

(19) World Intellectual Property Organization  
International Bureau



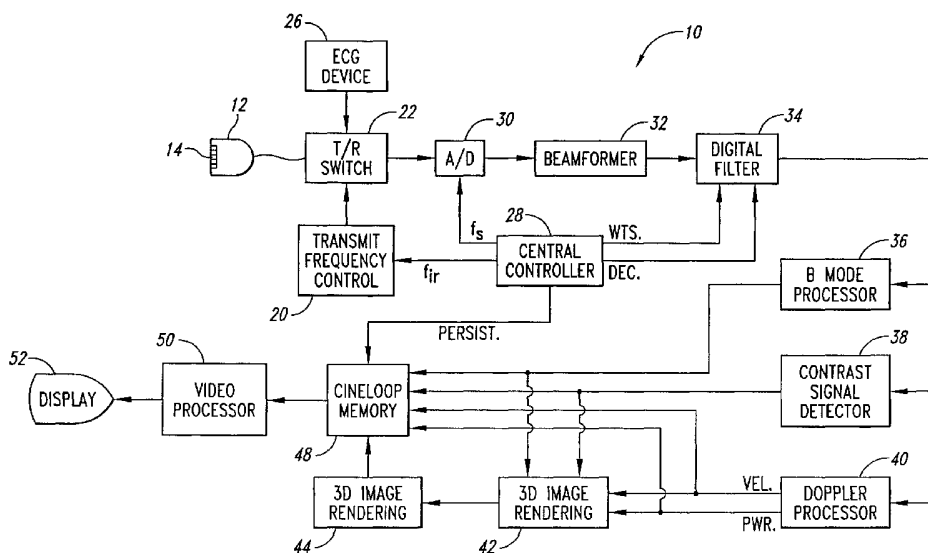
(43) International Publication Date  
26 June 2003 (26.06.2003)

PCT

(10) International Publication Number  
**WO 03/052453 A1**

- (51) International Patent Classification<sup>7</sup>: **G01S 7/52**, A61B 8/00
- (21) International Application Number: PCT/IB02/05069
- (22) International Filing Date:  
29 November 2002 (29.11.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
10/025,200 18 December 2001 (18.12.2001) US
- (71) Applicant: **KONINKLIJKE PHILIPS ELECTRONICS N.V.** [NL/NL]; Groenewoudseweg 1, NL-5621 BA Eindhoven (NL).
- (72) Inventors: **SKYBA, Danny, M.**; Prof. Holstlaan 6, NL-5656 AA Eindhoven (NL). **DOLIMIER, Damien, J.-J.**; Prof. Holstlaan 6, NL-5656 AA Eindhoven (NL). **POWERS, Jeffry, E.**; Prof. Holstlaan 6, NL-5656 AA Eindhoven (NL).
- (54) Title: **ULTRASONIC IMAGING SYSTEM AND METHOD FOR DISPLAYING TISSUE PERFUSION AND OTHER PARAMETERS VARYING WITH TIME**
- (74) Agent: **CHARPAIL, François**; Internationaal Octrooibureau B.V., Prof. Holstlaan 6, NL-5656 AA Eindhoven (NL).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— with international search report

[Continued on next page]



(57) Abstract: A method and system for displaying a parametric image showing tissue perfusion includes an ultrasonic imaging system coupled to an ECG device. The ECG device triggers the imaging system to obtain contrast image data showing tissue perfusion at a respective predetermined time during each of a plurality of heartbeats. Parametric image data for discrete locations in the area of interest such as the myocardium is determined from the temporal contrast data acquired during reperfusion of the tissue in the area of interest. The parameters are mapped to a display value such as color to produce a parametric perfusion ultrasound image. Sequences of images may be produced which depict both perfusion characteristics and dynamic wall motion of the myocardium in a common image sequence.



---

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

Ultrasonic imaging system and method for displaying tissue perfusion and other parameters varying with time

This invention relates to diagnostic ultrasonic imaging, and, more particularly, to a system and method for displaying tissue perfusion and other time-varying parameters.

5           Ultrasonic diagnostic imaging systems are capable of imaging and measuring the physiology within the body in a completely noninvasive manner. Ultrasonic waves are transmitted into the body from the surface of the skin and are reflected from tissue and cells within the body. The reflected echoes are received by an ultrasonic transducer and processed to produce an image or measurement of blood flow. Diagnosis is thereby possible with no  
10   invasion of the body of the patient.

          Materials known as ultrasonic contrast agents can be introduced into the body to enhance ultrasonic diagnosis. Contrast agents are substances that strongly reflect ultrasonic waves, returning echoes which may be clearly distinguished from those returned by blood and tissue. One class of substances which has been found to be especially useful as an  
15   ultrasonic contrast agent is gases, in the form of tiny bubbles called microbubbles. Microbubbles strongly backscatter ultrasound in the body, thereby allowing tissues and blood containing the microbubbles to be readily detectable through special ultrasonic processing.

          Although microbubbles can be simply very small bubbles of a suitable gas, microbubbles can also be very small bubbles of gas coated with a thin biodegradable coating  
20   or shell. These coated microbubbles typically have diameters between 0.1 and 4.0 microns and a specific density about 1/10 of the density of water. Coated microbubbles are normally suspended in an aqueous solution for infusion into the blood stream. Coated microbubbles have the advantage of being stable in the body for a significant period of time, as the shells serve to protect the gases of the microbubbles from diffusion into the bloodstream. The size  
25   of the microbubbles may be chosen to enable the microbubbles to pass through capillary beds in the body. Therefore, microbubble contrast agents can be used for imaging the body's vascularized tissues, such as the walls of the heart, since the contrast agent can be injected into the bloodstream and will pass through veins, arteries and capillaries with the blood supply until filtered from the blood stream in the lungs, kidneys and liver.

Although coated microbubbles can survive in the body for an extended period, they can also be selectively destroyed. More specifically, at moderately high sound pressure amplitudes, acoustic pressure waves can cause the shells of coated microbubbles to rupture, freeing the bubbles to behave as non-coated microbubbles by quickly diffusing into the bloodstream. U.S. Patent No. 5,813,613 to Averkiou, *et al.*, which is incorporated herein by reference, discloses a technique for using the destruction of microbubbles as described above to provide a measure of tissue perfusion. Basically, the Averkiou, *et al.* technique involves transmitting a high intensity ultrasonic pulse to a selected sample volume in the body, thereby destroying the microbubbles at that location. After the microbubbles in the sample volume have been destroyed, the blood that contained the destroyed microbubbles flows out of tissues at that location, and new blood containing microbubbles reperfuses these tissues. After a given period of reperfusion another high intensity pulse is transmitted with the received echoes indicating the microbubble concentration at the sample volume after the given period of reperfusion. This pulse destroys the microbubbles a second time, and a different reperfusion period is allowed to pass and another high intensity pulse transmitted to determine the microbubble concentration after the different period of reperfusion. The cycle is repeated for a plurality of reperfusion period and the measurements thus taken are plotted to produce a reperfusion curve showing the rate of reperfusion of the tissue at the sample volume.

While this technique is effective for measuring the perfusion rate and producing a reperfusion curve for a specific sample volume, it would be desirable to be able to make and display the results of perfusion measurements for a large region of tissue and not just a particular sample volume location. Such a capability would enable the rapid diagnosis the perfusion rate of a significant region of tissue such as the myocardium, enabling the clinician to quickly identify small regions of tissue where perfusion is problematic due to ischemia or other bloodflow conditions.

A method and system displays a parametric contrast image of the perfusion rate of anatomy in an image, depicting the rate of reperfusion for a significant area or volume of tissue in the body simultaneously. A single static parametric perfusion image may be produced, or a sequence of parametric perfusion images produced to illustrate changes in the perfusion rate over time. Ungated or gated images may be used, enabling the parametric display to be keyed to specific phases of the heart cycle. Multiple parameters can be

combined in a single parametric image, if desired. The inventive technique may be used with bolus contrast injections or with a continuous infusion of the contrast agent.

5 In accordance with the different embodiments of the invention the act of acquiring temporal ultrasonic echo information comprises flashing the region of interest with high MI ultrasound energy, then acquiring temporal ultrasonic echo information over a period of time with low MI ultrasound energy or the act of acquiring comprises acquiring ultrasonic echo information at periodically triggered intervals or the act of acquiring comprises acquiring a real time sequence of ultrasonic image information or the act of acquiring comprises selecting image information from the real time sequence which relates to  
10 a specific phase of bodily activity.

In accordance with the different embodiment of the invention, the act of producing a 2 or 3 dimensional image comprises mapping perfusion parameters to a range of display parameters or the act of producing comprises mapping perfusion parameters to a range of display colors.

15 In an embodiment of the invention, the act of identifying temporal echo information corresponding to common locations in the region of interest further comprises identifying the region of interest by automated border detection.

20 Fig. 1 is a block diagram of an ultrasonic imaging system according to one embodiment of the invention.

Fig. 2 is a schematic drawing showing a B-mode image of a myocardium obtained using the system of Figure 1.

25 Fig. 3 illustrates the acquisition of a sequence of real time image frames for parametric imaging.

Fig. 4 illustrates gated (triggered) acquisition of a sequence of frames for parametric imaging.

Fig. 5 depicts a sequence of real time images over several heart cycles.

30 Figs. 6a, 6b, and 6c illustrate sequences of images for unique phases of the heart cycle assembled from the images of the sequence of Figure 5.

Figs. 7a-7d illustrate the delineation of a region of interest in an image using assisted border detection.

Figs. 8a and 8b illustrate the masking of a region of interest.

Figs. 9a and 9b illustrate a preferred technique for quantifying pixel values in a region of interest.

Fig. 10 illustrates the selection of pixel values from a plurality of images for the determination of a perfusion curve for the pixel location.

5 Fig. 11 illustrates the plotting of a perfusion curve from image data.

Fig. 12 illustrates the fitting of a smooth curve to the perfusion curve of Figure 11.

Figs. 13a and 13b illustrate the mapping of perfusion parameters to a color scale and a two dimensional image.

10 Fig. 14 illustrates a real time display of parametric perfusion images corresponding to different phases of a heart cycle.

An ultrasonic diagnostic system 10 constructed in accordance with the principles of the present invention is shown in Figure 1. An ultrasonic scanhead 12 includes an array 14 of ultrasonic transducers that transmit and receive ultrasonic pulses. The array may be a one dimensional linear or curved array for two dimensional imaging, or may be a two dimensional matrix of transducer elements for electronic beam steering in three dimensions. The ultrasonic transducers in the array 14 transmit ultrasonic energy and receive echoes returned in response to this transmission. A transmit frequency control circuit 20 controls the transmission of ultrasonic energy at a desired frequency or band of frequencies through a transmit/receive ("T/R") switch 22 coupled to the ultrasonic transducers in the array 14. The times at which the transducer array is activated to transmit signals may be synchronized to an internal system clock (not shown), or they may be synchronized to a bodily function such as the heart cycle, for which a heart cycle waveform is provided by an ECG device 26. As explained in greater detail below, when the heartbeat is at the desired phase of its cycle as determined by the waveform provided by ECG device 26, the scanhead is commanded to transmit an ultrasound beam. The ultrasonic energy transmitted by the scanhead 12 can be relatively high energy (high mechanical index or MI) which destroys or disrupts contrast agent in the image field, or it can be relatively low energy which enables the return of echoes from the contrast agent without substantially disrupting it. The frequency and bandwidth of the ultrasonic energy generated by the transmit frequency control circuit 20 is controlled by a control signal  $f_a$  generated by a central controller 28.

Echoes of the transmitted ultrasonic energy are received by the transducers in the array 14, which generates echo signals that are coupled through the T/R switch 22 15 and digitized by analog to digital ("A/D") converters 30. The A/D converters 30 sample the received echo signals at a sampling frequency controlled by a fs signal generated by the central controller 28. The desired sampling rate dictated by sampling theory is at least twice the highest frequency of the received passband, and might be on the order of at least 30-40 MHz. Sampling rates higher than the minimum requirement are also desirable.

The echo signal samples from the individual transducers in the array 14 are delayed and summed by a beamformer 32 to form coherent echo signals. The digital coherent echo signals are then filtered by a digital filter 34. In this embodiment, the transmit frequency and the receiver frequency are individually controlled so that the beamformer 32 is free to receive a band of frequencies which is separate from the transmitted band. The digital filter 34 bandpass filters the signals, and can also shift the frequency band to a lower or baseband frequency range. The digital filter could be a filter of the type disclosed in U.S. Patent No. 5,833,613.

Filtered echo signals from tissue are coupled from the digital filter 34 to a B mode processor 36 for conventional B mode processing. The B mode image may be created from echoes returning from nondestructive ultrasonic imaging pulses. As discussed above, pulses of low amplitude, high frequency, and short burst duration will generally not destroy the microbubbles.

Filtered echo signals of a contrast agent, such as microbubbles, are coupled to a contrast signal detector 38. The contrast signal detector 38 preferably separates echoes returned from harmonic contrast agents by the pulse inversion technique, in which echoes resulting from the transmission of multiple pulses to an image location are combined to cancel fundamental signal components and enhance harmonic components. A preferred pulse inversion technique is described in U.S. patent 6,186,950, for instance, which is hereby incorporated by reference. The detection and imaging of harmonic contrast signals at low MI is described in U.S. patent 6,171,246, the contents of which is also incorporated herein by reference.

The filtered echo signals from the digital filter 34 are also coupled to a Doppler processor 40 for conventional Doppler processing to produce velocity and power Doppler signals. The outputs of these processors may be displayed as planar image, and are also coupled to a 3D image rendering processor 42 for the rendering of three dimensional images, which are stored in a 3D image memory 44. Three dimensional rendering may be

performed as described in U.S. Pat. No. 5,720,291, and in U.S. Pat. Nos. 5,474,073 and 5,485,842, all of which are incorporated herein by reference.

The signals from the contrast signal detector 38, the processors 36 and 40, and the three dimensional image signals from the 3D image memory 44 are coupled to a Cineloop® memory 48, which stores image data for each of a large number of ultrasonic images, as explained in greater detail below. The image data are preferably stored in the Cineloop memory 48 in sets, with each set of image data corresponding to an image obtained at a respective time. The sets of image data for images obtained at the same time during each of a plurality of heartbeats are preferably stored in the Cineloop memory 48 in the same group. Thus, as explained below, the image data in a group can be used to display a parametric image showing tissue perfusion at a respective time during the heartbeat. The groups of image data stored in the Cineloop memory 48 are coupled to a video processor 50, which generates corresponding video signals for presentation on a display 52. The video processor 50 preferably includes persistence processing, whereby momentary intensity peaks of detected contrast agents can be sustained in the image, such as described in U.S. Pat. No. 5,215,094, which is also incorporated herein by reference.

The manner in which perfusion can be displayed in a parametric image will now be explained with reference to Figures 2-14. An image 60 is obtained from a region of interest, preferably with the aid of the microbubbles used as contrast agents, as shown in Figure 2. The anatomy shown in Figure 2 is the left ventricle 62 of a heart, although it will be understood that the region of interest can encompass other tissues or organs. The left ventricle 62 is surrounded by the myocardium 64, which has inner and outer borders, 66, 68, respectively, that defines as an area of interest, the perfused myocardium 64. The myocardium can be distinguished for analysis by segmentation either manually or automatically using conventional or hereinafter developed techniques, as described below.

Figure 3 illustrates a real time sequence 70 of images of the myocardium which have been acquired with a contrast agent present in the heart. The image frames in the sequence are numbered F:1, F:2, F:3, and so on. The sequence is shown in time correspondence to an EGG waveform 72 of the heart cycle. It will be appreciated that during a heart cycle 10, 20, 30, 40 or more images may be acquired, depending upon the heart rate and the ultrasound system frame rate. In one embodiment of the present invention the acquired sequence 70 of images is stored in the Cineloop memory 48. In accordance with the principles of the present invention, during one interval 74 of images, high MI pulses are used to acquire the images. This is typically an interval of 1-10 image frames. The use of the high



intensity transmit pulses substantially disrupts or destroys the microbubbles in the image plane or volume. In this discussion these high MI frames are referred to as "flash" frames. At the end of this interval 74 low MI pulses are used to image subsequent image frames over several cardiac cycles delineated by interval 76 as the contrast agent reinfuses the myocardium. The sequence of images shows the dynamics of the cardiac cycle as well as contrast replenishment over many heart cycles.

Instead of acquiring a continual real time sequence of images, images can be selected out of a real time sequence at specific times in the cardiac cycle. Figure 4 illustrates this triggered acquisition, in which the arrows 78 indicate times triggered from the EGG waveform 72 at which images are acquired at a specific phase of the heart cycle. The arrow 80 indicates the time when one or more flash frames are transmitted, followed by an interval 76 during which low MI images are acquired. In this example only one image is acquired and stored in Cineloop memory during each cardiac cycle. The user sets the trigger timing to determine which part of the cardiac cycle to capture with the triggered images. When these images are replayed from Cineloop memory in real time, they do not show the dynamics of the cardiac cycle, as the heart is at the same phase of the cardiac cycle during each image. The sequence does show contrast replenishment in the triggered images acquired during the low MI interval 76.

Figures 5 and 6a, 6b, and 6c illustrate the assembly of multiple single-phase sequences from a real time continuous acquisition sequence. Figure 5 illustrates the continuous real time sequence as was shown previously in Figure 3. The dashed lines 82 represent the divisions between different heart cycles. The illustrated images are low MI images which have been preceded by one or more flash frames (not shown). Circles 84a indicate the time of acquisition triggered by the ECG waveform 72; the image in these circles are seen to be coincident with the QRS waveform 86. These triggered images are assembled in a sequence of images at this phase of the heart, as shown by image sequence 84a in Figure 6a. In a similar manner, triggered images are selected from the real time sequence at other phases of the heart cycle as shown by circles 84b and 84c. These triggered images are assembled into other sequences of images of their respective heart phases as shown in Figures 6b and 6c. This triggering may be done in real time, or in a post-processing operation in which the real time sequence of Figure 5 is captured in Cineloop memory and the triggered sequences of Figures 6a, 6b, and 6c are subsequently assembled from the stored real time sequence.

The area of interest in the image, in this example the myocardium, may optionally be delineated by assisted border detection as shown in Figures 7a-7d. Figure 7a illustrates a contrast image sequence 90 which may be a real time sequence 70 or a triggered sequence 80. From the image sequence 90 the user selects an image 92 which shows relatively well defined endocardial and epicardial borders. This image 92 is shown enlarged in Figure 7b. The selected image is then processed by assisted border detection, as described in U.S. patent [application serial number 09/732,613], entitled "Automated Border Detection in Ultrasonic Diagnostic Images," the contents of which is hereby incorporated by reference. Automated or assisted border detection acts to delineate the myocardium with a border 94 as shown in Figure 7c. The border outline 94 on the selected image is then used to delineate the border on other images in the sequence 90, as shown in Figure 7d. Alternatively, the borders may be drawn on the other images in the sequence by processing them individually with the automated border detection algorithm. The area of interest where perfusion is to be represented parametrically is now clearly defined for subsequent processing. If desired, the area of interest may be further defined by a mask 96, as shown in Figure 8b, in which the area within the border trace is masked. All pixels under the mask are to be processed in this example, while pixels outside of the mask are not processed parametrically.

Figures 9a and 9b illustrate a preferred technique for processing the pixels within the area of interest. As Figure 9b shows, for each pixel within the area of interest a mean image intensity value is calculated for a pixel and its surrounding eight neighboring pixels. Pixel values are calculated in this manner for each pixel in the myocardium 98 in this example, and the process is repeated for every pixel in the same location for each image in the sequence as shown for images 102, 104, 106 in Figure 10. The common location pixel values are, at least conceptually, then plotted graphically as a function of time and mean intensity as shown in Figure 11, which shows a plot of the common location pixel values intersected by arrow 100 in Figure 10. The common location pixels are then used to develop a perfusion parameter for display in a two- or three-dimensional image of the area of interest. In a preferred embodiment, parameters are produced by fitting the plotted values to a curve 10 of the form:

$$I(t) = A(1 - \exp^{-B \cdot t}) + C$$

where A is the final curve intensity, B is proportional to the initial slope of the curve, and C is a floating constant. A drawn curve 110 of this form is illustrated in Figure 12.

Parameters may then be formed using the values A, B, and combinations thereof (A\*B, A/B, etc.) as shown below.

Figure 13a-13b illustrate the creation of a parametric image from a parameter value of the form  $A*B$  using the curve characteristics described above. In the table of Figure 13a, the first two columns indicate the locational coordinates of pixels in a two dimensional image. For three dimensional images a third coordinate will be used. The  $A*B$  parameter value for each pixel location is represented in the third column. The range of parameter values, represented by the color bar 112 calibrated from zero to 255 between Figures 13a and 13b, is then used to encode (map) each parameter value to a color, brightness, or other display characteristic. The colors are then displayed in their respective locations in a two or three dimensional parametric image 120, as shown in Figure 13b, in which the perfusion of the myocardium of the heart is parametrically displayed.

The techniques of the present invention may be used to produce a single static image 120 as shown in Figure 13b, or they may be used to produce a sequence of parametric images which may be displayed in sequence or in real time. For instance, Figure 14 illustrates a sequence of parametric perfusion images from different phases of the heart cycle, as indicated by the arrows drawn from points on the ECG waveform 72 to individual images in the sequence 130. Each parametric image in the parametric image sequence 130 can be formed by a different one of the different phase sequences of Figures 6a, 6b, and 6c, for instance. The images of Figure 6a are used to produce parametric image 130a, the images of Figure 6b are used to produce parametric image 130b, and the images 11 of Figure 6c are used to produce parametric image 130c. When sequence 130 is played in full or partial real time, it will reveal the changing perfusion in the various locations in the myocardium during the different phases of the heart cycle. This image sequence thus reveals both myocardial perfusion information and the dynamics of wall motion of the endocardium in the same diagnostic image sequence.

In organs where perfusion is not as strongly related to the heart cycle, such as perfusion in the liver, kidney, a transplanted organ, or limb of the body, triggering may not be practical and perfusion images will be made during one or more selected reperfusion periods following flash image frames. Parametric images may be used for diagnoses such as tumor detection, where the parameter in the tumor will cause the image to "light up" from reperfusion faster than normal surrounding tissue. Parameters other than that shown for the curve equation given above may be used. For instance, the perfusion parameter could be based upon the error or variance of the actual acquired data (Figure 11) from a smooth curve such as curve 110. The techniques of the present invention may be used with either bolus injection of the contrast agent, or with continuous infusion of the agent. An example of

practice of the present invention with a bolus injection is tumor diagnosis in the liver.

Following a bolus injection a tumor in the liver will "light up" as it is infused with the flow of contrast agent from the hepatic arterial blood supply. Normal tissue in the liver lights up at a later time when the bolus of contrast agent enters the liver through the portal vein. At this later time the tumor will appear similar to or less bright than the surrounding normal tissue. Temporal parametric images will reveal these differences in perfusion at the different phases of this diagnostic process.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

## CLAIMS:

1. A method of providing a parametric ultrasound image of perfusion in a region of interest, comprising:

perfusing the region of interest with a contrast agent;

acquiring temporal ultrasonic echo information over a period of time as the

5 region of interest is perfused with the contrast agent;

identifying temporal echo information corresponding to common locations in the region of interest;

calculating a perfusion parameter from the identified temporal information at each common location; and

10 producing a two or three dimensional image of the region of interest in which locations in the region of interest are depicted by calculated perfusion parameters.

2. The method of claim 1, wherein the act of acquiring comprises flashing the region of interest with high MI ultrasound energy, then acquiring temporal ultrasonic echo  
15 information over a period of time with low MI ultrasound energy.

3. The method of claim 1, wherein the act of producing comprises producing a sequence of two or three dimensional parametric images.

20 4. The method of Claim 3, wherein the region of interest comprises the myocardium, wherein producing comprises producing a sequence of parametric images for different phases of the heart cycle,  
wherein the sequence of parametric images depicts both cardiac perfusion characteristics and wall motion.

25

5. The method of claim 1, wherein the act of calculating further comprises fitting a curve to the identified temporal information at each common location and utilizing a characteristic of the curve to calculate a perfusion parameter.

6. The method of claim 1, wherein the act of calculating a perfusion parameter comprises calculating a perfusion parameter for display from at least two other perfusion parameters.

5 7. An ultrasonic diagnostic imaging system for generating a parametric ultrasonic image of perfusion of blood in tissue in a region of interest, the system comprising:

a scanhead having an array transducer for scanning a region of interest;

a beamformer coupled to selectively apply transmit signals of high and low intensity to the transducer and to receive echo signals from the transducer and to generate  
10 output signals corresponding thereto;

a contrast signal detector which acts to identify contrast echo signals;

a processor coupled to the contrast signal detector and responsive to temporal sequences of contrast echo signals from discrete locations in the region of interest, the processor being operable to develop perfusion parameters relating to the discrete locations;

15 and

a video processor receiving the perfusion parameters and producing image data in which the perfusion parameters are spatially represented.

8. The system of claim 7, wherein the temporal sequences are real time image  
20 sequences.

9. The system of claim 7, further comprising a sensor which senses a cyclical bodily function, wherein the temporal sequences are triggered sequences in synchronism with the cyclical bodily function.

25 10. The system of claim 7, wherein the temporal sequences are acquired in response to low intensity transmit signals and following an interval of high intensity transmit signals.

30 11. The system of claim 7, wherein the processor further comprises an automated border detection processor which acts to delineate the region of interest in an ultrasound image.

12. The system of claim 7, wherein the video processor comprises an image processor responsive to the perfusion parameters which acts to map the perfusion parameter values to a display variable.

5 13. The system of claim 7, wherein the processor is further operable to determine perfusion parameters by fitting temporal contrast echo signals to perfusion curves.

14. The system of claim 9, wherein the sensor comprises a heart cycle sensor, and wherein the video processor acts to produce a sequence of perfusion parametric images  
10 relating to phases of the heart cycle.

15. The system of Claim 7, wherein the region of interest comprises a volumetric region, and wherein the video processor acts to produce image data for a three dimensional region.

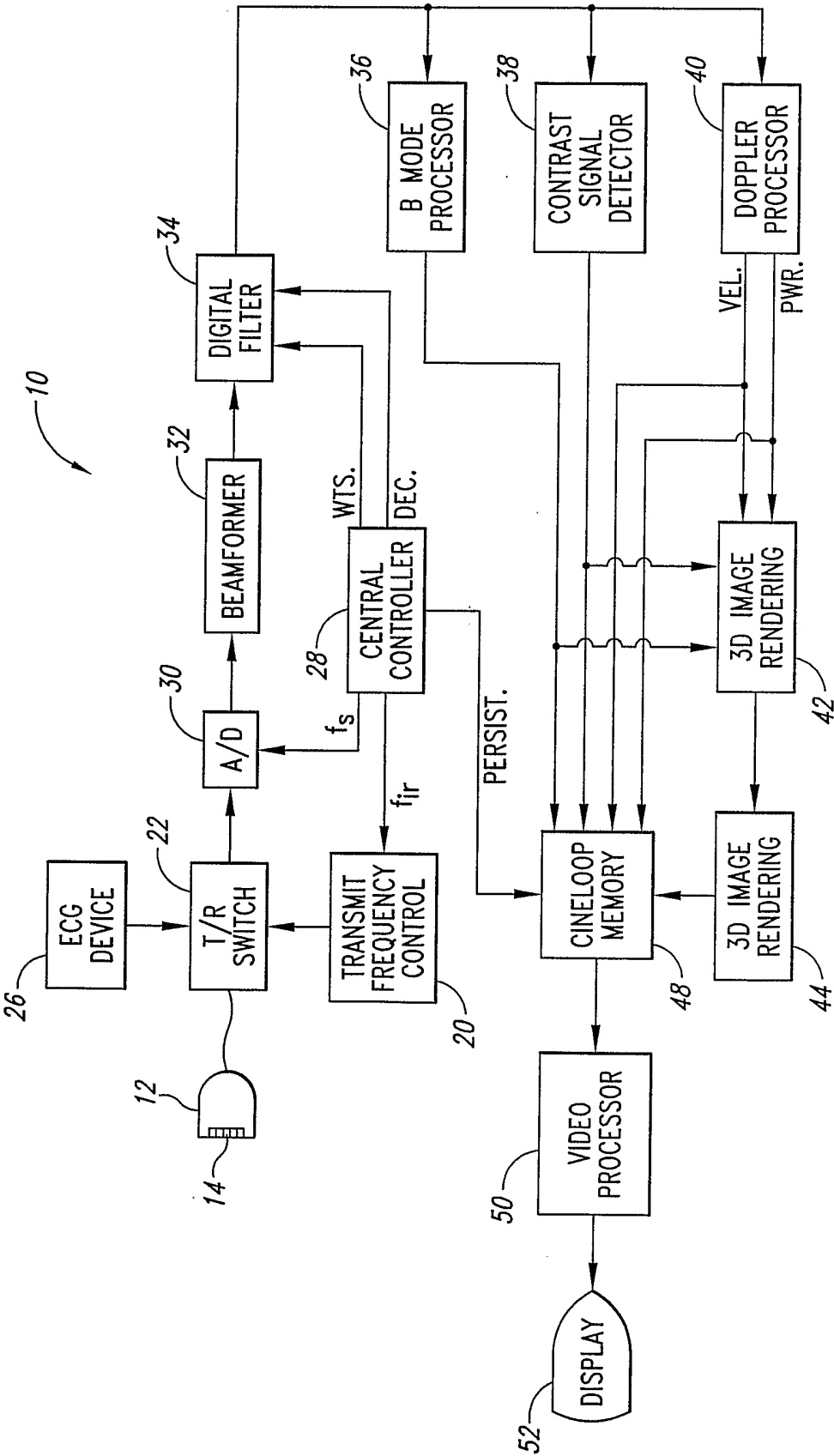
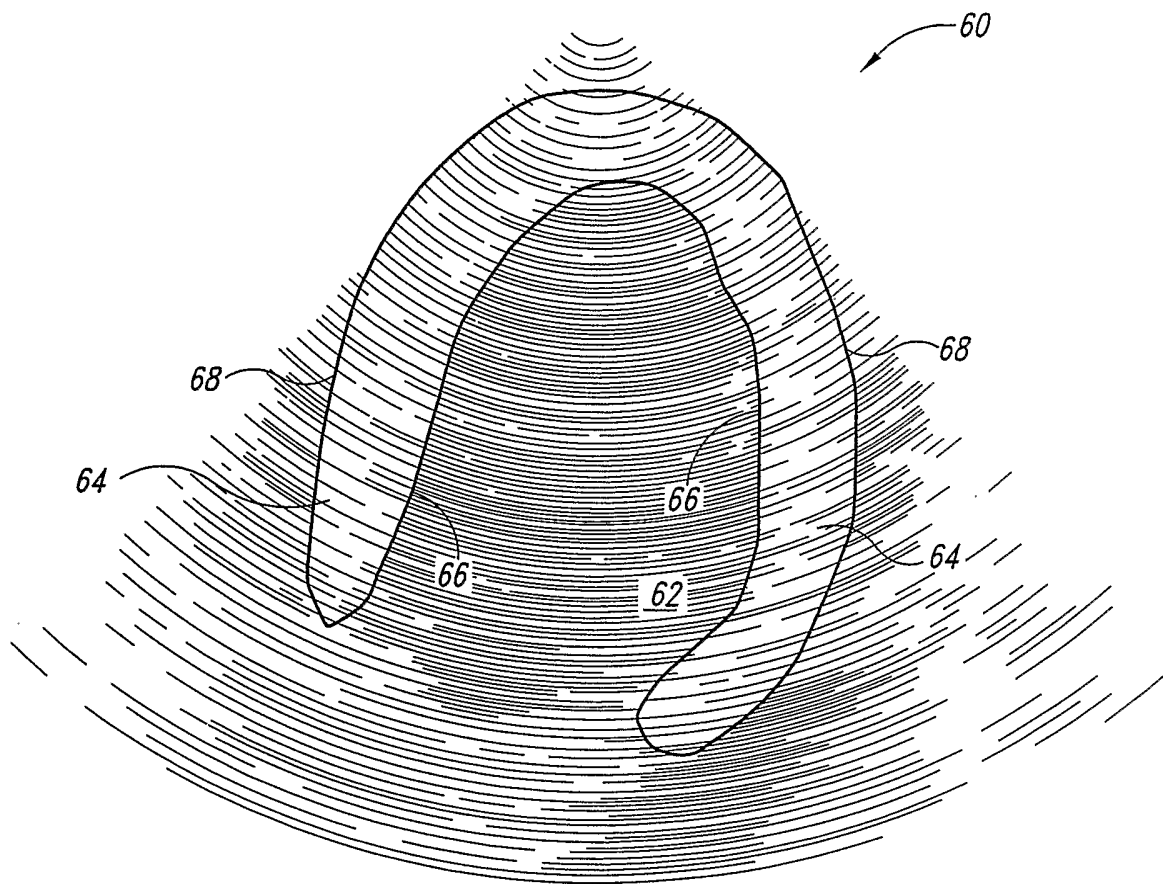


Fig. 1



2/11

*Fig. 2*

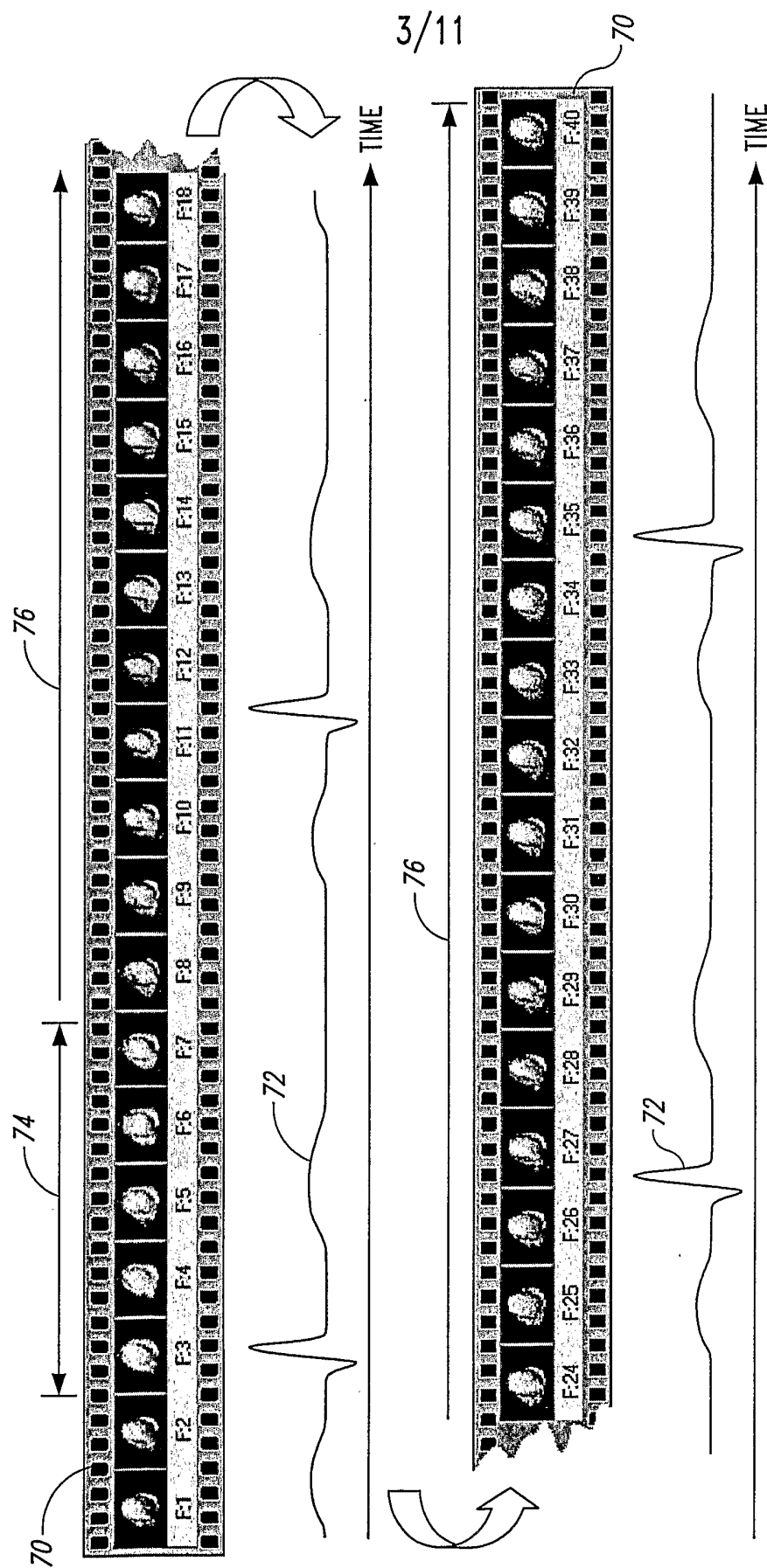


Fig. 3

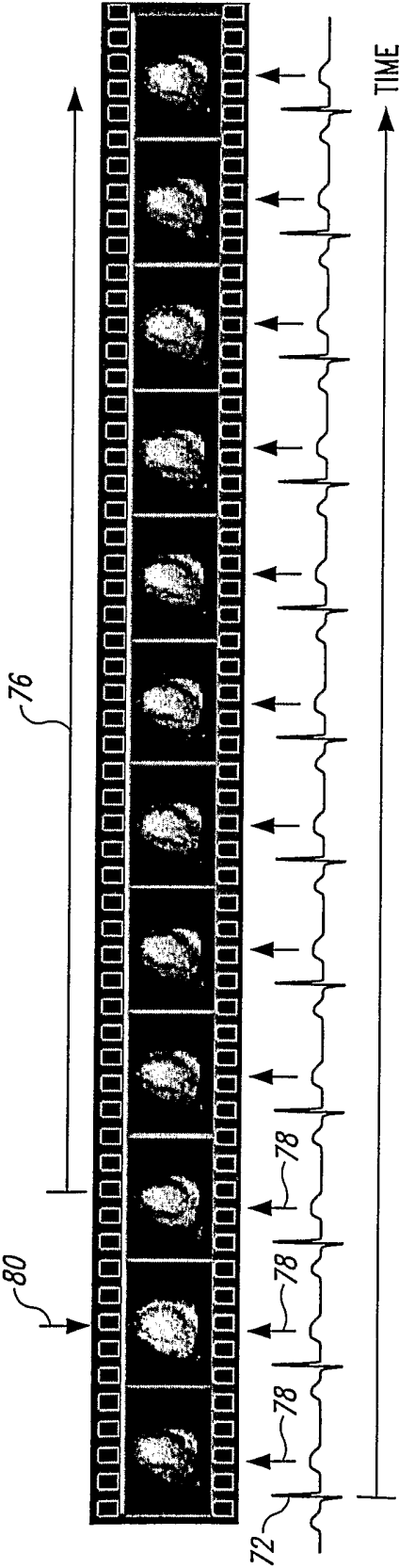


Fig. 4

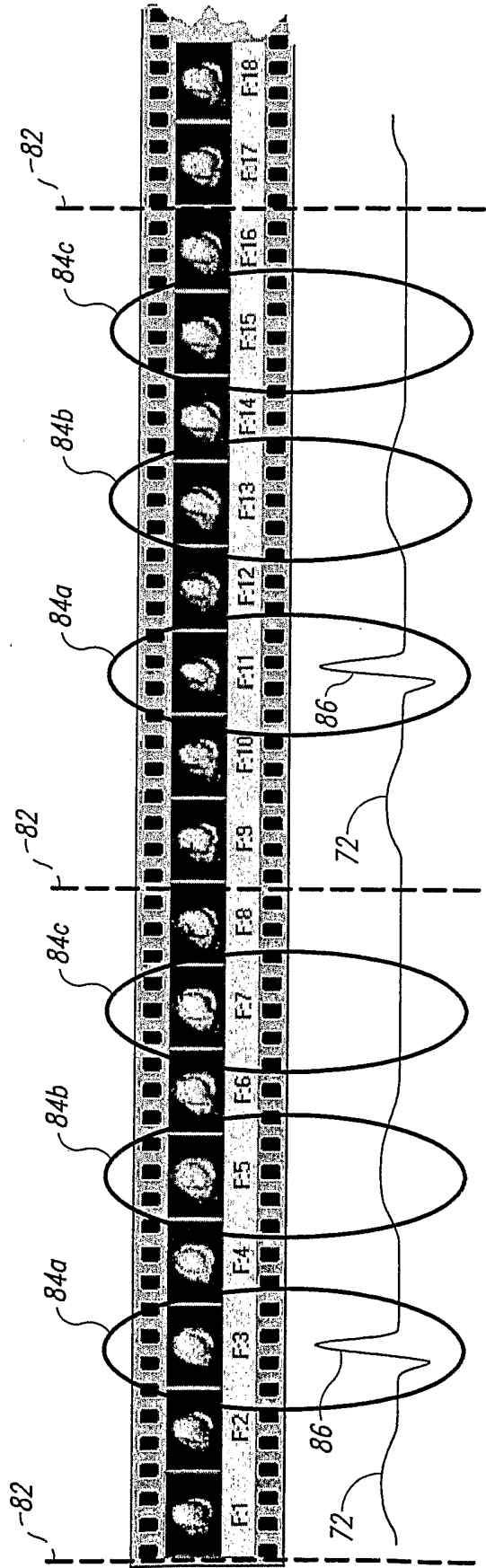


Fig. 5

Fig. 6A

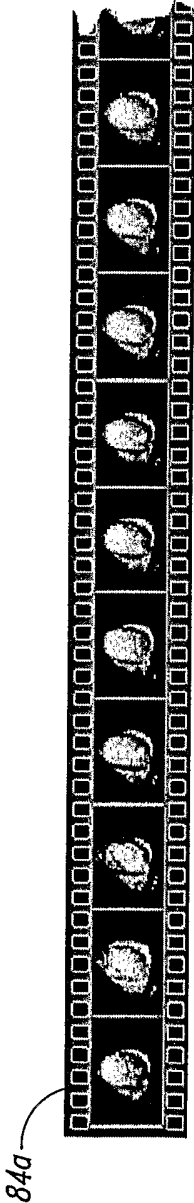


Fig. 6B

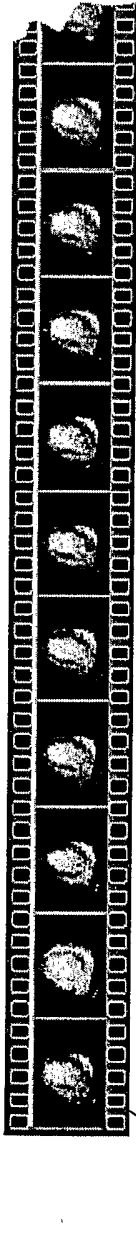
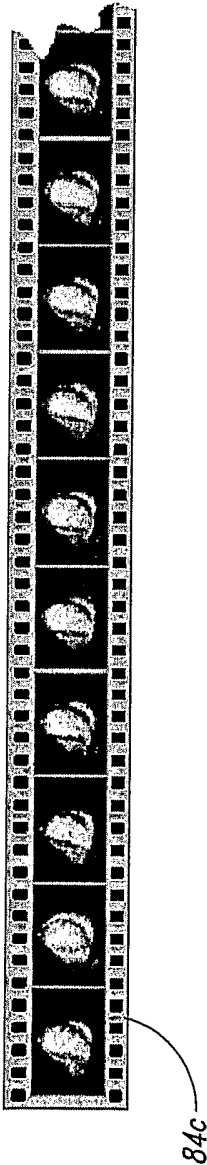


Fig. 6C



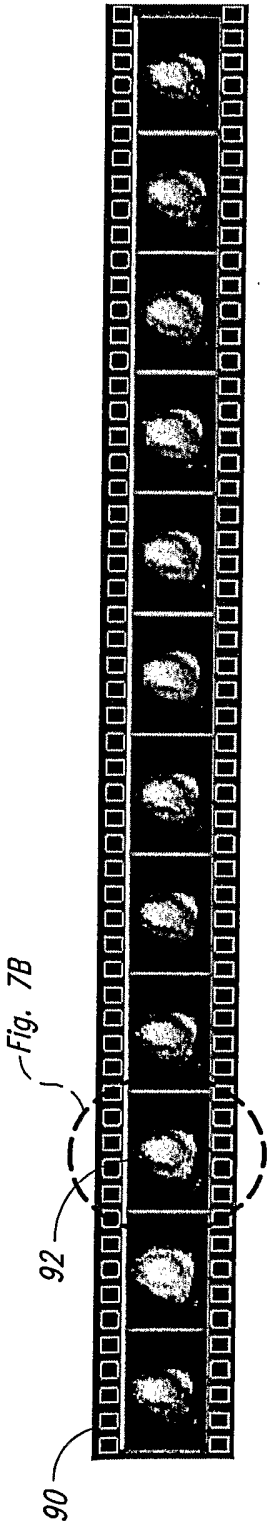


Fig. 7A

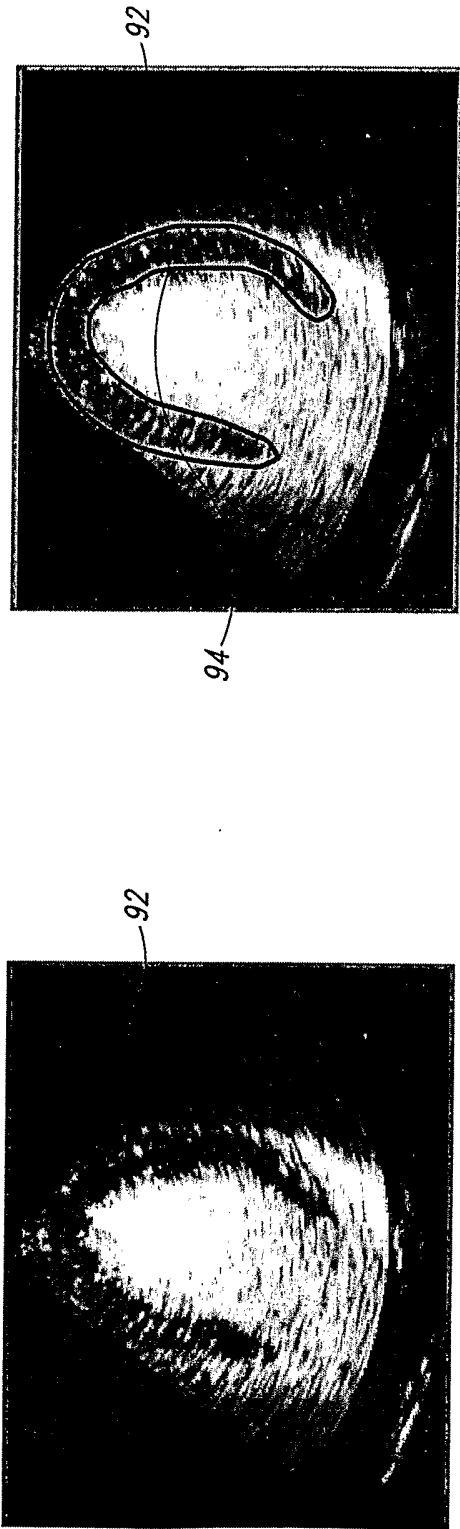


Fig. 7C

Fig. 7B

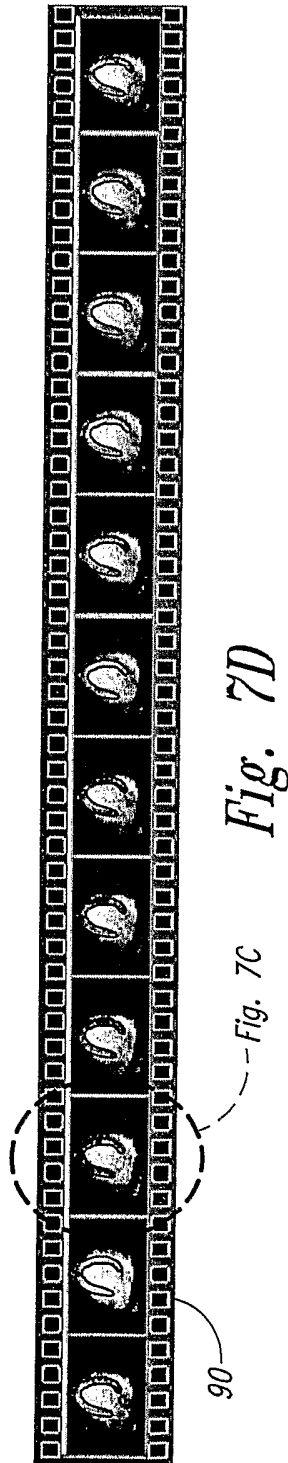
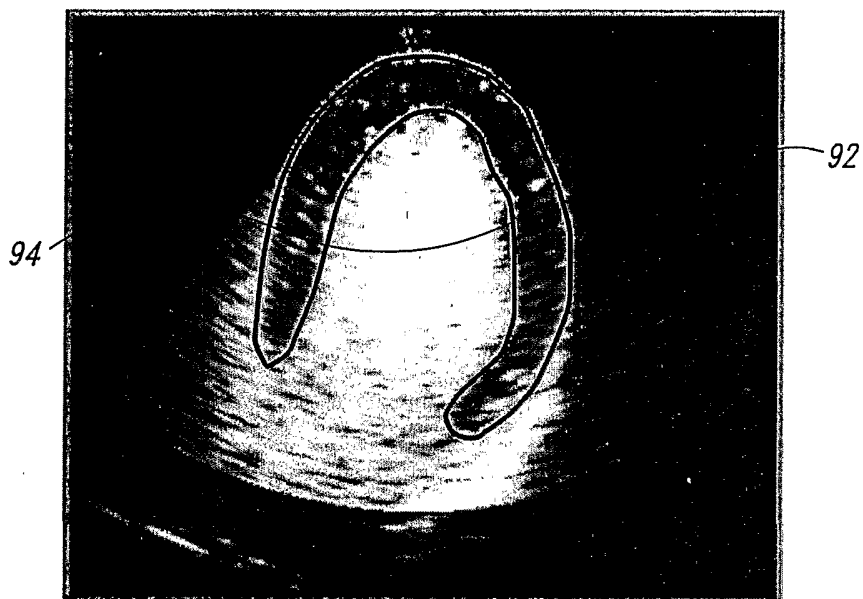
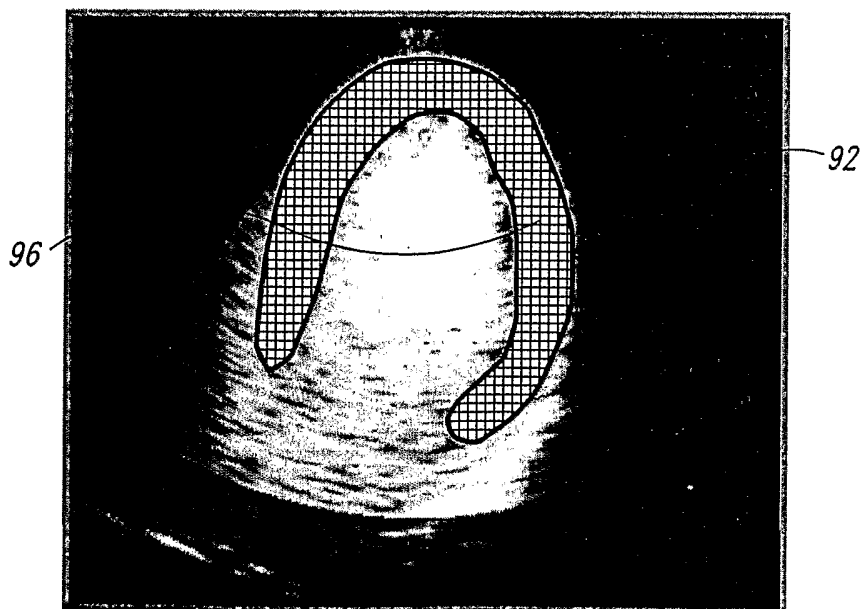


Fig. 7C

7/11

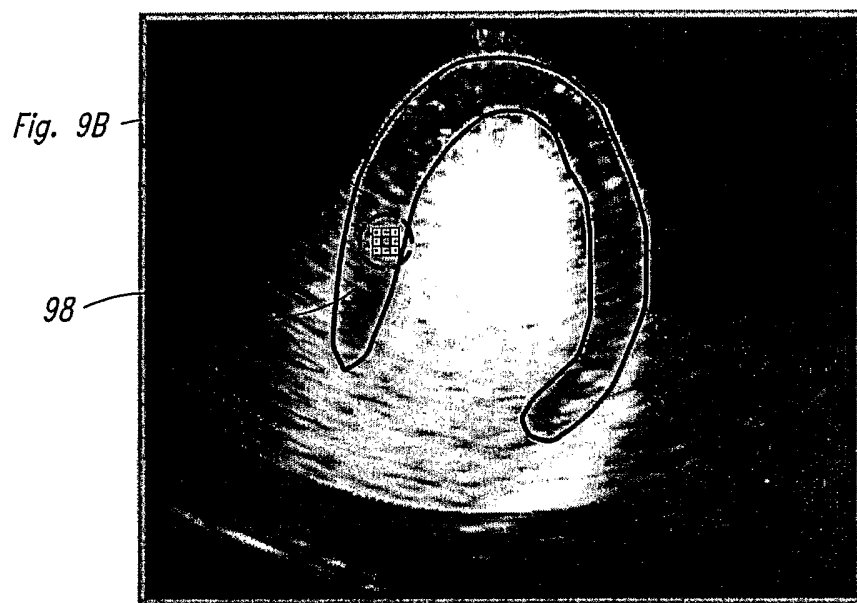


*Fig. 8A*

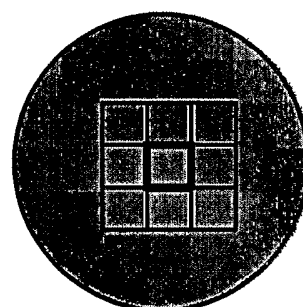


*Fig. 8B*

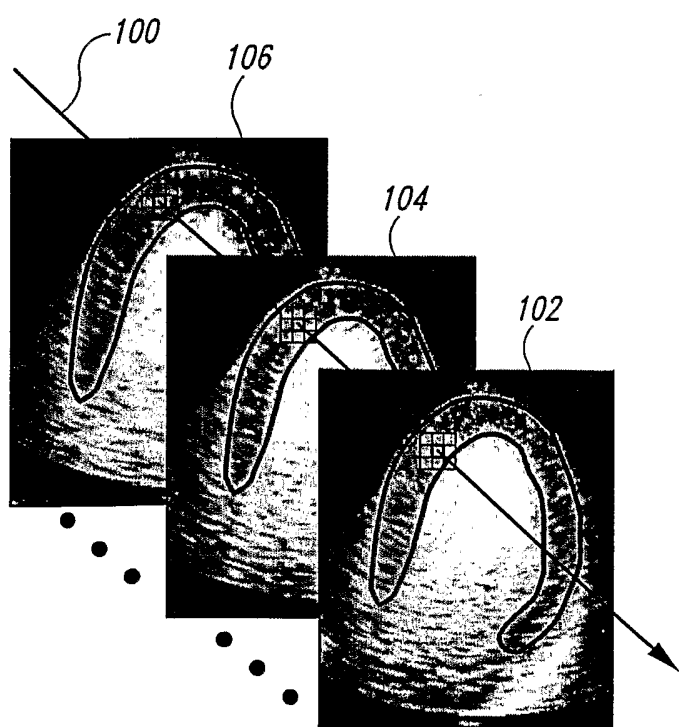
8/11



*Fig. 9A*

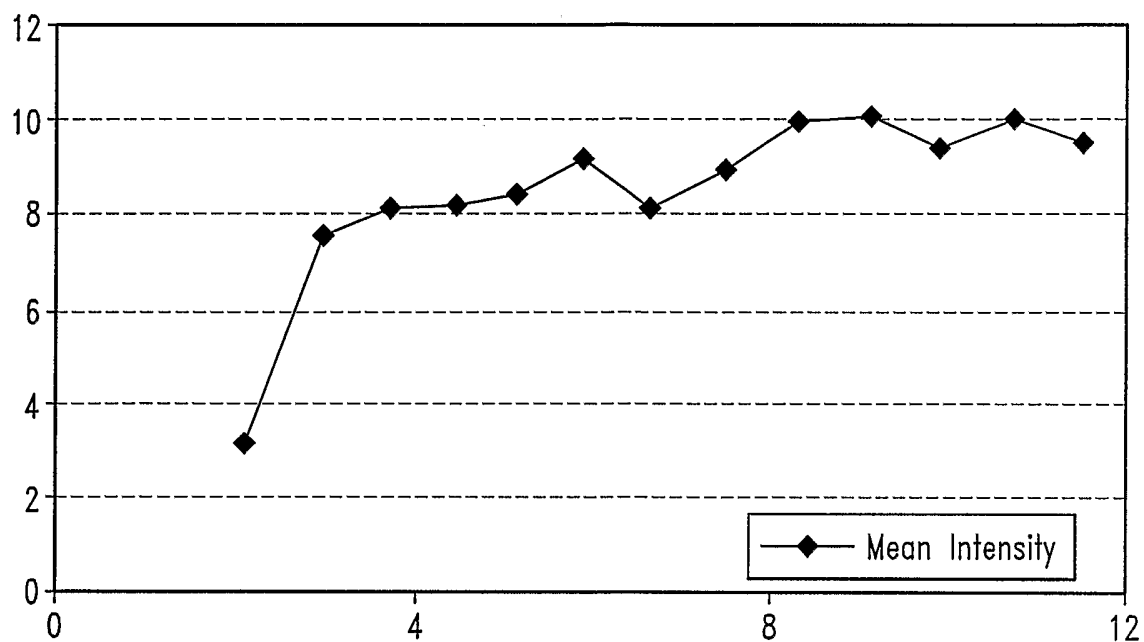
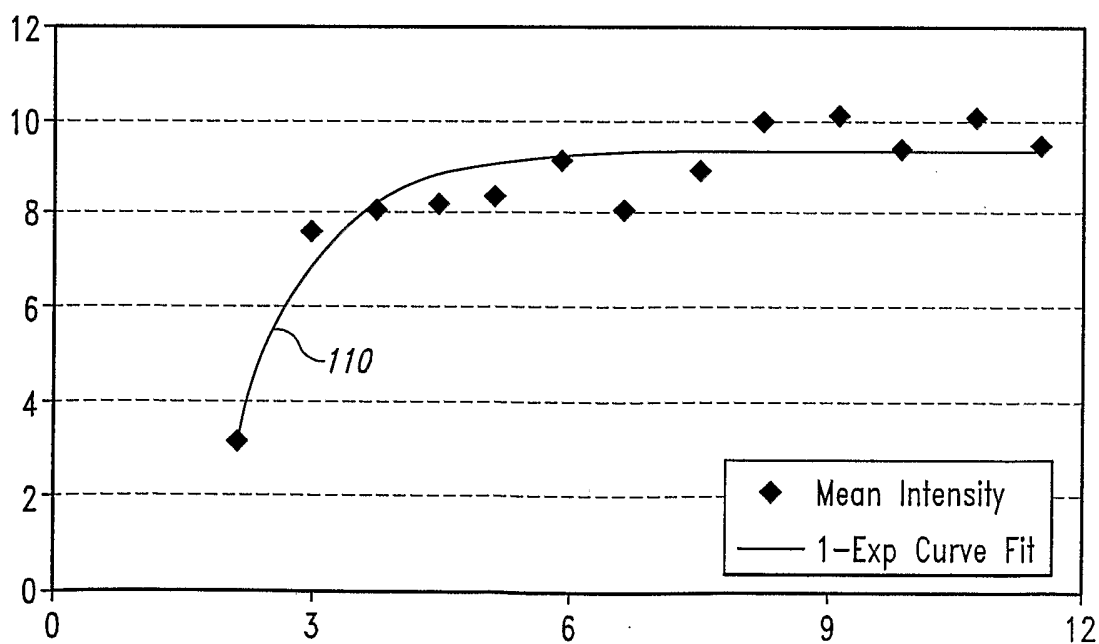


*Fig. 9B*



*Fig. 10*

9/11

*Fig. 11**Fig. 12*



10/11

PIXEL X COORDINATE	PIXEL Y COORDINATE	PARAMETER VALUE A*B	COLOR VALUE
100	100	19.7	200
100	101	21.0	210
100	102	19.7	200
...	...	...	...
175	157	1.3	10
175	158	1.7	17
...	...	...	...
203	50	2.3	19
203	51	2.7	21
...	...	...	...

Fig. 13A

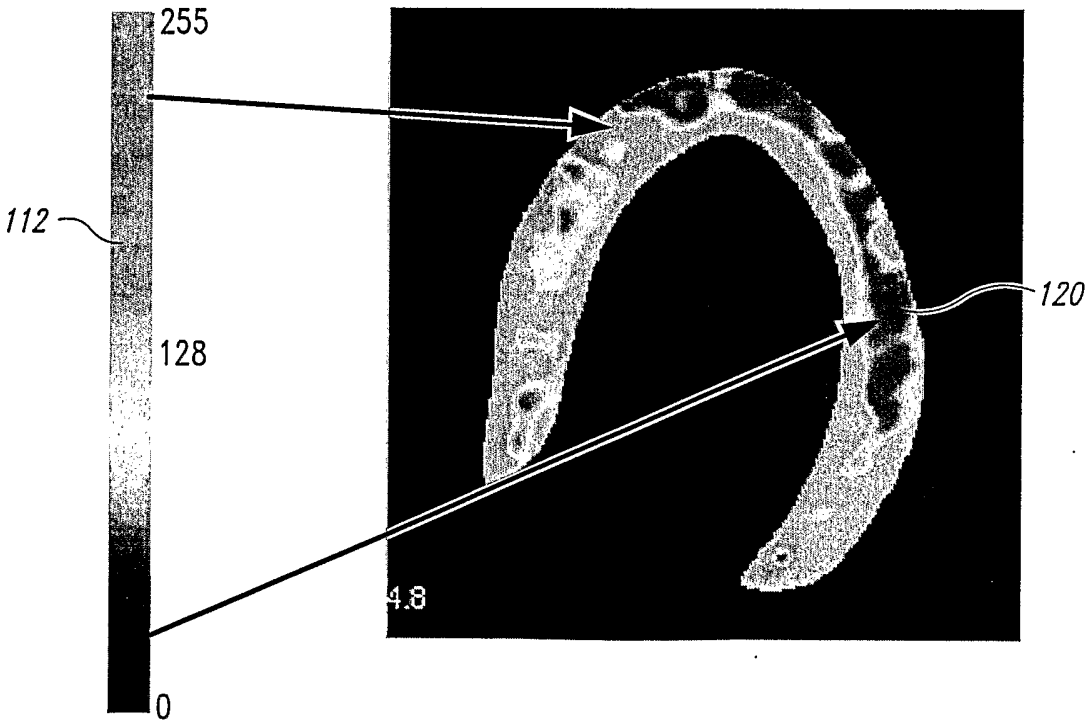


Fig. 13B

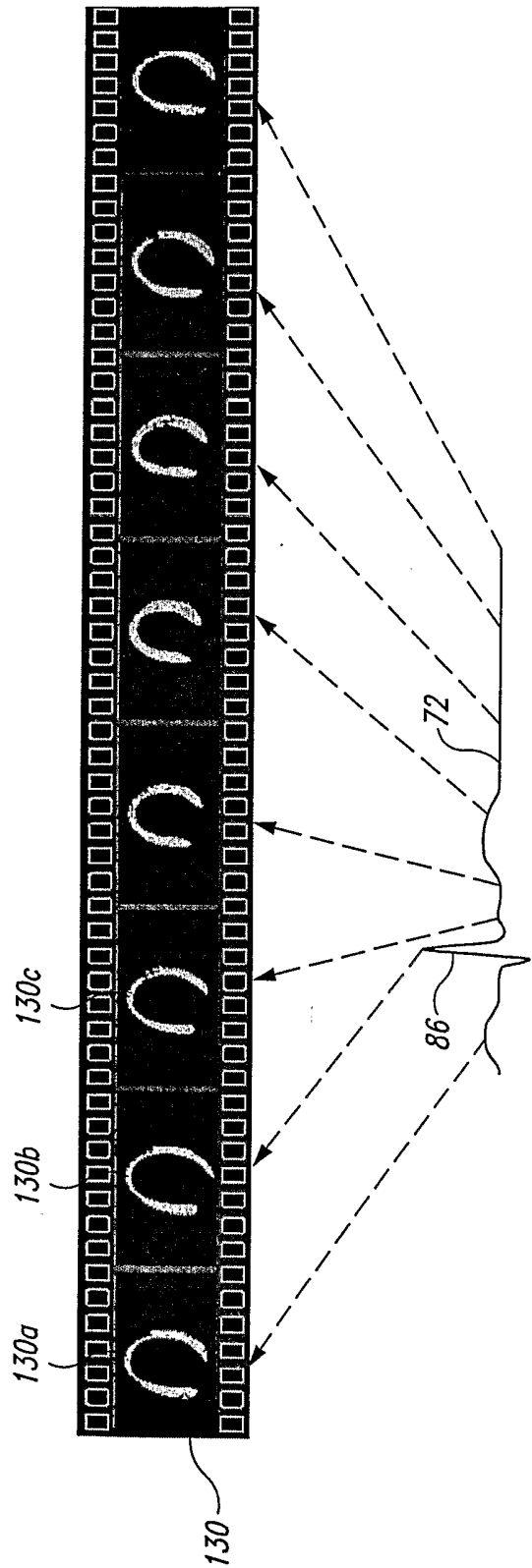


Fig. 14

# INTERNATIONAL SEARCH REPORT

PCT/IB 02/05069

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 G01S7/52 A61B8/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01S A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	H. BECHER, P. BURNS: "Handbook of Contrast Echocardiography, Chapter IV" June 2000 (2000-06), SPRINGER, FRANKFURT AND NEW YORK XP002231613 page 158, left-hand column, paragraph 1 page 164 -page 170 figures 9-13	7-15
X	H. BECHER, P. BURNS: "Handbook of Contrast Echocardiography, Chapter III" June 2000 (2000-06), SPRINGER, FRANKFURT AND NEW YORK XP002231614 page 95-97 page 108 page 111	7-15

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

20 February 2003

Date of mailing of the international search report

11/03/2003

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Reuss, T

# INTERNATIONAL SEARCH REPORT

PCT/IB 02/05069

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	H. BECHER, P. BURNS: "Handbook of Contrast Echocardiography, Chapter II" June 2000 (2000-06), SPRINGER, FRANKFURT AND NEW YORK XP002231619 page 50, right-hand column, paragraph 1 page 52, right-hand column page 54, left-hand column, paragraph 1 page 72-78 ----	7-15
X	H. BECHER, P. BURNS: "Handbook of Contrast Echocardiography, Chapter I" June 2000 (2000-06), SPRINGER, FRANKFURT AND NEW YORK XP002231620 page 23; figure 23 ----	7-15
X	J. SKLENAR ET.AL.: "Parametric Imaging for Myocardial Contrast Echocardiography..." COMPUTERS IN CARDIOGRAPHY, vol. 25, 16 September 1998 (1998-09-16), pages 461-464, XP010314381 ----	7,9,12,13
Y	the whole document ----	8,10,11,14,15
P,X	US 6 398 736 B1 (SEWARD JAMES B) 4 June 2002 (2002-06-04) abstract; figures 1-3,5-8 column 1, line 32 -column 2, line 50 column 4, line 30 -column 5, line 35 column 7, line 8-17 column 9, line 7 -column 10, line 59 column 12, line 26-67 column 14, line 28-39 ----	7,15
Y	US 5 833 613 A (AVERKIOU MICHALAKIS ET AL) 10 November 1998 (1998-11-10) cited in the application ----	8,10,14,15
A	abstract; figures 4,9-13 column 2, line 17-29 column 3, line 13-42 column 4, line 8-10 column 4, line 60-66 column 5, line 50-54 column 7, line 9 -column 8, line 37 column 9, line 14-54 column 11, line 30 -column 12, line 17 ----	9,12
Y	US 6 106 465 A (WANG JOHN S ET AL) 22 August 2000 (2000-08-22) abstract; figure 1 column 1, line 6 -column 2, line 56 column 10, line 29-57 -----	11

# INTERNATIONAL SEARCH REPORT

patent family members

PCT/IB 02/05069

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
US 6398736	B1	04-06-2002	US	2002128554 A1	12-09-2002
US 5833613	A	10-11-1998	US	2002040189 A1	04-04-2002
			US	2002055681 A1	09-05-2002
			US	5908389 A	01-06-1999
			US	6315729 B1	13-11-2001
			US	5879303 A	09-03-1999
US 6106465	A	22-08-2000	NONE		

# INTERNATIONAL SEARCH REPORT

PCT/IB 02/05069

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-6  
because they relate to subject matter not required to be searched by this Authority, namely:  
The method described in claims 1-6 contains a surgical step (injection of an ultrasound contrast agent into the blood stream). Such subject matter need not to be searched by the ISA (Art. 17(2)(a)(i) and Rule 39.1(iv), PCT).
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.