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(71) Applicant: **NORWEGIAN UNIVERSITY OF
SCIENCE AND TECHNOLOGY (NTNU)** [NO/NO];
Sem Sælands vei 14, N-7491 Trondheim (NO).

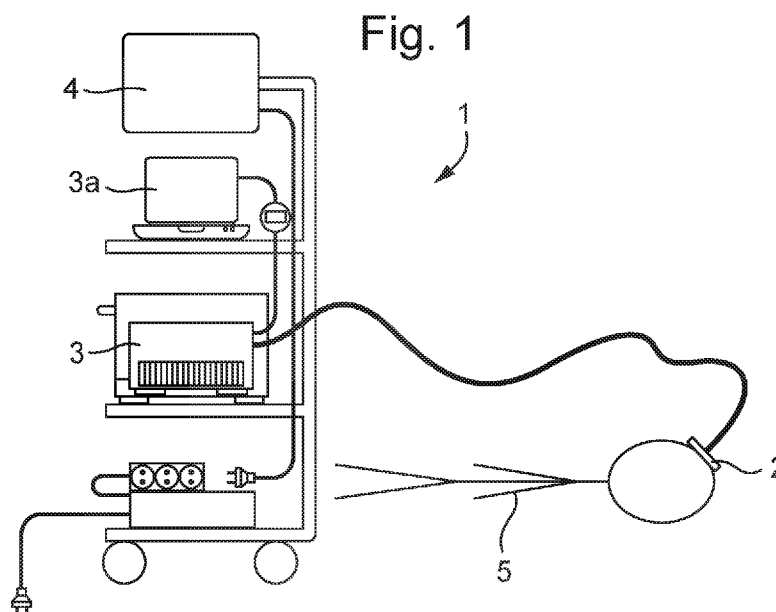
(71) Applicant (for MG only): **WILSON, Timothy James**
[GB/GB]; Delms, St Bride's House, 10 Salisbury Square,
London Greater London EC4Y 8JD (GB).

(72) Inventors: **TORP, Hans**; Arnebyvegen 13, 7024 Trond-
heim (NO). **SETERNESS, Arne**; Prestegårdsveien 10,
7051 Trondheim (NO). **MATTSON, Erney**; Fjordgata 28,
7010 Trondheim (NO). **HISDAL, Jonny**; Disengrenda 24b,
0587 Oslo (NO). **PETTERSEN, Erik Mulder**; Brinken 7,
4630 Kristiansand (NO).

(74) Agent: **DEHNS**; St Bride's House, 10 Salisbury Square,
London EC4Y 8JD (GB).

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(54) Title: ULTRASOUND BLOOD-FLOW MONITORING



(57) Abstract: The invention provides a method for monitoring peripheral microcirculation in a vertebrate animal subject undergoing or recovering from surgery, wherein said method uses unfocused ultrasound pulses to determine a characteristic of blood flow within in the minor peripheral vasculature of the subject and said characteristic or the profile of said characteristic over time is indicative or predictive of a change in the peripheral microcirculation of the subject. The invention further provides a method for monitoring or predicting the onset of and/or progression of dysfunction of the microvasculature and/or a response to treatment thereof in a vertebrate animal subject, wherein said method uses unfocused ultrasound pulses to determine a characteristic of blood flow within in the minor peripheral vasculature of the subject and said characteristic or the profile of said characteristic over time is indicative or predictive of dysfunction of the microvasculature or response to treatment thereof or variation in said characteristic or a profile of said characteristic over time is indicative or predictive of dysfunction of the microvasculature or is indicative or predictive of a change in the dysfunction of the microvasculature or response to treatment thereof.

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Ultrasound Blood-Flow Monitoring

BACKGROUND OF THE INVENTION

This invention relates to apparatus and methods for characterising or monitoring blood flow using ultrasound.

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Various techniques have been used to analyse blood flow in human or animal subjects. These include laser Doppler scanning, near-infrared spectroscopy, and Doppler ultrasound imaging. However, such analyses must typically be performed by a skilled technician, who must be present with the patient throughout. The equipment for carrying out such analyses can also be very expensive (e.g., over one million U.S. dollars for a 3D ultrasound imaging system). Such techniques are therefore not well suited to the unattended monitoring of patients in settings such as hospital wards or at home.

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The present invention seeks to provide a better approach.

SUMMARY OF THE INVENTION

From a first aspect, the invention provides a method for determining a characteristic of blood flow in a vertebrate animal subject, the method comprising:

transmitting ultrasound pulses into the subject from an ultrasound transducer that is fastened to the subject;

receiving reflections of the ultrasound pulses at the ultrasound transducer;

generating pulse-Doppler response signals from the reflections; and

processing the pulse-Doppler response signals to determine a characteristic of blood flow within the subject.

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From a second aspect, the invention provides a system for determining a characteristic of blood flow in a vertebrate animal subject, the system comprising:

an ultrasound transducer;

a fastener or an adhesive layer for fastening the ultrasound transducer to the subject; and

a controller,

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wherein the controller is configured to:

control the ultrasound transducer to transmit ultrasound pulses into the subject;

sample reflections of the ultrasound pulses received at the ultrasound transducer;

generate pulse-Doppler response signals from the reflections; and

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process the pulse-Doppler response signals to determine a characteristic of blood flow within the subject.

Thus it will be seen that, in accordance with these aspects, rather than a skilled operator
5 having to manually hold an ultrasound transducer against the subject, an ultrasound transducer is fastened to the subject. This can facilitate the monitoring of blood flow over an extended period of time, without requiring the expense of a human operator attending the subject continually during the data collection process. Preferably the ultrasound transducer will be fastened to the subject on an external surface of the subject and thus
10 will be non-invasive (i.e. fastening will preferably not involve a surgical procedure).

The ultrasound transducer may be fastened to the subject by chemical and/or mechanical means.

15 In one set of embodiments, the ultrasound transducer is bonded to the subject using an adhesive layer. This adhesive layer may be applied to a transducer element of the ultrasound transducer such that it lies between the transducer element and the subject. The ultrasound pulses may travel through the adhesive layer. In this case, the use of separate ultrasound gel may be unnecessary. Alternatively, the adhesive layer may bond
20 a housing of the ultrasound transducer to the subject. Ultrasound gel may then be applied separately to eliminate any air gap between a transducer element and the subject. The adhesive layer may be able to bond the ultrasound transducer to the subject with a force that is greater than the weight of the ultrasound transducer.

25 In some embodiments, the system comprises a fastener for fastening the ultrasound transducer to the subject, such as the skin of the subject. The ultrasound transducer is preferably designed for external use. The fastener is preferably non-invasive. The fastener may comprise one or more straps, which may be of fabric, plastic, or any other flexible material. One or more straps of the fastener may be sized for securing, alone or in
30 combination, around a limb, head, digit or other body part of the subject. The fastener may comprise an elasticated portion or a spring or other means for applying a compressive force to part of the subject's body. The fastener may have a surface for contacting the skin of the subject. The fastener may be configured to use friction, alone or in conjunction with other means such as an adhesive, to secure the ultrasound transducer resiliently in place
35 against the subject. The fastener may comprise a clip. The fastener may comprise a mount for receiving the ultrasound transducer. The fastener may be bonded or secured to the ultrasound transducer—e.g., such that a tool is required to separate the ultrasound

transducer from the fastener non-destructively. In other embodiments, the ultrasound transducer may be releasably secured to the fastener—e.g., retained only by friction.

The ultrasound transducer may be configured to transmit unfocused ultrasound pulses.

5 The ultrasound pulses may be plane-wave pulses. (The skilled person will appreciate that, in practice, the wavefront may not be exactly planar—e.g., due to imperfections in the transducer, or due to interference (e.g., refraction and diffraction) as the waves travel, or due to the finite extent of the wavefront, and the expression “plane-wave” should be understood accordingly.) The transducer preferably has no acoustical lens.

10

The controller may be configured to generate a pulse-Doppler response signal from one or more transmitted ultrasound pulses wherein the pulse-Doppler response signal aggregates reflections from across a region in the subject that has substantially the same width as the transmitted pulse received at the region. The system may have a receive
15 beam, or spatial sensitivity region, that is coincident with a transmit beam. The receive beam may have a width or diameter that is substantially equal to, or at least half, a width or diameter of the transmit beam, at a depth at which the characteristic of blood flow is determined. The transmit beam and receive beam may both be unfocused. The characteristic of blood flow may be determined for an aggregate blood flow through a
20 plurality of blood vessels. This contrasts with conventional array-based Doppler blood-flow imaging systems that use a focused receive beam (e.g., using delay-and-sum beamforming techniques) to analyse blood flow within a very small region, typically lying within the width of a single artery (e.g., having a beam width of under 0.5 mm at the focal point).

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The ultrasound transducer may comprise a plurality of transducer elements—e.g., arranged in a linear or rectangular array. Signals received at the plurality of transducer elements may be summed without any delay (in contrast with conventional delay-and-sum beamforming), and the pulse-Doppler response signals may be generated from the
30 summation of the signals received at each respective transducer elements.

However, in one set of embodiments the ultrasound transducer is a single-element transducer. The (single) transducer element may be a piezoelectric element. The same element in the ultrasound transducer may transmit and receive ultrasound. This enables
35 the cost of the transducer to be kept low. The transducer may emit ultrasound from a planar face. The planar face may have a width (e.g., a maximum, minimum or mean width) that is large compared with each transducer element in traditional array-based

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ultrasound transducers—for example, having a width of at least 2 mm, 5 mm, 10 mm, 20 mm or more. Compared with a wavelength of the ultrasound pulses transmitted from the transducer, the width of this transmitting surface may be 10 wavelengths, 50 wavelengths, or even 100 wavelengths or more. (Wavelengths, as referred to herein, may be

5 understood as relating to waves travelling in soft human tissue—e.g. waves travelling at 1540 m/s.) A ratio of width to wavelength of ten, twenty, fifty times or more can help to provide a more uniform beam, which is desirable for providing responses from different depth regions that are comparable in volume. The transducer may transmit ultrasound energy in a substantially uniform beam—i.e., having a constant or near-constant cross-

10 section in the propagation (depth) direction, at least up until a maximum depth at which reflections are processed to determine the characteristic of blood flow. The transducer (or a transmitting face thereof) may have any shape, but in one set of embodiments it is circular or rectangular. It may therefore transmit a circular or rectangular cylindrical beam into the organism—e.g., a circular beam having a diameter of approximately 5 mm or

15 approximately 10 mm.

The characteristic of blood flow may be determined from reflections received from a region within the subject.

20 By not focusing the transmit beam, and by using a transducer much larger than a transmitted wavelength (e.g., ten times or more), the intensity of the ultrasound pulses may be substantially uniform across this region. This would not typically be possible with a focused transmit beam, the intensity of which would vary across the region, and across individual blood vessels. Similarly, by not focusing the receive beam, the reflections may

25 be aggregated substantially uniformly from across the whole region. This would not typically be possible with a focused receive beam, which has only a small spatial sensitivity region.

A lateral extent of the region within the subject may be determined by the shape of the

30 transducer or a transmitting face thereof. An axial position or extent of the region (i.e., in the propagation direction, also referred to herein as the depth direction) may be determined by the duration of each pulse (e.g., being at least half the pulse duration) and by a time delay at which the reflections are sampled, after the transmission of each pulse. As explained in more detail below, reflections from a plurality of different (e.g., non-

35 overlapping) regions may be sampled and processed to generate separate respective Doppler signals; these reflections may be received from one or more common transmitted pulses – i.e., they may all cover substantially the same time period. Range-gating may be

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used to control the axial extent of the (or each) region. In some embodiments, the region has a depth of between 0.15 mm to 1 mm. The region may have a diameter or minimum width of approximately 5 mm, 10 mm or 20 mm.

- 5 The system is particularly well suited to determining a characteristic of blood flow close to the transducer. This is because a broad, unfocused beam means that the reflection from each blood cell is relatively weak. The region may therefore have a maximum distance from the transducer, in the propagation direction, that is less than a width (e.g., a maximum, minimum or mean width) of the transducer or transducer element, or that is no
10 more than two, three, five or ten times this width.

The ultrasound transducer may comprise a housing—e.g., of plastic or metal. The ultrasound transducer may be substantially cuboid or substantially a circular cylinder. It may be disc-shaped. It may have a minimum, maximum or average diameter or width that
15 is between 5 mm and 50 mm, or between 10 mm and 20 mm.

The housing may comprise an electromagnetic shielding layer, e.g., a metal layer, which may partially or wholly surround one or more electronic components or conductors in the transducer. The shielding may provide a Faraday cage for the transducer. The ultrasound
20 transducer may be connected to the controller by an electrical or fibre-optic cable. The cable may be electromagnetically shielded—e.g., being a tri-axial cable. The use of electromagnetic shielding for the transducer has been found to be particularly important in some embodiments because the signal-to-noise ratio from a broad, unfocused beam can be much lower than in traditional medical ultrasonography.

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The pulses may have a wavelength that is smaller than a diameter or width of the ultrasound transducer. In order to transmit plane waves with a uniform intensity, a wavelength of the pulses may be at least ten times smaller than a minimum, maximum or average diameter or width of the transducer or a transmitting face of the transducer. The
30 pulses may have a frequency, or include a frequency component, in the range 5 MHz to 20 MHz—for example, around 8 MHz or 16 MHz. A balance may need be struck between the greater penetration depth of a longer wavelength (e.g., approximately 40 mm at 8 MHz, compared with 20 mm at 16 MHz) and the greater resolution of a shorter wavelength. Similarly, a balance may need to be struck in the diameter of the transducer
35 whereby it supports transmit and receive beams that are broad enough to capture all the blood vessels across a region of interest while being sufficiently small to fasten conveniently to the subject.

The ultrasound transducer may be flat—i.e., shallower in height than its maximum diameter or width. In particular, the ultrasound transducer may comprise a housing for an ultrasound transducer element, wherein the housing comprises or defines a planar window for passing ultrasound signals from the transducer element to outside the housing. An average (mean) height or a maximum height of the housing, perpendicular to said window, integrated over the area of the window, may be less than a maximum diameter or width of the window. The housing may be rigid. The housing may be a single piece of metal or plastics material. The housing may wholly or partially surround the transducer element. The ultrasound transducer may have additional components, such as lead and a flexible strain relief for the lead, which may be distinct from the housing and which may extend beyond a height equal to the maximum diameter or width.

From a further aspect, the invention provides a medical ultrasound transducer comprising:
an ultrasound transducer element, for transmitting ultrasound signals; and
a housing for the transducer element,

wherein:

the housing comprises or defines a planar window for passing ultrasound signals from the transducer element; and
the housing has an average height, perpendicular to said window, over the area of the window, that is less than a maximum diameter or maximum width of the window.

Features of any other aspect may be features of this aspect also. In particular, the ultrasound transducer may have only a single transducer element. The ultrasound transducer may comprise a fastener or an adhesive layer for fastening the ultrasound transducer to the subject.

The ultrasound transducer unit may be used in a monitoring system as disclosed herein.

In one set of embodiments, the ultrasound transducer of this aspect or earlier aspects may define a rectangular window of approximately 5 mm x 16 mm. The average height of the ultrasound transducer may be approximately 8 mm. In another set of embodiments, the ultrasound transducer may define a circular window of approximately 10 mm diameter. The average height of the ultrasound transducer may again be approximately 8 mm.

The transducer may be configured to be fastened to a subject with the planar window substantially parallel to the subject's skin. A transmitting face of the transducer element

may be parallel to the planar window defined by the housing. In this way, the ultrasound pulses may be transmitted substantially perpendicularly to the subject's skin. However, in other embodiments, a transmitting face of the transducer element may be inclined to the planar window—for example, at an angle of between 5 and 45 degrees, such as at approximately 30 degrees or 45 degrees. This can facilitate the determining of a characteristic of blood where the blood is flowing broadly parallel to the planar window. This is because the pulse-Doppler response signals represent only those components of velocity that are perpendicular to the face of the transducer element, so flow parallel to the face does not give rise to any Doppler shift.

10

The ultrasound transducer may comprise one or more piezoelectric elements. The element may comprise a polymer or a ceramic or a polymer-ceramic composite. It may comprise lead zirconate titanate (PZT). In a preferred set of embodiments, the element comprises a ceramic (e.g., $\text{PbZr}_x\text{Ti}_{1-x}\text{O}_3$ for x having a value between 0 and 1) that is doped with ions. It is preferably doped with acceptor ions (e.g., K^+ , Na^+ , Fe^{+3} , Al^{+3} or Mn^{+3})—i.e., a so-called “hard” piezoelectric ceramic. It may comprise Pz26 (Navy Type I PZT-4), Pz28 (Navy Type III PZT-8) or Pz24 from FerroPerm™ (Meggitt™). In some embodiments, the element has a clamped dielectric constant that is less than 500 or less than 250—e.g., around 240 or less.

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The applicant has found that a PZT material having a lower dielectric constant than “soft” PZT materials, doped with donor ions, such as Pz27 and PZ29 from FerroPerm™ (Meggitt™) can advantageously be employed in certain embodiments of the present invention to provide an ultrasound transducer that is easier to drive electrically for a given thickness and area of the transducer. In particular, a hard ceramic transducer has been found to be particularly well suited for use in a single-element Doppler transducer; this is because the typically larger aperture area of such a transducer, compared with the transducer elements in conventional array-based medical ultrasound transducers, results in a lower electrical impedance, for a given choice of piezoelectric material. This reduced impedance (which can make the transducer more complex to drive) can be mitigated by using a harder material.

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In some embodiments, the ultrasound transducer may comprise impedance tuning circuitry. However, by using a hard ceramic transducer, some embodiments may avoid the need for impedance tuning circuitry in the ultrasound transducer. Thus, in some embodiments, the ultrasound transducer does not contain any tuning transformer.

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The characteristic of blood flow may relate to the velocity of the blood flow. It may relate to a component of velocity parallel to a transmission axis of the ultrasound transducer, or perpendicular to a transmission face of the ultrasound transducer. The characteristic may be any statistical measure derived from a set of velocity measurements over space and/or over time. It will be appreciated that any reference to “velocity” herein may refer to a component of velocity along a transmission or reception axis of the ultrasound transducer, and may therefore, in some cases, be represented by a scalar value (which may be signed or unsigned, depending on context).

The characteristic of blood flow may relate to the total blood flow within a region, which may be a cylindrical region, such as a circular or rectangular cylinder. The region may span the transmit beam and/or receive beam of the system. (It will be appreciated that references to cylinders and other shapes represent an idealised situation, and, in reality, the nature of ultrasound propagation in the animal medium means these shapes are only approximate, and may have soft, rather than hard, boundaries).

The characteristic may be a spatial-maximum velocity (parallel to the transmission axis) within a region. This may be determined, for example, by determining the maximum frequency-shift over all frequency shifts (or just positive or negative shifts) within a time-gated depth range that are above a minimum frequency-signal strength threshold. The characteristic may instead be derived from a set of spatial-maximum velocities determined at a succession of times. This set may represent a velocity trace of a spectrogram. The characteristic may be a time-maximum (VMax), time-minimum (VMin), or time-averaged mean (VMean) of the spatial-maximum velocity over a period of time; the period of time may be fixed or variable; it may be shorter or longer than one heartbeat—for example, between 5 and 30 seconds, such as 7 or 8 seconds, or it may be equal to one heartbeat. The characteristic may be a pulsatile index (PI), a resistivity index (RI), velocity area under the curve, an end diastolic velocity (VED), heart rate, blood flow volume through a region, or any other measure derived from the pulse-Doppler response signals. The characteristic may be a first or second order statistic of any of these parameters.

The characteristic may be evaluated repeatedly at intervals, which may be regular or irregular intervals. In some embodiments, one value of the characteristic may be estimated every time a new pulse-Doppler response signal is generated, or every 5 milliseconds, or every 10 milliseconds, (e.g., when the characteristic is a spatial-maximum), or every heartbeat or every 1, 5, 10 or 60 seconds (e.g., where the characteristic is VMax), . A set of one or more heartbeats may be identified that satisfy a

quality criterion – e.g., that the gradient of the positive and/or negative velocity traces satisfies a predetermined condition – thereby defining a set of valid heartbeats. The characteristic may be time-averaged over this set of valid heartbeats, or the characteristic may be such a time-average.

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A value (e.g., a current value) of the characteristic may be displayed on a display device – e.g., as a number - or a set of historic values may be displayed. A plot over time may be generated from a series of values, and may be displayed on a display device. The plot may be superimposed with a spectrogram.

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The controller may be configured to apply a noise filter or clutter filter to the pulse-Doppler response signals, to reduce contributions from stationary or slow-moving tissue, or from thermal noise. In some embodiments, the pulse-Doppler response signals are complex-demodulated. The response signals are preferably shifted to baseband.

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Removing clutter signals with a clutter filter helps to detect where blood is present. Tissue Doppler, for example, is a conventional approach to imaging tissue velocity (e.g., of heart muscle), but since the signal from non-blood tissue is typically thousands of times stronger than signals from blood, moving blood will not be visible in a tissue Doppler display. The clutter filter enables blood flow to be detected. In some embodiments, a combination of signal power and a frequency characteristic (after clutter filtering) may be used to determine if there is blood present, as well as the direction and velocity of the blood.

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25 Data representing a Doppler frequency spectrum, or a velocity spectrum, may be generated from a set of one or more of the pulse-Doppler response signals. The frequency or velocity spectrum may represent all blood flow through a region, as described herein—optionally all blood flow above a lower velocity bound and/or below an upper velocity bound. A succession of spectra may be calculated over time.

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In some embodiments, the controller may process positive Doppler shifts from one or more of pulse-Doppler response signals separately from negative Doppler shifts. The controller may calculate, from one or more pulse-Doppler response signals, a first envelope from positive Doppler shifts, and a second envelope from negative Doppler shifts, corresponding to blood flow towards or away from the ultrasound transducer, respectively, within a region of the subject. The controller may use an autocorrelation operation to identify heartbeats from the pulse-Doppler response signals. It may assign a

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quality metric to each heartbeat. The quality metric may depend on a similarity of the pulse-Doppler response signal or signals, or data derived therefrom, such as a frequency or velocity spectrum, for a respective heartbeat to the pulse-Doppler response signal or signals, or data derived therefrom, for a preceding heartbeat—e.g., the immediately
5 preceding heartbeat. Where two heartbeats are similar, the quality metric may be high, indicating that the heartbeats have been correctly identified with high confidence. The controller may evaluate the characteristic of blood flow only over those heartbeats that satisfy a quality criterion—e.g., for the quality metric exceeds a threshold level. Periods of time covering signals that are not identified as heartbeats with sufficiently high confidence
10 may be excluded from a time window over which the characteristic of blood flow is determined. This can improve the reliability of the determined value or values.

In one set of embodiments, the characteristic may be determined over a set of frequencies that includes only positive frequencies (corresponding to frequencies higher
15 than those of the transmitted pulses before demodulation), so that only flow in a direction having a component towards the transducer is included. In another set of embodiments, the characteristic may be determined over a set of frequencies that includes only negative frequencies (corresponding to frequencies lower than those of the transmitted pulses before demodulation), so that only flow in a direction having a component away from the
20 transducer is included. The system may calculate two sets of values of the characteristic of blood flow, one for positive frequency shifts and another for negative frequency shifts, for blood flow within the same region. The system may comprise a display and may be configured to display one or more values of the characteristic for positive frequency shifts and one or more values of the characteristic for negative frequency shifts, for blood flow
25 within the same region. These values may be displayed simultaneously—e.g., on different parts of the display. In this way, a physician can choose to monitor flow in just one direction, by looking at the relevant values on the display—this may be useful if, for example, one particular major artery is of interest in a region. In some embodiments, a maximum or mean speed towards the transducer and a maximum or mean speed away
30 from the transducer, over a common time period, and within a common region, may be displayed, or may be displayable in response to an input from a user.

The idea of determining a characteristic of blood flow through a region respectively for two different directions at the same time is believed to be novel. In particular, conventional
35 colour Doppler imagery does not allow such a distinction to be made, as it typically represents only an average velocity (averaged over the whole frequency spectrum) at a particular point.

From a further aspect, the invention provides a method for determining a characteristic of blood flow in a vertebrate animal subject, the method comprising:

- transmitting ultrasound pulses into the subject from an ultrasound transducer;
- 5 receiving reflections of the ultrasound pulses at the ultrasound transducer from a region in the subject;
- generating pulse-Doppler response signals from the reflections; and
- processing the pulse-Doppler response signals to determine a first value of a characteristic of blood flow within the region for blood flowing towards the ultrasound
- 10 transducer over a time period, and to determine a second value of the characteristic for blood flowing away from the ultrasound transducer over said time period.

From another aspect, the invention provides a system for determining a characteristic of blood flow in a vertebrate animal subject, the system comprising:

- 15 an ultrasound transducer;
 - a controller,
- wherein the controller is configured to:
- control the ultrasound transducer to transmit ultrasound pulses into the subject;
 - sample reflections of the ultrasound pulses received at the ultrasound transducer;
 - 20 generate pulse-Doppler response signals from the reflections; and
 - process the pulse-Doppler response signals to determine a first value of a characteristic of blood flow within the region for blood flowing towards the ultrasound transducer over a time period, and to determine a second value of the characteristic for blood flowing away from the ultrasound transducer over said time period.

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Each pulse-Doppler response signal may be processed to determine a respective first value and a respective second value from the same pulse-Doppler response signal.

- The first value and/or the second value may be stored in memory, or output over a
- 30 network interface, or displayed on a display device – e.g., numerically or graphically.

A first sequence of such first values and a second sequence of such second values may be determined over time. The first and second sequences may comprise values of the characteristic at common time periods across the sequences.

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Features of other aspects and embodiments disclosed herein may be combined with these aspects. In particular, the ultrasound transducer may be fastened to the subject. It may be a single-element ultrasound transducer.

- 5 From another aspect, the invention provides a method of monitoring blood flow in a vertebrate animal subject, the method comprising:
- transmitting unfocussed plane-wave ultrasound pulses into the subject, along a transmission axis, from a single transducer element of a single-element ultrasound transducer that is fastened to the subject;
 - 10 receiving reflections of the ultrasound pulses at the single transducer element from a region in the subject;
 - generating a succession of pulse-Doppler response signals from the reflections over time;
 - processing each pulse-Doppler response signal to determine a first respective
 - 15 spatial-maximum velocity value for blood flowing through the region towards the single transducer element, and to determine a second respective spatial-maximum velocity value for blood flowing through the region away from the single transducer element;
 - identifying heartbeats from said spatial-maximum velocity values;
 - assigning a quality metric to each identified heartbeat;
 - 20 identifying a subset of the spatial-maximum velocity values for which the assigned quality metric exceeds a threshold level;
 - monitoring values from the subset of spatial-maximum velocity values over time;
 - and
 - determining when a set of one or more values from the subset of spatial-maximum
 - 25 velocity values satisfies a predetermined alert criterion, and, in response to said determining, signalling an audible or visual alert.

From a further aspect, the invention provides a system for monitoring blood flow in a vertebrate animal subject, the system comprising:

- 30 a single-element ultrasound transducer, having a single transducer element, for fastening to the subject;
- a controller,
- wherein the controller is configured to:
- control the ultrasound transducer to transmit unfocussed plane-wave ultrasound
 - 35 pulses, along a transmission axis, from the single transducer element into the subject when the ultrasound transducer is fastened to the subject;

- sample reflections of the ultrasound pulses received at the single transducer element from a region in the subject;
- generate a succession of pulse-Doppler response signals from the reflections over time;
- 5 process each pulse-Doppler response signal to determine a first respective spatial-maximum velocity value for blood flowing through the region towards the single transducer element, and to determine a second respective spatial-maximum velocity value for blood flowing through the region away from the single transducer element over said time period;
- identify heartbeats from said spatial-maximum velocity values;
- 10 assign a quality metric to each identified heartbeat;
- identify a subset of the spatial-maximum velocity values for which the assigned quality metric exceeds a threshold level;
- monitor values from the subset of spatial-maximum velocity values over time; and
- determine when a set of one or more values from the subset of spatial-maximum
- 15 velocity values satisfies a predetermined alert criterion, and, in response to said determining, signal an audible or visual alert.

A first amplitude envelope representing blood flow towards the transducer may be determined, and second amplitude envelope of blood flow away from the transducer may

20 be determined. The first and second envelopes may be displayed on a display—e.g., as respective graphs over time. They may be overlaid on a display of a spectrogram, which may show positive and negative frequencies.

The first and second values may be determined for all blood flow with the region over the

25 time period (within the limits of the detection capability of the system), or only for all blood flow above a respective lower velocity limit and/or below a respective upper velocity limit.

In some embodiments, the characteristic may be determined over a set of frequencies that excludes frequencies in a band around zero (corresponding to frequencies close to

30 the carrier frequency of the transmitted pulses before demodulation). This may be achieved by applying a high-pass filter (e.g., with a cut-off frequency of between around 50 Hz to around 500 Hz) to the pulse Doppler response signals, shifted to baseband. In this way, reflections from stationary or slow-moving "clutter" can be rejected.

35 In general, it is expected that at least some embodiments of the invention may be able to reliably monitor blood flows having velocity components (parallel to an axis of the

ultrasound beam) of around 1 cm/second or higher—e.g., flows in a range of around 3, 4 or 5 cm/s to 20 cm/sec or higher.

5 Data representing the characteristic may be stored in a storage medium and/or displayed on a display device and/or output over a network or other data connection. The system may comprise a memory for storing data representing the determined characteristic—e.g., for storing a series of values over time. The system may comprise a display device, such as a monitor, for displaying one or more values of the characteristic, such as a live display of the maximum velocity (VMax) over a time window.

10

A plurality of characteristics may be determined, and may be displayed, for blood flow within a single region—optionally separately for positive and negative frequency shifts.

15 The system may comprise a monitoring subsystem and may monitor the characteristic of blood flow over time. It may determine a series of values, each relating to blood flow through a region at a different point in time—e.g., velocity values. These points in time may span an interval longer than a minute, or longer than 30, 60, 120 or 240 minutes or more. The series of values may be monitored by the monitoring subsystem.

20 A signal may be generated if a set of one or more of the values satisfies a predetermined criterion. The criterion may include one or more conditions. The system may be configured so that all of which must be met for the signal to be generated, or so that the signal is generated when any one or more of the conditions is met. A condition may be that a value of the series of values drops below a threshold amount (which may be fixed or determined relative to one or more earlier values). A condition may be that a value of the series of values exceeds a threshold amount (which may be fixed or determined relative to one or more earlier values). A condition may be that the series of values drops or rises faster than a threshold rate. A condition may relate to a frequency component of the series of values. A condition may be that a frequency component, lying within a
30 predetermined frequency range, is present in the series of value, or is not present in the series of value, or has an amplitude over time that rises or falls past a threshold level or that has a gradient exceeding a threshold gradient. In some embodiments, the predetermined frequency range may encompass a pulse (heartbeat) frequency of the subject. However, in other embodiments, the pulse (heartbeat) frequency of the subject
35 may always or at times lie outside the predetermined frequency range. It may be a frequency range whose upper frequency is half, or a quarter, or less, of the pulse rate of the subject—for example, the frequency range may be 3-7 Hz, whereas the subject's

- 15 -

pulse rate may be in the range 60 to 100 bpm, or 40 to 150 bpm, for example, depending on age, species and physical condition). As explained below, such a monitoring system may be useful for monitoring oscillations in blood flow measurements that don't correspond directly to the subject's heartrate.

5

The signal may cause an alarm to be raised—e.g., by sounding an audible or visual alert (a flashing light, a message on a display screen, etc.) or by sending a message over a network connection. The system may be a patient monitoring system—e.g., for bedside use in hospital, in an operating theatre, a general-practitioner (GP)'s office, or in a
10 patient's home. The series of values may be monitored for a period of time longer than a minute, or longer than 30, 60, 120 or 240 minutes or more.

In other embodiments the characteristic of blood flow in the subject is monitored discontinuously, although preferably at a frequency which provides clinically useful
15 information. For instance, the characteristic of blood flow in the subject may be actively monitored (i.e. ultrasound pulses are transmitted into the subject) for a 5, 10, 15, 30, 45, 60, 120 or 240 second period and these monitoring periods may be interspaced by a non-monitoring period of 1, 2, 3, 4, 5, 10, 15, 30, 45 or 60 minutes. During the non-monitoring period it may be preferable if ultrasound pulses are not transmitted into the subject. The
20 duration of the periods of monitoring and/or the periods of non-monitoring may be adjusted to account for changes in the subject's medical status. For instance, subjects in a critical or deteriorating condition may have longer and/or more frequent monitoring, whereas non-critical, stable or improving subjects may have shorter and/or less frequent monitoring. Such adjustments may be made by a clinician or may be made automatically
25 based on the output from the ultrasound monitoring itself or other medical data collection devices and systems which are assessing the subject's condition concurrently. In this way total ultrasound exposure for the subject may be minimised and/or the amount of data produced may be kept manageable.

30 In some embodiments, reflections of the ultrasound pulses are sampled from each of a plurality of regions within the subject. Respective values, or series of values, of the characteristic of blood flow in the respective region may be determined for each of the regions. Each characteristic may represent reflections from all the blood flow within the region, optionally between lower and/or upper velocity limits.

35

These regions may be at a plurality of different distances from the transducer—e.g., from a plurality of pairwise-abutting or pairwise-overlapping or spaced-apart regions. Each

region may have a substantially uniform thickness in the depth direction, which may be between 0.15 mm and 1 mm or 2 mm—for example, around 0.8 mm. The thickness will equal $N\lambda/2$, where N is the number of periods (cycles) in the transmitted pulse; in some embodiments, the value of N may be in the range 2 to 10. In some embodiments, the wavelength of the transmitted pulses may be in the range 0.1 - 0.5 mm—for example, 0.3 mm. The regions may all have the same thickness. Each region may be a circular or rectangular cylinder. The regions may span different respective depths or depth ranges. The regions may be arranged coaxially along a transmission axis of the ultrasound transducer. Each region may cover one continuous depth range. In one set of embodiments, the plurality of regions are contiguous, and together cover one aggregate depth range—e.g., from 0 or 5 mm to 30 or 40 mm.

A furthest region from the transducer may be at a maximum distance from the transducer, in the propagation direction, that is less than a maximum, minimum or mean diameter or width of the transducer, or that is no more than two, three, five or ten times this diameter width. The maximum distance could be 5 mm, 10 mm, 20 mm or 40 mm. The maximum distance may depend on the clinical application of interest; for monitoring cerebral circulation, it might be 40 mm, whereas for monitoring peripheral circulation in a digit it might be 10 mm.

Respective values of the characteristic may be determined for each of a plurality of regions from reflections of the same ultrasound pulses. In other words, a single pulse may contribute to the determining of a characteristic of blood flow at a first depth range and of the same characteristic of blood flow at a second depth range which may be distinct from (i.e. not overlap) the first depth range. This is not done in conventional pulsed-wave Doppler systems.

Values of the characteristic at two or more different depths may be compared; for example, a ratio, or other comparison operation, may be calculated. Outputs of this comparison operation may be displayed or monitored. They may provide a clinically-significant indicator which may be used for generating alerts by a monitoring system. In some embodiments, an aggregated value (e.g., mean or sum) from a plurality of depths may be generated, and may be output.

In some embodiments, the pulse-Doppler response signals may be processed to determine, for each of a plurality of depths or depth ranges, a respective sequence of values, over time, of a measure representative of blood flow relative to the ultrasound

transducer, within the subject at the respective depth or depth range. Each depth or depth range may correspond to a different respective region, as described above. This measure may, for example, be a power-weighted average (e.g., mean) frequency shift or velocity, or a frequency shift (or velocity) of maximum amplitude over one or more pulse-Doppler response signals. The measure may be evaluated at regular intervals—e.g., every 5 milliseconds. A graphical representation of the sequences of values may be displayed to a human operator. This can allow a human operator to identify one or more depths or depth ranges of interest from the plurality of depths or depth ranges. Values may be displayed for each of a set of depths or depth ranges that divides a viewing range into regular intervals—e.g., for every 1 mm interval from 5 mm to 35 mm. The values may be displayed as respective pixel intensities. A first axis may represent depth. A second axis may represent time.

The display may be similar to a conventional colour M-mode plot, but representing flow velocities at common time periods at multiple depths (i.e., generated from reflections of the very same Doppler pulse or pulses at multiple depths), rather than conventional approaches which use different pulses to acquire information at different respective depths. Moreover, the present approach does not require an array transducer, but can, at least in some embodiments, be generated with a single-element transducer.

20

It will be appreciated that the measure representative of blood flow may have a zero value or a low value at depths where no blood flow is present.

The operator may provide, as input, an indication of these one or more depths or depth ranges of interest to the controller. The controller may then process the pulse-Doppler response signals, or data derived therefrom, to determine respective values of one or more characteristics of blood flow for the indicated one or more depths or depth ranges. The characteristic(s) may be as described elsewhere herein—e.g., maximum velocity over a time window. The size of the depth range may be variable, and may be received as an input from the operator, in addition to the location of the depth range. For example, an operator may move a cursor to input upper and lower depth markers so as to select the range 20 mm – 25 mm for further processing, or to select the range 10 mm – 30 mm.

Embodiments of the system disclosed herein may have no conventional two-dimensional or three-dimensional imaging capability (e.g., no B-mode imaging). This graphical display provides a mechanism by which an operator can nevertheless view a “one-dimensional image”, even from a single-element transducer, which can allow the operator to identify a

depth of interest. For example, a depth that exhibits strong blood flow in the displayed values of the measure may be indicative of the presence of an artery at that depth.

From another aspect, the invention provides a method for determining and representing
5 blood flow in a vertebrate animal subject, the method comprising:
transmitting ultrasound pulses into the subject from an ultrasound transducer;
receiving reflections of the ultrasound pulses at the ultrasound transducer;
generating pulse-Doppler response signals from the reflections;
processing the pulse-Doppler response signals to determine, for each of a plurality
10 of depths or depth ranges, a respective sequence of values over time, of a measure that
is representative of blood flow within the subject, relative to the ultrasound transducer at
the respective depth or depth range, wherein the sequences comprise values
representative of blood flow at common time periods across the plurality of depths or
depth ranges; and
15 displaying a graphical representation of the sequences of values to a human
operator.

From a further aspect, the invention provides a system for determining and representing
blood flow in a vertebrate animal subject, the system comprising:
20 an ultrasound transducer;
a controller; and
a display,
wherein the controller is configured to:
control the ultrasound transducer to transmit ultrasound pulses into the subject;
25 sample reflections of the ultrasound pulses received at the ultrasound transducer;
generate pulse-Doppler response signals from the reflections;
process the pulse-Doppler response signals to determine, for each of a plurality of
depths or depth ranges, a respective sequence of values over time, of a measure that is
representative of blood flow within the subject, relative to the ultrasound transducer at the
30 respective depth or depth range, wherein the sequences comprise values representative
of blood flow at common time periods across the plurality of depths or depth ranges; and
control the display to display a graphical representation of the sequences of values
to a human operator.

35 Features of other aspects disclosed herein may be features of embodiments of these
aspects also.

It will be seen that this enables an operator to visualise simultaneous blood flow (i.e., flow within one time period) at multiple depths at once. This can allow for easy identification of a region or regions of interest. The nature of these regions may depend on the clinical context—e.g., being a depth range that contains a significant artery, or being a superficial
5 depth range that is deeper than the capillaries (where flow will typically be too low to detect) but higher than any major arteries.

In some embodiments, the method may further comprise receiving, from the human operator, an input identifying a depth or depth range of interest. It may further comprise
10 monitoring a characteristic of blood flow at said depth or depth range of interest. The characteristic may be a characteristic as described elsewhere herein. In some embodiments, the system may be configured to receive inputs identifying a plurality of depths or depth ranges of interest, and may be configured to determine a characteristic of blood flow at each depth or depth range of interest.

15 The plurality of depth ranges may be contiguous; they may span a range—e.g., from 0 mm to 40 mm. They may each have a depth of 1 mm, 2 mm or less, thereby providing a resolution of 1 mm, 2 mm or finer.

20 At each depth, two sequences of values may be determined—a first sequence relating to positive frequency shifts, and a second sequence relating to negative frequency shifts. Values from the two sequences may be represented independently on the graphical display. For example, for a particular time period and depth, if the value of the second
25 sequence is zero, or below a threshold, a first colour (e.g., red) may be used to represent the value from the first sequence. If the value of the first sequence is zero, or below a threshold, a second colour (e.g., blue) may be used to represent the value from the second sequence. If both values are non-zero, or above a respective threshold, a third colour (e.g., white) may be used to represent both values. If both values are zero, or
30 below respective thresholds, a fourth colour (e.g. black) may be displayed. Such an approach allows an operator to distinguish between a region with zero flow and a region with equal flow in both directions. Conventional colour Doppler imagery does not allow such a distinction to be made, as it typically represents only the average velocity (averaged over the frequency spectrum) at a point.

35 In some embodiments, the common time periods may be between 1 and 100 milliseconds—e.g., around 5 milliseconds. The time periods may be uniform and contiguous, such that new values for the sequences are determined at regular intervals.

The values may be displayed in a rolling time window, with older values (e.g., more than 7 seconds old) being removed from the display as new values are displayed.

5 The operator may use this display when positioning and/or fastening the ultrasound transducer. Thereafter, the system may automatically monitor the characteristic of blood flow at the selected depth range or ranges, without the need for further human intervention. In some embodiments, the system may monitor, over time, the respective sequence of values of the measure that is representative of blood flow, and may detect any displacement of the transducer relative to the subject from these values. This may be
10 done using pattern matching or other appropriate image processing techniques. The system may compensate for such displacement by adjusting the depth(s) or depth range(s) of interest by a corresponding amount.

15 In any of the aspects disclosed herein, the controller may store data representative of, or derived from, the pulse-Doppler response signals over a period of time, which may span minutes, hours or days. This can allow a physician to view a graphical representation of the data and/or select a depth range and/or view a representation of the characteristic of blood flow, all using historic data, rather than live data.

20 In some embodiments, the controller may calculate a quality value for each of a plurality of depths or depth ranges. This may be based on comparing heartbeat waveforms (e.g., from a velocity envelope) as described above, or any other appropriate way. The controller may select a depth or depth range at which to determine the characteristic of blood flow based on the quality value—e.g., selecting a depth that gives the highest
25 quality signal.

In some embodiments, the controller may be configured to monitor blood flow at a first depth to display or monitor information relating to flow at the first depth, and to monitor blood flow at a second depth, different from the first depth, as a reference to detect a fault
30 condition. The second depth may contain a blood vessel (e.g., an artery) that is larger than any blood vessel that is present at the first depth, within the ultrasound receive beam, or that contains faster-flowing blood than any blood vessel that is present in the beam at the first depth. This can be useful, as it can be expected that blood flow should be possible at the second depth throughout a monitoring period, whereas the blood flow at
35 the first depth may vary and may sometimes drop below the noise floor due to physiological changes such as vasoconstriction. Loss of signal at the second depth may then be used to detect a fault condition, such as the transducer having been knocked out

of the position; an alarm may be signalled in response. The use of the reference signal can prevent false alarms that might otherwise occur if only the first depth were monitored for a fault condition.

- 5 In general, the pulses are preferably transmitted at intervals—preferably at regular intervals. A pulse repetition frequency of around 10 kHz may be used. The transmitted pulses are preferably sine-wave pulses having a common carrier frequency. A pulse-Doppler response signal may be generated from the reflections of just one pulse (e.g., a long pulse). However, in order to provide useful depth resolution, each pulse needs to be
- 10 brief, and will therefore typically be too short to allow Doppler frequency shifts to be measured from the reflection of just a single pulse. (The bandwidth of a single pulse might typically be around 1 MHz, whereas the Doppler shift from a blood cell in the region could be around 1 kHz.) Therefore, each value of the characteristic of blood flow is preferably determined from the reflections of a plurality of pulses (for example, around fifty
- 15 pulses). A respective set of one or more samples may be obtained from each of a plurality of pulses, and this plurality of samples may then be used to generate a pulse-Doppler response signal, or a frequency or velocity spectrum, or other derived data, which may be processed to estimate a value of the characteristic.
- 20 The system, and its controller, may comprise one or more processors, DSPs, ASICs, volatile memory, non-volatile memory, inputs, outputs, etc. as will be appreciated by one skilled in the art. Some or all of the operations described herein may be carried out by, or under the control of, software stored in a memory and executing on one or more processors in the controller or monitoring system. The system may be a single unit or it
- 25 may be distributed—e.g. with one or more operations being performed remotely from the living organism, such as on a remote server. A sampling module in the controller may comprise an amplifier and/or an ADC and/or one or more filters and/or demodulators.

- In particular, in some embodiments, the controller may comprise two separate units—i.e.
- 30 a first unit and a second unit. The first unit may control the transducer and sample the reflections. The second unit may determine the characteristic of blood flow from the pulse-Doppler response signals. The first unit or the second unit may sample the reflections of the pulses. The two units may communicate over a wired link, such as a USB cable, or a wireless link, such as a Bluetooth™ connection. In particular, the first unit may send data
- 35 representing the pulse-Doppler response signals (preferably after bandpass filtering and complex demodulation) to the second unit, preferably wirelessly. The first unit may comprise a power supply, such as a battery. The first unit may comprise the ultrasound

transducer, e.g., within a common housing—preferably a solid housing such as a box.

The first unit may comprise means for fastening the first unit to a patient, such as a strap or an adhesive pad or region, or any other suitable fastener. The second unit may

comprise a display. The second unit may be a mobile telephone (cell phone) or a tablet

5 computer or other portable device. By dividing the system in this way, the first unit can be a portable sensor unit, which can easily be attached to a patient without the inconvenience of wired leads, and can be relatively low-cost, because it need only comprise a relatively basic microcontroller, while the more-complex processing of the response signals can be carried out on a more powerful device.

10

The operations described herein need not necessarily be performed close in time to one another. In particular, the reflected ultrasound signals may be acquired at a first period in time, and then processed at a later period of time, which may be hours or days apart.

15 The present system has many applications—e.g., neonatal monitoring, operative and post-operative care, monitoring cerebral circulation, monitoring peripheral circulation, monitoring microcirculation, monitoring for sudden blood loss in an emergency setting, etc.

20 The blood circulatory system of vertebrate animals is a closed system of conduits (blood vessels) and a pump (the heart) which circulate blood around the body as a means to deliver oxygen and nutrients to the tissues and remove carbon dioxide and the waste products of metabolism from the tissues. Functionally, the system may be considered to have two parts – the pulmonary circulation (which supplies blood to the lungs) and the
25 systemic circulation (which supplies blood to all parts of the body except the lungs). As used herein, the parts of the systemic circulation outside of the torso may be termed the peripheral circulation. Anatomically, blood is pumped by the heart through arteries, then arterioles and, in mesenteric beds, metarterioles, to the capillaries where its soluble and/or gaseous contents equilibrate with the interstitial fluids of the tissues. Blood exits
30 the capillaries into venules and then flows into the veins which lead back to the heart.

The larger arteries closest to the heart are elastic as a consequence of collagen and elastin filaments in the tunica media interspersing layers of smooth muscle cells. In contrast, smaller arteries, which draw blood from the elastic arteries and ultimately feed
35 the arterioles (distributing arteries) are predominantly muscular in structure and do not have multiple layers of elastic tissue. Instead, the muscular arteries have a single prominent elastic layer, the internal elastic lamina, that forms the outermost part of the

tunica intima of such vessels and which separates the tunica intima from the tunica media. Elastic arteries, the larger muscular arteries and the larger veins are of a size which requires a dedicated blood supply. This supply is provided by the vaso vasorum.

- 5 The term “minor vasculature”, as used herein, encompasses the distributing arteries (muscular arteries), veins of equivalent size in the subject of interest, arterioles, metarterioles, capillaries, and venules. The term “major vasculature” encompasses the blood vessels larger than the distributing arteries, veins of equivalent size in the subject of interest, arterioles, metarterioles, capillaries, and venules. The minor vasculature may be
10 divided into smaller vessels which are not supplied by the vaso vasorum and larger vessels which are.

- For the present purposes, blood flow within the small arteries feeding directly into the arterioles, the arterioles, metarterioles, capillaries, venules, and small veins fed directly by
15 the venules is considered to be the “microcirculation” and these vessels may therefore be termed “microvessels” or the “microvasculature”. The microvasculature is not supplied by the vaso vasorum. Blood flow in the larger vessels (arteries and veins) is in contrast termed the “macrocirculation”.

- 20 “Arterial microcirculation” may be considered to be blood flow in the small arteries feeding directly into the arterioles and the arterioles. “Venous microcirculation” may be considered to be blood flow in the venules and the small veins fed directly by the venules. “Arterial microvasculature”, “arterial microvessels”, “venous microvasculature” and “venous microvessels” should be interpreted accordingly.

25

Features of other aspects disclosed herein may be features of embodiments of these aspects also.

- 30 Characteristics of blood flow have been used to monitor and/or analyse the physiology of healthy vertebrate animals and to diagnose, monitor or predict the progression of disease and pathological conditions and/or treatment responses in such subjects. The methods, systems and apparatus described herein may be applied to such contexts.

- 35 The inventors have further recognised that the characteristics of blood flow in the peripheral circulation/vasculature (e.g. circulation in/vasculature of the head, limbs (legs, shoulders, arms, feet, hands, fingers and toes) may be determined in accordance with at least some methods of the invention and/or using at least some of the systems and

apparatus of the invention and such information may contribute advantageously to the monitoring and/or analysis of the physiology of healthy vertebrate animals and to the diagnosis, monitoring or prediction of the progression of disease and pathological conditions and/or treatment responses in such subjects. Any of the above defined groups
5 of blood vessels may be investigated in such embodiments.

The inventors have further recognised that the characteristics of blood flow in the superficial circulation/vasculature (circulation/vasculature in proximity to the skin's surface, e.g. less than about 20mm, 15mm, 10mm, 9mm, 8mm, 7mm, 6mm, 5mm, 4mm, 3mm,
10 2mm or 1mm from the epidermis) may be determined in accordance with at least some methods of the invention and/or using at least some of the apparatus of the invention and such information may contribute advantageously to the monitoring and/or analysis of the physiology of healthy vertebrate animals and to the diagnosis, monitoring or prediction of the progression of disease and pathological conditions and/or treatment responses in
15 such subjects. Any of the above defined groups of blood vessels may be investigated in such embodiments.

Thus, in certain embodiments at least some of the methods of the invention are for determining a characteristic of blood flow in the peripheral circulation (e.g. in the
20 superficial peripheral circulation, the peripheral minor vasculature, the peripheral arterial microvasculature, the superficial peripheral minor vasculature, or the superficial peripheral arterial microvasculature) of a vertebrate animal subject. In these embodiments the ultrasound transducer is fastened to the surface (e.g. skin) of the subject at a site which is not on the torso of the subject, e.g. a site on a limb (e.g. shoulder, arm, leg, hand, foot,
25 toe, finger, paw, wing, fin, tail), neck or head (e.g. ear, nose, tongue, cheek, scalp, forehead). Some aspects of the invention provide suitable fastening means.

The inventors have further recognised that by determining the characteristics of blood flow in multiple blood vessels simultaneously the information obtained may contribute
30 advantageously to the monitoring and/or analysis of the physiology of healthy vertebrate animals and to the diagnosis, monitoring or prediction of the progression of disease and pathological conditions and/or treatment responses in such subjects. A plurality of vessels of one or more of the above defined groups of blood vessels may be investigated in such embodiments. It may, in certain embodiments, be particularly advantageous to determine
35 blood flow in a plurality of vessels of the minor vasculature, e.g. arterial microvessels simultaneously. The minor vasculature and/or microvessels, in particular the arterial

microvessels, of the peripheral circulation may be targeted in these embodiments. More specifically, in these embodiments superficial vessels may be targeted.

5 In these embodiments references to determining the characteristics of blood flow in multiple blood vessels simultaneously includes determining the characteristics of blood flow in a plurality of vessels within a region at a certain depth/depth range and/or determining the characteristics of blood flow in one or more vessels within a plurality of depths/depth ranges within the region. This is discussed in more detail above.

10 In further embodiments the characteristics of blood flow in multiple blood vessels may be determined simultaneously from anatomically distant sites, e.g. the shoulder/upper arm and the hand or the head and the foot. A comparison of blood flow characteristics at each site may offer further insights into the diagnosis, monitoring or prediction of the progression of disease and pathological conditions and/or treatment response.

15 Thus, in certain embodiments at least some of the methods of the invention are for determining a characteristic of blood flow in multiple vessels, e.g. multiple vessels of the minor vasculature or multiple arterial microvessels or one or more of both, simultaneously. In these embodiments the ultrasound transducer is fastened to the surface (e.g. skin) of
20 the subject at a site which contains a plurality of blood vessels, e.g. a plurality of vessels of the minor vasculature or a plurality of arterial microvessels or one or more of both, within range of the transducer. Some aspects of the invention provide suitable fastening means.

25 Thus, from a further aspect, the invention provides a method for determining a characteristic of blood flow in a vertebrate animal subject, the method comprising:

transmitting ultrasound pulses into the subject from an ultrasound transducer that is applied to an external surface of the subject;

30 receiving reflections of the ultrasound pulses at the ultrasound transducer from at least one region within the subject, said at least one region containing a plurality of blood vessels;

generating pulse-Doppler response signals from the reflections; and

processing the pulse-Doppler response signals to determine a characteristic of the blood flow through the plurality of vessels in said at least one region.

35

The invention extends to a system configured to implement such a method.

- 26 -

In one embodiment said method is a method for determining a characteristic of blood flow in the minor vasculature of a vertebrate animal subject, the method comprising:

transmitting ultrasound pulses into the subject from an ultrasound transducer that is applied to an external surface of the subject;

5 receiving reflections of the ultrasound pulses at the ultrasound transducer from at least one region within the subject, said at least one region containing a plurality of vessels of the minor vasculature;

generating pulse-Doppler response signals from the reflections; and

10 processing the pulse-Doppler response signals to determine a characteristic of the blood flow through the plurality of vessels of the minor vasculature in said at least one region.

In one embodiment the method is a method for determining a characteristic of blood flow in the arterial microvasculature of a vertebrate animal subject, the method comprising:

15 transmitting ultrasound pulses into the subject from an ultrasound transducer that is applied to an external surface of the subject;

receiving reflections of the ultrasound pulses at the ultrasound transducer from at least one region within the subject, said at least one region containing a plurality of arterial microvessels;

20 generating pulse-Doppler response signals from the reflections; and

processing the pulse-Doppler response signals to determine a characteristic of the blood flow through the plurality of arterial microvessels in said at least region.

25 The ultrasound transducer may be applied to the external surface manually (e.g., being held in place by a human operator), but preferably it is fastened to the external surface.

In any embodiment of this aspect plurality of vessels contained within said region(s) may be within the peripheral circulation and/or the superficial circulation and said methods determine a characteristic of the blood flow through said plurality of vessels.

30

In certain specific embodiments the region(s) containing a plurality of blood vessels does not contain an artery and/or a vein of the major vasculature. In other specific embodiments the region(s) containing a plurality of blood vessels does not contain an artery and/or a vein whose walls are supplied by a vaso vasorum.

35

The vessels targeted by at least some of the methods of the invention will be vessels having a flow which may provide clinically useful information, e.g. in the specific clinical

contexts described herein. This is typically blood vessels having a flow rate sufficient to be detectable in the pulse-Doppler response signals, e.g. a flow rate of greater than 1cm/s, e.g. greater than 3-4cm/s. In certain embodiments the vessels targeted will be those with a flow rate of less than 60cm/s, e.g. less than 50cm/s, 45cm/s, 40cm/s, 35cm/s or 30cm/s. Due to the differing sizes of the subjects to which at least some of the methods of the invention may be applied, different vessels may be targeted in order to obtain clinically useful information, but in certain embodiments this will not be arteries and/or a veins of the major vasculature, in particular arteries and/or a veins whose walls are supplied by a vasa vasorum. In adult human subjects, the vessels targeted are typically the muscular arteries, in particular those directly feeding the arterioles, and the arterioles.

It should further be noted that characteristics of blood flow determined in certain areas of the vasculature may provide insight into the characteristics of blood flow in other areas of the vasculature. The inventors have, in particular, recognised that characteristics of blood flow in the arterial microvasculature (especially the peripheral arterial microvasculature) can provide information on the characteristics of blood flow in the microcirculation (especially the peripheral microcirculation) more generally, and especially in the context of microvascular dysfunction (e.g. as observed in subjects with sepsis and associated with diabetes mellitus types 1 and 2, Raynaud's phenomenon, systemic sclerosis, hypertension, peripheral artery disease, chronic renal failure, hypercholesterolemia, hyperlipidaemia, obesity and hypertension).

Features of other aspects disclosed herein may be features of embodiments of these aspects also.

In healthy tissues the microvasculature of the tissue is able to control blood flow within it sufficiently to meet the tissue's needs for oxygen and nutrients and the removal of waste products and CO₂. In certain diseases and conditions the microvasculature becomes dysfunctional and can no longer meet those needs adequately. Diseases and pathological conditions which are associated with microvasculature dysfunction include, but are not limited to, diabetes mellitus types 1 and 2, Raynaud's phenomenon, systemic sclerosis, hypertension, peripheral artery disease, chronic renal failure, hypercholesterolemia, hyperlipidemia, obesity and hypertension. Thus dysfunction may arise from a restriction in blood flow upstream of the area of dysfunction (e.g. due to a stenosis) which cannot be compensated by regulation of the tone of the vessels of the microvasculature and/or because of an inability of the microvasculature to regulate the

tone (peripheral resistance) of its vessels in response to increased or decreased tissue demands.

The inventors have recognised that some aspects of the invention have particular utility in the clinical treatment of dysfunction of the microvasculature, more specifically in the early and accurate of detection of subjects with or at significant risk of dysfunction of the microvasculature and in the monitoring of this dysfunction as it progresses and/or responds to treatment (e.g. surgical and/or pharmaceutical intervention). More specifically the inventors have recognised that characteristics of blood flow in the minor vasculature, e.g. the arterial microvasculature (especially the peripheral minor vasculature, e.g. peripheral arterial microvasculature) can provide information on the characteristics of blood flow in the microcirculation (especially the peripheral microcirculation) in the context of microvascular dysfunction (especially peripheral microvasculature dysfunction), e.g. associated with diabetes mellitus types 1 and 2, Raynaud's phenomenon, systemic sclerosis, hypertension, peripheral artery disease, chronic renal failure, hypercholesterolemia, hyperlipidemia, obesity and hypertension.

Thus, from a further aspect, the invention provides a method for monitoring or predicting the onset of and/or progression of dysfunction of the microvasculature and/or a response to treatment thereof in a vertebrate animal subject, said method comprising

transmitting ultrasound pulses into the subject from an ultrasound transducer that is applied to an external surface of the peripheral anatomy of the subject;

receiving reflections of the ultrasound pulses at the ultrasound transducer from at least one region containing at least one blood vessel of the minor peripheral vasculature, preferably a plurality thereof;

generating pulse-Doppler response signals from the reflections; and processing the pulse-Doppler response signals to determine a characteristic of blood flow in the minor peripheral vasculature of the subject;

monitoring the characteristic of blood flow over time; and optionally establishing a profile of said characteristic over time;

wherein the characteristic or the profile of said characteristic over time is indicative or predictive of dysfunction of the microvasculature or response to treatment thereof or variation in said characteristic or a profile of said characteristic over time is indicative or predictive of dysfunction of the microvasculature or is indicative or predictive of a change in the dysfunction of the microvasculature or response to treatment thereof

The invention extends to a system configured to implement such a method. In particular, the system is configured to transmit unfocused ultrasound pulses. The ultrasound pulses may be plane-wave pulses.

- 5 In certain embodiments the characteristic of blood flow in the subject is monitored over time continuously. In other embodiments the monitoring over time takes place repeatedly at a frequency which provides clinically useful information, e.g. as described above. In this embodiment the monitoring phases are interspaced with periods where monitoring does not take place. Preferably, ultrasound is not transmitted into the subject during the non-
10 monitoring phases.

- In accordance with these aspects of the invention the characteristic of blood flow may be monitored in any blood vessel, or vessels, in the minor peripheral vasculature of the subject having a flow rate sufficient to be detectable in the pulse-Doppler response
15 signals.

- In certain embodiments the blood vessel, or vessels, are those at a site on a limb (e.g. arm, shoulder, leg, hand (e.g. inside or back or between thumb and forefinger), foot, toe, finger, paw, wing, fin, tail), neck or head (e.g. ear, nose, tongue, cheek, scalp, forehead).
20

- In other embodiments the characteristic of blood flow may be monitored in any blood vessel, or vessels, in the peripheral microvasculature of the subject having a flow rate sufficient to be detectable in the pulse-Doppler response signals.

- 25 It may be advantageous in certain embodiments to monitor a characteristic of blood flow in the arterial microvasculature. In this regard the inventors have recognised that characteristics of blood flow in the arterial microvasculature (especially the peripheral arterial microvasculature), the vasculature slightly upstream of the capillary beds, can provide information on the characteristics of blood flow in the microcirculation (especially
30 the peripheral microcirculation) more generally, and especially in the context of the microvascular dysfunction.

In any of these embodiments said vessels may be superficial vessels.

- 35 The blood vessel, or vessels, may be within a region of the subject displaying signs of microvascular dysfunction, e.g. regions of, or in proximity to, skin ulcers, gangrene, tissue necrosis, cyanosis, numbness and coldness.

The dysfunction of the minor vasculature may be dysfunction associated with diabetes mellitus types 1 and 2, Raynaud's phenomenon, systemic sclerosis, hypertension, peripheral artery disease, chronic renal failure, hypercholesterolemia, hyperlipidemia, obesity and hypertension.

The subject may be at risk of microvascular dysfunction, e.g. may be a subject which has diabetes mellitus types 1 and 2, Raynaud's phenomenon, systemic sclerosis, hypertension, peripheral artery disease, chronic renal failure, hypercholesterolemia, hyperlipidemia, obesity and/or hypertension.

In certain embodiments the subject does not have and/or is not at risk of sepsis or septic shock. In certain embodiments the subject is not an infant subject.

Treatment of microvasculature dysfunction may include treatments for the underlying causes, e.g. anti-diabetic, antihypertensive, cholesterol lowering and lipid lowering pharmaceutical treatments, angioplasty or bypass surgery and lifestyle changes (e.g. smoking cessation, calorie restricted diets and increased exercise).

The method may also be considered a method for obtaining information relevant to monitoring or predicting the onset of and/or progression of microvasculature dysfunction and/or a response to treatment thereof in a vertebrate animal subject. The methods described herein may be used alone as an alternative to other investigative techniques or in addition to such techniques in order to provide information relevant to monitoring or predicting the onset of and/or progression of microvasculature dysfunction and/or a response to treatment thereof in a vertebrate animal subject.

In certain embodiments the method further comprises a step in which the characteristic or the profile of said characteristic over time or the variation in said characteristic or the profile of said characteristic over time is used, alone or together with additional clinical information (e.g. from other methods), to diagnose microvasculature dysfunction or the extent or severity thereof, or to provide a prognosis for the onset of and/or progression of minor vasculature dysfunction in the subject, or to determine a response to the treatment of microvasculature dysfunction in the subject.

In these embodiments the characteristic or the profile of said characteristic over time or the variation in said characteristic or the profile of said characteristic over time may be

compared to reference data previously obtained from the same subject, e.g. reference data obtained prior to the onset of microvasculature dysfunction, or the commencement of a treatment or treatment cycle or from a time earlier in said treatment. Divergence between the data sets may be indicative of a change in the dysfunction or response to treatment. Thus, the steps of comparing the test and reference data and determining whether or not they diverge (or correspond) may be performed using mathematical, or statistical techniques, and generally this will be implemented by software (i.e. it will be performed using a computer). Statistical or mathematical methods for performing such a comparison and determination of correspondence are well known and widely available in the art. In other embodiments correspondence (or divergence) may be assessed or estimated visually by the skilled person.

In other embodiments the characteristic or the profile of said characteristic over time or the variation in said characteristic or the profile of said characteristic over time may be compared to reference data previously obtained from a cohort of analogous subjects, e.g. a cohort which developed microvasculature dysfunction or which were previously determined as being at risk of microvasculature dysfunction or which were undergoing analogous clinical care for microvasculature dysfunction and/or a cohort of healthy subjects (subjects not displaying or at risk of the disease or pathological condition), i.e. a predetermined standard. In these embodiments correspondence (or divergence) between test data and reference data may be analysed as described above or by applying said test data to a mathematical model generated using the reference data. Such a mathematical model may be used to determine whether test data fits, or matches, a negative standard and/or a positive standard, e.g. whether it best fits, or best matches a negative and/or a positive standard. Mathematical methods for generating such models are well known. In other embodiments correspondence (or divergence) may be assessed or estimated visually by the skilled person.

The inventors have recognised that some aspects of the invention have particular utility in the monitoring of peripheral microvasculature function (circulation) during or following surgery, in particular vascular surgery. All surgical procedures carry a risk of damage, inadvertent or unavoidable, to the subject's vascular system. This can lead to microvascular dysfunction downstream of the damage. Monitoring characteristics of blood flow in the minor vasculature in certain areas (or area) on the subject allows clinicians to detect such dysfunction in the microvasculature and make suitable interventions to avoid or mitigate any compromise to the blood flow in the subject's microvasculature. In the specific context of vascular surgery, e.g. endovascular surgery, the outcome is typically to

restore blood flow to an area of the body which is experiencing a reduced or interrupted supply, e.g. because of stenosis or traumatic damage. Monitoring characteristics of blood flow in the minor vasculature in certain areas (or area) on the subject allows clinicians to confirm that blood flow in the microvasculature has been restored or has not been further
5 compromised.

From a further aspect, the invention provides a method for monitoring peripheral microcirculation in a vertebrate animal subject undergoing or recovering from surgery, said method comprising

10 transmitting ultrasound pulses into the subject from an ultrasound transducer that is applied to an external surface of the subject;

receiving reflections of the ultrasound pulses at the ultrasound transducer from at least one region containing at least one blood vessel of the minor peripheral vasculature, preferably a plurality thereof;

15 generating pulse-Doppler response signals from the reflections; and

processing the pulse-Doppler response signals to determine a characteristic of blood flow in the minor peripheral vasculature of the subject;

monitoring the characteristic of blood flow over time; and optionally

establishing a profile of said characteristic over time;

20 wherein variation in said characteristic or the profile of said characteristic over time is indicative or predictive of a change in the peripheral microcirculation of the subject.

The invention extends to a system configured to implement such a method. In particular, the system is configured to transmit unfocused ultrasound pulses. The ultrasound pulses
25 may be plane-wave pulses.

In certain embodiments the characteristic of blood flow in the subject is monitored over time continuously. In other embodiments the monitoring over time takes place repeatedly at a frequency which provides clinically useful information, e.g. as described above. In this
30 embodiment the monitoring phases are interspaced with periods where monitoring does not take place. Preferably, ultrasound is not transmitted into the subject during the non-monitoring phases.

In certain embodiments the surgery is vascular surgery, e.g. endovascular and open
35 vascular surgery. More specifically the surgery may be angioplasty or bypass surgery. In these embodiments the area of microcirculation to be monitored may be downstream of the artery undergoing surgical intervention. It may be advantageous to monitor an area

previously determined to have microvasculature dysfunction as a consequence of the vascular defect being addressed by the surgical intervention in question (e.g. an area in vicinity of a skin ulcer which has been attributed to a defect in an upstream artery). In this way revascularisation of the dysfunctional area may be confirmed. In these embodiments
5 the characteristic of blood flow to be determined may be determined in an area of the minor vasculature which comprises the target area of microcirculation or which is upstream of the target area of microcirculation and downstream of the artery undergoing surgical intervention.

10 During advanced endovascular or open vascular surgery, it may be advantageous to monitor circulation in the microvasculature of the lower limb musculature. This kind of surgery involves major arteries in the pelvis becoming blocked with endovascular or other surgical equipment and can lead to compromised circulation in the lower limb musculature with development of necrosis in the musculature and in some instances the need for
15 major limb amputation. This could be reduced or prevented with constant/intermittent monitoring of the circulation in the microvasculature of the lower limbs by following a characteristic of the blood flow in the minor vasculature.

The method may also be considered a method for obtaining information relevant to
20 monitoring microcirculation in a vertebrate animal subject undergoing or recovering from surgery. The methods described herein may be used alone as an alternative to other investigative techniques or in addition to such techniques in order to provide information relevant monitoring microcirculation in a vertebrate animal subject undergoing or recovering from surgery.

25 In certain embodiments the method further comprises a step in which the variation in said characteristic or the profile of said characteristic over time is used, alone or together with additional clinical information (e.g. from other methods), to diagnose microvasculature dysfunction in a vertebrate animal subject undergoing or recovering from surgery or the
30 extent or severity thereof, or to provide a prognosis for the onset of and/or progression of microvasculature dysfunction in the subject.

In these embodiments the characteristic or the variation in said characteristic or the profile of said characteristic over time may be compared to reference data previously obtained
35 from the same subject, e.g. reference data obtained prior to the surgery or from a point earlier in the surgery. Divergence between the data sets may be indicative of a change in the microcirculation of the subject. Thus, the steps of comparing the test and reference

data and determining whether or not they diverge (or correspond) may be performed using mathematical, or statistical techniques, and generally this will be implemented by software (i.e. it will be performed using a computer). Statistical or mathematical methods for performing such a comparison and determination of correspondence are well known
5 and widely available in the art. In other embodiments correspondence (or divergence) may be assessed or estimated visually by the skilled person.

In more specific embodiments the method may involve an alarm or indicator, in particular an automated alarm or indicator, occurring when change in the microcirculation of the
10 subject (as indicated by a characteristic of blood flow in the minor peripheral vasculature) passes a certain threshold value, e.g. a value which may be indicative or predictive of microvasculature dysfunction or a significant risk thereof.

In accordance with these aspects of the invention the characteristic of blood flow may be
15 monitored in any blood vessel, or vessels, in the minor peripheral vasculature of the subject having a flow rate sufficient to be detectable in the pulse-Doppler response signals.

In certain embodiments the blood vessel, or vessels, are those at a site on a limb (e.g.
20 arm, shoulder, leg, hand (e.g. inside or back or between thumb and forefinger), foot, toe, finger, paw, wing, fin, tail), neck or head (e.g. ear, nose, tongue, cheek, scalp, forehead).

In other embodiments the characteristic of blood flow may be monitored in any blood vessel, or vessels, in the peripheral microvasculature of the subject having a flow rate
25 sufficient to be detectable in the pulse-Doppler response signals.

It may be advantageous in certain embodiments to monitor the characteristic of blood flow in arterial microvasculature. In this regard the inventors have recognised that characteristics of blood flow in the arterial microvasculature (especially the peripheral
30 arterial microvasculature), which is the vasculature slightly upstream of the capillary beds, can provide information on the characteristics of blood flow in the microcirculation (especially the peripheral microcirculation) more generally, and especially in the context of the microvascular dysfunction.

35 In any of these embodiments said vessels may be superficial vessels.

- 35 -

In a further aspect the invention provides a method for treating or preventing dysfunction of the microvasculature in a vertebrate animal subject, said method comprising

transmitting ultrasound pulses into the subject from an ultrasound transducer that is applied to an external surface of the peripheral anatomy of the subject;

5 receiving reflections of the ultrasound pulses at the ultrasound transducer from at least one region containing at least one blood vessel of the minor peripheral vasculature, preferably a plurality thereof;

generating pulse-Doppler response signals from the reflections; and

10 processing the pulse-Doppler response signals to determine a characteristic of blood flow in the minor peripheral vasculature of the subject;

monitoring the characteristic of blood flow over time; and optionally

establishing a profile of said characteristic over time;

wherein the characteristic or the profile of said characteristic over time is indicative or predictive of dysfunction in the microvasculature or variation in said characteristic or a

15 profile of said characteristic over time is indicative or predictive of dysfunction in the microvasculature or is indicative or predictive of a change in the dysfunction of the subject's microvasculature;

diagnosing dysfunction of the microvasculature or determining the likelihood of dysfunction occurring in said subject or progressing in said subject and treating said

20 subject with a clinical intervention suitable for treating or preventing dysfunction of the microvasculature or reducing the likelihood of dysfunction occurring.

Clinical intervention suitable for treating or preventing dysfunction of the microvasculature may include anti-diabetic, antihypertensive, cholesterol lowering and lipid lowering

25 pharmaceutical treatments, angioplasty or bypass surgery and lifestyle changes (e.g. smoking cessation, calorie restricted diets and increased exercise).

The features described above in connection with the methods for monitoring or predicting the onset of and/or progression of dysfunction of the microvasculature and/or a response

30 to treatment thereof apply mutatis mutandis to this aspect.

In a further aspect the invention provides a method of surgery in a vertebrate animal, said method comprising monitoring microcirculation in the subject by

35 transmitting ultrasound pulses into the subject from an ultrasound transducer that is applied to an external surface of the peripheral anatomy of the subject;

receiving reflections of the ultrasound pulses at the ultrasound transducer from at least one region containing at least one blood vessel of the minor peripheral vasculature, preferably a plurality thereof;

- generating pulse-Doppler response signals from the reflections; and
 - 5 processing the pulse-Doppler response signals to determine a characteristic of blood flow in the minor peripheral vasculature of the subject;
 - monitoring the characteristic of blood flow over time; and optionally
 - establishing a profile of said characteristic over time;
- wherein variation in said characteristic or the profile of said characteristic over time is
- 10 indicative or predictive of a change in the microcirculation of the subject.

In a further aspect the invention provides a method of post-surgical treatment in a vertebrate animal, said method comprising monitoring microcirculation in a subject recovering from surgery by

- 15 transmitting ultrasound pulses into the subject from an ultrasound transducer that is applied to an external surface of the peripheral anatomy of the subject;
- receiving reflections of the ultrasound pulses at the ultrasound transducer from at least one region containing at least one blood vessel of the minor peripheral vasculature, preferably a plurality thereof;
- 20 generating pulse-Doppler response signals from the reflections; and
- processing the pulse-Doppler response signals to determine a characteristic of blood flow in the minor peripheral vasculature of the subject;
- monitoring the characteristic of blood flow over time; and optionally
- establishing a profile of said characteristic over time;
- 25 wherein variation in said characteristic or the profile of said characteristic over time is indicative or predictive of a change in the microcirculation of the subject

- The features described above in connection with the methods for monitoring microcirculation in a subject undergoing or recovering from surgery apply mutatis
- 30 mutandis to this aspect.

- In other aspects the dysfunction of interest may be considered minor vasculature dysfunction, e.g. as characterised by reduced or irregular blood flow in the minor vasculature. The above discussion with respect to microvasculature dysfunction applies
- 35 mutatis mutandis to such aspects, but any reference to microvascular or the like should be replaced by minor vasculature or the like as appropriate in the context.

- 37 -

Features of other aspects disclosed herein may be features of embodiments of these aspects also.

5 In some embodiments of any of the aspects disclosed herein the ultrasound transducer may comprise a heater, such as an electrical heating element or filament, or an infrared light source. This can prevent vasoconstriction of blood vessels due to cold, and therefore provide more accurate or consistent measurements of the characteristic of blood flow.

10 From a further aspect, the invention provides a medical ultrasound transducer comprising:
an ultrasound transducer element for transmitting ultrasound signals into a region of tissue of a vertebrate animal subject; and
a heater, distinct from the ultrasound transducer element, for heating said region of tissue.

15 Features of other aspects and embodiments may be combined with this aspect.

The ultrasound transducer may comprise a thermostat for maintaining a target temperature in, or adjacent, said region of tissue. The ultrasound transducer may comprise control circuitry for controlling the heater—e.g. based on signals from the
20 thermostat. The ultrasound transducer may be configured to receive an electrical current and/or signal from a controller, e.g., over an electrical lead, which may be used to control the heater. The ultrasound transducer may be configured to send a signal from the thermostat to a controller.

25 In some embodiments of any of the aspects disclosed herein the ultrasound transducer may comprise a force sensor. The ultrasound transducer or a separate controller may comprise a detector configured to process signals from the force sensor to determine when a contact force between the ultrasound transducer and the subject exceeds a threshold level. This can be useful to prevent restricting blood flow due to excessive
30 pressure from the ultrasound transducer, and therefore provide more accurate or consistent measurements of the characteristic of blood flow. Small vessels close to the skin are especially vulnerable to compression.

From a further aspect, the invention provides a medical ultrasound system comprising:
35 an ultrasound transducer comprising i) an ultrasound transducer element for transmitting ultrasound signals into a vertebrate animal subject, and ii) a force sensor for measuring a contact force between the ultrasound transducer and the subject;

a detector configured to detect when the contact force between the ultrasound transducer and the subject exceeds a threshold; and

an alert subsystem configured to output an alert when the contact force between the ultrasound transducer and the subject exceeds a threshold.

5

Features of other aspects and embodiments may be combined with this aspect.

The force sensor may use any appropriate sensor technology. It may comprise conductive rubber or plastic with electrodes embedded in the rubber or plastic, or it may comprise a strain gauge or a piezoelectric sensor.

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The detector may be part of a controller as described elsewhere herein, or it may be built into the ultrasound transducer—e.g., inside a housing of the ultrasound transducer.

The alert subsystem may be part of the ultrasound transducer. For example, the ultrasound transducer may conveniently comprise a light, a sounder, or other output for alerting the user when the contact force exceeds a threshold. Alternatively, the alert subsystem may be separate from the ultrasound transducer—e.g., comprising a software app on a user's smartphone that is configured to notify the user when the contact force is too high.

20

The various characteristics of blood flow which may be monitored in accordance with aspects of the invention may include Pulsatile index (PI), Resistivity Index (RI), velocity, Max velocity (Vmax), Mean velocity (Vmean) and the Velocity Time Integral (VTI) (velocity area-under the curve), end diastolic velocity, peak diastolic velocity. In certain embodiments these metrics may be combined with other circulatory metrics, e.g. blood pressure (arterial, venous, diastolic, systolic) to form an index or a derivatised metric in order to better resolves trends and patterns. Such indices are considered characteristics of blood flow which may be monitored in accordance with aspects of the invention. In some contexts it may be advantageous to measure blood flow velocity and blood pressure (e.g. arterial blood pressure) concurrently and monitor an index of blood pressure/velocity as the characteristic of blood flow in accordance with the invention.

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Some or all of the characteristics of blood flow recited herein may exhibit periodic behaviour in accordance with the heartbeat of the subject and in accordance with respiration rate. In certain embodiments oscillations or periodic patterns in these basic characteristics, having frequencies that do not correlate with the subject's heart rate or

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respiration rate (i.e., that are higher or lower in frequency than the heart rate or respiration rate), may be the profile of said characteristic over time which is established and used as the basis for the methods for monitoring for or predicting the onset or progression of a disease or pathological condition and/or a response to treatment in accordance with aspects of the invention. The frequency of said oscillations may be, for example, 0.005-0.5 Hz, e.g. 0.008-0.5, 0.01-0.5, 0.015-0.5, 0.02-0.5, 0.025-0.5, 0.03-0.5, 0.035-0.5, 0.04-0.5, 0.045-0.5, 0.05-0.5, 0.055-0.5, 0.06-0.5, 0.065-0.5, 0.07-0.5, 0.075-0.5, 0.08-0.5, 0.085-0.5, 0.09-0.5, 0.095-0.5, 0.1-0.5, 0.2-0.5, 0.3-0.5, 0.4-0.5, 0.005-0.008, 0.005-0.01, 0.005-0.015, 0.005-0.02, 0.005-0.025, 0.005-0.03, 0.005-0.035, 0.005-0.04, 0.005-0.045, 0.005-0.05, 0.005-0.055, 0.005-0.06, 0.005-0.065, 0.005-0.07, 0.005-0.075, 0.005-0.08, 0.005-0.085, 0.005-0.09, 0.005-0.095, 0.005-0.1, 0.005-0.15, 0.005-0.2, 0.005-0.25, 0.005-0.3, 0.005-0.35, 0.005-0.4, or 0.005-0.45 Hz. Any and all ranges which may be derived from any of the range endpoints recited above are expressly contemplated. In infant subjects the frequency of interest may be around 0.08 Hz, e.g. 0.01 to 0.2, 0.02 to 0.18, 0.03-0.16, 0.04-0.14, 0.05-0.12, 0.06-0.1, or 0.07-0.09 Hz. Any and all ranges which may be derived from any of the range endpoints recited above are expressly contemplated. For adults the frequency of interest may be around 0.02, e.g. 0.005-0.1, 0.008-0.08, 0.01-0.06, 0.012-0.05, 0.014-0.04, 0.016-0.03, 0.018-0.025 or 0.019-0.022 Hz. Any and all ranges which may be derived from any of the range endpoints recited above are expressly contemplated.

These oscillations in blood flow are referred to in the art as flowmotion or flow oscillations and are believed to arise via the effects of vasomotion: the oscillation in tone of blood vessels. Vasomotion, or at least certain elements thereof, may follow physiological rhythms, and may vary in different vascular beds in healthy subjects. Local cellular mechanisms in the vessel wall and autonomic neural activity both contribute to the phenomenon. Organ metabolic needs may also influence vasomotion. In the brain, such oscillations may be associated with or arise from cerebral haemodynamic autoregulation. There is evidence that vasomotion is altered under pathological conditions, including circulatory failure, hypertension and diabetes mellitus, and in sick infants more generally. The oscillations in blood flow characteristics which may be used in accordance with the invention (e.g. those which are associated with or arise from vasomotion oscillations and/or cerebral haemodynamic autoregulation) may be determined from readings of the above mentioned characteristics over time by the Fourier transformation (e.g. Fast Fourier transformation) or complex demodulation of such readings. This is well described in the art. Inter alia, the frequency and/or amplitude of these oscillations may be determined and used as the characteristic of blood flow, or profile thereof, monitored in accordance

with the invention. In certain embodiments such information, and/or the blood flow characteristics or profiles thereof per se, may be used together with blood pressure measurements, e.g. arterial blood pressure measurements.

5 In certain embodiments the characteristic of blood flow which may be monitored in accordance with aspects of the invention may be a secondary characteristic which arises during or following a dynamic physical procedure performed by the or on the subject. In these contexts variation in a primary characteristic of blood flow (e.g. Pulsatile index (PI), Resistivity Index (RI), velocity, Max velocity (Vmax), Mean velocity (Vmean), Velocity
10 Time Interval (VTI), end diastolic velocity, peak diastolic velocity during or following the procedure compared to the primary characteristic in the subject prior to the procedure (e.g. the extent of variation upon commencement or the recovery of the primary characteristic to baseline) is monitored. Dynamic procedures may be devised by the skilled person without undue burden. Merely as examples dynamic tests may include in
15 following: valsalva manoeuvre, forced respiration test, static handgrip exercise, cold pressor test, leg-rise test and passive elevated arm test. More specifically, the dynamic procedure may investigate maximal relative variations of PI (or any of the above variables) between measurement at rest (e.g. 30 sec), measurement with passive elevated arm (e.g. 30 sec) and measurement at rest (e.g. 30 sec). Time to return to baseline may also be
20 measured. PI (or other variable) Normalisation-time: measurement of the PI (other variable) on the hand at rest, during leg-rise-test (e.g. 1, 2 or 5 minutes) and again at rest. Time to return to baseline is measured. Maximal relative variations of mean velocity between measurement at rest, measurement during leg-rise-test (e.g. 1, 2 or 5 minutes) and again at rest. Time to return to baseline may also be measured.

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The subject may be any human or a non-human vertebrate, e.g. a non-human mammal, bird, amphibian, fish or reptile. In a preferred embodiment the subject is a mammalian subject. The animal may be a livestock or a domestic animal or an animal of commercial value, including laboratory animals or an animal in a zoo or game park. Representative
30 animals therefore include dogs, cats, horses, pigs, sheep, goats and cows. Veterinary uses of aspects of the invention are thus covered. The subject may be viewed as a patient. Preferably the subject is a human.

In certain embodiments the subject is a human adolescent or adult and in such subjects
35 the following blood vessels typically have the following lumen diameters: elastic arteries (greater than about 10 mm); muscular arteries (about 0.5 mm to about 10 mm); arterioles (about 30 μm to about 500 μm), metarterioles (about 15 μm to about 30 μm) capillaries

(about 1 μm to about 15 μm); venules (about 15 μm to about 500 μm), small veins (about 0.5 mm to about 10 mm); large veins (greater than about 10 mm).

- In a further aspect the clinical methods described above may comprise a further step of therapeutically treating said subject in a manner consistent with the assessment, diagnosis, prediction, prognosis made in order to alleviate, reduce, remedy or modify at least one symptom or characteristic of the disease/condition of interest (including the more specifically defined embodiments thereof) or to improve, mitigate, alleviate, reduce, remedy or modify the predicted clinical outcome or to accommodate the predicted clinical outcome, e.g. by providing palliative care. Such treatments may include administering a pharmaceutical composition, performing a surgical procedure, performing physiotherapy, and/or making lifestyle changes appropriate to treat the disease/condition of interest and/or alter or accommodate the predicted clinical outcome and/or adjusting the lifestyle of the subject in a manner appropriate to treat the disease/condition of interest or accommodate the predicted clinical outcome. In this regard, the invention can be considered to relate to methods for the therapeutic treatment of a disease/condition of interest (including the more specifically defined embodiments thereof) and for guiding and/or optimising such treatments.
- "Treatment" when used in relation to a disease or medical condition in a subject in accordance with the invention is used broadly herein to include any intervention which has a therapeutic effect, i.e. any beneficial effect in relation to the disease or on the condition. Thus included are pharmaceutical and surgical interventions but also lifestyle changes and physiotherapies. Thus, not only included are interventions which eradicate or eliminate the disease or condition, but also which provide an improvement in the disease or condition of the subject. Thus included for example, is an improvement in any symptom or sign of the disease or condition, or in any clinically accepted indicator of the disease or condition. Treatments thus includes both curative and palliative therapies
- "Response to treatment" includes any observable therapeutic effect, i.e. any beneficial effect in relation to the infection or on the condition. Thus, not only included is eradication or elimination of disease/condition, but also an improvement in the disease/condition of the subject. Thus included for example, is an improvement in any symptom or sign of the disease or condition, or in any clinically accepted indicator of the disease/condition. A response to treatment might, conversely, be expressed in terms of the lack of an observable therapeutic effect or limited therapeutic effect.

"Prevention" as used herein refers to any prophylactic or preventative effect. It thus includes delaying, limiting, reducing or preventing the disease/condition or the onset of the disease/condition, or one or more symptoms or indications thereof, for example relative to the disease/condition or symptom or indication prior to the prophylactic treatment.

5 Prophylaxis thus explicitly includes both absolute prevention of occurrence or development of the disease/condition, or symptom or indication thereof, and any delay in the onset or development of the disease/condition or symptom or indication thereof, or reduction or limitation of the development or progression of the disease/condition or symptom or indication thereof.

10

"Monitoring or predicting the onset or and/or progression of a disease or pathological condition" includes diagnostic and prognostic aspects. This may include concluding that a subject has a disease/condition and/or establishing the severity thereof. It may also include determining the likelihood (assessing the risk) of a disease/condition developing in

15 a subject or progressing or the rate at which progression will take place.

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Features of any aspect or embodiment described herein may, wherever appropriate, be applied to any other aspect or embodiment described herein. Where reference is made to different embodiments or sets of embodiments, it should be understood that these are not necessarily distinct but may overlap.

BRIEF DESCRIPTION OF THE DRAWINGS

Certain preferred embodiments of the invention will now be described, by way of example only, with reference to the accompanying drawings, in which:

25

Figure 1 is a diagram of an ultrasound monitoring system embodying the invention;

Figure 2 is a schematic diagram of functional elements of the monitoring system;

Figure 3 is a schematic diagram of a first embodiment of an ultrasound transducer;

Figure 4 is a schematic diagram of a second embodiment of an ultrasound transducer;

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Figure 5 is a simplified cross-section through a blood supply system and an ultrasound transducer;

Figure 6 is a simplified cross-section with the ultrasound transducer in a first orientation;

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Figure 7 is a simplified cross-section with the ultrasound transducer in a second orientation;

Figure 8 is a first screenshot of a display output from the ultrasound scanning system showing detailed information of neonatal cerebral circulation at a first depth;

Figure 9 is a second screenshot of a display output from the ultrasound scanning system showing detailed information of neonatal cerebral circulation at a second depth;

Figure 10 is a schematic diagram of a fastener for a patient's digit, embodying the invention, not applied to a patient;

5 Figure 11 is a schematic diagram of the fastener for a patient's digit, applied to a patient's big toe;

Figure 12 is a ghosted diagram of the fastener applied to the patient's big toe;

Figure 13 is a schematic diagram of a text set-up used to characterise different ultrasound transducer materials for transducers for use in systems embodying the
10 invention;

Figure 14 is a plan-view schematic diagram of a circular ultrasound transducer element for use with embodiments of the invention;

Figure 15 is a plan-view schematic diagram of a rectangular ultrasound transducer element for use with embodiments of the invention;

15 Figure 16 is a circuit diagram of tuning circuitry in an ultrasound transducer for use with embodiments of the invention;

Figure 17A is an exploded ghosted projection view of an ultrasound transducer for use with embodiments of the invention;

Figure 17B is a vertical cross-sectional view of the ultrasound transducer;

20 Figure 17C is a ghosted side view of the ultrasound transducer;

Figure 18 shows two horizontally-aligned plots of measured electrical impedance (magnitude and phase against frequency) of three piezoelectric materials;

Figure 19 shows two horizontally-aligned plots of measured electrical impedance (magnitude and phase against frequency) of three piezoelectric materials within
25 respective completed transducer assemblies;

Figure 20 shows beam profiles of two different transducers;

Figure 21 is a plot of amplitude against time for envelopes of received echoes with five different transducers;

Figure 22 is a plot of power against frequency for received echoes with the five
30 different transducers;

Figures 23a and 23b are graphs of flow velocity in the radial artery of a test subject taken every 5 minutes using laser Doppler fluxometry, pulse-Doppler and unfocussed ultrasound Doppler recordings and the correlation between the laser Doppler fluxometry and unfocussed ultrasound Doppler recordings;

35 Figure 24 shows Dresponse curves for HR, MAP, Doppler flow of the radial artery, skin pulp blood flow measured with laser Doppler fluxometry and unfocussed ultrasound Doppler upon cold induction test;

Figure 25 shows peripheral blood flow during constriction of the arterioles in the fingers of patients undergoing a cold pressor test recorded with 3 different techniques: 1) conventional Doppler measuring blood flow in the radial artery in the lower arm; 2) unfocused Doppler ultrasound in accordance with the invention measuring flow in arterioles and small arteries feeding the arterioles of the finger from at least 2mm depth; and 3) laserDoppler measuring microcirculation in a thin layer of the skin within 2mm of the surface; and

Figure 26 shows angiogram/CT scans of the iliac artery of a patient presenting with claudication (microvasculature dysfunction) and screenshots of a display output from an unfocused ultrasound scanning system embodying the invention showing blood flow velocity traces from the minor vasculature of the pulp of the patient's big toe before angioplasty (A and D; stenosis highlighted by arrow) after angioplasty of a first stenosis in the iliac artery (B and E), before angioplasty of a second stenosis in the iliac artery (C; stenosis highlighted by arrow), and after angioplasty of the second stenosis (F). Blood flow velocity in the minor vasculature of the toe increases following each surgical intervention indicating the surgical intervention has improved microvascular dysfunction in this patient.

Figure 27 shows angiogram/CT scans of the thigh and leg arteries of a patient with diabetes and an associated foot ulcer (microvascular dysfunction) and screenshots of a display output from an unfocused ultrasound scanning system embodying the invention showing combined Doppler signals obtained from a range of depths (approx. 2-15 mm) and velocity traces obtained from different sub-ranges within that range in the minor vasculature of the pulp of the patient's big toe before angioplasty (A) and after angioplasty (B). It was not possible to obtain stable blood flow readings from the minor vasculature of the patient prior to angioplasty (i.e. state of microvascular dysfunction) but, in contrast, robust and stable readings were seen following angioplasty (i.e. following normalisation of microvascular dysfunction).

DETAILED DESCRIPTION

Figure 1 shows a medical-ultrasound monitoring system 1, including an ultrasound transducer 2, a controller 3, an interaction terminal 3a, and a display device 4, for us in monitoring blood flow within a human or animal subject 5.

The ultrasound transducer 2 is connected to the controller 3 by a wire. The controller 3 is connected to the interaction terminal 3a and to the display device 4. The interaction terminal 3a may comprise a laptop computer and/or a control panel comprising a

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keyboard or trackball. The interaction terminal 3a may have its own display screen (e.g., where it is a laptop computer), however this is primarily for use by a researcher or administrator. In normal use, display output to a clinician will be shown on the display device 4, which may be an LCD monitor.

5

The transducer 2 contains a single piezoelectric transducer element. In use, the transducer 2 transmits a succession of ultrasonic plane-wave pulses and receives reflections of the waves, at the same transducer element, under the control of the controller 3. The transducer 2 can be fastened to a subject 5 by one or more straps,
10 adhesive pads, clips, etc.

The transducer 2 can be fastened to a subject 5 by a clinician or technician and then left unattended for a period of minutes, hours or days, during which the monitoring system 1 monitors and records and/or analyses blood flow within the subject 5. The monitoring
15 system 1 may output data such as a real-time plot of a blood flow curve from a particular region within the subject 5 on the display 4. It may also signal an alert if a predetermined criterion is met, such as if the blood flow drops rapidly. The alert may show on the display 4 (e.g., comprising a textual message or numerical value, or a flashing icon), or by another visual means (e.g., a strobe light), or audibly (e.g., from a siren or loudspeaker),
20 or be sent to another device over a network connection, or a combination of these.

Various embodiments of the system 1 can, for example, be used to monitor cerebral circulation in a premature baby, or to monitor peripheral circulation after an operation, or for many other situations where changes in blood flow can provide a useful indication of
25 the clinical condition of the subject 5.

Figure 2 shows more details of the system 1. The controller 3 contains a central processing unit (CPU) 6. This CPU 6 may include one or more processor chips, microcontrollers, DSPs, FPGAs and/or other processing means. A transmit/receive switch
30 unit 7 in the controller 3 is connected to the transducer 2. This switch unit 7 can switch between a transmitting mode and a receiving mode, under control of software executing on the central processing unit 6. The switch unit 7 passes electrical signals representing received ultrasonic reflections to a low-noise amplifier (LNA) 8 in the controller 3, which amplifies the received reflection signals. The LNA 8 outputs to an analogue-digital
35 converter (ADC) 9 in the controller 3, which samples and digitises the received reflections from each pulse. The system 1 also includes memory (not shown) storing software

instructions for execution by the CPU 6, and for storing data representing received data and the results of computations performed by the CPU 6.

In use, the transducer 2 can be controlled by the CPU 6 to transmit plane wave pulses
5 (e.g., pulses one microsecond long) at a predetermined carrier frequency (e.g., 8 or 16 MHz) and at a predetermined pulse repetition rate (e.g., 10 kHz). The switch unit 7 switches between a transmitting mode and a receiving mode, at the repetition rate (e.g., 10 kHz), in order to receive echoes from each pulse at the transducer 2. The frequency spectrum of the received reflections will depend on the range of movement of tissue,
10 relative to the transducer 2, in the regions within the subject 5 that are covered by the transmit and receive beams of the transducer 2. In contrast to conventional array-based beam-forming transducers, the single transducer element here gives a substantially cylindrical transmit beam, and a receive beam that is coincident with the transmit beam.

15 From the ADC, the sampled reflections (pulse-Doppler response signals) pass to a filter and complex demodulator unit 10 which bandpass filters and demodulates the digitised signals. The demodulated pulse-Doppler response signals are then sent to the CPU 6 for processing.

20 The CPU 6 may calculate measures related to the blood flow, and send data related to the blood flow to the display device 4 (which may be separate from the controller 3, or may be integral to it), via an input/output (I/O) unit 11, for displaying to a user. The CPU 6 may analyse blood flow at just one depth range, or at multiple different depth ranges simultaneously.

25

In an alternative embodiment, the demodulated pulse-Doppler response signals are passed directly to an external output device (which could be a mobile telephone or tablet computer, or a networked server) via the input/output (I/O) unit 11, and the external output device can analyse the response signals. The I/O unit 11 may comprise a wireless-
30 communication unit, such as a Bluetooth™ radio. The external output device may store and/or display derived metrics from the response signals.

In some embodiments, the ultrasound transducer 2 may be integrated with the controller 3 in a common housing, rather than being connected by a wire. The controller 3 may then
35 conveniently be very compact. It may be battery powered. In this way, the combined controller 3 and transducer 2 form a highly portable sensor unit. The sensor unit

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preferably transmits demodulated signals to a separate output device, for processing; this allows the controller 3 to have a relatively basic CPU 6, allowing it to be made at low cost.

5 The CPU 6 and/or an external output device may process the demodulated response signals to obtain values related to blood flow within the subject 5 using some of the techniques described below.

10 The interaction terminal 3a may be used by an operator to control the ultrasound transmission and processing, or to control the processing and display of information, or to configure alerts, or to perform any other actions. The terminal 3a may be a permanent part of the system 1, or it may be used only during a configuration or initialisation phase, and removed once the system 1 is in a monitoring phase.

15 Some embodiments may also dispense with the display 4, and instead output audible alerts (e.g., from a loudspeaker), or send data over a network connection to a central interface system, e.g., located at a nurses station remote from the subject 5.

20 Figure 3 shows the transducer 2 in more detail. A metal or plastic housing 30 contains a piezoelectric transducer element 31. The transducer element 31 may be a circular disc or may be rectangular, or any other appropriate shape. It may be a ceramic transducer, made of PZT (lead zirconate titanate) or a PZT-epoxy composite. Single crystal technology may be used. The transducer element 31 is mounted between a backing layer 32 and an acoustic-impedance matching layer 33. Wires 34 lead from the transducer 2 towards the monitoring system 1. The transducer 2 may include an electrical-impedance
25 matching component 35 such as a helical coil. The transducer 2 is preferably wider than it is tall—e.g., approximately 10mm in diameter, width or length, with the housing 30 being approximately 8mm high (excluding any cable strain relief). This can reduce the chance of it being knocked when fastened to the subject 5.

30 Figure 4 shows a variant transducer 2', in which the primed reference numerals refer to corresponding features as the same-numbered labels in Figure 3. The principal difference, compared with the transducer 2 of Figure 3, is that the transducer element 31' is inclined, relative to the housing 30'. It may be inclined at any angle—e.g., 30 or 45 degrees from a planar window 40 defined by the base of the housing 30' (aligned with horizontal in the
35 Figure 4). Such a transducer 2' is useful for getting Doppler signals from blood vessels that are nearly parallel to the window 40, since the angle increases the component of motion perpendicular to the face of the transducer element 31'. In this example, the

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transducer element 31' is rectangular, 5mm x 16mm, and the height of the housing 30' is 8mm. However, any appropriate dimensions may be used.

5 In use, any void between the acoustic coupling layer 33 and the subject 5 will typically be filled with an acoustic gel, applied by the operator. The gel may, in some instances, be adhesive and may be sufficient to fasten the transducer 2, 2' to the subject 5. In other embodiments, a mechanical fastening is used.

10 Figure 5 shows a branching blood vessel system 50 in cross section. The blood vessel system 50 may be a few millimetres or a few centimetres below the surface of the skin of the subject 5. The ultrasound transducer 2 at the left side of Figure 5 is mechanically or adhesively fastened to the subject 5. It transmits plane wave pulses into the subject 5 in a substantially cylindrical beam (e.g., a circular cylinder or a rectangular cylinder, depending on the shape of the transducer element). The axis of the cylinder runs from left to right in
15 Figure 5. Returning reflections are sampled after each pulse. One sample is obtained for each of a set of cylindrical sample volumes 51a – 51k in the subject 5, with the delay after the transmission of the pulse determining how far each sample volume 51a – 51k is from the face of the transducer 2.

20 The transducer 2 is an unfocused transducer, without any acoustical lens. It has considerably larger dimensions than many prior-art focused transducers or array transducers—e.g. a circular disc with diameter 10 mm. It generates a uniform beam with substantially constant cross section in the depth direction—e.g. a cylindrical beam with diameter of approximately 10 mm, in the near field. The spatial sensitivity in receive is
25 also substantially coincident with the transmit beam, so that the cross-sectional area of the sample volume will be much larger, compared with a traditional focused or beam-formed receive beam—approximately 10 mm again. This means that the system 1 can capture blood flow signals from a much larger area than a focused single-element transducer or a beam-forming array transducer does. This means that the probe location
30 and orientation are less critical. A drawback with the broad beam compared to a focused beam, is that the signal from each individual blood cell becomes weaker. This introduces a limitation in the maximum depth that can be measured. Typically, range-gating will be used to limit response signals to regions that have a maximum distance from the transducer 2 that is in the same order of magnitude as a width of the transducer 2; for
35 example, 0.5cm to 4cm deep.

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Response samples from each pulse are collected, for each volume 51a – 51k, and are filtered and complex demodulated by the demodulator unit 10 to give a respective baseband pulse-Doppler response signal for each volume 51a – 51k.

- 5 By using a multi-gated Doppler technique, the response signal can be split into a large number of Doppler signals, each representing components of blood flow perpendicular to the ultrasound beam within a thin "slice" or volume 51a – 51k. The thickness d of the slices is given by the length of the transmitted pulse: $d = N * \lambda / 2$, where N is the number of periods in the transmitted pulse and λ is the ultrasound beam wavelength (e.g., 0.1 - 0.3 mm). Typical values for the thickness d are 0.15 mm to 1 mm (e.g., 0.5 mm). By frequency analysis of a series of the pulse-Doppler response signals from each volume 51a – 51k (for example, by fast Fourier transform), a Doppler frequency spectrum is obtained, where the power density of each frequency component is given by the number of blood cells with a specific velocity component perpendicular to the transducer 2. A new Doppler frequency spectrum may be calculated every 5 milliseconds, for example.

The size of the spatial sensitivity region (receive beam width), b , in conventional focused ultrasound is given by

$$20 \quad b = D * \lambda / A = D / Nw,$$

where D is distance from the transducer, λ is the wavelength (e.g., 0.1 - 0.3 mm), A is the size (diameter) of the transducer, and Nw is the size of the transducer in # wavelengths. Typically, $Nw = 20$ -100 in conventional focused systems.

25

In the present system 1, however, the receive beam width is approximately equal to the diameter, A , of the transducer 2. This may therefore be fifty times larger (2,500 times larger in area) than the receive spot size of a typical convention system.

- 30 By using a transducer 2 with only one element, rather than an array, which would typically have 100-200 elements, it is not possible to steer the focus. Traditionally, such a single-element Doppler instrument would be designed with an elongate focus, which is obtained by using a high f-number, i.e. the probe diameter A is substantially less than the intended focal depth D . The beam width in the focal point will then be $D * \lambda / A$, where λ is the ultrasound beam wavelength. Typical values for a 10 MHz probe would be $\lambda = 0.15$ mm, $D = 10$ mm, $A = 3$ mm, which would give a beam width of 0.45 mm. By instead using an unfocused, disc shaped transducer, without acoustical lens, having considerably larger

dimensions than in the prior art (e.g. a circular disc with diameter 10 mm), the present system 1 has a uniform transmit beam, with constant cross section in the depth direction. The spatial sensitivity in receive will also be constant within the beam width, so that the cross sectional area of the sample volume will be much larger, compared to a focused
5 beam.

For each volume 51a – 51k, the blood flow is analysed in aggregate for all the blood vessels that pass through that volume. The distribution of velocities may, in some cases, allow signals from different vessels to be distinguished from each other within one volume
10 (e.g., where there is some flow towards the transducer 2 and some flow away from the transducer 2). However, in general, unlike conventional Doppler flow analysis, where a single vessel is identified by an operator in a B-mode image, and the transmit and/or receive focus is then placed just on that vessel, for Doppler processing, in the present system 1, there is no two- or three-dimensional imaging and no focusing of a transmit or
15 receive beam on a particular vessel.

Figure 6 shows the transducer 2 in a first orientation, with an exemplary volume 51 (typically a shallow cylinder or cuboid) intersecting the blood vessel system 50. In the case, a strong Doppler-shifted signal will be detected from the two branching arterioles
20 that pass through the volume 51 substantially perpendicular to the face of the transducer 2.

Figure 7 shows the transducer 2 in a second orientation, with a different exemplary volume 51' intersecting the blood vessel system 50 at a different angle. The same major
25 vessels (which account for the majority of the blood flow) are intersected in the first and second orientations. The steeper angle means that the Doppler shifts will be of lower amounts, but the larger length of the main vessels within the volume 51' mean that a stronger signal may be received. Where it is desired to monitor vessels that are nearly parallel to the front window of the transducer, a transducer 2' with an inclined element 31',
30 as shown in Figure 4, may be preferable.

Figure 8 is a screenshot of a graphical output that can be displayed on the display screen 4, showing the results of processing, by the CPU 6, of the Doppler response signals.

35 The data in Figures 8 and 9 relate to the cerebral circulation of a baby. However, the same user-interface may equally be used when monitoring other types of patient and other blood vessels, such as when monitoring adult peripheral circulation.

An upper rectangle 80 contains a plot of the power-weighted mean frequency, at different depths, over time. The vertical axis represents depth from the front of the transducer 2, here ranging from 0mm to 35mm. The horizontal axis represents time from the start of a receive buffer, and, in this example, ranges from 0 to 7 seconds. The plot is updated at regular intervals. Each pixel represents a depth range (corresponding to a particular sample volume 51a – 51k as shown in Figure 5) over a unit of time. In the original output, each pixel is shaded in red, blue or white, where red indicates that all of the Doppler response signal (after appropriate filtering) at that depth range was positively shifted, indicating flow towards the transducer 2; blue indicates that all of the Doppler response signal (after appropriate filtering) was negatively shifted, indicating flow away from the transducer 2; and white indicates both positive and negative frequency shifts, indicating that the region contains at least one vessel portion carrying blood towards the transducer and at least one other vessel portion carrying blood away from the transducer. In the period shown in Figure 8, the original colour output is broadly orange, with variation between lighter and darker shades of orange. It will be appreciated that the Doppler response signal may first be filtered to remove contributions from stationary or near-stationary tissue (clutter filtering), using standard techniques. The intensity of each pixel represents a power-weighted mean frequency at the respective depth range and time period; this may be calculated from a Fourier transform of the response signals, or, more efficiently, by using autocorrelation to calculate the first moment of the power spectrum. Black therefore represents zero flow (any movement is under the noise floor).

The upper rectangle 80 effectively presents a one-dimensional “image” of the blood flow at different depths from the transducer 2, over time. This allows an operator who understands the anatomy of the subject 5 to position the transducer 2 so that one or more vessels of interest are within the transmit and receive beam, and to verify visually from the plot that proper alignment has been achieved.

A lower rectangle 81 contains a velocity spectrum, which shows velocity, here ranging from -25 cm/sec to +25 cm/sec, against time, here ranging from 0 to 7 seconds. The grayscale intensity at each pixel represents the signal strength in the respective velocity bin at the respective time interval. Positive and negative envelope traces are automatically calculated, based on a threshold minimum velocity-signal strength, and can be included on the plot, as shown by the upper (originally red) and lower (originally blue) lines, respectively, in Figure 8. The velocity spectrum can be derived from the Fourier frequency spectrum, because frequency and velocity are linearly related by the Doppler equation:

$\Delta f = 2 \cdot f_0 \cdot v \cdot \cos(\theta) / c$. where Δf is Doppler shift frequency, f_0 is the ultrasound transmission frequency, v is the blood cell velocity, $\cos(\theta)$ is the cosine of the angle between the ultrasound beam and the flow direction, and c is the speed of sound in soft tissue. It will be appreciated that “velocity”, “frequency shift” and “frequency” (e.g., at
5 baseband) can therefore be used interchangeably, and the use of one of these terms herein should be seen, wherever appropriate, as also extending to an equivalent expression using one of the other terms—e.g., a reference to a “velocity spectrum” also encompasses a “frequency spectrum”.

10 The velocity data in the lower rectangle 81 is generated from the Doppler response signals at a particular depth range. This depth range may be specified by an operator or may be identified automatically by the system 1 (e.g., based on an automated comparison of respective quality values, as described below, for respective depths from a set of depths).

15

In Figure 8, the operator has move and sized a rectangular selection marker 82 on the upper rectangle 80 to provide an input to the system 1 of the range of interest for the velocity plot in the lower rectangle 81. The size and location of the selection marker 82 can be adjusted by the operator. In this example, it indicates a depth range of 10mm to
20 15mm.

To the right of the screenshot, a panel 84 provides values of Vmax, Vmean, VED, PI, RI, HR and a Quality value, independently for the positive frequency spectrum and the negative frequency spectrum in the range of interest. Each of these values is a
25 characteristic of blood flow in the region of interest. These values are calculated for every valid heartbeat in the seven-second time buffer of the velocity plot. The CPU 6 first generates the envelope traces (applying a threshold to identify velocity signals that have a strength are above a minimum floor), representing the spatial-maximum of velocity, in each direction, over the depth range of interest in each time period (e.g., every 5
30 milliseconds). It then identifies rising edges by applying a gradient threshold to the envelope traces over a minimum time period. These provide candidate heartbeats. The CPU 6 then compares successive heartbeats by autocorrelation of the envelope signals and generates a percentage quality value for each heartbeat based on how similar it is to the preceding heartbeat. This quality value may be derived from the height of a peak in
35 the autocorrelation, or in any other appropriate way. Candidate heartbeats below a threshold quality are excluded from the calculations. The values of Vmax, Vmean, VED, PI, RI, HR and Quality are then calculated for each valid heartbeat and are then averaged

over the seven-second time buffer, using only those heartbeats that meet the quality threshold. Vmax is the maximum trace velocity over the valid heartbeats. Vmean is the mean trace velocity over time. VED is the end diastolic trace velocity, averaged over the valid heartbeats. PI is the pulsatility index. RI is the resistance index. HR is the heart rate
5 in beats/minute. The Quality measure is a percentage value which is an average of the individual heartbeat Quality values over all of the valid heartbeats in the seven-second time buffer.

Of course, other durations of time buffer may be used – e.g., anywhere between 5 – 60
10 seconds, and other derived values may be displayed, including first or second order statistics of any of the parameters detailed above.

The lower velocity plot 81 in Figure 8 shows a strong signal flowing towards the transducer 2, from one or more arteries, and a weaker venous signal from blood flowing
15 away from the transducer 2. This is consistent with the generally orange shade in the original colour upper depth plot 80 at the depth range of interest, formed of a mix of red pixels (flow only towards the transducer 2) and some white pixels (flow in both directions).

This ability to distinguish flow in both directions, in the upper plot 80, from zero flow may
20 be especially useful to the clinician. By contrast, conventional colour Doppler plots are based on the mean velocity, averaged over all frequency shifts, positive and negative. Such a mean velocity value cannot discriminate between bidirectional flow, and zero or low flow. This is not normally a problem in conventional Doppler scans, because the receive beam is focused on a single vessel. However, in the context of the broad,
25 unfocused receive beam of the present system 1, which will typically capture signals from multiple vessels, the display methodology described here is extremely valuable.

Figure 9 shows the same data in the upper plot 80, but here the operator has set the rectangular selection marker 82 deeper and to a smaller range—approximately 23 –
30 26mm. The velocity plot 81 shows that the vessels at this depth exhibit a similar heartbeat cycle to those in Figure 8, but with a higher Vmax systolic velocity and a lower VED end diastolic velocity.

The controller 3 may be configured to test calculated values (e.g., a succession of Vmax
35 values) against an alert criterion. It may do this repeatedly at intervals. It may signal an alert if, for example, Vmax falls below a preset threshold and/or falls or rises faster than a

preset gradient. In some embodiments, a detailed display similar to that of Figure 8 need not be provided, and instead a simpler alert system may be provided.

5 In some embodiments, the controller 3 calculates a Fourier transform of V_{max} (e.g., by fast Fourier transform) to identify different frequency components in V_{max} . It may monitor one or more frequency components or ranges outside the normal heartbeat. It may signal an alert if such a frequency component satisfies an alert condition, such as diminishing in intensity below a preset level or faster than a preset rate.

10 Figure 10 shows a digit clip fastener 170 for attaching an ultrasound transducer, similar to the transducer 2 of Figure 3 (albeit potentially minus the housing 30) to a digit—i.e., a finger or toe—of a human or animal subject. This can be useful for monitoring purely the microcirculation, since the fingers and toes contain only minor arteries.

15 The clip fastener 170 comprises an upper jaw 171 and a lower jaw 172, connected by a sprung hinge 173. The upper and lower jaws 171, 172 define a proximal opening 174 which is urged shut by the sprung hinge 173. An electrical lead 175 extends from the clip fastener 170 for connecting the clip fastener 170 to a controller 3.

20 Figure 11 shows the clip fastener 170 in position on a big toe 180 of a human subject's right foot.

Figure 12 shows the position of a single-element ultrasound transducer 2 inside the lower jaw 172 of the clip fastener 170. The transducer 2 is positioned so as to contact the skin of
25 a digit inserted in the clip fastener 170, and the system 1 can control the ultrasound transmission and reception so as to monitor blood flow within part or all of a cylindrical region 190 in front of the transducer 2.

The sprung hinge 173 is preferably designed to apply sufficient pressure to keep the clip
30 fastener 170 from becoming easily dislodged, but not so much pressure that the microvessels are constricted.

In some embodiments, the clip fastener 170 may have a force sensor (not shown) within the upper or lower jaw 171, 172 which measures a contact force between the jaw 171,
35 172 and the digit. This may allow an operator to adjust the tension in the sprung hinge 173 to an optimal level.

In some embodiments, the clip fastener 170 has an electrical heating element (not shown) within the lower jaw 172, adjacent the ultrasound transducer 2. It may also have a thermometer for measuring temperature adjacent the digit. Signals may be sent over the lead 175 to and from the controller 3 for controlling the heating element so as to maintain
5 a temperature within a desired range so as to avoid temperature-induced vasoconstriction in the digit.

Figures 13 to 22 relate to an experimental set-up of a transducer system embodying the invention, and results obtained therefrom. The results compare the performance of
10 various different piezoelectric materials that may be used in the piezoelectric transducer element of the system. As explained below, hard PZT materials—especially Pz24—have been found to be particularly effective, although other ceramic and/or polymer and/or composite piezoelectric materials may nevertheless be used in some embodiments.

15 The transducers that were tested are suitable for use in a system shown in Figure 1 & 2. However, for characterising the transducer 200 performance, experimental set-ups, such as the pulse-echo set-up shown in Figure 13, were used.

Fabricated transducers 200 were characterized by electrical impedance measurements,
20 acoustic beam profile measurements and acoustic pulse-echo measurements. Electrical impedance was measured in air and in water using a network analyzer (Rohde & Schwarz ZVL, Munich, Germany).

Two-way sensitivity of the transducers was investigated in a pulse-echo set-up of Figure
25 13. A single-element transducer 200 was connected to a controller 201 (a Manus EIM-A produced by Aurotech Ultrasound AS, Tydal, Norway). A computer 202 is connected to the scanner using an Ethernet network cable. The transducer 200 was directed towards an 18 mm diameter stainless steel sphere 203 positioned for maximal reflection, 157 mm from the transducer 200. The controller/scanner 201 was used to drive the transducer
30 200, and acquire the received echoes. Received pulses were transferred to the computer 202, to be stored and analyzed in Matlab.

Using another set-up (not shown), beam profiles were also measured, in an Onda AIMS III measurement tank (Onda Corp. Sunnyvale, CA), controlled by Onda AIMS Soniq 5.2
35 software. The transducers 200 were driven by a Panametrics 5052PR Pulser Receiver (Olympus Corp. Waltham, MA). The resulting sound beams were scanned laterally at a fixed distance, using an Onda HGL-0200 hydrophone with an AG-2010 Preamplifier,

calibrated in the frequency range 1 to 20 MHz. The output was digitized at 250 MSa/s in a Picoscope PS5244A analog to digital converter (Pico Technology, St Neots, UK), and digitized pulses transferred to a computer to be stored and analyzed in Matlab.

5 Three common piezoelectric materials were studied for use in pulsed wave Doppler ultrasound embodying the invention, where high sensitivity is required, while bandwidth is less important. A large transducer aperture, 80 mm², results in a low electrical impedance, making the transducers challenging to drive with conventional electronics and cables. Air-backed transducers with electrical tuning circuitry and cable assembly were made using
10 the piezoelectric materials Pz24, Pz27, and Pz29. Pz24 is a hard PZT, with dielectric constant of 240, the other materials are soft PZT with dielectric constants around 1000. It was found that the transducer made with Pz24 gave 2 dB better two-way sensitivity compared to those made with the other PZT-variants. The improved performance is explained by the higher electrical impedance from using Pz24.

15

Doppler measurements are a common diagnostic ultrasound technique used to detect blood flow or muscle movement. Echoes scattered by the red blood cells carry information about the velocity of the blood. These echoes are weak, so the transducer should have a high sensitivity, while a large bandwidth and short pulse length are less important. The
20 study described in the following paragraph compares a variety of possible single element ultrasound transducers optimized for high sensitivity and demonstrates the particular suitability of Pz24.

Three different piezoelectric materials were tested, Pz29, Pz27 and Pz24 (Meggitt A/S,
25 Kvistgaard, Denmark). Soft piezoelectrics, e.g. Pz29 and Pz27, having large dielectric constant ϵ_r , are commonly used in medical ultrasound applications. However, for a single-element Doppler transducer having a large aperture area, embodying the present invention, the resulting high capacitance and low impedance may be hard to drive electrically, especially through a long, thin cable. Hence, for this particular application, a
30 hard piezoelectric with lower ϵ_r , e.g. Pz24, might be preferred.

All transducers in the study were designed for an 8 MHz centre frequency. The transducer designs were optimised for high sensitivity with less requirements to the bandwidth, so a solution with one acoustic matching layer in front and air backing was chosen. The
35 matching layer thickness was set to be a quarter of the wavelength in the matching layer material. Two different geometries were investigated, one rectangular and one circular.

The active element of the rectangular transducers was 16 mm by 5 mm, while that of the circular transducers was 10 mm diameter, giving equal active aperture areas.

Piezoelectric materials with high coupling coefficients were selected to achieve high sensitivity. Conventional soft PZT materials, Pz27 and Pz29 were chosen due to their frequent use in medical ultrasound transducers. However, for a 8 MHz centre frequency the surface area 80 mm² is large. This gives a low electrical impedance, which making the active elements hard to drive. To investigate the effect of this, a “hard” PZT material, Pz24, with low dielectric constant, was also tested. A list of the central material properties is given in the following table.

Property	Unit	Pz24	Pz27	Pz29
Electromechanical coupling coeff. k_t	(-)	0.508	0.469	0.524
Piezoelectric constant d_{33}	pC/N	149	425	574
Clamped dielectric constant $\epsilon_{33r}^S/\epsilon_0$	(-)	239	914	1220
Dielectric Loss $\tan\delta$	(-)	0.002	0.017	0.016
Density	kg/m ³	7700	7700	7460
Longitudinal wave velocity	m/s	4851	4331	4498
Characteristic acoustic impedance	MRayl	37.35	33.35	33.56

An electrical tuning network was implemented to match the electrical impedance to 50 Ω . The one-dimensional Mason model was used to design models for encapsulation of the transducers.

15

The piezoelectric plates and discs came polarized in the thickness direction and had silver painted electrodes. A matching layer of Eccosorb MF112 (Laird N.V. Geel, BE) was lapped down to the desired thickness. The matching layer was made larger than the piezoelectric, to act as support when mounting the transducer in the housing. This allows the piezoelectric element to be air-backed and have unclamped edges.

20

After lapping, the matching layer was covered with a tape-mask, sputtered with a seed layer of chrome to promote adhesion, before sputtering on a conductive layer of gold. The PZT was bonded to the sputtered matching layer using epoxy (Scotch-Weld Epoxy Adhesive DP460, 3M, Maplewood, MN). Conductive silver epoxy was used to connect wires to the electrode on the back of the PZT and to the gold sputtered on the matching layer. Silver epoxy was chosen to allow easy assembly and avoid localized heating from a soldering iron, which could cause de-poling.

25

Figure 14 shows a circular transducer 210 having an active piezoelectric element 213 of 10 mm diameter and a matching layer which has a sputtered surface 212 and an unsputtered surface 213. Wires were bonded using silver epoxy at two bonding points
5 214.

Figure 15 shows a rectangular transducer 220 having a 5 mm x 16 mm rectangular active piezoelectric element 223 and a matching layer which has a sputtered surface 222 and an unsputtered surface 223. Wires were bonded using silver epoxy at two bonding points
10 224.

A stereolithographic 3D-printer was used to print the models designed in SolidWorks.

Figures 17A, 17B, 17C show the completed transducer stack from various views. The
15 stack, including the circular transducer 210, was assembled in a bottom compartment of a main housing 240, with tuning electronics located in an upper compartment of the main housing 240. A flat disc 241 was put on the top to seal the upper compartment after assembly.

20 The transducers were electrically matched to 50 Ω , by adding a parallel inductor and a transformer, and the housed transducers were electrically shielded to reduce pick-up of environmental noise. This was achieved by sputtering a layer of chrome and then gold, covering the whole transducer assembly. The finished transducer was connected to a tri-axial cable, where the two inner conductors were interconnected with the piezoelectric,
25 and the outer conductor was connected to the shielding of the transducer housing.

Figure 16 is a circuit diagram of the shielded transducer with tuning components and cable. The LC circuit represents the cable. The whole diagram is enclosed in a Faraday cage, consisting of the outer shield of the tri-axial cable and the chrome-gold enclosing
30 the transducer housing.

For the study, five transducers were fabricated and characterized. Three were made with a rectangular aperture, two using Pz27 and one with Pz29, and two with a circular aperture, one with Pz29 and one with Pz24.

35

Figure 18 shows the measured electrical impedance of the three piezoelectric materials, without matching layers, measured in air. The Pz24 sample is circular, while the Pz27 and

Pz29 samples are rectangular. The surface area of the three elements are close to equal, and therefore comparable. Note the higher impedance in the Pz24 sample.

Figure 19 shows the measured electrical impedances of the finished transducer assemblies, including tuning circuitry and a cable, measured in water. These transducers have a single acoustic matching layer, are electrical tuned to 50Ω , and have similar cable lengths.

Figure 20 shows the beam profiles of two transducers. The left panel is for the Pz27 transducer having a rectangular aperture made from, while the right panel is for the Pz29 transducer having a circular aperture. All were measured at 3 mm distance from the transducer surface, with $100 \mu\text{m}$ lateral resolution.

The pulse echo measurement set-up of Figure 13 was used to compare the sensitivities of the transducers. The envelope of the received signals was acquired after around $210 \mu\text{s}$, corresponding to 157 mm distance between the transducer and reflector.

Figure 21 shows the envelopes of the received echoes.

Figure 22 shows corresponding power spectra.

The envelope verifies that the distance between transducer and reflector was the same, and gives an indication of the signal to noise ratio.

For all the studied transducers, the relatively large surface area of the aperture (compared with elements used in conventional array-based transducers) results in a low impedance, which may make the transducers difficult to drive. It was predicted that the 'hard' Pz24 material, with its low dielectric constant, would be easier to drive. This is seen in the electrical impedance results in Figure 18. However, after tuning with transformers, the finished transducers show similar electrical impedances. The slightly lower phase of the two circular transducers in the resonance region may be explained by imprecise thickness of the matching layer, or by the tuning components.

After tuning, the impedance magnitude at 8 MHz was between 20 and 40Ω and the phase within ± 25 degrees, for all transducers, when measured in water. For all transducers, tuning circuitry was able to move the impedance into a region suitable for conventional driving electronics. However, this tuning has to be placed at the transducer

end of the cable, thereby increasing its size and weight, which may not always be acceptable. The impedance measurement on the Pz24 transducer demonstrate how this material can be chosen to achieve a higher impedance, avoiding a tuning transformer.

- 5 The beam profiles in Figure 20 show small regions with reduced radiated energy. This corresponds to the positions 214, 224 where wires were connected to the back-electrode of the PZT using silver epoxy. This absorbed some energy, causing a 3 dB reduction in transmitted energy. This result demonstrates that the influence of the wire connection is not negligible, a careful application of silver epoxy is important to minimize the influence
10 on the transducer vibrations, while ensuring a secure connection.

From Figure 21, it can be seen that the peak of the transducers named "Rect PZ27 #2" and "Rect PZ29" have a slight offset compared to the others. This is explained by a small inaccuracy in the positioning of the measurement setup, and does not influence the
15 results.

When comparing the spectra in Figure 22, it can be seen that the two transducers with rectangular aperture made with Pz27 are not identical. The transducer "Rect PZ27 #2" has an uneven top with its peak at 6.8 MHz, while the transducer "Rect PZ27 #1" has a
20 flatter top. The difference at 8 MHz is 1 dB, and may be explained by process variations, e.g. inaccuracies in thicknesses of the matching and bonding layers. The third rectangular transducer "Rect PZ29" displays the same uneven top as the transducer "Rect PZ27 #2", and has 0.6 dB higher sensitivity than "Rect PZ27 #1". This can be explained by the higher coupling coefficient, k_t , of the Pz29 material.

25

Of the transducers with a circular aperture, the transducer made with Pz24 yielded a 2 dB-improved sensitivity over the transducer made with Pz29. The lower permittivity of Pz24 gives a higher electrical impedance, which for this large element area makes it easier to drive.

- 30 The transducers made with a circular aperture have an overall higher sensitivity than the rectangular transducers, due to the different beam pattern from the two geometries. Overall, the transducers performed well, with signal strength 75 to 85 dB above the recorded noise level. The -3dB bandwidth for the transducers was found to between 30% and 40%, which is suitable for the pulsed wave Doppler application they were targeted at.

35

In summary transducers made from three different piezoelectric materials were studied. The transducers were targeted at pulsed Doppler applications, embodying the invention,

where high sensitivity may typically be required, while the bandwidth requirement may be less important. The resulting large aperture area causes a low impedance, which is challenging for the driving electronics.

- 5 Two conventional soft PZT materials with high coupling coefficients, Pz27 and Pz29, were compared to a hard PZT, Pz24, with low dielectric constant. The results show that using the hard Pz24 makes it feasible to increase the sensitivity by 3 to 5 dB compared to the other materials and/or to dispense with tuning circuitry, thereby resulting in a lower manufacturing cost for the transducers.

10

CLINICAL EXAMPLES

Example 1 – Analysis of microvascular circulatory changes

15 *Background*

Microvascular physiological responses or endothelial functions as vaso-constriction or -dilatation and vasomotion, are well studied in healthy as well as in diabetic subjects. A range of non-invasive methods has been developed and is shown to adequately assess vasomotor responses. There are a number of potential devices and techniques that are in
20 use to evaluate microcirculatory function, i.e. transcutaneous oxygen tension (TcPO), skin pulp blood flow (i.e. laser Doppler fluxometry), iontophoresis or capillaroscopy. These techniques, as of today, need further development to optimally cover their clinical purposes due to lack of standardization and official guidelines which results in large differences in methodology and reduces reproducibility and comparability between studies
25 performed.

The present study was performed to compare and validate a novel flat unfocused ultrasound probe in accordance with at least some aspects of the invention (Earlybird) against already well-known clinical and laboratorial applicable devices intended for the
30 analysis of microcirculatory changes, i.e. radial artery Doppler, laser Doppler fluxmetry and photoplethysmography. The device consists of one acoustic element. Over the whole area of the acoustic element the device can measure blood flow velocities in the small arteries feeding the arterioles and the arterioles themselves at depths ranging from 0.2 to 4.0 cm. The blood flow velocity was measured at the skin pulp and evaluates the
35 microcirculation function in that vicinity. The probe is easy to use, more stable, user independent and cheaper to produce than already existing devices. It is therefore interesting to evaluate the flat unfocused ultrasound probe against already well-known

devices designed for the analysis of microcirculatory changes due to different physiologic stimuli in healthy individuals.

Design/method

5 In this study a novel flat unfocused ultrasound probe (Earlybird) was evaluated. Earlybird consists of three main parts: transducer, scanner and user interface. The transducer converts an electric signal burst into acoustic energy, which is transmitted into the patient, reflected and collected by the transducer. The pulse is ten wavelengths at the nominal frequency 7.8 MHz, and it is transmitted at a rate of 8 kHz. The circular, single-element
10 transducer (probe) is manufactured by Imasonic SAS (France). The material exposed to the patient is an epoxy resin, which is USP class VI approved. Between the probe and skin is a hydrogel standoff, with a thickness of three millimeter (HydroAid, Kikgel, Poland). The probe simultaneously records signals from 2mm to 40mm depth in slices perpendicular to the skin surface. This makes it possible to detect blood flow in all layers
15 from skin to bone simultaneously. The probe is connected to an ultrasound scanner (generic OEM Manus EIM-A produced by Aurotech Ultrasound AS, Tydal, Norway). A computer is connected to the scanner using an Ethernet network cable, and is used as user interface and display. The data collected is showed in real time as a Doppler spectrum (Matlab, Mathworks, Massachusetts, U.S.A), stored to a disk and enabled for
20 later re-examination. The ultrasound probe is not yet CE-marked but approved by Norwegian health authorities to be tested at volunteered patients and healthy individuals.

Ten healthy volunteers, six males, median age 39 years (range 18 – 64) participated in the test of the probe. Median BodyMassIndex (BMI) 23,5 (range 20,3 – 30,3). Two of the
25 test persons use antihistamines (desloratidin 5 mg or cetirizinhydroklorid 10mg). One person has a minor form of thalassemia without any complications. Prior to the examination, six persons had drunk coffee and two had drunk tea.

All tests were performed in one session and took place in a study room with a room
30 temperature between 23-26 °Celsius. Lightning was dimmed. The participants were comfortably clothed. The measurements were done with the test persons in supine position in a bed with the head slightly elevated. The bed was draped with a warming blanket. The test persons achieved a normo-temperature-state.

35 A well-equipped vascular physiological laboratory was used. Several simultaneous recordings were performed. A standard three diverted ECG and mean arterial blood flow velocity ($\text{cm} \cdot \text{sec}^{-1}$) in the right radial artery (except in one person were the left radial artery

was used) was recorded with a 10 MHz pulsed Doppler probe (SD-50; GE Vingmed Ultrasound, Horten, Norway). Continuous blood pressure was recorded as finger arterial pressure recordings by a photoplethysmographic volume-clamp method (Finometer; FMS Finapres Medical Systems BV, Amsterdam, The Netherlands). Skin pulp blood flow was measured with laser Doppler fluxmetry (LDF; Periflux PF 4000; Perimed AB, Jarfalla, Sweden) and with photoplethysmography (PPG; STR Teknikk, strteknikk.no, Aalesund, Norway). Respiration motion was recorded by nostril temperature sensors detecting in- and out-flow (STR Teknikk, strteknikk.no Aalesund, Norway). Heart rate was derived from the ECG. All data were assessed simultaneously and recorded at 1000 Hz in LabChart (ADINSTRUMENTS, Dunedin, New Zealand).

Each subject successively recorded a five minutes baseline and four different test protocols, each protocol repeated twice; (1) forced respiration, (2) static handgrip exercise, (3) valsalva manoeuvre and (4) cold pressor test. Between each protocol a sufficient pause was held for the subject to recover completely. The baseline recording was performed while the subject was resting at comfortable bed in a quiet room for five minutes.

1: While executing the forced respiration test the subjects inhaled or exhaled on the command of an instructor. The test started with 30 seconds of rest with normal breathing, followed by a cycle of 60 seconds with forced respiration with sequences of 4 seconds of inhalation and 4 seconds of exhalation. At the end the subject was asked to breath normally for an additional 30 seconds.

2: Before starting the static handgrip exercise the subjects were familiarized with the equipment. A test of maximum contraction on the handgrip dynamometer was performed and the highest produced force was noted. The subjects were able to visually control the force and were instructed to hold a 50 % of their maximum force during the test period. The static handgrip exercise recording consisted of 30 seconds of rest, 60 seconds of 50 % of maximum produced force, followed by 30 seconds of rest.

3: The valsalva test started with 30 seconds of normal breathing. The subjects then followed a total cycle of 60 seconds containing of two sequences of 15 seconds of valsalva manoeuvre and 15 seconds of rest. The valsalva maneuver was performed as a maximal expiratory effort maintained against closed airways. Intrathoracic pressure was not measured during the exercise. The protocol ended with 30 seconds of normal breathing.

4: The cold pressor test was performed by immersing the left hand in ice-water for the scheduled time. The test started with recording of 30 seconds of rest with the left hand by the side of the test person. The left hand, contralateral to the hand equipped with the recording equipment, was then lowered into a combination of ice and water for 60 seconds, followed by 30 seconds of recording while the hand was left to rest in room temperature.

All data recordings from Labchart were combined and synchronized with the Doppler flow curves from the novel unfocused ultrasound probe (Earlybird) recorded in MatLab. The mean values for all of the test subjects were pooled. The data were normalized. Curves were then plotted in SigmaPlot version 13.0. Correlation between the different curves were calculated for each recording,

Results

Baseline readings of flow velocity in the radial artery were taken every 5 minutes using each technique (Earlybird, laserDoppler fluxometry and pulse-Doppler recordings). An example of baseline recordings from subject 7 is shown in Figure 23a. Correlation was 0.97 (range 0.9-1.0) (Figure 23b). Figure 24 shows response curves upon cold induction test (HR, MAP, Doppler flow of the radial artery, skin pulp blood flow measured with laser Doppler fluxometry and EarlyBird Doppler).

As can be seen, the novel flat unfocused probe (EarlyBird) is capable of detecting vasomotion and vasomotor response upon different physiological stimuli at least as well as other comparable devices.

Example 2 – Analysis of blood flow in the peripheral circulation of healthy subjects undergoing cold pressor test – comparison of analytical techniques

The monitoring of blood flow in the small arteries feeding the microcirculation using unfocused Doppler ultrasound in accordance with at least some aspects of the invention provides useful blood flow characteristics of the microcirculation which are not seen with conventional techniques (Figure 25).

In this example, peripheral blood flow during constriction of the arterioles in the fingers of patients undergoing a cold pressor test (as described in Example 1) were recorded with 3

different techniques: 1) conventional Doppler measuring blood flow in the radial artery in the lower arm; 2) unfocused Doppler ultrasound in accordance with the invention measuring flow in arterioles and small arteries feeding the arterioles (arterial microcirculation) of the finger from at least 2mm depth; and 3) laserDoppler measuring
5 microcirculation in a thin layer of the skin within 2mm of the surface.

Results are shown in Figure 25. Reduction in flow is evident for all three measurements, however, the mid panel (unfocused Doppler) shows a characteristic change in waveform occurring from timepoint 35 sec (initiation of cold pressor), indicating an oscillatory
10 collapse in the tone of the arterioles. Thus the invention provides greater and more useful information on the characteristics of microcirculation in response to stimulus.

Example 3 – Analysis of blood flow in the peripheral circulation of subjects with microvascular dysfunction undergoing surgical intervention

15

Patient 1

This patient was a 65 year old male presenting with claudication, i.e. microvasculature dysfunction in the lower limbs arising from stenosis in an upstream blood vessel. As shown in Figure 26 (D) the velocity of the pulsatile (arterial) blood flow in the minor
20 vasculature of the pulp of the patient's big toe, as measured by an ultrasound system of the invention, was modest providing further evidence of microvasculature dysfunction in the lower limbs. As shown in Figure 26 (A) angiogram/CT scans of the iliac artery of the patient revealed a stenosis. Angioplasty of that stenosis resulted in significantly increased arterial blood flow in the minor vasculature of the big toe, but flow velocity as measured by
25 an ultrasound system of the invention was still considered low and remained indicative of continued microvasculature dysfunction. This led to further analysis of the angiogram and the detection of a further suspected stenosis. Angioplasty at this location resulted in a more than doubling of the arterial blood flow in the minor vasculature of the big toe. Under conventional protocols it is likely that this second stenosis would have been
30 identified only after the patient was assessed following the conclusion of the first surgery, thus requiring a second surgical intervention at another time. The present invention therefore prevented the risks and costs of a second surgical intervention in this patient.

This study shows how an ultrasound system of the present invention may be used to
35 monitor peripheral microcirculation in a vertebrate animal subject undergoing or recovering from surgery and guide treatment. It also shows how an ultrasound system of

the present invention may be used to detect and monitor microvascular dysfunction more generally.

Patient 2

- 5 This patient was an 80 year old male with diabetes and associated renal failure and foot ulcer, i.e. evidence of microvascular dysfunction. As shown in Figure 27 (A) angiogram/CT scans of the thigh and leg arteries revealed multiple significant occlusions (arrows). As shown in Figure 27 (B), following angioplasty these occlusions were rectified. Figure 27 further shows that using an ultrasound system in accordance with the invention arterial
- 10 blood flow readings from the minor vasculature of the patient (pulp of the big toe) were highly unstable prior to angioplasty (i.e. state of microvascular dysfunction) but, in contrast, robust and stable readings in arterial flow were seen following angioplasty (i.e. following normalisation of microvascular dysfunction).
- 15 This study shows how an ultrasound system of the present invention may be used to detect microvascular dysfunction by determining blood flow characteristics in peripheral minor vasculature (unstable readings) and monitor that dysfunction (stabilisation of readings following treatment to rectify that dysfunction). This study also shows how an ultrasound system of the present invention may be used to monitor peripheral
- 20 microcirculation in a vertebrate animal subject undergoing or recovering from surgery.

Patient 3

- This patient was an 80 year old female presenting with claudication, i.e. microvasculature dysfunction in the lower limbs arising from stenosis in an upstream blood vessel.
- 25 Angiogram/CT scans of the iliac artery of the patient revealed a stenosis. An ultrasound system of the invention was used to measure blood flow velocity in the arteria dorsalis pedis before, during and after angioplasty of the stenosis. Arterial blood flow velocity in the arteria dorsalis pedis was significantly increased following the procedure indicating successful revascularisation and reduction in microvascular dysfunction (data not shown).
- 30 This study shows how an ultrasound system of the present invention may be used to monitor peripheral microcirculation in a vertebrate animal subject undergoing or recovering from surgery. It also shows how an ultrasound system of the present invention may be used to detect and monitor microvascular dysfunction more generally.

CLAIMS

1. A method for monitoring peripheral microcirculation in a vertebrate animal subject undergoing or recovering from surgery, said method comprising
 - transmitting unfocused ultrasound pulses into the subject from an ultrasound transducer that is applied to an external surface of the subject;
 - receiving reflections of the ultrasound pulses at the ultrasound transducer from at least one region containing at least one blood vessel of the minor peripheral vasculature, preferably a plurality thereof;
 - generating pulse-Doppler response signals from the reflections; and
 - processing the pulse-Doppler response signals to determine a characteristic of blood flow in the minor peripheral vasculature of the subject;
 - monitoring the characteristic of blood flow over time; and optionally
 - establishing a profile of said characteristic over time;wherein variation in said characteristic or the profile of said characteristic over time is indicative or predictive of a change in the peripheral microcirculation of the subject.
2. A method for monitoring or predicting the onset of and/or progression of dysfunction of the microvasculature and/or a response to treatment thereof in a vertebrate animal subject, said method comprising
 - transmitting unfocused ultrasound pulses into the subject from an ultrasound transducer that is applied to an external surface of the peripheral anatomy of the subject;
 - receiving reflections of the ultrasound pulses at the ultrasound transducer from at least one region containing at least one blood vessel of the minor peripheral vasculature, preferably a plurality thereof;
 - generating pulse-Doppler response signals from the reflections; and
 - processing the pulse-Doppler response signals to determine a characteristic of blood flow in the minor peripheral vasculature of the subject;
 - monitoring the characteristic of blood flow over time; and optionally
 - establishing a profile of said characteristic over time;wherein the characteristic or the profile of said characteristic over time is indicative or predictive of dysfunction of the microvasculature or response to treatment thereof or variation in said characteristic or a profile of said characteristic over time is indicative or predictive of dysfunction of the microvasculature or is indicative or predictive of a change in the dysfunction of the microvasculature or response to treatment thereof

3. The method of claim 1 or claim 2, wherein the region is at a site which
 - (i) is not in the torso of the subject;
 - (ii) is in a limb, neck or head; or
 - (iii) is in a shoulder, arm, leg, hand, foot, toe, finger, paw, wing, fin, tail, ear, nose, tongue, cheek, scalp, forehead.
4. The method of any one of claims 1 to 3, wherein said blood vessel of the minor vasculature is a vessel of the arterial microvasculature.
5. The method of any one or claims 1 to 4, wherein said blood vessel is a vessel of the superficial circulation.
6. The method of any one of claims 1 to 5, wherein said characteristic of blood flow is a characteristic of blood flow through a plurality of vessels.
7. The method of any one of claims 1 to 6, wherein the ultrasound transducer has only a single transducer element.
8. The method of any one of claims 1 to 7, comprising transmitting the ultrasound pulses as plane-wave pulses.
9. The method of any one of claims 1 to 8, wherein the pulse-Doppler response signals aggregate reflections from across a region in the subject, wherein the region has a width that is substantially equal to a beam width of the transmitted ultrasound pulses at the region.
10. The method of any one of claims 1 to 9, wherein the ultrasound transducer is mechanically fastened to the subject.
11. The method of any one of claims 1 to 10, wherein the characteristic of blood flow is the maximum velocity or the time-averaged mean velocity, over the time period, parallel to a transmission axis of the ultrasound transducer.

12. The method of any one of claims 1 to 11, wherein the characteristic of blood flow is the Pulsatile index (PI), Resistivity Index (RI), velocity, Max velocity (Vmax), Mean velocity (Vmean) and the Velocity Time Integral (VTI) end diastolic velocity, peak diastolic velocity, vasomotion oscillations or a combination thereof.
13. The method of any one of claims 1 to 12, wherein said indicative profile is a low frequency oscillation in one or more of said characteristics of blood flow over time.
14. A method for treating or preventing dysfunction of the microvasculature in a vertebrate animal subject, said method comprising
- performing the method of any one of claims 2 to 13, wherein the characteristic or the profile of said characteristic over time is indicative or predictive of dysfunction in the microvasculature or variation in said characteristic or a profile of said characteristic over time is indicative or predictive of dysfunction in the microvasculature or is indicative or predictive of a change in the dysfunction of the subject's microvasculature;
- diagnosing dysfunction of the microvasculature or determining the likelihood of dysfunction occurring in said subject or progressing in said subject and treating said subject with a clinical intervention suitable for treating or preventing dysfunction of the microvasculature or reducing the likelihood of dysfunction occurring.
15. The method of claim 14, wherein said clinical intervention is selected from anti-diabetic, antihypertensive, cholesterol lowering and lipid lowering pharmaceutical treatments, angioplasty or bypass surgery and lifestyle changes.
16. A method of surgery in a vertebrate animal, said method comprising monitoring microcirculation in the subject by performing the method of any one of claims 1 and 3 to 13.
17. A method of post-surgical treatment in a vertebrate animal, said method comprising monitoring microcirculation in a subject recovering from surgery by performing the method of any one of claims 1 and 3 to 13.
18. The method of claim 16 or claim 17 wherein the surgery is vascular surgery, preferably endovascular surgery or open vascular surgery.

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Fig. 1

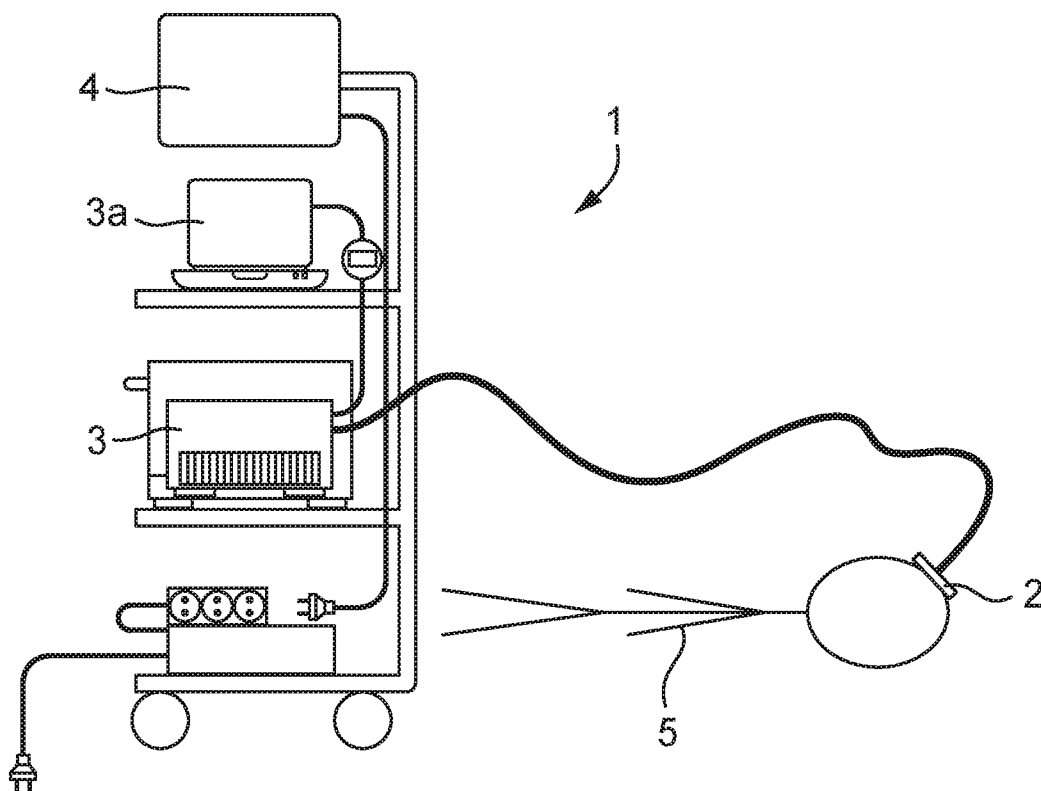
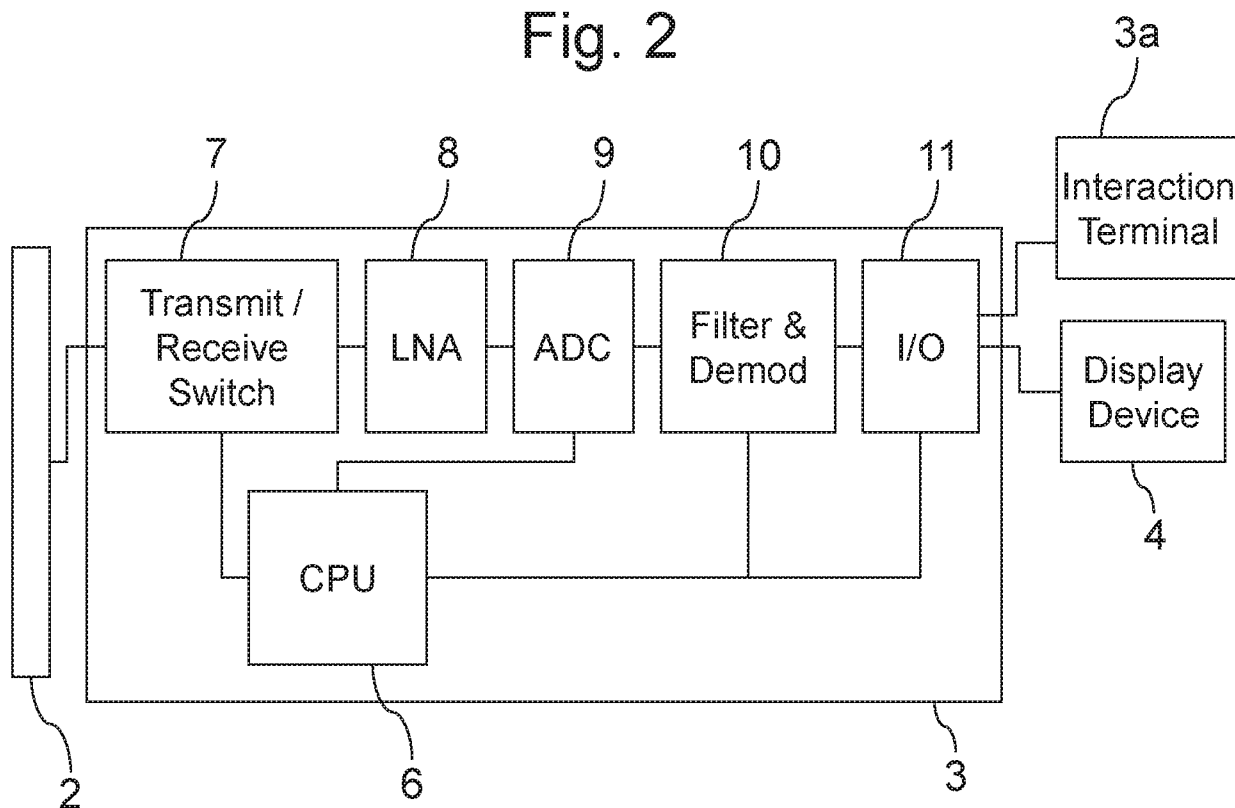


Fig. 2



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Fig. 3

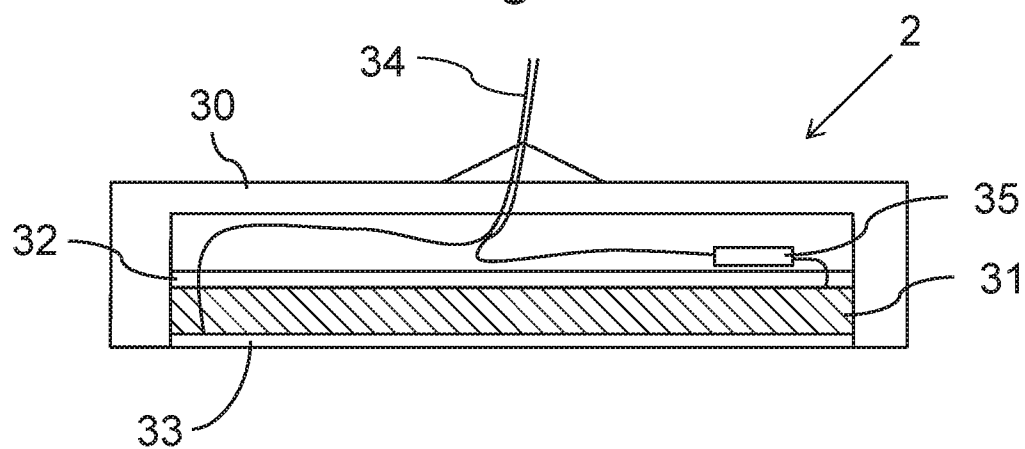


Fig. 4

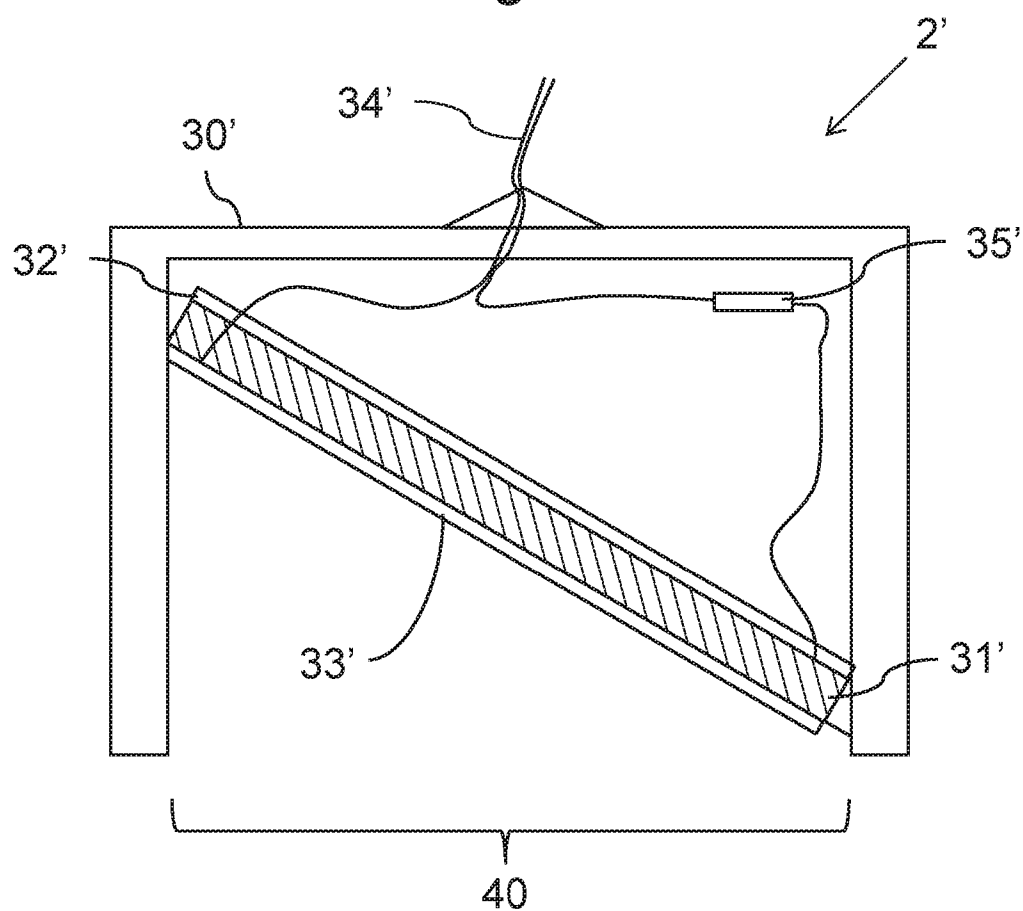


Fig. 5

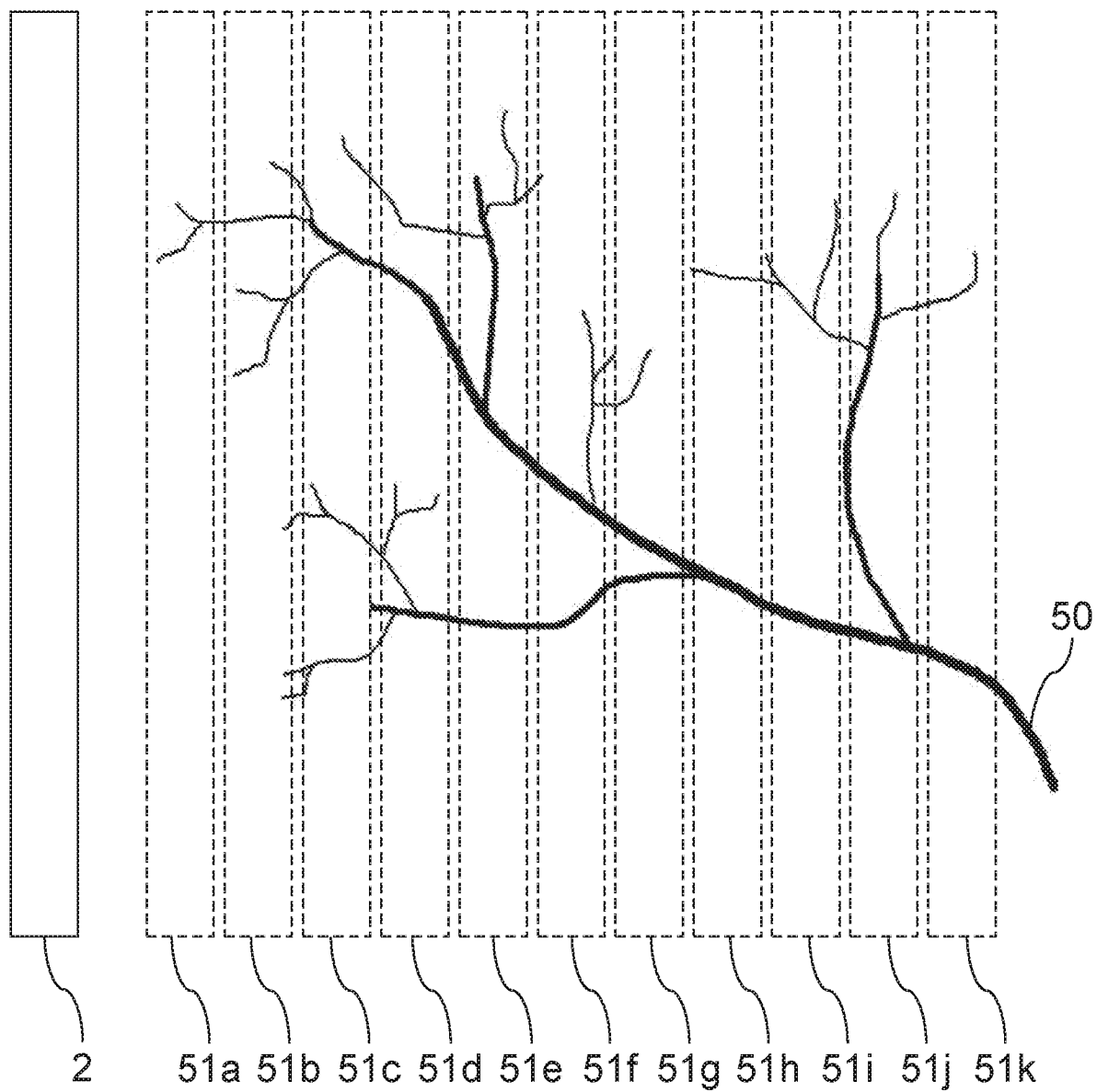


Fig. 6

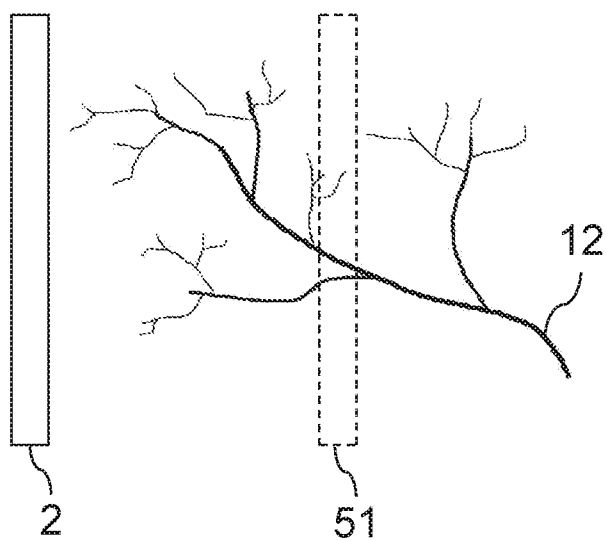


Fig. 7

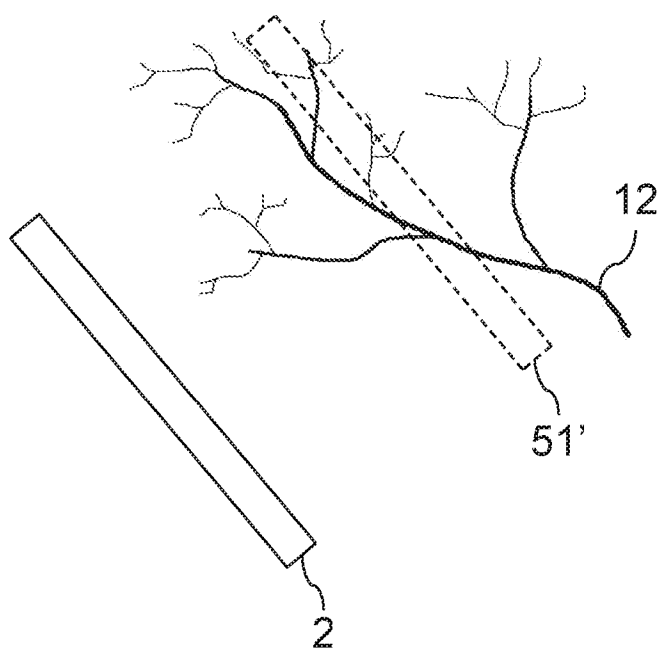
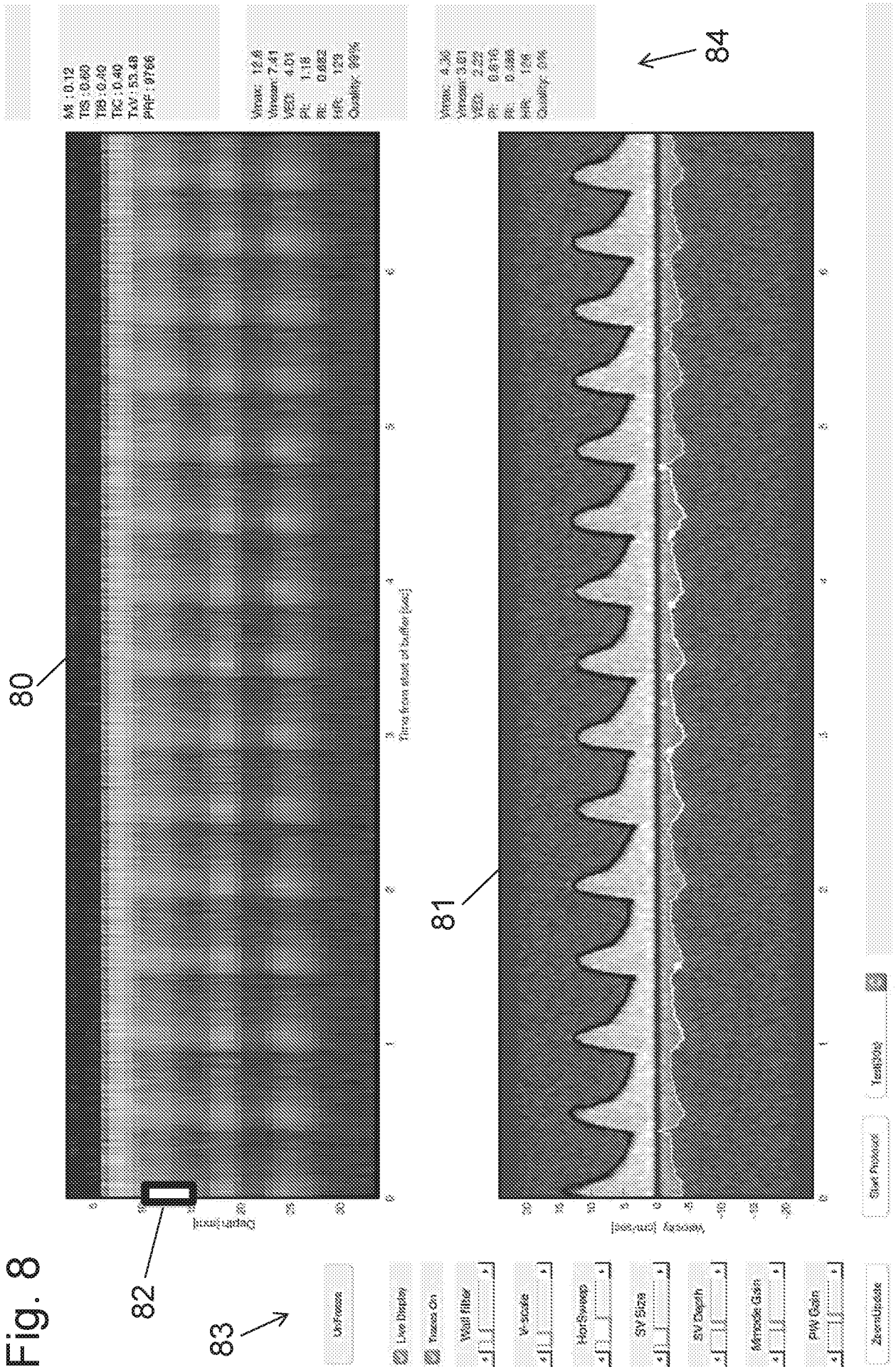
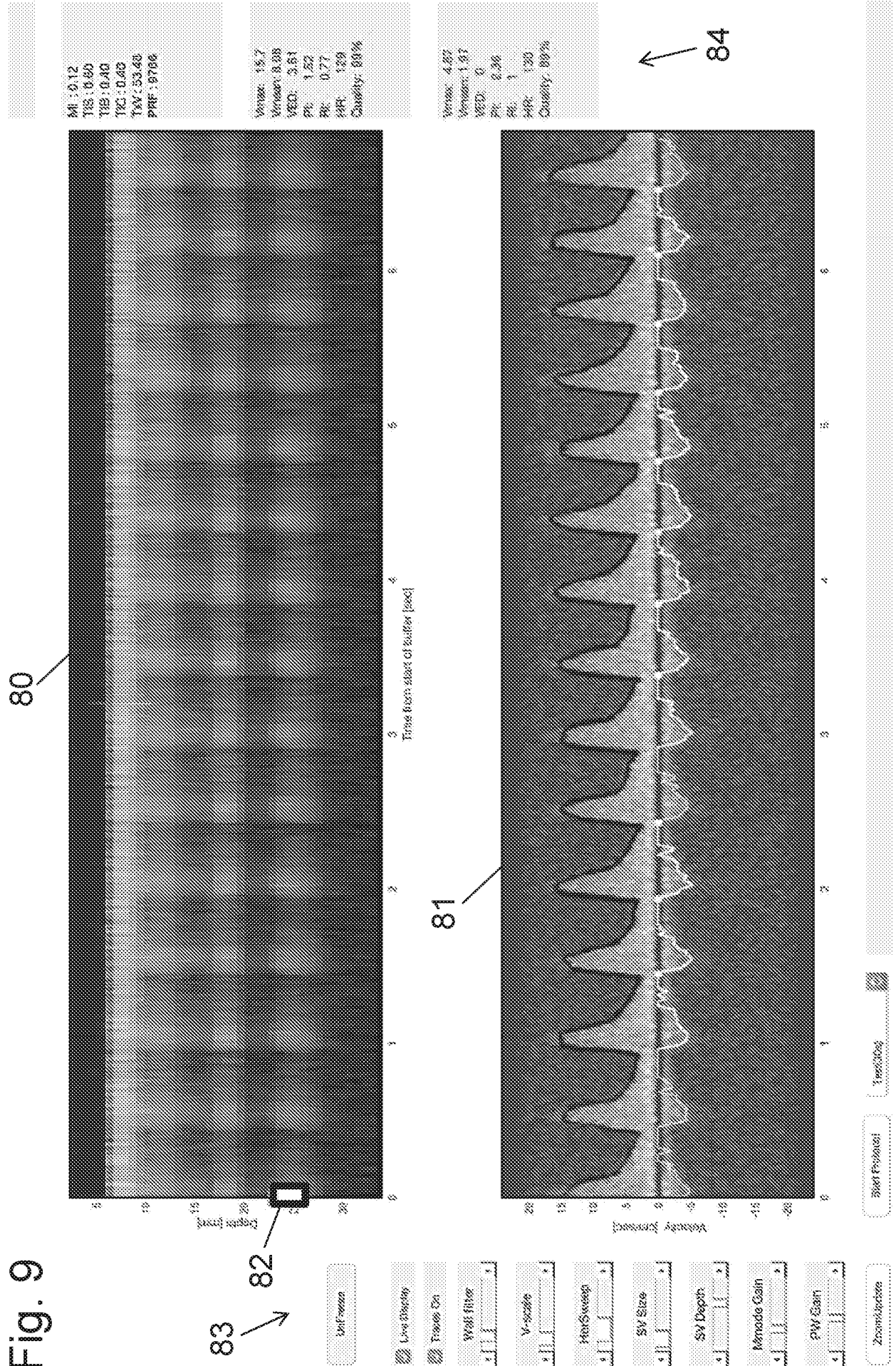


Fig. 8



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Fig. 9



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Fig. 10

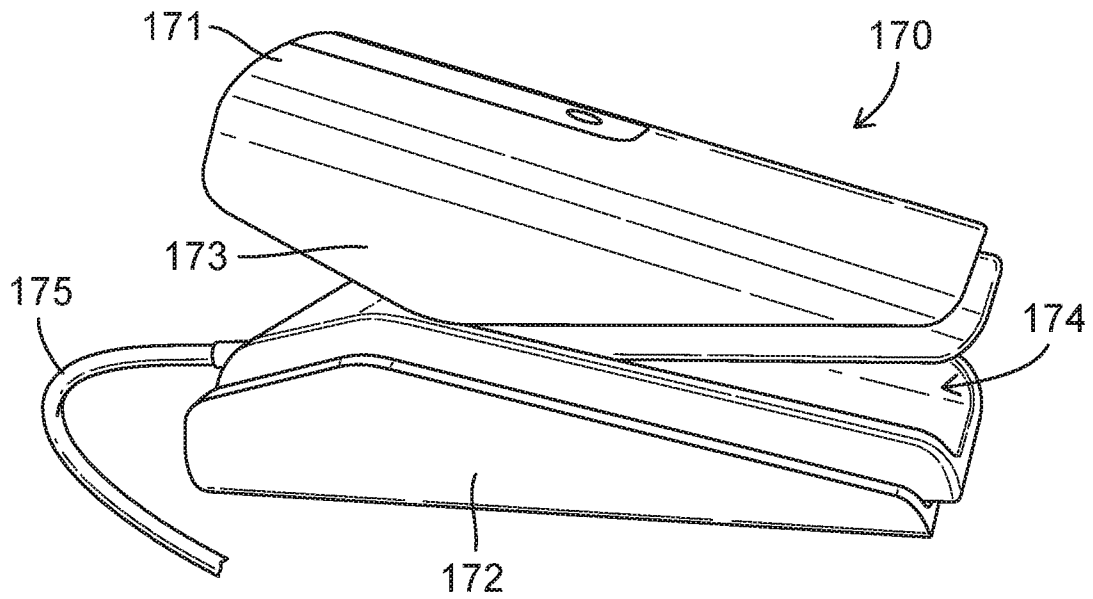
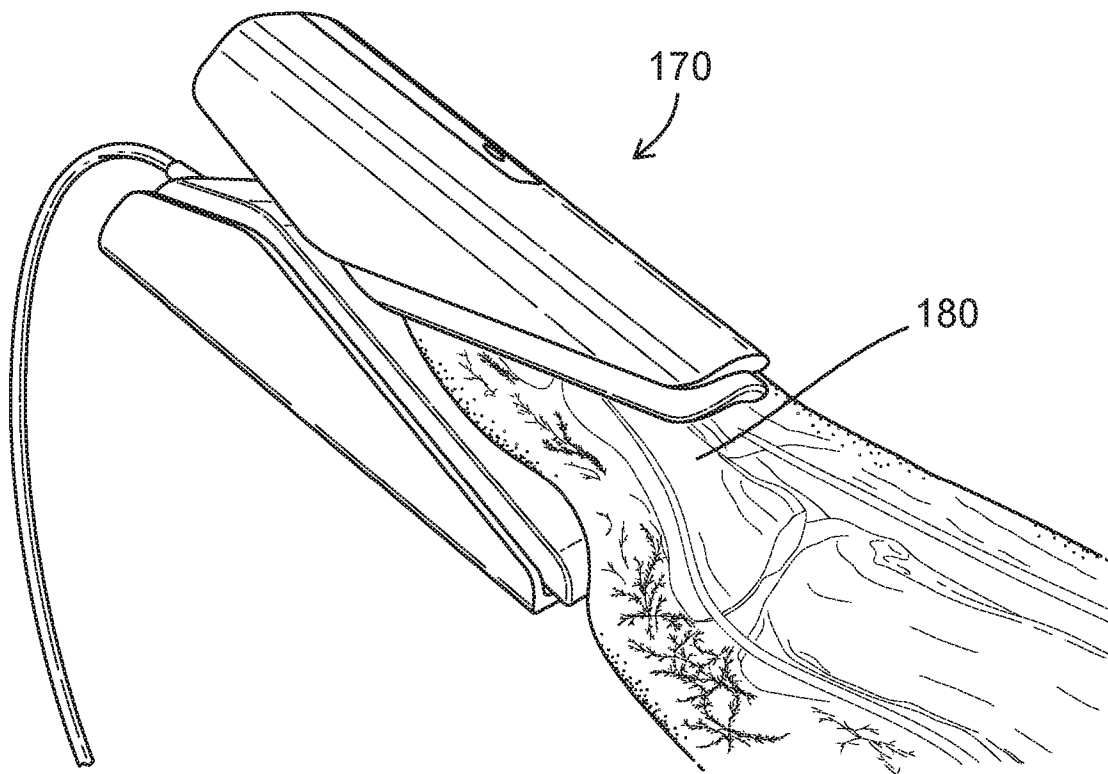
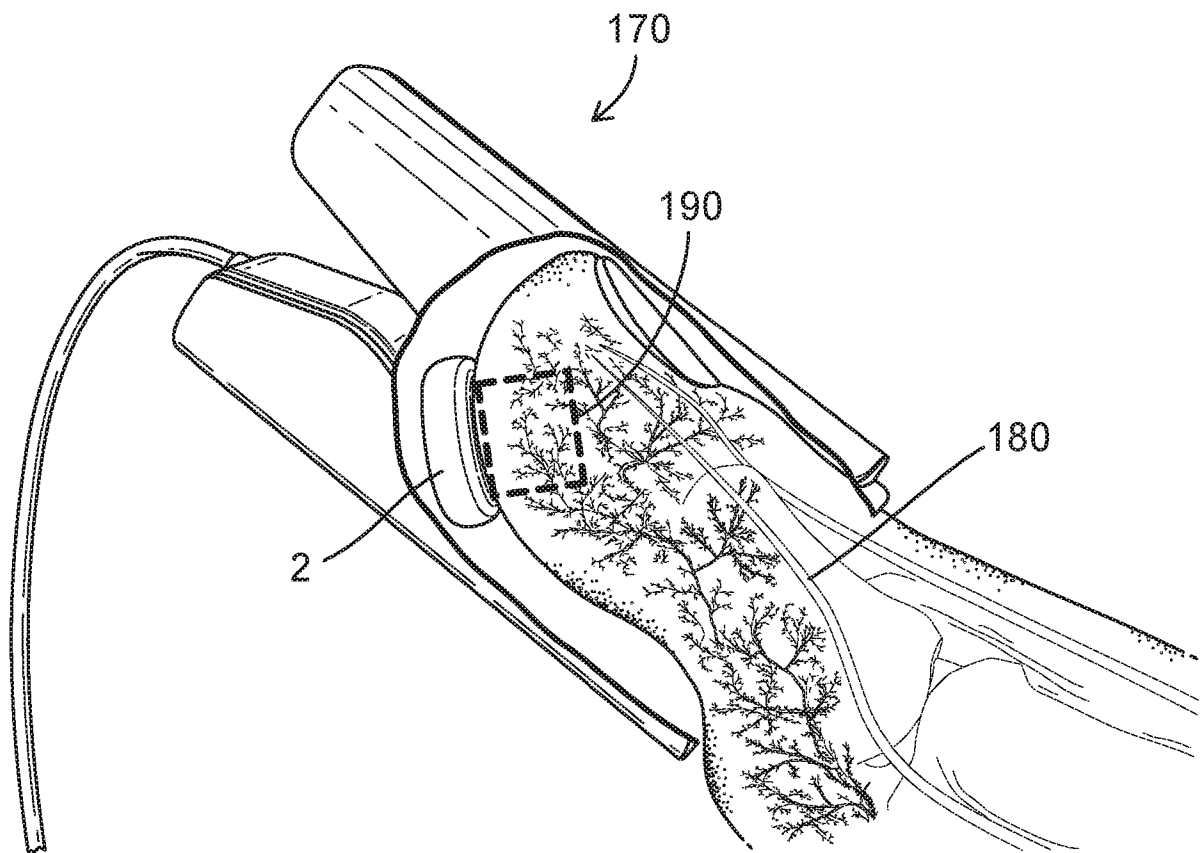


Fig. 11



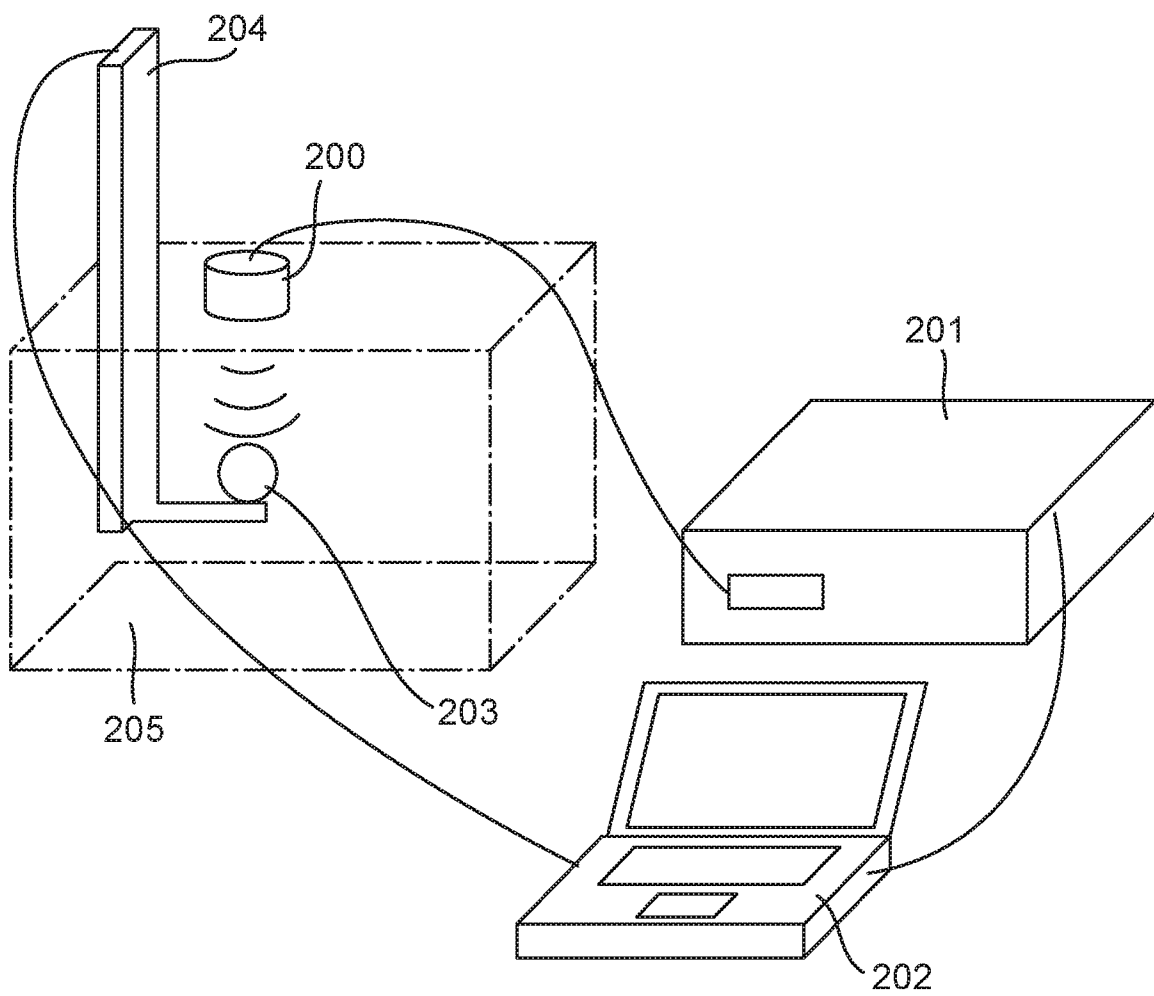
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Fig. 12



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Fig. 13



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Fig. 14

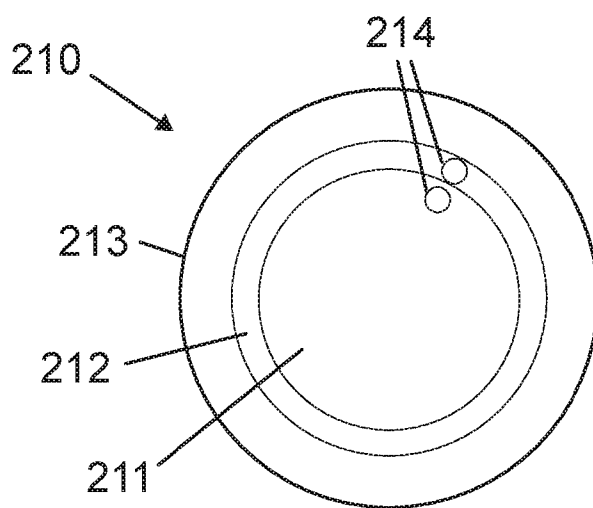


Fig. 15

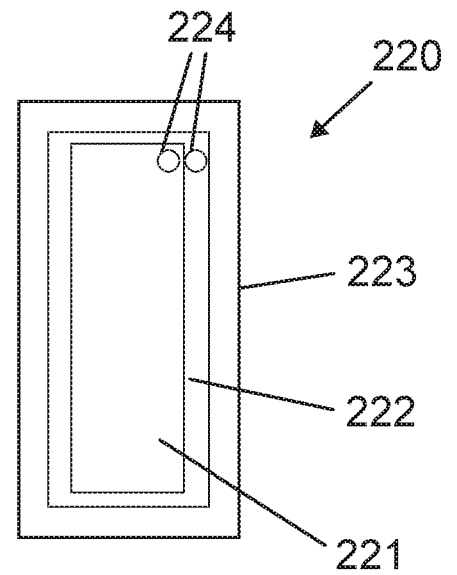
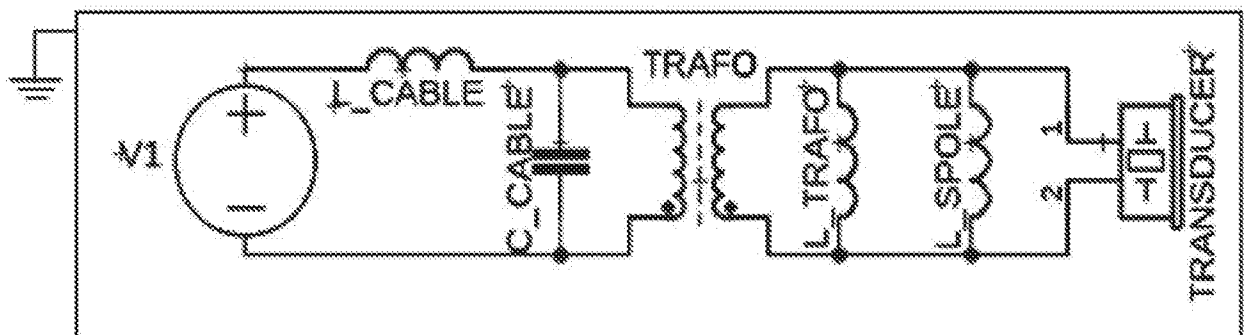


Fig. 16



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Fig. 17A

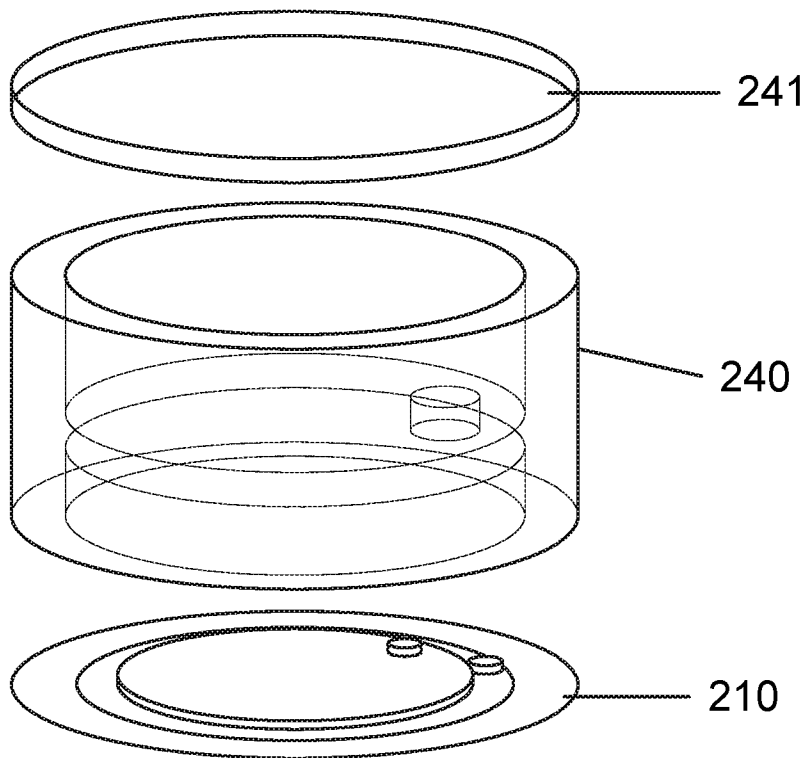


Fig. 17B

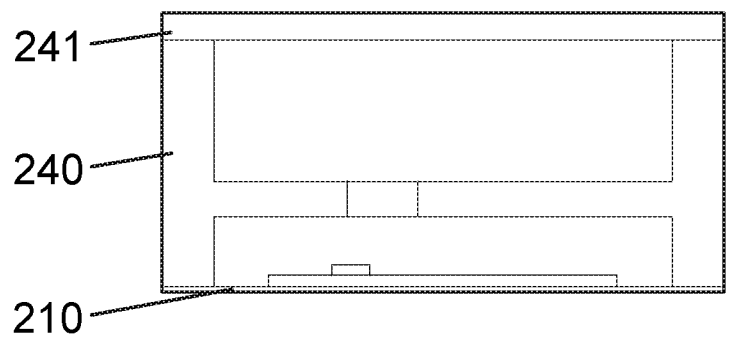


Fig. 17C

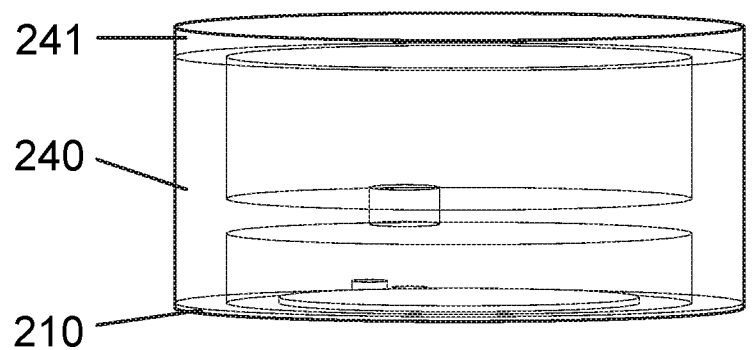


Fig. 18

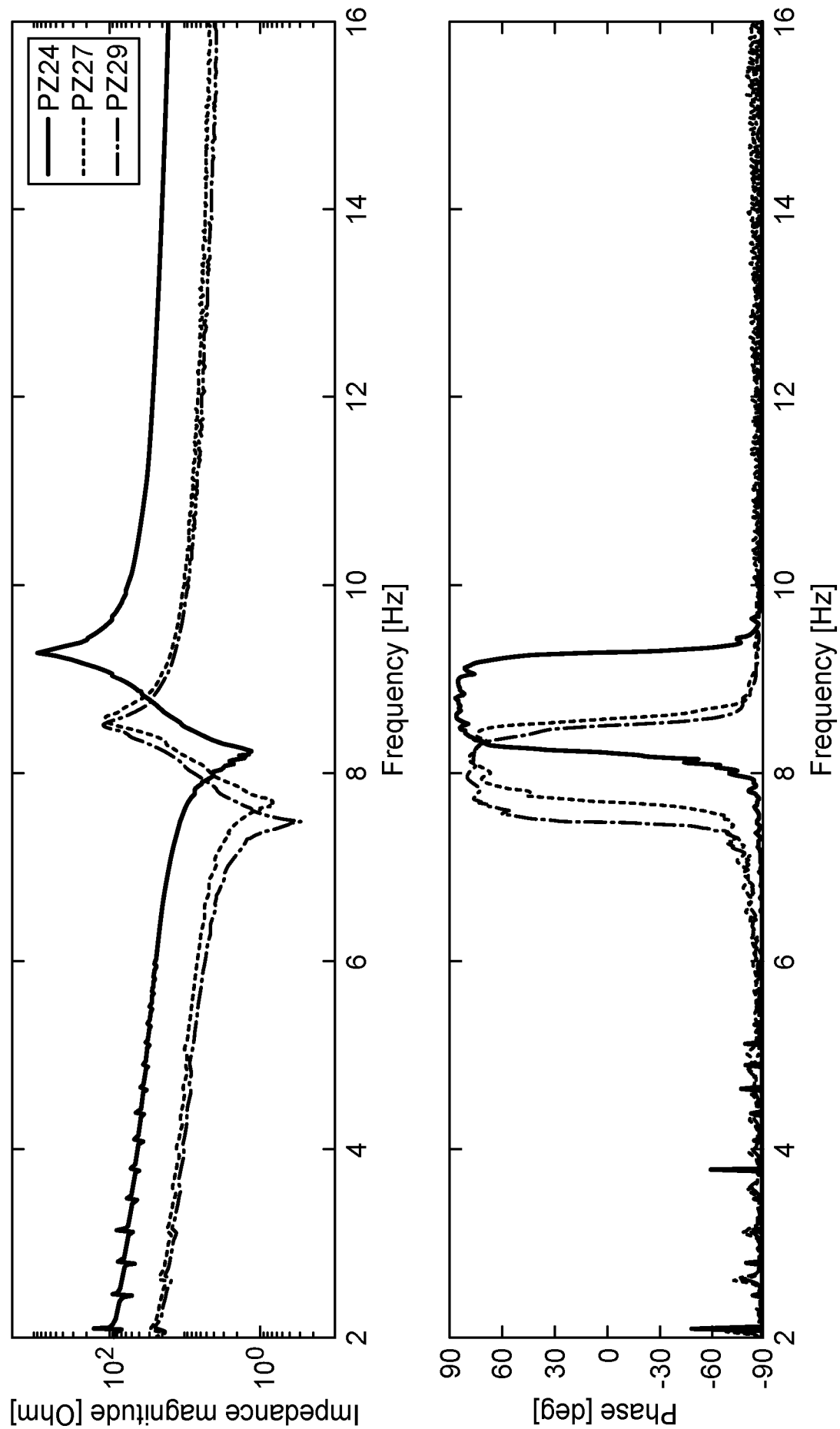


Fig. 19

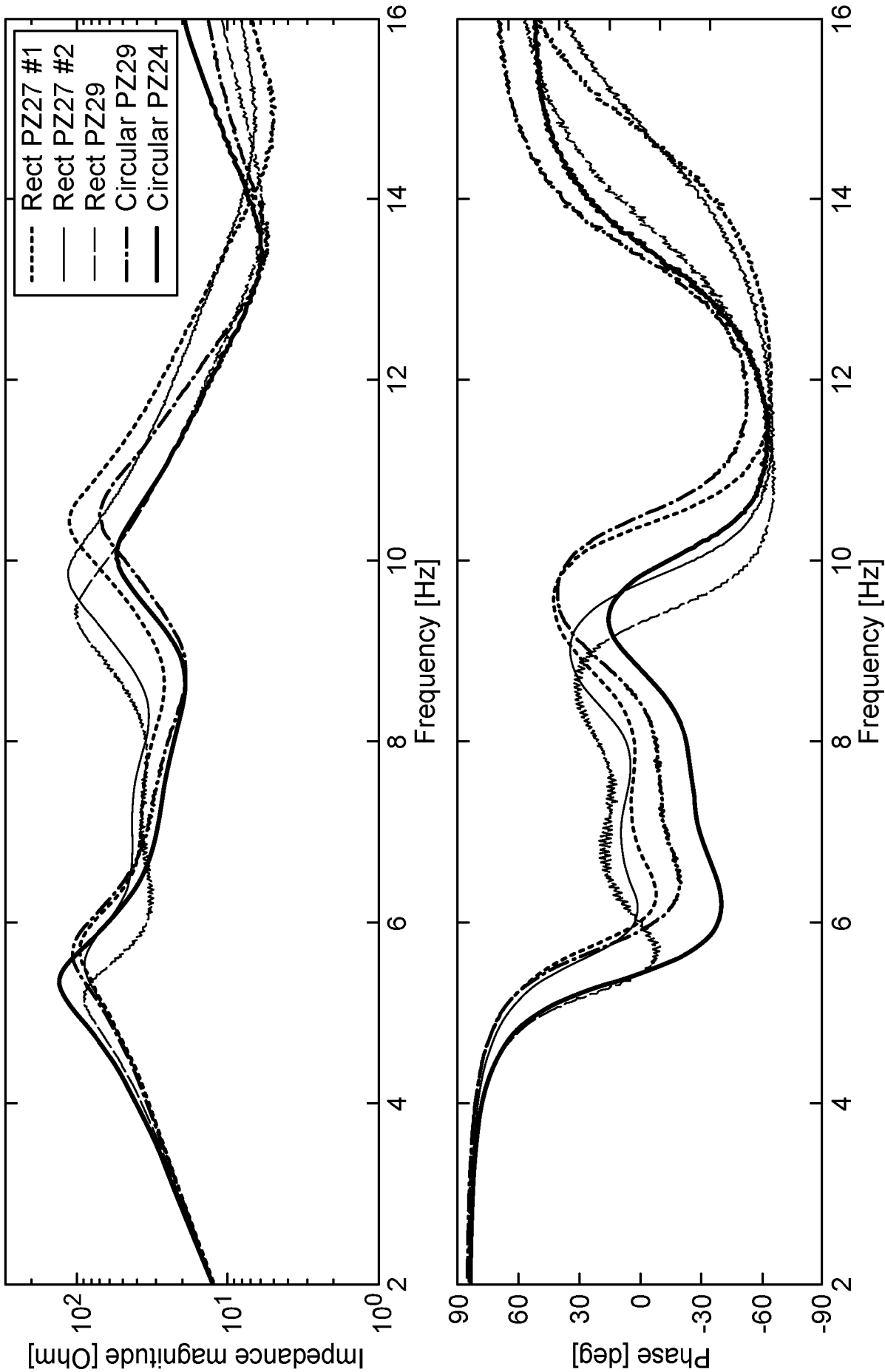
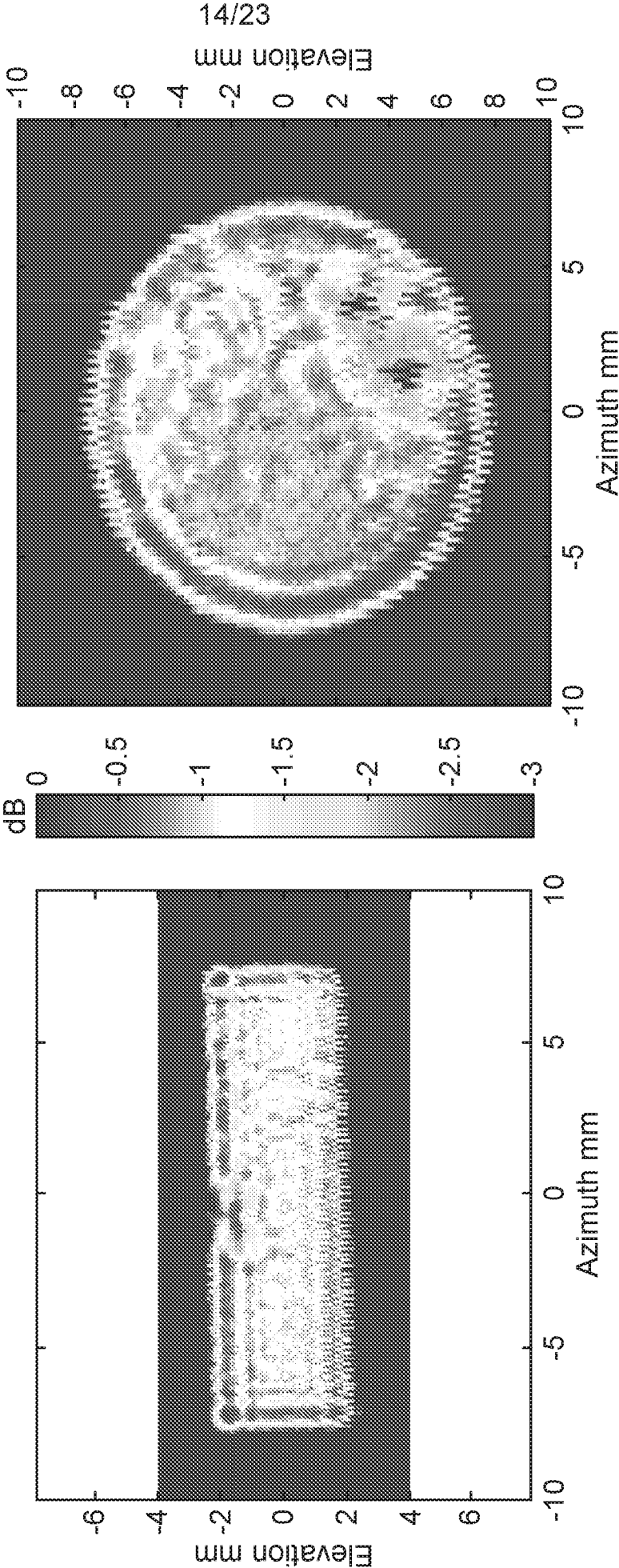


Fig. 20



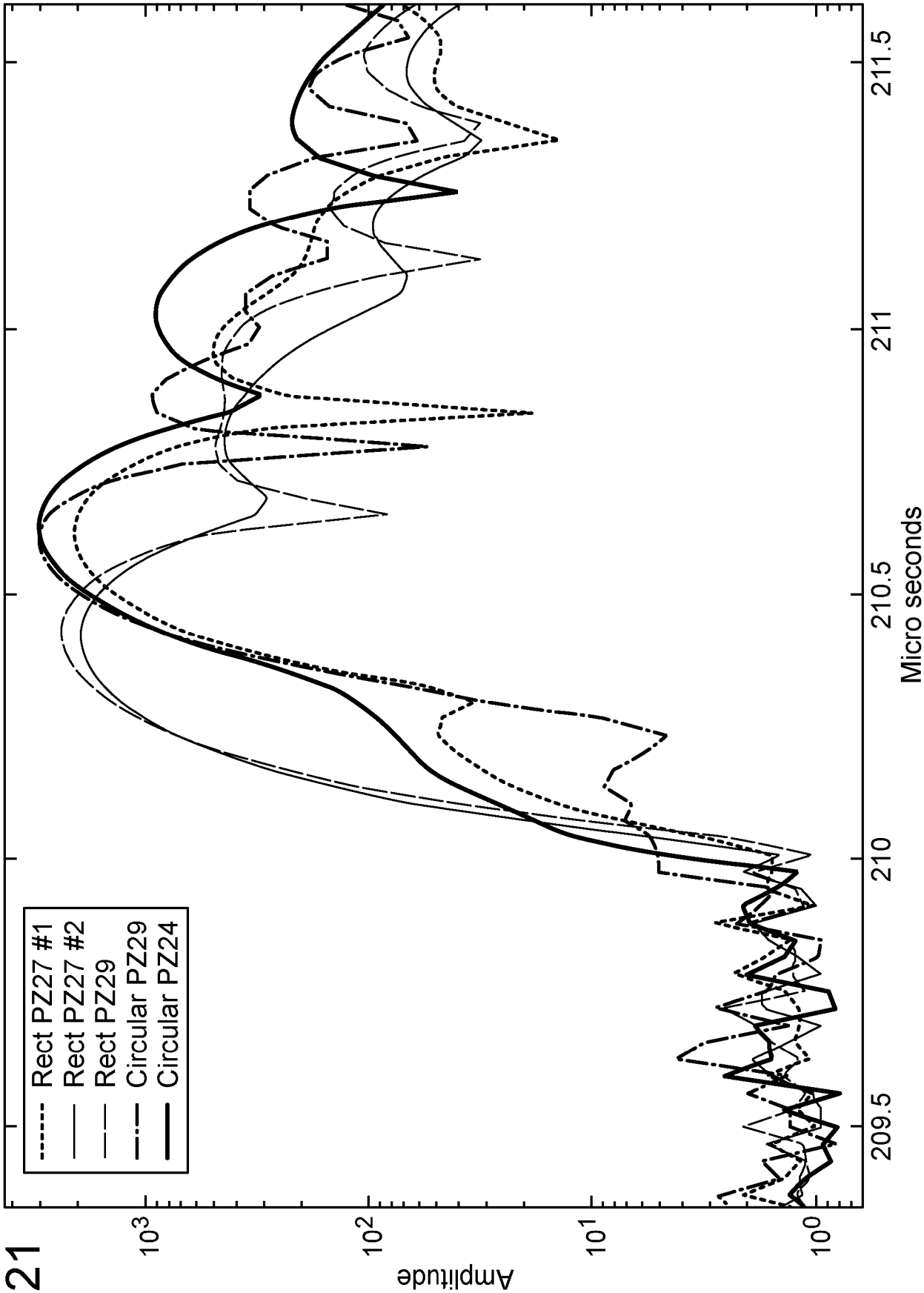
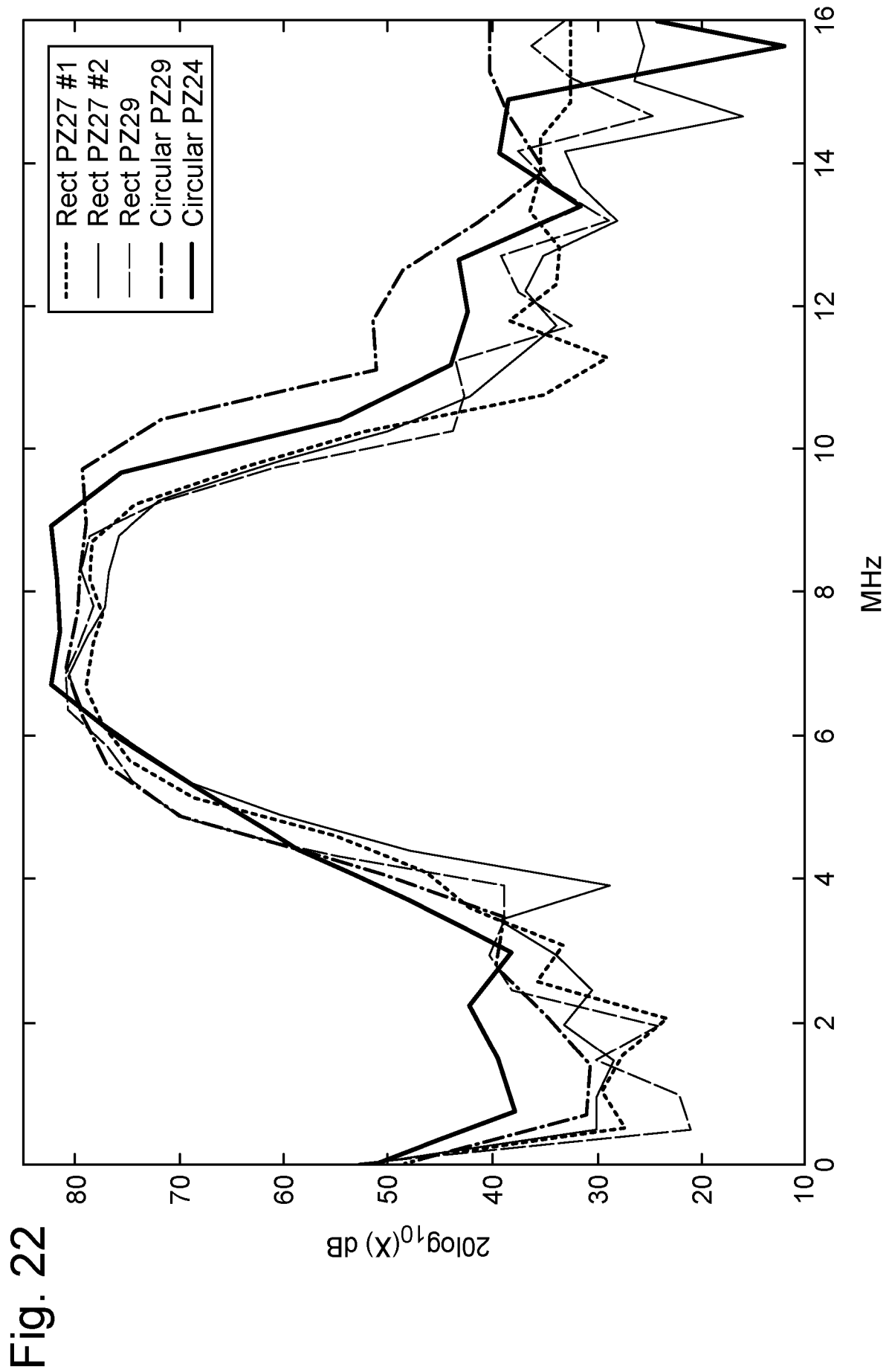


Fig. 21

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Fig. 23A

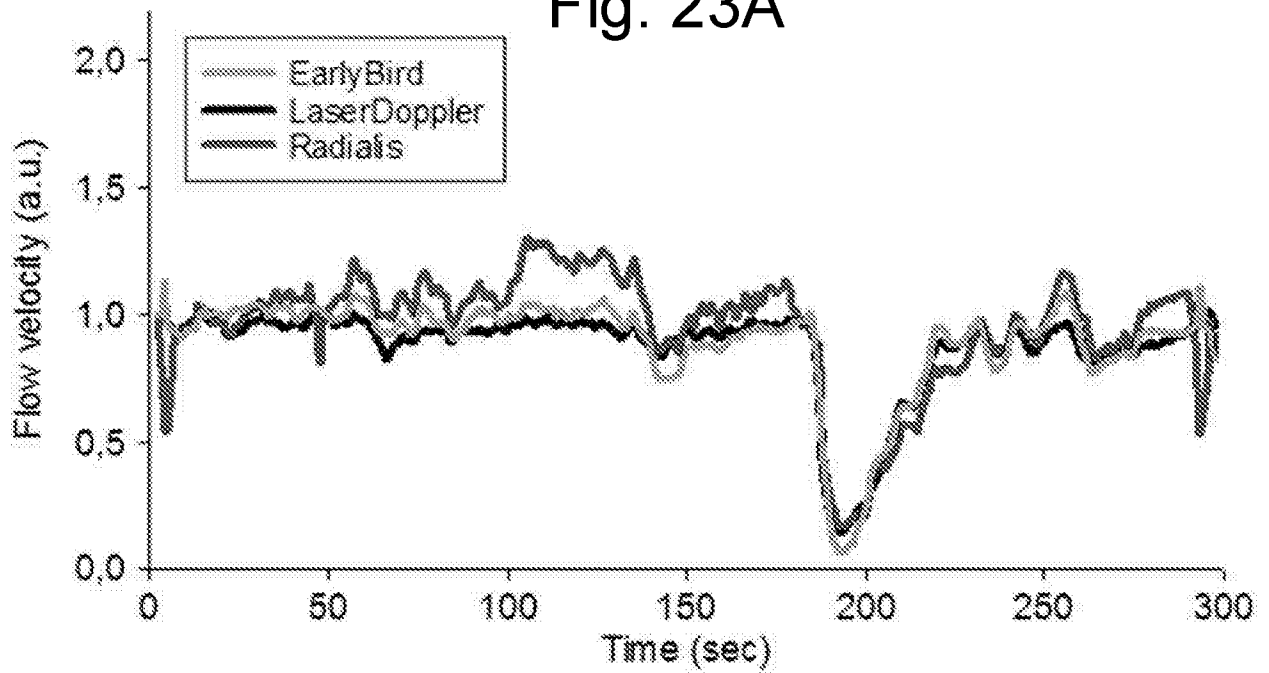
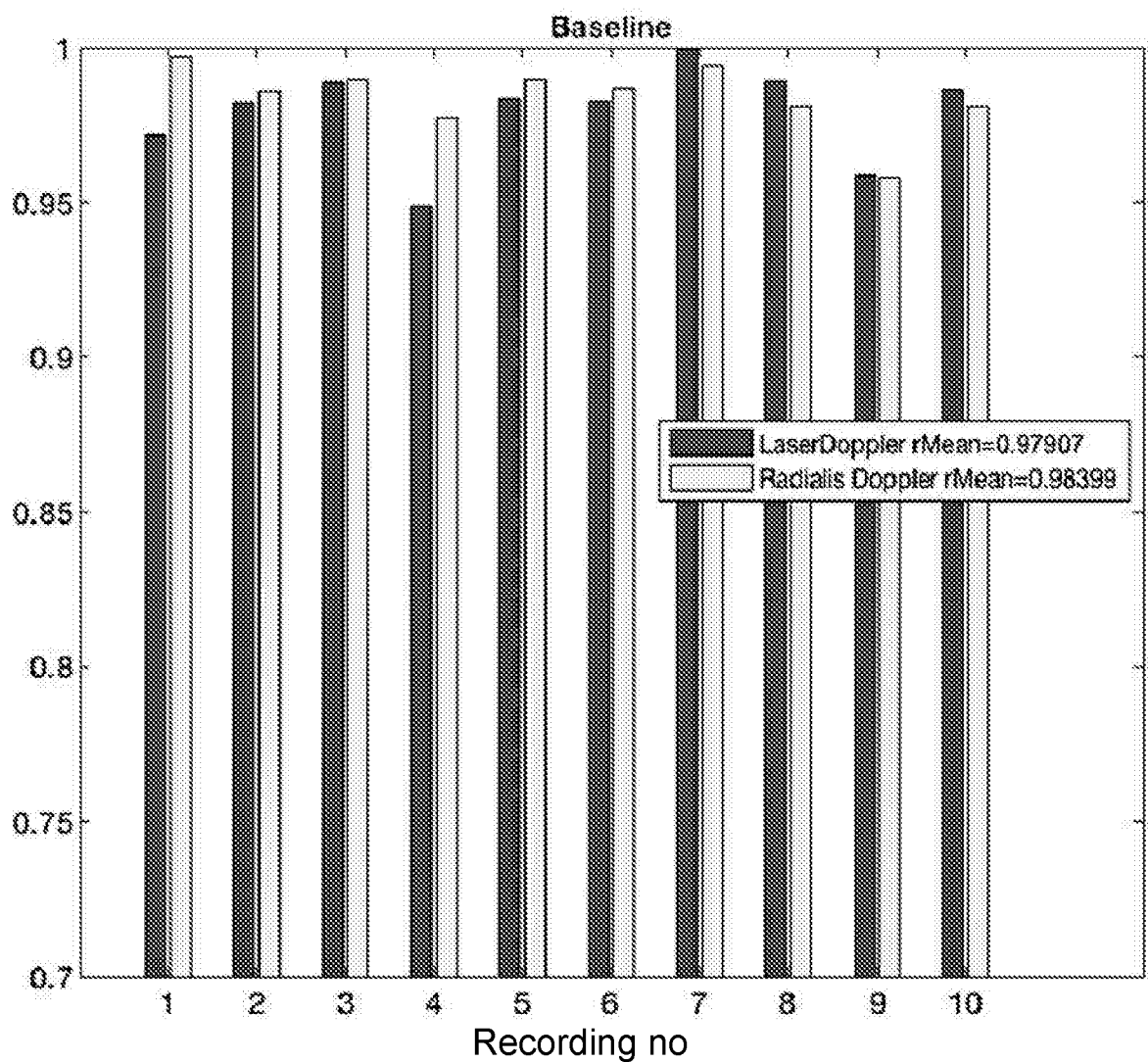


Fig. 23B



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Fig. 24

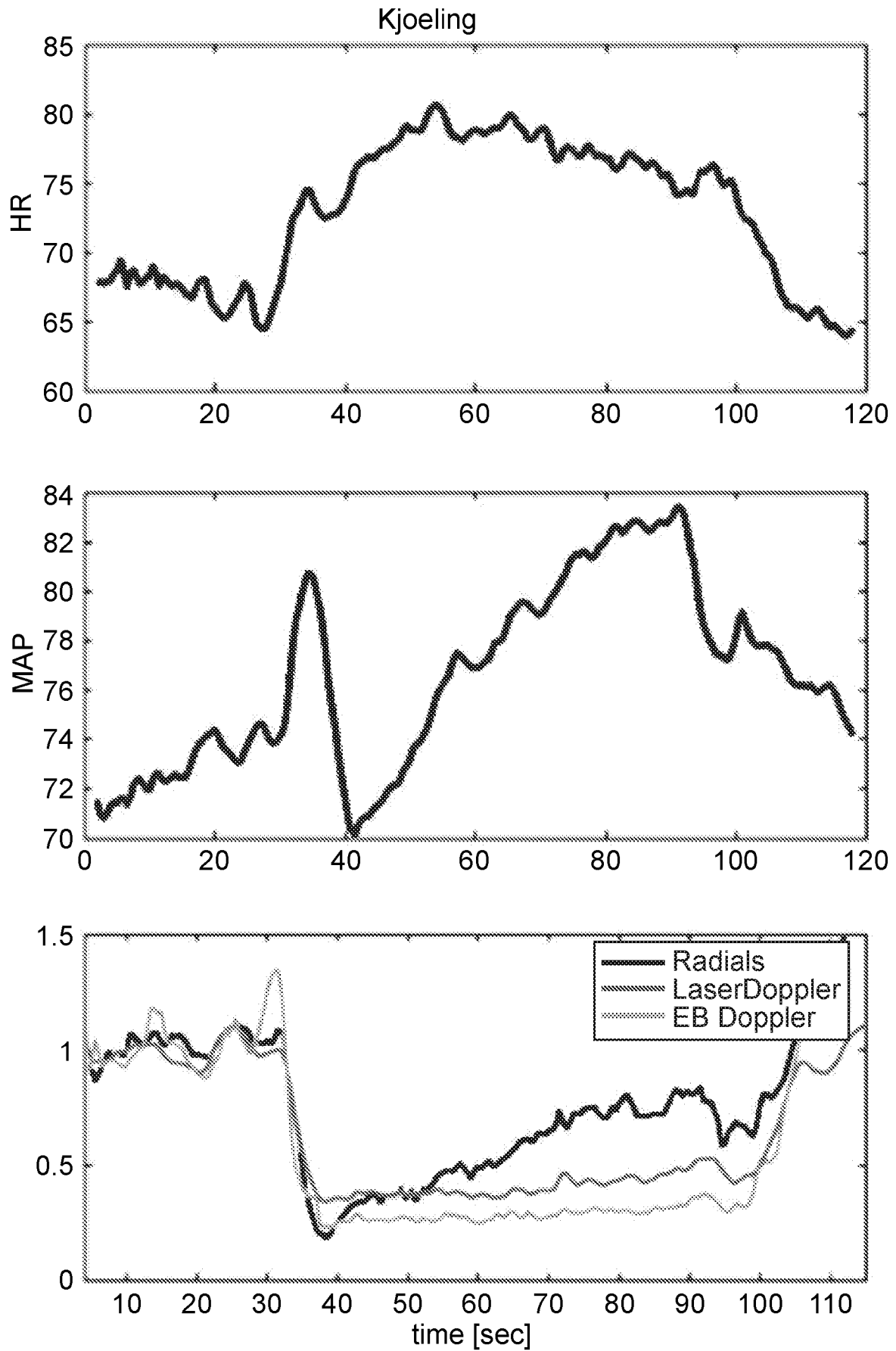


Fig. 25

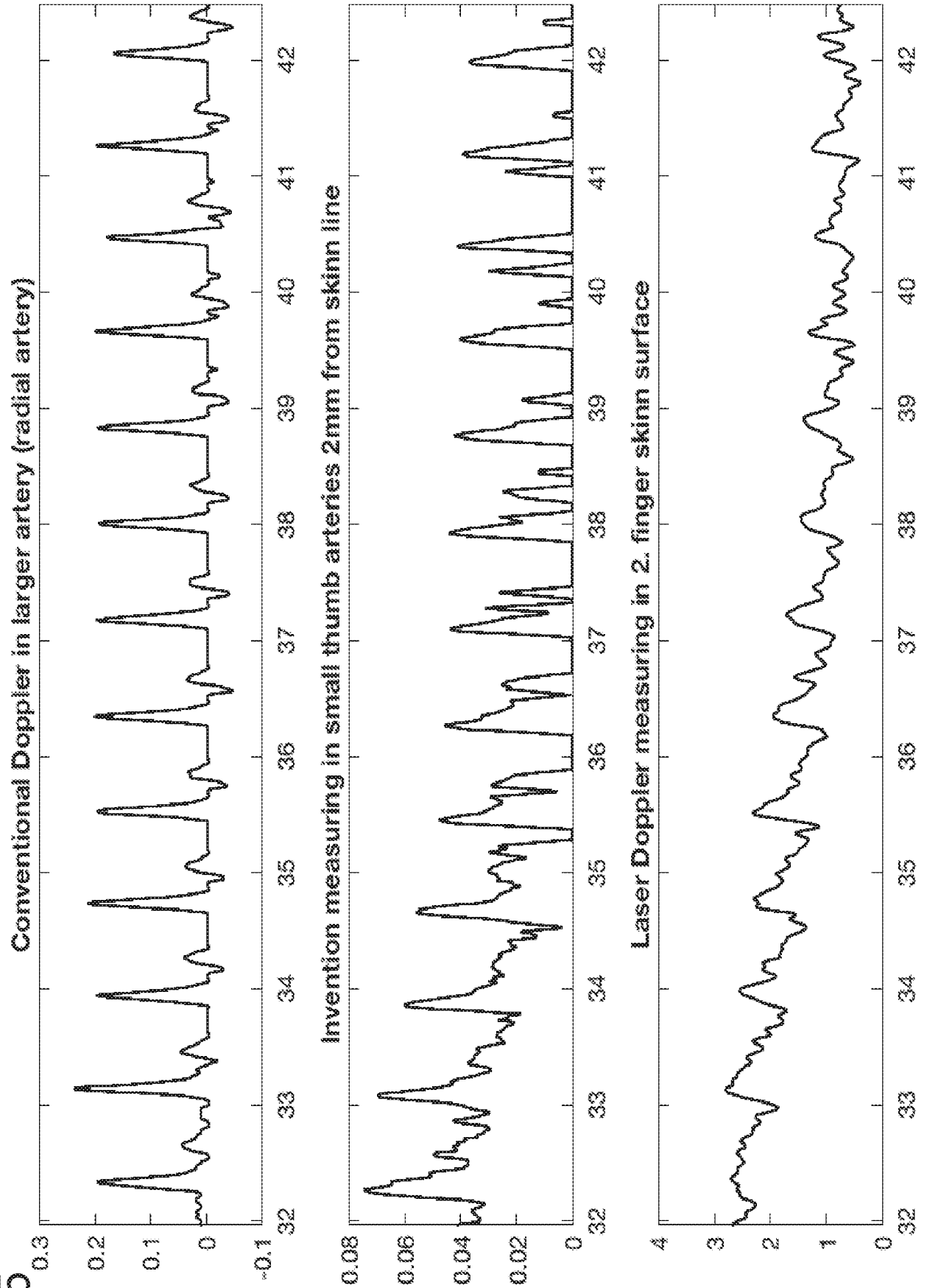


Fig. 26A

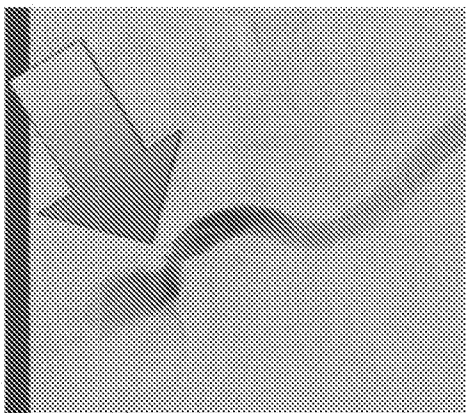


Fig. 26B



Fig. 26C

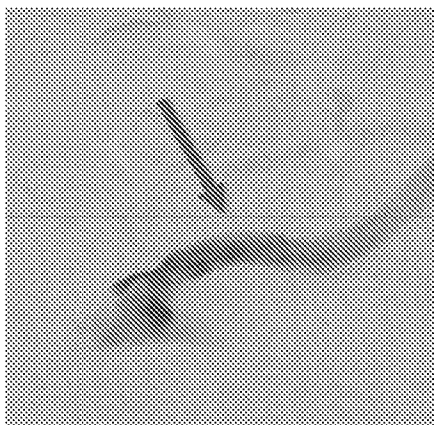


Fig. 26D

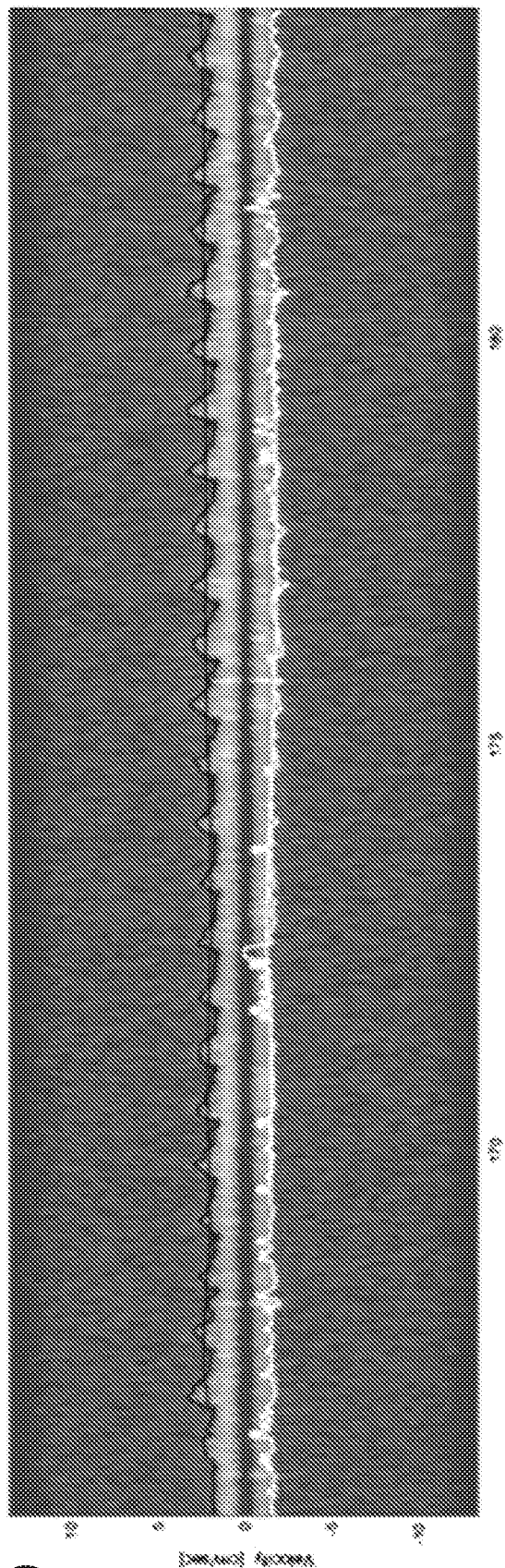


Fig. 26E

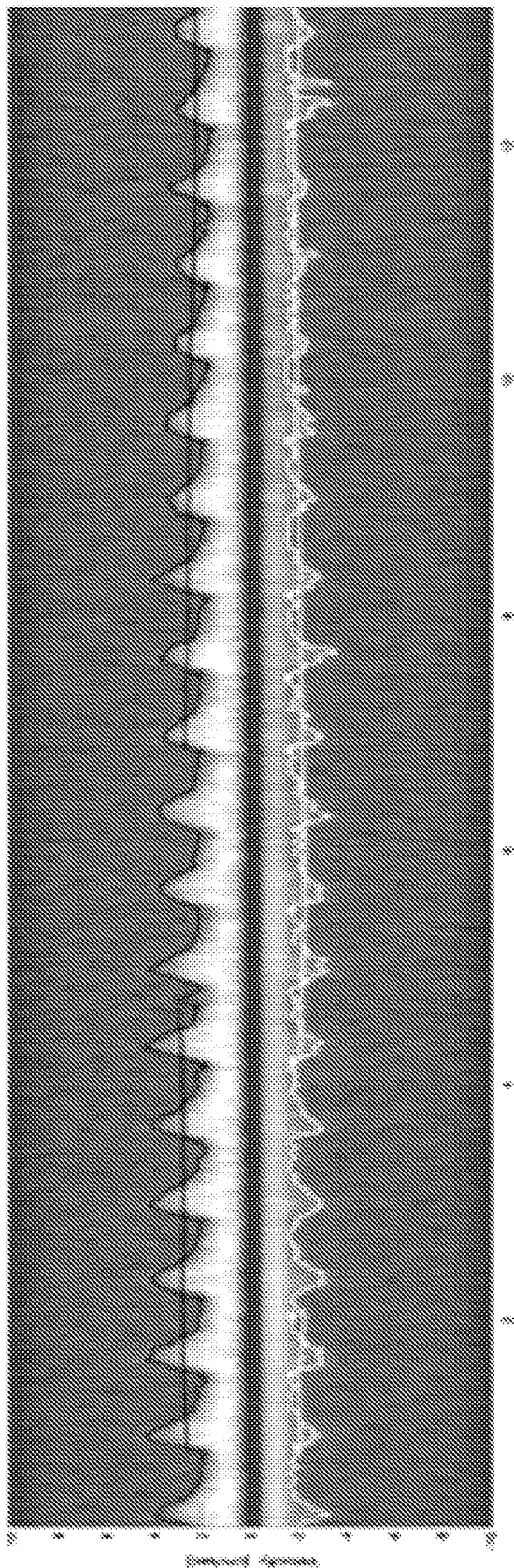
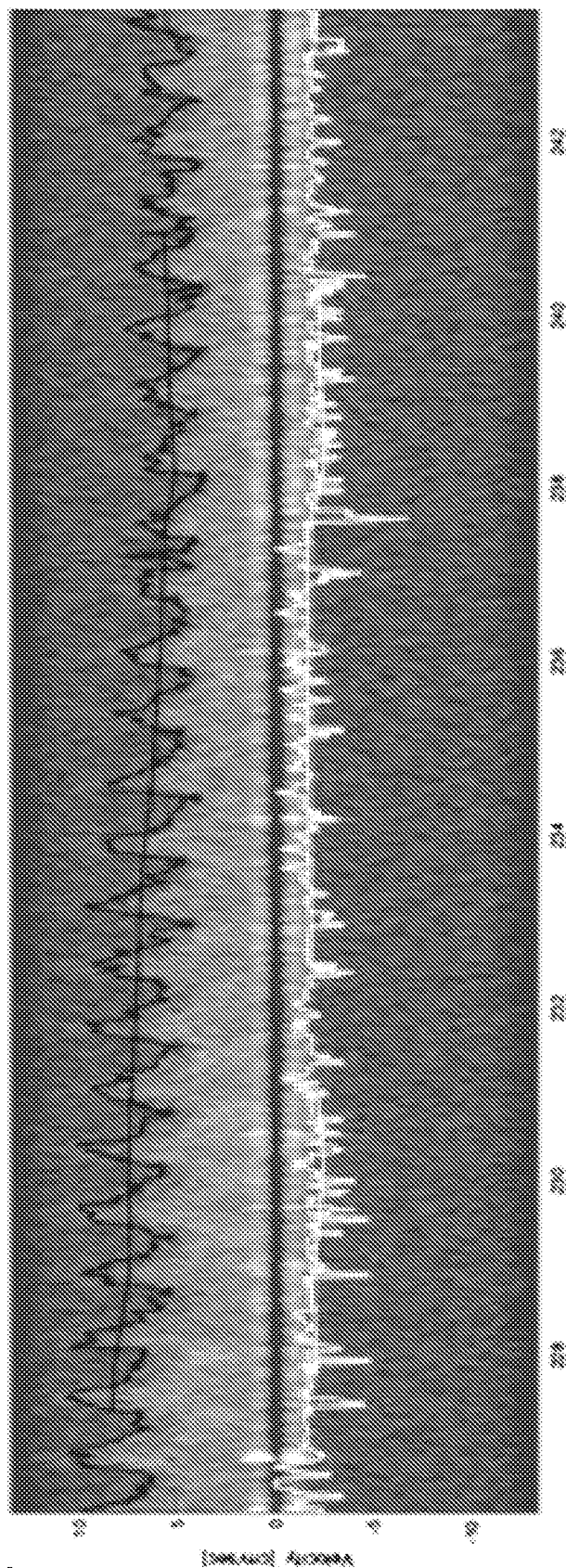


Fig. 26F



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Fig. 27A

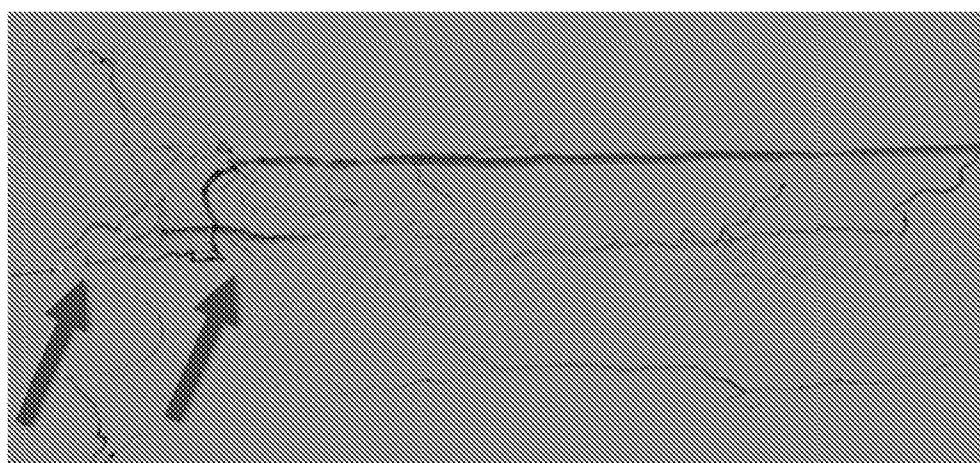
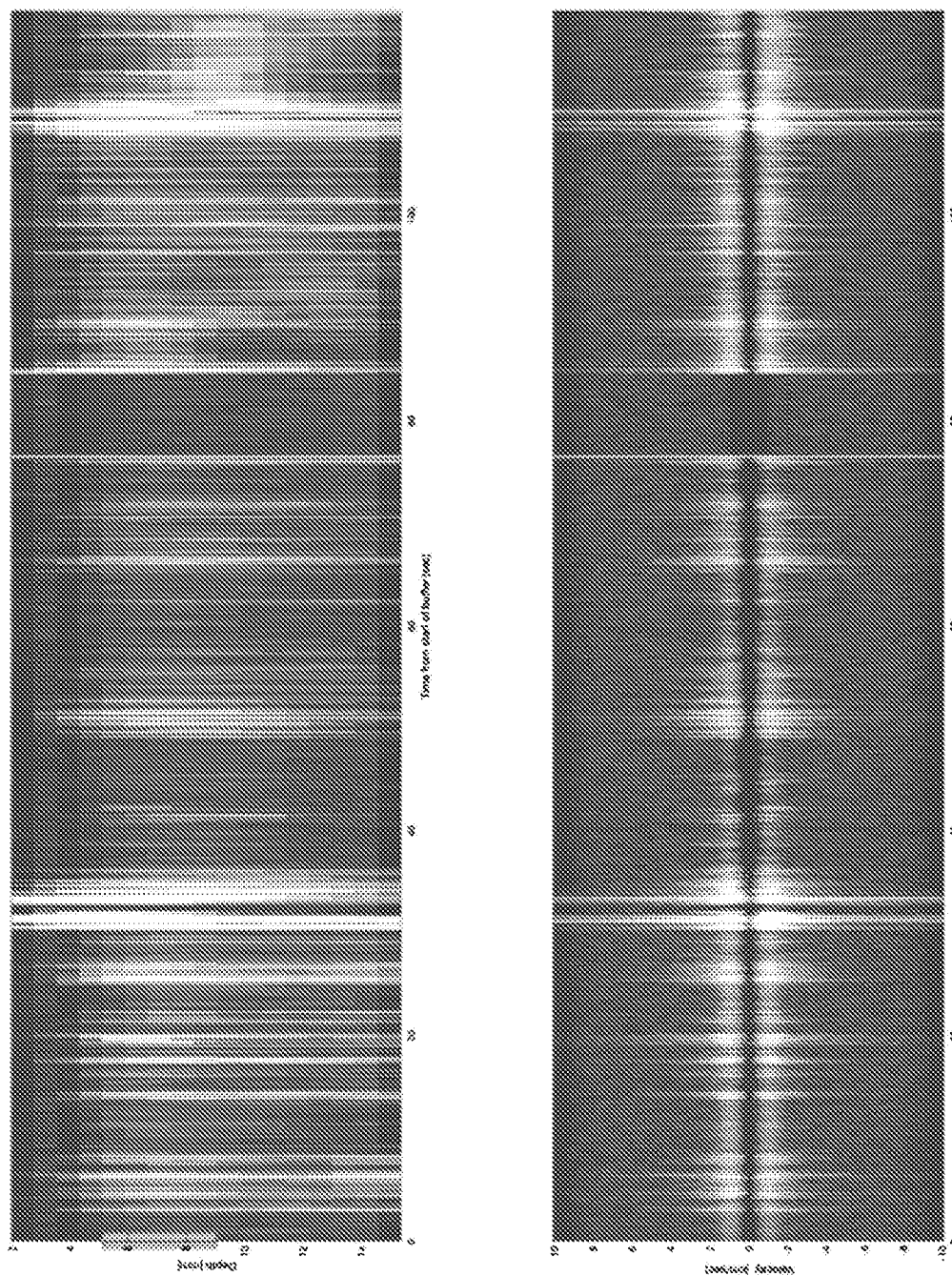
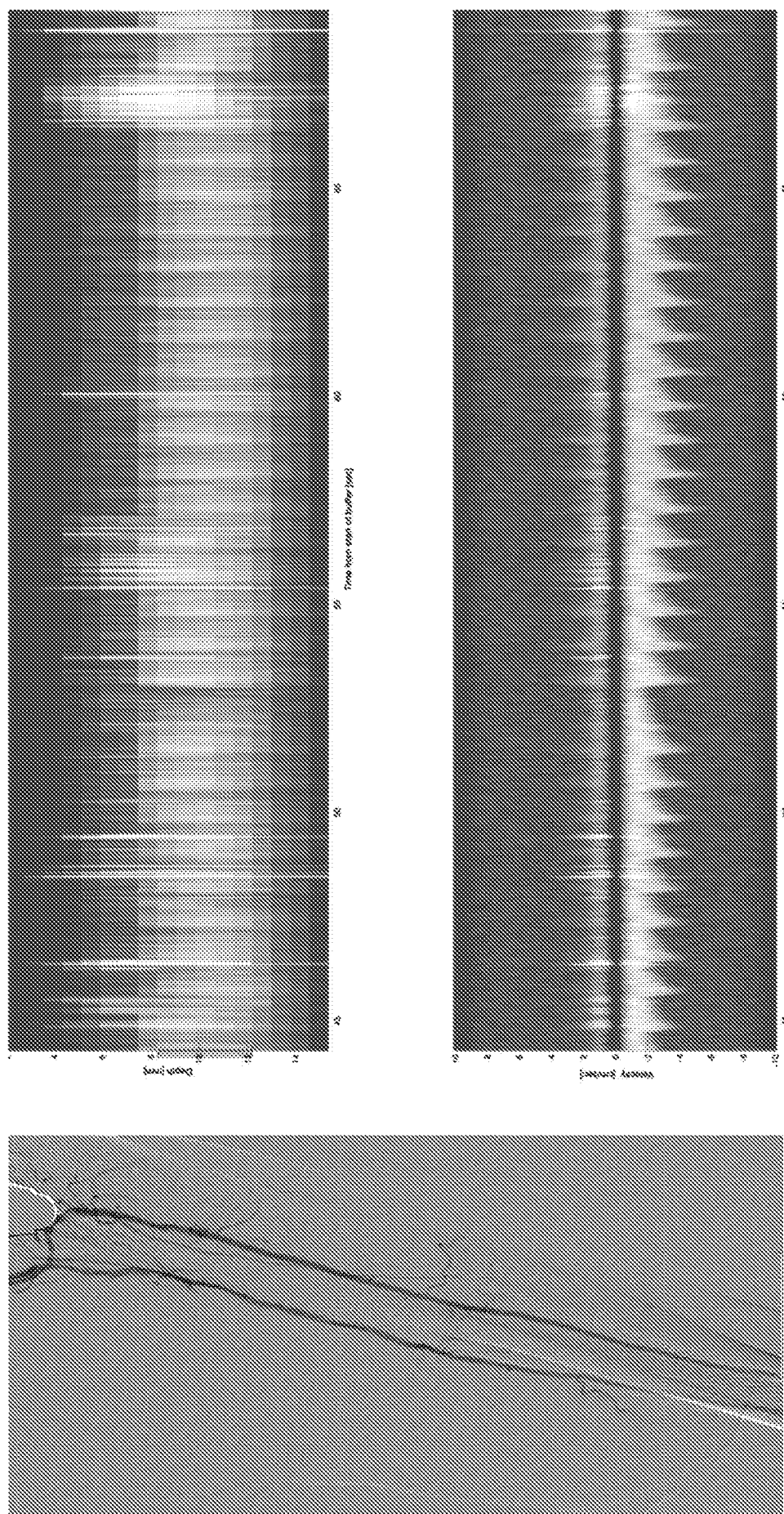


Fig. 27B



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/050341

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61B8/06 A61B8/08
ADD.

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)

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 practicable, search terms used)

EP0-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/326379 A1 (DAIGLE RONALD ELVIN [US] ET AL) 31 December 2009 (2009-12-31) paragraphs [0017], [0019], [0073], [0083], [0085], [0090] figure 2	1
A	----- S. M. BURNS ET AL: "Design for an Ultrasound-based Instrument for Measurement of Tissue Blood Flow", BIOMATERIALS, ARTIFICIAL CELLS AND ARTIFICIAL ORGANS, vol. 17, no. 1, 11 January 1989 (1989-01-11), pages 61-68, XP055585100, US ISSN: 0890-5533, DOI: 10.3109/10731198909118269 abstract -----	1

☐ Further documents are listed in the continuation of Box C.

☒ See patent family 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 application or patent 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

3 May 2019

Date of mailing of the international search report

21/05/2019

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Willig, Hendrik

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2019/050341

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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.: 2-18
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 2-18 define diagnostic methods practised on the human or animal body and methods for treatment of the human or animal body by therapy and surgery in the sense of Rule 39.1(iv) PCT. For the reasons it is referred to Item III in the Written Opinion of the International Searching Authority.
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 No. III Observations where unity of invention is lacking (Continuation of item 3 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 fees, this Authority did not invite payment of additional fees.
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 and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2019/050341

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009326379	A1	31-12-2009	CA 2728998 A1 30-12-2009
			CN 102123668 A 13-07-2011
			DK 2303131 T3 04-05-2015
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			JP 5858783 B2 10-02-2016
			JP 2011526181 A 06-10-2011
			KR 20110027806 A 16-03-2011
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			WO 2009158399 A1 30-12-2009
