial blood flow (MBF) can be quantitated using myocardial contrast echocardiography (MCE) by measuring the rate of microbubble replenishment after their initial destruction by ultrasound during a constant infusion of contrast. For this purpose, triggered harmonic images need to be acquired at different pulsing intervals, and subsequently aligned, averaged, and background subtracted. Pulsing intervals vs. video-intensity plots can then be generated for each pixel in the image and fitted to an exponential function to yield the myocardial blood volume (A) and the mean microbubble velocity (β).

Power Modulation is a new technology that was designed to produce real-time MCE using low power emission. This approach offers the unique opportunity to assess microbubble replenishment kinetics in real-time, by using short high power impulses to destroy the microbubbles and then observing their reappearance in real-time, at low power.

To test the ability of real-time MCE with PESDA to quantitate MBF, we studied 12 instrumented dogs with coronary stenosis (non flow limiting at rest) at rest, during hyperaemia and during occlusion. Real-time MCE-derived A and β were compared to radiolabeled microspheres (μS). At baseline A (12.9±3.2 vs. 13.3±2.7), β (0.38±0.25 vs. 0.34 ± 0.16 s^{-1}) and μS-MBF (0.78 ± 0.34 vs 0.85 ± 0.36 ml/min/g) were similar in the ischemic (IZ) and non-ischemic zone (NIZ). During occlusion, A, β and μS-MBF decreased in the IZ (to 2.6 ± 2.26, 0.10 ± 0.08 s^{-1} and 0.17 ± 0.19 ml/min/g, all $p<0.01$ vs. baseline), whereas they were unchanged in the NIZ. During stenosis and adenosine infusion, A decreased in the IZ (to 8.38 ± 4.39, $p<0.005$ vs. baseline), but not in the NIZ. By contrast, β and μS-MBF increased in the NIZ (to 1.02 ± 0.27s^{-1} and 2.66 ± 0.65 ml/min/g, $p< 0.005$ vs. baseline), but did not vary in the IZ. β and A*β were found to be highly correlated with μS-MBF (r= 0.88 and 0.80 respectively). Both MCE-derived β and MCE-derived β endocardium/epicardium ratio correlated strongly with both μS-MBF and μS-MBF endocardium/epicardium ratio (respectively, r=0.77, and r= 0.79).

These data demonstrate that the use of power modulation real-time MCE allows for the accurate quantification of absolute MBF in vivo and our study suggest that it has sufficient spatial resolution to resolve endocardial blood flow and endo/epi ratio to detect myocardial ischemia.

NEW USE OF CONTRAST ENHANCED ASSESSMENT OF CAROTID WALL INTIMAL-MEDIAL THICKNESS: INITIAL OBSERVATIONS

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Background

Intimal-medial thickness (IMT) of the common carotid artery (CCA) has been extensively used as a marker of early or diffuse atherosclerosis and correlates well with left ventricular hypertrophy (LVH), a profound risk factor for cardiovascular events. The posterior CCA wall has been used for this evaluation, but the anterior wall evaluation has been neglected because of poor visualization. We have previously investigated the benefit of contrast agents in enhancing luminal-wall interface for the calculation of left ventricular mass. We, for the first time, report the use of Optison TM, (Mallinckrodt, St. Louis, MO) to visualise the CCA and assess both intimal-medial thickness and the presence of carotid artery plaque.

Methods

We performed carotid ultrasound in 13 unselected patients with a total of 20 individual carotid examinations. IMT of the anterior and posterior CCA walls and external and internal diameters of the CCA were performed and measured on digitised 2-D and M-mode images at end diastole. Measurements of CCA thickness were not made at the site of a discrete plaque, though additional observations were made in a smaller number of examinations to evaluate for enhanced determination of plaque thickness and characterisation. Atherosclerosis was defined as the presence of discrete plaque in the bulb, internal or common carotid artery.

Results

The use of contrast enhanced-ultrasound revealed a statistically significant improvement in determination of anterior wall IMT with contrast aided measurement ($p<0.0001$). The posterior wall IMT and carotid internal diameter determinations were significant with p values of 0.0477 and 0.008, respectively. There was no significant difference in determination of external carotid vessel diameter measurements ($p<0.954$).

Conclusions

Contrast enhanced ultrasound allows statistically significant improved assessment of both anterior and posterior IMT. It is also useful in identifying morphology and presence of atherosclerotic plaques by enhancing the endothelial-luminal borders in complex lesions. This technique may insure more complete assessment of CCA intimal medial thicknesses and carotid atherosclerosis especially when visualization is suboptimal. Additionally, in large scale clinical trials designed to assess the effects of lipid lowering therapies on carotid IMT, the use of contrast enhanced images may provide more accurate data and reduce the number of data points required to produce statistically significant results.

SONOGRAPHIC ASSESSMENT OF PERFUSION DEFICITS IN ACUTE MIDDLE CEREBRAL ARTERY INFARCTION USING TRANSCRANIAL GREY-SCALE HARMONIC IMAGING TECHNIQUE

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Background and Purpose

First reports indicate the possibility to display cerebral perfusion deficits in acute ischemic stroke, using transcranial grey-scale harmonic imaging with ultrasound contrast agent (UCA) bolus injection. We performed a prospective patient study to investigate this approach.

Methods

Within 12 h and 72 ±6 h after onset of symptoms, 22 consecutive patients suffering from acute middle cerebral artery infarction, were investigated with transcranial grey-scale harmonic imaging technique after UCA bolus injection (Levovist™). The findings were compared with those of cranial computed tomography (CCT) and normalised time-intensity curves in regions of interest of both affected and unaffected hemisphere were analysed.

Results

14/22 patients suffered from MCA occlusion as diagnosed by duplex sonography. 11/22 patients had a symptomatic, high graded extracranial stenosis or occlusion of the internal carotid artery (ICA). The lesion patterns were 20 territorial infarctions and two lacunar infarctions. The median initial NIH-stroke scale score was 15 points. Corresponding to the area of infarction demarcated in CCT, in 11/14 patients with sufficient insonation conditions, a markedly hypointense area, representing the perfusion deficit, could be visualised by grey-scale harmonic imaging. In a total of 28 hemispheres, we found a sensitivity and specificity of 78.6% and 92.9%, respectively for harmonic imaging in predicting the occurrence and localisation of a final infarction. In 8/11 patients the slope and the area under the curve (AUC) of the time-intensity curves were significantly diminished in the area of infarction in comparison with the reference area.

Conclusions

It is possible to display cerebral perfusion deficits with transcranial grey-scale harmonic imaging and UCA-bolus injection. Hypoperfusion can be evaluated by analysing the corresponding time-intensity curves.

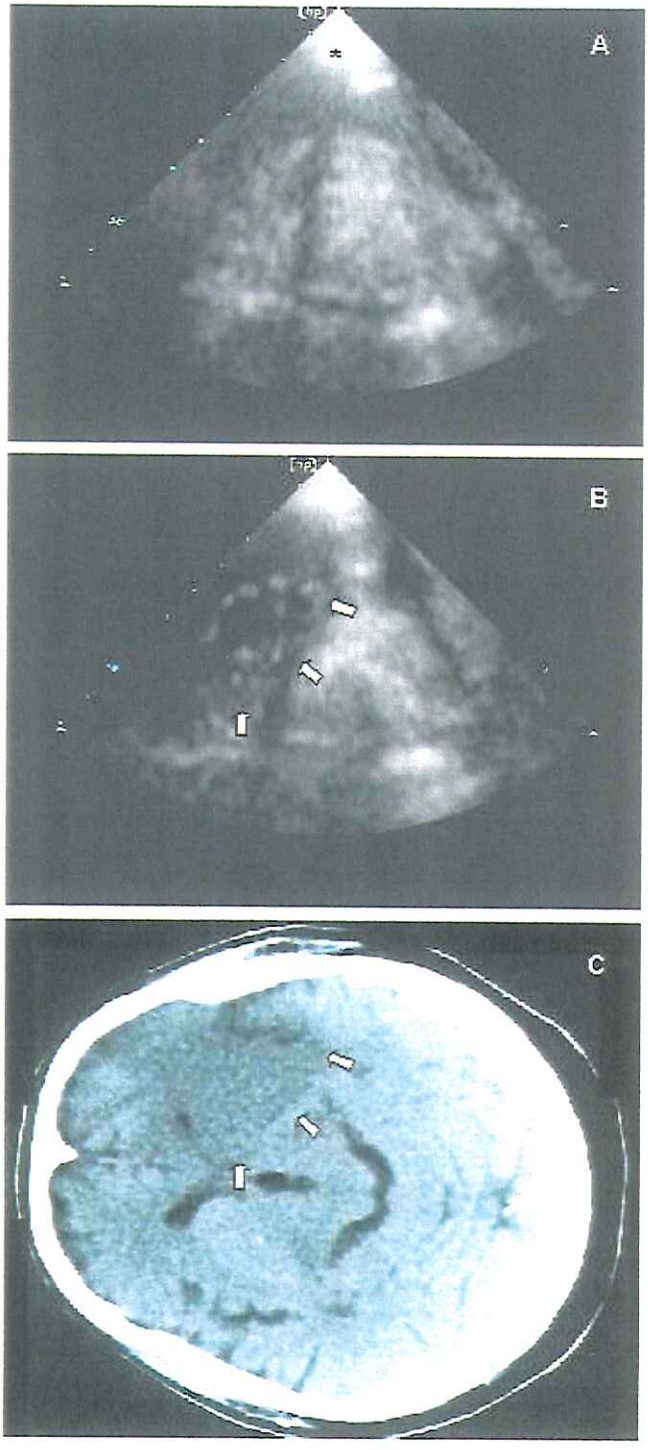

Figure 1

A. Patient GL, suffering from a territorial infarction after distal ICA occlusion: Grey-scale harmonic imaging scan after 5ml, 400mg/ml Levovist™ intravenously (2 h after onset of symptoms). Unaffected hemisphere.

B. Corresponding symptomatic hemisphere with acute MCA and ACA infarction. Note the infarction as hypointense area.

* : near field artifact

C. Cranial CT scan of patient GL with demarcation of the middle cerebral artery infarction in the left hemisphere (9 h after onset of symptoms).

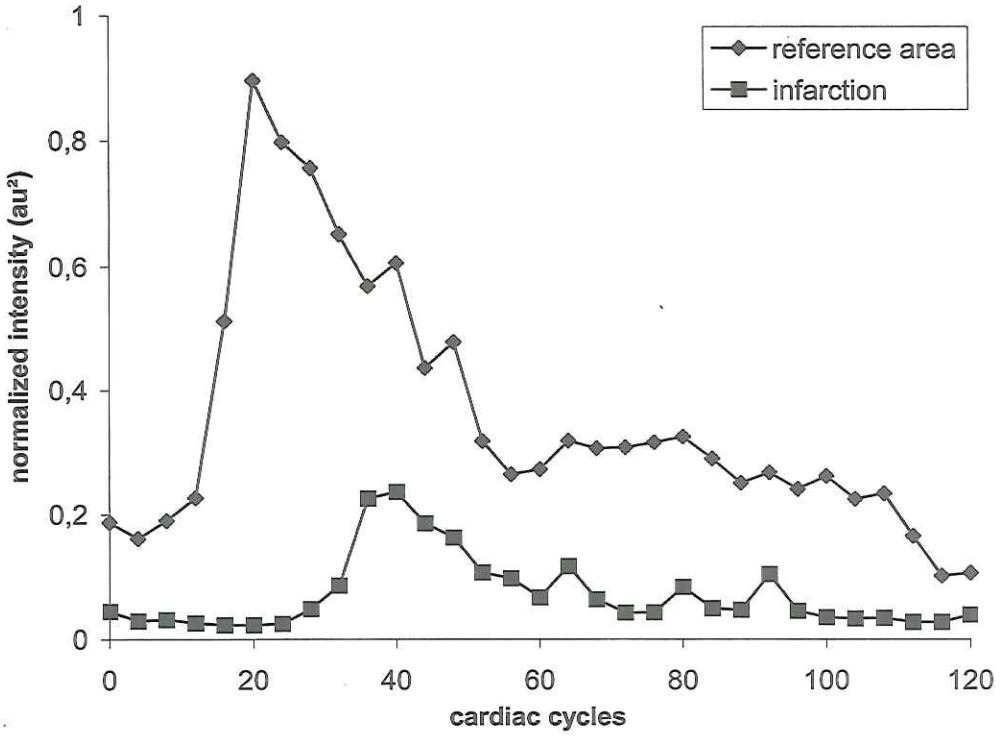

Figure 2

Time-intensity curves, of the area of infarction and the reference area

(patient GL, space-occupying territorial infarction after distal ICA occlusion), 2 h after onset of symptoms: Note the delay and inferiority of contrast enhancement within the area of infarction, compared to the reference area.

ULTRAHARMONICS: A NEW DETECTION TECHNIQUE FOR ULTRASOUND CONTRAST AGENTS

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Harmonic Imaging is a technique that was largely developed for use with ultrasound contrast agents. The hope was that microbubbles would have a strong second harmonic response in comparison to the second harmonic response of the tissue. This assumption proved to be not entirely correct. Although harmonic imaging provided an improvement, the non-linear properties of tissue caused sufficient generation of second harmonic signals which in many cases, "masked" the microbubble response. Newly developed techniques have been focused at minimising the non-linear tissue component. These techniques include high-MI modes, such as Harmonic Power Doppler, and more recently, low-MI modes, such as Power Modulation and Pulse Inversion.

Recently, a new contrast detection modality called Ultraharmonics has been introduced. Like Harmonic Power Doppler, it is a high-MI technique. However, instead of using multiple pulses with a wall filter to remove unwanted tissue harmonic signal, the signal is removed with an RF filter. It has been discovered that encapsulated microbubbles emit broadband energy when fragmented (i.e., not just at the harmonics). Simulations using the Gilmore-Akulichev equation indicate free microbubbles also emit strong broadband energy at medium-MI levels (0.5 or so). However, tissue only has sufficient energy at the harmonics of the transmit signal. If the RF filter is placed between the second and third harmonic, unwanted tissue signal can be reduced dramatically. This technique is made possible by a broadband transducer called the s3, which has a bandwidth sufficient enough to allow signals to be transmitted at 1.3MHz, and received at 3.6MHz.

Ultraharmonics enjoys many benefits as a detection technique. Compared to Harmonic Power Doppler, motion artifacts are minimised making it much easier to use in practice. Additionally, Ultraharmonics has excellent resolution. The higher receive frequency and higher line density increase the lateral resolution. Axial resolution is also improved at the higher receive frequency. Long transmit pulses can be used without compromising axial resolution and therefore sensitivity can be maintained.

POWER DOPPLER

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Power Doppler was the first, and remains the most popular method for the imaging of myocardial perfusion with ultrasound. While many of its shortcomings have been overcome by the advent of newer techniques such as pulse inversion and pulse inversion Doppler, these methods have not rendered power Doppler obsolete. Indeed, there are still situations where power Doppler is the imaging method of choice. This presentation will attempt to explain power Doppler and identify its principal strengths.

Power Doppler methods arose from the observation that high MI ultrasound is capable of disrupting bubbles. When the shell is broken, free gas is released which is driven to resonance by the sound field, producing a strong, highly non-linear echo of brief duration. These gas bubbles are unstable, and within a very short time diffuse into the surrounding medium. How long this takes is crucial to the efficacy of power Doppler: the shorter the better. Although the physics is too complicated for us to resolve a precise picture of the process, we know that bubbles of highly diffusible, highly soluble gases (such as air) disappear more quickly than those containing lower solubility gases such as perfluorocarbons, and we know that exposure to more intense, lower frequency (i.e., higher MI) ultrasound also speeds bubble dissolution.

The major challenge in myocardial perfusion imaging is to suppress the rather strong echo from the myocardial tissue. Because the echo from a disrupting bubble is rich in harmonics, harmonic imaging might seem the obvious detection method. However, at the high MI necessary to disrupt the bubbles, propagation (or "tissue") harmonic produces an intense echo from the muscle itself. It is therefore well known to be necessary to use some sort of subtraction procedure to image myocardial contrast agent. This requires registration of a baseline image with post contrast ones, a procedure that is time consuming, operator dependent and never completely effective.

In essence, power Doppler performs this subtraction in real time. A series of two or more pulses are transmitted in rapid succession into tissue, in much the same way as they are for conventional colour Doppler. The first pulse begins bubble disruption, so that the echo from the second pulse is much weaker; typically the bubble and its echo have gone by the third or fourth. Successive echoes are subtracted, so that power Doppler detects the difference between echoes. For stationary tissue, power

Doppler gives nothing, for a disrupting bubble a large signal is produced. The image thus produced is really an image of 'decorrelation', that is, the degree of change in the echoes between pulses. Because the entire bandwidth of the signal is used, the method can produce images of very high resolution. Because the echo from a bubble disrupting is stronger than that which it gives when not disrupting, it is a very sensitive, in fact at present the most sensitive, way to detect bubbles in high dilution when hidden by tissue. The method is typically implemented as an overlay to a greyscale image, which might be in fundamental or harmonic mode.

There are, however, problems. For perfusion imaging, this is not a real time method. Once bubbles have been destroyed in the microcirculation, it takes a number of seconds for new bubbles to reperfuse the imaged area, so triggering is necessary. If the tissue moves between pulses, its echo decorrelates (which is, in fact, the Doppler effect), producing a signal seen as a flash artifact. The key is to arrange the bubble echo to decorrelate faster, so that the sequence of pulses can be sent before the tissue has had time to move. This requires a high pulse repetition frequency and is one reason that air-based agents work so well with power Doppler. It is also possible to use harmonic filtering to help with tissue motion suppression, though this is limited by the same tissue harmonic effect described above. Practical expedients to subdue motion artifact will be discussed: these include careful attention to the trigger timing, for which the onset of the t-wave is a good starting point. It often appears that power Doppler images have a lower dynamic range than greyscale ones, but it should be appreciated that this is not a fundamental consequence of the method, but rather a reflection of the way in which it is implemented in many scanners. The power Doppler dynamic range should be placed against that of the final, subtracted image when comparing it to greyscale harmonic imaging. Perhaps the most fundamental physical limitation of the method is the requirement that bubbles must be disrupted in all regions of the field of view in order to see perfusion in all the imaged segments. The transmit field is not, however uniform, the peak intensity (and therefore the MI) decreasing with depth and lateral location in the sector. New transducer and transmitter technology is required to address this problem effectively; it is not clear to many manufacturers that this investment would currently be justified.

Power Doppler performs best when sensitivity to contrast, rather than real time imaging, is the major objective. It is also best with air-based agents and when tissue motion is not too severe. It is heavily dependent on the uniformity of the transmit field, something that a new generation of beam formers may be able to help with. It is the method of choice for destruction-reperfusion imaging when accuracy is valued over speed. It remains the most popular approach to perfusion imaging because of its intuitive and, compared to other methods, relatively consistent performance. It has many proponents, who keep it in reserve for whenever low MI, real time methods fail.

LOW MI NON-LINEAR IMAGING TECHNIQUES FOR REAL-TIME DETECTION OF PERFUSION USING CONTRAST MICOBUBBLES

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Detection of perfusion with contrast agents was first performed with techniques requiring high amplitudes (or Mechanical Index, MI), like Harmonic Power Doppler. Those techniques relied on the signals from bubble destruction and thus the echoes increased in amplitude with increasing MI. To counter the excessive destruction of contrast microbubbles, triggered imaging was used where an image is acquired once per cardiac cycle. In the last two years *real-time* techniques were developed. In cardiology the real-time techniques offer wall motion monitoring in addition to perfusion information, and in radiology they offer observation of liver and other organ perfusion. In order to avoid bubble destruction very low MI's are used (0.1-0.2) and to suppress tissue echoes only the non-linear part of the echoes are detected. At such low MI's, bubble echoes contain non-linear components while tissue does not, making perfusion detection possible.

Some of the low MI non-linear techniques used today for real time detection of perfusion are: Pulse Inversion (PI), Amplitude Modulation (AM), and Sub-Harmonic Imaging (SHI). With PI and AM it is required that 2 or more pulses of alternating sign or amplitude are transmitted down each line. With SHI one pulse is adequate but two or more pulse versions combined with PI may also be beneficial in eliminating the linear (fundamental) signals. Since for real time imaging a low MI is needed the echoes from the perfused tissue have small amplitudes. Both PI and AM techniques are very well suited for small signals because they eliminate the strong linear components, thus emphasising the non-linear ones. In addition, the elimination of the linear components with these techniques also results in improved effective axial resolution.

In PI the odd harmonic components are eliminated and the even are enhanced. In a system where only fundamental and second harmonic components are present, the fundamental is eliminated and the second harmonic is kept. Variations of PI include more than 2 pulse ensembles (like Power Pulse Inversion), and combination of the inverted echoes that results in incomplete cancellation of the fundamental to enhance the overall signal in a desirable way. In AM the differential nonlinearity between two states (a low and a high) is detected. In the limiting case where one state is low enough that may be considered linear and the other state is non-linear, AM effectively subtracts the scaled linear fundamental component from the 2^{nd} pulse echoes, thus leaving in only the non-linear components. AM, like PI, offers increased effective resolution.

One difference between PI and AM is that PI eliminates all of the fundamental and other odd harmonic components in the echoes whereas in AM both fundamental (only its non-linear part) and harmonic components are kept. The *non-linear* fundamental component in AM is the result of the unequal excitation states. The harmonic components represent energy that originated from the fundamental component. Another way of stating this is that the fundamental component in a non-linear system is non-linear as well. Since in AM two different states (a high and a low) are subtracted, the non-linear fundamental components do not cancel. Hence, it is possible to use pulses in AM that are at the centre of the transducer bandwidth and form an image based solely on the fundamental component.

The most important factor for a real-time perfusion study is low MI. Unless there is minimal bubble destruction, perfusion will not be detected no matter how good the detection technique is. Another important factor is the use of a uniform sound field so that bubbles in both shallow and deep regions are exposed to roughly the same excitation amplitude. This is achieved by using deeper focal zones i.e., by placing the focus at the bottom of the image sector. The received gain also plays an important role due to the low amplitude of both the transmit signal and returned echoes. In order to effectively detect these low amplitude echoes the received gain must be maximised. Since PI and AM are multi-pulse techniques tissue motion (between pulses) is an important factor to be considered. The use of higher pulse repetition frequencies (PRF) greatly reduces motion artifacts.

Theoretical simulations and clinical data will be used in this presentation to give physical basis and demonstrate the above non-linear detection techniques for real-time perfusion imaging. The importance of various imaging parameters will be explained, and some basic steps on how to set-up an ultrasound system for a perfusion study will be presented.

HIGH RESOLUTION HARMONIC IMAGING OF CONTRAST AGENTS WITH IMPROVED FRAME RATES

Lewis (Tom) Thomas, Kathy Quiroz, Patrick Phillips, Rob Steins, Greg Holley, and Joanne Otsuki

Acuson

The objective of any contrast agent detection technique is to maximize the specificity of the detection technique to the agent. Usually this means either increasing the signal received from the agent or suppressing signals from tissue. Contrast agents exhibit a stronger second order response to ultrasound than tissue, therefore, imaging of contrast agents by detecting the second order response of the agent to ultrasound has become common. Initially, the second order response of the agent was detected by simply filtering the received RF signal to select frequency components near twice the transmitted frequency. Later approaches used multiple (usually two) pulses of opposite polarity transmitted along the same line and the coherent summation of the received signals from each pulse to cancel the linear response. These cancellation techniques allow some overlap of the transmitted frequency spectrum and the received second harmonic spectrum, allowing increased bandwidth of the received signal and therefore improved resolution with minimal sacrifice of specificity.

The approach presented here also uses a cancellation technique to suppress the linear response of tissue and contrast agents while detecting the second order response. However, instead of using two pulses of opposite polarity transmitted along the same line, a single pulse is used on each transmit line and the polarity of this pulse is alternated on adjacent lines. Using dual receive beams, collocated signals arising from opposite polarity transmit pulses are received and these signals are coherently added together, resulting in suppressed sensitivity to the linear response of both tissue and contrast agents while enhancing sensitivity to the second order response.

The approach outlined here offers the advantage of being able to vary the line spacing of the transmit lines, gaining the ability to increase frame rate with minimal decrease in specificity to contrast agent. The implementation is complicated by the fact that with spatially distinct transmit beams of opposite polarity, the phase of the two received beams may not be exactly opposite. Fortunately, the phase errors can be calculated and corrected before combining the two receive signals, resulting in excellent specificity with improved frame rates. These techniques are particularly valuable for maintaining specificity during low MI non-destructive continuous imaging of contrast agents, precisely the imaging situation where frame rate is most valuable.

SUPER-HARMONIC IMAGING FOR IMPROVED CONTRAST DETECTION

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For ultrasound contrast agents (UCA), harmonic imaging has nowadays become fundamental since current contrast imaging methods are dominantly based on the harmonic response of UCA and mainly the second harmonic response. The differentiation between the perfused tissue and the UCA is the challenge for UCA-imaging and is described by contrast to tissue ratio (CTR). Currently, due to the limited bandwidth of the transducers only the second harmonic response of UCA is selectively imaged producing images with a superior quality than fundamental images, but still degraded and not optimal because of the harmonic generation in the path tissue and thus giving a limited CTR. We demonstrate in this study by mean of theory and measurements that the CTR increases when the harmonic number increases as shown in the figure below. To take advantage of these higher harmonics (termed here super harmonics and include third, fourth, fifth and ultraharmonics), we have developed a new phased array transducer containing two different types of elements arranged in an interleaved pattern (odd and even elements). The elements can operate separately and at a distinct frequency enabling separate transmission and reception modes. The odd elements operate at typically 2.8 MHz centre frequency and 80% bandwidth. The even elements have a centre frequency of 900 kHz with a 50% bandwidth. In-vitro measurements using this dual frequency probe show an increase of 40 dB of the CTR for super harmonic components over the conventional second harmonic system. The increase in CTR is in agreement with the calculations using existing models for the response of encapsulated bubbles and known theory of non-linear propagation. A clinical pilot study was also carried out and demonstrated the efficacy of superharmonics for myocardial perfusion.

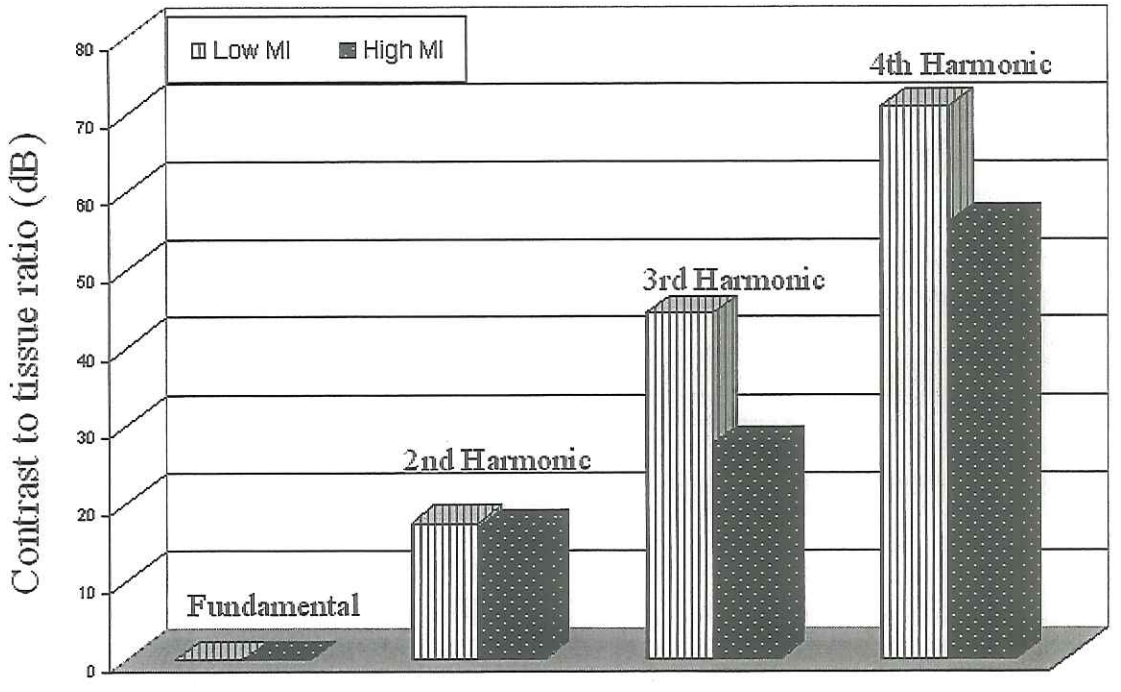

Figure. Simulation of the contrast to tissue ratio for a low and a high MI.

An ensemble of encapsulated gas bubbles was interrogated using a 1.7 MHz, 3-cycles ultrasound wave through an attenuating medium (attenuation of 0.7 dB/MHz/cm and B/A of 6.75).

LIVER PHASE MICROBUBBLES: SPECIFICITY IS THE KEY

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Why might this approach work?

It is known that some microbubbles are selectively retained within the liver and spleen after completion of the vascular phase. The agents with well-documented evidence of this are Levovist (Schering), Sonazoid (Nycomed Amersham), Sonavist (Schering), and BR14 (Bracco). Whatever the mechanism, it is clear that certain microbubbles enter a liver and spleen specific phase after completion of blood pool enhancement. They thus have kinetics analogous to SPIO agents in MR. Just as in MR, thus, liver specific agents could be useful both in increasing specificity, as many benign liver lesions contain normal liver tissue (eg focal nodular hyperplasia, regenerating nodules) while malignant lesions do not.

From an imaging aspect, the key point is that the microbubbles are widely distributed and stationary (or near stationary) in the tissue parenchyma at this time. They cannot therefore be detected using conventional Doppler enhancement. Non-linear modes, which can detect stationary microbubbles, are needed, and a number of alternatives are now available. The best choice involves consideration of many factors, including the ultrasound equipment available, the clinical problem being addressed, and the microbubble being used. Currently, these modes can basically be divided into modes, which detect resonance effects, such as second harmonic and pulse/phase inversion imaging, and modes, which rely on microbubble disruption producing a loss of correlation of successive ultrasound pulses. A great advantage of "disruptive" or loss of correlation based modes (such as "SAE" or "ADI") is that it is easy to capture a conventional and a microbubble specific image at the same time, which may be particularly useful if we are trying to increase specificity as we can study the distribution of microbubbles within and without a lesion.

Liver phase imaging does indeed improve specificity

Results so far are highly encouraging. Our own group has studied the late phase distribution of the microbubble Levovist (5 minutes after injection) using SAE. In this study, we observed significant and marked differences in the uptake between different lesion types. Metastases and HCC showed low uptake in every case. Hemangiomata also showed significantly low uptake, but with more variability,

some cases showing only slightly less signal than the adjacent liver. By comparison, all cases of FNH exhibited uptake at a level similar or identical to the adjacent liver. A complete separation was observed between FNH and other lesion types, and this was observed both objectively and subjectively suggesting that the technique could be used as a diagnostic test for FNH. As the only other condition which showed intralesional SAE at a level comparable with the adjacent liver was hemangioma (in some cases), it may also be that the presence of marked late phase SAE is a useful marker for the benign nature of a lesion.

Further work from our group using Levovist with ADI supports these findings, and also suggests that areas of fatty sparing can be characterised in a similar fashion. This is strongly supported by data from a major study using Levovist and phase inversion from Albrecht et al in Berlin. Similar findings are also seen using the newer liver specific microbubbles, particularly Sonazoid. Further studies are clearly needed, however, particularly in determining, how reliable this method is in distinguishing HCC from nodular regeneration.

Why characterisation is so important

The characterisation of liver lesions, and in particularly the accurate diagnosis of benign liver lesions is a very important part of liver imaging. It is a problem, which has become probably more, rather than less, straightforward as the sensitivity of ultrasound has improved and clinicians and patients have become rightly more demanding of accurate diagnoses. Examples include the problem of a common, incidental lesion found on ultrasound (such as haemangiomas, or focal steatosis / fatty sparing), the characterisation of rarer lesion types (such as focal nodular hyperplasia or adenomas), and the distinction between hepatocellular carcinoma and nodular regeneration in a cirrhotic liver. Although in skilled hands, ultrasound can characterise lesion types with reasonable accuracy, it is rarely possible to make an completely definitive assessment with non-cystic lesions on a single conventional ultrasound. Correlative imaging, follow-up or biopsy are often necessary. A liver phase microbubble ultrasound, which could be performed at the same attendance by a single sonologist, could in principle be a highly cost-effective and practical way of reducing the need for further tests, and reassuring patients and clinicians if a diagnosis can be made using it. Even where the use of microbubbles merely aids decision making, by altering the prior probability (in a Bayesian sense) that a lesion is benign or malignant, this could be helpful in clinical management.

Could the late phase be the most useful time to scan?

There are several attractive features to late phase scanning. A key factor is its simplicity. Whereas "vascular phase" imaging usually requires 2 people (one to inject and one to scan) a late phase scan can be performed by one individual. Contrast can be injected in normal lighting conditions – even outside the scanning room - with the patient relaxed and comfortable. Particularly with the newer

imaging modes such as ADI, it is then a simple matter to acquire a few images several minutes after injection.

This is not to say that in some situations vascular phase imaging, especially using the newer harmonic modes can help to improving specificity. There is certainly evidence that "interval delay" imaging can characterise hemangiomas, as they typically show peripheral nodular enhancement and centripetal infilling. However, with this important exception, it is arguable that vascular phase imaging adds relatively little of clinical value to characterisation if a careful high quality baseline Doppler study has been performed. "Vascular" lesions can be enhanced, but the utility of this is debatable. It is also not clear if an interval delay approach is actually more accurate than a late phase image. By contrast, late phase imaging adds complementary and unique "microbubble specific" information to a conventional scan.

LIVER-SPECIFIC LATE PHASE: SENSITIVITY IS THE KEY

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Despite its routine clinical use in the diagnosis of focal liver lesions, ultrasound has only a moderate detection rate of primary and metastatic liver tumours. The sensitivity of US in the detection of solitary focal liver lesions lies between 53% and 84%. Most lesions missed on US are either small (the sensitivity for detecting lesions < 1 cm is only 20%) or almost isoechoic and thus mainly reflect the relatively poor contrast between lesion and normal liver parenchyma.

The main disadvantage of sonography in comparison to CT or MR imaging in this application so far was the lack of contrast agents for liver ultrasound. CT and MR imaging rely heavily on contrast agents for detection and characterisation of focal liver lesions. Liver-specific contrast agents for MR-imaging have recently become available and MR imaging using these agents is now considered the most sensitive non-invasive modality for detecting liver metastases.

In recent years sonographic contrast agents which can be used for liver imaging have become available. Some of these agents (e.g. Levovist, Schering AG; Sonavist, Schering AG; Sonazoid, Nycomed Amersham; BR14, Bracco SPA) have liver-specific properties, i.e. they accumulate in normal liver parenchyma late after the injection and after clearance from the blood pool. This late phase enhancement is liver-specific as it spares many focal lesions such as metastases in the same way as liver-specific MR agents do. Although the precise mechanism of the late microbubble accumulation is not established for all agents displaying this feature, the temporal course and the distribution suggest interaction with the reticuloendothelial system, and Kupffer-cell up-take has been proven for some of these agents.

Visualisation of this late phase requires contrast-specific imaging techniques such as phase or pulse inversion. When scanned in phase inversion during the late phase, normal liver parenchyma shows strong enhancement. As the enhancement spares metastases, these stand out as echo-poor or almost echo-free enhancement defects. This improves the conspicuity of metastases markedly and improves their detection. Two larger series have systematically studied the influence of late phase enhancement with Levovist on the sensitivity in the detection of individual metastases. These studies showed an improvement from 63% and 71% to 91% and 88% respectively. In an on-going study we are

comparing contrast enhanced ultrasound in the late phase of Levovist with dual phase spiral CT. Preliminary results show almost identical sensitivity values (89% and 91% respectively) suggesting that contrast enhanced US may be equivalent to dual phase spiral CT in detecting liver metastases.

Common benign lesions such as haemangiomata, focal fatty change/sparing and focal nodular hyperplasia on the other hand show considerable contrast enhancement in the late phase which is similar to that of normal liver. These lesions can often not reliably be differentiated from metastases on unenhanced US and many patients with benign lesions therefore go to CT or MR to rule out metastases. Contrast enhanced late phase pulse inversion imaging can identify these benign lesions. In the ATL multicentre study, specificity was thus increased from 59% to 88%. With the use of contrast enhancement, ultrasound can correctly identify benign liver lesions and these patients no longer require CT. We therefore think that contrast enhanced late phase sonography is particularly well suited to rule out metastases. Patients with a negative contrast ultrasound should not require further liver imaging in the future.

VASCULAR PHASE IMAGING FOR SENSITIVITY IS THE KEY

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The therapeutic approach to both primary (i.e. hepatocellular carcinoma; HCC) and secondary (i.e. metastatic lesions) focal liver malignancies has dramatically changed in the last few years : new modalities such as percutaneous ablative therapies (ethanol injection, PEI; radiofrequency, RF; laser; microwaves)) and liver transplantation (OLT) have been introduced, in addition or in competition with pre-existing modalities, i.e. surgical resection, systemic chemotherapy, segmental chemoembolisation, hypoxic perfusion, etc... Thus, in order to decide on the appropriate therapeutic choice, accurate detection and intrahepatic staging (i.e. high sensitivity) by means of imaging modalities is mandatory. In most cases ultrasound is the first imaging modality, but, due to patients' limitations (obesity, gas, poor collaboration, etc…) and technical limitations (small lesion size, poor contrast resolution, etc…), the sensitivity of unenhanced sonography is generally lower than that of triphasic helical CT, contrast-enhanced MR and intraoperative sonography.

For HCCs, the reported detection rate of sonography varies widely from 46% to 95% for lesions measuring less than 2 cm in diameter, and from 82% to 93%. for HCCs between 2 and 3 cm, while it goes down to 59 – 68% for infiltrative and atypical HCCs. Bi- or triphasic helical CT is reported to achieve a detection rate of 89-92%, slightly inferior to that of intraoperative US (94 - 96%).

For the most frequent type of liver metastases (hypovascular lesions) sensitivity rates of 57% - 92% (as low as 20% for lesions smaller than 1 cm) for sonography, 65 – 87% for conventional contrast-enhanced CT, 85 – 90% for MR with liver-specific contrast agents and 90-95% (50% for lesions smaller than 1 cm) for intraoperative US have been reported.

Since July 2000 we have been performing a clinical study comparing the sensitivity of contrast enhanced US (CEUS) with that of contrast – enhanced biphasic or triphasic helical CT. CEUS is performed following intravenous administration of a second generation US contrast agent (Sonovu™ , Bracco, Milan, Italy) (2.4 - 4.8 ml), using contrast specific-software, either coherent contrast imaging (Acuson, Mountain View, USA) or phase inversion (Siemens, Erlangen, Germany), in continuous mode with very low MI (0.1 - 0.2) in order to avoid microbubble disruption and study dynamically the Vascular Phase. This consists of an arterial phase (15 – 25 sec), an early portal phase (45 – 60 sec) and a complete portal phase (90 – 120 sec).

In the group of 28 patients with known liver cirrhosis and elevated serum levels of AFP, SGOT and SGPT and with at least one questionable nodule found with B-mode sonography, sensitivity of CEUS

and of CT are almost equivalent: in 25/28 cases the detection rate has not showed differences (58 vs. 58 lesions), while in 3 patients conspicuity of CT has been superior (3 vs. 11 lesions) mostly due to the typical limitations of US (obesity, technical difficulty to perform panoramic scans of the entire liver, etc…). The typical vascular pattern of HCCs (high and rapid peak of enhancement in the arterial phase, followed by a relatively quick "wash out" in the portal phase) has been visualised in 54/61 HCCs, while in the remaining 7 inhomogeneous enhancement with CEUS has been related to necrotic changes. Similar enhancement modality has been found in 3 patients with hypervascular liver metastases from neuroendocrine tumours, with detection rate equivalent to that of helical CT (9 out of 9 lesions).

Vascular phase and continuous mode are likely of crucial importance for the detection of multifocal hypervascular liver lesions.

In a group of 14 patients with known history of colorectal, gastric or breast cancer, CEUS using the same vascular phase (minor signs of vascularity in the arterial phase, enhancement equivalent to that of the normal liver in the early portal phase and hypovascularity in the full portal phase) has achieved a much higher detection rate compared with that of helical CT: in 8/14 patients, 20 – 100 % more numerous metastatic foci have been detected by CEUS than by CT, with size ranging from 5 to 15 mm.

Using this technique, also the detection of hypovascular lesions during the early and full portal phases is achievable with high accuracy, likely comparable to that previously reported in the late phase of air-based contrast agents.

ULTRASOUND CONTRAST AGENTS: IMAGING THE VASCULAR PHASE

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Information about the blood flow to a liver lesion is an integral component of diagnosis of a focal liver mass on CT and MR scan. Performed routinely with intravenous contrast agents, these scans are non-specific without the blood flow information provided with contrast agent injection. Conventional ultrasound with Doppler may in some patients provide comparable information to that obtained on CT and MR scan. Unfortunately, however, Conventional Doppler is frequently unsatisfactory in large patients and for the study of deep and small liver masses.
The addition of microbubble contrast agents to enhance the Doppler signal from blood and the use of specialised imaging techniques, such as pulse inversion imaging, allow for exceptional vascular imaging of liver masses with ultrasound.

Vascular imaging with microbubble contrast agents is performed while the contrast agent is present within the vascular volume. Beginning at the time of injection, this imaging will usually last for about 2 to 3 minutes. Bolus injection of a small volume of agent is optimal.

Objectives of vascular imaging are two-fold:

- To depict in real-time the vascularity of a liver lesion and
- To predict the relative vascular volume of a lesion as compared to the adjacent liver.

Vascularity features include:

- the presence of vessels,
- their distribution
- their number and
- their morphology.

To allow for depiction of long and continuous lengths of lesional vessels, a low MI non-destructive technique is optimal. A high MI technique which destroys bubbles as they appear within the imaging plane will prevent visualization of any significant length of lesional vessels.
Perfluorocarbon contrast agents are optimal for vascular imaging as they produce non-linear harmonic oscillation with exposure to a low MI ultrasound field.

Vascular volume features are most commonly obtained with a higher MI using an ***interval delay technique.*** At the peak of arterial enhancement, the mechanism on the ultrasound machine is frozen for an interval of 8 to 10 seconds. During this interval, the contrast agent will continue to perfuse the liver and the lesion under study. A brief reinsonation with a high MI destructive mode will disrupt the accumulated bubbles, often in a single frame. This produces a bright but brief enhancement in proportion to the volume of bubbles accumulated during the delay. Comparison of the enhancement of the liver lesion to the enhancement of the adjacent liver will provide an assessment of their relative vascular volumes.

Images obtained after an interval delay are optimally stored as short cineloops, which allow for review on a single frame basis. The first frame is usually the most valuable as the bubble destruction is most often complete following this single frame, appearing as a bright ***single frame flash.*** If a large volume of a perfluorocarbon contrast agent is given, however, bubble destruction on the first frame may involve only the near field, with destruction in the mid and far fields occurring on successive frames. This has the effect of appearing as if a veil has been dropped over the image and we refer to this multiple frame observation as ***the greyscale veil.***

Vascular volume assessments, in comparison to vascularity assessments, may be performed with both the air containing and the perfluorocarbon contrast agents. Both classes of contrast agent will disrupt with a high MI and some bubble destruction will also occur even with a lower MI level. These destructive techniques are more sensitive than are the vascular imaging techniques such that evidence of accumulated microbubbles may occur even in the absence of documented flow.

Timing of interval delay sequences is essential to provide a complete documentation of the enhancement features of a liver mass. We routinely perform an interval delay sequence at the peak of arterial enhancement. Further interval delays are then performed on the basis of the result of the arterial phase interval delay. To obtain information about the contrast agent volume within a lesion in later phases of enhancement, we inject a separate bolus, and perform delays of 30 seconds, 60 seconds, and 90 seconds. Longer delays, to show slow filling of a lesion such as a hemangioma, may also be performed but are technically more challenging and often less rewarding. Portal venous phase imaging is optimal at 50 to 70 seconds following injection.
In the future, we are hopeful that it will not be necessary to perform interval delay techniques for vascular volume assessments. Rather, improved low MI techniques will be able to show in real-time the accumulation of the microbubbles over time.

A summary of our vascular imaging in commonly encountered liver lesions follows.
Hemangioma – shows marginal vascularity, often in clumps and pools. Interval delay shows

peripheral nodular enhancement of brighter intensity than seen in the adjacent enhancing liver with centripetal progression on longer interval delays.

HCC – shows profuse and diffuse vascularity often with aberrant morphology. Interval delay shows enhancement equal to and more often in excess of the adjacent liver in the arterial phase with more rapid washout in the portal venous phase of enhancement.

Metastases – are variable depending on the vascularity of the primary lesion. Most commonly these lesions show sparse and often marginal vascularity. Interval delay shows no or weak enhancement or may show marginal enhancement without centripetal progression. Metastases from a vascular primary are often similar to HCC on contrast enhancement.

FNH – is a hyperarterialized mass often showing a stellate vascular pattern, a large and tortuous feeding artery and a non-enhancing scar.

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ASSESSMENT OF VASCULARITY IN HEPATIC TUMOURS USING CONTRAST-ENHANCED DYNAMIC FLOW

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Introduction: Dynamic Flow by TOSHIBA Power Vision 8000 is a technique developed to represent blood flow with high resolution images based on the wide Band Doppler technique. Without contrast agent Dynamic Flow can visualise blood flows with high resolution, avoid blooming, and accurately express small blood flow. With contrast agent Dynamic Flow can visualise Perfusion Signal in capillary vessel. Dynamic Flow can accurately visualise small vessels and visualise perfusion with less blooming, which helps the understanding of hemodynamics and the correct localisation of perfused area.

Purpose: The aim of this study was to evaluate ultrasound findings of hepatic tumours by using Dynamic Flow with contrast agent, Levovist (Schering AG, Germany).

Materials and Methods: Forty-two patients with hepatic tumours untreated before examinations were examined with Dynamic Flow after intravenous bolus injection of 300mg/ml, 2.5g of Levovist. These tumours included seventeen hepatocellular carcinomas (HCCs, 21-158mm in diameter, mean diameter 61mm), four intrahepatic cholangiocarcinomas (23-70mm, 48mm), ten metastatic tumours (11-90mm, 36mm), six hemangiomas (26-118mm, 63mm) and five focal nodular hyperplasias (23-86mm, 41mm). All HCCs and intrahepatic cholangiocarcinomas were resected and confirmed with histopathological examinations. Ultrasound images were recorded on digital videotape or hard disk recording system. Contrast enhancement appearances including tumour vessels (intratumoral tortuous or irregular formed vascular images) or intratumoral perfusion images in early vascular phase and perfusion defect in delayed phase were analysed.

Results: In HCCs, tumour vessel images were depicted in sixteen tumours (94%) and fifteen (88%) showed diffuse or mosaic perfusion images in early vascular phase. In delayed phase, thirteen (76%) showed perfusion defect images. In intrahepatic cholangiocarcinomas, one tumour showed tumour vessel

like vasculature and diffuse perfusion image, whereas three lesions demonstrated punctated or linear vascular images and no perfusion image. In metastatic tumours, no obvious tumour vessel or perfusion image were depicted in any tumours, while nine tumours revealed only punctated or short linear vessel images located in the tumour margin predominantly in early vascular phase. All six hemangiomas showed no vascular images in the tumour, but marginal spotty enhancement patterns with fill-in and enhanced area remaining in delayed phase were observed. Focal nodular hyperplasias revealed spoke-wheel like vascular images in three and central scar images in three lesions.

Conclusions: Contrast-enhanced ultrasound using Dynamic Flow with Levovist will be a new useful technique for differential diagnoses of hepatic tumours.

FUTURE ENHANCEMENTS FOR CONTRAST ECHOCARDIOGRAPHY

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Over the last few years, there have been several advancements in the area of contrast echocardiography. A major area of research has been in understanding the interaction between ultrasound and microbubbles. This increased knowledge has fuelled equipment manufacturer's progress and has resulted in the invention and introduction of new imaging modalities, at low-MI's as well as high-MI's. New non-linear detection techniques (e.g., Pulse Inversion, Power Modulation) focused on improving the signal/noise ratio (i.e., contrast/tissue ratio) at low-MI's has resulted in real-time visualization of ultrasound contrast agents. Insights into microbubble destruction from the work of the Thoraxcentre (de Jong et al) and UCDavis/UVA (Ferrara et al) as well as others has led to improvements in high-MI techniques. Recently, new high-MI B-mode imaging techniques (Ultraharmonics) and improvements in Harmonic Power Doppler have been introduced.

Agilent Technologies offers three imaging techniques for MCE research; Power Modulation, Ultraharmonics and Harmonic Angio. Power Modulation offers wall motion information simultaneously with myocardial opacification and easy image acquisition due to its real-time capabilities. Ultraharmonics is easy to use and offers very high resolution imaging with minimal artifacts. Harmonic Angio offers excellent sensitivity. When used in combination with the s3 transducer, designed to produce a more uniform power field, these modalities offer a major advancement for contrast echo.

Despite these and other advancements, contrast echo has still been slow in clinical acceptance, partially because there are unresolved issues with the system and transducer technology. For system technology, the important parameter of bubble/tissue ratio always needs to be improved. Signal to noise ratio is paramount but there are several noise sources other than non-linear tissue signals. These sources include "flash" artifact for multi-pulse techniques, system thermal noise, imperfect matching of transmit waveforms and imperfect RF filtering. Reducing these noise sources will improve sensitivity and ease-of-use because system settings will become less critical.

For transducer technology, bandwidth is a critical factor. Bandwidth on the s3 transducer enables Ultraharmonic imaging but further increases in bandwidth will allow exploration of higher harmonics, which could increase sensitivity (i.e., bigger signals in the system for same returned signal from the

bubble). Increased bandwidths will further allow for destruction of microbubbles at lower frequencies and imaging at higher frequencies to increase resolution. The future of transducers also involves phased matrix probes, similar to those from Volumetrics. These transducers offer the promise of 3D imaging but also allow for elevation control of the transmit focus. The ability to electronically steer the elevation focus in the same manner as the lateral focus will allow for increased depth-of-field (i.e., more uniform power field) as well as the ability to more tightly focus the transmit beam for localised bubble destruction.

There are also clinical issues to be resolved before myocardial contrast echo becomes a routine procedure. The manner(s)in which MCE data is displayed and the way MCE is used for coronary artery disease detection need to be determined. Reproducibility is critical in serial studies and stress exams. System software must better integrate MCE with stress protocols to improve consistency and accuracy. Since many existing CAD detection techniques (i.e., Dobutamine, exercise) change the hemodynamics of the patient and effect the LV contrast concentration and the amount of attenuation, the slope and plateau of the reperfusion curves are necessarily affected, which complicates quantification. On-line quality measures need to be added to ensure that these effects are either corrected for or mitigated. Once data is acquired, it must be presented in an intuitive manner. Parametric imaging or alternate displays based on quantification may reduce complexity and help diagnosis.

A FAST ROTATING PHASED ARRAY FOR REAL-TIME THREE-DIMENSIONAL DATA ACQUISITION, PRINCIPLE OF OPERATION AND CLINICAL RESULTS

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Introduction

A fast rotating phased array transducer was designed in order to scan a conical section of the heart at high scan rates. The array has 64 elements with a pitch of .21 mm. The central frequency is 2.8 MHz, while the bandwidth allows for harmonic imaging. The rotating part has a diameter of 15 mm. The rotating transducer is connected to a stationary cable by means of a 82 contact slip ring device. Typical rotation rate is 240-480 rpm.

Data acquisition

Data is acquired in a period of 10 seconds using a GE Vingmed System V mainframe and stored in a PC. The rotation of the probe requires no additional interfacing.

Data processing

The data is stored as a sequence of frames in their raw (polar) format i.e. range versus scan angle. The frames are linearly related to rotation angle. The data set is thus fully described in a spherical co-ordinate system. The rotation speed is recovered by a cross-correlation of a reference plane with the total data set, yielding azimuth defined by rotation. Volume reconstruction in the classical Cartesian co-ordinate system is obtained by defining a XYZ grid, mapping this grid in the spherical domain and subsequent interpolation of the data onto the grid points. Because of the equal spacing of the data in the spherical domain this process is performed by a fast look-up table algorithm. The resulting cubical data set is in raw format accessible for three-dimensional analysis packages.

A clinical need in echocardiography is the estimation of left ventricular volumes. The contours of the left ventricle are traced in the raw data frames without any scan conversion. The LV volume, contained in the sequence of contours along the azimuth direction in the spherical domain, can be obtained directly using a spherical volume integral.

Another advantage of processing in the spherical domain is the fusion of multiple heartbeats into a synthesised single heartbeat. This can be achieved by realignment of the spherical data in the azimuth range using the ECG as synchronisation. Asynchronous probe rotation produces a random interleaved volume sampling.

Application of contrast

The rotation of the probe sometimes results in a partial loss of definition of one of the lateral LV walls. This hampers the tracing of the ventricular boundary. Opacification of the ventricular chamber by contrast material will improve the success rate of the tracing procedure.

Ultrasound contrast enhancement of the myocardium is difficult to detect when the interrogating beam is destroying the material. Due to the continuous rotation of this probe the spatial average of the beam is reduced by two orders of magnitude except in the centre of the scanned volume. We hope to prove that with this probe in real-time the volumetric distribution of the contrast material in the myocardium can be obtained.

Conclusion

We propose that the construction and analysis of three-dimensional data sets obtained from a fast rotating sector scanner is performed in the spherical co-ordinate system, produced by the probe itself. The procedure is efficient, accurate and time saving.

Applications of contrast material will enhance the accuracy of LV-volume estimation and allow for non-destructive analysis of the three-dimensional distribution of the material over time.

WIDE-BAND CONTRAST IMAGING TECHNOLOGIES

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Recently, there have been a growing number of reports concerning the usefulness of contrast echo imaging as a result of the expanding clinical application. Contrast Echo imaging permits myocardial and hepatic parenchymal perfusion to be clearly visualised and is useful for the diagnosis of ischemic heart disease and hepatic cancer, as well as for assessing the effectiveness of therapy for hepatic cancer. Contrast Echography is rapidly moving from the research phase to the clinical phase. High spatial resolution and high contrast resolution, as well as high sensitivity with superior real-time characteristics, are required in the contrast echo imaging method. For the abdominal region, in particular, the depiction of fine blood vessels is of great diagnostic importance. We describe wide-band imaging technologies that have been developed to achieve high spatial and contrast resolution based on wide-band transmission/reception.

In Gray-scale Second Harmonic method and Pulse Inversion method, tissue images based on tissue harmonic components cannot be separated from the echoes from contrast agent. This means that the THI components limit the level of detection of contrast agent. The conventional Colour Doppler and Harmonic Doppler methods, on the other hand, are able to visualise the signals from contrast agent alone, although these methods suffer from a number of limitations such as a low frame rate and poor spatial resolution which limit their diagnostic usefulness.

Dynamic Flow is a high-quality, high-sensitivity contrast imaging technique based on Toshiba's Wide-Band Doppler technology. While the conventional Colour Doppler method employs narrow-band transmission with a long burst wavelength, Dynamic Flow uses transmission pulses with a bandwidth as wide as that for B-mode. It also receives wide-band signals including both the fundamental and harmonics for imaging. Although wide-band transmission causes the Doppler spectrum to widen and makes it difficult to differentiate between tissue components and blood-flow components, resulting in increased motion artifacts, tissues can be successfully separated from blood-flow using the Doppler Digital Image Optimiser (DIO). The remaining clutter components are further reduced by Adaptive Image Processing (AIP). AIP is an algorithm in which B-mode images can be optimally combined with wide-band transmitted/received Doppler signals on a pixel-by-pixel basis.

Dynamic Flow realises high-resolution contrast images to be superimposed on high-quality B-mode images

Rate Subtraction images are obtained by performing transmission twice in the same direction and then differentiating the received RF signals. Through subtraction, constant surrounding tissue signals can be eliminated in order to selectively detect the non-constant contrast-agent signals. Rate Subtraction Imaging makes it possible to detect and visualise signals from bubbles alone with the same image quality as in gray-scale harmonic imaging.

As the basic technologies for realising Contrast Echo imaging with higher sensitivity and a wider bandwidth, we are developing a new ultrasound transducer, which employs piezoelectric single-crystal elements. A prototype transducer with piezoelectric single-crystal elements has achieved an electromechanical coupling factor approximately 13% higher than that of conventional ceramic transducers. In addition, the acoustic impedance, which is an important factor in acoustic coupling with the target tissues, is approximately 30% closer to that of the living body compared with conventional transducers.
This prototype transducer permits the detection of wide-band signals from contrast media with higher sensitivity.

With the expansion of the clinical application of contrast echo method, we must focus on ease of use, real-time imaging capabilities, and high-quality imaging techniques. The imaging techniques and wide-band ultrasound transducer technology that we have developed are expected to further improve the diagnostic usefulness of contrast echography.

A SIMPLE MODEL OF THE VASCULAR NETWORK FOR THE ANALYSIS OF DESTRUCTION REPERFUSION MEASUREMENTS

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Quantification of myocardial blood flow using the destruction-reperfusion method [1] is rapidly being adopted as a standard technique. Most researchers have been analysing the contrast recovery curve by fitting it to a single exponential curve:

$$S(t) = A\left(1 - e^{-t/\tau}\right).$$

They are following the analysis used by Wei *et al* [1], which implicitly followed the single perfectly-mixed tank model used in the classical indication-dilution method in physiology (see, for example, [2]). The perfectly-mixed tank yields the correct results in that (1) the initial slope of the contrast recovery curve is proportional to the total volumetric flow into the region of interest and (2) final enhancement level (the asymptote) is proportional to the blood pool volume in the ROI. However, the exponential curve correlates poorly with experimentally measured data sets, a phenomenon also observed in radioactive tracer washout studies. The explanation is simply that a network of blood vessels is far from resembling a single perfectly mixed tank. One approach to address this has been to model the vascular network as a number of mixing tanks in parallel [3]. For intravascular contrast agents, an alternative model based on parallel non-interconnecting pipes carrying plug flow may be more realistic than one based on mixing tanks. We will demonstrate that theoretically these pipes can represent a very general class of vascular networks in destruction-reperfusion studies. This will be illustrated with simple cases such as a single pipe with arbitrary flow profile and a vascular network generated using a fractal algorithm. The contrast recovery curve can be easily calculated from any specified networks. Like the single and multiple perfectly mixed tanks, the parallel pipes model also results in the well-known relationships between the initial slope and flow rate and between the asymptote and blood volume. However, the shape of the contrast curve is variable and is determined by the probability distribution of transit times. The inverse problem has also been solved: a contrast recovery curve can be uniquely decomposed into a probability distribution of blood flow pathways characterised by the transit time. In the study of vascular networks modified by ischemic injury and tumour angiogenesis, such a distribution may provide diagnostic information in addition to total volumetric flow and blood volume.

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THE FUTURE

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The major challenge for contrast agent imaging is to detect echoes from bubbles with high sensitivity and in real time, without detecting tissue, even if the tissue is moving. At the same time, an imaging method should be capable of disrupting the bubbles in a uniform and controlled way, so that reperfusion can be imaged and flow measured.

The challenge for development of the contrast agents themselves is to produce a population of bubbles whose size distribution is controlled and stable, even after cardiac and pulmonary passage. The bubbles should be easily induced into coherent non-linear oscillation in the systemic circulation, with as few bubbles disrupting as possible. At the same time, they should be capable of disruption by ultrasound of a higher intensity. The threshold of destruction should be as sharp as possible, probably meaning that the population of bubbles should have uniform properties, including size. The bubbles should be stable after mixing but before injection, and neutrally buoyant so that they can be infused easily without separating from the suspension. They should be either pure blood pool agents, or, if for example they persist during the post vascular phase in the liver or spleen parenchyma, they should do so relatively slowly so that an unambiguous blood pool phase is produced.

Although progress continues to be made on both fronts, it is clear that the recent development in contrast imaging technology have been the most dramatic. Yet it is likely that current non-linear contrast methods only scratch at the surface of what is possible. The major focus is on the controlled induction of stable non-linear oscillation of the bubbles and the detection of the echoes which result. Both are strongly influenced by the exact form of the bubble excitation, which is likely to be the focus of more work in the immediate future. Whereas the majority of current methods for detecting non-linear bubble oscillation use a two or more phase or amplitude modulated pulses, a general understanding of the way in which non-linear echoes result from a sequence of pulses with both forms of modulation is just emerging. Combining phase and amplitude modulation using Doppler methods offers the opportunity to explore higher bubble harmonics, and new means to separate tissue harmonics from bubble echoes. This will enable us to use higher MI's without the tissue harmonic interfering with the contrast image. This will, however, only be possible when we have bubbles that

produce continuous non-linear echoes without disruption at reasonably high MI's (say, 0.5). Such a development would offer a significant improvement in image signal-to-noise ratio.

It is remarkable that we have done so well with bubbles that were designed with nothing but the crudest notion of how they would behave acoustically. Now that we can specify how we would like a bubble behave in an ultrasound field, can we expect the agent manufacturers to build a better bubble for us? There are already signs that they can. For example, by uncoupling the means for the bubble's physical stability from that of its acoustic stability, we might expect bubbles to undergo stable non-linear oscillation at low MI, but disappear quickly when hit with a high MI pulse. At present we would choose a perfluorocarbon agent for one role, an air for the other. A population of bubbles that have a very narrow distribution of properties would also represent a useful advance, perhaps finally opening the way to pressure measurement with contrast agents. Finally, the notion of targeting bubbles to specific tissue, or of using them as vehicles for drug delivery, is slowly edging towards reality, as new bubble designs emerge with shell structures specifically manufactured for therapy applications.

It is clear, however, that the major obstacle to progress in our field at the moment does not come from imaging technology or bubble development, but from the US drug regulatory authorities. For no reason clear to us, not a single ultrasound contrast agent has been approved to date for routine clinical use. The collaboration between academic research, pharmaceutical development and the imaging industry for ultrasound contrast is unlikely to be sustained unless some progress comes soon from this quarter.

A CONTROLLED TEST OF AUTOMATED PERFUSION ASSESSMENT TECHNIQUES

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2 Acuson Corp, Mountain View, CA

Background

Currently available contrast agent (CA) perfusion imaging methods use either triggered high power imaging or live low power imaging. These techniques have problems with cumbersome acquisition and low signal to noise respectively.

Objective

To implement and test two new automated techniques for perfusion imaging.

Method

An Acuson Sequoia (Mountain View, CA, USA) ultrasound scanner was modified to create new destructive modes which allowed fast, synchronised transitions to the imaging mode, Coherent Contrast Imaging (CCI).

Two new imaging methods were developed and implemented. The first, Triggered Interval Sequencing (TIS), runs through a user-defined sequence of triggering intervals which combines imaging and destruction pulses. This method is faster, easier to use and destroys the CA more efficiently than current methods. The splitting of the imaging (CCI) and destruction (MBD) pulses makes it possible to image with reduced power (Mechanical Index, MI) to minimise collateral destruction close to the transducer, improving both imaging and destruction homogeneity compared to existing techniques.

The second method, Destruction Wash-In (DWI), combines ECG-synchronised CA destruction with triggered imaging every heartbeat after the destructive pulses. This allows for the use of higher MI than live perfusion imaging and thus better signal to noise ratio. DWI also makes it easier to visually appreciate the in-flow of the contrast agent during acquisition than with other techniques.

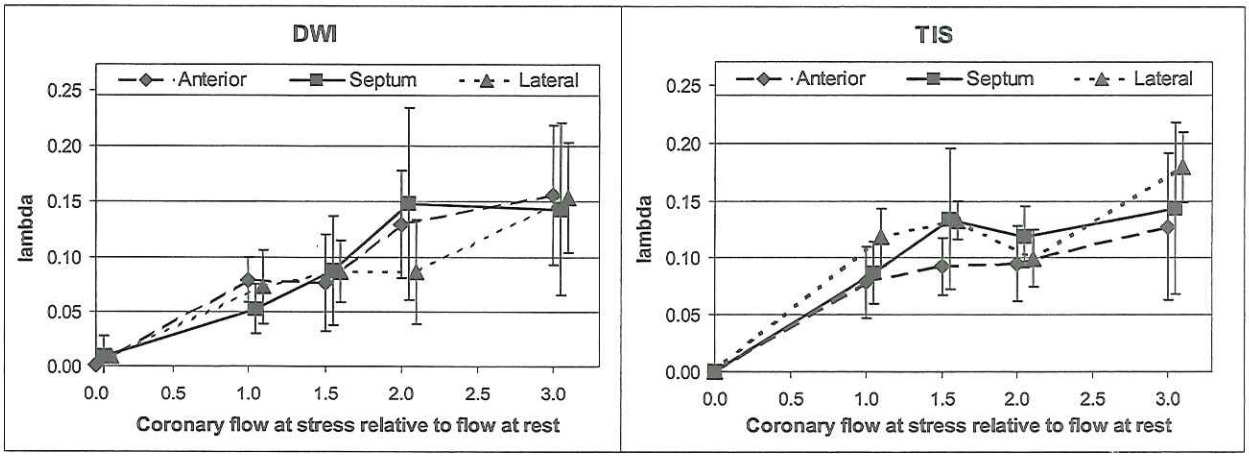
TIS and DWI were tested in a series of five open-chest pig experiments where the flow in the LAD and LCx arteries was controlled with a snare. CA (Sonazoid, Nycomed Imaging AS, Oslo) was infused and stress was applied with dobutamine. Digital images were stored from TIS and DWI measurements at rest and at five different flow levels during stress.

Results

For four different regions of interest in the myocardium the mean of the linearised intensities was calculated and fitted to an exponential in-flow curve

$$(I = I_0 + C\,(1\text{-}e^{-\lambda t})).$$

Temporal analysis results are shown below as the mean results of all animals. Standard deviation values are therefore a combined result of individual animal variations in cardiac physiology and anatomy, variations in coronary arterial flow during data acquisition, and measurement and model fitting variations/errors.



Conclusion: The new imaging methods simplify the perfusion imaging procedure and the calculated time constants may be used as an indirect measure of perfusion level. Direct comparisons of the results from the two techniques are difficult due to different destruction methods and different analysis techniques used for the different methods.

The DWI technique has potential advantage in clinical use due to the frequent (every heartbeat) feedback to the sonographer compared to TIS (every eighth heartbeat). The TIS technique may give better results, in terms of perfusion assessment, in patients with poor imaging windows due to the possibility of using higher power, and may have some advantage over DWI since it does not require total non-destructive imaging.

FRACTAL MODELLING OF MICROBUBBLE DESTRUCTION RE-PERFUSION IN UNRESOLVED VESSELS

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Ultrasound contrast agents can be used to *detect* the microcirculation. In this study, we ask the question whether they can help *characterise* it. Unlike normal vessels, vascular network in malignant angiogenesis and revascularised ischemic tissue is disorganised and chaotic. Most tumours develop a chaotic vascular network rather than an ordered vascular system with the hierarchical vessel arrangement that one finds in an organ such as the kidney. The assessment of the tumour microvasculature is particularly important for anti-angiogenic therapies, which target the blood supply of tumours. Assessment of microvascular morphology and blood flow is difficult due to the small vessel sizes (< 100 μm) and low blood velocities (below about 10 mm/sec). Only using contrast agents can flow in these vessels be detected.

Our objective is to determine whether the form of a destruction re-perfusion curve with ultrasound contrast agents can reveal morphological information about the microcirculation. This is investigated by generating a computational model of a vascular tree and its flow, into which different degrees of structural randomness are introduced. Two fractal models are developed having different degrees of structural randomness - mimicking the morphology of organised and disorganised vascular trees. Flow is simulated and the expected destruction re-perfusion response is evaluated for the two vascular models. The destruction re-perfusion curves of the kidney and the tumour model have the same initial slope and asymptote that correspond to the same flow rate and vascular volume, but have different transition curves. This difference, which is due to the transit time distribution, may characterise the organisation of the vessels.

The form of the destruction re-perfusion curve may offer important information about microvascular morphology. This finding may have implications for characterisation of neovascular tissue in cancer and ischemic heart disease.

AIR BUBBLES DETECTION AND SIZING METHOD USING HIGHER HARMONICS

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Detection and characterisation of circulating emboli in the blood stream is of high clinical importance for decision making after surgery. A new approach involving the non-linear properties of gas bubbles is presented in this study.

An In-Vitro set-up was developed to generate a uniform stream of calibrated air bubbles with diameter ranging from 20μm to 200μm. The backscattered echo from these bubbles was measured using low frequency transducers operating at 130kHz and 250kHz and at moderate acoustic pressure (lower than 60kPa). The experimental and theoretical results showed that depending on the transmitted frequency and the bubbles' sizes, higher harmonic components could be produced (Figure 1). Non-resonant bubbles scatter either linearly when their sizes are far away from the resonance size or nonlinearly at the second or third harmonic frequency when their sizes are getting close to the resonance size. Resonant bubbles or bubbles very close to the resonance size are able to scatter at higher harmonic frequencies (fourth and fifth). In conclusion, the technique proposed allows the detection and sizing of circulating air bubbles over a wide range of diameters by monitoring their higher harmonic emissions and can offer the possibility to differentiate them from particulate emboli.

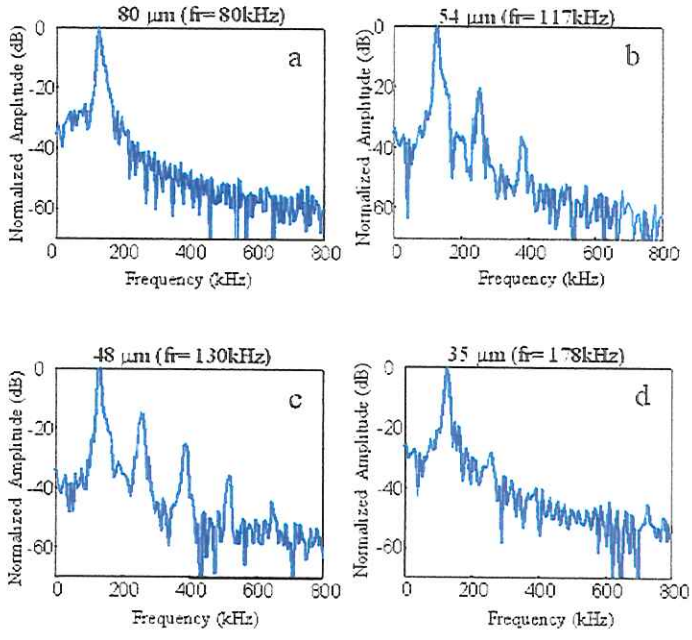

Figure 1. Frequency Spectra of scattered echoes for different bubble diameters insonified at 130kHz: (a) 80 μm; (b) 54μm; (c) 48μm and (d) 35μm.

IN VITRO COMPARISON OF SECOND HARMONIC, PULSE INVERSION AND POWER DOPPLER FOR ULTRASOUND CONTRAST AGENT DETECTION

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Introduction

Detection strategies for ultrasound contrast agents exploit two properties of the contrast agent, non-linear scattering and bubble destruction. Destruction increases with output power, and detection modalities based on destruction such as Power Doppler (PD) perform best at high output power. Because PD destroys contrast bubbles, intermittent operation is required. Non-linear scattering occurs at all output levels, but in order to be able to perform continuous (i.e. non-intermittent or "real time") imaging, the Mechanical Index (MI) must be lowered to minimise bubble destruction. Detection of non-linear echoes can be done by a band-pass filtering a single pulse at the Second Harmonic (SH) frequency, or by Pulse Inversion (PI) which uses summation of inverted transmit pulses to eliminate odd harmonic components from the received echoes. In this study we wanted to investigate the relative performance of SH, PI and PD under ideal conditions *in vitro*.

Experiments and methods

The experimental set-up is described in [1]. The set-up consisted of a tissue-mimicking phantom with a contrast filled channel. A System Five® ultrasound scanner (GE Vingmed Ultrasound, Horten, Norway) with a 2.5 MHz phased array probe (FPA_2.5 MHz) was used to acquire RF-data at varying output power. The contrast agent used was Sonazoid™ (Nycomed Amersham, Oslo, Norway), and the experiments were performed with stationary contrast, i.e. without flow. For each beam direction in the image, 6 short pulses were transmitted at a pulse repetition frequency of 2.5 kHz. The 6 pulses had alternating pressure polarity. Pulse 1, 3 and 5 started with a positive half cycle, whereas pulse 2, 4 and 6 started with a negative half cycle. The transmitting frequency was 1.54 MHz, and the fractional bandwidth of the pulses was 60 %.

From each RF-data set, a SH image was obtained using a single negative pulse (pulse #4). A PI image was computed by summing two consecutive inverted pulses (pulse #2 + pulse #3) and a PD image was computed by subtracting two negative pulses (pulse #2 – pulse #4). Since the SH, PI and PD images are computed from the same data set, a relative comparison of the different modes under the same conditions and on the same contrast population is possible. The SH, PI and PD images were filtered by a bank of band-pass filters. The filters had bandwidth 0.8 MHz, and centre frequency varying from 1.5 to 3.5 MHz. The intensity levels for tissue and contrast were extracted from 2 reference regions in the

filtered images. The optimal filter for each mode and MI level was determined based on maximum Contrast-to-Tissue Ratio (CTR). The corresponding Contrast-to-Noise Ratios (CNR) were computed by extracting the thermal noise levels from acquisitions made with the transmit power supply disconnected.

Results

Curves of CTR and CNR vs. MI for all 3 modes with optimal filters are plotted in Figure 1. For all output levels, PI performs better than SH, in terms of both CTR and CNR. At low output power (MI< 0.15), both PI and SH give better CTR than PD, but as MI increases, the CTR of PD improves due to increased bubble destruction. At high output levels (MI>0.4), the CTR of PD increases above PI. At MI>0.6, both CTR and CNR are higher for PD than for PI.

The corresponding optimal filter frequencies are listed in Table 1. For single-pulse detection it is optimal to use a second harmonic filter. The optimal centre frequency for SH decreases gradually as MI increases. This can be explained by increased harmonic signal generated from non-linear propagation in tissue. For PI, the optimal filter at low MI is a second harmonic filter. For increasing MI, the optimal frequency decreases to about 2.3 MHz at medium MI and below 2.0 MHz for high MI. The reason for this is that the destruction of contrast agent becomes more dominating than the non-linear scattering from bubbles. At low MI, PD performs poorly regardless of filter choice. At higher MI, a fundamental filter is preferable for PD. The fundamental filter gives approximately the same CTR as a harmonic filter, but there is a gain in CNR of up to 10 dB.

Conclusions. For real time imaging at low output levels, the results show that PI performs better than SH and PD. At higher output levels where destruction of contrast agent gives a larger contribution to the pulse to pulse changes, PD become superior to PI. The performance of all modes can be optimized by careful choice of frequency filter. Until now, second harmonic filters have been considered best for Power Doppler imaging. In our experiment, we observe that fundamental filtering will significantly improve CNR in PD relative to second harmonic filtering.

References

[1] J. Kirkhorn et al "Comparison of Pulse Inversion and Second Harmonic for Ultrasound Contrast Imaging". To appear in*: Proc. IEEE Ultrasonics Symposium*, San Juan, Puerto Rico, October 2000. Pre-print available at: http://www.ifbt.ntnu.no/~johank/1B-3.pdf

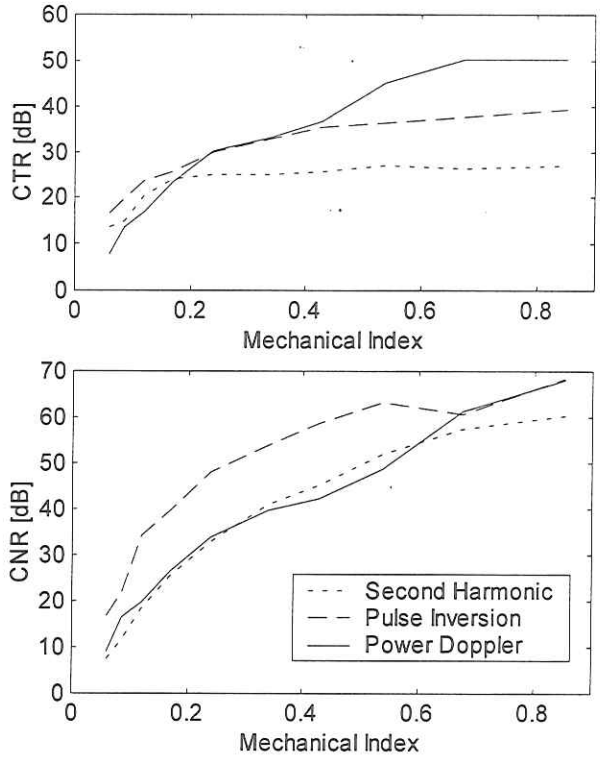

Figure 1. Contrast-to-Tissue Ratio (CTR) and Contrast-to-Noise Ratio (CNR) vs. output power (Mechanical Index) for Second Harmonic, Pulse Inversion and Power Doppler. The frequency filters were chosen for optimal CTR, and corresponding filter frequencies are listed in Table 1.

Table 1. Optimal centre frequencies for frequency filters.

Output power	Second Harmonic	Pulse Inversion	Power Doppler
Low (MI<0.15)	3.3	3.2	2.5
Medium (0.15<MI<0.4)	3.1	2.3	1.8-2.0
High (MI>0.4)	2.9	1.7-2.0	1.5-1.8

POTENTIAL QUANTIFICATION ERRORS ASSOCIATED WITH CONTRAST DETECTION TECHNIQUES

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Many novel signal-processing techniques have now evolved for use in the detection of ultrasound contrast agents. Beyond left ventricular opacification, it is envisioned that these techniques will enable the observation and quantification of myocardial perfusion. However, in many cases the specialised detection techniques may also potentially incur measurement errors in the determination of relative concentration levels of contrast agent in various areas of the image.

A principal cause of such measurement error is due to acoustic target motion, in techniques, which use multiple lines for the detection of contrast agent. Such motion can cause falsely increased video levels due to moving tissue being incorrectly portrayed as contrast agent. Additionally, rapidly moving contrast agent, such as is present in the Mitral valve area of the left ventricle, can be represented in stronger video intensities than in blood pool areas having an identical contrast agent concentration, but lower velocity.

A paper will be presented that will draw upon clinical images and in *in vitro* measurements to describe these potential quantification errors in contrast measurement techniques.

BUBBLE DISSOLUTION AND NUCLEI FORMATION ABOVE THE SHELL-DISRUPTION THRESHOLD OF ULTRASOUND CONTRAST AGENTS

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The application of short, high-intensity acoustic tone bursts to ultrasound contrast agents can result in shell disruption or even bubble fragmentation [P.A. Dayton, et. al., IEEE UFFC, Vol.26, No.1, 1999]. If the bubble contents are freed from the stabilising shell material, the bubble will then shrink as gas dissolves into the surrounding fluid [P.J.A. Frinking, et. al., JASA Vol.105, No.3, 1999 & W.T. Shi, et. al., UMB Vol.26, No.6, 2000]. We have used active acoustic scattering techniques to track the dissolution of freed microbubbles at high acoustic pressures. Using a 5 MHz transducer, we expect that the bubbles should pass through a region of resonance in which the scattering amplitude actually increases momentarily as the bubble dissolves. Our measurements of dissolving microbubbles appear to confirm this notion. At higher pressure amplitudes, free bubbles can also be generated from the pre-existing nuclei in the solution by inertial cavitation. The newly generated bubbles will also dissolve in the medium and show typical scattering signals. We have modelled our dissolution data using a distribution of free microbubbles, taking into account the possible nucleation of microbubbles. We have found that a bimodal bubble size distribution is often needed to account for the scattering signals. A fast decaying scattering signal is attributed to small, sub-micron-sized bubbles, while a resonance-like feature in the scattering signal is attributed to bubbles larger than a micron. In some cases, small bubbles appear to be nucleated during the initial tone burst without the accompanying dissolution signals from contrast microbubbles. Contrast microbubbles with perfluorocarbon gas, such as OptisonTM, exhibit a much longer dissolution time compared to those with air content, as expected.

Effect of nonlinear incident pulse propagation distortion on nonlinear contrast agent scattering

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Introduction

It is well known that propagation of pressure pulses in tissue at typical frequencies and amplitudes used in medical ultrasound imaging is a nonlinear process. Contrast agents for medical ultrasound imaging are typically gas-filled bubbles encapsulated in a thin shell. The nonlinearity of scattering from a gas bubble in water was first analyzed by Lord Rayleigh [2] and the nonlinear scattering from various medical ultrasound contrast agents has been studied by numerous authors.

The Numerical Model

Nonlinear propagation: A simulation tool for nonlinear wave propagation has been developed in our group and is used to calculate the distorted pulses. The program makes use of the Operator Splitting method with separate operators for diffraction, absorption, and distortion. The linear diffraction operator is solved by methods of Finite Differences while the distortion is based upon Burgers' one-dimensional equation. Absorption is taken care of in the frequency domain and for tissue it is typically proportional to the frequency. The nonlinear simulation program gives results which are in agreement with results from linear wave propagation when the nonlinearity parameter in the program is set equal to zero. The program also gives results which are in reasonable accordance with measurements done with wave propagation through beef.

Contrast agent scattering: Simulations for bubble radius oscillations and acoustic scattering are done using the numerical model developed by Angelsen *et al* [1]. The model includes an equation for the relation between pressure and radial strain in a thin shell encapsulating the gas bubble. This model also allows for a constant speed of sound in the medium surrounding the bubble, thus taking radiation losses from the bubble into account, but is otherwise very similar to the well known Rayleigh-Plesset equation.

Method

Pressure pulses filtered around a center frequency are propagated an arbitrary distance using the nonlinear simulation program. Inspection of the resulting distorted pulses shows that for focal pressure amplitudes at the order of a few hundred kPa, the nonlinear propagation effect manifests itself mainly as a second harmonic component. Distorted pulses are then used as input in the simulation program for nonlinear contrast agent scattering.

Results

Simulations done, driving the contrast bubble with pertinent levels of a second harmonic component relative to the fundamental component, reveals that the nonlinear scattered pressure from the bubble may be significantly affected and diminished by the distortion of the driving pulse.

The effect on the second harmonic component of the scattered pressure pulse can to some extent be explained as the result of a linear process, *i.e.* first exposing the bubble to the fundamental component of the distorted driving pressure, then to the second harmonic component which has a phase angle relative to the fundamental component, and finally summing the two contributions to get the total scattered field. The effect on the higher harmonic components in the scattered pressure pulse is a result of the mixing of the two frequency components in the driving pressure and is hence nonlinear.

[1] B.A.J. Angelsen, T.F. Johansen, and L. Hoff. Simulation of gas bubble scattering for large mach-numbers. *1999 IEEE Ultrasonics Symposium Proceedings*, 1:505–508, 1999.

[2] Lord Rayleigh. On the pressure developed in a liquid during collapse of a spherical cavity. *Phil. Mag.*, 34:94–98, 1917.

B-MODE TRANSRECTAL ULTRASONOGRAPHY(TRUS) COMPARED WITH LEVOVIST® ENHANCED COLOUR DOPPLER(CD-TRUS) FOR THE DIAGNOSIS OF PROSTATECANCER.

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This study was sponsored by Schering AG, Germany.

Objectives

To increase detection-rate and improve clinical staging as well as biopsy specificity and sensitivity using additional CD-TRUS imaging with and without contrast medium (Levovist).

Methods

219 participants with PSA-levels above 3 ng/ml were recruited within the screening arm of the Rotterdam section of the ERSPC (European randomised study of screening for prostate cancer). These participants were randomised into a control group (n=104) and a contrast (Levovist) group (n=94). In both the control and Levovist group regular B-mode TRUS and DRE (digital rectal examination) was performed. In the Levovist group an additional CD-TRUS was used to obtain vascular images of the prostate before and after intravenous administration of Levovist (300 mg/ml). Subsequently both groups received standard sextant biopsy and if a lesion was seen on B-mode or CD-TRUS an additional 7^{th} biopsy was taken. Analysis of the blood vessel architecture was performed using a vascularity status. Imaging results were intra-individually related to the histologic findings obtained from needle biopsy and compared between the groups.

Results

In both groups the PSA range and the volume as well as the age distribution was divided normally. In the Levovist group 40 cancers (43%) and control group 31cancers(30%) were detected (p=0.06). Comparing B-Mode results showed a difference in sensitivity as well as specificity. B-mode in Levovist group resulted in 81% specificity and 35% relative sensitivity.
In the control group this was respectively 87% and 30%. Looking at the results in the Levovist group B-mode combined with CD-TRUS resulted in 74% specificity and 63% relative sensitivity.
Using the CD-TRUS 11 more cases of prostate cancer were found. These were not seen on the B-Mode TRUS but were seen on CD-TRUS using Levovist. In only 2 cases a lesion was found on B-mode TRUS that was not seen on CD-TRUS. Furthermore in the control group the number of

additional 7th biopsies was 18. In 6 (33%) cases cancer was found. In the Levovist group 29 extra biopsies were taken resulting in finding 18 cases (62%).

Conclusions

Due to an increase of the number of extra 7th biopsies in the Levovist group the specificity is lower than in the control group. But by using Levovist more cases of prostate cancer were detected resulting in a higher relative sensitivity (63% vs. 30%).

IMPROVED DIFFERENTIATION OF TESTICULAR TUMORS WITH THE USE OF CONTRAST MEDIUM LEVOVIST

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Purpose

Based on the fact that malignant neovascularisation can be considered as a marker of tumour's aggressivity, the aim of the study was improved detection and differentiation between various types of testicular tumours with the use of contrast medium Levovist (Schering AG, Berlin).

Material

Levovist was administered in 65 men aged 23-67 with testicular tumours 7-36 mm in diameter (39 seminomas, 17 embryonal cell carcinomas, 6 teratocarcinomas, 3 men with metastatic lesions – 1 leukaemia, 2 lymphomas). Testical tumours were divided into sub-groups: under 15 mm in diameter (31 lesions) and over 15 mm in diameter (34 lesions) – long axis.

Methods:

Ultrasound examinations were performed with ATL Philips 3000 and ATL Philips 5000 linear wideband transducers 5-10 MHz and 5-12 MHz. Levovist was administered in doses 2,5 g (suspension 300 mg/mL), speed of infusion 2 mL/sec.

All men were first examined with B-mode, Colour Doppler and Power Doppler. Then Levovist was administered and second ultrasound examination was performed for 10 minutes. All ultrasound examinations were videotaped and later on reviewed by two independent blinded readers. 62 out of 65 testicular masses were verified and confirmed in surgery. 3 men with metastatic lesions (1 leukaemia, 2 lymphomas) were diagnosed by laboratory findings and the result was unknown for the ultrasonographer.

The following diagnostic criteria were taken into consideration:

- enhancement scale (0-4 points) with the use of Colour Doppler and Power Doppler after Levovist administration
- time of peak enhancement (0-1 sec, 1-120 sec, 121-240 sec, 241-480 sec, over 481 sec) obtained after Levovist administration.

Results

- In the group of seminomas (39 patients) the largest number of lesions (36 = 92,3%) were enhanced for under 2 points and all seminomas presented peak enhancement in the time of under 120 seconds.
- In the group of embryonal cell carcinomas (17 patients) the largest number of lesions (15 = 88,2%) were enhanced for 2 points and over. 16 embryonal cell carcinomas (94,1%)
- presented peak enhancement in the time of under 120 seconds.
- In the group of teratocarcinomas (6 patients) all lesions were enhanced for 2 points and over and all of them presented peak enhancement in the time of over 121 seconds.
- In the group of metastatic lesions (3 patients) all lesions were enhanced for under 2 points and all of them showed peak enhancement in the time of under 120 seconds.
- In testical tumours under 15 mm in diameter (31 lesions) 29 lesions (93,5%) were enhanced below 2 points and all of them presented peak enhancement in the time of under 120 seconds.
- In testical tumours over 15 mm in diameter (34 lesions) all of them were enhanced for over 2 points and 32 lesions (94,1%) presented peak enhancement in the time of over 121 seconds.
- Average contrast enhancement obtained after Levovist administration: teratocarcinomas 3,16 , embryonal cell carcinomas 2,11 , metastatic lesions 0,66 , seminomas 0,64 points.
- Average contrast enhancement obtained after Levovist administration: testical tumours under 15 mm in diameter – 0,67, testical tumours over 15 mm in diameter – 2,61 points.
- *Conclusions:* Marked increase in vascular enhancement was typical for teratocarcinomas (3,16) and embryonal cell carcinomas (2,11). Marked increase in vascular enhancement was more typical for testicular tumours over 15 mm in diameter (2,61) than for testicular tumours under 15 in diameter (0,67). Cross sections and adjacent vessels were only seen in teratocarcinomas and embryonal cell carcinomas. Longer persistence time (over 121 seconds) was observed only in teratocarcinomas. Longer persistence time (over 121 sec) was more typical for testicular tumours over 15 mm in diameter (94,1%).

The administration of Levovist can be considered useful in initial differentiation between types of testicular tumours, particularly in the improved differentiation between teratocarcinomas and seminomas. The degree of vascularity depends also on the size of the tumour, not only histologic features.

NEW LOW POWER CONTRAST IMAGING TECHNOLOGIES ALLOW THE DIFFERENTIATION OF RENAL MACRO- AND MICROCIRCULATION

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Background. Recently available echo-contrast specific imaging technologies required intermittent imaging modalities at high emission power due to low contrast sensitivity at low emission power and considerable bubble destruction at higher power levels (1). It has been shown that increasing trigger intervals allow the assessment of bubble replenishment kinetics following ultrasound induced destruction of microbubbles and therefore this technique allow the assessment of blood flow (2). Since the acquisition of replenishment curves in the clinical scenarios is a time consuming procedure, susceptible to artifacts and lacks of clinical practicability intermittent imaging technique at high emission power has been limited to initial experimental studies. In contrast to those technologies the new imaging modalities Power Pulse Inversion (PPI) and Pulse Inversion (PI) using low emission power are almost non-destructive to microbubbles. Therefore PPI and PI allow the simultaneous assessment of tissue perfusion and organ function (3).

The aim of this study was to evaluate 1) whether PPI and PI allow the visualization of different vessel compartments in real-time and 2) whether PPI and PI allow to distinguish between macro- and microcirculation using the contrast replenishment concept.

Methods

The experiments were performed using a model for isolated perfused kidneys. The kidneys of German farm pigs (mean weight: 25 kg ± 2 kg) were surgically explanted and inserted into a perfusion circuit (Fig. 1). The arterial flow was kept constant at 45ml/min. Definity™, an octafluoropropane ultrasound contrast agent, was constantly infused at 0.12ml/min. To avoid recirculation of the contrast agent the microbubbles were filtered by means of two dialysis cartridges installed downstream of the insonation area. Efficiency of the filter process was observed by means of a second ultrasound transducer (T2) behind the filter section. PPI (12 Hz) and PI-Imaging (25Hz) was performed by means of an ATL-HDI 5000 Ultrasound machine. In this study we used a kidney model to study contrast replenishment in macro- and microcirculation since these vessel compartments are clearly separated. The major feeding arteries are located in the renal hilum, split up into smaller arteries in the medulla whereas the renal cortex contains essentially microvasculature (Fig. 2). Moreover, renal perfusion is mainly directed from the inside towards the outside of the organ and a single inlet respectively outlet vessel (A. and V. renalis) allows easy experimental manipulation in a perfusion circuit. The kidneys were insonated in a

transversal plane that included the cortex and the medulla as well as the renal hilum (T1). At steady state of tissue enhancement two bursts were emitted at high emission power (MI: 1.2) in order to destroy as many microbubbles as possible. Immediately after the destruction sequence contrast replenishment was evaluated at lowest possible emission power (MI: 0.09). Various Regions of interest were placed in the renal cortex and in the area of the segmental arteries to compare contrast replenishment in macro- and microcirculation. Replenishment curves obtained in these vascular regions were fitted by the exponential function: $y = A\ (1\text{-}e^{-\beta t})$ in which β represents the velocity parameter and A the signal amplitude parameter.

Results

During continuous infusion of contrast in both imaging modalities inhomogeneous distribution of contrast signals was observed in the area of the renal hilum. Strong signals were visible in structures resembling feeding arteries (Aa. segmentales, Aa. interlobares, Aa arcuatae). Application of contrast resulted in a visually homogenous enhancement of the cortex in PPI and PI. The emission of the high-power bursts resulted in homogenous appearing of PI and PPI signals of maximum intensities assessable in the entire kidney. Following the "flash"-sequence a strong reduction of signal intensities was observed in both imaging modes whilst particular vessel structures could still be observed in the renal hilum. In consecutive imaging frames signal enhancement was first noted in the hilar arteries (Aa. segmentales and Aa. interlobares), then, with a substantial delay in the renal cortex. Contrast replenishment curves could be obtained in all analysed segments. At same flow A was significantly higher in bigger arteries (PPI: mean A = 18.97 dB ± 1.41 dB; PI: mean A = 34.1 dB ± 2.42 dB) compared to cortex (PPI: A = 10.22 dB ± 2.11 dB; $p<0.001$; PI: mean A = 27.28 dB ± 3.31 dB; $p<0.001$). ß at same flow was found to be significantly higher in the arteries (PPI: mean $\beta = 5.5 \pm 1.8$; PI: mean $\beta = 1.2 \pm 0.16$) as compared to the cortex (PPI: mean $\beta = 0.36 \pm 0.17$; $p<0.001$; PI: mean $\beta = 0.53 \pm 0.12$; $p<0.001$) as well.

Conclusion

PPI and PI allow the visualization of different vessel compartments and the assessment of contrast replenishment rate in different tissue compartments in real-time. Contrast replenishment rate in macro- and microvasculature differs significantly. Low-power-techniques allow to distinguish between macro- and microcirculation. New imaging technologies might take advantage of this fact by selectively displaying contrast agent in the macro- and microcirculation applying replenishment kinetics.

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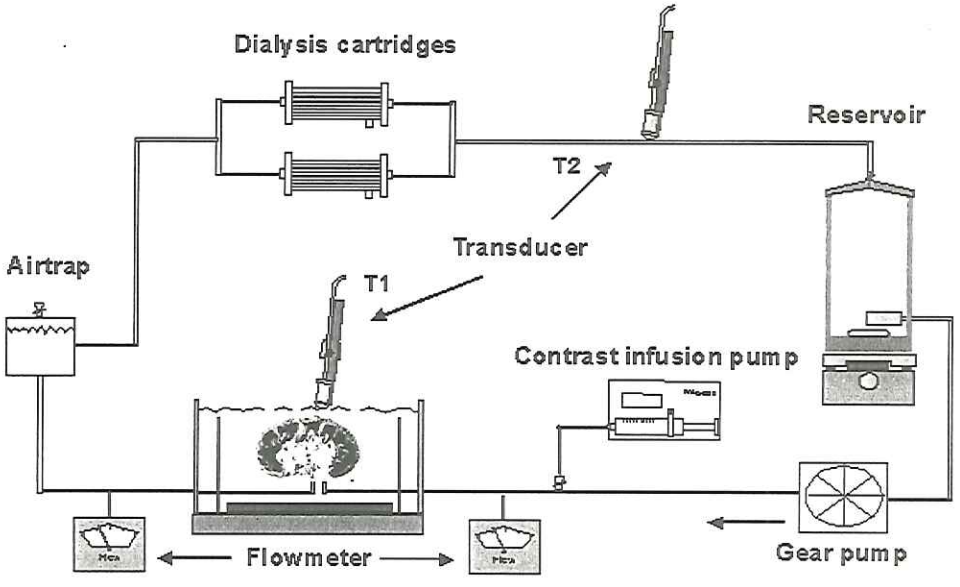

Figure 1. Simplified sketch of the kidney perfusion model

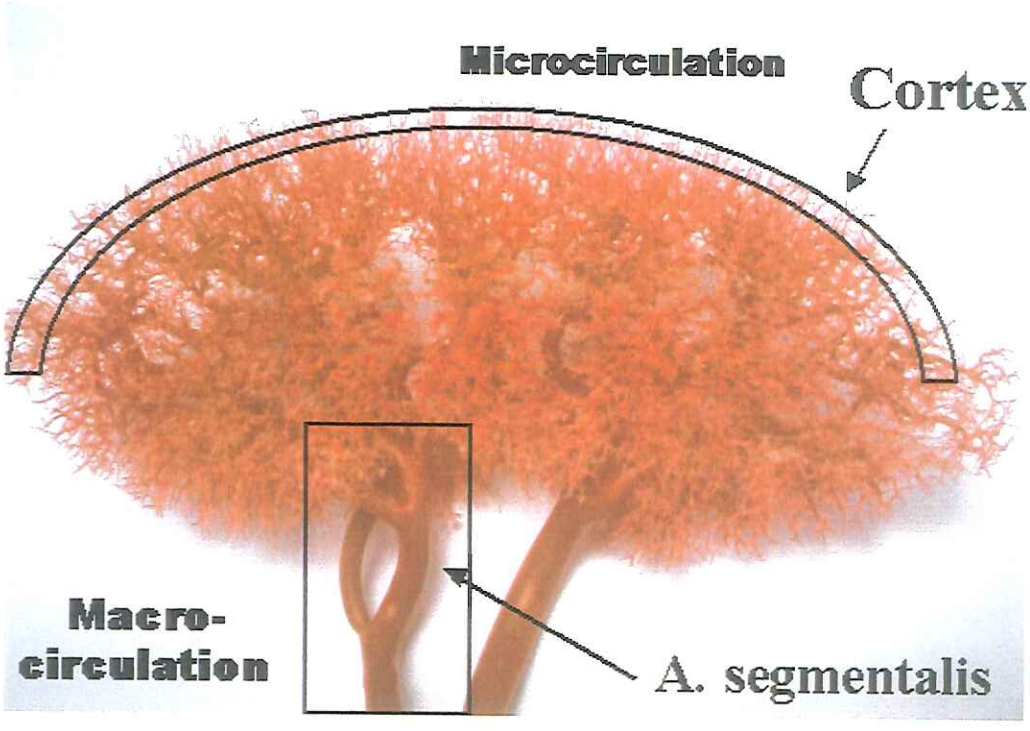

Figure 2. In the kidney macro- and microcirculation are clearly separated

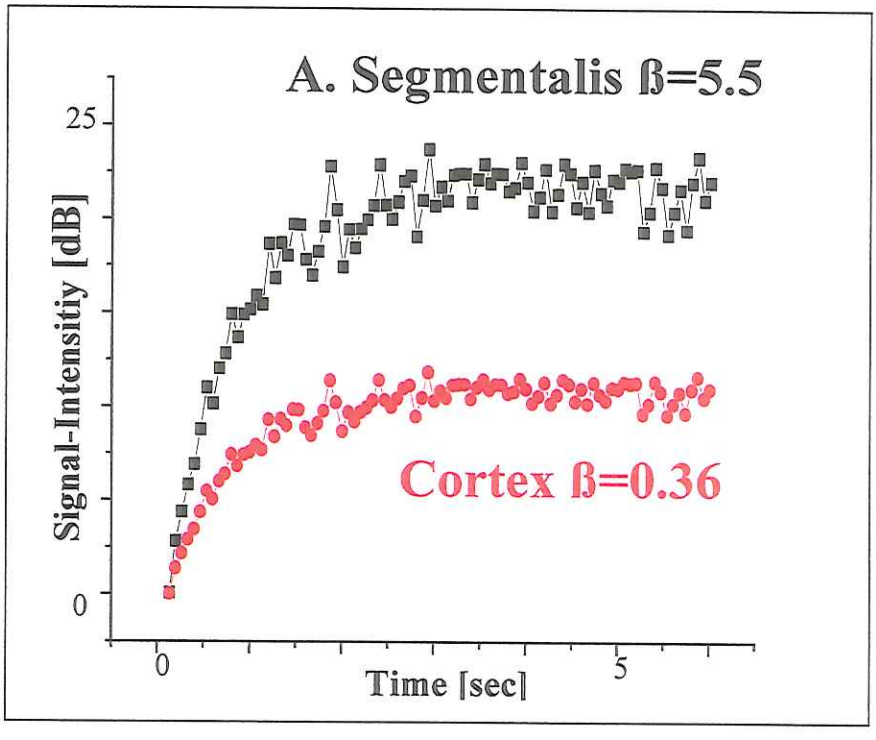

Figure 3. The two time intensity curves demonstrate the replenishment in the macro- and microcirculation in PPI. Compared to renal cortex the amplitude of the signal intensities in the arteries is clearly higher. Secondly parameter ß representing the microbubble velocity is clearly higher in the macrocirculation as well.

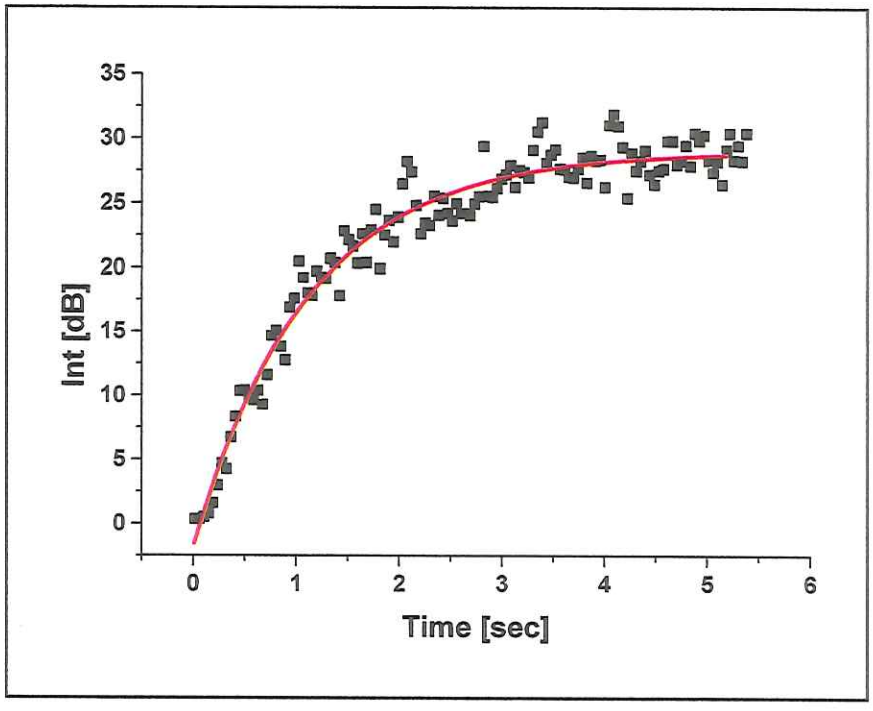

Figure 4. Example of a contrast replenishment curve of the renal cortex recorded in PI. Good agreement was found between the mathematical model $y = a\,(1\text{-}e^{-\beta t})$ and the replenishment data.

the β- and F-values on infusion rate (p=0.058 and p=0.206, respectively). For all volunteers, parameter images could be generated (figure 2).

Conclusions

It is possible to display the UCA refill kinetics in human cerebral microcirculation after microbubble destruction by transcranial ultrasound. Transcranial grey-scale harmonic imaging may allow a quantitative approach to cerebral perfusion that can be visualised by parameter images.

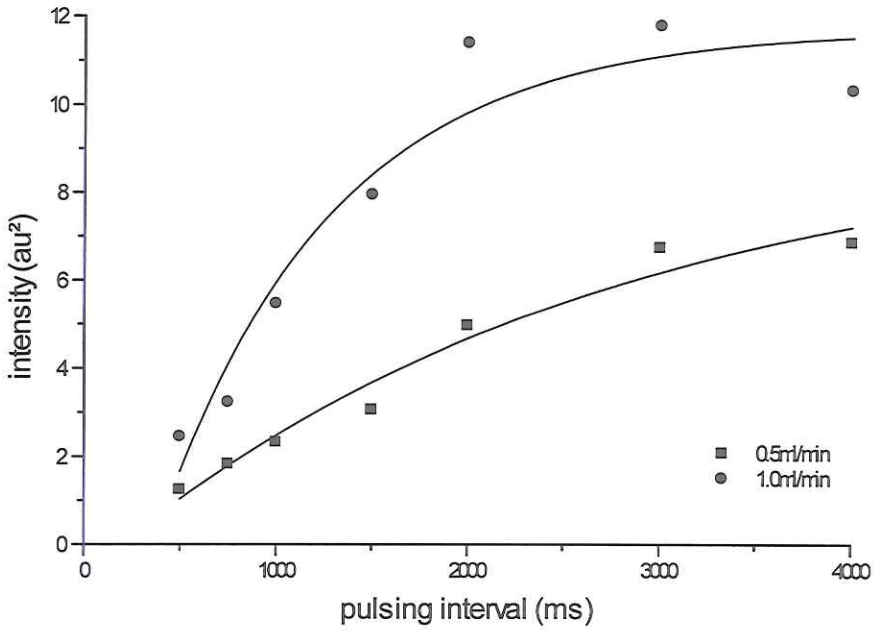

Figure 1. Intensity (au²) versus pulsing interval (ms) curves of 0.5 ml/min and 1.0 ml/min infusions of Optison™ (mean values, n=10). The ROI was specified to the ipsilateral thalamus.

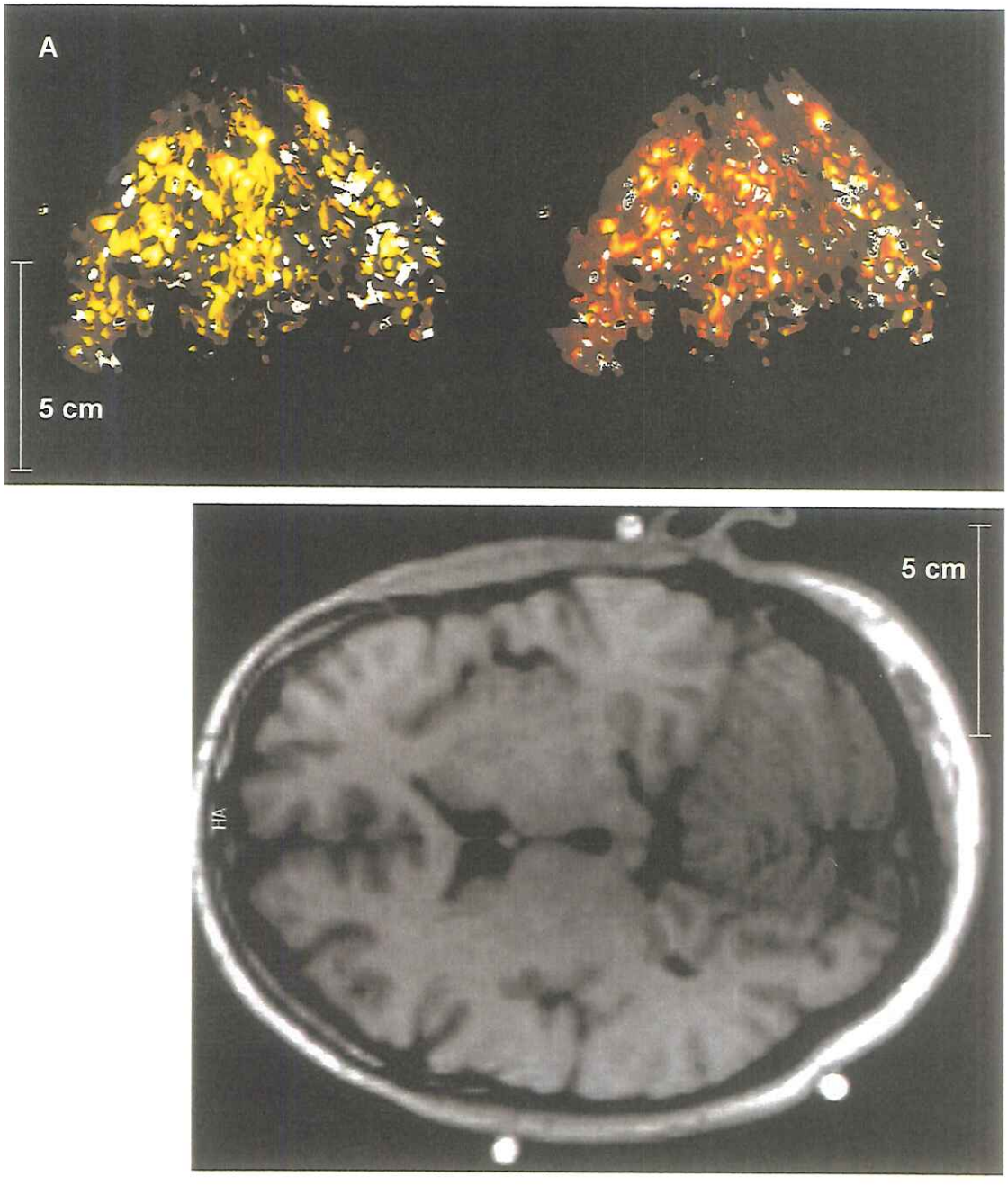

Figure 2. Parameter images (UCA infusion rate: 1.0 ml/min).
A: rate constant [β]. B: F-value. (Bright colors represent higher values)
C: Axial MRI scan (T1) in a comparable plane.

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CONTRAST-ENHANCED VOIDING UROSONOGRAPHY [VUS] FOR THE DIGANOSIS OF VESICOURETERORENAL REFLUX IN CHILDREN – AN UPDATE

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Introduction

Voiding urosonography [VUS] with the intravesical administration of the US contrast medium Levovist® [*Schering AG, Berlin*] has been shown to be a practical method with high diagnostic accuracy of vesicoureterorenal reflux [VUR] when compared to the radiological reflux diagnostic modalities, voiding cystourethrography [VCUG] and radionuclide cystography [1-4]. In Heidelberg, VUS is being carried since 5 years and over 700 children have undergone this examination. Currently, about 2000 children at various other centres in Europe have had VUS.

Purpose

[1] To find out the extent of reduction of VCUGs after adding VUS to the diagnostic algorithm of VUR. [2] To compare both types of phase inversion imaging [PII] modalities, tissue [THI] and contrast [CHI] harmonic imaging, with the fundamental imaging [FI] mode in contrast-enhanced VUS.

Patients and Methods

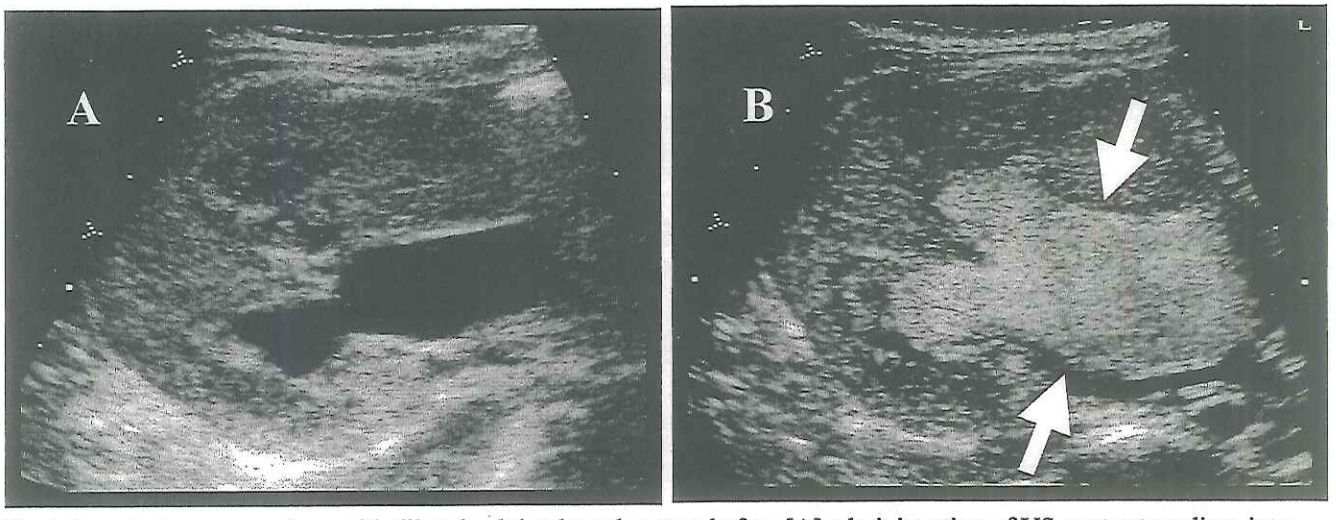
[1] Over two years 449 children were referred for diagnosis of possible VUR. The selection of a particular reflux examination was based on pre-defined criteria. VUS was performed primarily in girls and follow-up cases. The indications for a VCUG were as follows: [a] boys' first examination for VUR, [b] specific request for urethra or bladder imaging, [c] girls when VUR was diagnosed in the VUS and no VCUG had been done in the past, [d] technically inadequate VUS. [2] A total of 54 children presenting for diagnostic examination of VUR underwent a standard US of the urinary tract in FI. This was followed by intravesical administration of Levovist®. The post-contrast US was conducted, in both FI and PII [CHI +/- THI] modalities.

Results

[1] VCUGs were carried out primarily in 141 cases. VUSs were performed in 239 patients. In 69 of these patients a VCUG followed during the same examination session. Thus 239/449 patients

underwent only VUS, resulting in the reduction of the VCUGs by 53%. [2] In all, 248 pairs or trios of images were available for comparison. The delineation of both the retrovesical space and renal pelvis was found to be best with THI in 84% and 96%, respectively. From 27 kidney-ureter units of 22 [41%] children with reflux, 41 pairs or trios of images were compared. The refluxing microbubbles were much more conspicuous in PII [THI=100%, CHI=93%]. In 8 kidney-ureter units reflux was detected only with PII.

Conclusion [1] The implementation of VUS as part of the routine diagnostic imaging modality for VUR significantly reduced the VCUGs, thus cutting down by almost half the number of children that would have been exposed to ionising radiation. [2] The visualization of the urinary tract and detection of microbubbles is significantly improved with both types of phase/pulse inversion harmonic imaging modalities. When both FI and PII options are available, we recommend PII for contrast-enhanced VUS.



The kidney in transverse plane with dilated pelvi-calyceal system before [A] administration of US contrast medium into the bladder. Post-contrast the microbubbles have refluxed from the bladder into the pelvicalyces [arrows].

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NON-INVASIVE DETERMINATION OF CARDIAC OUTPUT BY CONTRAST ECHOCARDIOGRAPHY – AN INDICATOR DILUTION TECHNIQUE: WORK IN PROGRESS

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Background

Cardiac output (CO) is a significant hemodynamic parameter used to assess global myocardial performance. Measurement of CO is especially useful in the treatment of critically ill patients with depressed myocardial function. Thermodilution indicator dilution technique, a widely accepted method used for measuring cardiac output, is safe, easy to perform, reproducible and reasonably accurate.

The thesis on which indicator dilution theory is based maintains that a given concentration of an "indicator", introduced into the circulation, varies proportional to the time the indicator stays in the circulation. The following simplified equation describes basic indicator dilution theory $Q = I / c.t$ where flow (Q) equals the quantity of indicator (I) divided by the mean concentration of the indicator (c) times the interval between the appearance and disappearance of the indicator (t).

In practice, a fluid bolus of known quantity and temperature (concentration) is rapidly introduced into the venous circulation. The transit interval of the bolus between an upstream injection site and a downstream sensing site, and the ensuing change in its temperature is measured. The resultant temperature/time change is calculated, converted into flow and displayed as a monoexponential time/temperature curve. The physiologic result in the flow/time relationship is cardiac output.

Previous work in 1984 by DeMaria, et al., has shown the feasibility of generating a monoexponential videodensitometry-based indicator dilution curve using echo contrast correlated to thermodilution cardiac output. Gentile, et al., in 1997 correlated several videodensitomic parameters, obtained from measurement of the videodensitometric time-intensity LV opacification curve, and cardiac index.

Early feasibility investigations performed at our institution showed that the use of current concentrations and doses that were used to produce LVO to evaluate wall motion, were too intense for

cardiac output applications. Doses of undiluted Optison (0.3cc) produced B-mode videointense images that:

a. attenuated far field content
b. persisted too long (permitting recirculation)
c. reduced frame capture limits
d. produced maximum intensities that were "out of range" of the software measuring capability

To avoid these limitations, we plan to capitalise on the stability of the second generation contrast agents; maximise the image quality associated with the non-destructiveness of using harmonic imaging using a low mechanical index, we employed a new and practical dosing regimen.

Hypothesis

Optison, a second generation contrast agent, was used to measure cardiac output. A bolus containing a known quantity (concentration) of Optison was rapidly introduced into the circulation through a central view. As the ultrasonically sensitive, gas containing microbubbles pass through a relatively low power ultrasonic beam, the bubbles begin oscillating (contracting and expanding) and in the process reflect (scatters) and re-reflect off each other within the cardiac chambers. The amplified acoustic signal, generated by this reflection process produces a videointense (bright) image on the ultrasound display. With continued exposure (time) the image becomes progressively less videointense (darker) as fewer bubbles are available to illuminate the image. This change in videointensity over time is calculated, converted into concentration and ultimately flow and as with thermodilution, a typical monoexponential time/intensity curve is generated. The physiologic result in the flow/time relationship is correlated to cardiac output.

Methods

With IRB approval and informed consent, five patients were enrolled into the study. Only ICU patients, who underwent right heart catheterization (Swan-Ganz catheter), as part of their prescribed care, were recruited.

After obtaining appropriate hemodynamic data, a thermodilution cardiac output, consisting of three 10cc room temperature injections of 0.9%NS, was performed and served as a baseline value. Cardiac output values fell within 10% of each other for all patients enrolled. Routine 4-view 2-D echocardiographic views were obtained and used as a visual reference for evaluating wall motion and overall LV function.

As the first step, calibration or dose response measurements were then performed. Each patient received three (3) sets of injections. Each set consisted of three (3) individual 10cc boluses of 0.9% normal saline (NS), similar to the thermodilution technique, for 90cc. Each set consisted of varying concentrations (fixed volume) of Optison and NS. The first set contained 1 part contrast to 300 parts (1/300) NS; the second, three (3) parts contrast to 300 parts (1/100) NS and the third was five-(5) parts contrast to 300 parts (1/60) NS. The purpose of the varying concentrations was to calibrate a time/intensity response, to the videointensity associated with a known quantity of contrast. Continuous LV images (frames) were collected just before injection, during maximum LV opacification and continued until near complete washout from the LV. The total number of frames collected to produce a measurable time/intensity curve depended upon the HR and LV function, but averaged about 350 to 400 frames. Collection times varied between 25 and 120 seconds. Low mechanical index (MI), relatively low frame rates and minimum image acquisition depth settings were necessary to collect a large number of frames for long collection times.

Analysis

The digital dose-response videointensity images, collected from the three concentrations of contrast/saline injectate, were analysed on a System 5 GE using software developed for this application. Analysis of each injection consisted of overlaying an electronic cursor, of known area, (region of interest) onto a single LV frame containing contrast information. Once selected, the videointensity content of the region of interest was automatically calculated for all frames collected for an individual injection and was displayed as a monexponential curve representing the change in mean concentration over the collection period. Five discrete parameters were measured on each curve. These parameters include:

a) Peak intensity
b) Time to peak intensity
c) Intensity Half-Time
d) Time Intensity Integral
e) Maximum Duration

Discussion

The results of the calibration and correlation studies will be shown. The discussion will include methods of curve analysis and statistical averaging.

IS SONOVUE ™ INJECTION HELPFUL FOR VASCULAR CHARACTERISATION OF LIVER METASTASES?

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We studied whether the haemodynamic distribution of BR1 (SonoVueTM, Bracco, Milan, Italy), after IV bolus administration, in the liver is useful for optimal characterisation of liver metastases using contrast enhanced harmonic imaging at Low Mechanical index.

Nine patients with suspected liver metastases were scanned first without contrast and subsequently following IV bolus administration of 2.4ml of BR1. Contrast enhanced images were obtained from the whole liver 20 to 30 seconds (arterial phase), 60 to 90 seconds (portal phase) and at each minute up to 6 minutes (late vascular phase) from bolus administration using Contrast Coherent Imaging Technique from Sequoia commercial equipment (Acuson, Mountain View, CA) and MI between 0.2 to 0.4. Lesion enhancement pattern and overall vascularity were assessed and quantified using DATA Pro software (Noesis, Les Ulis, France). Triphasic helicoidal CT scans were obtained in all patients.
CT identified hypovascular metastases in 6 cases and hypervascular metastases in 3 cases.
BRI arterial and portal phase haemodynamic distribution allowed differentiation of vascular pattern in all cases. Later phase did not exhibit differences in contrast enhancement between different metastases. Besides BR1 arterial and portal phase, distribution pattern helped in detecting lesion of 3 mm which were not visible on late phase scans.
Quantification confirmed these observations with increased signal to noise ratio in all cases: hypervascular lesions presented an increased grey scale intensity in arterial phase compared to normal tissue, while hypovascular lesions had a reduced grey scale intensity compared to normal tissue in portal phase.
Ultrasound contrast imaging demonstrated a greater number of tiny lesions than unenhanced sonography or CT scan.
For detection and characterisation of liver metastases, the study of arterial and portal phase hemodynamic distribution of the US contrast agent allows a diagnosis comparable to CT scan. Late phase did not give additional information and did not allow the complete detection of tiny metastases with possible consequences for the patient..

NON-DESTRUCTIVE SUBHARMONIC IMAGING

James Chomas, Paul Dayton, Donovan May, Kathy Ferrara

Destruction-based contrast agent imaging can be used to estimate blood perfusion in a region of interest by first destroying the microbubbles in the region and then monitoring the refresh of microbubbles using a non-destructive pulse sequence. An optimal non-destructive imaging technique should minimise relative expansion and wall velocity of the bubble, as well as use a minimum number of cycles while maintaining a satisfactory signal to noise ratio with which the microbubbles can be detected. Subharmonic imaging is a strong candidate for imaging within these restraints. Modelling of a contrast agent in conjunction with optical experimental techniques is used to find the optimal imaging parameters for non-destructive subharmonic imaging.

The model that is used is a modified Rayleigh-Plesset model that accounts for the shell, re-radiation effects, and non-ideal nature of the gas. The model is used to predict the transmission pressure threshold as a function of pulse length, transmission centre frequency, and bubble initial radius. The effect of initial radius is significant, with the optimal bubble size being 2.5 um for 2.4 MHz insonation. A 2.5 um bubble has a predicted linear resonance of 1.2 MHz, suggesting that the optimal transmission frequency is twice the predicted bubble resonance frequency. Furthermore, the subharmonic threshold is inversely related to resting radius, with small bubbles requiring a higher pressure than large bubbles.

A high-speed optical system capable of 10 nsec temporal resolution and 100 nm spatial resolution is employed to experimentally observe the effect of bubble initial radius, transmission pressure, and transmission frequency on subharmonic response. The relative expansion of bubbles observed with the optical system is in strong agreement with that predicted by the model. The subharmonic threshold is observed by the optical system to be similar to that predicted by the model. Insonifying a bubble with the resonant frequency of the bubble cannot generate subharmonic oscillations without destroying the bubble, due to the destruction pressure threshold being lower than the subharmonic pressure threshold. On the contrary, insonifying a bubble with a frequency that is approximately twice the resonant frequency of the bubble can generate subharmonic oscillations without destroying the bubble.

OPTIMAL DETECTION METHODS FOR SONAZOID

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Various imaging methods have been suggested to enhance the echoes from contrast agent bubbles relative to tissue. Most of these methods are based on the strong non-linear response of a bubble in a sound field. This presentation will discuss some of these methods, linking the effects to the behaviour of the bubble.

A simulation program in *Matlab* was used to calculate the response of a contrast agent bubble exposed to an ultrasound pulse. Such calculations of bubble oscillation and scattered sound pulses illustrate the physical mechanisms behind the imaging methods.

The contrast agent bubbles are enclosed in a shell. This alters the response of the contrast agent bubbles compared to free bubbles, and the effect of this shell is discussed. The simulations are done using shell properties estimated for Nycomed's contrast agent Sonazoid.

The imaging methods studied include:

1. Second harmonic imaging
2. Imaging at higher harmonics
3. Non-linear frequency mixing
4. Pulse inversion
5. Pulses with different amplitudes
6. Sub- and ultraharmonics
7. Acoustic destruction of bubbles

Tissue itself is a non-linear medium at the sound amplitudes used in diagnostic imaging, and the first five of the effects above are found in both tissue and bubbles. But the non-linear responses of the bubbles are stronger, and these five effects work by enhancing bubble echoes compared to tissue. The last two effects, *subharmonics* and *acoustic destruction*, are believed to be unique for bubbles, although sidelobes in the transmitted pulse spectrum and tissue motion can cause similar effects in the echoes.

As a conclusion, *subharmonics*, *ultraharmonics* and *acoustic destruction* have a potential to give unique detection of contrast agent bubbles *in vivo*. However, the optimal imaging method for Sonazoid, or any other contrast agent, is probably not invented yet, and it will be very interesting to see what the future brings.

Ultrasound contrast agents and the importance of nonlinearities

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Many modern uses of microbubble ultrasound contrast agents rely on the highly nonlinear response of the bubbles to a driving ultrasonic field: harmonic, subharmonic, and ultraharmonic imaging as well as pulse inversion or bubble destruction are salient examples. A quantitative modeling of the sound emission of strongly driven microbubbles is crucial for our understanding and future optimization of contrast agents. Recently, we have developed a model that describes the concentration of sound energy in the very close vicinity of the collapsed bubble (a few diameters of the bubble in its collapsed state). High pressures, shear stresses, and liquid temperatures are expected to occur in relatively small volumes over a short time. Over these distances (largely in the intermediate-field rather than the far-field part of the sound wave), ultrasound could be a powerful tool for therapeutic applications such as directed drug delivery, ultrasound-induced cell lysis, or gene transfer, which all rely on the great mechanical forces a strongly driven bubble can induce.

While the nonlinear dynamical response of the bubble is faithfully represented in the model (using the Keller equation), the extreme conditions spawned by the compressibility contrast of the two-phase system potentially induce other effects that are not included in a straightforward approach to sound emission. In particular, nonlinear propagation and nonlinear damping of the outgoing wave should be taken into consideration.

We have investigated the importance of these effects. Depending on the desired application, aspects of total energy expenditure or of spectral energy distribution are central. In general, total energy balances (cross sections) and the detectable (low-frequency) part of the emitted spectrum show a moderate to negligible dependence on the aforementioned nonlinear wave dynamics (the nonlinear propagation of the *driving* wave, however, is crucial for the spectral properties).

Moreover, we find that it is precisely the nonlinearity of strongly driven bubble dynamics that allows for relatively simple calculations of the emitted sound even at intermediate-field distances to the bubble; for small driving pressures (linearized dynamics) the computations would be considerably more difficult. Thus, strong nonlinearity sometimes makes our lives easier.

SONO-SCINTIGRAPHY – DETECTION OF ISOLATED BUBBLES AND QUANTIFICATION OF EXTREMELY LOW CONCENTRATIONS

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In recent years a number of techniques for sensitive detection of ultrasound contrast agents (microbubbles) have been developed. Compared to other imaging modalities, these methods allow diagnostic contrast imaging with relatively small amounts of contrast agent. But even the small concentrations routinely used in clinical procedures still contain many (up to many hundred) bubbles per volume of a single ultrasound pulse, although the most sensitive ultrasound imaging modes are able to detect a single, isolated microbubble in that volume. Therefore, possible ways for contrast imaging and quantification have been explored at very low bubble concentrations, i.e. at least hundred times lower than those used today.

The useful range of bubble concentrations is determined by several requirements:

1. Bubbles must be isolated, at most one at a time must be within a pulse volume.
2. Higher image resolution (high frequency, narrow beam, short pulses) means smaller pulse volume, i.e. an increased upper limit of local bubble concentrations.
3. Statistical fluctuations of the local bubble concentration must be kept small, either by avoiding too small concentrations, or by averaging over time or over sample points in a region of interest.

Other (systematic) errors can be taken into account at least approximately. The coincidence of two or more bubble signals can be statistically corrected as long as the concentration is below the upper limit of 1 bubble per resolution cell. Counting rates in tissue are also influenced by the effective beam cross section, which decreases with increasing beam attenuation and must be calibrated for the particular transducer. In practice, the main uncertainty comes from insufficient knowledge of tissue attenuation.

Fortunately, it turns out that suitable parameter combinations can be found in the lower MHz range, where imaging depth in tissue is sufficient for many medical applications. A relative counting error of 1 ... 10 % in a single run will typically result from statistical fluctuations of the local bubble concentration. A trade-off between spatial and/or temporal averaging over several runs allows some reduction of this relative error. Although it also reduces spatial and/or temporal resolution of Sono-Scintigraphy, in this respect the method should still be superior to similar techniques used in Nuclear Medicine. The most sensitive acoustical detection modes seem to be those which are destroying the

microbubbles during detection, but this 'decay' is controlled by the investigator and does neither cause logistic problems nor the environmental and other hazards, as do radioactive isotopes of short or long half-life.

First in vivo results obtained with conventional Colour Doppler will demonstrate the principle. Improvements can be expected when other recently introduced modes for contrast imaging are used.

A 5-PULSE SEQUENCE FOR HARMONIC AND SUB-HARMONIC IMAGING

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Introduction

Contrast agent specific imaging modes fall into two categories: non-linear imaging modes and destructive imaging modes. While non-linear imaging modes provide higher frame rates, destructive imaging modes exhibit a better signal-to-noise ratio in many cases [1]. Pulse sequences with more than 2 pulses may overcome current limitations of non-linear imaging modes and, therefore, give access to new flow and perfusion imaging techniques [2,3].

In the following, a 5-pulse sequence will be discussed. The sequence consists of 5 broadband pulses that have the same magnitude spectrum but different phase spectra. This sequence in combination with a signal processing that is based on weighted summation and demodulation suppresses the fundamental (1st harmonic) while keeping the 2nd and 3rd harmonic as well as sub-harmonics.

Pulse Sequences

2-pulse sequence.

It is well known that a 2-pulse sequence, where the 2 transmitted pulses have a phase shift of 180 degrees, are useful for 2nd harmonic imaging. Longer pulse sequences, where every other transmit pulse is shifted by 180 degrees in phase, can be used to improve the signal-to-noise ratio or to expand the broadband cancellation of the fundamental to Doppler imaging techniques [2,3]. The 3rd harmonic, however, cannot be imaged with 180°-sequences. There is evidence that sub-harmonics can be imaged with phase inversion (pulse inversion) techniques, but such approaches have not been sufficiently explored, yet.

3-pulse sequence

Transmitting 3 pulses with different (carrier) phases offers more space for phase-sensitive signal processing approaches. It is obvious that summing up the echoes resulting from a symmetrical 3-pulse sequence (0°, 120°, 240°) cancels out the 1st harmonic. Unfortunately, also the 2nd harmonic is suppressed because doubling the phases of the transmit pulses leads to the same phase symmetry (0°, 240°, 480°=120°).

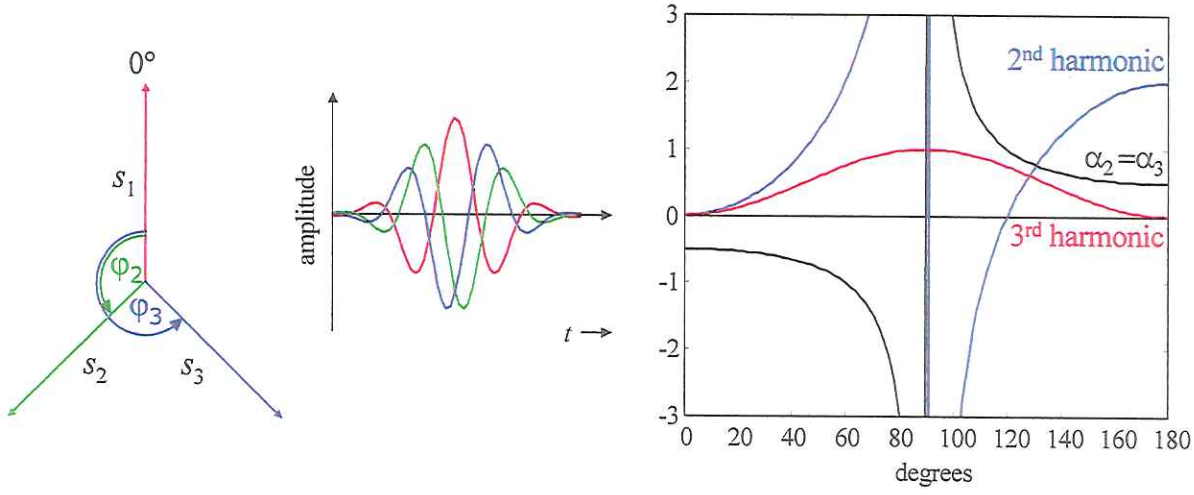

Fig. 1: Left: Vector diagram of a 3-pulse sequence, $\varphi_2 = -\varphi_3$. Middle: Transmit pulses, $\varphi_2 = 72°$. Right: Normalized amplitudes for the 2nd and the 3rd harmonic and weights α_2 and α_3 as a function of φ_2.

The key to a detection of 2nd and 3rd harmonic signals with 3-pulse sequences is a non-equidistant phase distribution. In the following, we will consider 3-pulse sequences with three transmit pulses s_1, s_2, s_3 that exhibit the symmetry $\varphi_1 = 0$, $\varphi_3 = \varphi_2$. Since the phases are not equidistant, a weighted summation has to be performed to eliminate the fundamental. If e_1, e_2, e_3 are the echoes resulting from the three transmit pulses, the summation can be written as $e = \alpha_1 e_1 + \alpha_2 e_2 + \alpha_2 e_3$. For simplicity we choose $\alpha_1 = 1$. The pulses are illustrated in Fig. 1. Given that α_2 and α_3 are chosen appropriately, the summation leads to a suppression of the first harmonic (fundamental) while the 2nd harmonic and the 3rd harmonic are kept. The amplitudes for the 2nd and 3rd harmonics as well as the weights α_1 and α_2 can be calculated. The values are shown in Fig. 2. $\varphi_2 = 180°$ is the regular phase inversion sequence with one 0° pulse and two 180° pulses. It is important to note that α_1 and α_2 should be close to 1. Otherwise, the echoes will not be used efficiently, and the values for the normalised amplitudes of the higher harmonics are rather due to scaling than to an efficient detection of harmonics.

5-pulse sequence

$\varphi_2 = 72°$ degrees and $\varphi_2 = 144°$ are of special interest because both values give the same ratio between the detected 2nd and 3rd harmonic and provide a good compromise with respect to the detection of both harmonics. The same angles occur if we consider an equidistant 5-pulse sequence (0°, 72°, 144°, 216°, 288°). Any combination of 3 pulses in such a 5-pulse sequence either forms a 72°-subset, e. g. 0°, 72°, 144°, or a 144° subset, e. g. 0°, 144°, 288°. In total, 5 different 72°-subsets and 5 different 144°-subsets can be derived from a 5-pulse sequence. For each of these 10 subsets, a weighted summation yields a subset-echo, where the fundamental is eliminated. After demodulation (envelope detection),

the 10 A-lines are averaged to form one new A-line of the harmonic image. More details can be found in [4].

Data Acquisition

We acquired data with a Siemens Sonoline® Elegra equipped with a 7.2 MHz linear Array. For each beam line, 5 pulses with different phases were transmitted at a high pulse repetition frequency of more than 5 kHz. Instead of gaussian shaped pulses as shown in Fig. 1, 2 cycle square wave pulses were used. Although these pulses to not match well the desired magnitude and phase spectra, the approximation turned out to be good enough to show the feasibility of the proposed method. Rf data was acquired on a tissue-mimicking phantom. The phantom has a vertical, cylindrical hole that was filled with Levovist®. Also, a string target was fixed in the centre of the hole. Only a small region of the phantom was scanned as shown in Fig. 2.

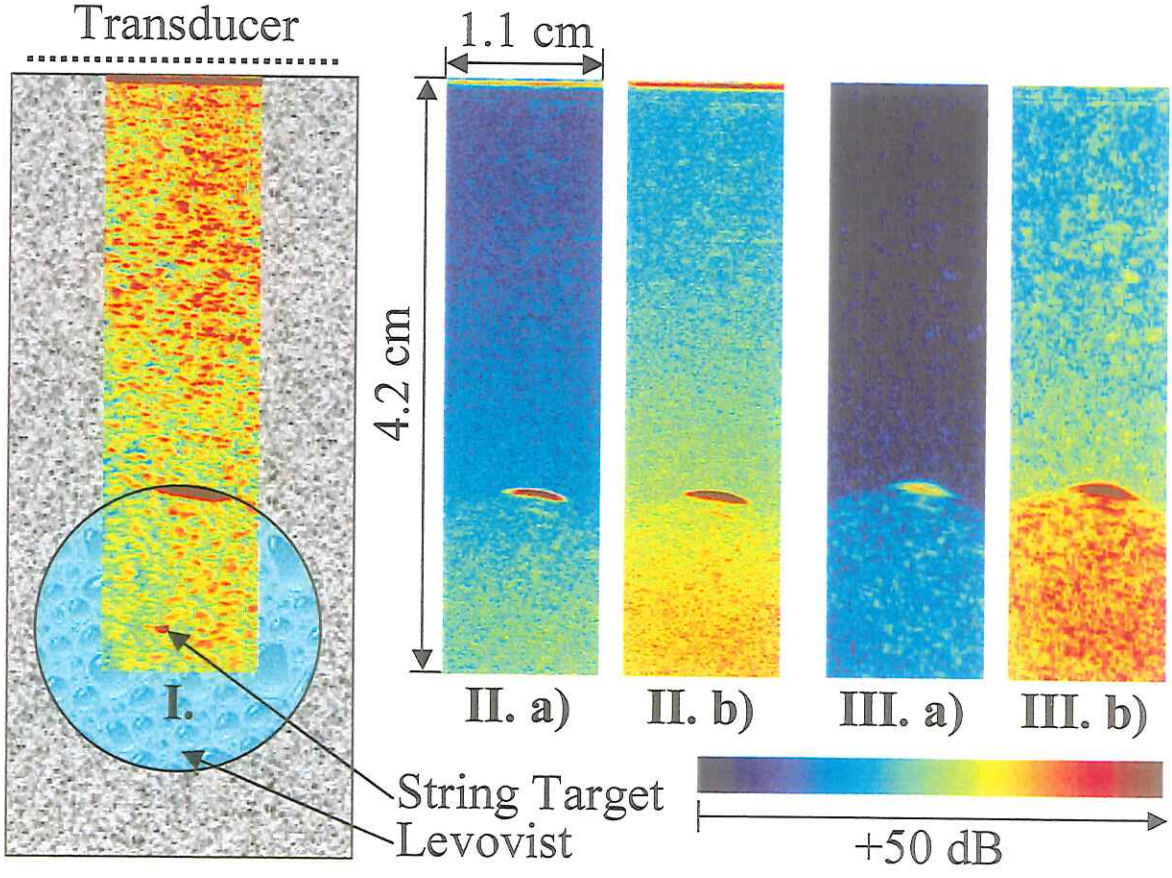

Figure 2.

Results

Fig. 2, I. shows the B-mode image over a dynamic range of 50 dB. The contrast between the contrast agent and the tissue in the B-mode image is –4 dB, i. e. the tissue shows a higher brightness than the contrast agent.

In the harmonic image, Fig. 2, II. a), the tissue is suppressed by about 26 dB in the near field. The incomplete suppression results from the non-ideal transmit pulses. The weights for the summation of the echoes where optimised to account for non-ideal phase shifts. The phase shifts between the transmit pulses, however, must be constant over a wide frequency range. Optimising the weights can only minimise the average phase error. Filters would be required to improve the overall phase response. Despite of these shortcomings, a broadband elimination of the fundamental can be observed. Fig. 2, II. a) also reveals that tissue harmonics are generated so that the brightness of the tissue increases over depth (Note that the brightness in the B-mode image, Fig. 2, I., decreases over depth.). The contrast between contrast agent and tissue is 14 dB in the harmonic image, i. e. an increase of 18 dB compared to the B-mode image. Fig. 2, II. b) shows the same data as Fig. 2, II. a), but with a 10 dB higher gain (brightness). Since the transmit frequency of 7.2 MHz is much higher than the resonance frequency of the microbubbles, almost no higher harmonics are generated by the contrast agent. Instead of higher harmonics, strong sub-harmonics are present in the spectrum.

A spectral analysis of the subset-echoes used for Fig. II. shows that the suppression of the fundamental was almost complete and that higher harmonics are below the noise floor. Therefore, a low-pass filter with a cut-off frequency of 6 MHz was applied to separate the high frequency noise from the sub-harmonic signal. The results are shown in Fig. 2, III. a) and b), where the gain (brightness) is 20 dB higher in b). The filtering obviously improves the contrast between the tissue and the contrast agent. The contrast in this sub-harmonic image is 18 dB, i. e. 22 dB higher than in the B-mode image.

An increase of image brightness over depth can also be noticed in the sub-harmonic image. This might be due to the fact that a second order non-linearity does not only create a 2^{nd} harmonic but also a base-band signal (0^{th} harmonic). Simulations have shown that this base-band signal leads to a speckle reduction in the harmonic images if the demodulated subset-echoes (after envelope detection) are averaged as proposed above [4]. The reason for the speckle reduction is that the base-band signal (0^{th} harmonic) and the 2^{nd} harmonic have a different phase relationship in the 10 subset echoes, since the phase of the 0^{th} harmonic is constant while the phase of the 2^{nd} harmonic depends on the phases of the transmit pulses. Therefore, the speckle patterns in the subset-echoes are different. The $SNR_{speckle}$, which is defined as the mean amplitude divided by the standard deviation of the amplitude, is 1.91 for fully developed speckle. The B-mode image in Fig. 2, I. exhibits an $SNR_{speckle}$ of 1.8 in the depth range 0.5 – 1 cm. A harmonic image derived from 1 subset-echo per beam line shows an $SNR_{speckle}$ of 1.85 in

the same depth range. After averaging the harmonic images from all 10 subset-echoes, the $SNR_{speckle}$ reaches values of about 3 and increases slightly over depth.

Conclusions

We have shown that the proposed 5-pulse sequence is useful for harmonic and sub-harmonic imaging. Even though the transmit pulses did not match the desired magnitude and phase spectra well, the fundamental could be suppressed by 26 dB. Sub-harmonics generated by Levovist® were detected. Compared to the B-mode image, the sub-harmonic image shows an improvement in contrast agent / tissue contrast of 22 dB. In conclusion, the proposed technique shows potential to improve the bandwidth and SNR in harmonic images. Also some speckle reduction is achievable.

Future Work

Our future work will concentrate on the imaging of higher harmonics (2^{nd} harmonic, 3^{rd} harmonic) and on the combination of harmonic imaging and flow estimation. Since a high pulse repetition frequency is used, motion artifacts will be negligible in many cases. A 5-pulse sequence, however, can also be used to estimate axial flow velocities, since a compensation of the 5 different carrier phases converts the 5 echoes into a regular flow sequence. The information on the axial flow velocity is useful to improve the robustness of the harmonic images to motion artifacts. Approaches to a harmonic flow imaging technique similar to phase inversion Doppler are currently investigated.

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OVERVIEW OF GENE AND DRUG DELIVERY WITH ULTRASOUND

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Genetic engineering has made tremendous strides in the past decade in our knowledge of own genetic makeup. It is clear that for the foreseeable future, advances in medicine will be primarily driven by the development of new therapies made possible by these genetic engineering breakthroughs. It has also been shown that ultrasound, and especially ultrasound microbubbles, may play a major role in delivering and activating these therapeutic agents in the right place and time. This paper will briefly outline some of the potential applications for genetic medicine and ultrasound mediated delivery. It should be noted that all proposed applications deal with somatic gene therapy, which affects only the individual, not germ line therapy, in which future generations are affected and is much more controversial.

Most applications for ultrasound mediated gene and drug delivery focus on vascular related diseases. This is largely because microbubbles, and hence any drugs or genes that may be encapsulated in them, are restricted to remaining within the vascular system. This still allows addressing some of the biggest killers world-wide: ischemic injury, namely heart attack and stroke; and cancer.

The drugs currently under the most intense clinical development are related to angiogenesis, the growth of new blood vessels. In the case of ischemic injury, there is hope that with the proper therapy new blood vessels can be grown to bypass the stenotic area and provide adequate blood supply without major surgery. This especially holds promise for those affected with more diffuse disease that cannot be treated by bypass surgery or angioplasty, which can alleviate only localised lesions. For cancer the opposite effect is sought, namely to stop the development of new blood vessels triggered by the growth of a malignant lesion.

In the former case, blood vessel growth can be initiated by administering vascular endothelial growth factor (VEGF), but if administered generally would result in uncontrolled vascular growth in areas where it is not needed. However, to administer it directly to the injured myocardium, for example, would require multiple injections over a long period of time directly into the heart muscle, obviously a very invasive procedure. The role of genetic engineering then is to force local cells in the region of interest to produce the VEGF protein over an extended period of time, long enough to affect new

blood vessel growth. However, the gene itself must somehow be gotten into the cells and expressed, indicated by the production of VEGF.

One of the methods to accomplish this is to put the gene in a viral vector, or a deactivated virus, which uses the ability of a virus to infect cells, but in which the viral DNA has been replaced with the new engineered DNA. This works in a test tube but doesn't work in vivo very well as the virus is largely confined to the vascular system and cannot enter the intracellular fluid and hence infect the target cells.

This is where ultrasound and microbubbles may play a unique role. Ultrasound seems to change endothelial membrane properties to allow particles which would otherwise be trapped within the vascular system to enter the intracellular fluid, giving them access to the target cells. It has also been shown that microbubbles insonified with ultrasound enhances gene transfection, or incorporation of the new genetic material into the targeted cell. The combination of these effects produces a huge increase in overall gene transfection. The goal would then to be able to inject a genetically engineered drug, scan the region of injury releasing the gene into the intracellular space and grow new blood vessels to repair damaged tissue.

A brief review of some recent results from other labs will also be presented in the talk.

DRUG DELIVERY WITH MICROBUBBLES: INITIAL STEPS

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Apart from the effects of microbubbles on tissue, numerous studies on microbubble behaviour and applications for local drug delivery have already been carried out. Klibanov and co-workers have shown that 0.0001% volume microbubbles in blood (20 bubbles / millilitre) gives a strong backscatter signal and that patches of contrast microbubbles as small as 1x2 mm can be visualised. Porter and colleagues have demonstrated that, as theoretically predicted, higher frame rates and sonification frequencies near the resonance frequency result in greater bubble destruction. They likewise show that small (<5μm) microbubbles are preferentially destroyed. Furthermore, the biodistribution of albumin-shelled microbubbles has been examined before their approval for use by the Federal Drug Administration: particulate albumin has been shown to be taken up chiefly by the liver. Likewise, it has been shown that it is possible to target microbubbles to various cell types by attaching (fragments of) antibodies or active peptides to the bubble shell reviewed in. With such targeting methods, it has been shown possible to visualise both thrombi activated endothelium in vivo. Although, it may be possible to further increase the specificity of delivery techniques via such a targeting mechanism, local insonification may be sufficient for tissue selection. Also promising is data showing that ultrasound and contrast may increase gene delivery. Lawrie and co-workers have demonstrated that ultrasound (1 MHz, continuous wave, 0.4 W/cm^2, for 60s) increased lipofection of plasmid DNA in vitro in endothelial and smooth muscle cells when given after 30 minutes of the three hour transfection period. This effect was not due to heat. Shohet et.al. have demonstrated that ultrasound and microbubbles clearly enhanced gene delivery to the myocardium. These authors infused bubbles with adhered recombinant adenoviruses (2 ml, 1.2 x 10^9 β-gal units/ml). Transthoracic ultrasound (1.3 MHz, MI 1.5) was given for 3 frames every 4-6 cardiac cycles). The total ultrasound exposure was not reported. Reporter protein activity was increased ten-fold versus all controls in the heart. Extensive activity in the liver was noted, but not in skeletal muscle. All in all, if one combines existing data demonstrating that ultrasound and ultrasound/contrast enhance tissue permeability with the capability of local insonification or targeting, it seems that ultrasound in combination with contrast may prove to be a veritable, solution in the ongoing search for a local drug delivery technique. Considering the innumerable applications for local delivery of drugs and/or genes, research furthering the understanding of ultrasound contrast is significant and well warranted.

Despite these positive steps, much basic research is need before microbubble-mediated local drug delivery becomes a reality. Essential questions remaining to be answered include:

1) Is a hydrophilic substance attached to a microbubble released upon bubble rupture?
2) Is a hydrophobic substance captured in an oil layer within a bubble released upon bubble rupture?
3) Are these substances inactive before release but active subsequent to bubble rupture?
4) Does the coupled substance effect the behaviour of the bubble, in terms of its resonance, contrast and rupture?
5) Are entrapped/coupled substances taken up by endothelial cells? Is this process efficient?
6) Is it possible to meet dosing requirements with allowable dosages of microbubbles, i.e., how much of a drug can be delivered via a bubble and how many bubbles can be delivered before clearance?
7) Are histological effects induced by rupture of clinically relevant amounts of bubbles of physiological significance?
8) Is targeting necessary? Does it improve delivery efficiency?

Work in this field will benefit by studies clearly demonstrating rupture-induced release of a substance, its uptake and subsequent predicted activity in vitro and then in vivo. Tot achieve proof of principle any tracer is suitable, e.g., fluorescent markers, dyers, radioactivity, or reporter genes. To prove substance activity, it is advisable to choose a drug whose effects are well described.

GENE TRANSFECTION WITH SONOPORATION

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There has been a considerable degree of excitement in diagnostic ultrasound imaging with the introduction of new echo contrast agents. Recently, various in vitro and in vivo experiment have demonstrated that echo contrast agent microbubbles can be intentionally ruptured by diagnostic and therapeutic ultrasound. This acoustically induced destruction and collapse of the microbubbles produces a high amplitude response. Violent microstreaming can be produced during microbubble collapse. Researchers have hypothesised that these microjets or microstreaming could be applied to promote diffusion of drugs into various tissues and lesions. Additionally, drug-filled or drug-coated microspheres carrying a therapeutic compound may be targeted to specific tissues through the use of sonic energy, which is directed to the target area and causes the microspheres to rupture and release the therapeutic compound (1-3). Targeted drug delivery methods are particularly important where the toxicity of the drug is an issue. Specific drug delivery methods potentially serve to minimise toxic side effects, lower the required dosage amounts, and decrease costs for the patient. The most exciting application of this method is probably gene therapy (4-7).

Arterial occlusive diseases cause serious ischemic conditions in various organs, such as the heart, brain and leg. Therapeutic angiogenesis is believed to be beneficial for such conditions. Intramuscular injection of naked plasmid DNA encoding angiogenic growth factors offers a promising new approach for such purposes, however, only a small amount will pass through the cell membrane leading to low gene-transfer efficiency. Recent studies have shown that ultrasound can induce or increase cell membrane permeabilisation of various agents including genes. It is currently suggested that the major mechanism of this phenomenon is closely related with acoustic cavitation. High intensity of ultrasound is required to create cavitation within tissues such as the skeletal muscles and myocardium. As microbubble can lower cavitation threshold, it was postulated that commercially available ultrasonography contrast agent microbubbles could be used to increase gene transfection efficiency in vivo by relatively low intensity ultrasound-mediated microbubble destruction. We recently demonstrated that muscle tissue irradiated with ultrasound in the presence of albumin-coated, octafluoropropane gas-filled Optison microbubble can increase gene transfection by 10-folds compared to albumin-coated, air-filled Albunex microbubble. As Optison has a longer life span than Albunex as a bubble, gene transfection may be attributed to repeated or slower bubble destruction

during ultrasound irradiation resulting in greater number of cell membrane sonoporation. Systemic administration or local vascular delivery of microbubble have also been reported elsewhere (8-10), to induce localised extravascular leakage of genes leading to more uptake into surrounding tissue and cells.

Although further investigation should be performed to find the optimal type of gas-filled microbubble, already commercially available ultrasonography contrast agent, Optison, PESDA, Fluorogene, etc might be used as a modality for efficient gene delivery into cells for induction of angiogenesis and treatment of various diseases in the near future.

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MOLECULAR IMAGING AND TARGETED DRUG DELIVERY

Gregory M. Lanza, Dana R. Abendschein, Michael S. Hughes, Jon N. Marsh,Michael J. Scott, Ralph Fuhrhop, Jie Tan, Mark McLean, John S Allen,Patrick J. Gaffney and Samuel A. Wickline

Developments in molecular science now extend the horizon of non-invasive medical imaging from gross anatomical description to functional cellular and biochemical information. The emerging field of "molecular imaging" encompasses the non-invasive in vivo diagnosis of complex pathological processes by detection of unique molecular signatures. Moreover, localisation of specific biochemical epitopes with targeted contrast agents affords the opportunity for targeted delivery and deposition of therapeutics. Combining imaging with drug delivery permits verification and quantification of treatment, i.e. rational targeted therapy.

Successful targeted contrast agents must ideally have:

- long circulating half-life (ideally greater than 30-60 minutes).
- long residence time at targeted site.
- sensitive and selective binding to epitopes of interest.
- prominent contrast-to-noise enhancement.
- acceptable toxicity profile.
- ease of production and clinical use.
- applicability with standard commercially available imaging modalities.
- promise for adjunctive therapeutic delivery (ideal)

We have reported the development of a unique, multifunctional site-targeted emulsion-based contrast agent used to detect a broad range of molecular signatures. The agent is a nongaseous perfluorocarbon nanoparticle (~250 nm mean diameter) that have inherently poor acoustic reflectivity except when bound and concentrated on specific targets. We have reported large increases in signal-to-noise ratio for acoustic imaging of arterial thrombi in dogs and stretch induced tissue-factor expression within the carotid tunica media in pigs.

Recently, we have demonstrated a unique capability of these nanoparticles to deliver potent bioactive agents, such as chemotherapeutic agents, with enhanced efficiency to targeted tissues through a unique form of bioactive agent transfer into target cells, i.e. contact facilitated drug delivery. The results of this emerging technology for the detection and/or treatment of vulnerable atherosclerotic plaque, post-angioplasty restenosis and angiogenesis insolid tumours will be presented.

CLINICAL APPLICATIONS OF ULTRASOUND CONTRAST AGENTS

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Background

Ultrasound is the fastest growing segment of the clinical imaging modalities.

The advanced ultrasound imaging systems, coupled with the use of ultrasound contrast agents, provide a unique and unparalleled opportunity to define disease and monitor the effects of therapy.

Ultrasound Contrast Agents

Ultrasound imaging, in distinction to other non-invasive imaging modalities, has not traditionally incorporated the use of contrast agents. Today, all other non-invasive imaging modalities incorporate contrast agents in approximately 40 to 60% of clinical studies; particularly, for tissue/organ enhancement, perfusion or blood pool imaging. SPECT and PET, NMR, and CT, utilise contrast agents as a routine part of the clinical practice of medicine.

In part, the delay in the clinical deployment of contrast applications can be attributed to several factors: (1) the first commercially available ultrasound contrast agent was approved in the USA in 1994; a second-generation agent was approved in January 1998, (2) lack of educational efforts for the end-users, (3) "moving targets" with respect to ultrasound technology, and (4) governmental approval and reimbursement issues.

Clinical Applications of Contrast Agents

Transthoracic Imaging. Traditionally, 15-20% of all transthoracic echo images are technically inadequate for diagnostic clinical purposes [Beller GA, NEJM 2000; (20):1488-90]. Today while the technologic improvements in ultrasound software and hardware design have, in fact, reduced the "technically limited" exams, there exist a sizeable number of studies that are inadequate for diagnostic purposes. To illustrate the utility of ultrasound contrast agents, Reilly et al. (JACC 2000, 33(2):485-90) recently published a report describing the clinical utility of using contrast agents for improving the diagnostic yield in ICU patients. To quote…"Contrast Echo should be used in all suboptimal transthoracic echocardiograms…"

Further, a report by Malhotra et al. (J Am Soc Echocardiogr 2000;13:771-3),

"Is the Technically Limited Echocardiographic Study an Endangered Species? Endocardial Border Definition with Native and Tissue Harmonic Imaging and Optison Contrast: A Review of 2200 Cases."

To quote, "...The use of Optison contrast significantly enhanced border definition when imaging was performed in either fundamental or Native Tissue Harmonic Imaging Mode."

Stress Testing with Contrast Agents. Due to the inherent limitations of clearly defining the "true" endocardial surfaces with both transthoracic and stress echo images, the use of contrast agents have been shown to improve the diagnostic yield of the stress echo examination. The inter- and intra-observer variability is reduced, the false positive rate is reduced, and the overall positive predictive value is improved, substantially. From our laboratory at Rush-Presbyterian-St. Luke's Medical Center in Chicago, we observed an absolute increase of 13% (relative increase of 17%) increase in establishing the true positive predictive. Specifically, we determined the positive predictive values of performing stress echo for the determination of ischemic heart disease in the era of pre- and post-harmonic and contrast imaging.

Group A consisted of patients that underwent stress echoes in the era of pre-harmonics and pre-contrast and, Group B, consisted of patients who underwent stress echoes with harmonics and ultrasound contrast agents. The results indicated an absolute increase in the positive predictive value of 13% (relative increase of 17%) for the detection of coronary artery disease with the addition of harmonic imaging and contrast agents.

In addition, the number of false positives decreased with a corresponding increase in the overall percentage of positive studies. These results are consistent with a corresponding decrease in the number of false negative studies.

Cost effectiveness. The use of contrast enhanced stress echocardiography has resulted in improved patient care, reduction in redundant testing, and cost effective management of resources.

[LJ Shaw et al., Use of an Intravenous Contrast Agent (Optison) to Enhance Echocardiography: Efficacy and Cost Implications. Am J Man Care 1998;4:SP169-176, and Use of Intravenous Optison Contrast Echocardiography Reduces Downstream Research Use and Enhances Cost Savings. Acad Radiol 1998;5(suppl 1): S 250-1, discussion S252-3].

REAL TIME Perfusion Imaging

REAL TIME myocardial perfusion coupled with stress testing (exercise or pharmacologic) will permit the direct assessment of microvascular blood volume and flow. Based upon experimental data, contrast echo methods have been shown to quantitatively correlate to microvascular volumes (using radio-labelled RBC's and plasma) and microvascular blood flow (latex microspheres). Subsequently, confirmatory data from multiple centres has supported the clinical use of ultrasound contrast for perfusion imaging. From these reports, gated and REAL TIME perfusion imaging have been shown to be feasible and practical in clinical practice. The addition of perfusion imaging to stress testing will allow the "threshold" of detecting ischemic heart disease to go beyond the current standards of

detecting wall motion and wall thickening. The detection of abnormalities of microvascular perfusion should complement the current diagnostic and therapeutic management of patients with atherosclerotic heart disease.

Future Uses of Cardiovascular Ultrasound for the Diagnosis and Monitoring of Atherosclerosis

We plan to utilise ultrasound and associated tissue perfusion imaging, in patients with atherosclerosis to define the efficacy of therapy. Ultrasound contrast agents when used in conjunction with traditional imaging, will serve to enhance the intimal-media thickness of the carotid arteries and quantitatively assess perfusion of the heart and the kidneys. These ultrasound and contrast derived data, will be used to monitor the ongoing medical therapies currently used for atherosclerosis plaque stabilisation and regression.

Summary

A revolutionary change is occurring in the field of contrast ultrasound imaging. With the technologic advances in acoustic imaging and the availability of contrast agents, ultrasound imaging is now a true and equal partner to the traditional imaging modalities that provide a physiologic basis for the analysis of organ perfusion. Today, ultrasound contrast agents, serving as true intravascular markers of perfusion, provide an unparalleled ability to define cardiovascular physiology. The remarkable temporal and spatial resolution of ultrasound imaging provides a unique opportunity to quantitatively diagnosis and monitor therapies directed at the treatment of atherosclerosis.

OPTIMIZING THE LEFT VENTRICULAR ENDOCARDIAL BORDER DETECTION: HARMONICS, PULSE INVERSION OR CONTRAST?

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Background

The evaluation of regional and global left ventricular function is the most common clinical indication for echocardiogram. Thus, the visualization of left ventricular endocardial border (LVEB) is an essential component of the study. Fundamental imaging is frequently insufficient for this purpose. Novel echocardiographic modalities have been applied to improve the echocardiographic evaluation of LVEB detection but data regarding their comparative value, particularly against contrast-enhanced imaging, are few.

Methods

Endocardial visualization index was calculated in a group of 15 patients with insufficient endocardial border detection in fundamental imaging. The following modalities were directly compared in all patients: fundamental imaging (FI), tissue harmonic imaging (HI), pulse inversion imaging (PI), harmonic contrast-enhanced imaging (HC) and pulse inversion contrast-enhanced imaging (PC). Imaging was performed using ATL 5000HDI and bolus injections of 0.3-0.5ml Optison. The analysis of data was based on calculation of endocardial visualization index (EVI), defined as the average of scores for 18 segments imaged from the 3 standard apical projections. Individual scores for segments were assigned using 3-point scale: 0-invisible, 1- incomplete visualization, 2 - complete visualization.

Results

Interpretable images were obtained in all patients. HI and PI improved significantly the visualization of LVEB, however, the addition of contrast provided further improvement, most significant in the studies with poorest quality. The comparisons of EVI using different modalities are shown below.

	EVI	SD	P vs FI	P vs HI	P vs PI	P vs HC
FI	0,889	0,420		<0.0001	<0.0001	<0.0001
HI	1,463	0,429	<0.0001		0.23	0.35
PI	1,363	0,533	<0.0001	0.23		0.13
HC	1,593	0,387	<0.0001	0.35	0.13	
PC	1,807	0,205	<0.0001	0.018	0.005	0.014

Conclusions

Both unenhanced harmonic imaging and pulse inversion imaging markedly improve LVEB in technically difficult echocardiograms but contrast administration can provide additional benefit in most challenging studies, with pulse inversion being the most efficient detection modality.

MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY IN (SUB)ACUTE MYOCARDIAL INFARCTION

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In acute myocardial infarction, myocardial contrast echocardiography after intravenous application of a contrast agent may demonstrate not merely the presence of coronary occlusion and success of reperfusion, but also the extent of myocardial salvage after reflow. The absence of myocardial perfusion has been shown to be a strong predictor of complications and poor recovery of left ventricular function despite angiographically documented infarct-related coronary patency.

Intravenous myocardial contrast echocardiography has the potential for vastly increasing clinical indications of contrast echocardiography in the setting of acute and chronic myocardial infarction. Examples will be shown during this meeting.

MYOCARDIAL SEPTAL ABLATION IN HYPERTROPHIC CARDIOMYOPATHY GUIDED BY MYOCARDIAL CONTRAST ECHO

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Non surgical reduction of septal myocardial muscle using ethanol is a new promising treatment for patients with hypertrophic obstructive cardiomyopathy (HOCM). However, proper localisation and quantification of the septal infarction is crucial before ethanol is being injected. Since myocardial contrast echo is a clinical tool to determine "area at risk" which can be visualised alive. This technique is nowadays proposed to guide ethanol injection during cardiac catheterization.

We present a clinical case with severe HOCM. Myocardial contrast echo was used using a commercially available ultrasound machine (HP Sonos 5500) and Levovist as an ultrasound contrast agent.

The contrast agent was injected through the coronary catheter, which was put into a septal branch of the left descending coronary artery (LAD). A 0.014-inch guide wire was passed into this septal branch and subsequently a small angiographic balloon (usually 10 x 2 mm) was advanced over the wire. After inflation of the balloon 1 ml of Levovist was injected distally from the balloon, with simultaneous registration of Transthoracic echo in apical views.

Also LV outflow tract gradient was calculated from Doppler echocardiography and the site of initial turbulence was located in the LV outflow tract by colour Doppler.

This enabled us to determine the exact site of the septal infarct and its potential myocardial infarction size.

After this procedure 1 ml of ethanol was injected and the whole MCE procedure was repeated after 5 minutes. If there was satisfactory decrease of LVOT gradient, the balloon was deflated and the catheter system removed.

This case will illustrate our method during non-surgical septal reduction using MCE.

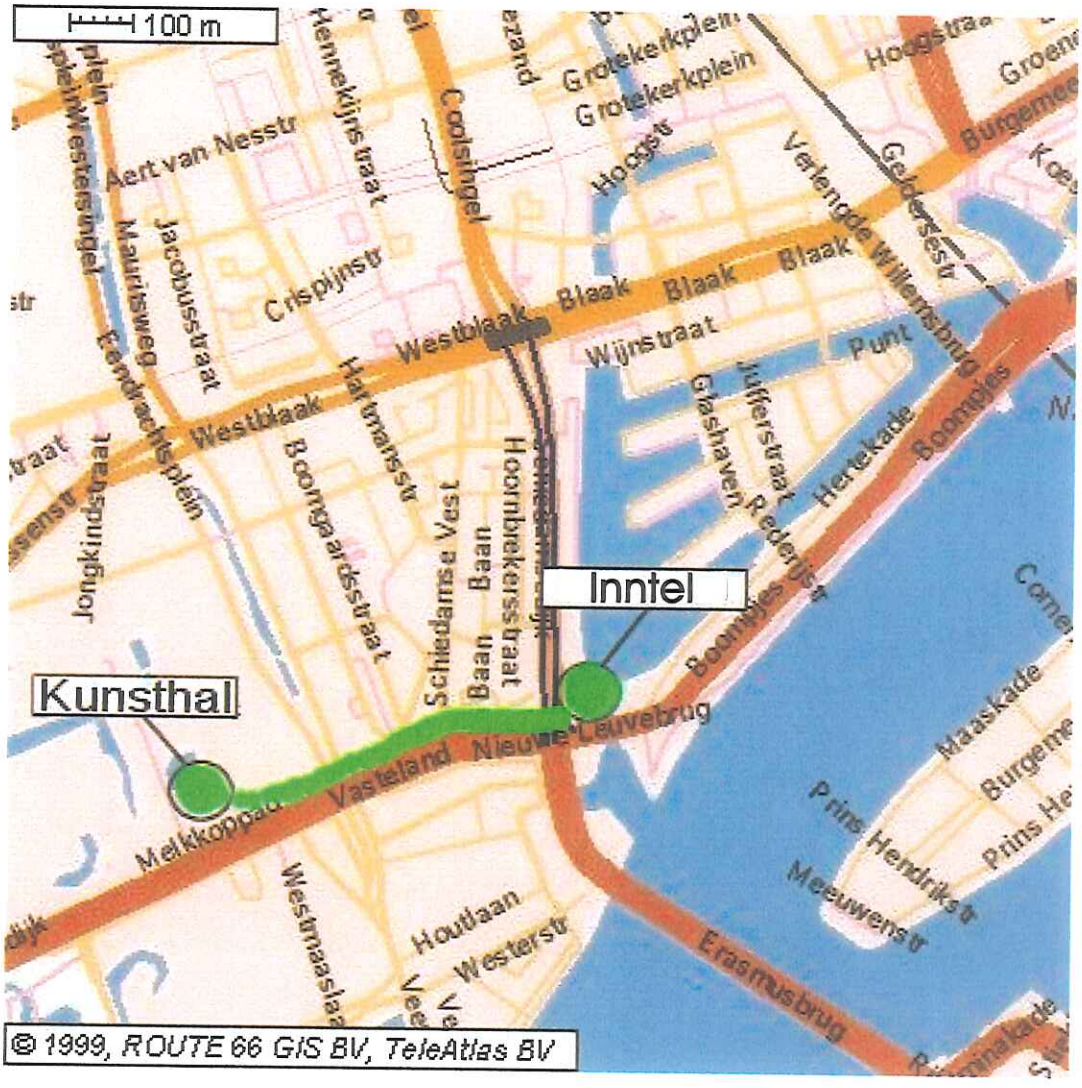
NO-REFLOW AFTER ACUTE MYOCARDIAL INFARCTION

L. Galiuto

Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy

One of the most promising applications of myocardial contrast echocardiography is that of in vivo imaging of post-ischemic coronary microcirculation. The diagnosis of microvascular patency status after acute myocardial infarction is of crucial importance to establish patient's prognosis. Furthermore, in the future, an early diagnosis of "no-reflow" despite successful recanalisation of the infarct related artery might lead to possible pharmacological prevention of this phenomenon. Myocardial contrast echocardiography (MCE) is the most promising available technique to study coronary microvascular network after acute myocardial infarction.

In this presentation, some clinical cases of post-ischemic reflow and no-reflow will be presented, along with their time-course of perfusion and function and with viability assessment.



Congress location: Inntel Hotel

From Central Railway Station
- by underground: 3rd stop (Central Station - Stadhuis - Beurs/Churchillplein - Leuvehaven)
- by taxi: about ten minutes

Social Event "Pictorial Imaging"

A ten minutes' walk from the Inntel or Tulip Inn brings you to Grand Café Hoboken (located between the Inntel and the Medical School of Erasmus University, and annex to the Kunsthal) where from 18:45 on drinks will be available. In the following hour you will be given the opportunity to visit the exposition "Meesterlijk Verzameld" (Masterly Collected). For more information about this collection, please see Kunsthal's press release on the next page. As from 20:15 an Indonesian dinner buffet will be served.

Route from the Inntel: Cross the road in front of the hotel. Go straight on. Cross two more streets. The second has traffic lights. After a while there is a fork. Keep right and proceed on the path that goes down. You will see the Kunsthal at your right-hand side. Thereafter turn right to enter the Grand Café Hoboken.

Masterly Collected
Five Centuries of European Painting: the Gustav Rau Collection
January 20 - April 16 2001

From January 20 through April 16 2001 the Kunsthal Rotterdam hosts a prestigious art collection: a hundred paintings from the collection of Gustav Rau. The exhibition 'Masterly Collected' will temporarily transform the Kunsthal into a 'Museum of European Art', with representative examples of all major movements throughout five centuries of European painting by such artists as Renoir, Monet, Degas, Fra Angelico, Morandi, Ribera, Watteau, Ruysdael, Macke, Canaletto, El Greco, Pourbus, Ter Borch, Gerard Dou, Cranach, Boucher, Millet, Courbet and Corot. Gustav Rau's wide-ranging collection, which is dominated by figurative art, contains works rarely if ever seen in one museum. Born in Stuttgart in 1922, Gustav Rau spent most of his life as a doctor in Africa. He founded a hospital in Zaire and launched an educational programme which benefits 30,000 children a year. Besides a doctor and a philanthropist, Rau is an art-lover who intends to donate his collection of more than 800 works to UNICEF in the near future. 'Masterly Collected' is currently on show at the Musée du Luxembourg in Paris, and will travel from the Kunsthal to New York's Metropolitan Museum of Art. This most prestigious show ever hosted by the Kunsthal and will be one of the main events taking place while Rotterdam is Cultural Capital of Europe in 2001.

A rare opportunity
'Masterly Collected' provides a rare opportunity for the public to see a number of less known paintings by famous artists. The French Impressionists and Post-Impressionists lead the field with six Monets, two Renoirs, two Degas, four Pisarros, three Sisleys, four Vuillards, two Bonnards and one painting each by Boudin, Signac and Caillebotte - an unprecedented gathering of masterpieces of this period of French art. Spain is represented by Ribera and an imposing 'Saint Dominic in Prayer' by El Greco. French eighteenth-century painters such as Greuze, Fragonard and Watteau feature prominently, so do the English portraitists Joshua Reynolds and Thomas Gainsborough, whose works are seldom seen in the Netherlands. Among the examples of Holland's 'Golden Age' are a rare portrait by Judith Leyster and a monumental work by Hendrick Ter Brugghen. The selection also includes paintings of superior quality by, among others, Frans Post, Gerard Dou, Gerard Ter Borch and Willem van Aelst. The Italian school makes a fine showing with two panels of an altarpiece from Fiesole by Fra Angelico and a superb David and Goliath scene by Guido Reni.

The exhibits have been selected by Marc Restellini, director of the Musée du Luxembourg in Paris.
An illustrated catalogue will accompany the exhibition and is published by Waanders Uitgevers; the English version by SKIRA.

With special thanks to the enlightened generosity of the principal sponsor of the exhibition, HAL Investments as well as to the other supporting sponsors, the Dutch Ministry of Education, Culture and Welfare, the City of Rotterdam, Rotterdam 2001 Cultural Capital, L'Ambassade de France aux Pays Bas, the Alliance Française and Stad Rotterdam Verzekeringen.

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Please state the Kunsthal's general information number: +31-10-4400301

6th EUROPEAN SYMPOSIUM ON ULTRASOUND CONTRAST IMAGING
25-26 JANUARY 2001, Rotterdam, The Netherlands

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FIRST ANNOUNCEMENT 2002:

7th EUROPEAN SYMPOSIUM ON ULTRASOUND CONTRAST IMAGING
24 and 25 JANUARY 2002, Rotterdam, The Netherlands.

Course Directors: Folkert Ten Cate, Nico de Jong and
David O. Cosgrove (Hammersmith- London)
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Internet:http://www.eur.nl/fgg/thorax/contrast

Rotterdam, January 2001

7 TH ULTRASOUND CONTRAST SYMPOSIUM

24 AND 25 JANUARY 2002

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