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(54) **ULTRASONIC DIAGNOSTIC IMAGING WITH HARMONIC CONTRAST AGENTS**

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(*) Notice: This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/481,814**

(22) Filed: **Jan. 11, 2000**

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Issued: **Jan. 13, 1998**
Appl. No.: **08/728,318**
Filed: **Oct. 9, 1996**

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(51) **Int. Cl.**
A61B 8/14 (2006.01)

(52) **U.S. Cl.** **600/458**; 600/437; 424/9.51; 424/9.52; 424/9.5; 367/7

(58) **Field of Classification Search** 600/437–457; 424/9.5, 9.51, 9.52

See application file for complete search history.

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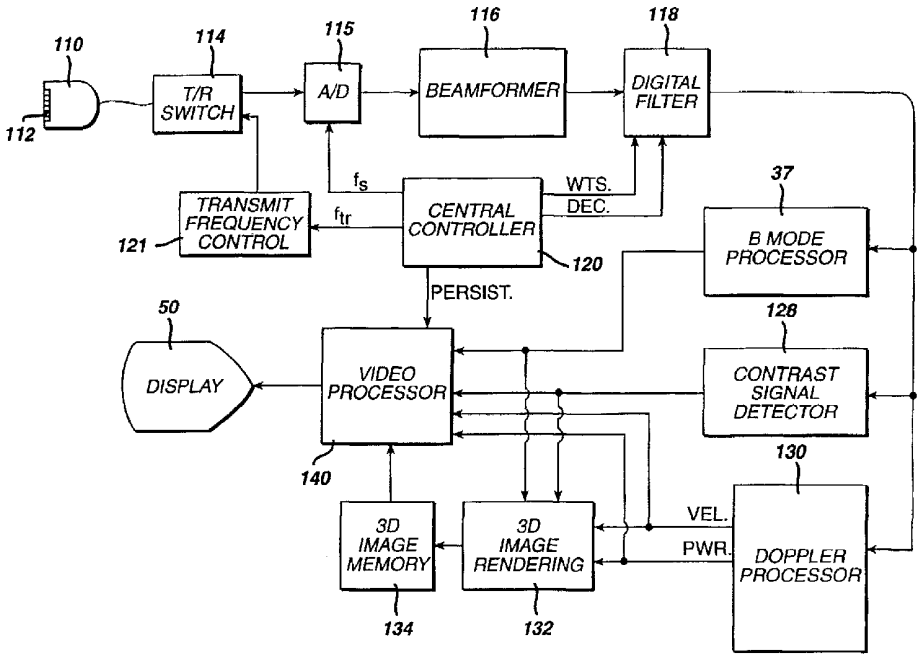
(57) **ABSTRACT**

Apparatus and methods are disclosed for the detection and imaging of ultrasonic harmonic contrast agents. The harmonic echo effect is detected through alternate polarity acquisition of harmonic contrast agent effects, which provides the benefits of suppressing the harmonic components of the transmitted signal while eliminating clutter.

25 Claims, 5 Drawing Sheets



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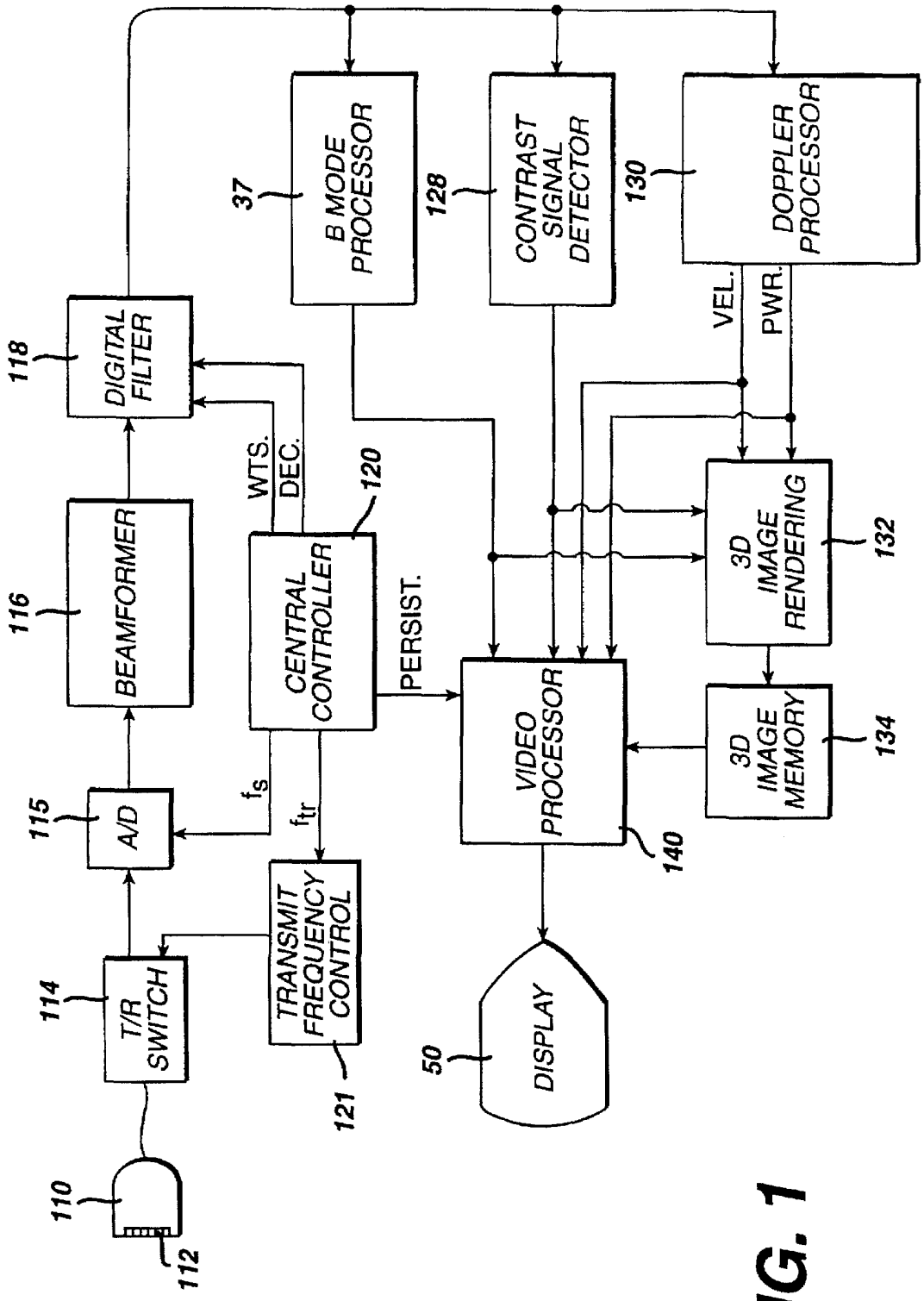
B MODE PROCESSOR
37
CONTRAST SIGNAL DETECTOR
128
DOPPLER PROCESSOR
130
VEL.
PWR.
DIGITAL FILTER
118
WTS.
DEC.
120
BEAMFORMER
116
CENTRAL CONTROLLER
PERSIST.
3D IMAGE RENDERING
132
VIDEO PROCESSOR
140
3D IMAGE MEMORY
134
A/D
115
f_s
f_{tr}
T/R SWITCH
114
TRANSMIT FREQUENCY CONTROL
121
DISPLAY
50
110
112

FIG. 1

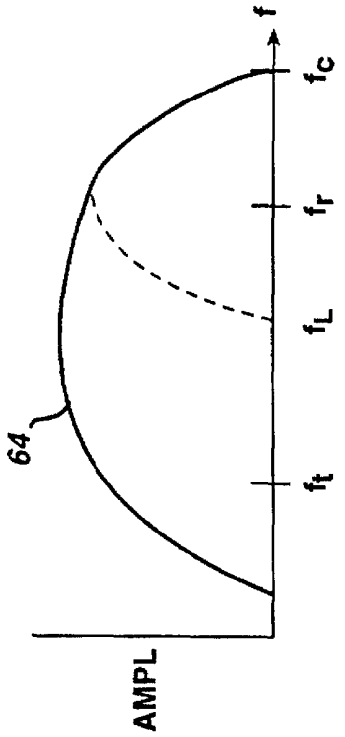

FIG. 2

FIG. 3

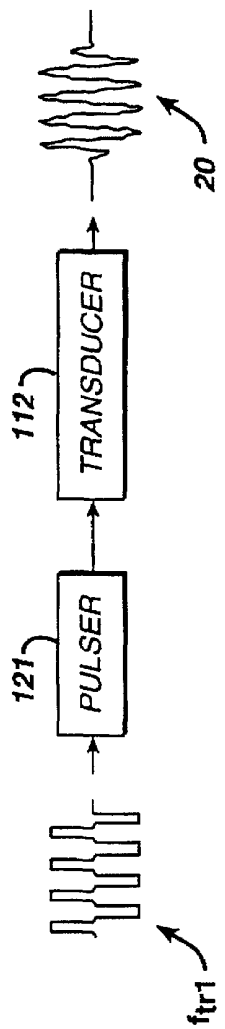

FIG. 4a

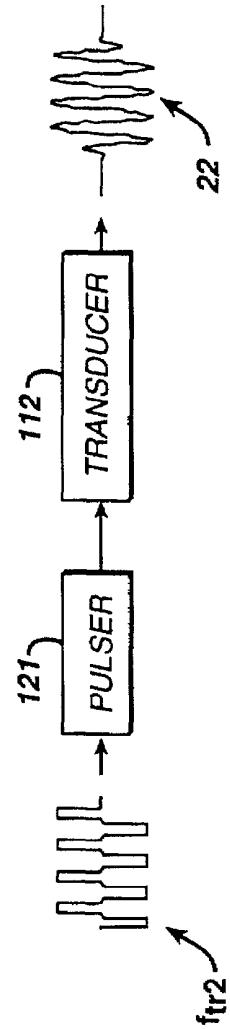

FIG. 4b

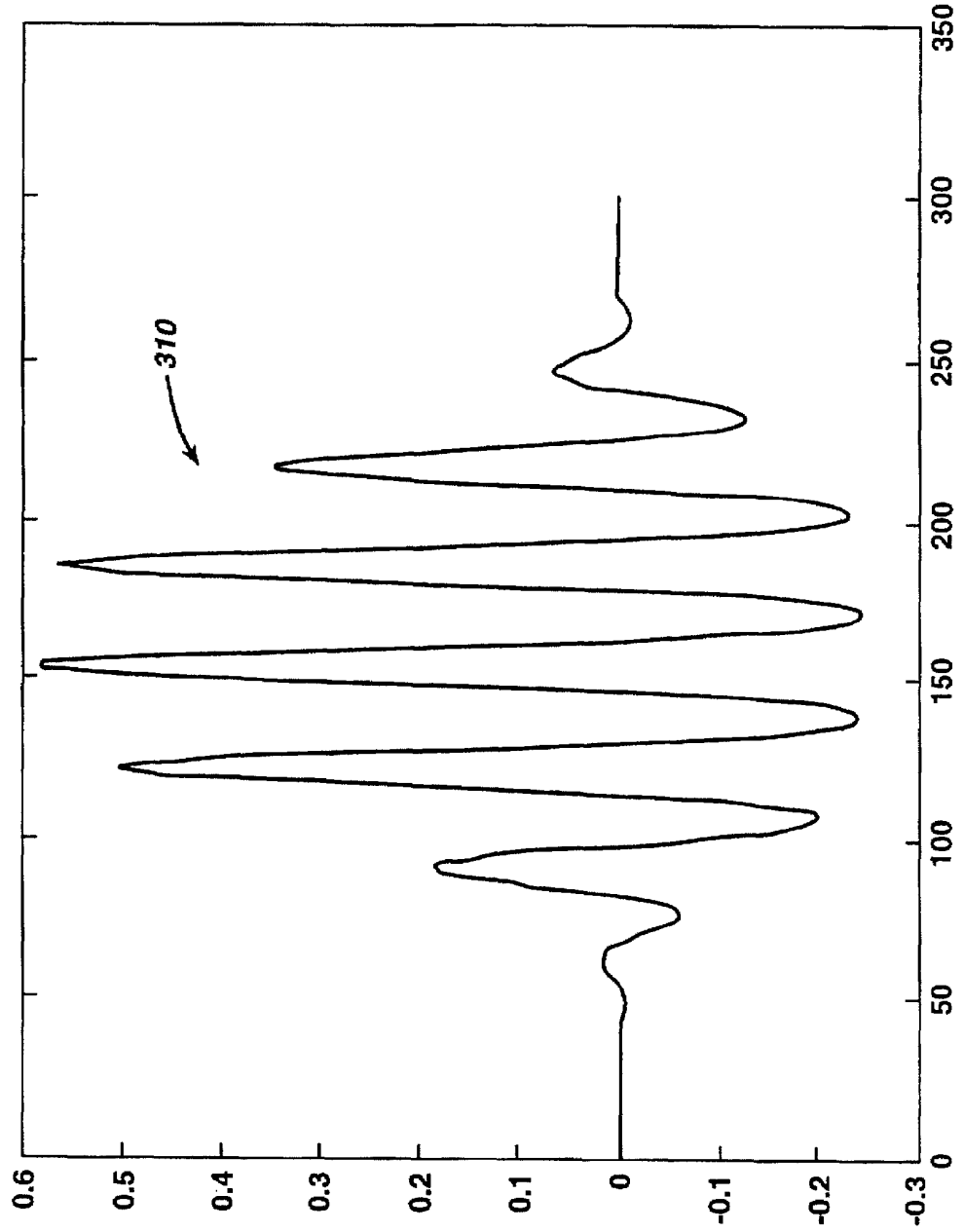

FIG. 5a

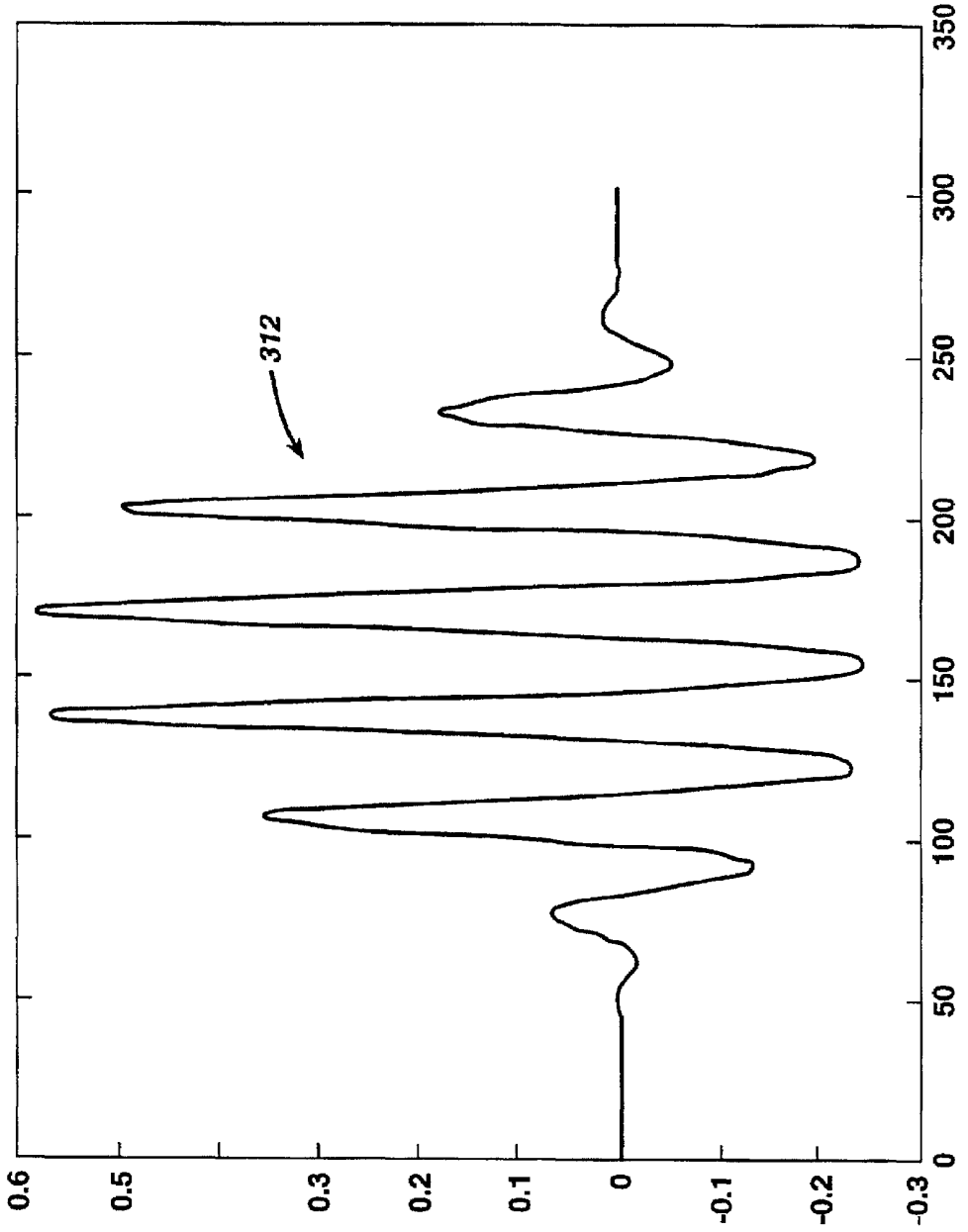

FIG. 5b

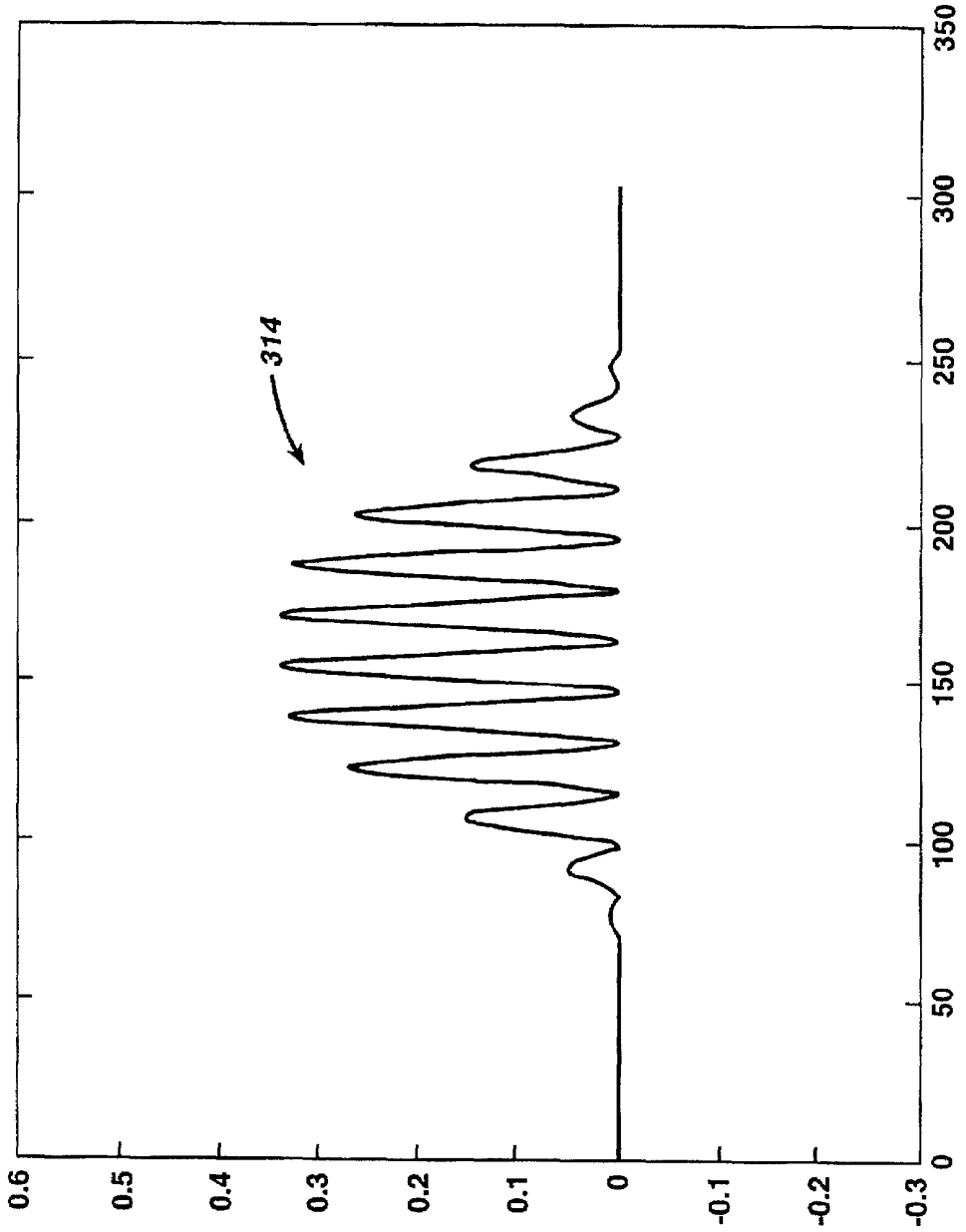

FIG. 5c

ULTRASONIC DIAGNOSTIC IMAGING WITH HARMONIC CONTRAST AGENTS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

This application claims the benefit of U.S. Provisional Application No. 60/005,009, filed Oct. 10, 1995.

This invention relates to ultrasonic diagnosis and imaging of the body with ultrasonic contrast agents and, in particular, to new methods and apparatus for ultrasonically detecting and imaging with contrast agents.

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 intervention into the body of the patient.

However materials known as ultrasonic contrast agents can be introduced into the body to enhance ultrasonic diagnosis. Contrast agents are substances which will strongly interact with 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 ultrasonic contrast agent is gases, in the form of tiny bubbles called microbubbles. Microbubbles present a significant acoustic impedance mismatch in comparison to tissue and fluids, and nonlinear behavior in certain acoustic fields which is readily detectable through special ultrasonic processing. In order to infuse bubbles into the body so that they will survive passage through the pulmonary system and circulate throughout the vascular system, gases have been stabilized in solutions in the form of tiny microbubbles. Microbubble contrast agents are useful for imaging the body's vascular system, for instance, as the contrast agent can be injected into the bloodstream and will pass through the veins and arteries of the body with the blood supply until filtered from the blood stream in the lungs, kidneys and liver.

One property of microbubble contrast agents currently under investigation is harmonic response. These harmonic contrast agents exhibit significant, detectable responses at frequencies which are harmonics of the transmitted ultrasonic frequency. This property is useful for clutter rejection of the received signals. When the transmitted frequency band is used as the received frequency band, echoes will be returned from the microbubbles, but also from surrounding tissue, the latter comprising clutter in the received echo signals. But with harmonic contrast agents, reception occurs at harmonic frequencies, where fundamental band clutter from tissue is ignored. Since tissue generally reflects very minimal harmonic components, the received harmonic band enables the microbubble echoes to be received with a high signal to noise ratio.

In accordance with the principles of present invention, a technique is provided for the detection and imaging of harmonic ultrasonic contrast agents. The harmonic contrast agent is insonified by alternate polarity transmitted pulses, and the echo signals received from the transmitted pulses are combined. The result is a suppression of harmonic components of the transmitted ultrasonic waves and the elimination of clutter.

In the drawings:

FIG. **1** illustrates in block diagram form apparatus constructed in accordance with the present invention which provides performance advantages for harmonic contrast agent detection;

FIGS. **2** and **3** illustrate passband characteristics used to explain the performance of the embodiment of FIG. **1**;

FIGS. **4**a and **4**b illustrates the alternate polarity pulsing of harmonic contrast agents; and

FIGS. **5**a–**5**c illustrate nonlinear response waveforms produced by alternate polarity acquisition of contrast agent echoes.

Referring to FIG. **1**, an ultrasonic diagnostic system for use with harmonic contrast agents in accordance with the present invention is shown in block diagram form. In this system an array transducer **112** of a probe **110** transmits ultrasonic energy and receives echoes returned in response to this transmission. The response characteristic of the transducer can exhibit two passbands, one around the central transmit frequency and another about the center of the received passband. For imaging harmonic contrast agents, a broadband transducer having a passband encompassing both the transmit and receive passbands is preferred. The transducer may be manufactured and tuned to exhibit a response characteristic as shown in FIG. **2**, in which the lower hump **60** of the response characteristic is centered about the center transmit frequency f_t, and the upper hump **62** is centered about the center frequency f_r of the response passband. The transducer response characteristic of FIG. **3** is preferred, however, as the single dominant characteristic **64** allows the probe to be suitable for both harmonic contrast imaging and imaging without harmonic contrast agents. The characteristic **64** encompasses the central transmit frequency f_t, and also the harmonic receive passband bounded between frequencies f_L and f_c, and centered about frequency f_r. A typical harmonic contrast agent can have a response such that transmission about a central transmit frequency of 1.7 MHz will result in harmonic returning echo signals about a frequency of 3.4 MHz. A bandwidth characteristic **64** of approximately 2 MHz would be suitable for these harmonic frequencies.

In FIG. **1** a central controller **120** provides a control signal f_{tr} to a transmit frequency control circuit or pulser **121** to control the center frequency and time of transmission of the transmitted ultrasonic energy. The transmit frequency control circuit pulses the elements of the transducer array **112** by means of a transmit/receive switch **114**.

Echoes received by the transducer array **112** are coupled through the T/R switch **114** and digitized by analog to digital converters **115**. The sampling frequency f_s of the A/D converters **115** is controlled by the central controller. The desired sampling rate dictated by sampling theory is at least twice the highest frequency f_c of the received passband and, for the preceding exemplary frequencies, might be on the order of at least 8 MHz. Sampling rates higher than the minimum requirement are also desirable.

The echo signal samples from the individual transducer elements are delayed and summed by a beamformer **116** to form coherent echo signals. The digital coherent echo signals are then filtered by a digital filter **118**. In this embodiment, the transmit frequency f_{tr} is not tied to the receiver, and hence the receiver is free to receive a band of frequencies which is separate from the transmitted band. The digital filter **118** bandpass filters the signals in the passband bounded by frequencies f_L and f_c in FIG. **3**, and can also shift the frequency

band to a lower or baseband frequency range. The digital filter could be a filter with a 1 MHz passband and a center frequency of 3.4 MHz in the above example. A preferred digital filter is a parallel arrangement of serially coupled multipliers and accumulators. This arrangement is controlled by the central controller **120**, which provides multiplier weights and decimation control which control the characteristics of the digital filter. Preferably the arrangement is controlled to operate as a finite impulse response (FIR) filter, and performs both filtering and decimation.

Filtered echo signals from tissue, generally filtered by a passband centered about or demodulated from the transmit frequency, are coupled to a B mode processor **37** for conventional B mode processing. Filtered echo signals of the harmonic contrast agent passband are coupled to a contrast signal detector **128** which performs pulse to pulse summation or integration of temporally discrete echoes from a given spatial location, amplitude or envelope detects the combined signals. Simple two pulse summation of the form P_1+P_2 may be employed where P_1 represents the echoes received following one pulse and P_2 represents the echoes received following another pulse. The combination of echoes from consecutive pulses may, if desired, be performed before the digital filter **118** rather than after, the decision being a matter of choice of system design.

The filtered echo signals from the digital filter **118** are also coupled to a Doppler processor **130** for conventional Doppler processing to produce velocity and power Doppler signals. The outputs of these processors are coupled to a 3D image rendering processor **132** for the rendering of three dimensional images, which are stored in a 3D image memory **134**. Three dimensional rendering may be performed as described in U.S. patent application Ser. No. 08/638,710, and in U.S. Pat. Nos. 5,474,073 and 5,485,842, the latter two patents illustrating three dimensional power Doppler ultrasonic imaging techniques. The signals from the contrast signal detector **128**, the processors **37** and **130**, and the three dimensional image signals are coupled to a video processor **140** where they may be selected for display on an image display **50** as dictated by user selection. The video processor preferably includes persistence processing, whereby momentary intensity peaks of detected contrast agents can be sustained in the image. One technique for providing persistence is through frame averaging, whereby new image frames are combined with previous frame information on a spatial basis. The combination can be done by weighting the contributions of the old and new frame information and the frame information can be combined in a recursive manner; that is, old frame information is fed back for combining with new frame information. A preferred persistence technique is the fast attack, slow decay technique described in U.S. Pat. No. 5,215,094, which can be applied to both Doppler and contrast agent images.

The apparatus of FIG. **1** performs alternate polarity pulse transmission as illustrated in FIGS. **4**a and **4**b. In the first transmission of FIG. **4**a, the central controller **120** provides a first polarity control signal f_{tr1} to the pulser **121**, which drives the transducer elements **112** to transmit a first polarity pulse **20**. For the second transmission of FIG. **4**b, the central controller **120** provides a second polarity control signal f_{tr2} to the pulser **121**, which drives the transducer elements **112** to transmit a second polarity pulse **22**.

The echoes received from microbubbles in response to these alternate polarity transmissions are shown in FIGS. **5**a and **5**b. FIG. **5**a illustrates an echo waveform **310** received from the first pulsing of a microbubble contrast agent. The nonuniform amplitudes on either side of the zero reference level illustrate nonlinear reflexive action of microbubbles in the presence of acoustic waves, as the microbubbles nonlinearly compress and expand. The echo waveform of **310** FIG. **5**a results from transmission of an ultrasonic pulse exhibiting a first polarity.

Following transmission of the ultrasonic pulse exhibiting the opposite polarity, the echo waveform **312** of FIG. **5**b results. This waveform is similarly nonlinear, but out of phase with the first waveform due to the change in pulse polarity. When the two waveforms are combined, a harmonic response is obtained, as shown in FIG. **5**c. The highly nonlinear waveform of FIG. **5**c is readily detected, causing the system to become highly sensitive to the contrast agent which produced the nonlinear echo responses.

A mathematical analysis of this effect and response is as follows. To detect the harmonic response of microbubbles, the harmonic component in the incident pressure wave must be suppressed. Based on the analytical solution of the dynamic motion of microbubbles, the primary component of the backscattering pressure magnitude is linearly proportional to the incident pressure and the harmonic component is quadratically proportional to the incident pressure p_i or $p_s(\omega) \alpha p_i$ and $p_s(2\omega) \alpha p_i^2$. Thus, neglecting the higher order terms, one may write the backscattering pressure magnitude $p_B(\omega)$ from a microbubble in a generic form

$$P_B(\omega)=k_1(\omega)p+k_2(\omega)p^2 \quad (1)$$

where k_1 and k_2 are parametrically related to the acoustic properties of the microbubble such as size, viscosity, surface tension, ambient pressure, etc.

Now assume that the microbubble is excited by two narrow band signals at different times but with the same magnitude p and at the same frequency ω, but with opposite polarity: $p_{i1}=p \cos \omega t$ and $p_{i2}=-p \cos \omega t$. Then the back-scattered pressure wave from $p_{i1}=p \cos \omega t$ is

$$p_{B1}(\omega,t)=k_1(\omega,t)p+k_2(\omega,t)p^2 \quad (2)$$

and from $p_{i1}=-p \cos \omega t$ is

$$p_{B2}(\omega,t+\delta t)=k_1(\omega,t+\delta t)p+k_2(\omega,t+\delta t)p^2 \quad (3)$$

Then the total backscattered pressure magnitude may be obtained by summing Equations (2) and (3),

$$S=p_{B1}+p_{B2}=(k_1(\omega,t)-k_1(\omega,t+\delta t))p+(k_2(\omega,t)+k_2(\omega,t+\delta t))p^2 \quad (4)$$

$$\approx 2k_2(\omega)p^2$$

Equation (4) shows that the primary component is eliminated if $k_1(\omega)$ and $k_2(\omega)$ do not change substantially in the time duration δt, where δt is small.

Assume the backscattering from microbubbles is quasi-stationary over T, where T is the pulse repetition interval. Therefore, the average nonlinear acoustic properties are not changed over time T, or

$$E\{k_1(\omega,t)\} \cong E\{k_1(\omega,t+T)\}$$

and

$$E\{k_2(\omega t)\} \cong E\{k_2(\omega,t+T)\}.$$

The relationship of Equation (4) will hold by summing the pulse echoes from two pulses which are time-diverse in T. The quasi-stationary assumption is valid for slow perfused flow, such as myocardial perfusion.

When the bandwidth of the incident pressure wave is wide, the wideband excitation wave P(t) may be represented by a Fourier series

$$P(t) = \sum_i A(\omega_i)\cos\omega_i t$$

Thus the backscattered pressure magnitude of the microbubbles from P(t) may be written as

$$P_{B1} = \sum_i k_1(\omega_i)A(\omega_i) + \sum_i k_2(\omega_i)A^2(\omega_i) \quad (5)$$

and the backscattered pressure magnitude of the microbubbles from −P(t) may be written as

$$P_{B2} = -\sum_i k_1(\omega_i)A(\omega_i) + \sum_i k_2(\omega_i)A^2(\omega_i) \quad (6)$$

Summing Equations (5) and (6), one may obtain

$$S = p_{B1} + p_{B2} = 2\sum_i k_2(\omega_i)A^2(\omega_i) \quad (7)$$

Again, the harmonic component is extracted and the primary component is eliminated.

Let us assume the nonlinearity in tissue is negligible. Since the backscattered pressure in a linear medium is linearly proportional to the incident pressure wave, the polarity of the backscattered wave will be changed as the polarity of the incident pressure wave is changed. Assuming the tissue is relatively stationary during the period of two consecutive pulses, summing the pulse echoes from consecutive pulses with opposite polarity will cancel the echo response from tissue. Thus, tissue clutter will be suppressed.

The concept of summing the pulse echoes from two pulses of opposite polarity may be generalized into processing echoes from multiple pulses with alternate polarity to maximize the sensitivity and minimize the variance, assuming the tissue is stationary during the pulsing interval. Let the pulse sequence be

$$P=\{p\ -p\ p-\ p\ p-\ p\ *\ *-p\ p\}$$

and the pulse echoes be

$$E=\{E_1\ E_2\ E_3\ E_4\ E_5\ E_6 \cdots E_n\}$$

Accumulating the partial sum of consecutive pairs of echoes results in

$$S = \sum_{j=1}^{n-1} E_j + E_{j+1} = 2(n-1)\sum_i k_2(\omega_i)A^2(\omega_i)$$

What is claimed is:

1. A method of ultrasonically detecting the ultrasonic response of an ultrasonic contrast agent comprising the steps of:

transmitting a first ultrasonic pulse to said ultrasonic contrast agent to cause a first harmonic response;

transmitting a second ultrasonic pulse of a different polarity than said first ultrasonic pulse to said harmonic contrast agent to cause a second harmonic response;

detecting said first and second harmonic responses; and

combining said first and second harmonic responses.

2. The method of claim **1**, wherein said step of combining comprises summing said first and second harmonic responses.

3. The method of claim **1**, wherein said step of combining comprises integrating said first and second harmonic responses.

4. The method of claim **1**, wherein said transmitting step comprises transmitting pulses which exhibit a pulse energy which is within a range which causes microbubbles of said ultrasonic contrast agent to oscillate without substantial microbubble destruction.

5. A method of ultrasonically detecting the nonlinear response of a substance within the body comprising the steps of:

transmitting at least three ultrasonic pulses into the body which exhibit first and second characteristics that cause a reduction in the linear echo response when echoes received in response to such pulses are combined;

receiving echoes in response to said ultrasonic pulses; and

combining said echoes to produce a nonlinear response.

6. The method of claim 5, wherein said step of receiving echoes comprises receiving echoes from a given location in the body.

7. The method of claim 5, wherein said ultrasonic pulses are transmitted in a sequence in which said first and second characteristics are alternated from pulse to pulse.

8. The method of claim 5, wherein said step of combining comprises summing pairs of echoes.

9. The method of claim 5, wherein said ultrasonic pulses are transmitted in a sequence in which said first and second characteristics are alternated from pulse to pulse; and

wherein said step of combining comprises summing pairs of echoes from successive pulses.

10. The method of claim 5, wherein said first and second characteristics comprise first and second polarities.

11. The method of claim 10, wherein said transmitted ultrasonic pulses are of the form {p −p p . . . }.

12. The method of claim 5, wherein said step of combining produces a sum result S which is substantially equal to

$$S = \sum_{j=1}^{n-1} (E_j + E_{j+1}),$$

where E_j and E_{j+1} are pulse echoes.

13. The method of claim 12, wherein the number of ultrasonic pulses which is transmitted is three.

14. A method of ultrasonically detecting the nonlinear ultrasonic response of a medium inside the body comprising the steps of:

transmitting a first ultrasonic pulse to said medium to cause a first echo response;

transmitting a second ultrasonic pulse to said medium to cause a second echo response;

transmitting a third ultrasonic pulse to said medium to cause a third echo response which is substantially the same as said first echo response; and

combining said first, second and third echo responses to produce a nonlinear response.

15. The method of claim 14, wherein said transmitted ultrasonic pulses are of the form {p −p p}.

16. The method of claim 14, wherein said step of combining produces a sum result S which is substantially equal to

$$S = \sum_{j=1}^{n-1} (E_j + E_{j+1}),$$

where E_j and E_{j+1} are pulse echoes.

17. A method of ultrasonically detecting the nonlinear response of a substance within the body comprising the steps of:

transmitting at least three ultrasonic pulses into the body in a sequence which is of the form $\{p -p p -p \ldots -p p\}$;

receiving echoes in response to said ultrasonic pulses which comprise a sequence of the form $\{E_1 E_2 E_3 E_4 \ldots E_{n-1} E_n\}$; and

accumulating said echoes to produce a nonlinear response.

18. The method of claim 17, wherein said step of accumulating comprises accumulating pairs of consecutive echoes.

19. The method of claim 17, wherein said step of accumulating produces a sum result S which is substantially equal to

$$S = \sum_{j=1}^{n-1} (E_j + E_{j+1}),$$

where E_j and E_{j+1} are pulse echoes.

20. A method of ultrasonically detecting the nonlinear response of a substance within the body comprising the steps of:

transmitting a sequence of at least three ultrasonic pulses into the body which exhibit a transmit characteristic which alternates from pulse to pulse;

receiving echoes in response to said ultrasonic pulses; and

combining said echoes to produce a nonlinear response.

21. The method of claim 20, wherein said pulses are transmitted to a given location in the body; and

wherein said step of combining reduces the primary component of said echoes and produces a harmonic response.

22. The method of claim 20, wherein said step of transmitting produces a sequence of echoes relating to a given location in the body in which the phase of the primary component of echoes produced by one transmit characteristic is out of phase with the phase of the primary component of echoes produced by the alternate transmit characteristic.

23. The method of claim 22, wherein said step of combining reduces the primary component of the combined echoes and produces a harmonic response.

24. The method of claim 23, wherein said transmit characteristic is a polarity differential from pulse to pulse.

25. The method of claim 23, wherein said transmit characteristic is a phase differential from pulse to pulse.

* * * * *

专利名称(译)	谐波造影剂的超声诊断成像		
公开(公告)号	USR43048	公开(公告)日	2011-12-27
申请号	US09/481814	申请日	2000-01-11
申请(专利权)人(译)	先进技术实验室，INC.		
当前申请(专利权)人(译)	先进技术实验室，INC.		
[标]发明人	HWANG JUIN JET SIMPSON DAVID HOPE		
发明人	HWANG, JUIN-JET SIMPSON, DAVID HOPE		
IPC分类号	A61B8/14		
CPC分类号	A61B8/06 A61B8/463 A61B8/481 G01S15/8963 G01S7/52038 G01S7/52039 G01S7/52041 G01S15/8959 G01S7/52026 A61B8/08 A61B8/488		
优先权	60/005009 1995-10-10 US		
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摘要(译)

公开了用于超声谐波造影剂的检测和成像的装置和方法。通过谐波对比剂效应的交替极性获取来检测谐波回波效应，这提供了抑制传输信号的谐波分量同时消除杂波的益处。