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(54) Title: A SYSTEM AND METHOD FOR CHARACTERIZING LESIONS AND BLOOD VESSEL WALLS USING MULTI–POINT PRESSURE MEASUREMENTS

(57) Abstract

The present invention relates to devices and methods determining tubular wall properties for improved clinical diagnosis and treatment. Advantageously, tubular wall characteristics are recorded that correspond to the distensibility and compliance of the tubular walls. More specifically, the invention provides for a quantitative determination of the pressure wave velocity (PWV) of blood vessels, thereby characterizing, *inter alia*, the Young modulus, the distensibility, the compliance and the reflection coefficient of aneurysms, lesioned and non–lesioned parts of blood vessels. The determined properties may be further used to evaluate the degree of calcification of lesioned and non–lesioned parts of blood vessels. These determined values can be calculated and reported in absolute terms as a ratio of the relevant paramater value in the lesion region to the parameter value in a non–lesion region of the same patient. Alternatively, the system may calculate and report a ratio of the relevant parameter determined in the lesion region of the patient to a "standard" average value of the relevant parameter as measured in a group of healthy people with similar physiology (age group, gender, vessel type, etc.). These values are used to determine the medically and economically optimal treatment method or combination of methods of choice, and to evaluate the effectiveness and success of the treatment of choices, during the procedure and with time. These methods allow measurement of early physiologic, i.e. functional, changes in the arterial wall. This allows for a level of therapy which presently does not exist in clinical medicine.

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A SYSTEM AND METHOD FOR CHARACTERIZING LESIONS AND BLOOD VESSEL WALLS USING MULTI-POINT PRESSURE MEASUREMENTS

CROSS REFERENCES TO RELATED APPLICATIONS

This Application claims the benefit of U.S. Provisional Application No. 60/071,255 filed on January 12, 1998 which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the field of medical diagnostic devices in general and to a system for intravascular characterizing blood vessel walls and lesions in particular.

2. Description of the Related Art

Vascular diseases are often manifested by reduced blood flow due to atherosclerotic occlusion of vessels. For example, occlusion of the coronary arteries supplying blood to the heart muscle is a major cause of heart disease. Invasive procedures for relieving arterial blockage such as bypass surgery and balloon dilatation with a catheter are currently performed relying on estimates of the occlusion characteristics and the blood flow through the occluded artery. These estimates are based on measurements of occlusion size and / or blood flow. Unfortunately, current methods of occlusion size compliance (rarely used), obstruction to flow and blood flow measurement have low resolution, are time consuming, require expertise in the interpretation of the results and are expensive. Thus, decisions on whether or not to use any of the blockage relieving methods and which of the methods should be used are often based on partial information.

Pressure, flow and geometry are three variables often measured in the cardiovascular system. Recent progress in probe miniaturization and improvements of the frequency

response of probe sensors have opened a whole new range of pressure and flow measurements that have been previously impossible to perform.

Atherosclerotic lesions may have different characteristics. Some lesions exhibit a variable degree of calcification while others have a fatty or thrombotic nature. Lesion characteristics together with vessel condition proximal and distal to the lesion are the major factors for determining the therapeutic procedure needed. Typically, the physician first selects the appropriate treatment method from among medication therapy, transcatheter cardiovascular therapeutics (TCT), coronary artery bypass grafting (CABG), or non-treatment. Recently, increasing number of patients are directed toward TCT. TCT starts with an interventional diagnosis procedure (mostly angiography), followed by the treatment of the patient with medication therapy, CABG or continuation of the TCT procedure with interventional treatment.

Numerous methods are currently available for treating various lesion types. Some of these methods are given hereinbelow, sequenced from "softer" to "heavier", relating to their ability to open calcified lesions; percutaneous transluminal angioplasty (PTCA), "Cutting balloon" angioplasty, directional coronary atherectomy (DCA), rotational coronary atherectomy (RCA), Ultrasonic breaking catheter angioplasty, transluminal extraction catheter (TEC) atherectomy, Rotablator atherectomy, and excimer laser angioplasty (ELCA). Often, stents are placed within the lesion so as to prevent re-closure of the vessel (also known as recoil). Mostly stent is placed after lumen predilatation PTCA. Stenting without predilatation is also performed at increasing rates, saving both costs and time. In some cases, e.g. carotid stenting, primary stenting is clinically superior. In this case, debris, produced by the dilatation are held in place by the stent, instead of flowing downstream and causing a stroke.

Lesion characteristics, together with vessel condition proximal and distal to the lesion, are used to determine the medically and economically optimal treatment method or combination of methods of choice.

A clinically important lesion characteristic is the lesion calcification level. A non-calcified arterial wall or lesion is usually a non-chronic, fat based plaque that may be treated

by medication therapy, or by the softer, less expensive, PTCA method. Heavily calcified lesion wall typically requires harder methods, such as ELCA. Furthermore, the vessel wall calcification level influences the decision whether to use a dilatation balloon prior to stenting.

For example, in cases of very soft lesions, the physician may elect not to use a dilatation balloon prior to stenting. In cases where the degree of calcification dictate the use of such a balloon, the vessel wall calcification level influences the optimal inflation pressure of the dilatation balloon.

Chapter 12 entitled "CALCIFIED LESIONS" of the book "The New Manual of Interventional Cardiology" (Eds. Mark Freed, Cindy Grines and Robert D. Safian, Physicians' Press, Birmingham, Michigan, 1996, pp. 251-261), discusses various methods for the assessment of the degree of vessel wall calcification and their importance in selecting a treatment method.

Decisions about post dilatation processes such as stent deployment for preventing wall recoil and restenosis, or radiation exposure for preventing restenosis caused by cell proliferation, are also influenced by vessel wall and lesion characteristics.

Unfortunately, while lesion geometry is evaluated by angiography, qualitative coronary angiography (QCA), or by intravascular ultrasound (IVUS), accurate information regarding the vessel wall structure and composition and the degree of calcification of the lesion and of the vessel wall sections neighboring the lesion is frequently unavailable due to technical limitations and the expense involved in obtaining this information. Similarly, for the same reasons, information about the total rate of blood flow through the lesioned vessel are frequently unavailable to the physician.

The available diagnostic methods for assessing vessel wall structure and degree of calcification may be categorized according to their "intervention complexity", as judged by the duration of the diagnostic procedure and the complexity of interpretation of the results, or to the measurement principle: either imaging or physiological measurements. These available diagnostic methods are listed in TABLE 1 hereinbelow.

TABLE 1

	High intervention complexity	Low intervention complexity
Imaging	IVUS Angioscopy	angiography angiography + QCA
Physiological flow measurements	Doppler velocity sensor	Pressure sensor

When angiography is used for calcification evaluation, an arc of at least 180 degrees of calcification is required to achieve identification of a mass of calcium and quantification of calcification is difficult. Thus, angiography demonstrates poor sensitivity for detecting mild to moderate lesion calcium, and only moderate sensitivity for extensive lesion calcium. For example, Jeffrey J. Pompa and Martin B. Leon show in an article entitled "A Lesion Specific Approach To New-Device Angioplasty" in "Textbook of Interventional Cardiology" published by W.B. Saunders (1993), that more than 10% of the lesions that were angiographically identified as calcified, were found by IVUS to be non-calcified.

IVUS is the most informative tool that provides reliable information about wall characteristics. IVUS provides a penetrating ultrasound image of the vessel wall. The lesion wall characteristics, including calcification zones can be assessed from this ultrasound image. Late works in IVUS interpolation present evaluation of wall elasticity by comparing vascular cross sections at different pressure levels. These methods are still within preliminary research and the combination and pressure measurement increases the complexity of the procedure, therefore prevents its wide implementation.

When standard balloon therapeutic methods have failed or are suspected to be ineffective, use of other methods is needed. Failures are due either to lesion rigidity or to complications such as coronary dissection or abrupt vessel closure. In undilatable lesions, where the lumen residual diameter is less than 50%, atherectomy and ablative devices are used. Decision making procedures for therapeutic strategy are based on characterization of

vessel rigidity/elasticity and more specifically on the calcification level and spread. Generally, the calcification level plays a major role, discriminating between deep and superficial calcification as described by Pompa and Leon.

However, the interpretation of the IVUS ultrasound image for assessing the degree of calcification is subjective and non-quantitative, requires a high degree of skill and expertise, and is subject to well known limitations of ultrasound methods such as, *inter alia,* shadowing and high cost. IVUS is also a time consuming procedure. Additionally, while IVUS provides some indication of lesion geometry and composition, it does not measure blood flow.

Consequently, currently IVUS is still primarily used for research purposes, and is not routinely used in the majority of catheter-labs due to its high cost, lack of expert personnel, and its being a time consuming procedure.

It frequently happens that even in angiographically normal blood vessel segments, the average plaque burden in the normal reference segment may comprise 40% of the total vessel cross-sectional area. This happens because with increasing plaque accumulation, there is a remodeling process whereby the vessel expands to accommodate the plaque load.

The inability of angiography to detect this occult disease is due to the presence of positive arterial remodeling and the diffuse nature of disease throughout the entire vessel length in many patients. There is therefore a need for a diagnostic method that can identify these "angiographically silent" diseased vessel segments for enabling timely treatment and/or monitoring of vessel disease propagation.

Endothelial cells, lining the internal vessel lumen are known to play an important function in lesion formation, plaque rupture, angiogenesis and additional clinical processes. The local combination of mechanical forces acting on the Endothelial cells and to some extent on the underlying cell tissues (including the smooth muscle cells and the intima) initiate and affect biological, clinically important processes.

The following mechanical stimulus are known to affect cellular activity in the vessel

wall:

-Pressure

-Fluid flow friction

-Circumferential strain

While pressure is routinely measured during interventional procedures and fluid flow friction (known as shear stress) may be derived from velocity profiles, derived from either external ultrasound measurements or from intravascular doppler measurement, no method is able to detect circumferential strain. The paper "Loading Paradigms - Intentional and Unintentional - for Cell Culture Mechanostimulus. Brown, D.T. et al., *Am J Med Sci* 316, 1998 "present the recent interest in the response of cells to the circumferential strain stimuli. Thus, the need exists for improved procedures and techniques for characterizing blood vessel walls and lesions which result in improved diagnosis and recommendations for treatment.

SUMMARY OF THE INVENTION

Lesion characteristics, together with vessel condition proximal and distal to the lesion, are used to determine the medically and economically optimal treatment method or combination of methods of choice. Systems and methods of use thereof have been designed which provide information regarding wall physiology fluid flow and characterization of lumen structure which provide for improved treatment of diseased or injured vascular structures. In the preferred embodiment, the system provides information from multiple points of measurement within the blood vessels, which allows assessment of wall structure, physiology and mechanical properties. Specifically, by determining the elastic properties of the blood vessels, one can calculate the distensibility and compliance of lesioned and non-lesioned parts of blood vessels. Comparisons of the values with standard values in people of similar age, gender, etc., or to the same patient, same procedure, values but in different vessels or different location within the same vessel, or to the same patient values over a range of time provide a means for assessment of disease and/or treatment over time. This also

provides a means for determining the most efficacious treatment, particularly with regard to those individuals which have occlusions of less than 50%.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be understood and appreciated more fully from the following detailed description taken in conjunction with the appended drawings in which like components are designated by like reference numerals:

Fig. 1 is a schematic isometric view of a system for characterizing lesioned and non-lesioned blood vessel walls, constructed and operative in accordance with a preferred embodiment of the present invention;

Fig. 1a is a schematic isometric view of a system for characterizing lesioned and non-lesioned blood vessel walls, constructed and operative in accordance with another preferred embodiment of the present invention;

Fig. 2 is a schematic functional block diagram illustrating the details of the system 1 of Fig. 1;

Fig. 2a is a schematic functional block diagram illustrating the details of the system 1.a of Fig. 1.a;

Fig. 3 is a schematic cross section illustrating the positioning of a pressure catheter of the system of Fig. 1 or 1a within a blood vessel during the operation of the system of Fig. 1 or 1a;

Fig. 3a is a schematic cross section illustrating the another positioning of a pressure catheter of the system of Fig. 1 or 1a across the stenosis, within a blood vessel during the operation of the system of Fig. 1 or 1a;

Fig. 4 is a schematic isometric view of an in-vitro system for characterizing lesioned and non-lesioned blood vessel walls, constructed and operative in accordance with a preferred embodiment of the present invention;

Fig. 5 is a schematic detailed illustration of the in-vitro tubing system 51 of Fig.4.;

Fig. 6 is a detailed schematic illustration of the experimental section 44 of Fig.4 and the positioning of the pressure sensors within a the latex tube during the operation of the system of Fig. 4;

Fig. 7 is a schematic cross section illustrating the positioning of the three pressure sensors of Procedure 1 and Method 1, within a lesioned or non-lesioned blood vessel;

Fig. 8 is a schematic cross section illustrating the positioning of the two pressure sensors of procedure 2, within a lesioned or non-lesioned blood vessel;

Fig. 9 is a schematic flow chart illustrating the steps of the method of determining the pressure wave velocity within a blood vessel from pressure data obtained simultaneously by three separate pressure sensors, in accordance with a preferred embodiment of the present invention;

Fig. 10 is a schematic flow chart illustrating the steps of the method of determining pressure wave velocity within a blood vessel from pressure data obtained simultaneously by two separate pressure sensors, using the level fitting procedure, constructed and operative in accordance with another preferred embodiment of the present invention;

Fig. 11 is a schematic flow chart illustrating the steps of the method of determining pressure wave velocity within a blood vessel from pressure data obtained simultaneously by two separate pressure sensors, using the optimal overlap procedure, constructed and operative in accordance with another preferred embodiment of the present invention;

Fig. 12a is a schematic flow chart illustrating the steps of the method (first approach) of determining pressure wave velocity within a blood vessel from pressure data obtained simultaneously by a fluid field (FF) pressure transducer system and one moving intravascular pressure sensor, constructed and operative in accordance with another preferred embodiment of the present invention;

Fig. 12b is a schematic flow chart illustrating the steps of the method (second approach) of determining pressure wave velocity within a blood vessel from pressure data

obtained simultaneously by a fluid field (FF) pressure transducer system and one moving intravascular pressure sensor, constructed and operative in accordance with another preferred embodiment of the present invention;

Fig. 13 is a schematic cross section illustrating the positioning of one moving intravascular pressure sensor and an FF pressure transducer system as described in Procedure 3, within a lesioned or non-lesioned blood vessel;

Fig. 14 is a schematic cross section illustrating the positioning of two intravascular pressure sensors and an FF pressure transducer system as described in Method 2, within a lesioned or non-lesioned blood vessel;

Fig. 15 is a schematic cross section illustrating the positioning of the two pressure sensors of Method 3, within a lesioned or non-lesioned blood vessel;

Fig. 16 is a schematic cross section illustrating the positioning of three pressure sensors within a pig carotid during an in-vivo experiment;

Fig. 17a-17d illustrates in-vivo pressure raw data acquired with two intravascular pressure sensors positioned within the pig carotid; b. applying Procedure 2.a to the raw data presented in a. and detecting the PWV based on 10% level fitting; c. applying Procedure 2.b to the raw data presented in a. and detecting the PWV based on optimal overlap between the two signals; d. using data of three pressure signals and applying Procedure 1 to derive PWV. All methods presented similar PWV values.

Fig. 18 illustrates the pressure wave velocity derived by Procedure 2.a on in-vivo pressure raw data acquired with two intravascular pressure sensors positioned within the pig coronaries (left circumflex). The numbers appearing on the graph indicate PWV in meter per sec as calculated for each stroke;

Fig. 19a-19d illustrates in-vitro pressure raw data acquired with three intravascular pressure sensors positioned within the experimental latex section; b. applying Procedure 1 to the raw data presented in a. and detecting the averaged PWV; c. applying Procedure 2.a to the

raw data presented in a. and detecting the PWV based on 10% level fitting on a series of strokes, yielding a PWV value for each stroke and the averaged PWV value. Both methods presented similar PWV values.

Fig. 20 is a schematic cross section illustrating the positioning of one intravascular pressure sensor and an FF pressure transducer system as described in Method 4, within a lesioned or non-lesioned blood vessel;

Fig. 21 is a schematic cross section illustrating the positioning of one moving intravascular pressure sensors and an FF pressure transducer system as described in Method 5, within a lesioned or non-lesioned blood vessel;

Fig. 22 is a schematic cross section illustrating the positioning of one moving intravascular pressure sensor and a FF pressure transducer system connected through the standard guiding catheter within a pig carotid during an in-vivo experiment;

Fig. 23a-23b illustrate the application of Procedure 3 to in-vivo pressure raw data acquired with a moving intravascular pressure sensor and FF pressure transducer positioned in point A and then B within the pig carotid. The numbers appearing on the graph indicate a procedural interim value as calculated for each stroke;

Fig. 24 illustrates the validation of the results presented in Figs. 23a-23b by applying Procedure 2.a to two intravascular pressure sensors within the pig carotid. The numbers appearing on the graph indicate PWV in meter per sec as calculated for each stroke;

Fig. 25a - 25b present the simultaneous raw data of FF and Radi pressures at proximal position;

Fig. 26a - 26b present the simultaneous raw data of FF and Radi pressures, at distal position;

Fig. 27 illustrates one pulse of the two FF pressure signals (proximal and distal);

Fig. 28 illustrates the application of the optimal overlap procedure on the signals of Fig. 27;

Fig. 29 illustrates one pulse of the two Radi pressure signals (proximal and distal);

Fig. 30 illustrates the application of the optimal overlap procedure on the signals of Fig. 27;

Fig. 31 is a schematic cross section illustrating the positioning of one moving intravascular flow probe and an FF pressure transducer system as described in Method 6, within a lesioned or non-lesioned blood vessel;

Fig. 32a-32b illustrates flow raw data [ml/min] acquired on the in-vitro system with an ultrasonic flowmeter probe positioned within the experimental latex section; b. illustrates in-vitro pressure [mmHg] raw data acquired with an intravascular pressure sensor probe positioned within the experimental latex section;

Figs. 33-34 illustrate the application of Procedure 3 to the flow and pressure raw data, detecting the PWV;

Figure 35 is a cross section illustrating the positioning of a single pressure transducer of procedure 5 and method 7, within a stenosed blood vessel;

Figure 36 is a cross section illustrating the positioning of a single pressure transducer of procedure 5 and method 7, within a pig carotid during an in-vivo experiment;

Figure 37 illustrates in-vivo pressure raw data acquired with a single pressure sensor positioned within the pig carotid;

Figure 38 illustrates the cepstrum of the pressure raw data presented in Fig. 37, calculated using the first step of procedure 5;

Figure 39 illustrates the final result of procedure 5, as applied to the raw data of Fig. 37;

Figure 40 illustrates the reflection coefficient calculation from the raw data presented in Fig. 37;

Figure 41 illustrates in-vivo pressure raw data acquired with a single pressure sensor positioned at a second position within the same pig carotid;

Figure 42 illustrates the cepstrum of the pressure raw data presented in Fig. 40, calculated using the first step of procedure 5; and

Figure 43 illustrates the final result of procedure 5, as applied to the raw data of Fig. 40.

Figure 44 illustrates the reflection coefficient calculation from the raw data presented in Fig. 41.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention relates to devices and methods determining tubular wall properties for improved clinical diagnosis and treatment. Advantageously, tubular wall characteristics are recorded that correspond to the distensibility and compliance of the tubular walls. More specifically, the invention provides for a quantitative determination of the pressure wave velocity (PWV) of blood vessels, thereby characterizing, *inter alia,* the Young modulus, the distensibility and the compliance of lesioned and non-lesioned parts of blood vessels. The determined properties may be further used to evaluate the degree of calcification of lesioned and non-lesioned parts of blood vessels. These determined values can be calculated and reported in absolute terms as a ratio of the relevant parameter value in the lesion region to the parameter value in a non-lesion region of the same patient. Alternatively, the system may calculate and report a ratio of the relevant parameter determined in the lesion region of the patient to a "standard" average value of the relevant parameter as measured in a group of healthy people with similar physiology (age group, gender, vessel type, etc.). In this second alternative, the system will include means for storing such standard averaged values of the relevant parameters such as a data-base stored in a suitable storage device included in the system (not shown). These methods allow measurement of early physiologic, i.e. functional, changes in the arterial wall. This allows for a level of therapy which presently does not exist in clinical medicine.

In understanding how to interpret such characteristics it will be appreciated that significant changes are observed in the hemodynamic characteristics of blood vessels with aging and/or disease-state such as hypertension and atherosclerosis. Basically, the large arteries dilate and stiffen, the collagen/elastin ratio increases, thus reducing the vessel distensibility. For example, the elastic modulus of the human aorta, more than doubles between the age of 20 and 60 years. The diameter of the human ascending aorta increases by 9% per decade, and the aorta wall thickened to a bigger extent, raising the ratio of vessel wall thickness to the vessel's radius. These processes result in an increased PWV within the vessel. Calcification of the vessel wall in particular regions causes significant increase in

PWV in the calcified region. Comparing the measured PWV to the statistically computed PWV provides a PWV ratio. These PWV measurements and the reported PWV ratio disclosed hereinabove may be useful in the detection of otherwise "angiographically occult" diseased vessel regions.

The present invention is embodied in a system for determining at least one viscoelastic parameter of a region of a blood vessel. The system comprises a flexible elongated member having a portion insertable into said blood vessel; means for simultaneously measuring the blood pressure in at least two predetermined positions along said longitudinal axis and for producing simultaneous pressure signals; and a processing unit connected to said means for measuring the blood pressure for receiving said pressure signals and for processing said simultaneous pressure signals to determine said at least one viscoelastic parameter.

Another embodiment of the present invention is found in a system for determining at least one viscoelastic parameter of a region of a blood vessel. The system comprises a flexible elongated member having a portion insertable into said blood vessel and a longitudinal axis; a plurality of pressure sensors, each of said plurality of pressure sensors being attached to said elongated member at a predetermined position along said longitudinal axis for simultaneously sensing the pressure at said positions and for producing pressure signals; and a processing unit connected to said plurality of sensors for receiving said pressure signals and for processing said pressure signals to determine said at least on viscoelastic parameter.

The present invention is embodied in a method for determining at least one viscoelastic parameter of a region of a blood vessel. The method comprises the steps of simultaneously measuring the pressure in at least two measurement points within said blood vessel to obtain data representing the variation of pressure with time at said at least two measurement points; calculating at least one viscoelastic parameter of said region from said data; and reporting said at least one viscoelastic parameter.

Yet another embodiment of the present invention is disclosed in a system for determining at least the pressure wave velocity and derived characteristics of a region of a blood vessel. The system comprises a flexible elongated member having a portion insertable into said blood vessel and a longitudinal axis; a plurality of pressure sensors, each of said plurality of pressure sensors being attached to said elongated member at a predetermined position along said longitudinal axis for simultaneously sensing the pressure at said positions and for producing pressure signals; and a processing unit connected to said plurality of sensors for receiving said pressure signals and for processing said pressure signals to determine said at least the pressure wave velocity and derived characteristics.

In another embodiment, a method for determining at least the pressure wave velocity and derived characteristics of a region of a blood vessel is disclosed. The method comprises the steps of simultaneously measuring the pressure in at least one measurement point within said blood vessel to obtain data representing the variation of pressure with time at said at least two measurement points; calculating said at least the pressure wave velocity of said region from said data; reporting said at least the pressure wave velocity and derived characteristics.

In another embodiment, a system for determining at least the pressure wave velocity and derived characteristics of a lesioned region of a blood vessel is disclosed. The system comprises a flexible elongated member having a portion insertable into said blood vessel; means for simultaneously measuring the blood pressure in at least one predetermined position along said longitudinal axis and for assessing simultaneous pressure signals; and a processing unit connected to said means for measuring the blood pressure for receiving said pressure signals and for processing said simultaneous pressure signals to determine said at least the pressure wave velocity and derived characteristics, and thereby recommend the best treatment needed.

In another embodiment, a system for determining at least the pressure wave velocity and derived characteristics of a region of a blood vessel, where a PTCA procedure has been applied. The system comprises a flexible elongated member having a portion insertable into

said blood vessel ; means for simultaneously measuring the blood pressure in at least one predetermined position along said longitudinal axis and for assessing simultaneous pressure signals; and a processing unit connected to said means for measuring the blood pressure for receiving said pressure signals and for processing said simultaneous pressure signals to determine said at least the pressure wave velocity and derived characteristics, and the efficacy of the PTCA applied intervention, or any other dilatation procedure.

In another embodiment, a system for determining at least the pressure wave velocity and derived characteristics of a lesioned region of a blood vessel, where a STENT was deployed. The system comprises a flexible elongated member having a portion insertable into said blood vessel ; means for simultaneously measuring the blood pressure in at least one predetermined position along said longitudinal axis and for assessing simultaneous pressure signals; and a processing unit connected to said means for measuring the blood pressure for receiving said pressure signals and for processing said simultaneous pressure signals to determine said at least the pressure wave velocity and derived characteristics, and the efficacy of the STENT deployment.

In yet another embodiment, a system for characterizing changes in a tubular conduit system within a living body for transferring fluids is disclosed. The system comprises a flexible elongated member having a portion insertable into said tubular conduit and a longitudinal axis; at least one pressure sensor being positioned along said elongated member at a predetermined location along said longitudinal axis for sensing the pressure and operative to generate a pressure signal representative of said sensed pressure at a plurality of points within said tubular conduit; a processing unit operatively connected in circuit to said at least one pressure sensor; a program for controlling said processor unit; said processor unit operative with said program to receive said pressure signal and to identify changes in the pressure signal; detect characteristics of said tubular conduit system being derived from changes in said pressure signal; recognize and assign a label to said characteristic.

The system as stated above wherein said at least one pressure sensor includes one pressure sensor movable relative to said tubular conduit; said pressure signal is representative of a plurality of pressure measurements taken over time a predetermined locations within said tubular conduit.

The system as stated above wherein said at least one pressure sensor includes two pressure sensors located in predetermined spaced-apart positions along said elongated member; said pressure signal is representative of a plurality pressure measurements taken simultaneously by said pressure sensors.

The system as stated above wherein said at least one pressure sensor includes three pressure sensors located in predetermined spaced-apart positions along said elongated member; said pressure signal is representative of a plurality pressure measurements taken simultaneously by said pressure sensors.

The system as stated above incorporating a B. CMOS implantable multiple pressure sensor chip of the type disclosed in "Full integration of a pressure sensor system into a standard B. CMOS process" pp. 211-214 of Sensor and Actuators A 67 (1998) published by Elsevier Science.

The system as stated above wherein said tubular conduit system is a blood vessel system; and said processor unit is operative to detect characteristics of a blood vessel wall wherein said characteristics of said blood vessel wall detected by said processor include vessel wall compliance and distensibility wherein said processor unit is operative to recognize wall calcification and thickening, thereby permitting occult disease identification wherein said processor unit is operative to recognize a low compliance thereby identifying weak vascular sections of said blood vessels.

Another embodiment includes a method for using a flexible elongated member having a portion insertable into said tubular conduit and a longitudinal axis, at least one pressure sensor being positioned along said elongated member at a predetermined location along said

longitudinal axis for sensing the pressure and operative to generate a pressure signal representative of said sensed pressure at a plurality of points within said tubular conduit, a processing unit operatively connected in circuit to said at least one pressure sensor, a program for controlling said processor unit, said processor unit operative with said program to receive said pressure signal to characterize changes in a tubular conduit system within a living body for transferring fluids. The method comprises the steps of sensing a pressure using said pressure sensor; generating a pressure signal representative of said sensed pressure at a plurality of points within said tubular conduit; identifying changes in the pressure signal; detecting characteristics of said tubular conduit system being derived from changes in said pressure signal; and recognizing and assigning a label to said characteristic.

Relationship of Measured Characteristics

The determination of the elastic properties of an artery is based on calculating the phase velocity of the pressure wave. It is noted that, actually, PWV is a complex number containing information on the phase velocity and the attenuation of the pressure wave. For simplicity of derivation the attenuation is initially ignored hereinbelow.

As a first approximation a linear model is assumed for the blood fluid equation based on the linearized Navier- Stokes equation. A linear model is also assumed for the vessel wall. This model is discussed in detail by William R. Milnor in Chapter 6 entitled "The Normal Hemodynamic State" of the book entitled "Hemodynamics", published by Williams & Wilkins, Maryland (1989) and is known as Womersley's model. The link between a vessel's phase velocity and elastic properties is already contained in the following simplified model.

Consider a cylindrical tube, assumed to represent a vessel, in which a gradient of pressure is present wherein **r** is the density of blood assumed to be incompressible, **A**(x,t) is the cross section area at a point **x** along the longitudinal axis of the cylinder at time **t**, and **w**(x,t) is the axial blood velocity, which is assumed to depend on **x** only. The model assumes

neither radial nor tangential blood velocities. The total pressure $\tilde{p}$ at a point **x** and time **t** is represented by the equation:

$$\tilde{p}(x,t) = p_0 + p(x,t)$$

wherein $\mathbf{p_0}$ is the hydrostatic pressure and **p(x,t)** is the excess pressure, generally referred to as the pressure hereafter.

Applying Newton's second law of motion, stating that mass times longitudinal acceleration equals the longitudinal force, and neglecting convecting acceleration, we use the expression $-\frac{\partial P}{\partial x}\Delta x$ representing the force on a volume element Δx to obtain equation 1.

$$\rho \frac{\partial w}{\partial t} = -\frac{\partial P}{\partial x} \qquad (1)$$

Equation 2 is the continuity equation:

$$\frac{\partial(\rho A)}{\partial t} = -\rho A \frac{\partial w}{\partial x} \qquad (2)$$

Wherein A is the instantaneous cross-section.

We assume that the instantaneous cross-section is a function of the instantaneous pressure

$$A = A(P) \qquad (3)$$

It is noted that A(0) is the cross-section for zero excess pressure. The latter assumption is equivalent to neglecting at least one viscoelastic and hysteresis behavior.

The distensibility **D** is defined as: $\mathbf{D} = \frac{1}{A}\frac{dA}{dP}$ wherein $\frac{dA}{dP}$ is the compliance.

For constant **r**, dividing both sides of Equation 2 by **r** and using the relation $\frac{\partial A}{\partial t} = \frac{dA}{dP}\frac{\partial P}{\partial t}$ we get equation 4:

$$D\frac{\partial P}{\partial t} = -\frac{\partial w}{\partial x} \qquad (4)$$

combining equations 1 and 4 the velocity w can be eliminated to give equation 5:

$$\frac{\partial^2 P}{\partial t^2} = C_w^{\,2}\frac{\partial^2 P}{\partial x^2} \qquad (5)$$

Wherein $C_w = (\rho \mathbf{D})^{-1/2}$ is the pressure wave velocity function. The wall is assumed to be purely elastic (that is viscoelasticity is negligible), thin, homogeneous and isotropic with Young modulus, E, and incompressible. Defining the Moens-Korteweg velocity:

$$C_0 = \sqrt{\frac{Eh}{2\rho r}} \cong \sqrt{\frac{Eh}{2\rho r_0}} \qquad (6)$$

where h is the wall thickness, r_0 the vessel radius at hydrostatic pressure, the pressure wave velocity is:

$$C_w = \frac{C_0}{\sqrt{1-\sigma^2}} \qquad (7)$$

PWV enables computation of the circumferential strain of the vessel wall. The inner side of the wall is covered by endothelial cells which are known to play a major role in the wall biology, e.g. plaque formation and rupture.

Wall smooth muscle cells are also affected by wall strain.

Assuming that the inner wall to be covered by N endothelial cells in the circumferential direction. The mean length of such cells is clearly $L_0 = 2\pi r_0/N$. The transmural pressure (difference between internal and external wall pressure) induces a variation of the radius dr, the distensibility is thus equal to:

$$D = \frac{1}{A}\frac{dA}{dP} = \frac{1}{\pi r^2}\frac{d\pi r^2}{dP} = \frac{2}{r}\frac{dr}{dP} \cong \frac{2}{r_0}\frac{dr}{dP}$$

Using the expression for L_0 above one obtains

$$D \cong \frac{2}{L_0}\frac{dL}{dP}$$

Since $D = 1/\rho c^2$, the PWV together with in-vivo pressure measurements yields the time-dependent strain $\varepsilon \equiv \frac{dL}{L_0}$ suffered by the endothelial cells:

$$\varepsilon = \frac{dP}{2\rho c^2}$$

When a better accuracy is needed, a more realistic mathematical model such as Womersley's blood vessel model can be used. Womersley's model is based on the linearized Navier-Stokes equation assuming incompressible blood and Newtonian behavior. The blood viscosity μ is constant, assuming a laminar blood flow. In Womersley's model, the vessel wall becomes an active component of the system. The dynamic behavior of the vessel wall is taken into account and has its own Newton equation for longitudinal and radial displacement. The Womersley number is defined as:

$$\alpha(\omega) = r_0\sqrt{\frac{\omega\rho}{\mu}} \tag{8}$$

where $\frac{\mu}{\rho}$ is the kinematic viscosity. The function F_{10} is defined in equation 9:

$$F_{10} \equiv \frac{2J_1(\alpha j^{3/2})}{\alpha j^{3/2} J_0(\alpha j^{3/2})} \tag{9}$$

F_{10} is a function of α and is therefore a function of ω. J_0 , J_1 are the Bessel functions of order 0 and 1, respectively.

The complex inverse velocity $\gamma(\omega)$ is defined for a pressure wave represented as $P_0 e^{j\omega t}$. After traveling a distance x the pressure wave will be transformed into $P_0 e^{j\omega(t-\gamma(\omega)x)}$.

The relation of the complex function $\gamma(\omega)$ to measurable quantities is

$[\gamma(\omega)]_{REAL} = \frac{1}{c(\omega)}$ and $[\gamma(\omega)]_{IMAGINARY} = \frac{-a(\omega)}{\omega}$, wherein the real part of $\gamma(\omega)$, Re [γ(ω)], is the inverse of the pressure wave velocity, and the imaginary part of $\gamma(\omega)$ is the negative of the pressure wave attenuation divided by the angular frequency ω (which is expressed in radian/second).

It is noted that, C_0 is the frequency-independent pressure wave velocity of the Moens-Korteweg formula (equation 8), while $c(\omega) \equiv 1/\gamma(\omega)$ is the frequency-dependent pressure wave velocity.

It is observed that, in-vivo, arteries are longitudinally tethered, meaning that the longitudinal motion of the arterial wall is strongly hindered compared to its radial motion. For complete tethering, Womersley's theory yields:

$$C_0^2\gamma^2(\omega) = \frac{(1-\sigma^2)}{(1-F_{10})} \qquad (11)$$

Thus, for determining hereinabove described properties of a blood vessel, the pressure wave velocity and the pressure wave attenuation have to be measured as a function of ω, yielding the complex function. The function $F_{10}(a)$ has been tabulated and tends to unity in the large a limit . Hence:

$$\lim_{\omega \to \infty} (\text{Re } [\gamma(\omega)]) = 1/C_w$$

In practice a Womersley number of at least 4 is sufficient for a good approximation.

Now, in the linear setting, the pressure wave, p(x,t) is composed of a forward and a backward moving wave denoted respectively, $p_f(x,t)$ and $p_b(x,t)$ and they linearly superpose: $p(x,t)= p_f(x,t) + p_b(x,t)$.

The forward-moving pressure wave $\Pi e^{j\omega t}$ measured at x=0 becomes upon traveling a distance x, $\Pi e^{j\omega(t-\gamma(\omega)x)}$ whereas the backward-moving wave is $R(\omega)\bullet\Pi e^{j\omega(t-\gamma(\omega)x)}$ where R(w) is the frequency dependent reflection coefficient, indicating reflection of the forward moving pressure wave from a distal obstacle (stenosis, vascular bed, bifurcation, etc). Upon Fourier decomposing the pressure wave into its harmonics, we have:

$$p(x,t)=\sum_{\omega}\Pi(\omega)e^{j\omega t}(1+R(\omega)e^{-j\omega\gamma(\omega)(2L-x)})$$

System Details

Reference is now made to Figs. 1, 1.a, 2 and 2.a. Figs. 1 and 1.a present a schematic isometric view of a system for determining the pressure wave velocity and the compliance and circumferential strain acting on wall cells of blood vessel lesion regions and non-lesioned regions, and other body conduits constructed and operative in accordance with the objects of the present invention. Fig. 2 and 2.a are schematic functional block diagrams illustrating the details of the system 1 of Fig. 1 and system 1.a of Fig. 1.a..

The systems 1 and 1.a include at least one pressure sensor catheter or guide wire 4, inserted into the vessel directly or via a catheter lumen 3 for measuring the pressure inside a blood vessel. The lumen catheter may be a guiding catheter of the type sold as 8F Archer coronary guiding catheter from Medtronic Interventional Vascular, Minneapolis, U.S.A. or a diagnostic catheter of the type sold as Siteseer diagnostic catheter, from Bard Cardiology, U.S.A., or a balloon catheter of the type sold as Supreme fast exchange PTCA catheter, by Biotronik GMBH & Co, U.S.A. or any other hollow catheter . Specifically, the systems of Figures 1 and 1a may include one, two or three pressure sensor catheters or guide wires 4 for measuring the pressure inside a blood vessel. An exemplary, but not limiting, embodiment of

a pressure sensor 4 having one sensor is a 3F one pressure sensor model, model SPC-330A, commercially available from Millar Instruments Inc., TX, U.S.A.; however, any other pressure catheter suitable for diagnostic or combined diagnostic / treatment purposes may be used, such as the 0.014 " guidewire mounted pressure sensor product number 12000 from Radi Medical Systems, Upsala, Sweden, or Cardiometrics WaveWire pressure guidewire from Cardiometrics Inc. an Endsonics company of CA, U.S.A. The two and three pressure sensor embodiments may also include combinations of the pressure sensors; however, a dual pressure catheter SPC-721 commercially available from Millar Instruments Inc., TX, U.S.A., may also be used.

The system 1 and 1.a may also include a fluid filled (FF) pressure transducer 31, i.e. model PX272 disposable pressure transducer by Baxter Healthcare Corporation, CA, USA, connected via the end of the guiding catheter 3. The fluid filled pressure transducer 31 is connected to the system 1, when additional pressure readings are needed, or in place of an intravascular pressure transducer, according to the defined study.

The system 1 and 1.a also includes a signal conditioner 23, such as a model TCB-500 control unit commercially available from Millar Instruments, or Radi Pressure Wire Interface Type PWI10, Radi Medical Systems, Upsala, Sweden , or other suitable signal conditioner. The signal conditioner 23 is suitably connected to the pressure sensor 4 for amplifying the signals of the pressure sensor. The system 1 further includes an analog to digital (A/D) converter 28 such as the NI E Series Multifunction I/O model PCI-MIO-16XE-10 commercially available by National Instruments, Austin, TX connected to the signal conditioner 23 and to the FF pressure transducer 31 for receiving the analog signals therefrom. The signal conditioner 23 may be integrated in the data acquisition card of the computer 20, or may also be omitted altogether, depending on the specific type of pressure sensors used. It will be appreciated by those skilled in the art of Digital Signal Processing that the implementation of a signal conditioner depends on the nature and character of pressure sensor, the signal transmission circuit leads, environmental factors and the nature and character of FF pressure transducer 31. It should be noted that either optical data transmission (e.g. Radi pressure sensor) or wireless communication (e.g. Siemens pressure transducer) may be used.

The system 1.a of Fig. 1.a also includes a standard cardiac catheterization system 22, such as Nihon Kohden Model RMC-1100, commercially available from Nihon Kohden Corporation, Tokyo, Japan. The signal conditioner 23 and the FF pressure transducer 31 are directly connected to the monitoring system 22. The system 1.a further includes an analog to digital (A/D) converter 28 connected to the output of the monitoring system 22 through a shielded I/O connector box 27, such as models NI SCB-68 or BNC-2090 commercially available from National Instruments, Austin, TX.

The systems 1 and 1.a also include a signal analyzer 20 connected to the A/D converter 28 for receiving the digitized conditioned pressure signals from the A/D converter 28. The signal analyzer 20 includes a computer 25 under the control of signal analysis software, and optionally a display 21 connected to the computer 25 for displaying text numbers and graphs representing the results of the calculations performed by the computer 25 and a printer 26 suitably connected to the computer 25 for providing hard copy of the results for documentation and archiving. It will be appreciated by those skilled in the art that the A/D converter 28 can be a separate unit or can be integrated in a data acquisition computer card installed in the computer 25. The computer 25 processes the pressure data, sensed by the pressure sensors 4 and acquired by the A/D converter 28 or the data acquisition card (not shown) and generates textual, numerical and/or graphic data that is displayed on the display 21.

It will further be appreciated that the choice of the computer 25, selection of the A/D converter and signal conditioner may vary and are not limited to the descriptions contained herein.

Preferably, the data displayed on the display 21 is calculated and displayed in real time for providing the operator of the pressure catheter 3 with information assisting him in the manipulation of the pressure catheter 3 within the patient's vascular system. The real time operation is particularly advantageous in cases where aneurysms are diagnosed and treated; e.g., by filling the aneurysm with a filling Material. In such case, both locations of the aneurysm may be defined by the altered (higher) compliance resulting from both local wall thinning and local dilatation comparing with neighbor segments. Treatment success may be indicated by

compliance decrease, due to wall thickening and cross-section area reduction. As well, the real time operation is particularly advantageous in cases where the pressure catheter used also includes a dilation balloon or any other ablation devices such a laser ablation device, a mechanical ablation device or an ultrasound ablation devices for relieving the obstruction. In such cases, the data provided in real time enables the physician to quantitatively assess the obstruction parameters before, during and after a therapeutic procedure, and to decide whether to proceed to use the dilation balloon or any other therapeutic device based on the data provided in real time.

The present apparatus and methods correspond to the diagnosis of various blood vessel characteristics including but not limited to vessel wall compliance and distnesibility, in general, and more particularly to wall calcification and thickening to allow occult disease identification, low compliance characteristics to identify weak vascular wall sections, detecting circumferential strain of vessel walls, and attend higher compliance characteristics relating to aneurysms. Diagnosis provided by the present invention not only provides initial guidance in implementing a treatment, but also allows for cooperative analysis of the vessel during treatments such as, but not limited to medication therapy, transcatheter cardiovascular therapeutics (TCT), coronary artery bypass grafting (CABG), or non-treatment. Additionally, numerous methods are currently available for treating various lesion types. Some of these methods are given hereinbelow, sequenced from "softer" to "heavier", relating to their ability to open calcified lesions; percutaneous transluminal angioplasty (PTCA), "Cutting balloon" angioplasty, directional coronary atherectomy (DCA), rotational coronary atherectomy (RCA), Ultrasonic breaking catheter angioplasty, transluminal extraction catheter (TEC) atherectomy, Rotablator atherectomy, and excimer laser angioplasty (ELCA). Often, stents are placed within the lesion so as to prevent re-closure of the vessel (also known as recoil). Mostly stent is placed after lumen predilatation PTCA. Stenting without predilatation is also performed at increasing rates, saving both costs and time. In some cases, e.g. carotid stenting, primary stenting is clinically superior. In this case, debris, produced by the dilatation are held in place by the stent, instead of flowing downstream and causing a stroke.

However, the data acquired and/or calculated by the computer 25 may also be stored in the computer's memory or in a suitable storage device included in the computer 25 (not shown) for later off-line calculations, statistics, patient long time monitoring and/or analysis and presentation. This can be useful for training and educational purposes at a later time.

Reference is now made to Fig. 3 and 3a. Fig. 3 is a schematic cross section illustrating the positioning of the guiding or diagnostic catheter 3, within the blood vessel of interest 30, during operation of the systems 1 and 1a of Figs. 1 and 1a, respectively. The guiding catheter (or diagnostic catheter) 3 with three pressure sensors 4a, 4b or 4c, are inserted into the vascular system of the patient using a standard connector 8 and standard methods and moved to reach the blood vessel of interest 30. Fig. 3 illustrates a cross section of an artery 30 having an arterial wall 32. The artery 30 may also include a stenotic obstruction 34 obstructing the blood flow through the artery 30. The pressure sensors may be located along the vessel, proximal (Fig. 3), distal, across or within the stenosis (Fig. 3a) in order to characterize the various regions of the vessel.

In-vitro Experimental System

Reference is now made to Figs. 4, 5 and 6 in which Fig. 5 is a schematic diagram representing an in-vitro experimental apparatus constructed and operative for determining flow characteristics in simulated non-lesioned and lesioned blood vessels, in accordance with an embodiment of the present invention. Fig. 2 is a schematic functional block diagram illustrating the functional details of a system including the apparatus of Fig. 5 and apparatus for data acquisition, analysis and display.

The fluidics system 51 of Fig. 5 is a recirculating system for providing pulsatile flow. The system 51 includes a pulsatile pump 42, model 1421A pulsatile blood pump, commercially available from Harvard Apparatus, Inc., Ma, U.S.A. The pump 42 allows control over rate, stroke volume and systole/diastole ratio. The pump 42 recirculates distilled water or other liquid solutions, such as glycerin water solution, to stimulate blood viscosity, from an input reservoir 15 to an output reservoir 14, according to the specification of the experiment.

The system 51 further includes a flexible tube 43 immersed in a water bath 44, to compensate for gravitational effects. The flexible tube 43 is made from Latex® and has a length of 120 cm. The flexible tube 43 simulates an artery. The flexible tube 43 is connected to the pulsatile pump 42 and to other system components by Teflon® tubes. All the tubes in system 51 have 4 mm internal diameter. A bypass tube 45 allows flow control in the system and simulates flow partition between blood vessels. A Windkessel® compliance chamber 46 is located proximal to the flexible tube 43 to control the pressure signal characteristics. A Windkessel® compliance chamber 47 and a flow control valve 48 are located distal to flexible tube 43 to simulate the impedance of the vascular bed.

Reference is now made to Fig. 6, which is a schematic cross sectional view illustrating a part of the fluidics system 51 in detail. Pressure is measured along the flexible tube 43 using a pressure measurement system including MIKRO-TIP pressure catheters 57,58 and 59, model SPR-524, SPC-721 or SPR-407 pressure catheter, connected to a model TCB-500 control unit, commercially available from Millar Instruments Inc., TX, U.S.A.. The catheters 57,58 and 59 are inserted into the flexible tube 43 via the connector 10, connected at the end of the flexible tube 43. The catheters 57,58 and 59 include pressure sensors 24A, 24B and 24C, respectively, for pressure measurements. It is noted that the number of pressure transducers used varies according to the experiment specifications. The system further included an artificial stenosis made of a tube section 55, inserted within the flexible tube 43. The tube section 55 is made from a piece of Teflon® tubing. The internal diameter 52 (not shown) of the artificial stenosis 55 may be varied by using artificial stenosis sections fabricated separately and having various internal diameter.

A fluid filled pressure transducer 31 is connected to the system 51 via the end of the guiding catheter 3, inserted into the flexible tube 43 via the connector 9. The fluid filled pressure transducer 31 is connected to the system 51, when additional pressure readings are needed, or in place of an intravascular pressure transducer, according to the defined experiment.

The system 51 of Fig. 5 also includes a flowmeter 11 connected distal to the flexible tube 43 and a flowmeter 12 connected to the bypass tube 45. The flowmeters 11 and 12 are suitably connected to the A/D converter 28. The flowmeters 11 and 12 are model 111 turbine flow

meters, commercially available from McMillan Company, TX, U.S.A.. In certain cases, an ultrasonic flowmeter model T206, commercially available from Transonic Systems Inc., NY, U.S.A. was used.

Reference is now made to Fig. 4. The system 41 includes the system 51. The system 41 also includes a signal conditioner 23, such as a model TCB-500 control unit commercially available from Millar Instruments. The signal conditioner 23 is suitably connected to the pressure sensors 24A, 24B and/or 24C for amplifying the pressure signals. The system 41 further includes an analog to digital (A/D) converter 28 connected to the signal conditioner 23 for receiving the conditioned analog signals therefrom. The system 41 also includes a signal analyzer 20 connected to the A/D converter 28 for receiving the digitized conditioned pressure signals from the A/D converter 28. The signal analyzer 20 includes a computer 25, a display 21 connected to the computer 25 under the control of signal analysis software for displaying text numbers and graphs representing the results of the calculations performed by the computer 25. A printer 26 is suitably connected to the computer 25 for providing hard copy of the results for documentation and archiving. The computer 25 processes the pressure data which is sensed by the pressure sensors 24A, 24B and 24C and acquired by the A/D converter 28 or the data acquisition card (not shown) and generates textual, numerical and graphic data that is displayed on the display 21.

Data acquisition of the below listed procedures was performed using a PC (Pentium 586) with an E series multifunction I/O board 28 model PC-MIO-16E-4, commercially available from National Instruments Inc., TX, U.S.A. The I/O board was controlled by a Labview graphical programming software, commercially available from National Instruments Inc., TX, U.S.A. 10 sec interval of pressure and flow data were sampled at 5000Hz, displayed during the experiments on the monitor and stored on hard disk. Analysis was performed offline using Matlab version 5 software, commercially available from The MathWorks, Inc., MA, U.S.A.

Alternate IVUS Catheter Embodiments

In accordance with another preferred embodiment of the present invention, the pressure sensor of the system of the present invention may also be incorporated into an IVUS catheter system such as IVUS catheter model 82700 available from Endosonics corp. U.S.A., and connected to a suitable signal analyzer. Thereby forming a system for performing IVUS and for determining the PWV, The distensibility and the compliance of blood vessel regions based on IVUS geometrical data and pressure readings is derived using the following relationship: D= (dA/ dP)/A where: A - crossection area available from IVUS, P pressure, D- distensibility

In accordance with another preferred embodiment of the present invention, the PWV, the distensibility and the compliance of blood vessel regions may be derived using IVUS geometrical data and FF pressure readings. The IVUS probe is inserted into the vessel of interest through a standard guiding catheter, serving simultaneously the FF pressure measurement system.

Applications of the Preferred Embodiments

In accordance with another preferred embodiment, an IVUS may replace a pressure sensor in each of the methods and embodiments presented. For example, in two pressure sensor, located apart application, IVUS replace each of the pressure sensors. It then allows to perform both compliance and reflection diagnostics described in this patent together with conventional IVUS tasks (Intravascular lumen and vascular wall imaging). In accordance with another preferred embodiment, Intravascular flow (IVF) sensor (e.g., Endosonics Doppler Flowire), a flow wave sensor of the type suitable for this purpose are the Flowwire catheters manufactured by Endosonics Corporation, U.S.A. in which the system uses doppler ultrasound technology to accurately measure arterial blood flow velocity providing functional lesion assessment. Such device provide for measurements suitable for the procedures of the present invention as sold commercially or preferably when modified to allow for frequency increases to 200 Hz may replace a pressure sensor in each of the methods and embodiments presented. For example, in two pressure sensor located apart application, IVF may replace each of the pressure sensors. It then allows to perform both compliance and reflection diagnostics described in this patent together with conventional IVF tasks (Intravascular velocity and flow measurements).

It will be appreciated by those skilled in the art that obtaining compliance and distensibility information about vessels using measurements of the PWV provide valuable diagnostic information in an area of medical practice with an increasing number of treatments available to the physician. One of the advantages of providing physicians with compliance values of different vessel regions relates to improving of stenting procedures. Usually, stenting is performed after pre-dilatation balloon angioplasty. If the compliance of the vessel region to be stented is known prior to stenting by using the devices and methods of the present invention as disclosed hereinabove, the physician may decide, based on the compliance values, whether a pre-dilatation procedure is required. In cases where the vessel wall compliance is high, this pre-dilatation procedure may be omitted, saving the time and the additional expense involved with the pre-dilatation procedure and decreasing the patient's risk and discomfort.

The physician may utilize the vessel characteristics obtained to avoid PTCA failure by identifying failure risks such as enhanced risk of vessel wall dissection in advance, and applying proper decision procedures prior to PTCA for choosing an adequate treatment a priori. It may serve for identifying occult lesions where vessel wall thickness and/or calcification increases, reducing compliance in specific regions. It may also serve, together with geometrical data (e.g. angiography) for the quantification of wall-cell-strains.

It is further noted that the system of the present invention can also be used for confirming stent deployment. After stent deployment, the compliance and distensibility of the stented vessel region will significantly decrease and the PWV in that region will significantly increase. Thus, the methods and systems of the present invention may be used to confirm stent deployment by determining the PWV, the distensibility and the compliance values in the stented region.

Additionally, the system can be adapted for use for characterizing aneurysms in blood vessels for diagnostic purposes. When the catheter is used for treating an aneurysm in a blood vessel, the system can be adapted for characterizing and localizing the aneurysm

before, during and after the therapeutic procedure. It may also serve for in process monitoring of the aneurysm filling process.

Another potential application of the multi-point pressure measurement system of the present invention is in the diagnostic evaluation of the feasibility of insertion of intra-aortic balloon pumps (heart-assist devices). In situations where the relevant vessel wall has low compliance, the use of such intra-aortic pump may be dangerous. The ability of the method and system of the present invention to provide a value for the compliance of the vessel segment makes it useful as a diagnostic method, which can be performed prior to pump insertion procedures. "Mapping" compliance values and providing the physicians with quantitative compliance data enable a better decision on whether pump insertion should be performed.

A further potential application of the system is in assisting the physician in selecting an appropriate stent. The compliance values determined for a lesioned vessel region by the devices and methods disclosed hereinabove for multi-point pressure measurements can be used for selecting the most appropriate stent that is desirable for deployment in that lesioned region.

Finally, while the present invention has been described with respect to blood vessel measurements, the system can be used within other tube-like structures having pulsatile liquid flow therein.

It will be appreciated that the present invention is not limited by what has been described hereinabove and illustrated in the various figures, and that numerous modifications, all of which fall within the scope of the present invention, exist.

Following, several procedures and methods will be presented, serving for computing the pressure wave velocity and thereby derived blood vessel characteristics. Examples utilizing these procedures and methods include in-vitro experiments performed using the

experimental system described above, but also in-vivo data on pigs and one human experiment.

In some of the methods presented below, multiple pressure measurements are required. The proximal measurement was collected using a fluid filled pressure transducer system 31 such as Baxter Model PX272, pressure monitoring kit from Baxter Healthcare Corporation, Ca, U.S.A.), connected to the guiding catheter of system 1 via the connector 8, or an intravascular pressure transducer 4 as described hereinabove.

SYSTEM IMPLEMENTATION METHODS AND PROCEDURES

The system uses various methods to derive the pressure wave velocity in a vessel, or in a stenosis or aneurysm area. The methods are based on five main data analysis procedures, which are described hereinbelow. Other data analysis procedures may be developed based on the principles, hereinbelow presented. The choice between procedures depends on the number of measurements performed and number and kind of transducer used. As used throughout the term "transducer" refers to the pressure sensor either alone or in combination with other components to which it is associated, such as the catheter or other fluid filled system. Various examples are described in the following methods. One can either use PWV as an independent indicative parameter, or derive the distensibility, compliance and time dependent wall-cell-strain of the studied vessel.

Procedure 1: Three pressure measurements

As presented hereinabove, the Fourier decomposition of the pressure wave in its harmonics, yields:

$$p(x,t)=\sum_{\omega}\Pi(\omega)e^{j\omega t}(1+R(\omega)e^{-j\omega\gamma(\omega)(2L-x)})$$

Assuming that the pressure is measured at three points, a distance Δ apart $(-\Delta,0,\Delta)$, we have three equations:

$$p(0,t) = p_2 = \sum_{\omega} p_2(\omega)e^{j\omega t} = \sum_{\omega} \Pi(\omega)e^{j\omega t}(1 + R(\omega)e^{-j2\omega\gamma(\omega)L})$$

$$p(-\Delta,t) = p_1 = \sum_{\omega} p_1(\omega)e^{j\omega t} = \sum_{\omega} \Pi(\omega)e^{j\omega t}(e^{j\omega\gamma\Delta} + R(\omega)e^{-j\omega\gamma(\omega)(2L+\Delta)})$$

$$p(\Delta,t) = p_3 = \sum_{\omega} p_3(\omega)e^{j\omega t} = \sum_{\omega} \Pi(\omega)e^{j\omega t}(e^{-j\omega\gamma\Delta} + R(\omega)e^{-j\omega\gamma(\omega)(2L-\Delta)}) \quad (18)$$

The coefficients $p_i(\omega)$ are obtained by Fourier transforming the three pressure signals. The resulting equation system to be solved is:

$$p_1(\omega) = \Pi(\omega)(e^{j\omega\gamma\Delta} + R(\omega)e^{-j\omega\gamma(2L+\Delta)}) \quad (19)$$

$$p_2(\omega) = \Pi(\omega)(1 + R(\omega)e^{-j\omega\gamma 2L}) \quad (20)$$

$$p_3(\omega) = \Pi(\omega)(e^{-j\omega\gamma\Delta} + R(\omega)e^{-j\omega\gamma(2L-\Delta)}) \quad (21)$$

Algebraic manipulation of equations 19,20 and 21, yields equation 22:

$$\frac{p_1(\omega) + p_3(\omega)}{p_2(\omega)} = 2\cos(\omega\gamma\Delta) \quad (22)$$

Since we know w and Δ we can obtain equation 23 for $\gamma(\omega)$:

$$\gamma(\omega) = \frac{1}{\omega\Delta}\arccos\left(\frac{p_1(\omega) + p_3(\omega)}{2p_2(\omega)}\right) \quad (23)$$

As explained hereinabove (equ. 12), the pressure wave velocity is the inverse of real $[\gamma(\omega)]$.

Reference is now made to Fig. 9 which is a schematic flow chart illustrating the steps of the method of calculating the (complex) propagation coefficient g(w) and the pressure wave velocity from pressure data obtained simultaneously and continuously by three separate pressure sensors in accordance with a preferred embodiment of the present invention. The distance between the first pressure sensor and the second pressure sensor is Δ and the distance between the second pressure sensor and the third pressure sensor is Δ.

After the guiding catheter 3 is positioned within a blood vessel at the place selected for performing a measurement as disclosed hereinabove and illustrated in Fig. 7, the system starts by digitizing the pressure signals received from the pressure sensors 4A, 4B and 4C (step 62) and transmitted to the computer to yield the digitized pressure signals $p_1(t)$, $p_2(t)$ and $p_3(t)$. The system computes the Fourier coefficients $p_1(w)$, $p_2(w)$ and $p_3(w)$ from the digitized pressure signals $p_1(t)$, $p_2(t)$ and $p_3(t)$ (step 64). The computation of step 64 can be performed using any suitable FFT program such as Matlab 5.1, The MathWorks, Inc., MA, U.S.A.

The system then directly computes $\gamma(\omega)$ from the equation:

$$\gamma(\omega) = \frac{1}{\omega\Delta}\arccos\left(\frac{p_1(\omega)+p_3(\omega)}{2p_2(\omega)}\right) \quad \text{(step 66)}$$

The pressure wave velocity function, $c(\omega)$, is then derived (step 68) using the relation $c(\omega) = \text{real}\,[1/\gamma(\omega)]$. The PWV value is defined as $PWV = c(\omega)|_{\omega\to\infty}$ (step 70). In practice, the asymptotic value of $c(\omega)$ is already attained for an equivalent Wormersley number of 5. Referring to the in-vivo example given hereinbelow, where a pig carotid was studied (internal diameter of 6-8 mm), the asymptotic value of PWV is reached at a frequency of around 4 Hz.

Note that the PWV is independent of the reflection coefficient. The reflection coefficient may be determined by dividing Eq. 19 by Eq. 20, yielding:

$$\frac{p_1(\omega)}{p_2(\omega)} = \frac{e^{j\omega\gamma\Delta} + R(\omega)e^{-j\omega 2L}e^{-j\omega\Delta}}{1 + R(\omega)e^{-j\omega\gamma 2L}}$$

If the value of L is independently known from a QCA or any other suitable method, and $\gamma(\omega)$ has been computed, the system uses the available value of L to compute $R(\omega)$ by solving the above equation.

The procedure was described for the case of equal spacing between the three transducers. A straight forward modification is applied to the procedure, when the spacing between the three transducers are not equal.

Procedure 2: Foot to Foot – dual pressure measurement

This procedure is based on the observed fact that during the steep rise in pressure, observed in early systole, henceforth denoted the "foot" of the pressure wave, the pressure wave has not yet returned from the reflecting sites. Therefore, two nearby points along an artery, have similar, in the mathematical sense, shapes at the onset of systole. However, due to the finite velocity of the pressure wave (PWV), the onset of systole is delayed by Δt, where $\Delta t = d / PWV$ and d is the distance between the two points. Thus knowing the distance between the points (e.g. through QCA) and the time delay Δt, the PWV is easily calculated. An additional benefit of considering the foot of the pressure wave is its relative robustness to measurement noise. This effect is obviously due to the large derivative of the curve. The proposed "foot-to-foot" procedures below exploit those properties.

2.a. Level fitting procedure

The "Level fitting" procedure involves estimation of the time delay between comparable levels of the pressure wave in the foot region. A level of L% is defined as follows. Let two pressure sensors be located at x and x+d, giving pressure readings $P_1(t)$ and $P_2(t)$. Then t_1 is the time at which $P_1(t)$ reaches a level of L% if:

$$P_1(t_1) = \min P_1(t) + \frac{L}{100} \bullet (\max P_1(t) - \min P_1(t))$$

where the maximum (minimum) is computed on a single heart pulse. A similar formula holds for the sensor at x+d, that is for $P_2(t)$. A typical operational level is 10-20%. Next, the time delay is $\Delta t = t_2 - t_1$, and the PWV=d/Δt.

Reference is now made to Fig. 10 which is a schematic flow chart illustrating the steps of the method of calculating the PWV from pressure data obtained simultaneously by two pressure sensors, located within a vessel d cm apart, in accordance with a preferred embodiment of the present invention.

After the guiding catheter 3 and the pressure sensors 4a and 4b are positioned within a blood vessel at the place selected for performing a measurement as disclosed hereinabove and illustrated in Fig. 8, the system starts by digitizing the pressure signals received from the pressure sensors (step 70) to yield the digitized pressure signals $p_1(t)$ and $p_2(t)$. The system then applies pre-conditioning steps to the digitized signals that include linear interpolation of the discrete signals. In addition, since the Fourier components of the pressure wave above 15 Hz are negligibly small, the measured signals are filtered out by means of a low-pass filter (FIR) at this frequency (step 72), thereby, partially eliminating measurement noise, as well.

The system then computes t_1 and t_2, the time at which $P_1(t)$ and $P_2(t)$ reaches a level of L%, respectively (step 74 and 76). If simultaneous pressure measurements with two pressure transducers are acquired, then the PWV may be derived as d/Δt (step 78), where d is the distance between the transducers and Δt is the time delay between corresponding points on the pressure-time curves as measured by the two transducers (e.g. 10%).

In other applications of this procedure, one may use for Δt the time delay between pressure maximums. Alternatively, one may choose the time delay between points at which the pressure attains a fixed, arbitrarily chosen, percentage of the full range of the pressure curve.

It is well known, that the PWV in arterial segment increases with pressure, which is an indication of gradual stiffening of the artery with pressure. Using well-established viscoelastic arterial models, the analysis of the PWV for several specified percentage of full range of the pressure enables one to compute the stiffness of the vessel wall.

2.b. Optimal overlap procedure

The idea of the "Optimal overlap" procedure is based on the observation that the foot of the pressure wave pulse $P_2(t)$ is mathematically similar to $P_1(t)$ but a delayed version of the latter. Thus we search for the best stretching coefficient b and the best delay Δt, for which the function foot of $\beta \bullet P_2(t + \Delta t)$ is globally close to the foot of $P_1(t)$. The reason for the appearance of the stretch coefficient b is the attenuation of forward moving pressure wave. Mathematically, we require minimum distance in L_2 norm, or equivalently a least square criterion. Thus, the least square optimal overlap procedure can be formulated as follows:

Let i be the index of N successive samples in the foot of the same heart beat (that is from onset of systole to, say 80%, of the maximum of the pressure wave $P_1(t)$) and t_i the corresponding sample times. The optimal overlap criterion reads:

$$\min_{\beta\ ,\ \Delta t} \sum_{i=1}^{N} \left(P_1(t_i) - \beta \bullet P_2(t_i + \Delta t) \right)^2$$

Carrying out the partial derivatives with respect to β and Δt, yields the set of implicit equations:

$$\beta = \frac{\sum_{i=1}^{N} P_1(t_1) \bullet P_2(t + \Delta t)}{\sum_{i=1}^{N} P_2^{\,2}(t_i + \Delta t)}$$

Let $P_2^{/}(t)$ be the derivative function of $P_2(t)$. Then the second non-linear and implicit equation reads:

$$\sum_{i=1}^{N} P_1(t_i) \bullet P_2^{/}(t_i + \Delta t) = \beta \bullet \sum_{i=1}^{N} P_2(t_i + \Delta t) \bullet P_2^{/}(t_i + \Delta t)$$

The calculated Δt allows one to derive the pressure wave velocity within the vessel between the two pressure sensors, separated by a distance d: PWV= d / Δt.

Reference is now made to Fig. 11 which is a schematic flow chart illustrating the steps of the method of calculating the PWV from pressure data obtained simultaneously by two pressure sensors, located within a vessel d cm apart, in accordance with a preferred embodiment of the present invention.

After the guiding catheter 3 and the pressure sensors 4a and 4b are positioned within a blood vessel at the place selected for performing a measurement as disclosed hereinabove and illustrated in Fig. 8, the system starts by digitizing the pressure signals received from the pressure sensors (step 80) to yield the digitized pressure signals $p_1(t)$ and $p_2(t)$. Since the Fourier components of the pressure wave above 15 Hz are negligibly small, the system filters out the measured signals by means of a low-pass filter (FIR) at this frequency (step 82). The low pass filter is preferably embodied in the software, however, an analog hardware version may be useful as well. The system then solves the system of equations presented hereinabove for Δt and β (step 84). PWV is then computed using the simple relationship PWV=d/Δt (step 86). Pressure measurement using a fluid field system may replace 4.a.

Procedure 3: Moving pressure measurement- first approach.

In this configuration, use is made of a single fluid-filled (FF) catheter or any other device which measures a parameter which is closely correlated with local the pressure at a specific site within the vessel and a single, moving, pressure sensor. The PWV is obtained in two stages: the pressure sensor is first located at a known distance d_1 from the tip of the FF catheter, denoted

point A, and a measurement is taken. The pressure sensor is subsequently moved to a distance d_2, denoted point B, and the measurement is repeated there.

Since the pressure pulse rapidly rises at onset of systole (the foot), as explained hereinabove, both the pressure sensor and the FF catheter curves exhibit a "foot". The foot of the fluid-filled catheter curve is, however, in general, different from the one of the pressure sensor (function of the FF catheter characteristics: "FF catheter transfer function"). The difference is twofold: the shape of the foots differ and, most importantly the foots start at different times, t and t+Δt. This time difference can be computed by applying the foot-to-foot procedure (using the level fitting version) for an arbitrary distance l: Δt=l/v. The first and the second measurement yield delays Δt_1 and Δt_2, respectively. The PWV is given by the formula:

$$PWV = \frac{d_1 - d_2}{\Delta t_1 - \Delta t_2}$$

This method uses the FF pressure catheter as a clock, for gating purposes, therefore has the advantage that it eliminates the need of any prior knowledge regarding the catheter characteristics. Also, the distance between the tip of the FF catheter and the pressure sensor is irrelevant. The procedure requires the knowledge of one distance - the distance d, between point A and B.

Instead of the FF catheter another type of pressure sensor or flow or a transducer tracking the diameter or crossection changes in time may serve. Examples for such a transducer tracking the diameter or crossection changes are IVUS catheter available from Endosonics or the guidewire designated "imaging core wire" described in the paper "First experience with imaging core wires"by Di Mario C, Akiyama T, Moussa I, Reimers B, Jang YT, Tobis J ., Colombo A published in the seminar of interventional Cardiology 1997 Narch ;2 (1) pages 69-73. Such an "imaging core wire" may be incorporated together with pressure and or doppler flow transducer on the same wire.

Reference is now made to Fig. 12a which is a schematic flow chart illustrating the steps of the method of calculating the PWV from pressure data obtained simultaneously by a FF pressure

catheter and one moving pressure sensor, where the FF pressure catheter is in a fixed location and the pressure sensor is measuring in two independent locations (d cm apart), in accordance with a preferred embodiment of the present invention.

After the guiding catheter 3 and the pressure sensor 4a are positioned within a blood vessel at the place selected for performing a measurement as disclosed hereinabove and illustrated in Fig. 13, the system starts by digitizing the pressure signals received from the FF pressure catheter and the sensor (step 90) to yield the digitized pressure signals $p_1(t)$ and $p_2(t)$. The system then applies the Procedure 2.a, presented hereinabove, with an arbitrary distance l to yield the time delay Δt_1 (step 92). Now the pressure sensor 4a, is moved a distance d, to point B. The system then digitizes the pressure signals received from the FF pressure catheter and the sensor (step 94) to yield the digitized pressure signals $p_1(t)$ and $p_2(t)$. The system then applies Procedure 2.a, presented hereinabove, with an arbitrary distance l to yield the time delay Δt_2 (step 96). The system now computes the PWV according to equation: $PWV=d / (\Delta t_2 - \Delta t_1)$.

Procedure 4: Moving pressure measurement - second approach.

In this configuration, use is made of a single fluid-filled (FF) catheter and a single pressure sensor. The PWV is obtained in two stages: the pressure sensor is first located at a known distance d_1 from the tip of the FF catheter, denoted point A and a measurement is taken. The pressure sensor is subsequently moved to a distance d_2 denoted point B, and the measurement is repeated there.

Although the clinical procedure corresponding to Algorithm 3 and 4 are mutual, the analysis approach is different. Here, we are taking advantage of the fact that the FF pressure catheter remains in a fixed location. Therefore any time shift between the first and second measurements is due to the time delay between those measurements. However the time shift between the two pressure sensor measurements involves both the time delay between the measurements and the time due to distance difference (d_2-d_1). These time differences can be computed by applying either Algorithm 2a, the foot-to-foot algorithm (using the level fitting

version) or Algorithm 2b, the optimal overlap version. The first and second calculations yield delays Δt_1 and Δt_2 respectively. The PWV is given by the formula:

$$PWV = \frac{d_1 - d_2}{-(\Delta t_1 - \Delta t_2)}$$

Again, the FF pressure catheter data are used as a clock, therefore avoiding the need of any prior knowledge regarding the catheter characteristics. Also, the distance between the tip of the FF catheter and the pressure sensor is irrelevant. The algorithm requires the knowledge of one distance - the distance d, between point A and B.

Instead of the FF catheter, another type of pressure sensor or flow or a transducer tracking the diameter or crossection changes in time may serve, as described hereinabove.

The ECG signal is another signal that may serve for gating in this procedure. Indeed its main advantage is that it is a routine and essential measurement in the catheterization lab, independent of the presented procedure. This means that a single movable pressure transducer may be used in conjunction with the existing ECG in order to derive the PWV and its derived parameters. This approach is elaborated in Method 5a.

Reference is now made to Fig. 12b, which is a schematic flow chart illustrating the steps of the method of calculating the PWV from pressure data obtained simultaneously by a FF pressure catheter and one pressure sensor. The FF pressure catheter is in a fixed location and the pressure sensor is measuring in two independent locations (1cm apart), in accordance with a preferred embodiment of the present invention.

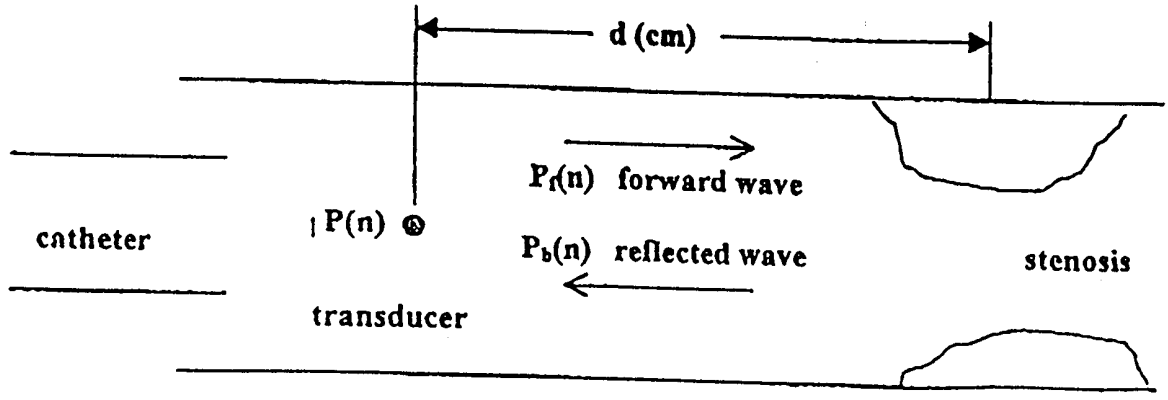
After the guiding catheter 3 and the pressure sensor 4a are positioned within a blood vessel at the place selected for performing a measurement as disclosed hereinabove and illustrated in Fig. 13, the system starts by digitizing the pressure signals received from the FF pressure catheter and the sensor (step 100) to yield the digitized pressure signals $p_1(t)$ and $p_2(t)$. Now the pressure sensor 4a, is moved a distance d, to point B. The system then digitizes the pressure signals received from the FF pressure catheter and the sensor (step 102)

to yield the digitized pressure signals $p_1(t)$ and $p_2(t)$. The system then applies the Algorithm 2a or 2b presented hereinabove, to the FF pressure data at point A and B, yielding the time delay Δt_1 (step 104). The system then applies Algorithm 2a or 2b presented hereinabove, to the pressure sensor data at point A and B, yielding the time delay Δt_2 (step 106). The system now computes the PWV (step 108) according to equation: PWV: $1/(\Delta t_2 - \Delta t_1)$.

PROCEDURE 5: Echo Detection Algorithm.

The shape of the pressure wave changes along the arterial system due to a multiplicity of factors: dispersion of the phase velocity, attenuation and reflection at obstacles due to a sudden change of flow impedance such as bifurcations, side branches, reflections from the vascular bed (arterioles and capillars) and occlusions along the path of the wave (stenosis). The presence of a stenosis dominates all the other reflecting sites. Even in the absence of stenosis, a pressure wave is always reflected, albeit weakly, because of the vascular bed.

The present algorithm exploit the reflection of the pressure wave and detects the duration of the echo using the cepstrum method (Oppenheim and Schafer "Discrete-Time Signal Processing" 1989 Prentice-Hall), a well-established mathematical technique in the field of signal processing. As in previous algorithm, a pressure transducer is inserted at a distance d from a stenosis according to the following experimental setup (the obstacle is a stenosis):



where P(n) is the measured pressure and $P_f(n)$, $P_b(n)$ are the (unknown) forward and backward waves as described hereinabove, sampled at time sample n, n=1..N where N is the number of samples.

The following relationship holds:

$$P(n)=P_f(n)+P_b(n-m)=P_f(n)\otimes[\delta(n)+R\bullet g(n-m)]$$

where

$\otimes$ is the discrete convolution operator;

δ is the discrete delta function;

g(n) is the response of the vessel for a distance of 2·d (to stenosis and back). It is implicitly assumed that g(n) is close to the delta function $\delta(n)$; it is also assumed that the energy dissipation along short section of a blood vessel is negligible, that is $\sum g(n)\approx 1$;

R is the reflection coefficient;

m is the integer part of (2·d/C), the time delay (in number of samples) of the reflected wave;

C is the PWV (pressure wave velocity);

In what follows, the cepstrum function of the minimum-phase component of the signal K(n), defined as the natural logarithm of P(n) in the algebra of formal polynomials (e.g. $p^2(n)\equiv P(n)\otimes P(n)$) is calculated. The method presented acts directly in time space, in contrast to the more conventional frequency space.

Detailed algorithm description:

First, the regular component Reg(n) and singular component Sng(n) of the cepstrum of the minimum-phase component of the pressure signal, K(n), are separated:

$$K(n)=Reg(n)+Sng(n)$$

Then, the following holds:

$$Sng(n)=\sum_{i=1}^{I}(-1)^{i+1}*R^i*\delta(n-i*m)/i,$$

Algorithm steps:

Step 1: Calculate the allpass component u(n) and the cepstrum K(n) of the minimum-phase component: P(n) = u(n) ⊗ exp(K(n)).

Step 2: Separate the regular Reg(n) and the singular Sng(n) component of K(n).

Step 3: Calculate the exponential function of Sng(n): q(n) = exp(Sng(n)).

Step 4: Since the first peak in q(n) contains the information about the forward wave and the second peak of q(n) contains the information about the reflected wave, the delay, τ, between the first and the second peak is estimated: $\tau = m \cdot f$ where m is the number of samples between peaks and f is the sampling frequence.

Step 5: Evaluate the pressure wave velocity by the formula: $PWV = 2 \cdot d/\tau$;

Step 6: The reflection coefficient R is evaluated by the following expression:

$$\sum_n q(n) \approx \sum_n^R * g(n) \approx R * \sum_n g(n) \approx R$$

PROCEDURE 5a: The distance to the obstacle is known.

When d, the distance to the stenosis, is known, a simple application of the above procedure yields the time delay by which the pressure wave velocity, C, is obtained:

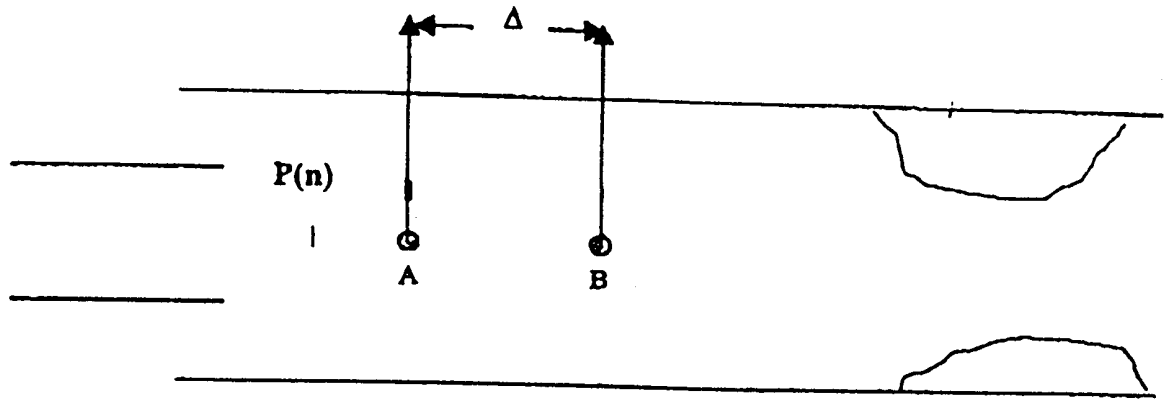
$$PWV = 2 * d / \tau$$

PROCEDURE 5b: The distance to the obstacle is not known.

When the distance d to the obstacle is unknown (for example for a healthy vessel), the procedure is applied twice upon moving the pressure transducer to two different positions, a and b, separated by a distance $\Delta = x_b - x_a$, with corresponding delays τ_a smf τ_b. The PWV is given by the formula:

$$C = \frac{2 \cdot \Delta}{(\tau_a - \tau_b)}$$

The experimental setup is:



METHOD NO. 1: Three pressure measurements

With reference to Fig. 7. Three pressure sensors 4a, 4b, 4c are inserted via a standard connector 8 into a standard guiding catheter 3 and located within the blood vessel of interest 30. The distance between pressure sensor 4a and 4b is equal to the distance between pressure sensor 4b and 4c. Simultaneous pressure data is acquired and analyzed. The method is demonstrated in Example 1, an in-vivo study on the carotid of a young pig, described hereinbelow.

Two pressure sensors 4a and 4b ,or 4a and 4c or 4b and 4c may be a dual pressure catheter or guidewire, i.e. two pressure sensor model spc-721, catalog no 803509, available from Millar.

Three pressure sensors 4a ,4b and 4c may also be incorporated on a single catheter or guidewire, i.e. using three pressure transducers adapted in a custom design configuration available from Millar Instruments Inc., Houston TEXAS. Obvious procedure modification may enable unequal distances between the sensors.

METHOD NO. 2: FF catheter and two pressure measurements.

The method is presented in Fig 14. A FF pressure system 31, connected to a standard guiding catheter 3, and two intravascular pressure sensors 4a and 4b are inserted via a standard connector 8 and located within the vessel of interest 30. The distance between the tip of the GC and the sensor 4a is equal to the distance between sensor 4a and sensor 4b.

Assuming the catheter characteristics (time delay and/or transfer function) are known or measured separately, the FF catheter signal is transformed to a signal replacing an actual measurement at the tip of the guiding catheter. The pressure wave velocity is derived by using the FF transformed signal as pressure input, one of the three expected inputs of Procedure 1, presented hereinabove.

METHOD NO. 3: Two pressure measurements

The method is described in Fig. 15. Two pressure sensors 4a and 4b are inserted into the blood vessel of interest 30 and positioned at point A and B, with a known distance L, 32 in between. Simultaneous pressure measurement with sensors 4a and 4b result in a time delay, proportional to the distance between the sensors and the pressure wave velocity. Both versions of Procedure 2 (2a and 2b) will detect the time delay and derive the pressure wave velocity. Both versions are demonstrated in Example 1, an in-vivo study on the carotid of a young pig.

Example 1: In-vivo experiment

With reference to Fig. 16, in-vivo experiment was performed on the carotid of a young (3 months old) pig using three pressure sensors 35, 36 and 37 inserted into the vessel via a standard 8F guiding catheter 38, and positioned 5cm apart. This case will serve us to demonstrate Procedure 1 and 2.

Reference is now made to Fig. 17. Procedure 2.a was run on the pressure raw data, two out of three available, presented in Fig.17a. The 10% level fitting was applied to both pressure signals resulting in a time delay equivalent to a PWV = 2.406 m/sec, shown in Fig. 17b. Procedure 2.b was applied to the same raw data. Moving one pressure signal to get an optimal overlap with the second pressure signal is shown in Fig. 17c., and result in a PWV = 2.415. The application of Procedure 2.a and 2.b was demonstrated on one heart beat, zooming on a single systole. In fact, these procedures may be generalized. Detection of the onset of systole is automatically carried out on a set of data containing multiple beats, yielding the PWV per beat, and its statistical properties (average, standard deviation, etc.). See Example 2 and 3, hereinbelow.

The same data set was analyzed using the three pressure procedure, Procedure 1, presented hereinabove, referring to all three pressure measurements within the vessel. Fig. 17d. presents the pressure wave velocity as a function of frequency. The monotonically increasing profile is consistent with the Wormesley theory. Since we are interested in the asymptotic value of this function, the average velocity is computed as an average of the data while neglecting the first and last two harmonics. The first two harmonics are not in the asymptotic range, and the last two harmonics are out of the range of acceptable accuracy due to measurement noise. The PWV resulting of this analysis is PWV=2.6. This result is in excellent agreement with the PWV derived hereinabove with Procedure 2.a and 2.b.

Example 2: In-vivo experiment

With reference Fig. 16, in-vivo experiment was performed within the coronaries of a different pig, on the left circumflex of a young (3 months old) pig using two pressure sensors 35 and 36 inserted into the vessel via a standard 8F guiding catheter 38, and positioned 6cm apart.

With reference to Fig. 18, Procedure 2.a was run on the pressure raw data (10 sec data) of 2 Radi pressure wires located 6 cm apart, and filtered by a lowpass filter of 30 Hz. The 10% level fitting was applied to both pressure signals resulting in a PWV = 5.7 m/sec.

Although the previous example presented an in-vivo carotid PWV of about 2.6 m/sec, this pig was in a better clinical condition and exhibited a PWV of 5.6 in the coronaries. The method is demonstrated in Example 4, an in-vivo experiment, using procedure 3 and in Example 5, on human data, using procedure 4.

Example 3: In-vitro experiment

Data were acquired on the in-vitro system described in Figs 4-6, with three Millar pressure sensors, separated by an equal distance of 12 cm. Fig. 19a presents the raw data and Fig. 19b illustrates the analysis with Procedure 1 resulting in a PWV of 13.17 m/sec. To validate this calculation, Procedure 2.a was applied to two out of three sensors. Fig. 19c presents the analysis of the same raw data with Procedure 2a, resulting in PWV of 13 m/sec.

METHOD NO. 4: FF catheter and one pressure measurement

Referring to Fig. 20, a FF pressure system 31, a standard guiding catheter 3 and a pressure sensor 4a are inserted into the blood vessel of interest 30. Assuming prior knowledge of the catheter characteristics (time delay and/or transfer function), the FF pressure signal is transformed. PWV is derived using Procedure 2 (either 2a or 2b) with the transformed FF signal and the pressure sensor signal.

METHOD NO. 5: FF pressure catheter and a single moving pressure sensor

The method is described in Fig. 21. A FF pressure system 31, a standard guiding catheter 3 and a single pressure sensor 4a are inserted into the blood vessel of interest 30 and positioned at point A. Data of pressure at point A are obtained. Than, the pressure sensor 4a is moved to B. Data of pressure at point B are obtained

Example 4: In-vivo experiment

Referring to Fig. 22, in-vivo experiment was performed on a pig carotid using a moving pressure sensor 36 inserted into the vessel via a standard 8F guiding catheter 38. Reference is now made to Figs. 23a and 23b. Procedure 3 was run on the pressure raw data. Figs. 23a and 23b present the results of Procedure 2.a. The level fitting procedure was applied twice, using as input the FF pressure signal and the Radi pressure signal: with Radi pressure sensor located 5 cm and 15 cm from the catheter tip. The pressure curves were filtered by a standard zero-phase 15Hz low-pass filter. The calculated time delays were: Δt_1=0.15/4.3387=0.0342 sec and Δt_2=0.05/-13.8413=-0.0036 sec. Resulting in:

$$PWV = \frac{0.15 - 0.05}{0.0342 - (-0.0036)} = 2.645 \ \ m/s$$

An independent validation of the above-calculated PWV is presented in Fig. 24. Applying Procedure 2.a to two Radi pressure sensors, yields a PWV of 2.38 m/s.

Example 5 Clinical results

As a further illustration of the method, we present the PWV calculation for the left coronary artery (LAD) of a sixty years old woman, using Procedure 4. The data were obtained in the course of a PCTA procedure using the system as described in Figure 1a 2a and 3. Procedure 3 was run on the pressure raw data presented in figure 25 (a,b) and 26 (a,b). The sampling rate was 1000 Hz. In figure 25, the simultaneous measurements of the FF and the radi , in proximal position, are presented, the distance between both transducers being 3 cm. Next, the radi was moved 3 cm distally (the FF-radi distance being now 6 cm) and an another simultaneous measurement was carried out about two minutes later. It is safe to assume that the physiological conditions did not change significantly. The measurements are presented in figure 26. For each heart beat, the following procedure should be repeated and averages taken in the end. First, the time shift, t_1, between the foot of two FF measurements for two arbitrary heart beats, one for each case, proximal and distal is calculated.

The method used was the optimal overlap procedure. Figure 27 presents the two FF measurements. The optimal coincidence graph is shown in figure 28 for that case. The time shift is found to equal : t_1=0.03/6 sec. The same procedure is carried for the two radis corresponding two the same beats (figures 29,30) and the time shift is: t_2=0.03/3.75 sec . The time shift between the two radis is thus t=0.03/3.75-0.03/6=0.003 sec and since the distance between the radis is 3 cm one finds: PWV = 0.03/0.003=10 meter/second.

METHOD NO. 5 a: Single pressure sensor and an electrocardiogram.

The method is based on a single pressure sensor and simultaneous ECG signal, measured at point A and point B, d cm apart within the vessel. The ECG signals (e.g. the R wave of a standard lead ECG) are used to derive the time shift between the measurements, Δt_1. The time shift is applied to the pressure data. Now we have two synchronized pressure data, and procedure 2 (2a or 2b) is applied to derive PWV and its parameters. As well, one could independently derive the time shift between the pressure measurements and calculate the PWV according to the following equation: PWV = $d/(\Delta t_2 - \Delta t_1)$. The single pressure may be a FF pressure catheter, a

catheter pressure transducer or any type of pressure sensor, flow sensor, diameter or crossection changes sensor, as described in procedure 3 hereinabove.

$$PWV=\frac{d}{\Delta t_2 - \Delta t_2}$$

METHOD NO. 6: FF pressure catheter with single flow sensor

Referring to Fig. 31, a FF pressure system 31, a standard guiding catheter 3 and a single velocity(or flow) sensor 5a , i.e FloWire doppler flow guidewire , catalog number 1400 available from Cardiometrics, an Endosonics corporation, are inserted into the blood vessel of interest 30 and positioned at point A. Data of FF pressure simultaneously is measured with flow at point A are acquired. Then, the flow sensor 5a is moved to point B. Data of FF pressure are simultaneously acquired with flow at point B. The PWV is derived by applying the principle of Procedure 3 to flow data acquired by a moving flow sensor, gated to the FF pressure catheter data. Another type of pressure traducer may replace FF pressure measurement, i.e. wavewire pressure guidewire catalog number 8400 available from Radi Medical systems, Upsala, Sweden or pressure sensor catheter model SPC-320 (catalog number 800-0509) available from Millar, Texas

Also any other device which measures a parameter which is closely correlated with pressure at a specific site within the vessel may take the gating rolerplacing the FF pressure catheter. For example it may be an Intravascular flow sensor or an IVUS. The ECG signal is another signal that may serve for gating. Not only it is a convenient signal, but it is also a standard and essential clinically significant measurement.

Flow and pressure transducers may also be incorporated within the same catheter or guidewire, i.e. model SPVC-663A catalog number 810-1029 available also from Millar.

Example 6: In-vitro experiment

Data were acquired on the in-vitro system described in Figs 4-6, with one ultrasonic flowmeter (model T206, by Transonic Systems Inc., NY, USA) probe and two pressure sensors.

The ultrasonic flowmeter probe was located at the proximal part of the flexible tube **43**, and the two pressure sensors were located distally to it. The distance between the flowmeter and the first pressure measurement was 31.5 cm. The distance between the flowmeter and the second pressure measurement was 22 cm. Fig. 32a illustrates a typical ultrasonic flowmeter raw data of one stroke. Fig. 32b illustrates a simultaneous pressure data. Figs. 33-34 illustrate the application of the Procedure 3 to both set of flow and pressure data (note that the flat aspect of the pressure data is due to the difference in scale between the pressure and flow): Dt_1=0.315/6.4299=0.049 sec, Dt_2=0.22/5.2407=0.042 sec and yielding $dt=Dt_1-Dt_2$=0.007 sec. The pressure wave velocity is, therefore, PWV=(0.315-0.22)/dt = 13.55 m/sec. This value of PWV is in an excellent agreement with the known pressure wave velocity within the in-vitro system. Finally, while the present invention has been described with respect to blood vessel measurements, the system can be used within other tube-like structures having pulsatile liquid flow therein. It will be appreciated that the present invention is not limited by what has been described hereinabove and illustrated in the various figures, and that numerous modifications, all of which fall within the scope of the present invention, exist.

METHOD NO. 7: Single pressure transducer

With reference to Figure 35. Pressure sensor 4 is inserted via a standard connector 8 into a standard guiding catheter 3 and located within the blood vessel of interest 30, proximal to a stenosis 31. When the distance between the pressure sensor and the stenosis is known (using angio, QCA, etc.) the PWV is calculated using a single pressure sensor and a single measurement as described in procedure 5a. The method is demonstrated in Example 7.

When the distance between the pressure sensor and the stenosis is unknown, the PWV is calculated using a single pressure sensor measuring at two locations along the vessel, proximal to the stenosis, as described in procedure 5b. The method is demonstrated in Example 8.

EXAMPLE 7: In-vivo experiment

Referring to Fig. 36, in-vivo experiment was performed on a pig carotid using a single pressure sensor 36, inserted into the vessel via a standard 8F guiding catheter 38. The pressure sensor 36, was located 5 cm proximal to an externally induced occlusion 37. The pressure raw data, presented in Fig. 37, was analyzed using procedure 5a. The results are presented in Figs. 38 and 39.

Fig. 38 presents the cepstrum of the raw data with a singular part appearance at τ=40.2 msec (step 1 of procedure 5a), and Fig. 39 presents the exponential function of the singular component with τ=39.2 msec. The derived PWV is : PWV=0.10/0.0402=2.49 msec, where the pressure wave is traveling to the stenosis and back a distance of 10 cm. This value is highly correlated to the PWV calculated for the same study with other methods, see examples 1 and 4 hereinabove.

Reference is now made to Fig. 40. Taking further procedure 5, the reflection coefficient is calculated and found to be 0.32. Referring to Stergiopulos, Spiridon, Pythoud and Meister, "On the wave transmission and reflection properties of stenoses", J. Biomechanocs, Vol. 29, No. 1, pp. 31-38, 1996, this value relates to a stenosis of about 85%, in accordance to the level of stenosis applied in the study.

EXAMPLE 8: In-vivo experiment

Referring to Fig. 36, in-vivo experiment was performed on a pig carotid using a single pressure sensor 36, inserted into a vessel via a standard 8F guiding catheter 38. The pressure sensor 36, was first located 7.5 cm (point a) and then 5 cm (point b, not shown) proximal to an externally induced occlusion 37. The relevant pressure raw data are presented in Fig. 37 and 41. The data was analyzed using procedure 5b. Referring to Figs. 42 and 43. Fig. 38 and 42 present the cepstrum of the raw data with a singular part appearance at τ=40.2 msec and τ=60.2 msec (step 1 of procedure 5), and Figs. 39 and 43 present the exponential function of the singular component with τ=39.2 msec and τ=59.45 msec.

The derive PWV is: $PWV=2\cdot d/(\tau_a-\tau_b)=0.05/(0.0602-0.0402)=2.5$ msec, where the distance between the points of measurement was 5 cm (2.5 cm each way) and the denominator represent the difference in the echo time from the two points. This value is highly correlated to the PWV calculated for the same study with other methods, see examples 1, 4 and 7 hereinabove.

Reference is now made to Fig. 44. Taking further procedure 5, the reflection coefficient is calculated and found to be 0.27. As stated hereinabove, this value relates to a stenosis of about 85%, in accordance to the level of stenosis applied in the study. The small decrease in the reflection coefficient value probably relates to the wave attenuation, as the distance to the stenosis is higher.

It will be understood that certain features and sub-combinations are of utility and may be employed without reference to other features and sub-combinations as they are outlined within the claims. While the preferred embodiments and applications of the invention have been described, it is apparent to those skilled in the art that the objects and features of the present invention are only limited as set forth in claims attached hereto.

What is claimed is:

1. A system for determining at least one viscoelastic parameter of a region of a blood vessel, the system comprising:

a flexible elongated member having a portion insertable into said blood vessel;

means for simultaneously measuring the blood pressure in at least two predetermined positions along said longitudinal axis and for producing simultaneous pressure signals; and

a processing unit connected to said means for measuring the blood pressure for receiving said pressure signals and for processing said simultaneous pressure signals to determine said at least one viscoelastic parameter.

2. A system for determining at least one viscoelastic parameter of a region of a blood vessel, the system comprising:

a flexible elongated member having a portion insertable into said blood vessel and a longitudinal axis;

a plurality of pressure sensors, each of said plurality of pressure sensors being attached to said elongated member at a predetermined position along said longitudinal axis for simultaneously sensing the pressure at said positions and for producing pressure signals; and

a processing unit connected to said plurality of sensors for receiving said pressure signals and for processing said pressure signals to determine said at least one viscoelastic parameter.

3. A method for determining at least one viscoelastic parameter of a region of a blood vessel, the method comprising the steps of:

simultaneously measuring the pressure in at least two measurement points within said blood vessel to obtain data representing the variation of pressure with time at said at least two measurement points;

calculating at least one viscoelastic parameter of said region from said data;

reporting said at least one viscoelastic parameter.

4. A system for determining at least the pressure wave velocity and derived characteristics of a region of a blood vessel, the system comprising:

a flexible elongated member having a portion insertable into said blood vessel and a longitudinal axis;

a plurality of pressure sensors, each of said plurality of pressure sensors being attached to said elongated member at a predetermined position along said longitudinal axis for simultaneously sensing the pressure at said positions and for producing pressure signals; and

a processing unit connected to said plurality of sensors for receiving said pressure signals and for processing said pressure signals to determine said at least the pressure wave velocity and derived characteristics.

5. A method for determining at least the pressure wave velocity and derived characteristics of a region of a blood vessel, the method comprising the steps of:

simultaneously measuring the pressure in at least one measurement point within said blood vessel to obtain data representing the variation of pressure with time at said at least two measurement points ;

calculating said at least the pressure wave velocity of said region from said data;

reporting said at least the pressure wave velocity and derived characteristics.

6. A system for determining at least the pressure wave velocity and derived characteristics of a lesioned region of a blood vessel, the system comprising:

a flexible elongated member having a portion insertable into said blood vessel ;

means for simultaneously measuring the blood pressure in at least one predetermined position along said longitudinal axis and for assessing simultaneous pressure signals; and

a processing unit connected to said means for measuring the blood pressure for receiving said pressure signals and for processing said simultaneous pressure signals to determine said at least the pressure wave velocity and derived characteristics, and thereby recommend the best treatment needed.

7. A system for determining at least the pressure wave velocity and derived characteristics of a region of a blood vessel, where a PTCA procedure has been applied. The system comprising:

a flexible elongated member having a portion insertable into said blood vessel ;

means for simultaneously measuring the blood pressure in at least one predetermined position along said longitudinal axis and for assessing simultaneous pressure signals; and

a processing unit connected to said means for measuring the blood pressure for receiving said pressure signals and for processing said simultaneous pressure signals to determine said at least the pressure wave velocity and derived characteristics, and the efficacy of the PTCA applied intervention.

8. A system for determining at least the pressure wave velocity and derived characteristics of a lesioned region of a blood vessel, where a STENT was deployed, the system comprising:

a flexible elongated member having a portion insertable into said blood vessel ;

means for simultaneously measuring the blood pressure in at least one predetermined position along said longitudinal axis and for assessing simultaneous pressure signals; and

a processing unit connected to said means for measuring the blood pressure for receiving said pressure signals and for processing said

the pressure wave velocity and derived characteristics, and the efficacy of the STENT deployment.

9. A system for characterizing changes in tubular conduit system within a living body for transferring fluids, said system comprising:

at least one flexible elongated member having a portion insertable into said tubular conduit and a logitudinal axis;

at least one pressure sensor being positioned along said elongated member at a predetermined location along said longitudinal axis for sensing the pressure and operative to generate a pressure signal representative of said sensed pressure at a plurality of points within said tubular conduit;

a processing unit operatively connected in circuit to said at least one pressure sensor;

a program for controlling said processor unit;

said processor unit operative with said program to receive said pressure signal and to:

identify changes in the pressure signal;

detect characteristics of said tubular conduit system being derived from changes in said pressure signal;

recognize and assign a label to said characteristic.

10. The system according to Claim 9 wherein:

said at least one pressure sensor includes one pressure sensor movable relative to said tubular conduit;

said pressure signal is representative of a plurality of pressure measurement taken over time a predetermined locations within said tubular conduit.

11. The system according to Claim 9 wherein:

said at least one pressure sensor includes two pressure sensors located in predetermined spaced-apart positions along said at least one elongated member;

said pressure signal is representative of a plurality pressure measurement taken simultaneously by said pressure sensors.

12. The system according to Claim 9 wherein:

said at least one pressure sensor includes three pressure sensors located in predetermined spaced-apart positions along said elongated member;

said pressure signal is representative of a plurality pressure measurements taken simultaneously by said pressure sensors.

13. The system according to Claims 9, 10, 11 or 12 wherein said tubular conduit system is a blood vessel system; and

said processor unit is operative to detect characteristics of a blood vessel wall.

14. The system according to Claim 13 wherein said characteristics of said blood vessel wall detected by said processor include vessel wall compliance and distensibility.

15. The system according to Claim 14 wherein said processor unit is operative to recognize wall calcification and thickening, thereby permitting occult disease identification.

16. The system according to Claim 14 wherein said processor unit is operative to recognize a low compliance thereby identifying weak vascular sections of said blood vessels.

17. The system according to Claim 13 wherein said characteristics of said blood vessel wall include detecting circumferential strain acting on blood vessel wall cells thereby monitoring drug treatment effects.

18. The system according to Claim 17 wherein said blood vessel wall cells are of the group consisting of endothelial cells and smooth muscle cells.

19. The system according to Claim 11 wherein said tubular conduit system is a blood vessel system such at least one pressure sensor measures blood pressure waveforms;

said processor unit is operative to:

detect characteristics of a blood vessel wall;

receive pressure signals representative of a predetermined portion of said blood pressure waveform;

determining a pressure wave velocity from said received pressure signals.

20. The system according to Claim 19 wherein said processor unit is operative to conduct a level fitting procedure including estimating a time delay between comparable levels in said predetermined portion of said blood pressure waveform to determine a pressure wave velocity.

21. The system according to Claim 19 wherein said processor unit is operative to perform an overlap procedure including estimating a best stretch co-efficient and a time delay between said predetermined portions of said blood pressure waveform.

22. The system according to Claim 10 wherein said tubular conduit system is a blood vessel system;

said at least one pressure sensor measures blood pressure waveforms and includes one pressure sensor;

said processor unit is operative to:

detect characteristics of a blood vessel wall;

receive pressure signals representative of a predetermined portion of said blood pressure waveform.

23. The system according to Claim 22 wherein said pressure sensor is movable with said blood vessel system;

said processor unit is operative to:

perform a level fitting procedure including determining an estimate of a time delay between comparable levels of said predetermined portion of said blood pressure waveform.

24. The system according to Claim 12 wherein said tubular conduit system is a blood vessel system;

said at least one pressure sensor measures blood pressure waveforms and includes three pressure sensors;

said processor unit is operative to:

detect characteristics of a blood pressure wall;

receive pressure signals representative of a predetermined portion of said blood pressure waveform.

25. The system according to Claim 24 wherein said processor unit is operative to:

perform Fourier decomposition procedure including determining a Fourier transform of said pressure signal from said three pressure sensors and determining a pressure wave velocity therefrom.

26. A method for using a flexible elongated member having a portion insertable into said tubular conduit and a logitudinal axis, at least one pressure sensor being positioned along said elongated member at a predetermined location along said longitudinal axis for sensing the pressure and operative to generate a pressure signal representative of said sensed pressure at a plurality of points within said tubular conduit, a processing unit operatively connected in circuit to said at least one pressure sensor, a program for controlling said processor unit, said processor unit operative with said program to receive said pressure signal to characterize changes in a tubular conduit system within a living body for transferring fluids, said method comprising the steps of:

sensing a pressure using said pressure sensor;

generating a pressure signal representative of said sensed pressure at a plurality of points within said tubular conduit;

identifying changes in the pressure signal;

detecting characteristics of said tubular conduit system being derived from changes in said pressure signal; and

recognizing and assigning a label to said characteristic.

27. The method according to Claim 26 wherein said tubular conduit system is a blood vessel system; and

said detecting step includes detecting characteristics of a blood vessel wall.

28. The method according to Claim 27 wherein said characteristics of said blood vessel wall detected in said detecting step includes vessel wall compliance and distensibility.

29. The method according to Claim 28 including the steps of:

recognizing wall calcification and thickening; and

permitting occult disease identification.

30. The method according to Claim 28 including the steps of:

recognizing a low compliance; and

identifying weak vascular sections of said blood vessels.

31. The method according to Claim 27 wherein said detecting step includes detecting circumferencian strain acting on blood vessel wall cells thereby monitoring drug treatment effects.

32. The method according to Claim 31 wherein said blood vessel wall cells are of the group consisting of endothelial cells and smooth muscle cells.

33. The method according to Claim 26 wherein said tubular conduit system is a blood vessel system such at least one pressure sensor includes two pressure sensors, said sensing step includes measuring blood pressure waveforms and said method including the steps of:

detecting characteristics of a blood vessel wall;

receiving pressure signals representative of a predetermined portion of said blood pressure waveform; and

determining a pressure wave velocity from said receive pressure signals.

34. The method according to Claim 33 including the steps of:

estimating a time delay between comparable levels in said predetermined portion of said blood pressure waveform to determine a pressure wave velocity.

35. The method according to Claim 33 including the steps of estimating a best vessel wall stretch co-efficient and estimating a time delay between said predetermined portions of said blood pressure waveform.

36. The method according to Claim 26 wherein said tubular conduit system is a blood vessel system;

said at least one pressure sensor includes one pressure sensor, said sensing step includes measuring blood pressure waveforms, said method further includes the steps of:

detecting characteristics of a blood pressure wall;

receiving pressure signals representative of a predetermined portion of said blood pressure waveform.

37. The method according to Claim 36 wherein said pressure sensor is movable with said blood vessel system, said method includes the steps of:

performing a level fitting procedure including determining an estimate of a time delay between comparable levels of said predetermined portion of said blood pressure waveform.

38. The method according to Claim 26 wherein said tubular conduit system is a blood vessel system;

said at least one pressure sensor includes three pressure sensors, said sensing step includes measuring blood pressure waveforms, said method includes the steps of:

detecting characteristics of a blood pressure wall;

receiving pressure signals representative of a predetermined portion of said blood pressure waveform.

39. The method according to Claim 38 including the steps of:

performing a Fourier decomposition procedure including determining a Fourier transform of said pressure signal from said three pressure sensors and determining a pressure wave velocity therefrom.

40. The method according to Claim 26 wherein said method includes:

repeating said sensing step, said generating step, said identifying step, said detecting step and said reconizing step at least once;

wherein said repeated steps are adapted to correspond to a predetermined one of a plurality of detecting and recognizing procedures.

41. The method according to Claim 26 wherein said at least one pressure sensor is movable and a controlled atoumatic moving system controls movement of said sensor, said method includes:

moving said sensor at a predetermined distance along said conduit.

42. The system according to claim 14 wherein said processor is operative to recognize an altered higher compliance thereby identifying an aneurysm.

43. A system for characterizing changes in tubular conduit system within a living body for transferring fluids, said system comprising:

at least one flexible elongated member having a portion insertable into said tubular conduit and a logitudinal axis;

at least one fluid flow sensor being positioned along said elongated member at a predetermined location along said longitudinal axis for sensing the fluid flow and operative to generate a fluid flow signal representative of said sensed fluid flow at a plurality of points within said tubular conduit;

a processing unit operatively connected in circuit to said at least one fluid flow sensor;

a program for controlling said processor unit;

said processor unit operative with said program to receive said fluid flow signal and to:

identify changes in the fluid flow signal;

detect characteristics of said tubular conduit system being derived from changes in said fluid flow signal;

recognize and assign a label to said characteristic.

44. The system according to Claim 43 wherein:

said at least one fluid flow sensor includes one fluid flow sensor movable relative to said tubular conduit;

said fluid flow signal is representative of a plurality of fluid flow measurement taken over time a predetermined locations within said tubular conduit.

45. The system according to Claim 43 wherein:

said at least one fluid flow sensor includes two fluid flow sensors located in predetermined spaced-apart positions along said elongated member;

said fluid flow signal is representative of a plurality fluid flow measurement taken simultaneously by said fluid flow sensors.

46. The system according to Claim 43 wherein:

said at least one fluid flow sensor includes three fluid flow sensors located in predetermined spaced-apart positions along said elongated member;

said fluid flow signal is representative of a plurality fluid flow measurements taken simultaneously by said fluid flow sensors.

47. The system according to Claims 43, 44, 45 or 46 wherein said tubular conduit system is a blood vessel system; and

said processor unit is operative to detect characteristics of a blood vessel wall.

48. The system according to Claim 47 wherein said characteristics of said blood vessel wall detected by said processor include vessel wall compliance and distensibility.

49. The system according to Claim 48 wherein said processor unit is operative to recognize wall calcification and thickening, thereby permitting occult disease identification.

50. The system according to Claim 48 wherein said processor unit is operative to recognize a low compliance thereby identifying weak vascular sections of said blood vessels.

51. The system according to Claim 47 wherein said characteristics of said blood vessel wall include detecting circumferential strain acting on blood vessel wall cells thereby monitoring drug treatment effects.

52. The system according to Claim 51 wherein said blood vessel wall cells are of the group consisting of endothelial cells and smooth muscle cells.

53. The system according to claim 48 wherein said processor is operative to recognize an altered higher compliance thereby identifying an aneurysm.

54. A system for characterizing changes in tubular conduit system within a living body for transferring fluids, said system comprising:

at least one fluid characteristic sensor being positioned in relation to said tubular conduit at a predetermined location for sensing the fluid characteristic and operative to generate a fluid characteristic signal representative of said sensed fluid characteristic at a plurality of points within said tubular conduit;

a processing unit operatively connected in circuit to said at least one fluid characteristic sensor;

a program for controlling said processor unit;

said processor unit operative with said program to receive said fluid characteristic signal and to:

identify changes in the fluid characteristic signal;

detect characteristics of said tubular conduit system being derived from changes in said fluid characteristic signal;

recognize and assign a label to said characteristic.

55. The system according to Claim 54 wherein:

said at least one fluid characteristic sensor includes one fluid characteristic sensor movable relative to said tubular conduit;

said fluid characteristic signal is representative of a plurality of fluid characteristic measurement taken over time a predetermined locations within said tubular conduit.

56. The system according to Claim 54 wherein:

said at least one fluid characteristic sensor includes two fluid characteristic sensors located in predetermined spaced-apart positions in relation to said tubular conduit;

said fluid characteristic signal is representative of a plurality fluid characteristic measurement taken simultaneously by said fluid characteristic sensors.

57. The system according to Claim 54 wherein:

said at least one fluid characteristic sensor includes three fluid characteristic sensors located in predetermined spaced-apart positions in relation to said said tubular conduit;

said fluid characteristic signal is representative of a plurality fluid characteristic measurements taken simultaneously by said fluid characteristic sensors.

58. The system according to Claims 54, 55, 56 or 57 wherein said tubular conduit system is a blood vessel system;

said fluid characteristic is of the group consisting of blood pressure, blood flow and blood vessel wall deformations from blood flow; and

said processor unit is operative to detect characteristics of a blood vessel wall.

59. The system according to Claim 58 wherein said characteristics of said blood vessel wall detected by said processor include vessel wall compliance and distensibility.

60. The system according to Claim 59 wherein said processor unit is operative to recognize wall calcification and thickening, thereby permitting occult disease identification.

61. The system according to Claim 59 wherein said processor unit is operative to recognize a low compliance thereby identifying weak vascular sections of said blood vessels.

62. The system according to Claim 58 wherein said characteristics of said blood vessel wall include detecting circumferential strain acting on blood vessel wall cells thereby monitoring drug treatment effects.

63. The system according to Claim 62 wherein said blood vessel wall cells are of the group consisting of endothelial cells and smooth muscle cells.

64. The system according to claim 59 wherein said processor is operative to recognize an altered higher compliance thereby identifying an aneurysm.

65. A system for characterizing changes in tubular conduit system within a living body for transferring fluids, said system comprising:

at least one vessel wall imaging sensor being positioned in relation to said tubular conduit at a predetermined location for sensing the fluid characteristic and operative to generate a vessel wall characteristic signal representative of said sensed vessel wall characteristic at a plurality of points within said tubular conduit;

a processing unit operatively connected in circuit to said at least one vessel wall imaging sensor;

a program for controlling said processor unit;

said processor unit operative with said program to receive said vessel wall characteristic signal and to:

identify changes in the vessel wall characteristic signal;

detect characteristics of said tubular conduit system being derived from changes in said vessel wall characteristic signal;

recognize and assign a label to said characteristic.

66. The system according to Claim 65 wherein:

said at least one vessel wall imaging sensor includes one vessel wall imaging sensor movable relative to said tubular conduit;

said vessel wall characteristic signal is representative of a plurality of vessel wall characteristic measurement taken over time a predetermined locations within said tubular conduit.

67. The system according to Claim 65 wherein:

said at least one vessel wall imaging sensor includes two vessel wall imaging sensors located in predetermined spaced-apart positions along said elongated member;

said vessel wall characteristic signal is representative of a plurality vessel wall characteristic measurement taken simultaneously by said vessel wall imaging sensors.

68. The system according to Claim 65 wherein:

said at least one vessel wall imaging sensor includes three vessel wall imaging sensors located in predetermined spaced-apart positions along said elongated member;

said vessel wall characteristic signal is representative of a plurality vessel wall characteristic measurements taken simultaneously by said vessel wall imaging sensors.

69. The system according to Claims 65, 66, 67 or 68 wherein said tubular conduit system is a blood vessel system;

said vessel wall characteristic is of the group consisting of blood pressure, blood flow and blood vessel wall deformations from blood flow; and

said processor unit is operative to detect characteristics of a blood vessel wall.

70. The system according to Claim 69 wherein said characteristics of said blood vessel wall detected by said processor include vessel wall compliance and distensibility.

71. The system according to Claim 70 wherein said processor unit is operative to recognize wall calcification and thickening, thereby permitting occult disease identification.

72. The system according to Claim 70 wherein said processor unit is operative to recognize a low compliance thereby identifying weak vascular sections of said blood vessels.

73. The system according to Claim 69 wherein said characteristics of said blood vessel wall include detecting circumferential strain acting on blood vessel wall cells thereby monitoring drug treatment effects.

74. The system according to Claim 73 wherein said blood vessel wall cells are of the group consisting of endothelial cells and smooth muscle cells.

75. The system according to claim 70 wherein said processor is operative to recognize an altered higher compliance thereby identifying an aneurysm.

FIG. 1

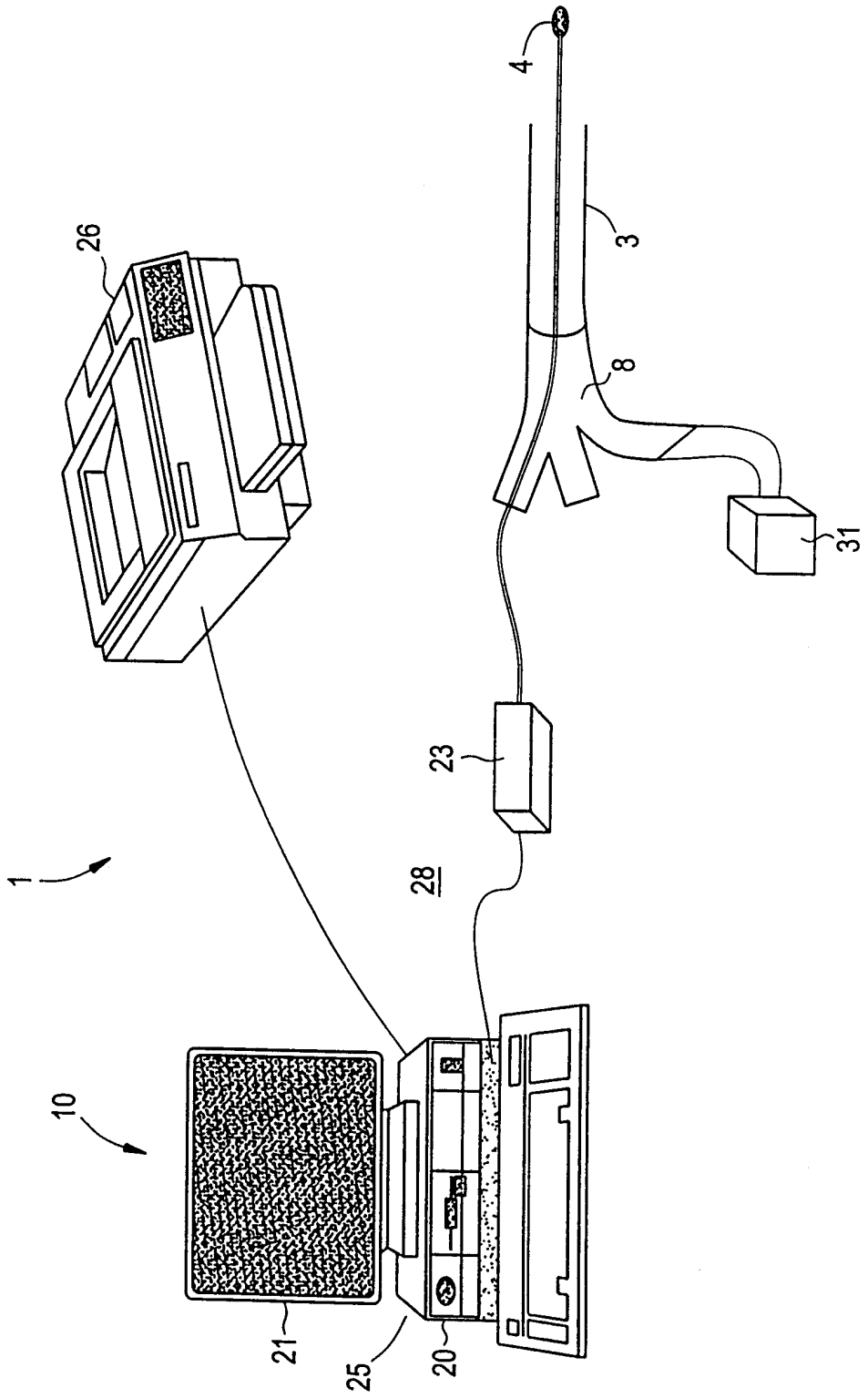


FIG. 1A

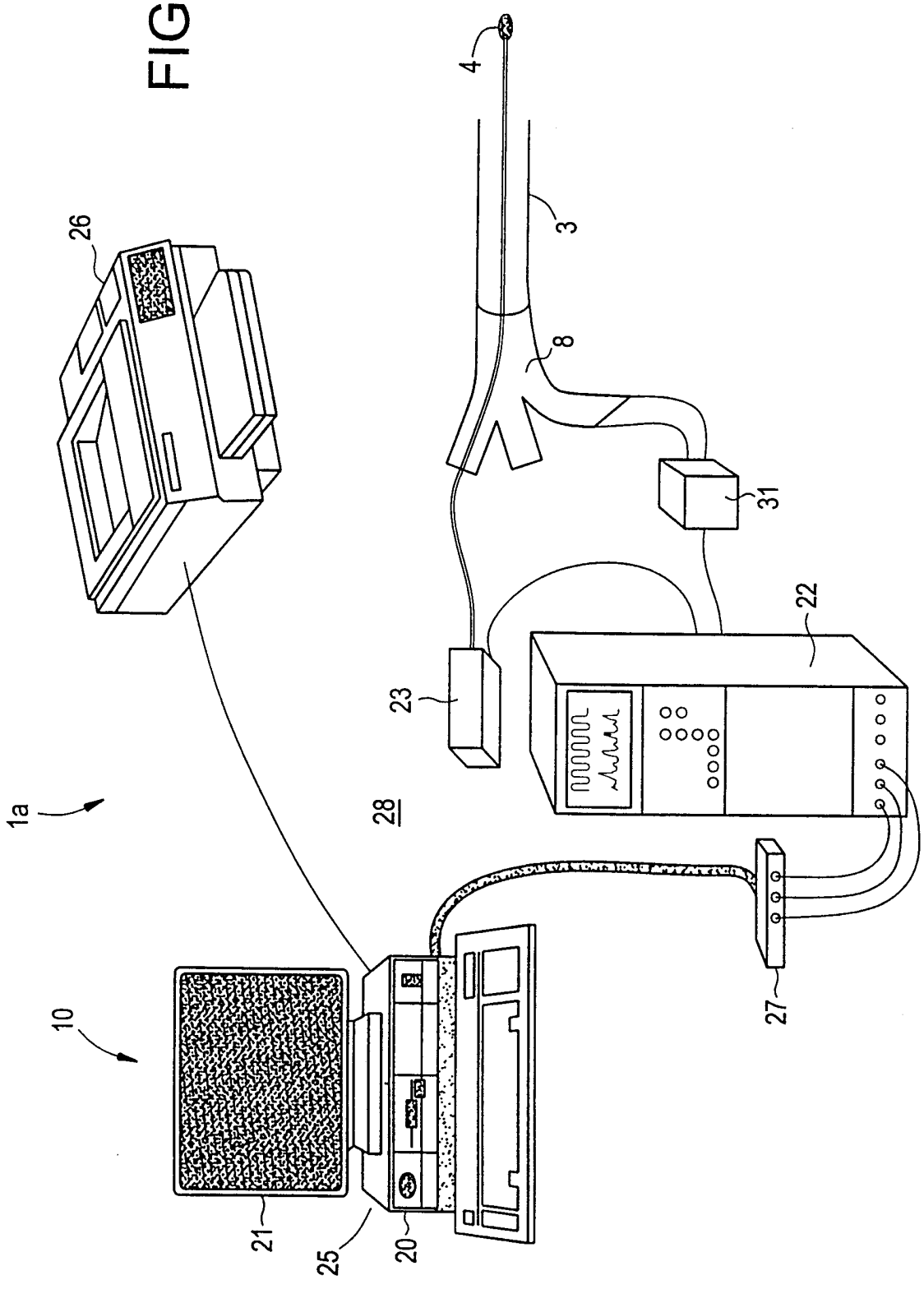


FIG. 2

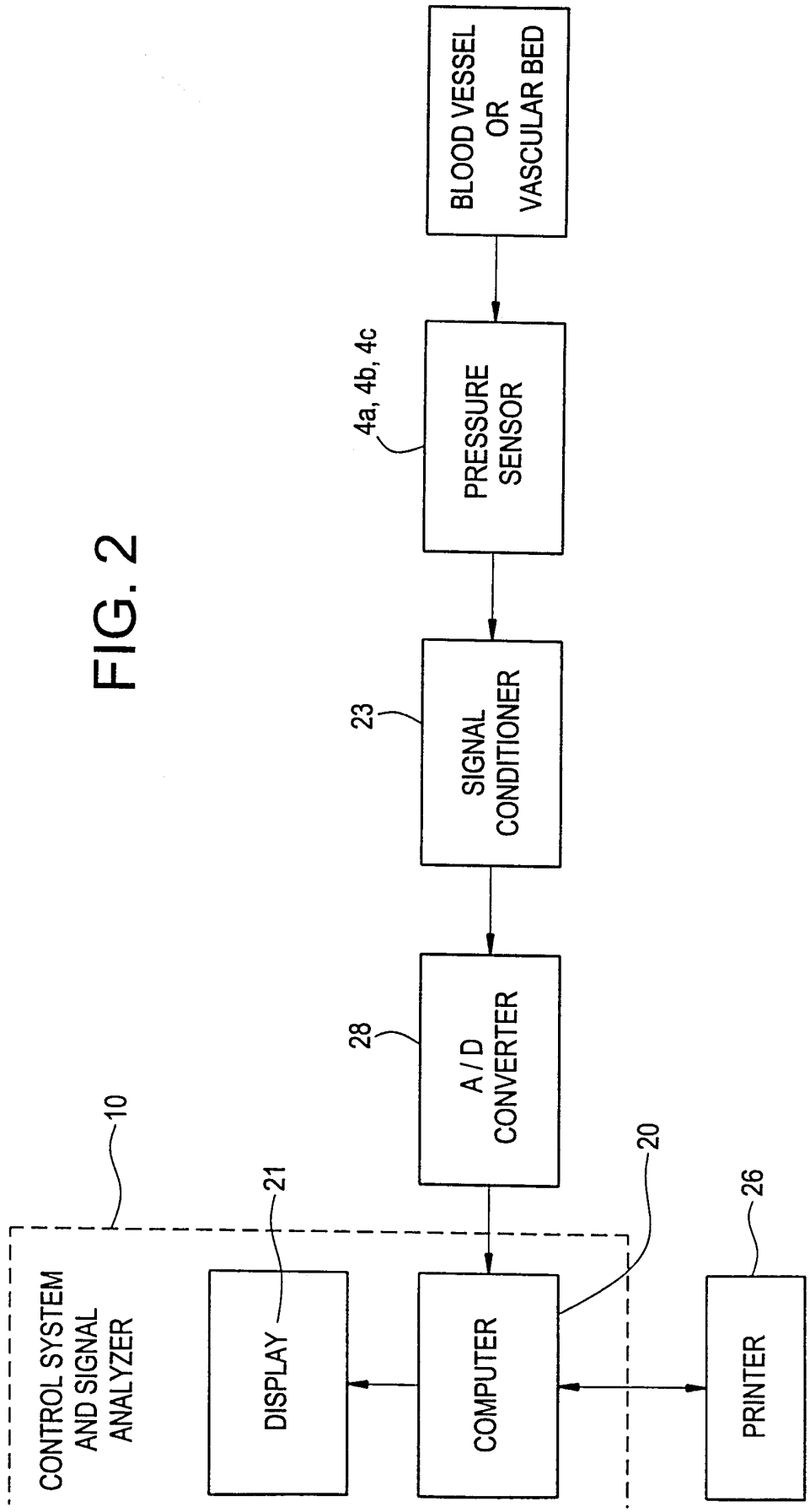

BLOOD VESSEL OR VASCULAR BED
4a, 4b, 4c
PRESSURE SENSOR
23
SIGNAL CONDITIONER
28
A / D CONVERTER
10
CONTROL SYSTEM AND SIGNAL ANALYZER
21
DISPLAY
COMPUTER
20
26
PRINTER

FIG. 2A

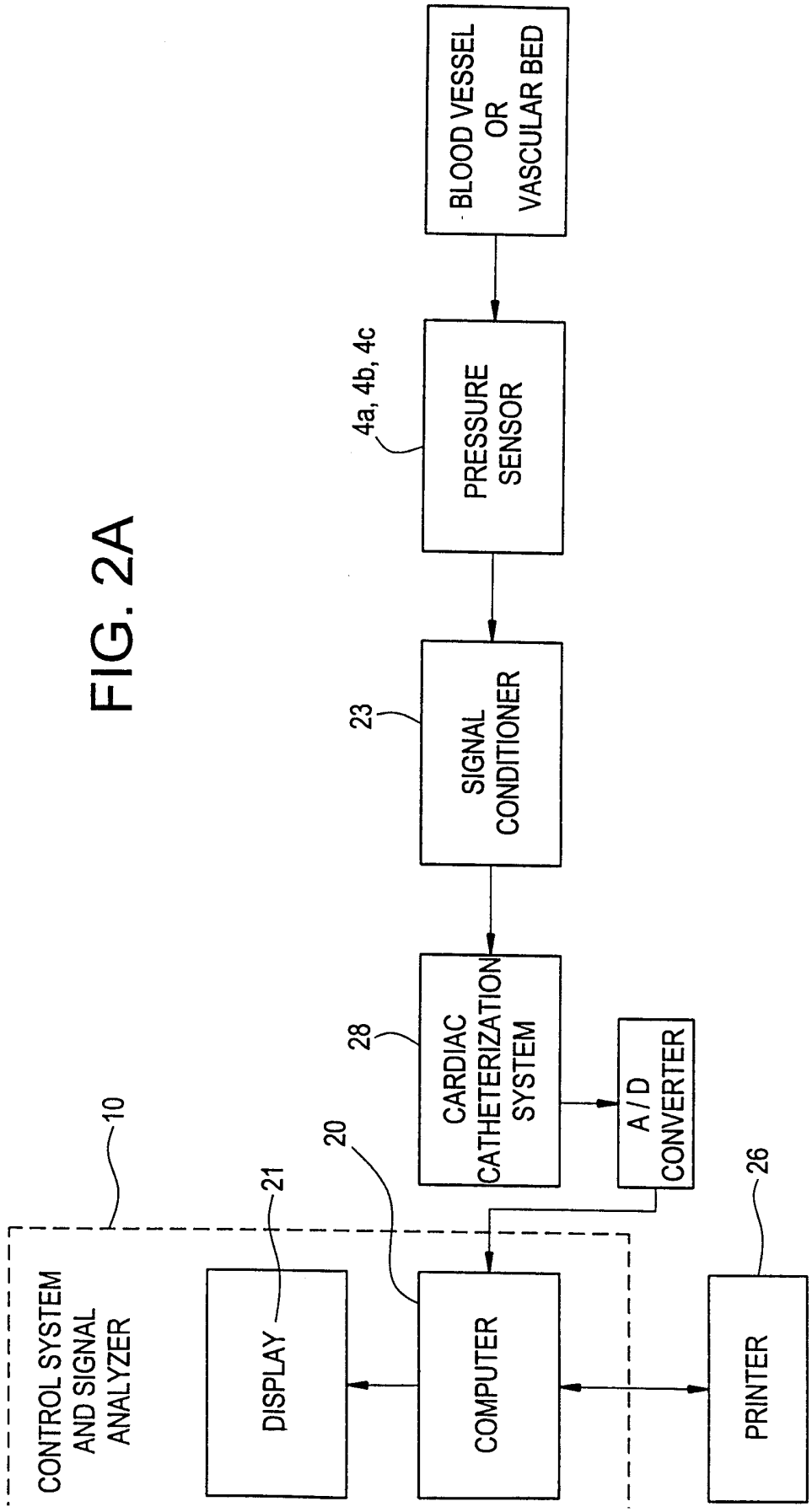

BLOOD VESSEL OR VASCULAR BED
4a, 4b, 4c
PRESSURE SENSOR
23
SIGNAL CONDITIONER
28
CARDIAC CATHETERIZATION SYSTEM
A / D CONVERTER
10
20
21
26
CONTROL SYSTEM AND SIGNAL ANALYZER
DISPLAY
COMPUTER
PRINTER

FIG. 3

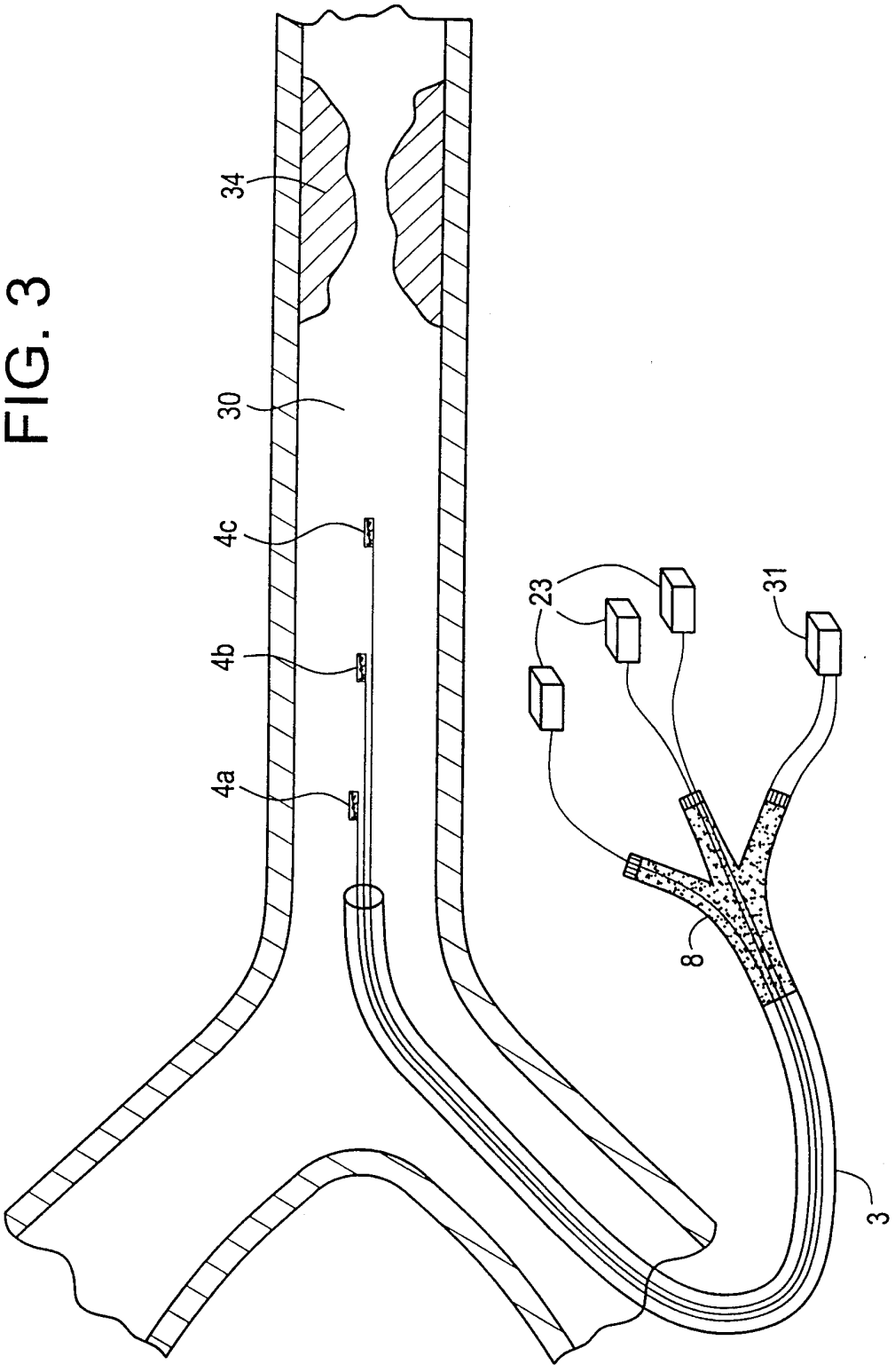


FIG. 3A

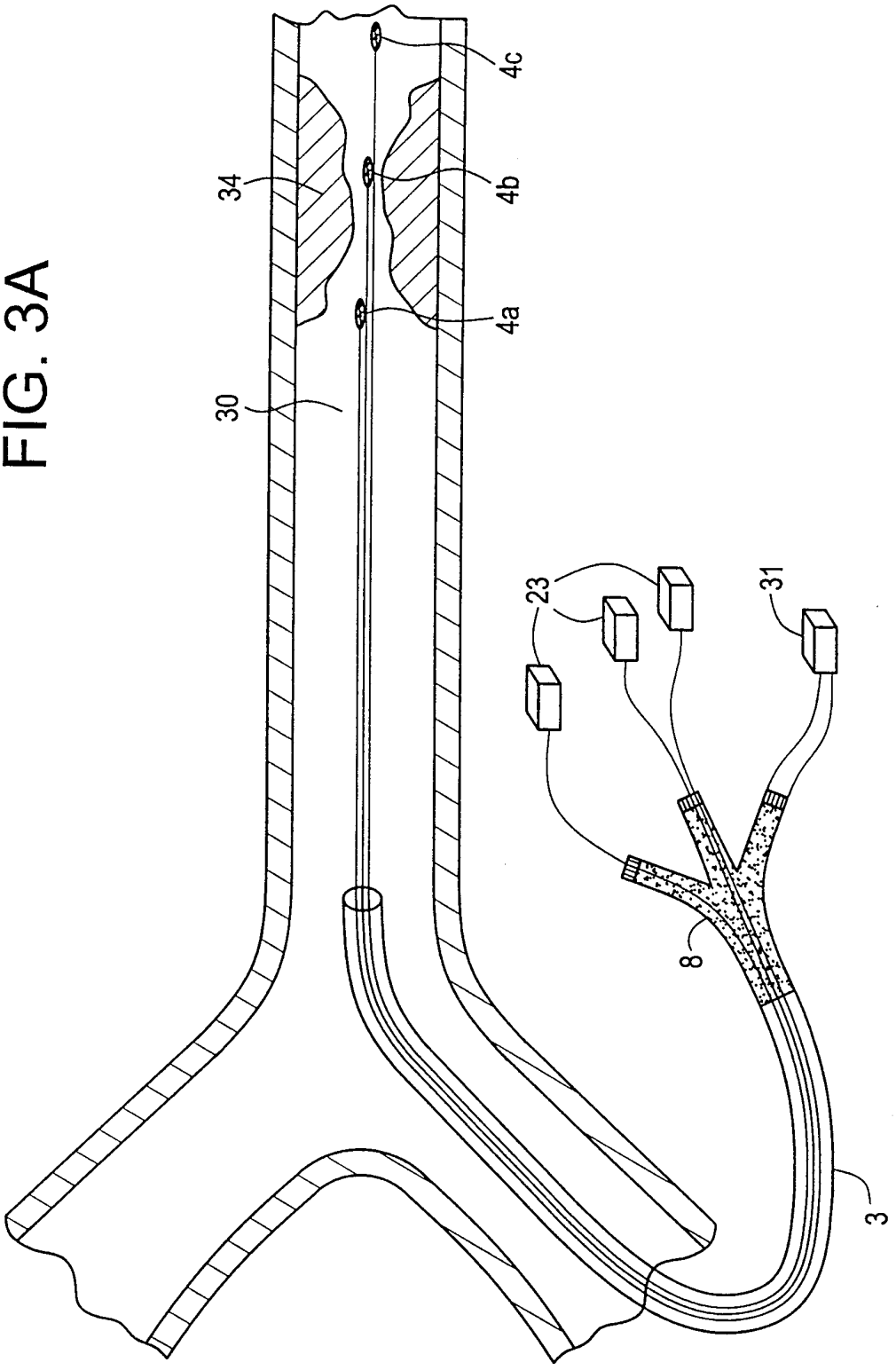


FIG. 4

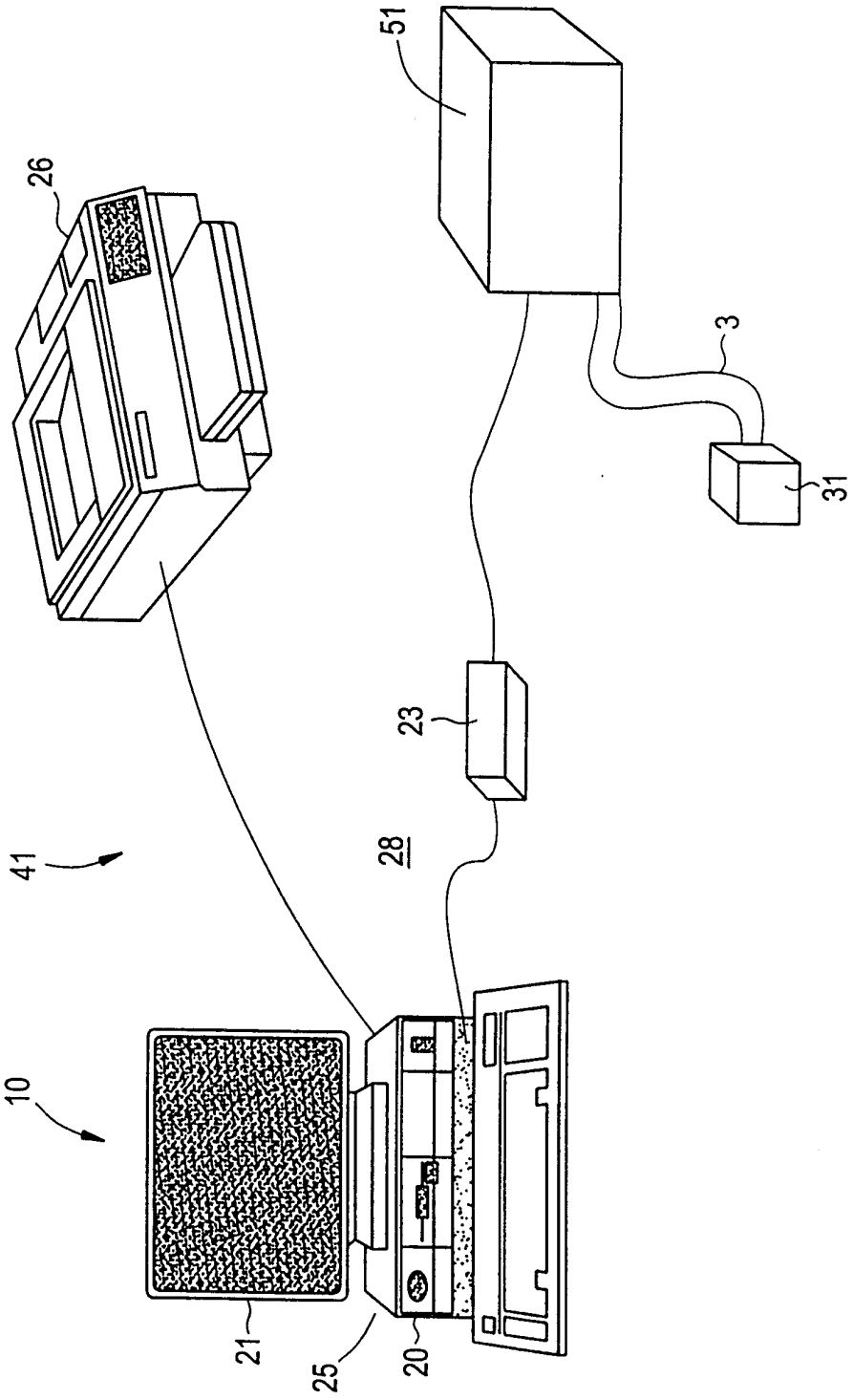


FIG. 5

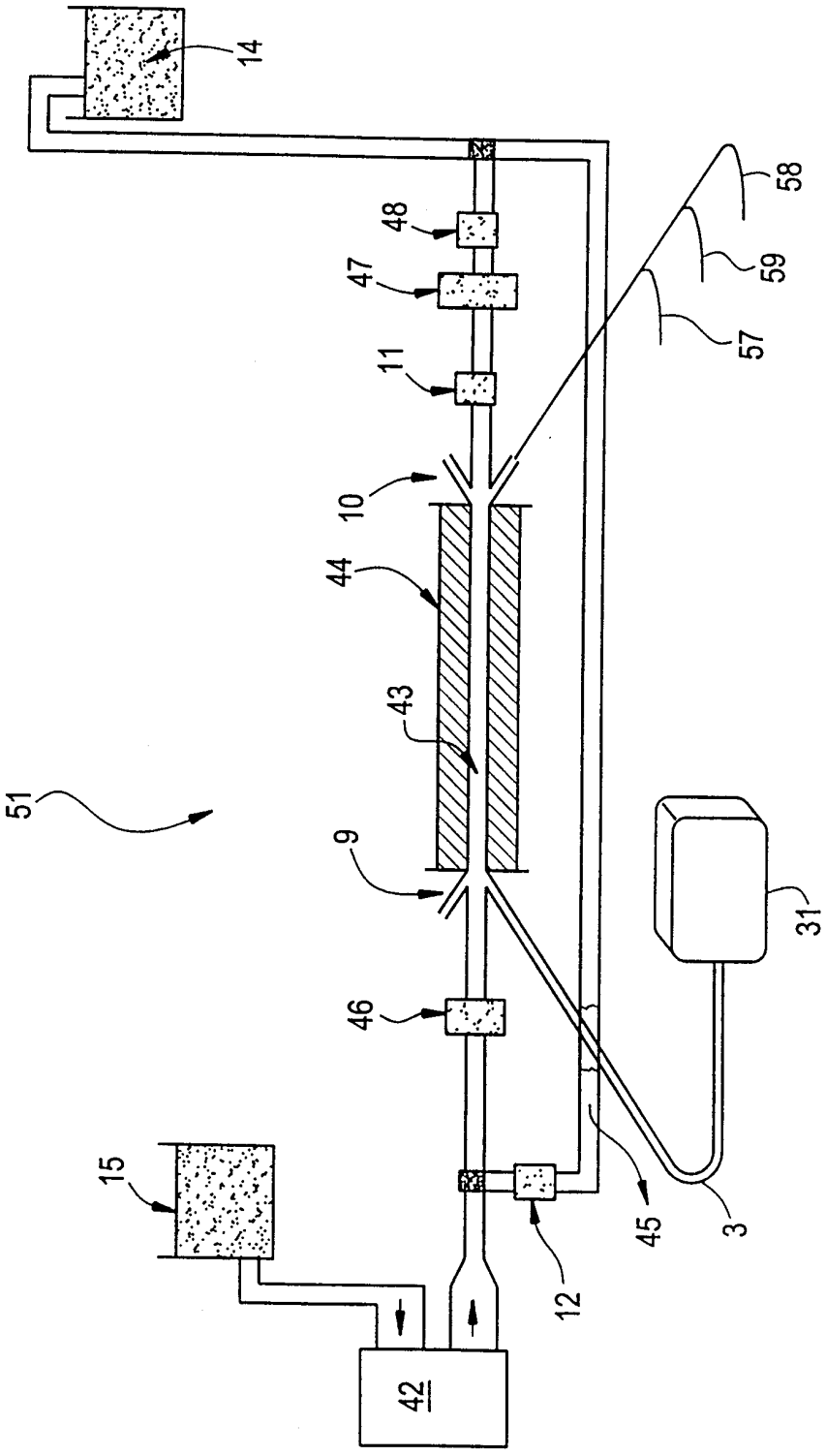


FIG. 6

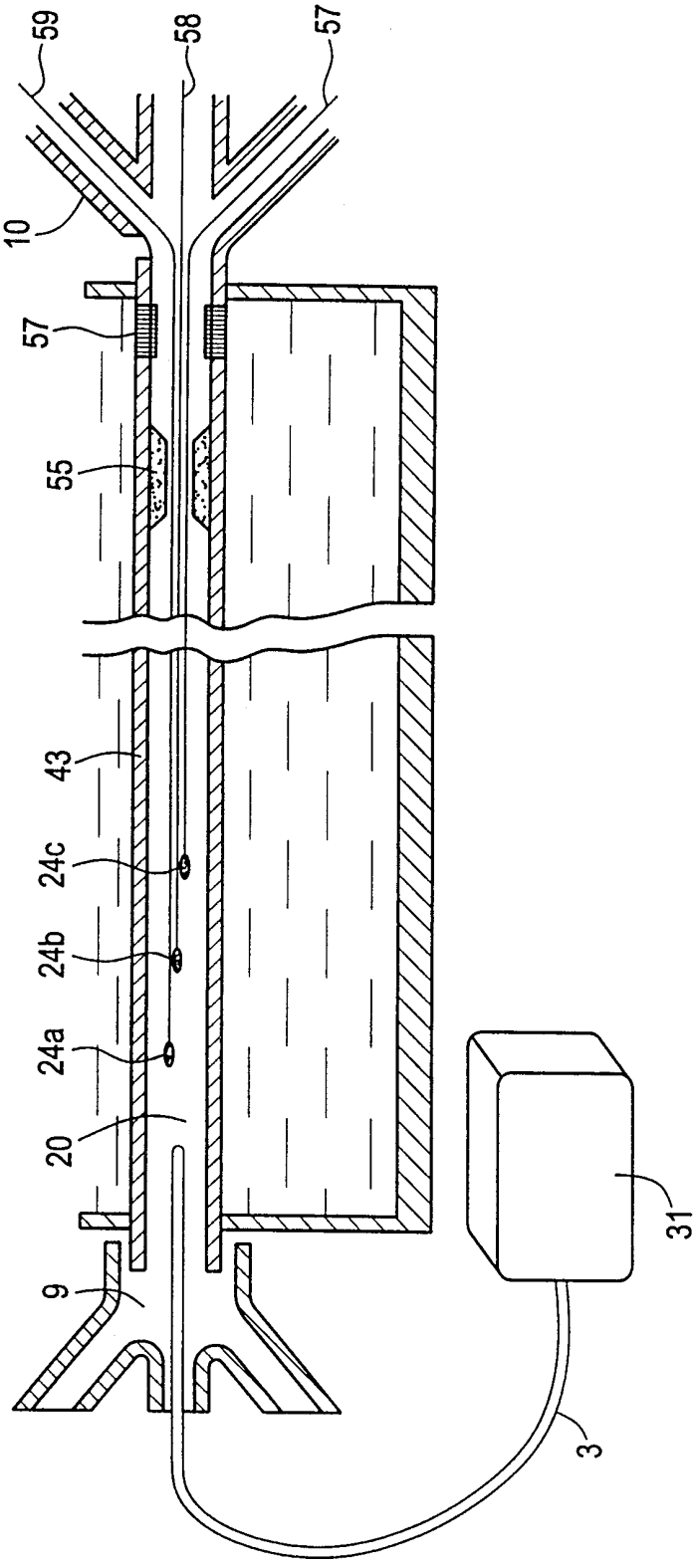


FIG. 7

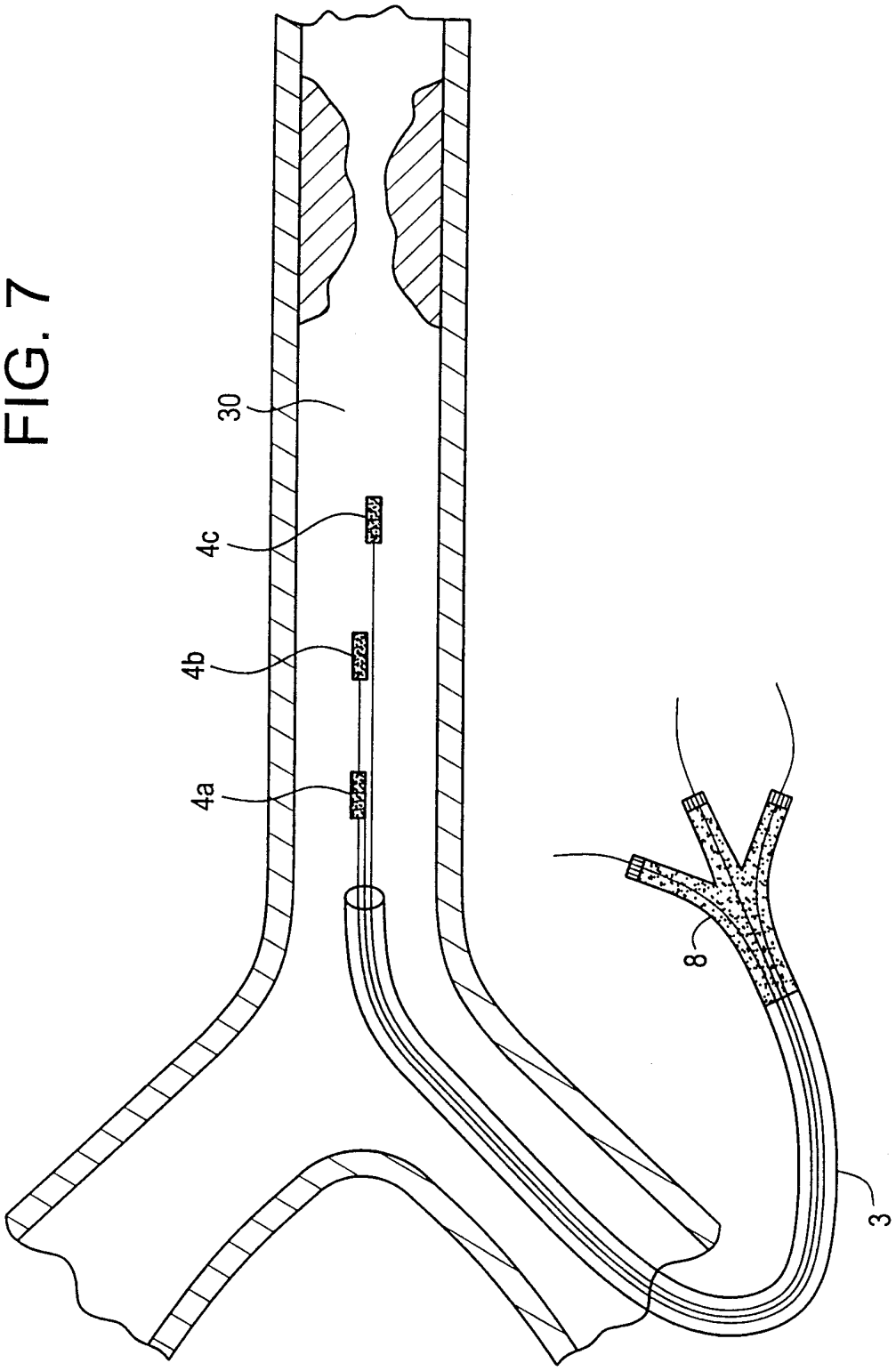


FIG. 8

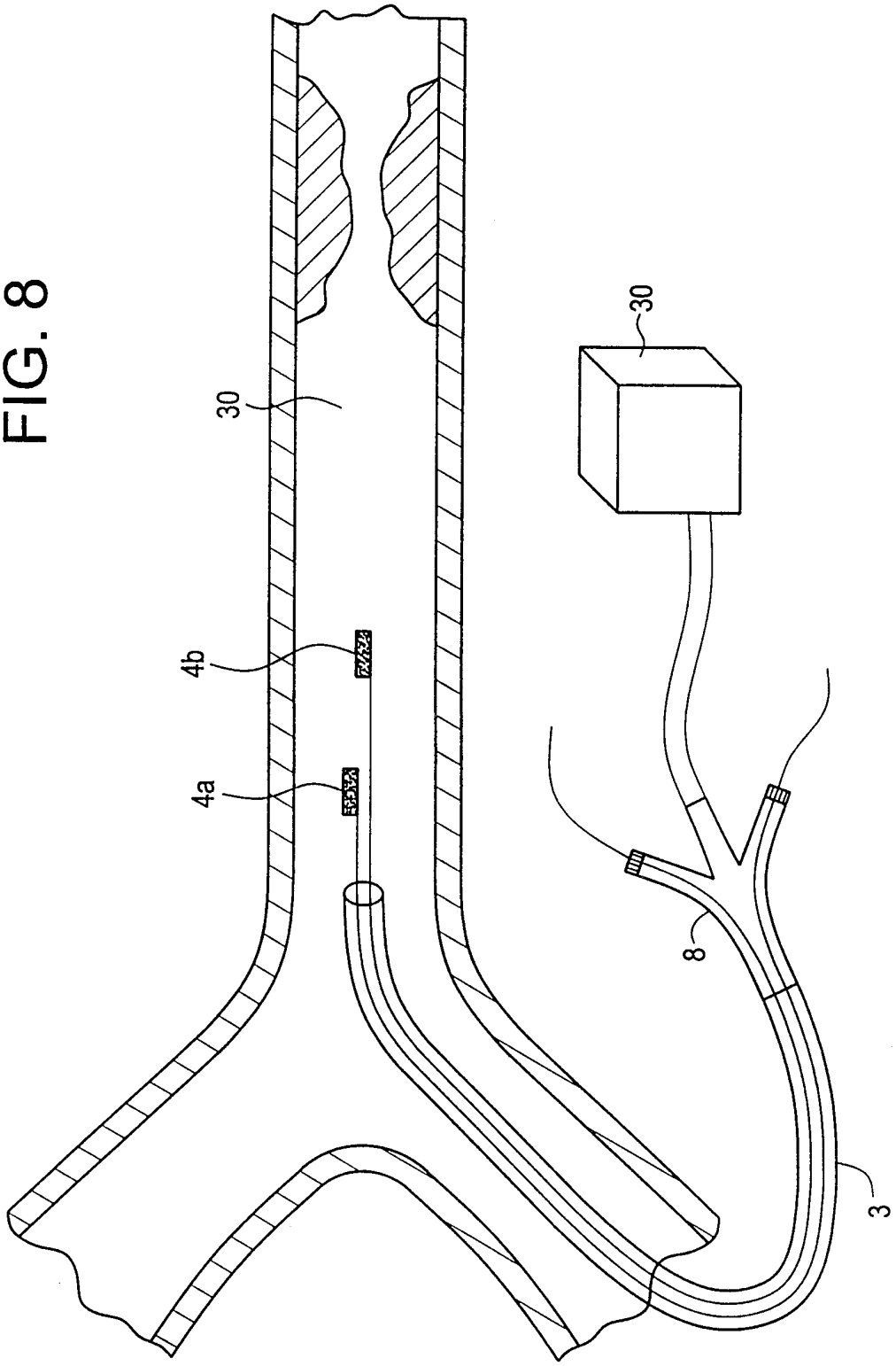


FIG. 9

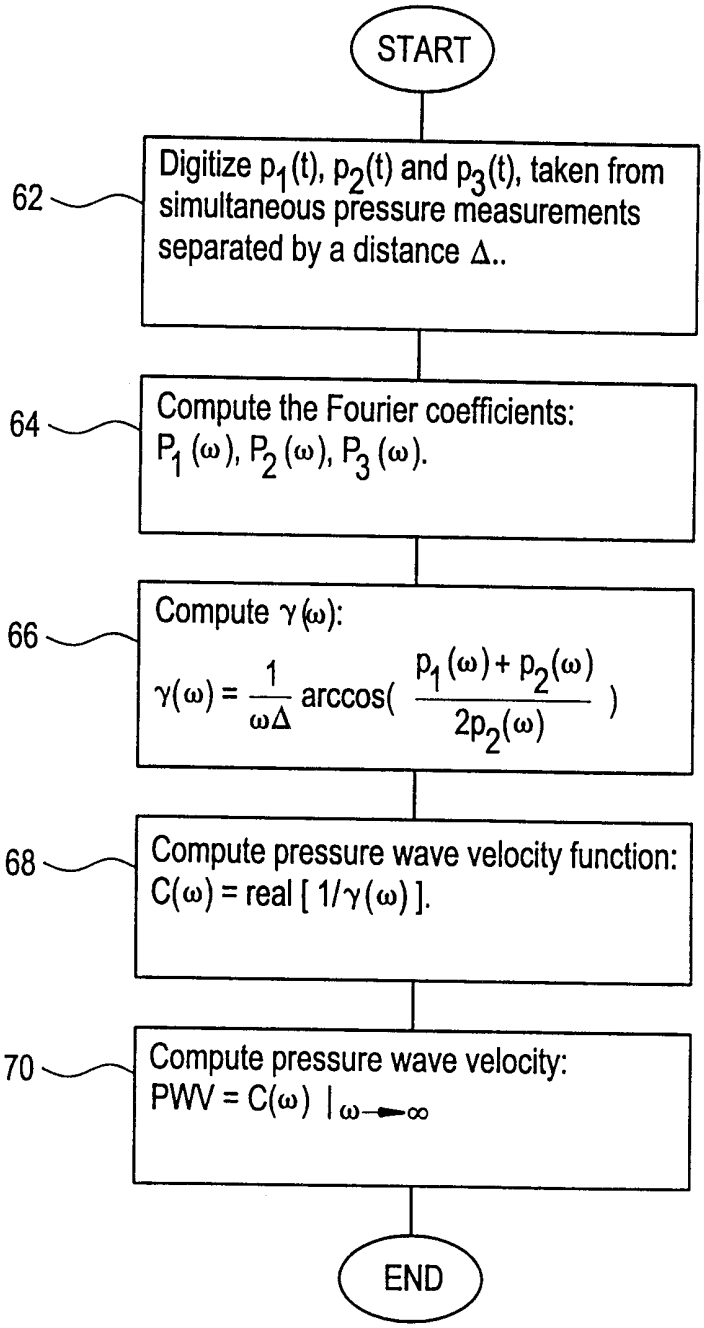

START
62
Digitize $p_1(t)$, $p_2(t)$ and $p_3(t)$, taken from simultaneous pressure measurements separated by a distance Δ..
64
Compute the Fourier coefficients: $P_1(\omega)$, $P_2(\omega)$, $P_3(\omega)$.
66
Compute $\gamma(\omega)$:
$\gamma(\omega) = \frac{1}{\omega\Delta} \arccos\left(\frac{p_1(\omega) + p_2(\omega)}{2p_2(\omega)} \right)$
68
Compute pressure wave velocity function: $C(\omega) = \text{real}\,[\,1/\gamma(\omega)\,]$.
70
Compute pressure wave velocity: $PWV = C(\omega)\,|_{\omega \to \infty}$
END

FIG.10

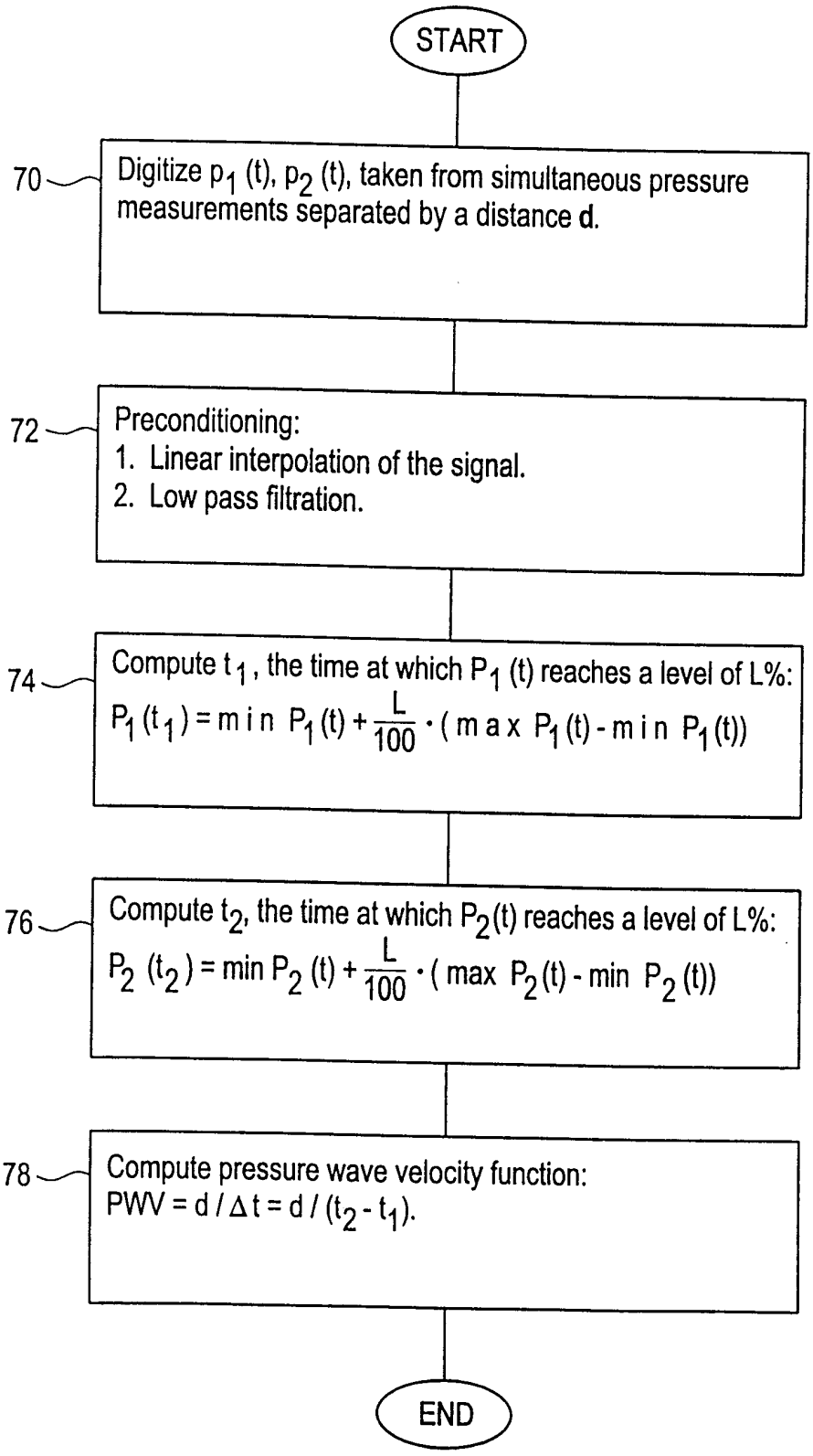

START
70
Digitize p_1 (t), p_2 (t), taken from simultaneous pressure measurements separated by a distance **d**.
72
Preconditioning:
1. Linear interpolation of the signal.
2. Low pass filtration.
74
Compute t_1, the time at which P_1 (t) reaches a level of L%:
$P_1(t_1) = \min P_1(t) + \frac{L}{100} \cdot (\max P_1(t) - \min P_1(t))$
76
Compute t_2, the time at which P_2(t) reaches a level of L%:
$P_2(t_2) = \min P_2(t) + \frac{L}{100} \cdot (\max P_2(t) - \min P_2(t))$
78
Compute pressure wave velocity function:
$PWV = d / \Delta t = d / (t_2 - t_1)$.
END

FIG. 11

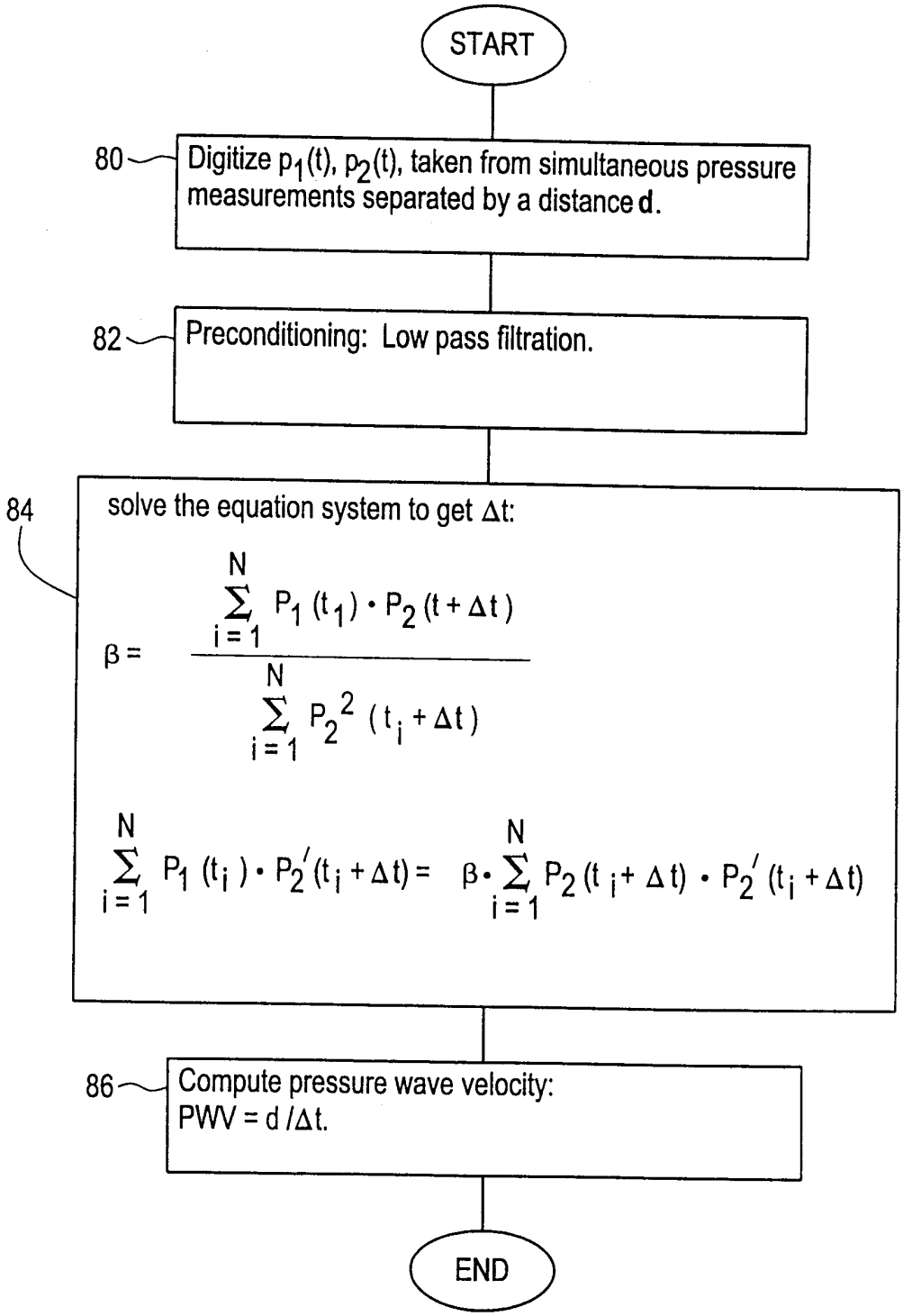

START
80
Digitize $p_1(t)$, $p_2(t)$, taken from simultaneous pressure measurements separated by a distance **d**.
82
Preconditioning: Low pass filtration.
84
solve the equation system to get Δt:
$\beta = \frac{\sum_{i=1}^{N} P_1(t_1) \cdot P_2(t+\Delta t)}{\sum_{i=1}^{N} P_2^2(t_i+\Delta t)}$
$\sum_{i=1}^{N} P_1(t_i) \cdot P_2'(t_i+\Delta t) = \beta \cdot \sum_{i=1}^{N} P_2(t_i+\Delta t) \cdot P_2'(t_i+\Delta t)$
86
Compute pressure wave velocity:
PWV = d /Δt.
END

FIG. 12A

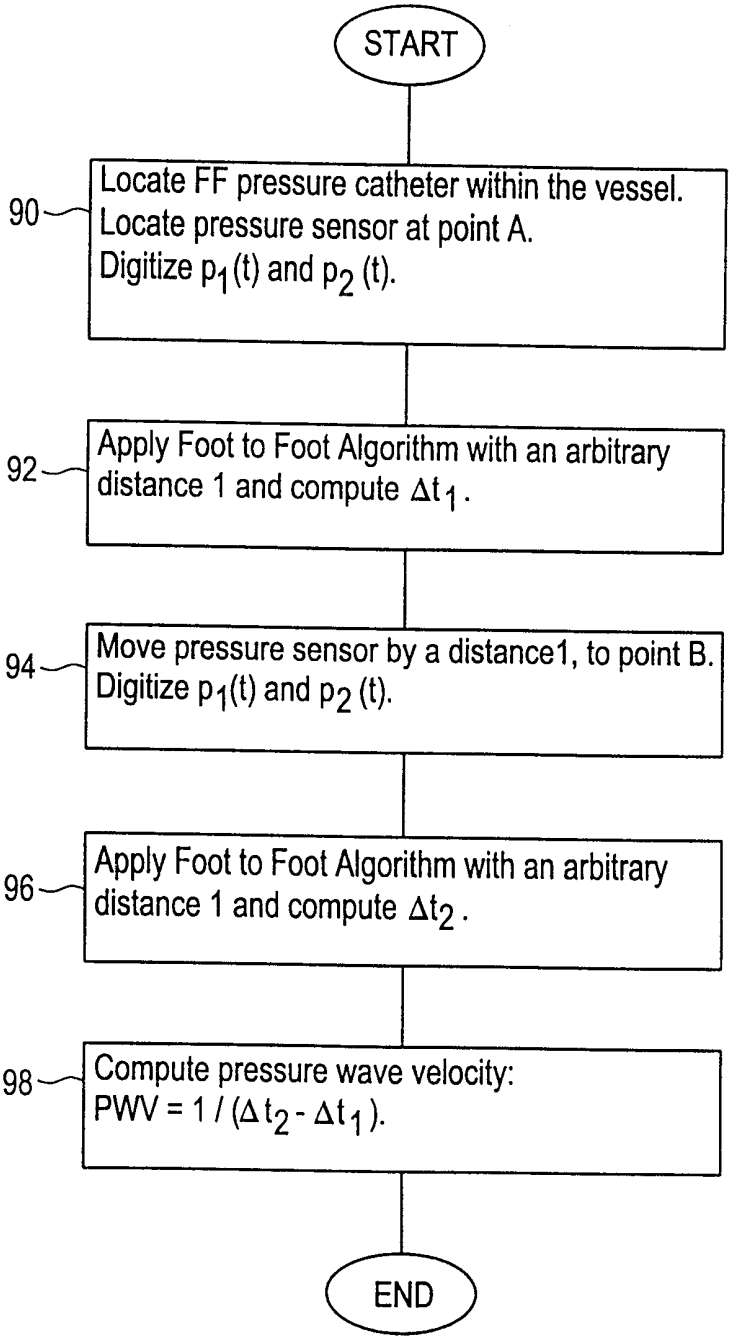

START
90
Locate FF pressure catheter within the vessel.
Locate pressure sensor at point A.
Digitize $p_1(t)$ and $p_2(t)$.
92
Apply Foot to Foot Algorithm with an arbitrary distance 1 and compute Δt_1.
94
Move pressure sensor by a distance1, to point B.
Digitize $p_1(t)$ and $p_2(t)$.
96
Apply Foot to Foot Algorithm with an arbitrary distance 1 and compute Δt_2.
98
Compute pressure wave velocity:
$PWV = 1 / (\Delta t_2 - \Delta t_1)$.
END

FIG.12B

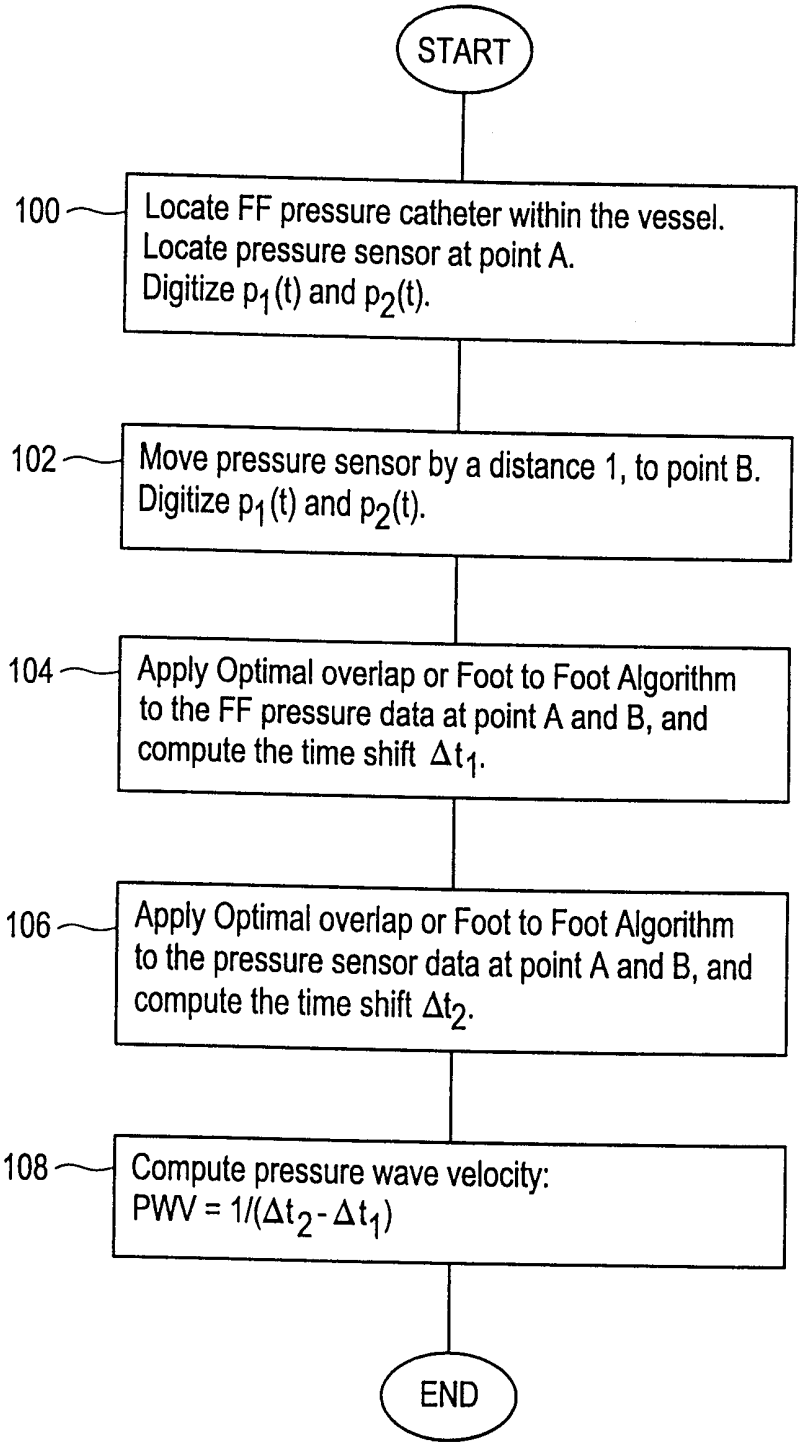

START
100
Locate FF pressure catheter within the vessel.
Locate pressure sensor at point A.
Digitize $p_1(t)$ and $p_2(t)$.
102
Move pressure sensor by a distance 1, to point B.
Digitize $p_1(t)$ and $p_2(t)$.
104
Apply Optimal overlap or Foot to Foot Algorithm to the FF pressure data at point A and B, and compute the time shift Δt_1.
106
Apply Optimal overlap or Foot to Foot Algorithm to the pressure sensor data at point A and B, and compute the time shift Δt_2.
108
Compute pressure wave velocity:
$PWV = 1/(\Delta t_2 - \Delta t_1)$
END

FIG. 13

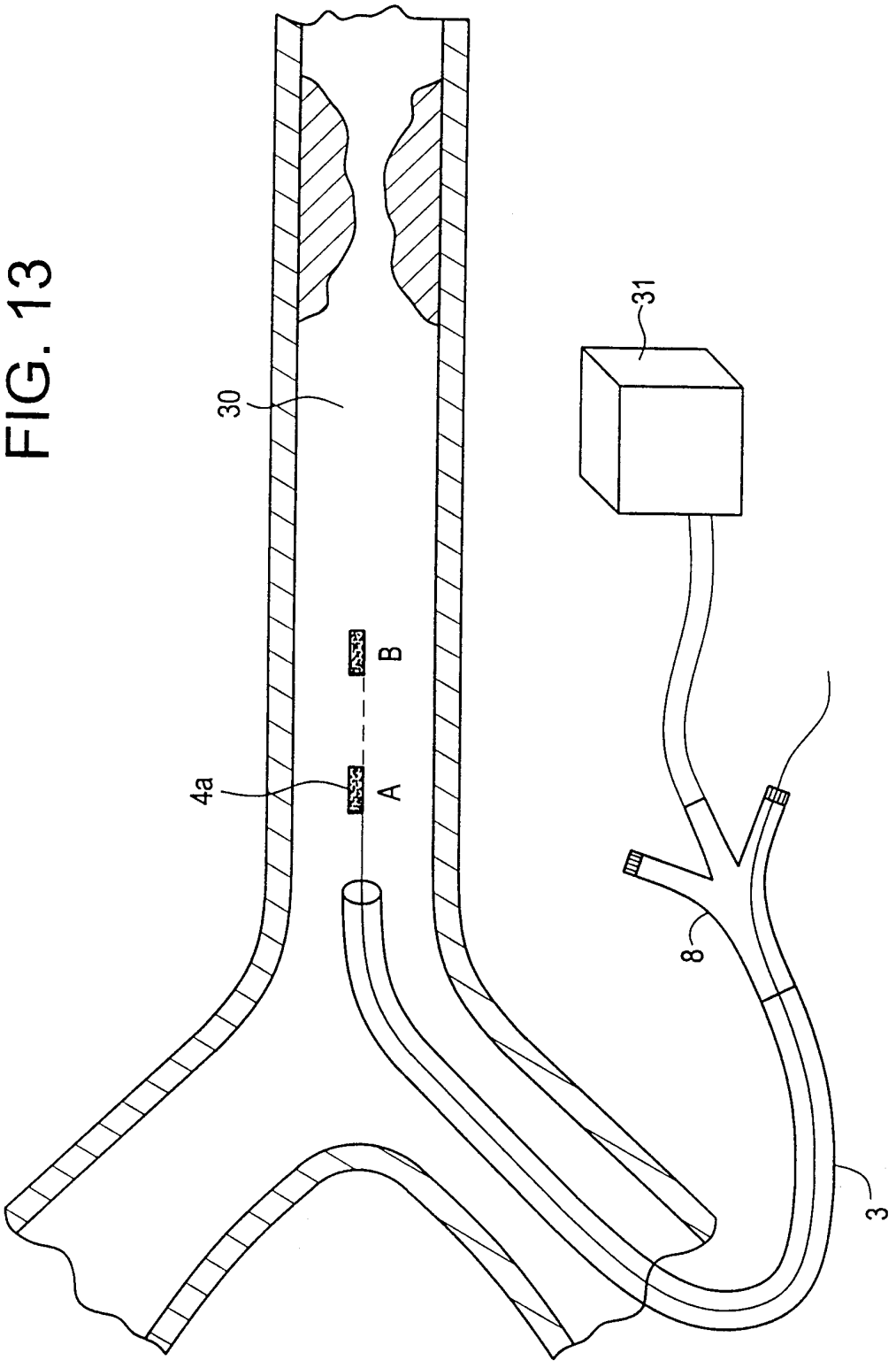


FIG. 14

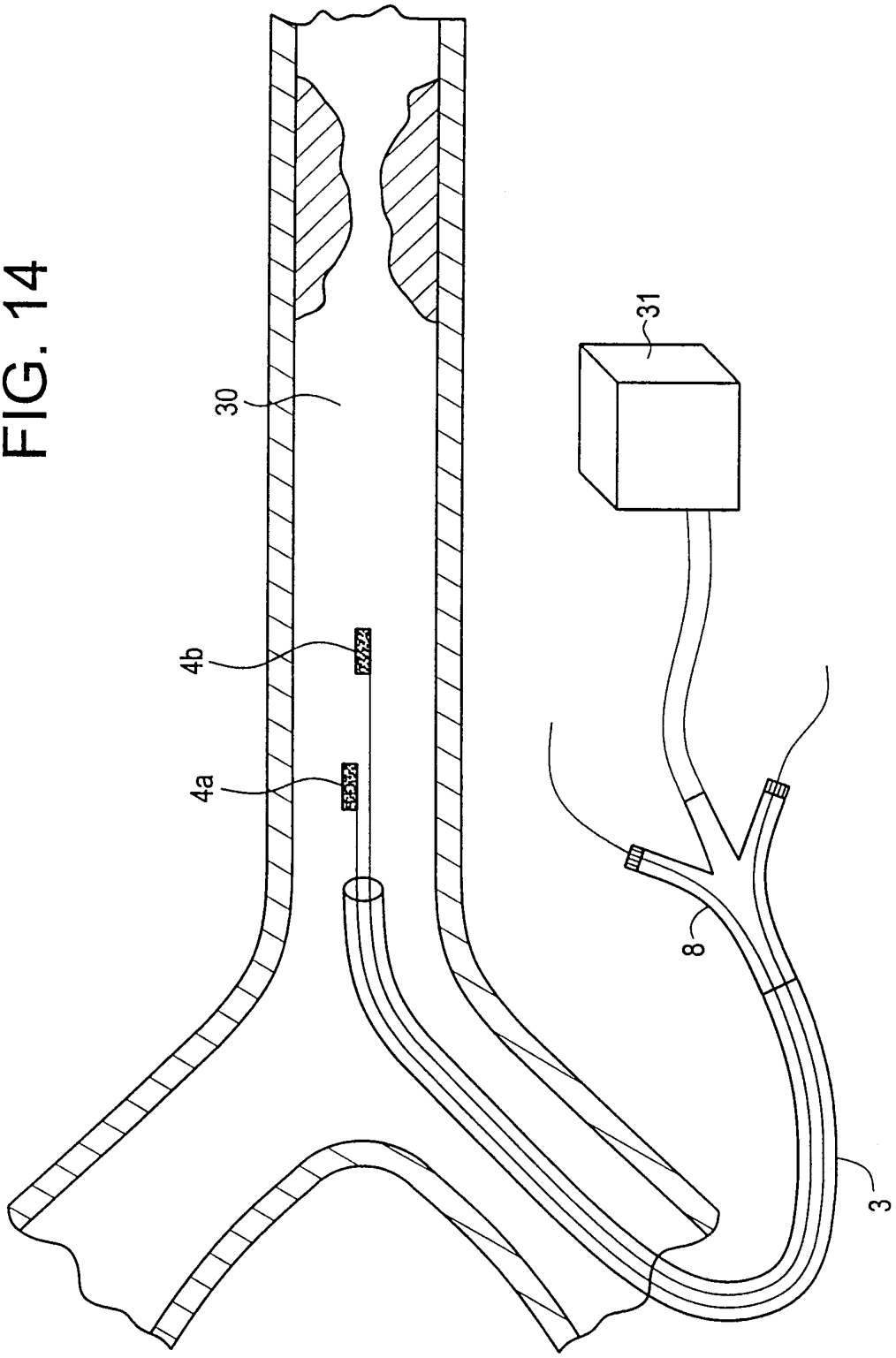


FIG. 15

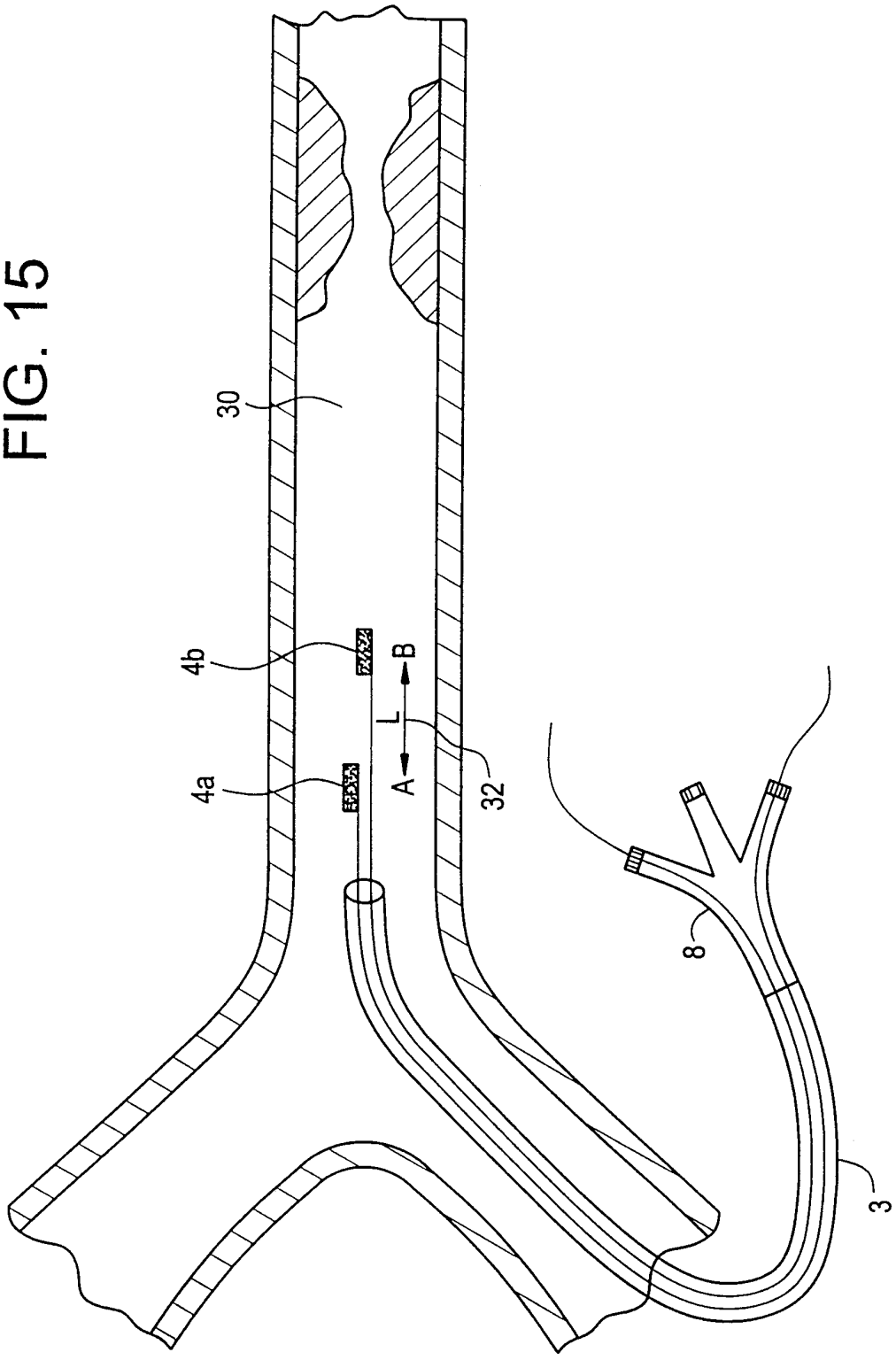


FIG. 16

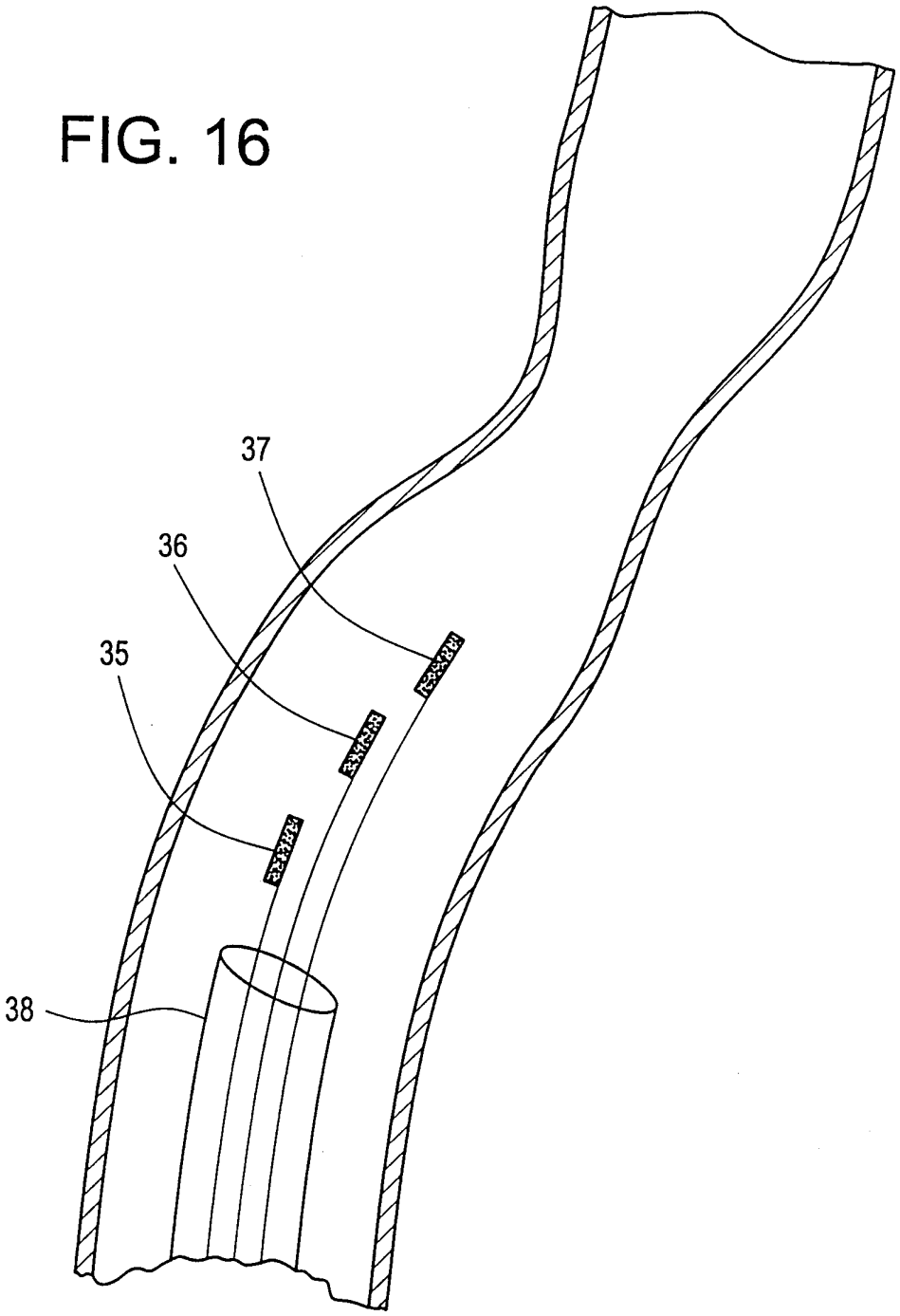


FIG. 17A

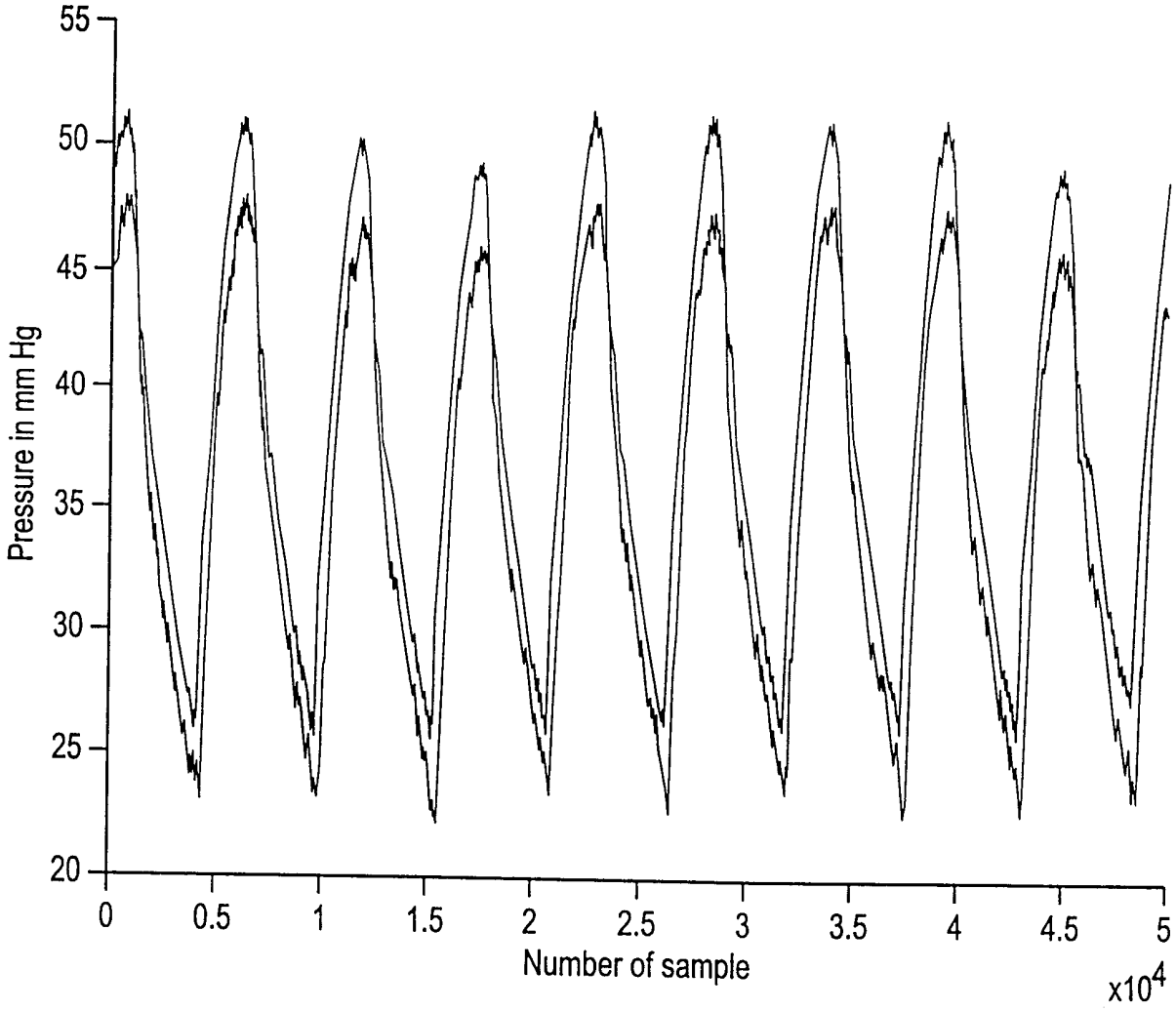

55
50
45
40
35
30
25
20
Pressure in mm Hg
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Number of sample
x10^4

FIG. 17B

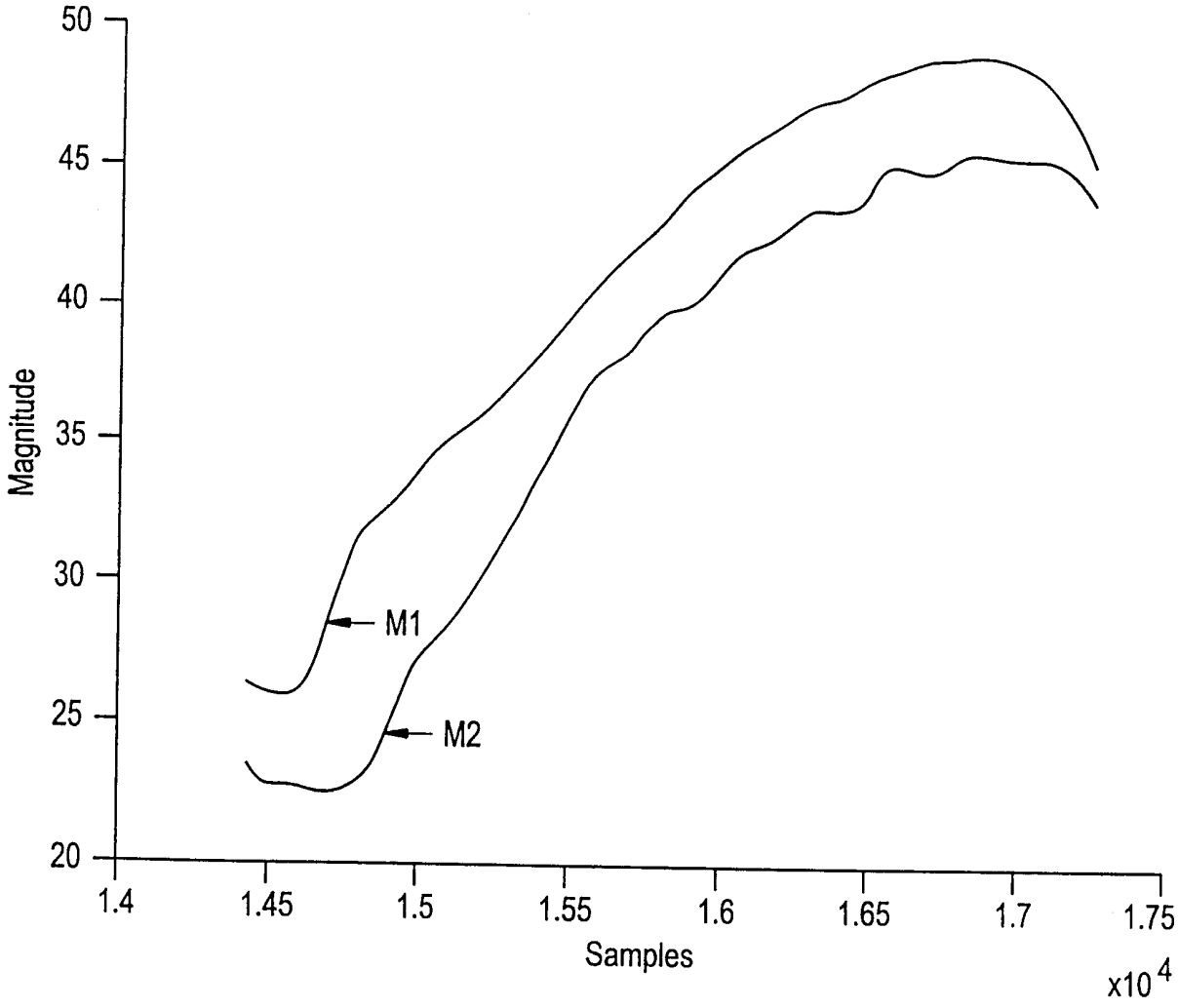

50
45
40
35
30
25
20
Magnitude
M1
M2
1.4
1.45
1.5
1.55
1.6
1.65
1.7
1.75
Samples
x10 4

FIG. 17C

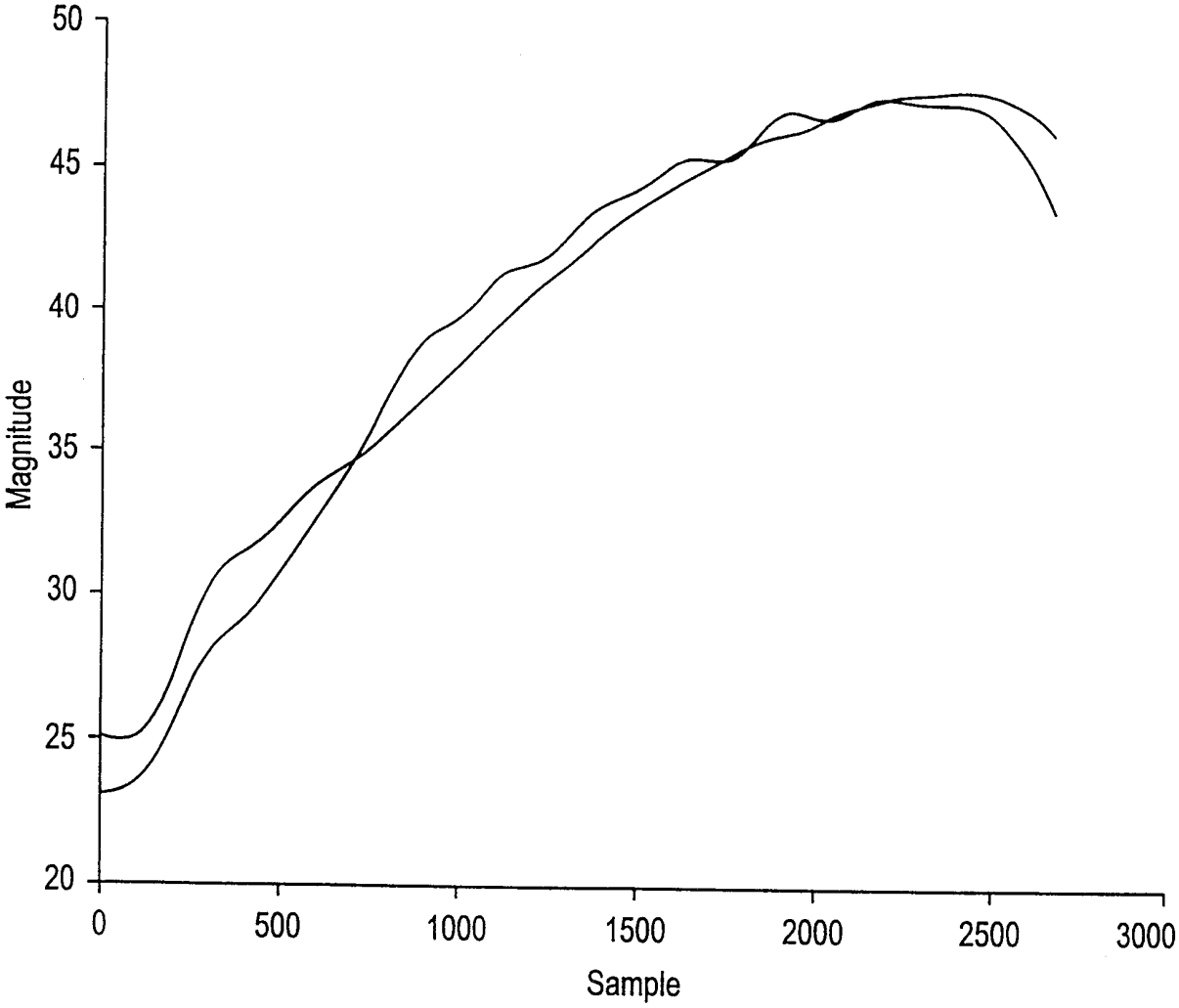
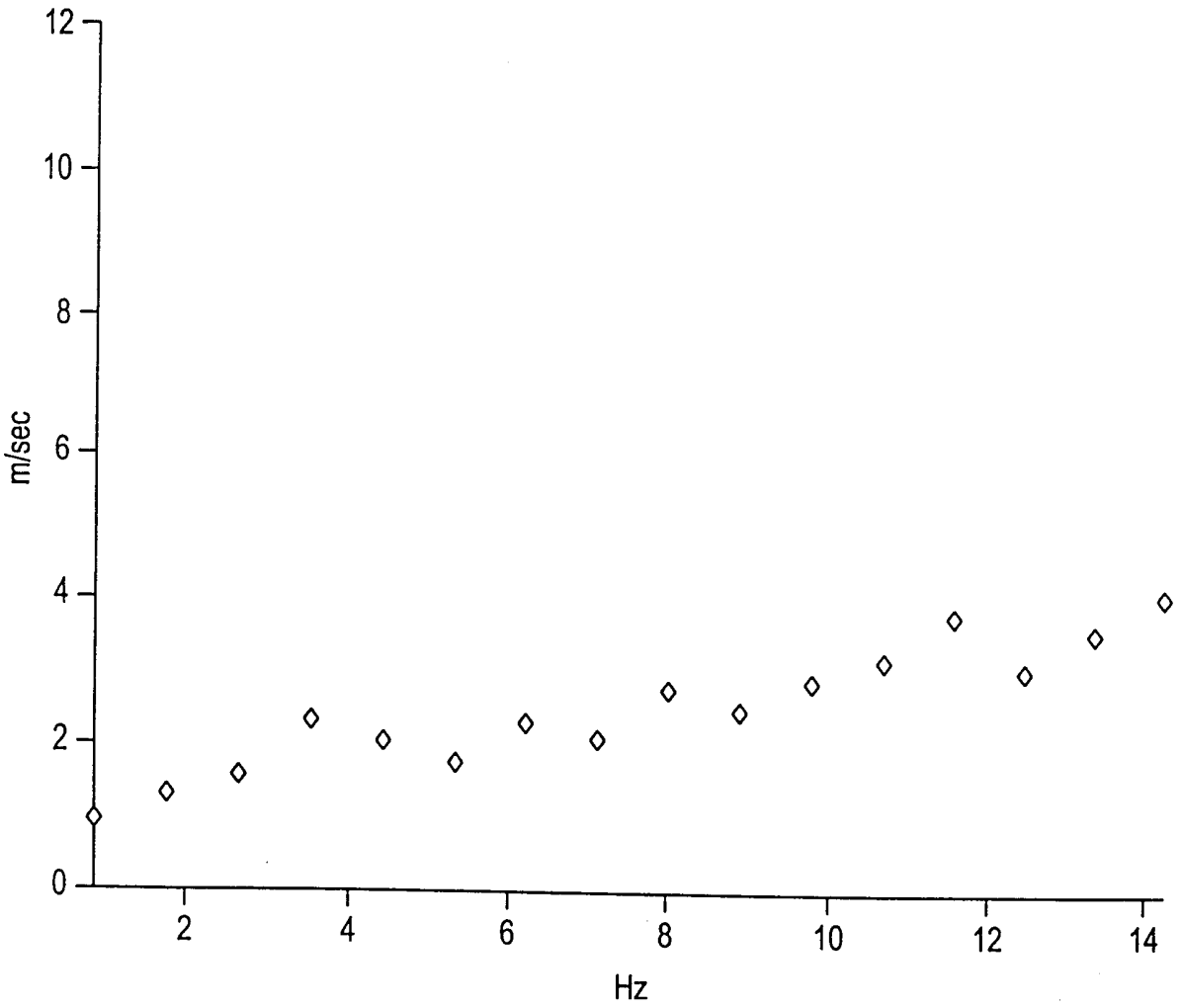

50
45
40
35
30
25
20
Magnitude
0
500
1000
1500
2000
2500
3000
Sample

FIG. 17D



Average velocity: 2.6025 m/sec

FIG. 18

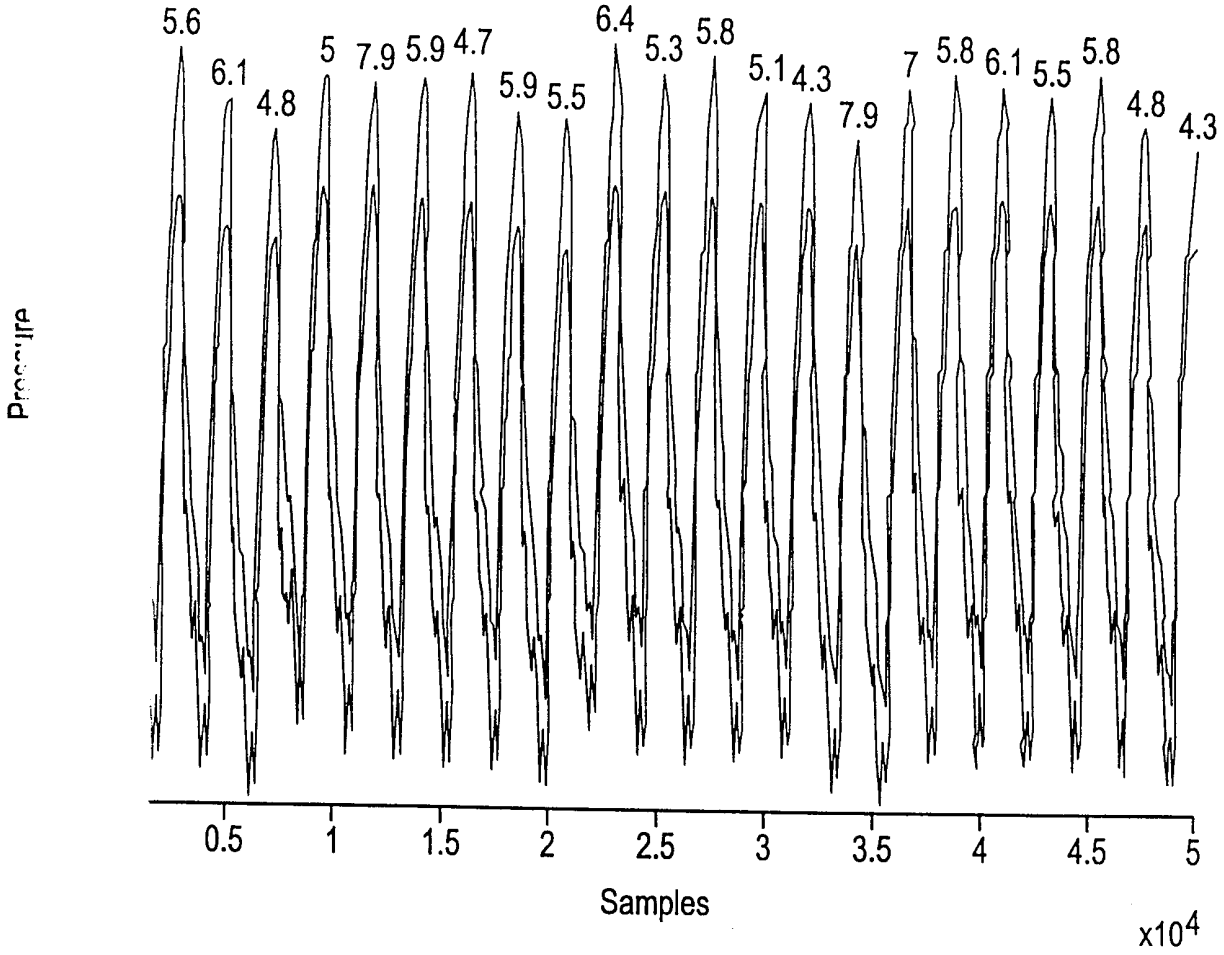

5.6
6.1
4.8
5
7.9
5.9
4.7
5.9
5.5
6.4
5.3
5.8
5.1
4.3
7.9
7
5.8
6.1
5.5
5.8
4.8
4.3
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Samples
x10^4

FIG. 19A

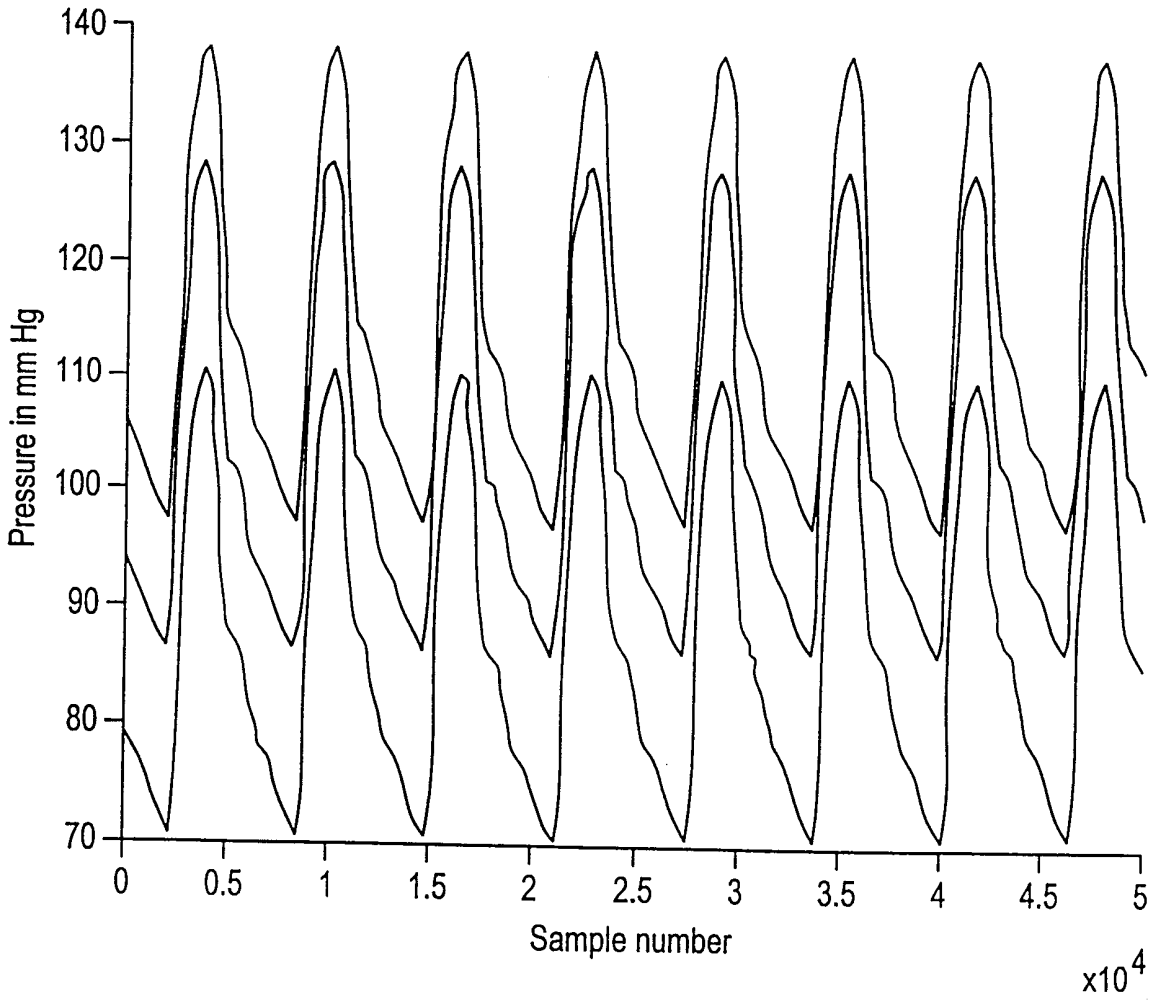

140
130
120
110
100
90
80
70
Pressure in mm Hg
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Sample number
x10^4

FIG. 19B

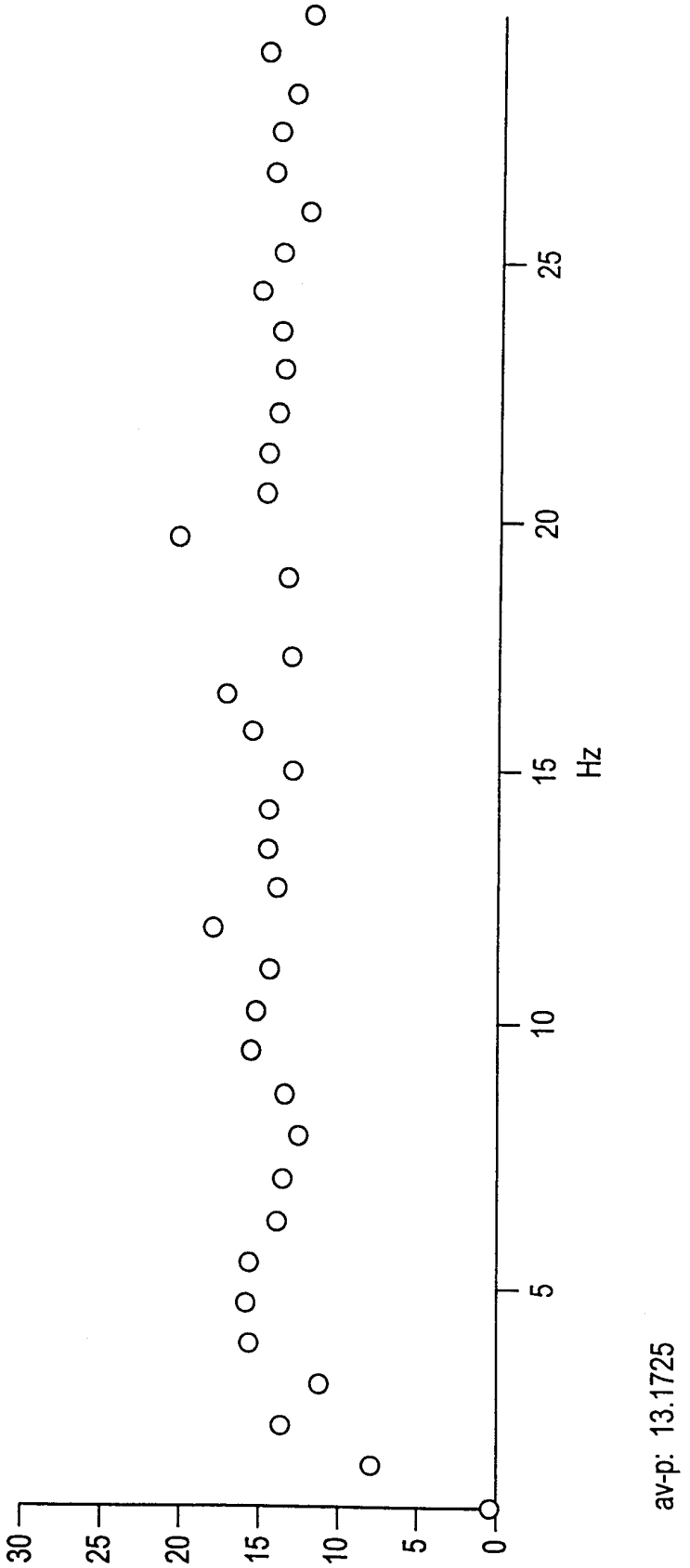


FIG. 19C

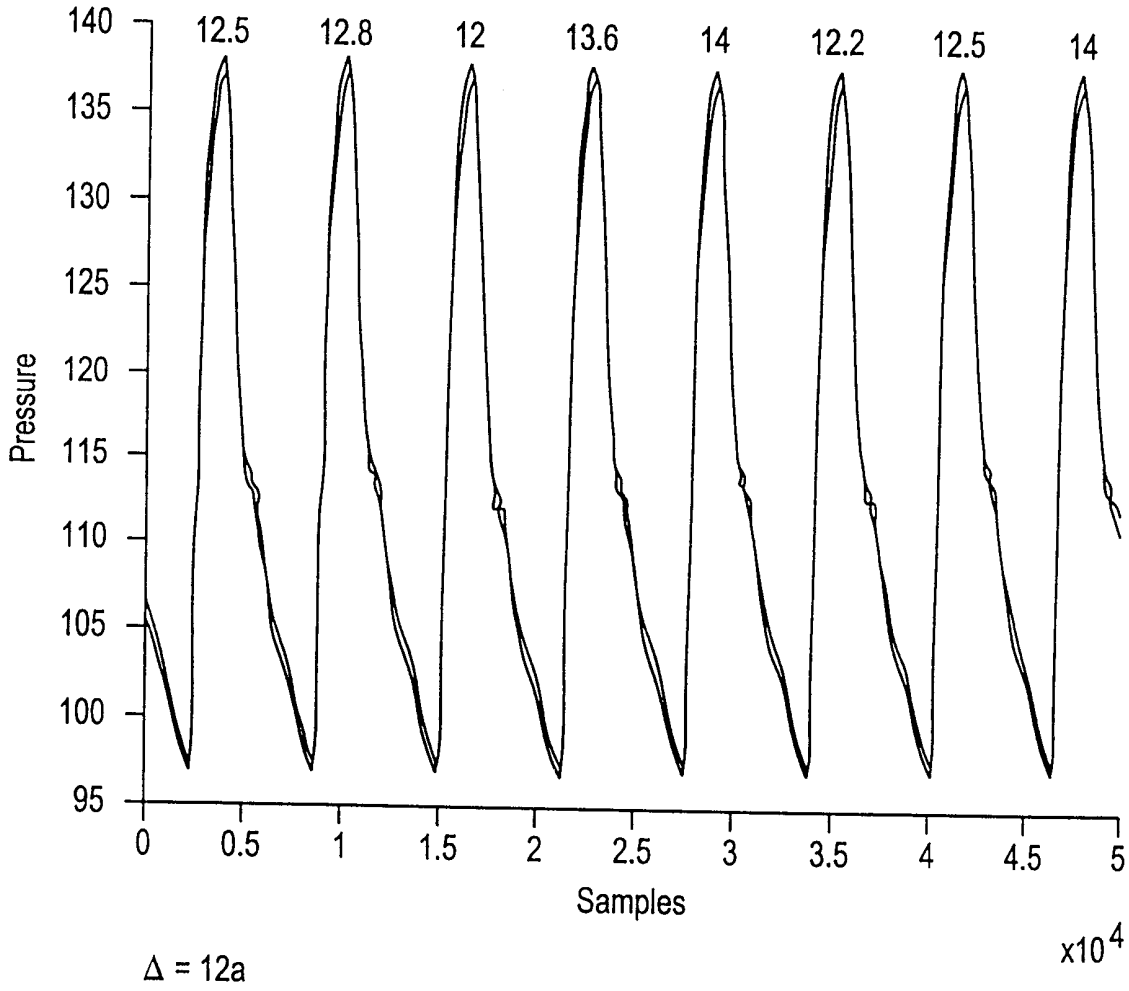

140
135
130
125
120
115
110
105
100
95
Pressure
12.5
12.8
12
13.6
14
12.2
12.5
14
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Samples
x10^4
Δ = 12a

FIG. 20

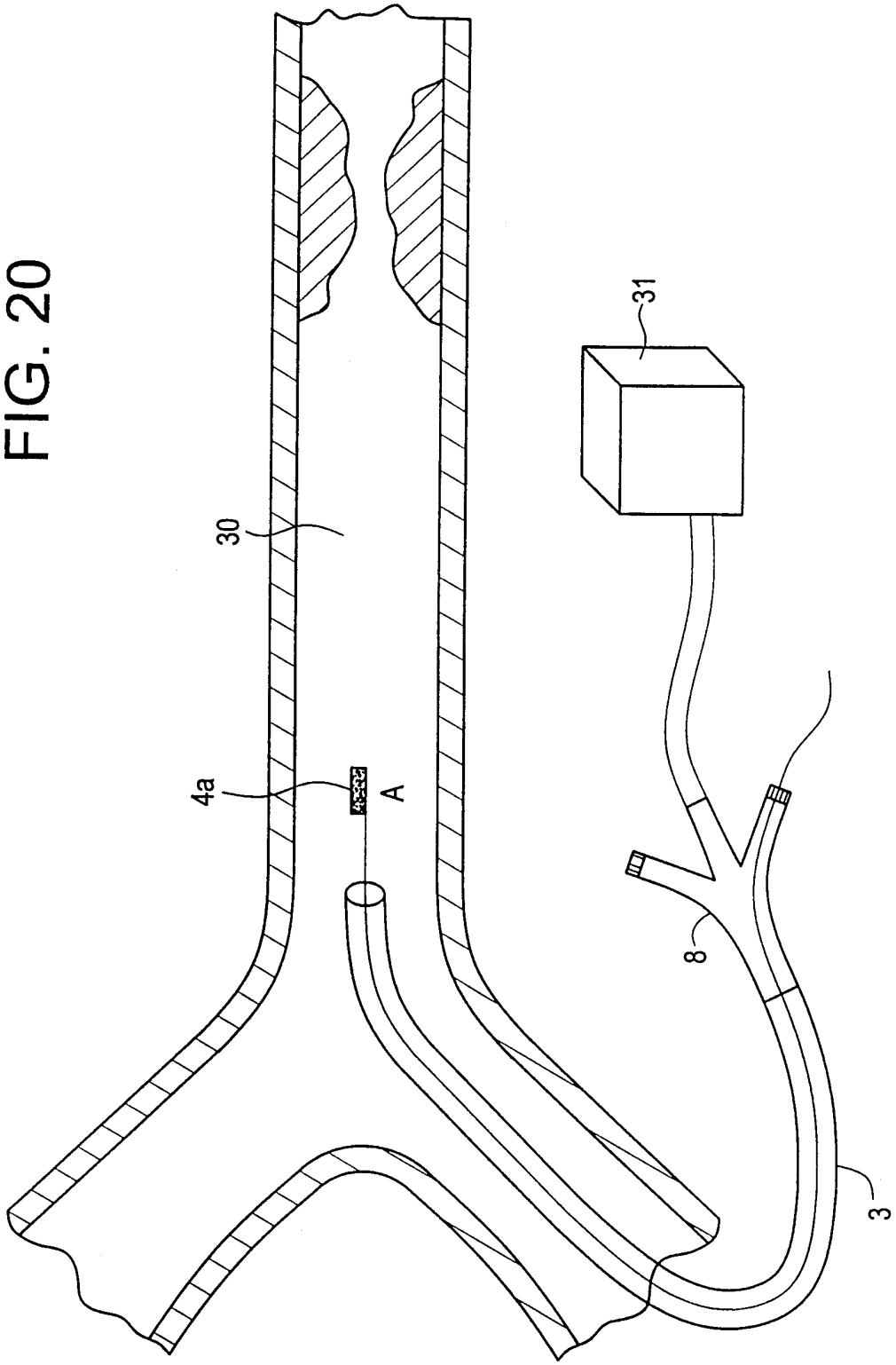


FIG. 21

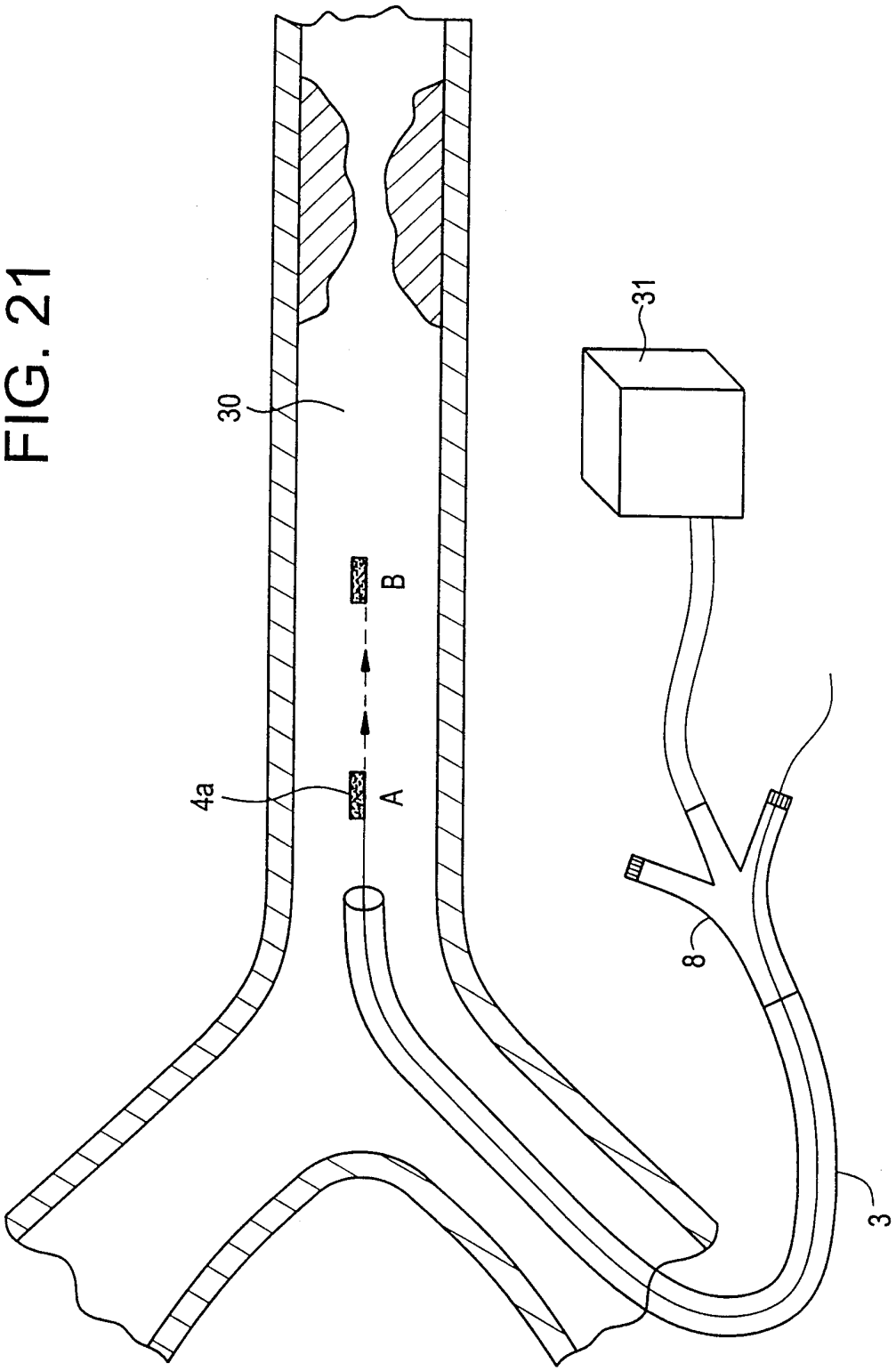


FIG. 22

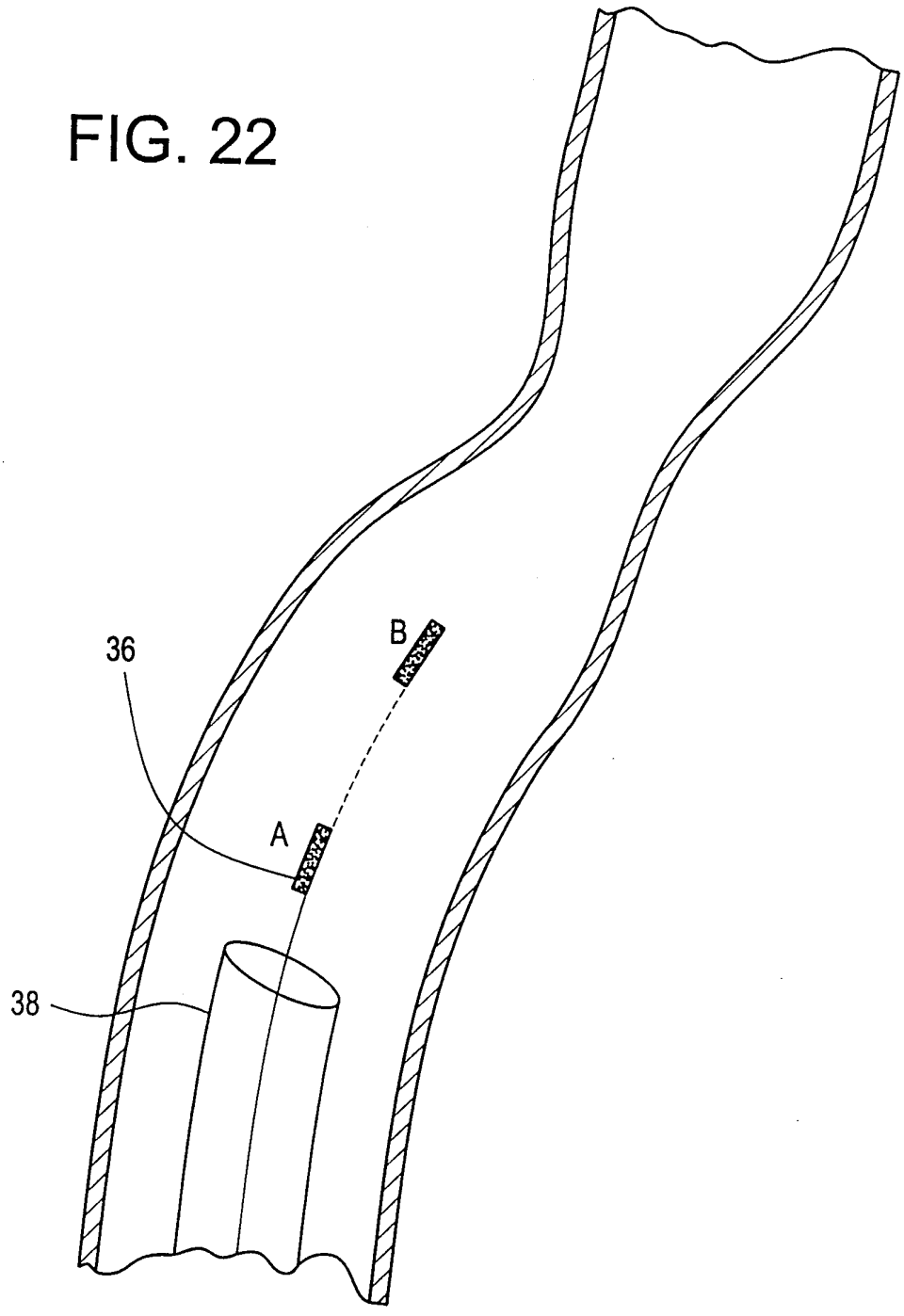


FIG. 23A

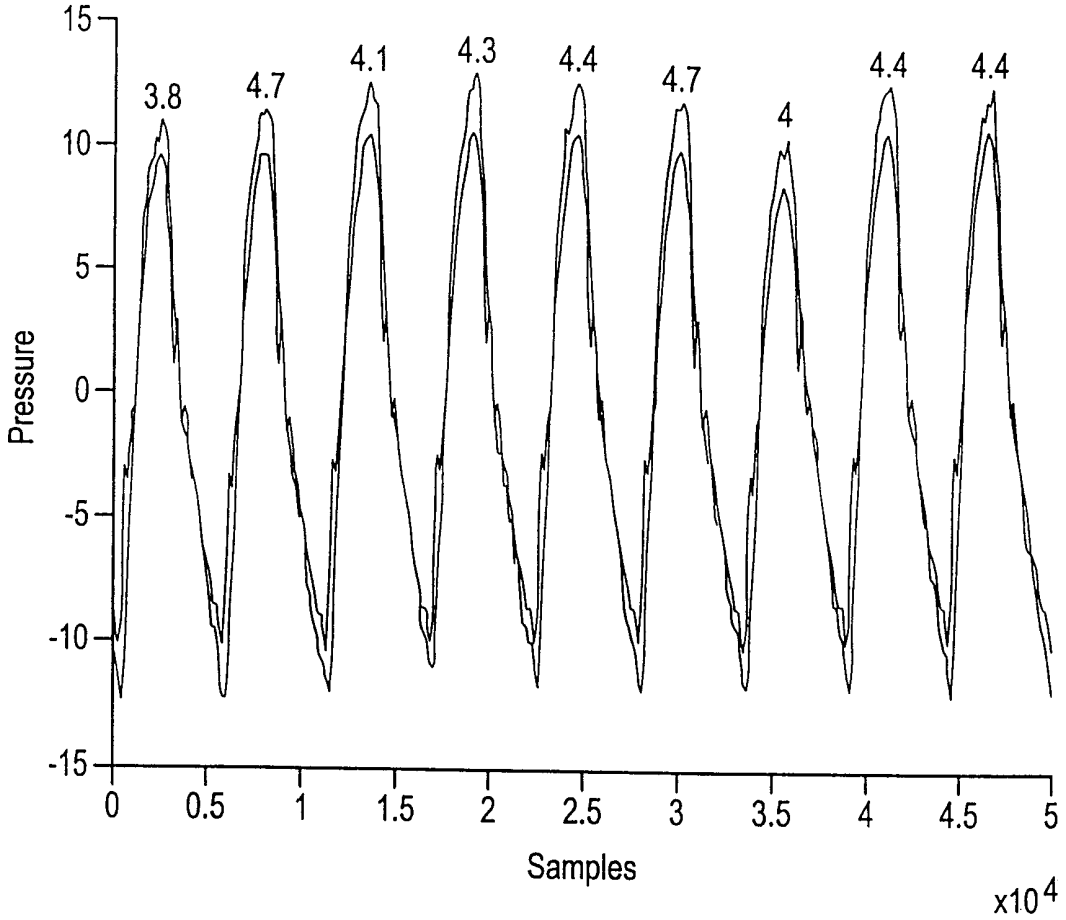

15
10
5
0
-5
-10
-15
Pressure
3.8
4.7
4.1
4.3
4.4
4.7
4
4.4
4.4
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Samples
x10 4

FIG. 23B

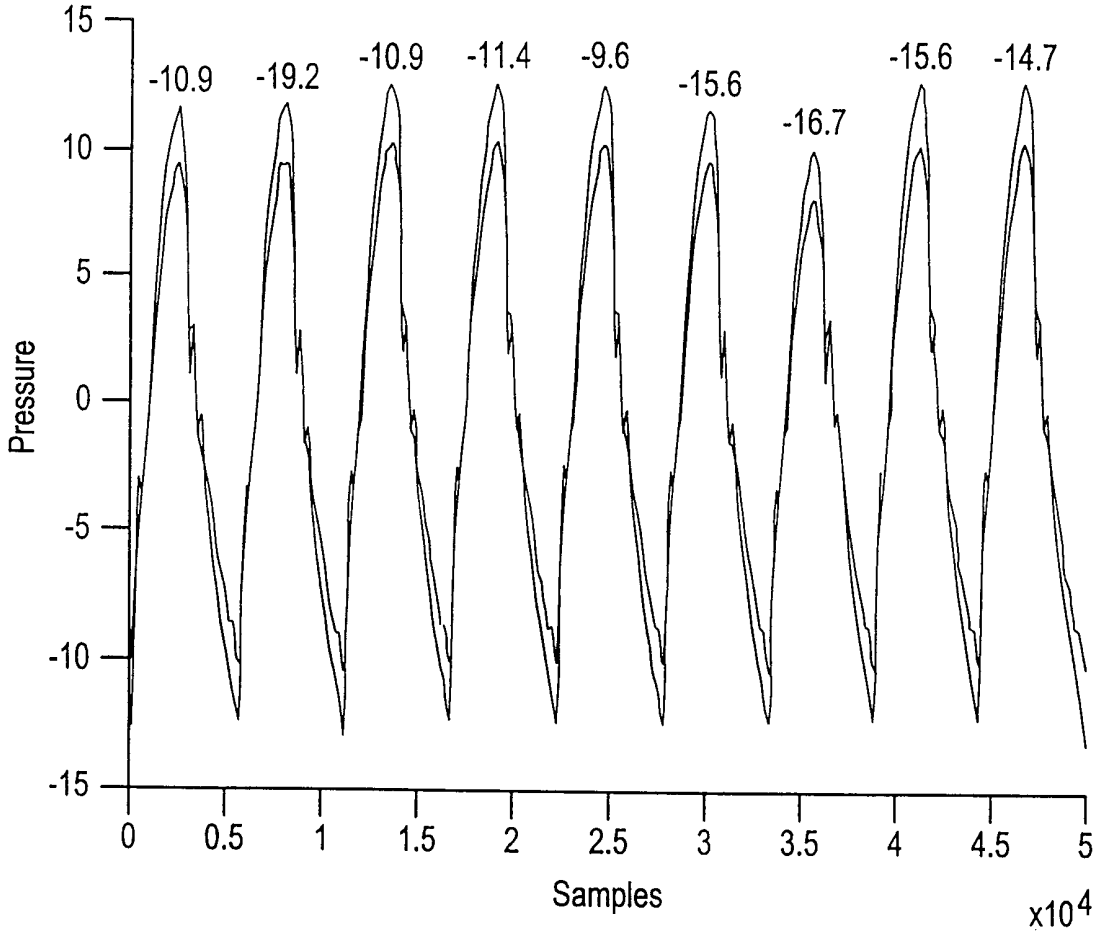

15
10
5
0
-5
-10
-15
Pressure
-10.9
-19.2
-10.9
-11.4
-9.6
-15.6
-16.7
-15.6
-14.7
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Samples
x10^4

FIG. 24

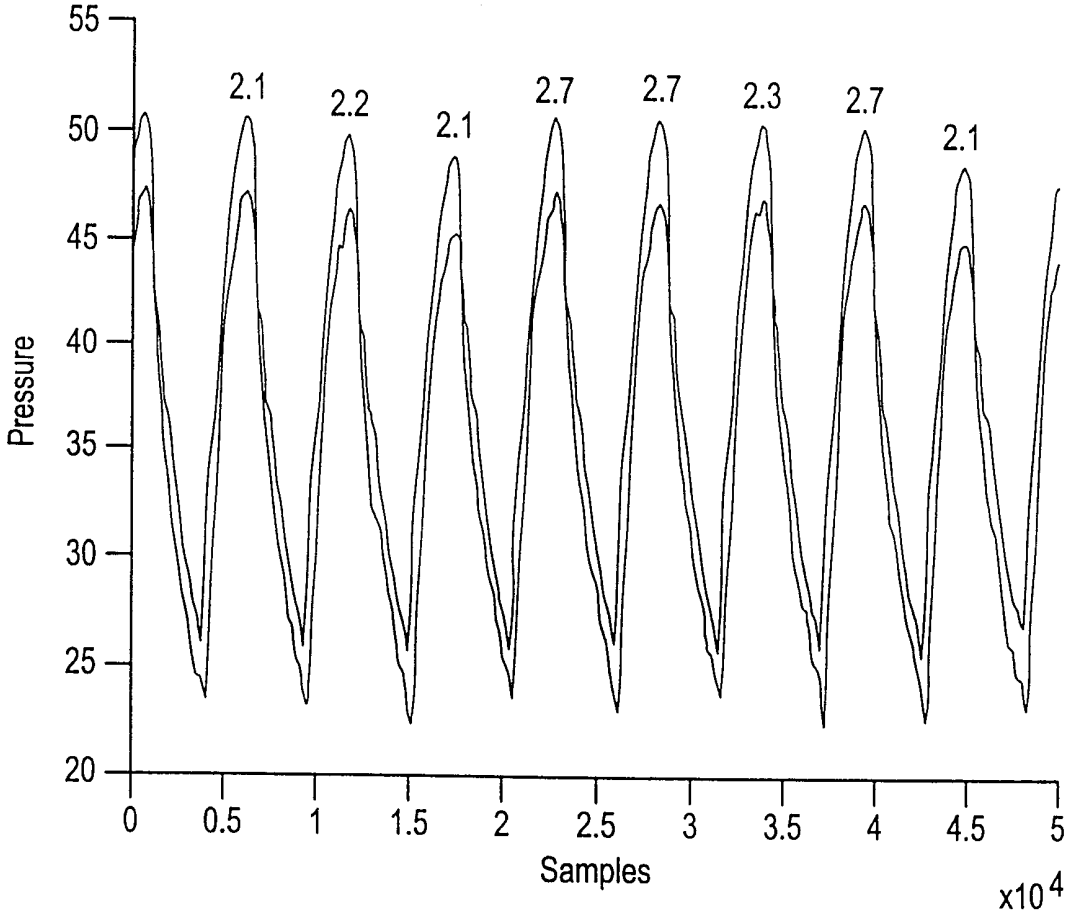

55
50
45
40
35
30
25
20
Pressure
2.1
2.2
2.1
2.7
2.7
2.3
2.7
2.1
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Samples
x10 4

FIG. 25A

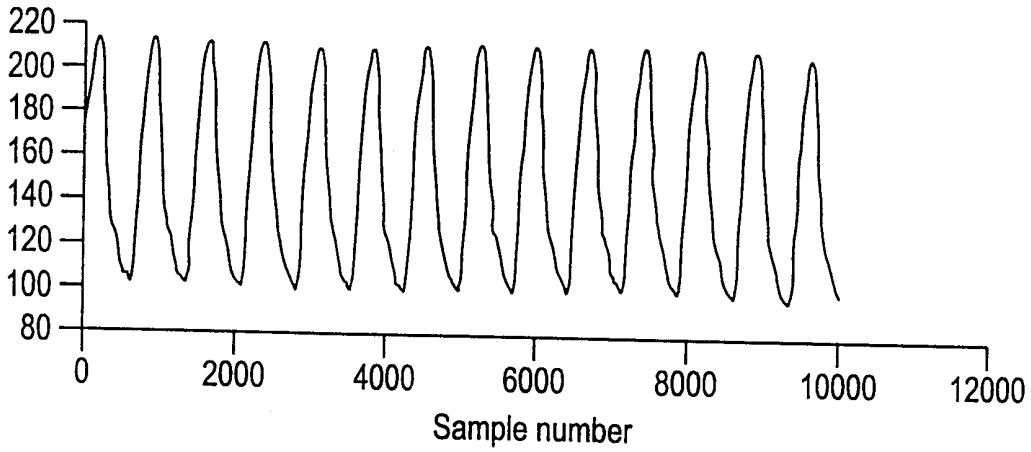


FIG. 25B

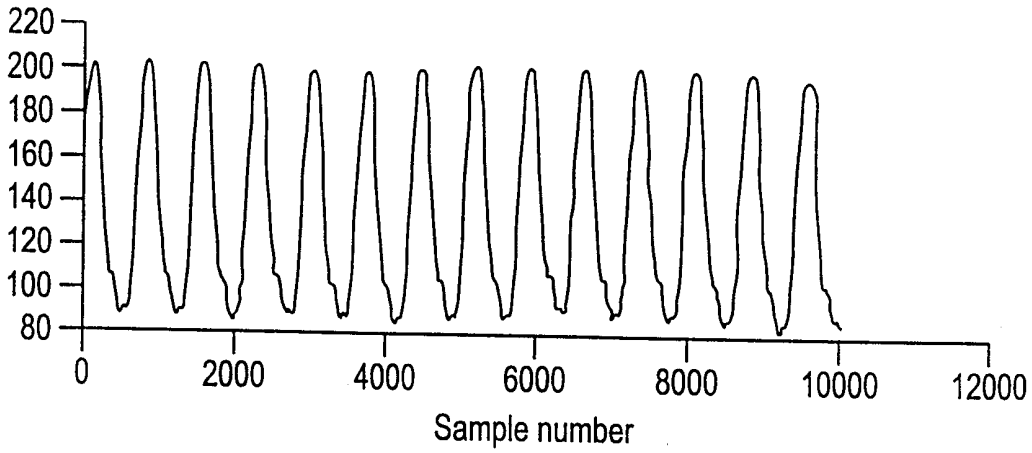


FIG. 26A

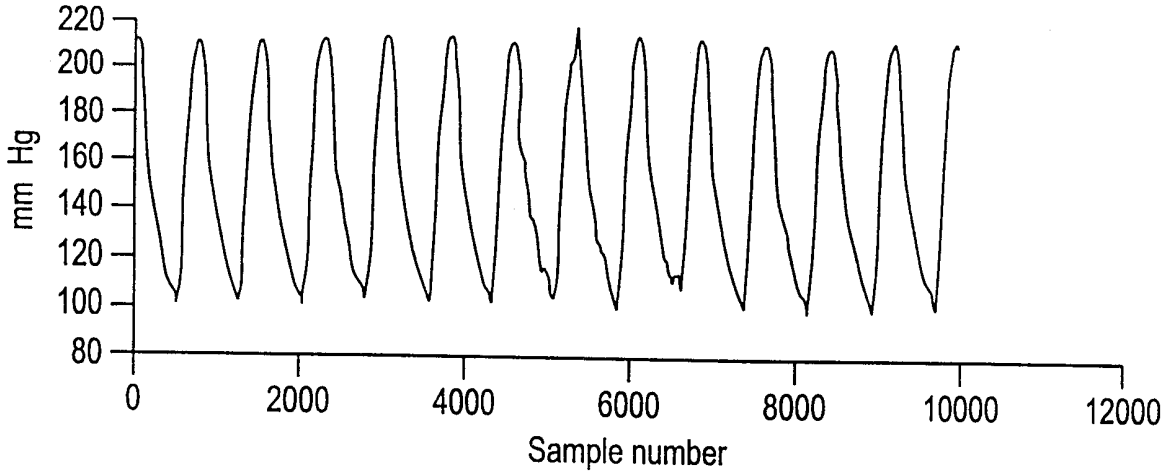


FIG. 26B

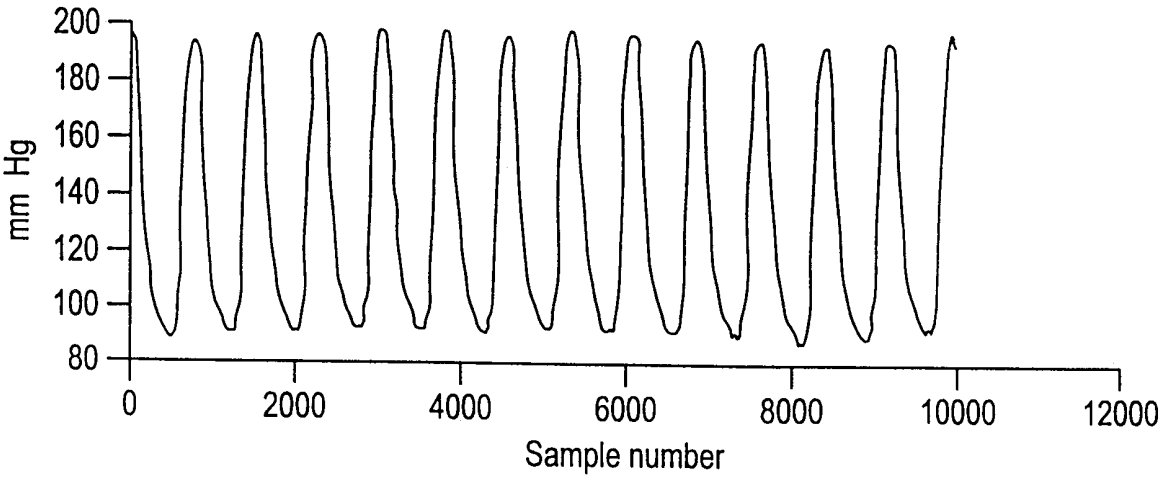


FIG. 27

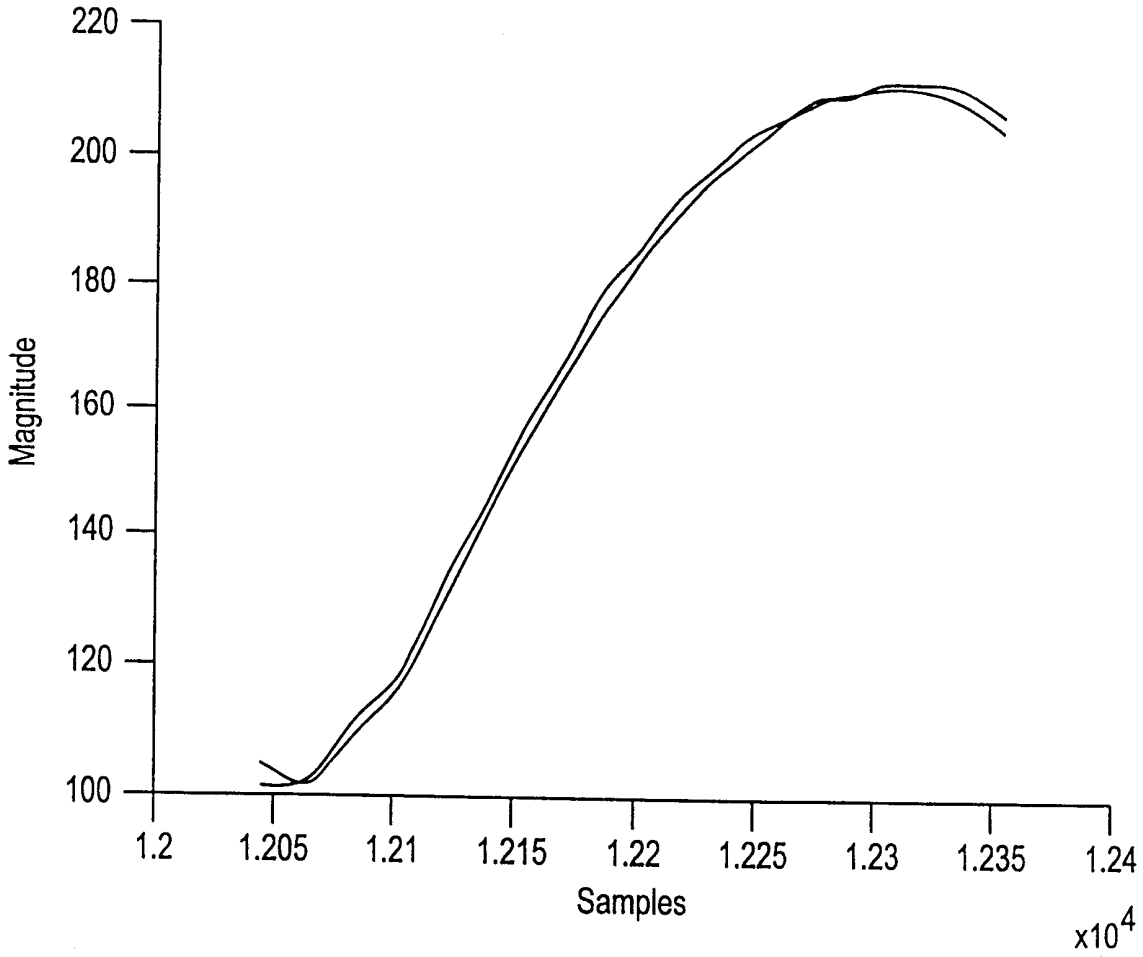

220
200
180
160
140
120
100
Magnitude
1.2
1.205
1.21
1.215
1.22
1.225
1.23
1.235
1.24
Samples
x10^4

FIG. 28

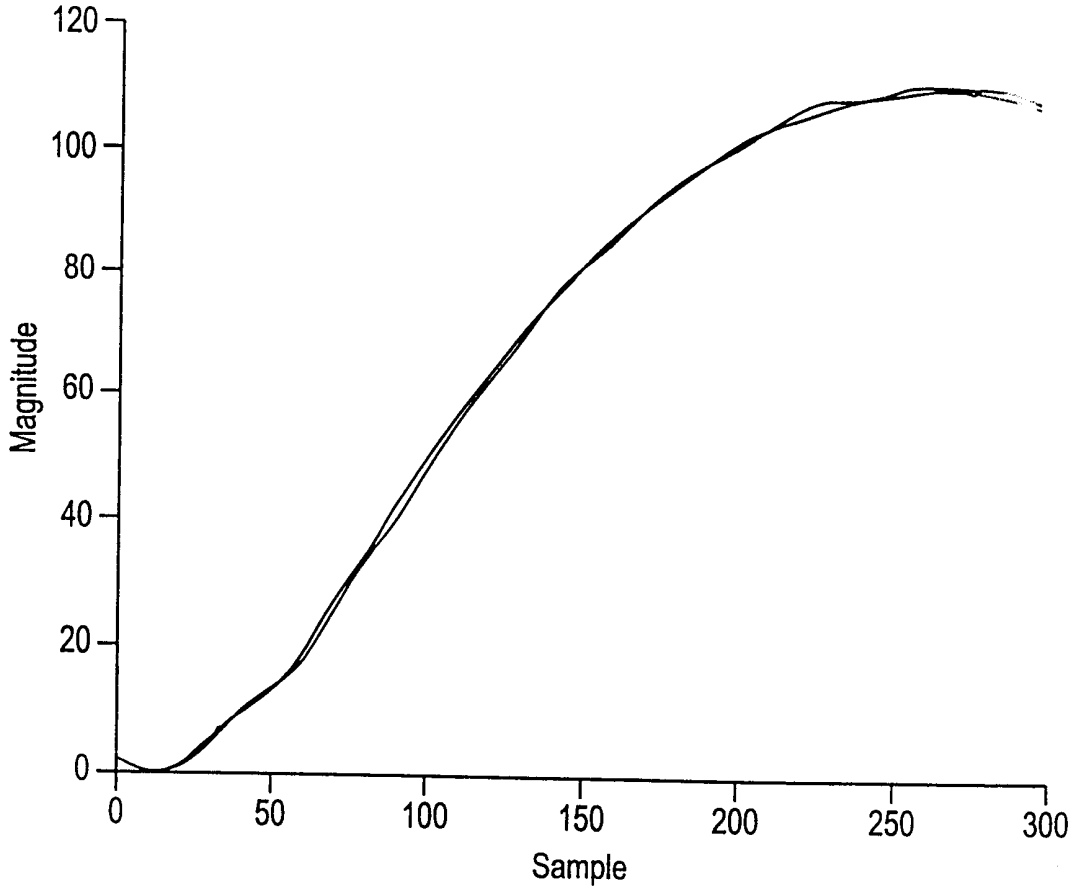


FIG. 29

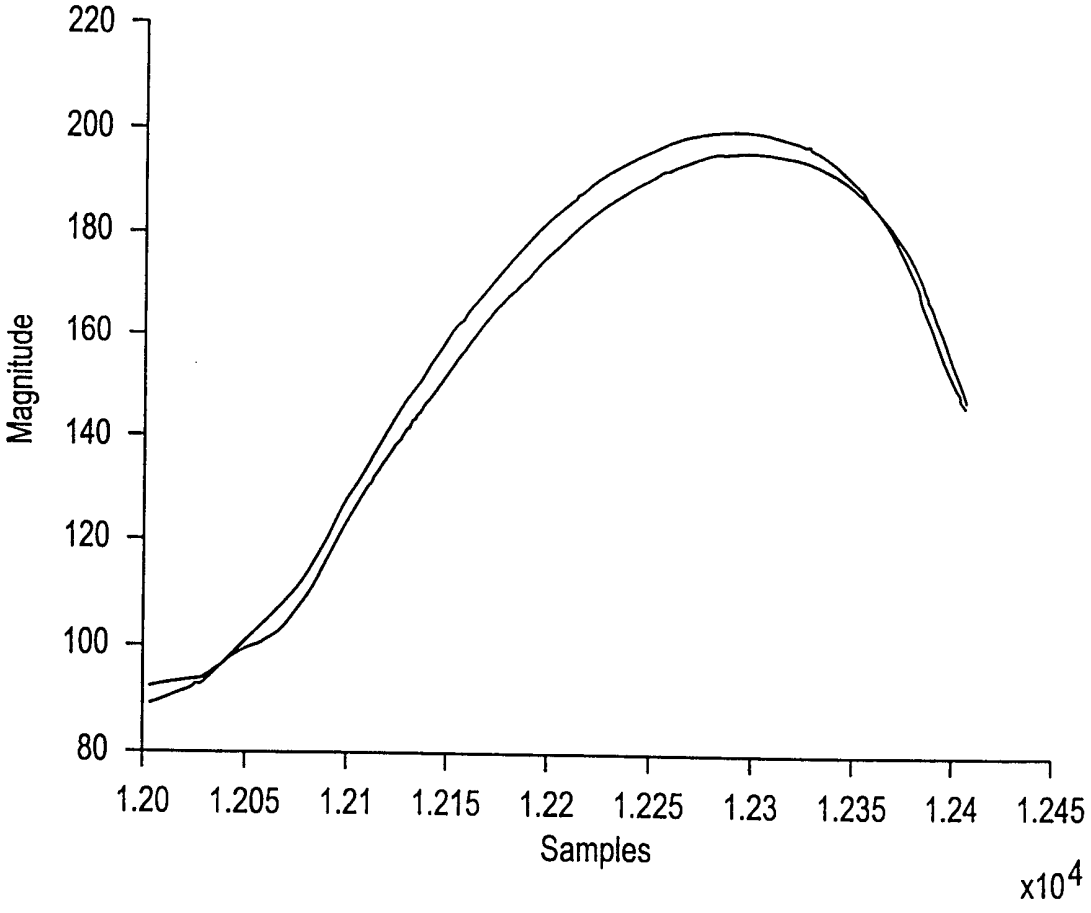

220
200
180
160
140
120
100
80
Magnitude
1.20
1.205
1.21
1.215
1.22
1.225
1.23
1.235
1.24
1.245
Samples
x10^4

FIG. 30

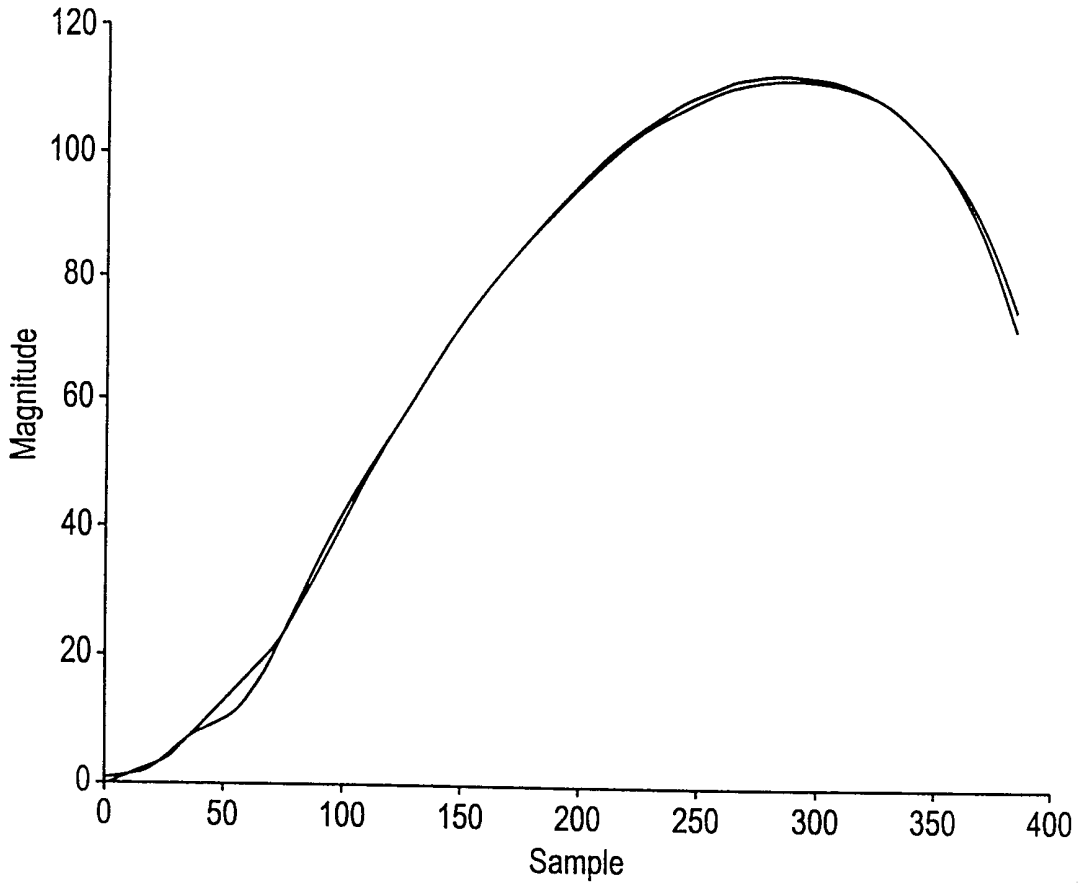

120
100
80
60
40
20
0
Magnitude
0
50
100
150
200
250
300
350
400
Sample

FIG. 31

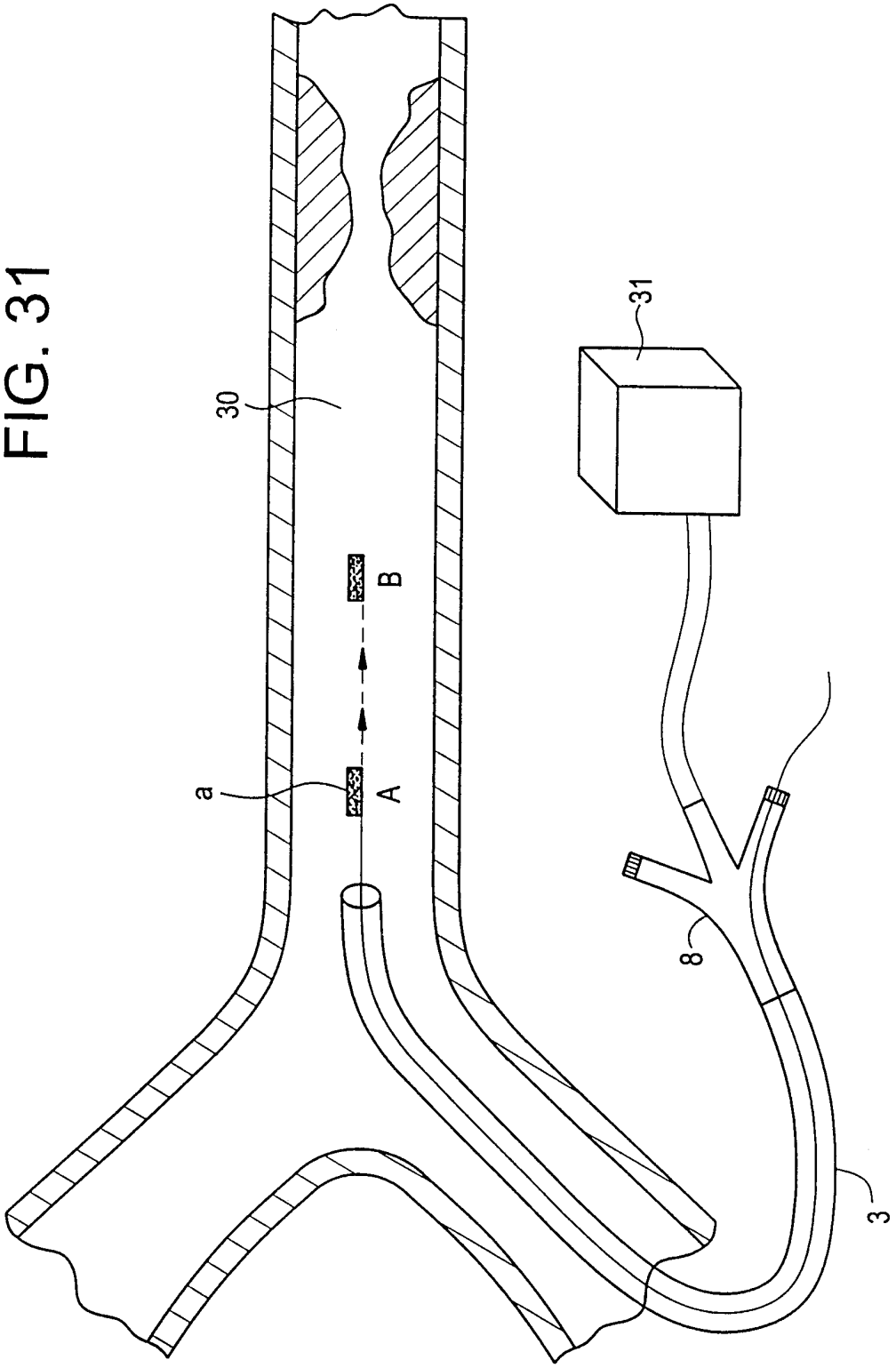


FIG. 32A

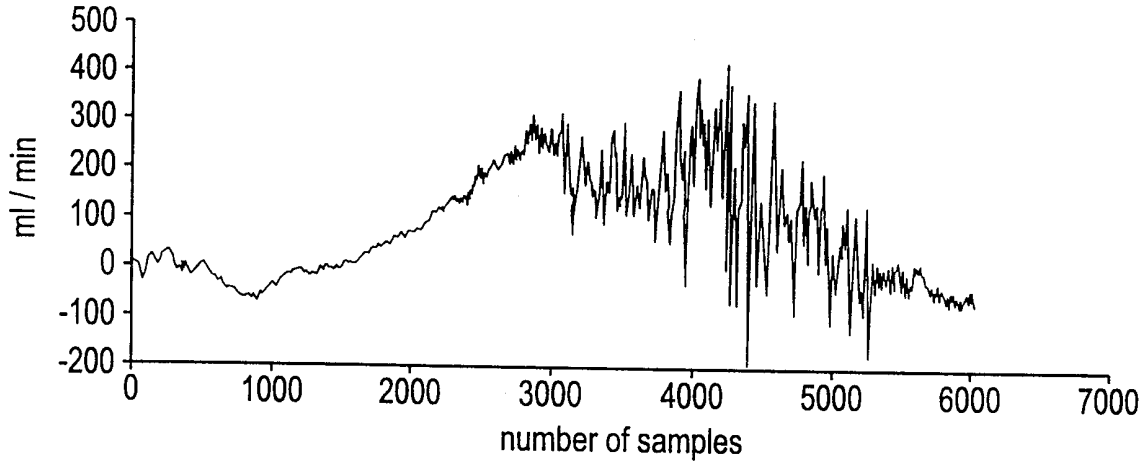


FIG. 32B

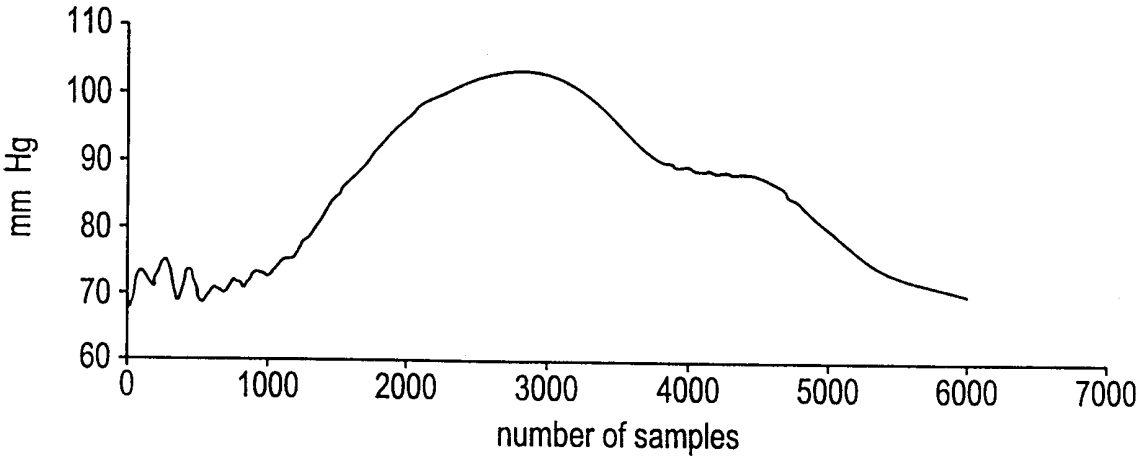


FIG. 33

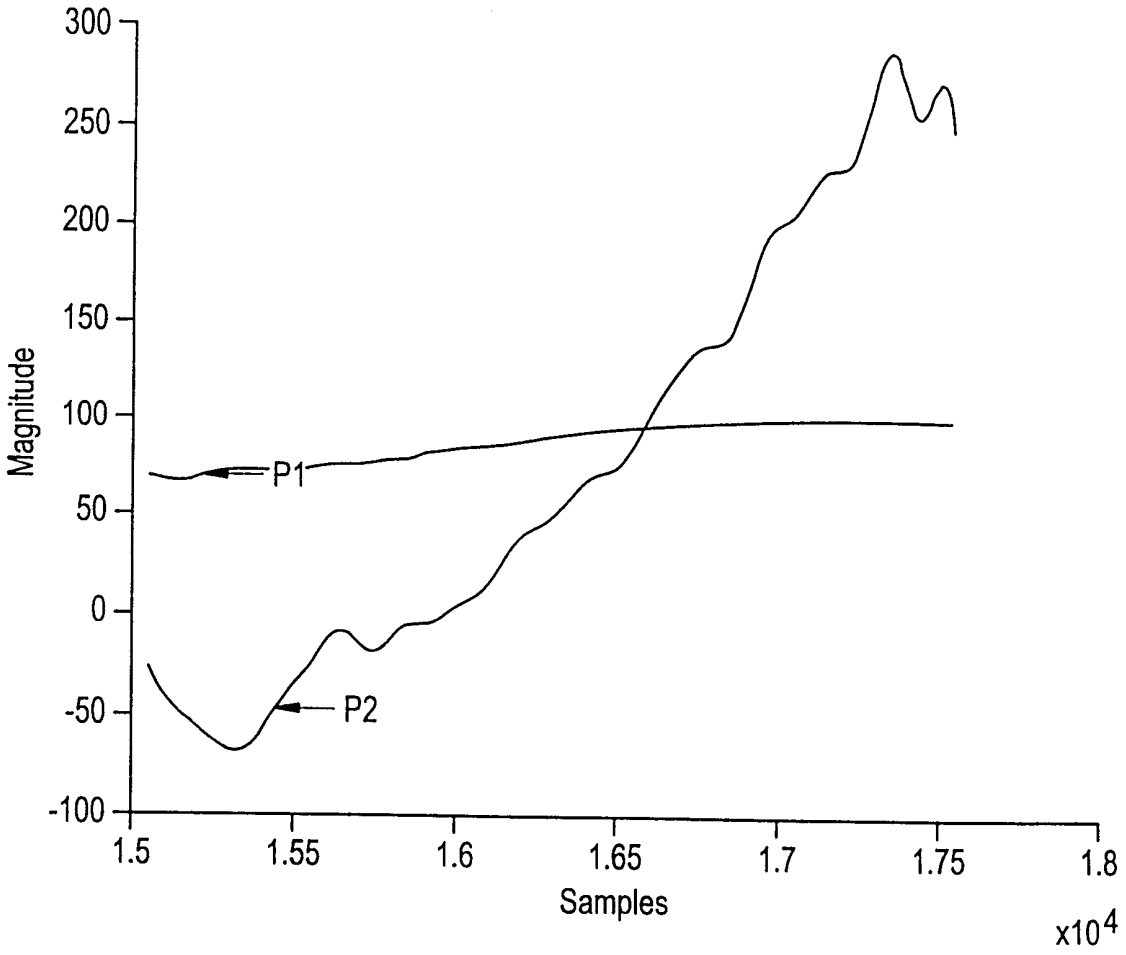

300
250
200
150
100
50
0
-50
-100
Magnitude
P1
P2
1.5
1.55
1.6
1.65
1.7
1.75
1.8
Samples
x10^4

FIG. 34

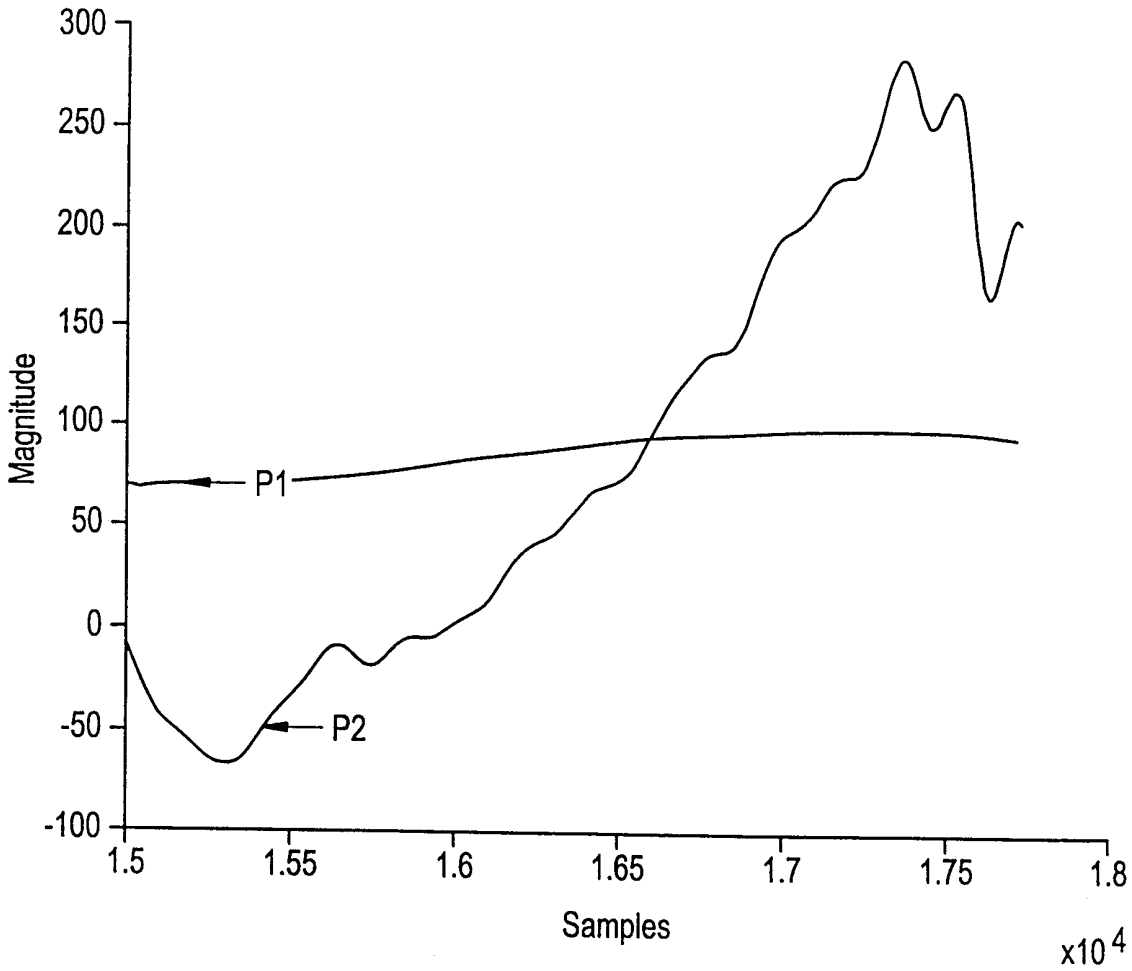

300
250
200
150
100
50
0
-50
-100
Magnitude
P1
P2
1.5
1.55
1.6
1.65
1.7
1.75
1.8
Samples
x10 4

FIG. 35

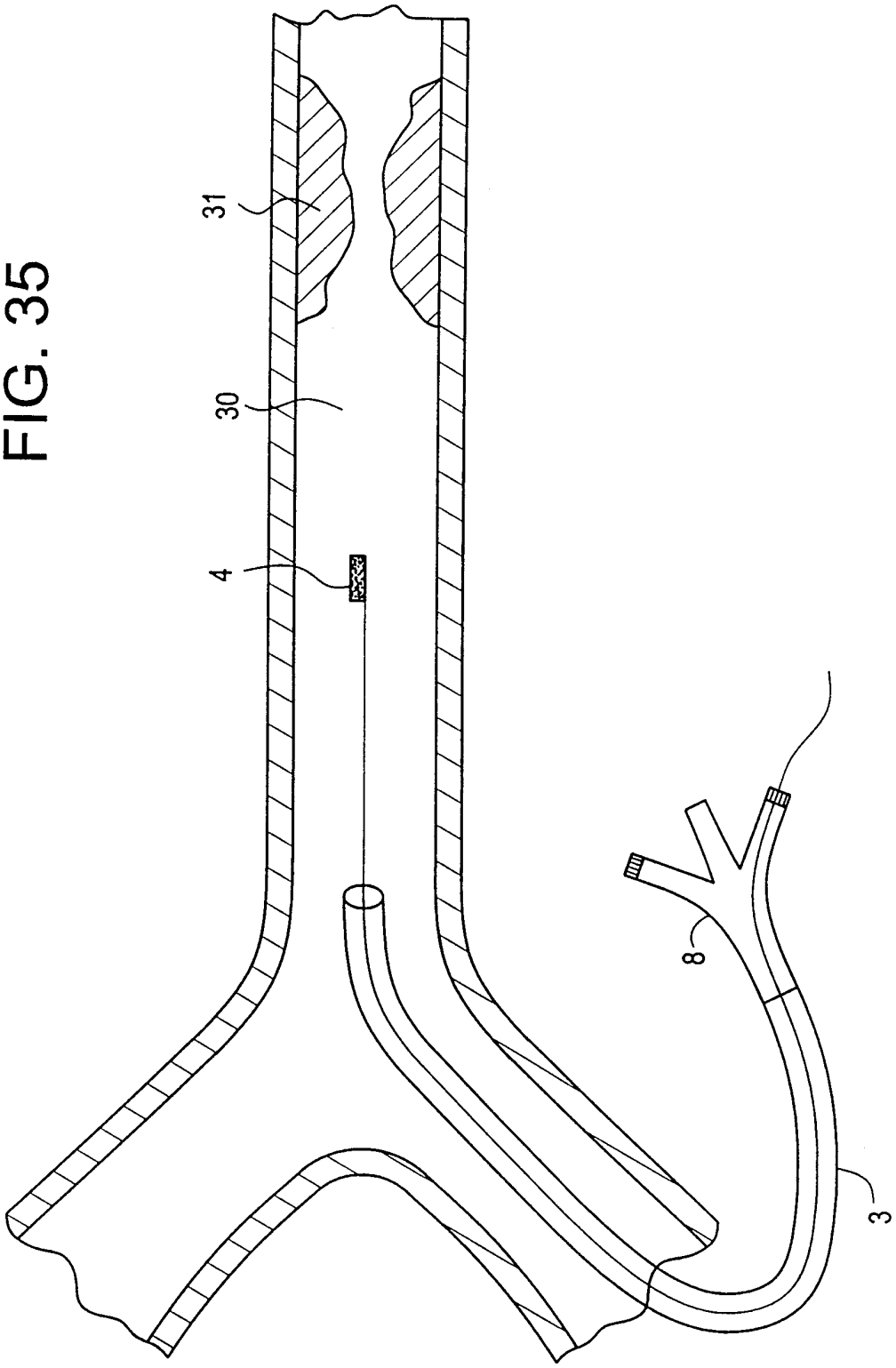


FIG. 36

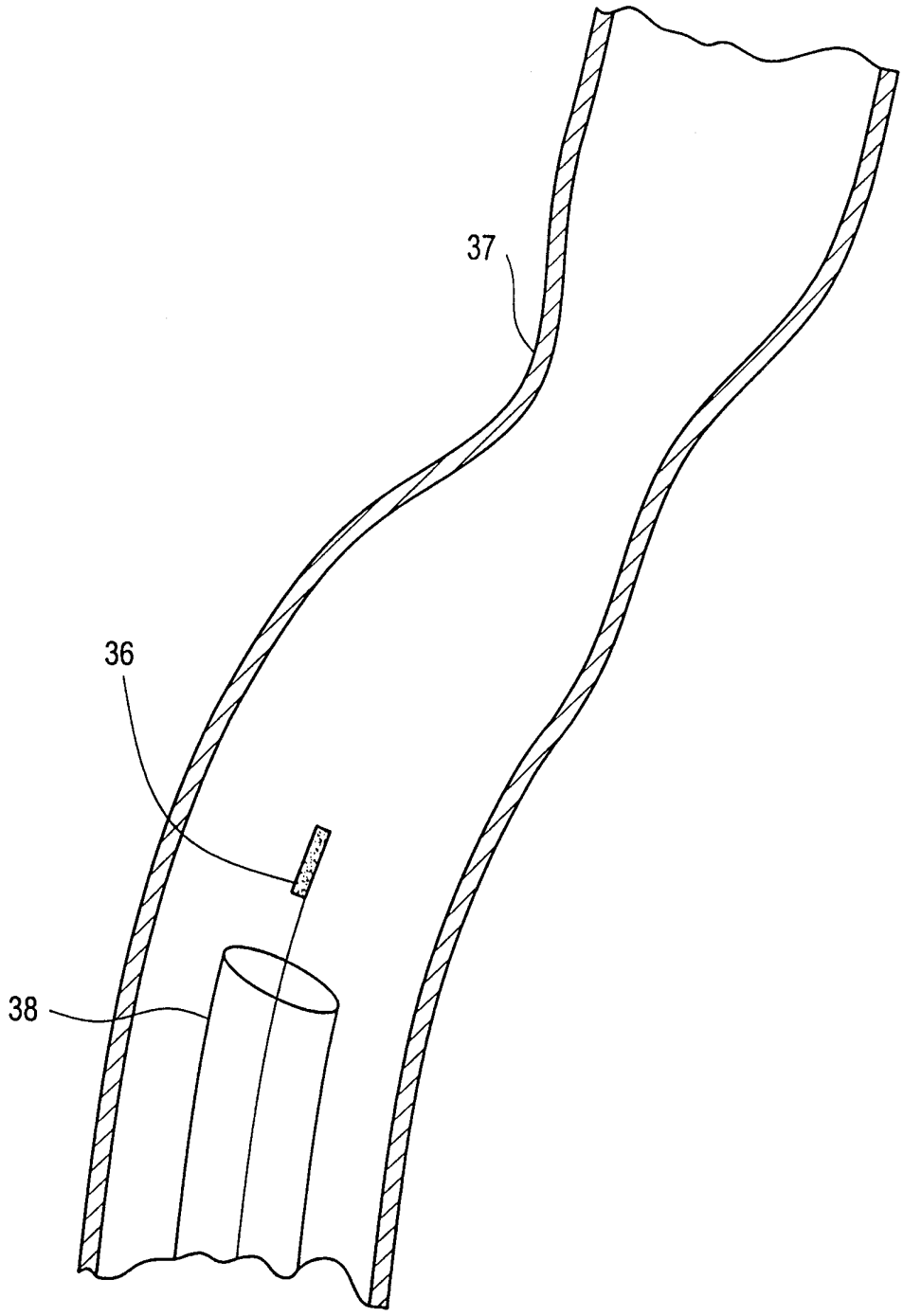


FIG.37

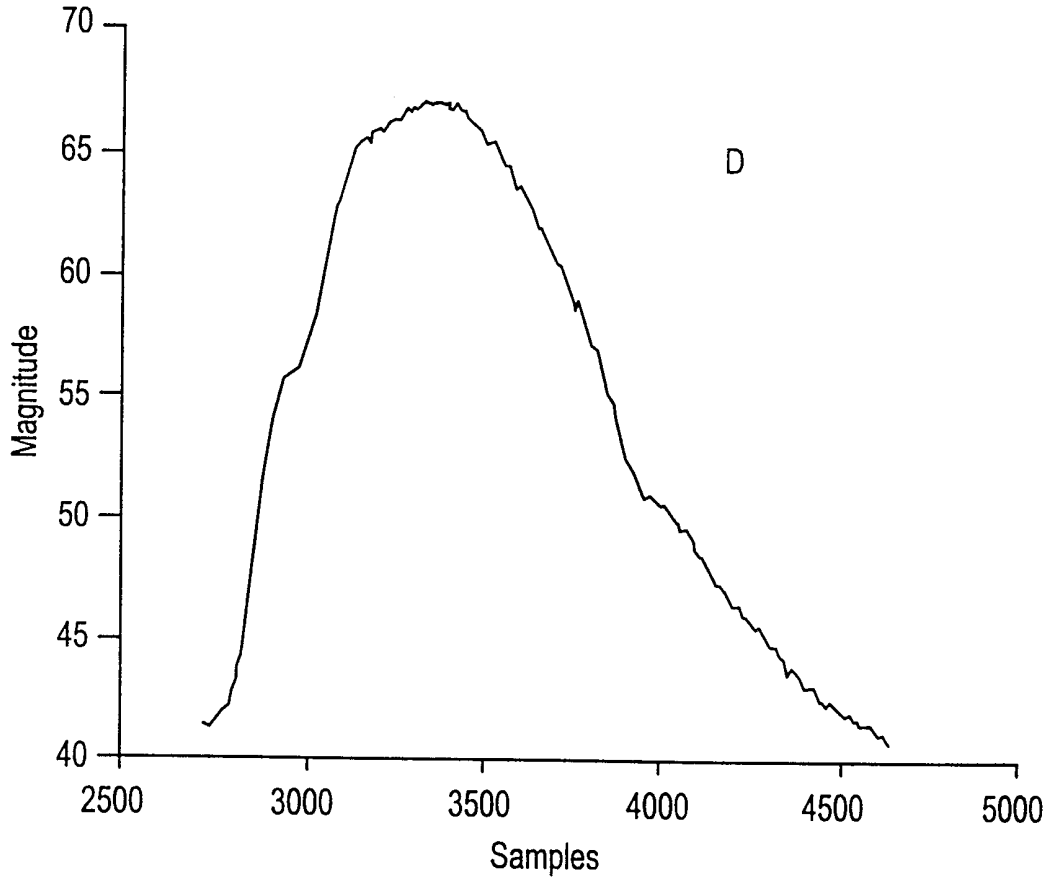

70
65
60
55
50
45
40
Magnitude
D
2500
3000
3500
4000
4500
5000
Samples

FIG.38

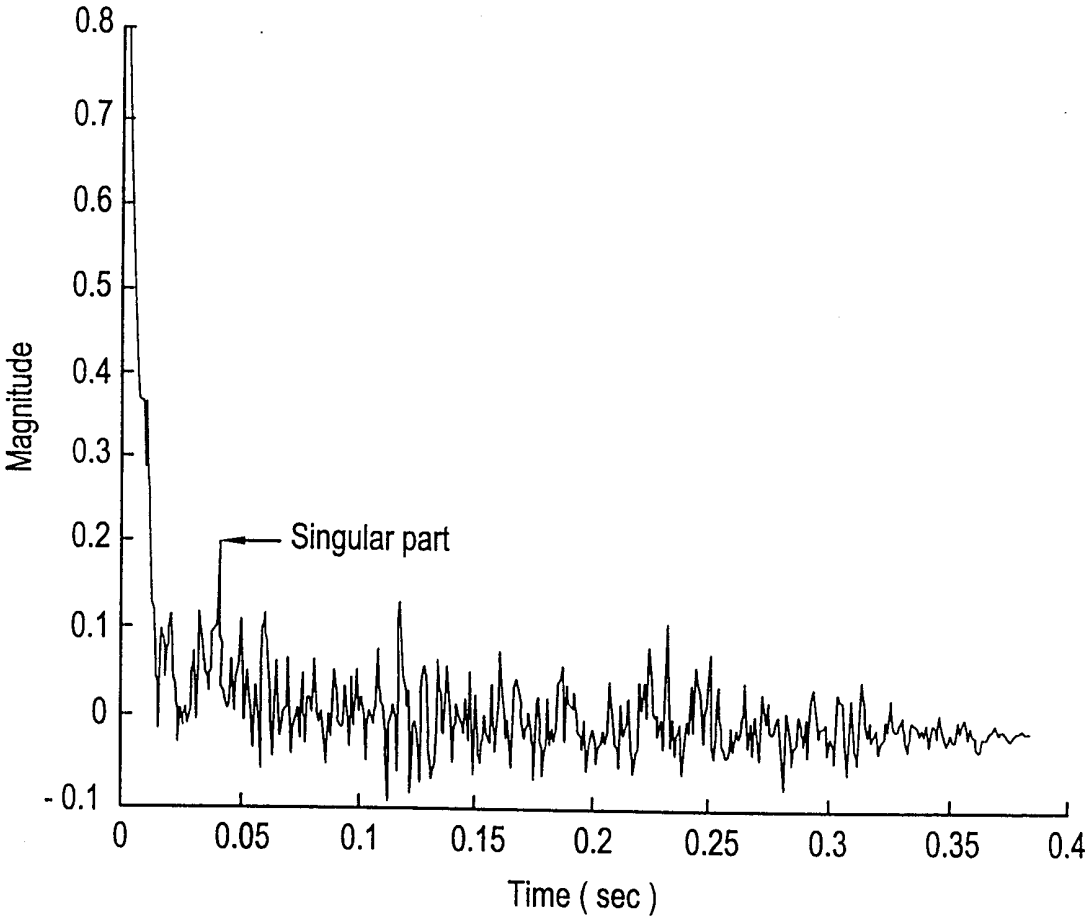

0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
- 0.1
Magnitude
Singular part
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
Time (sec)

FIG.39

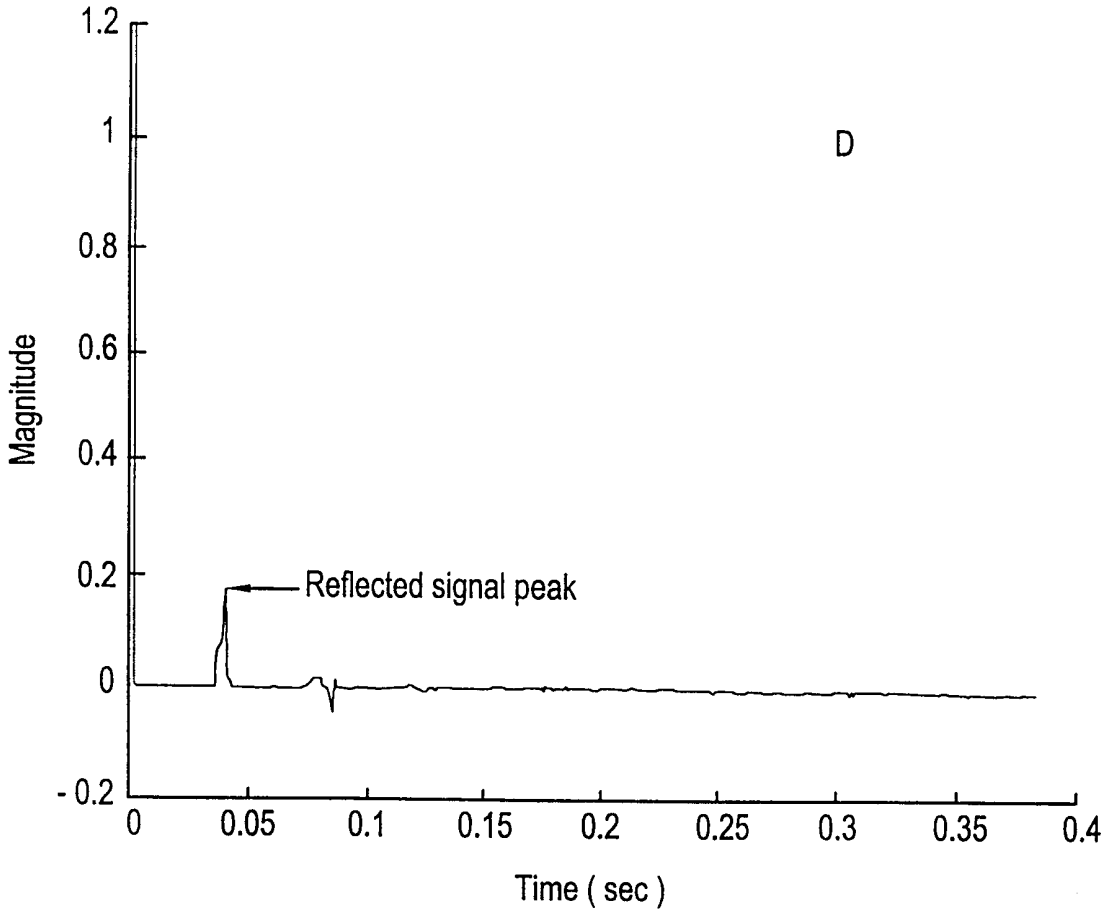

D
1.2
1
0.8
0.6
0.4
0.2
0
- 0.2
Magnitude
Reflected signal peak
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
Time (sec)

FIG. 40

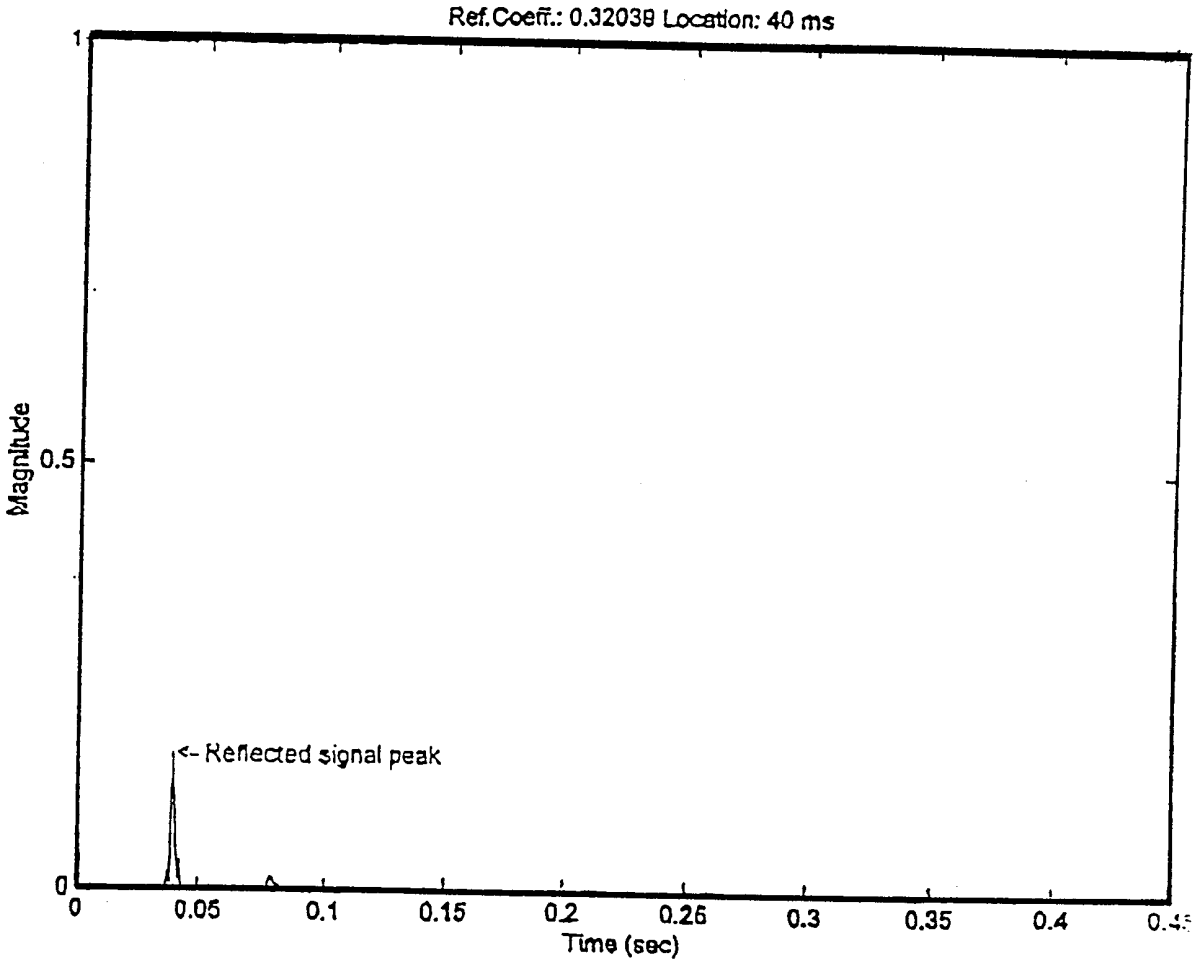

Ref.Coeff.: 0.32038 Location: 40 ms
Magnitude
1
0.5
0
<- Reflected signal peak
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
Time (sec)

FIG.41

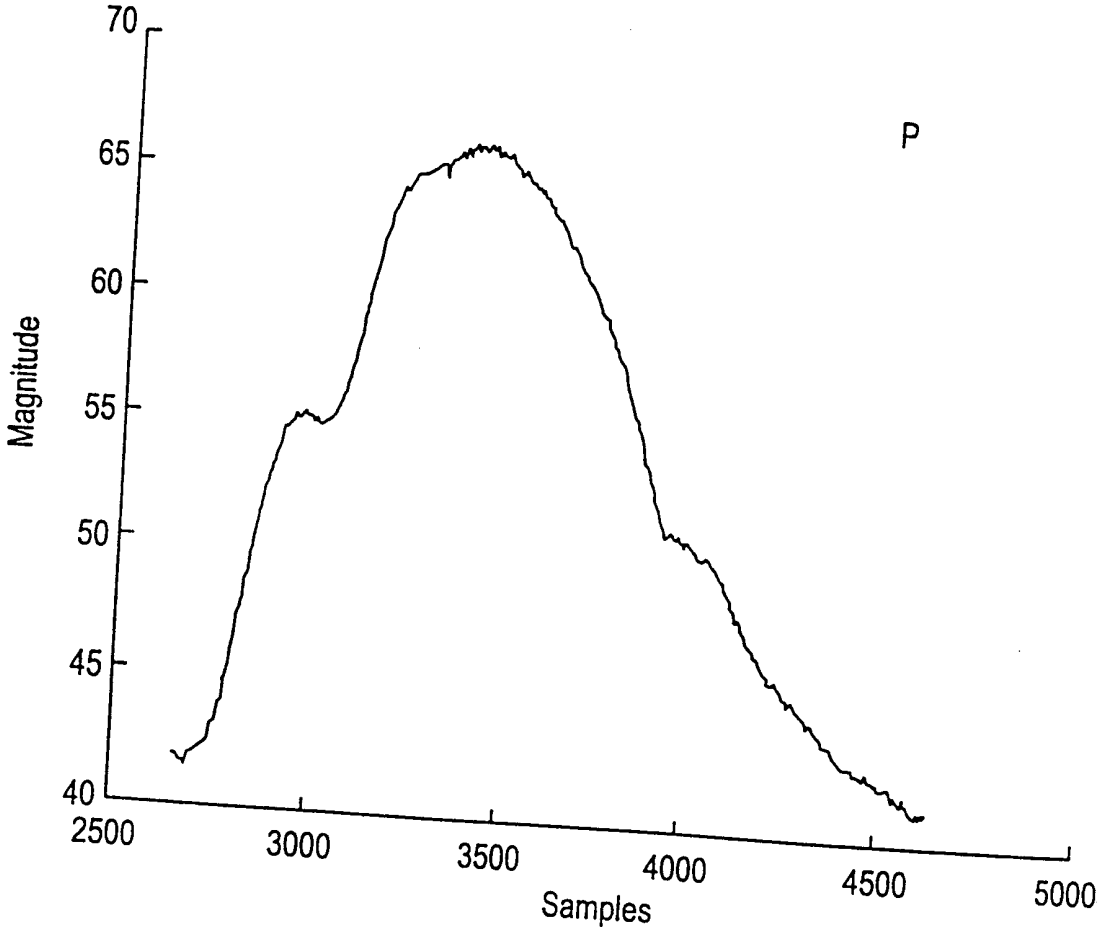

70
65
60
55
50
45
40
Magnitude
P
2500
3000
3500
4000
4500
5000
Samples

FIG.42

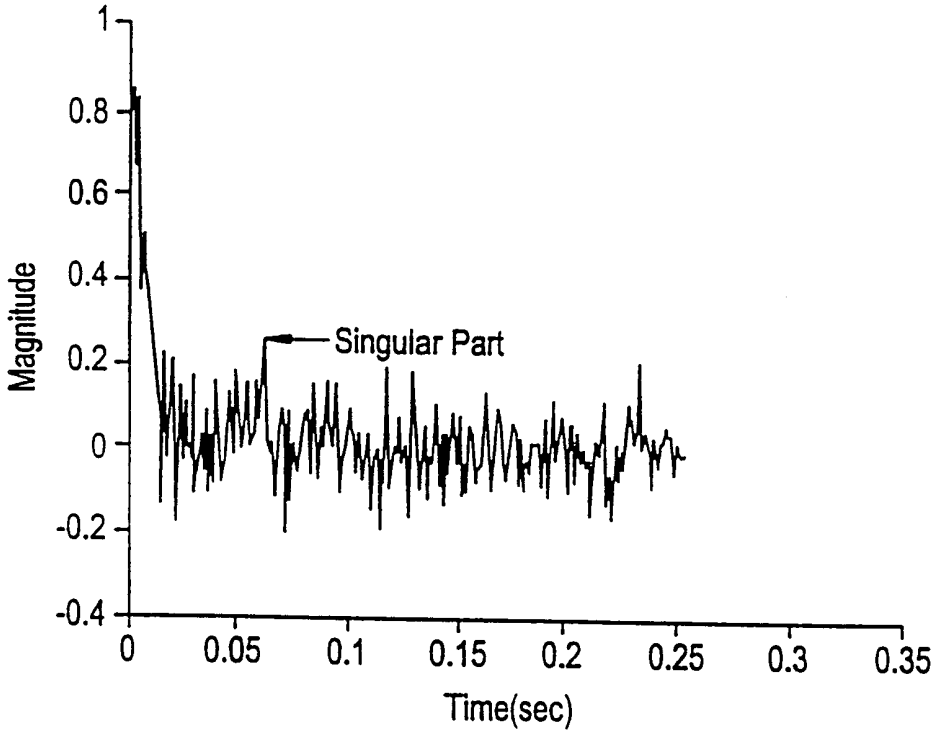

Magnitude
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
Singular Part
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
Time(sec)

FIG. 43

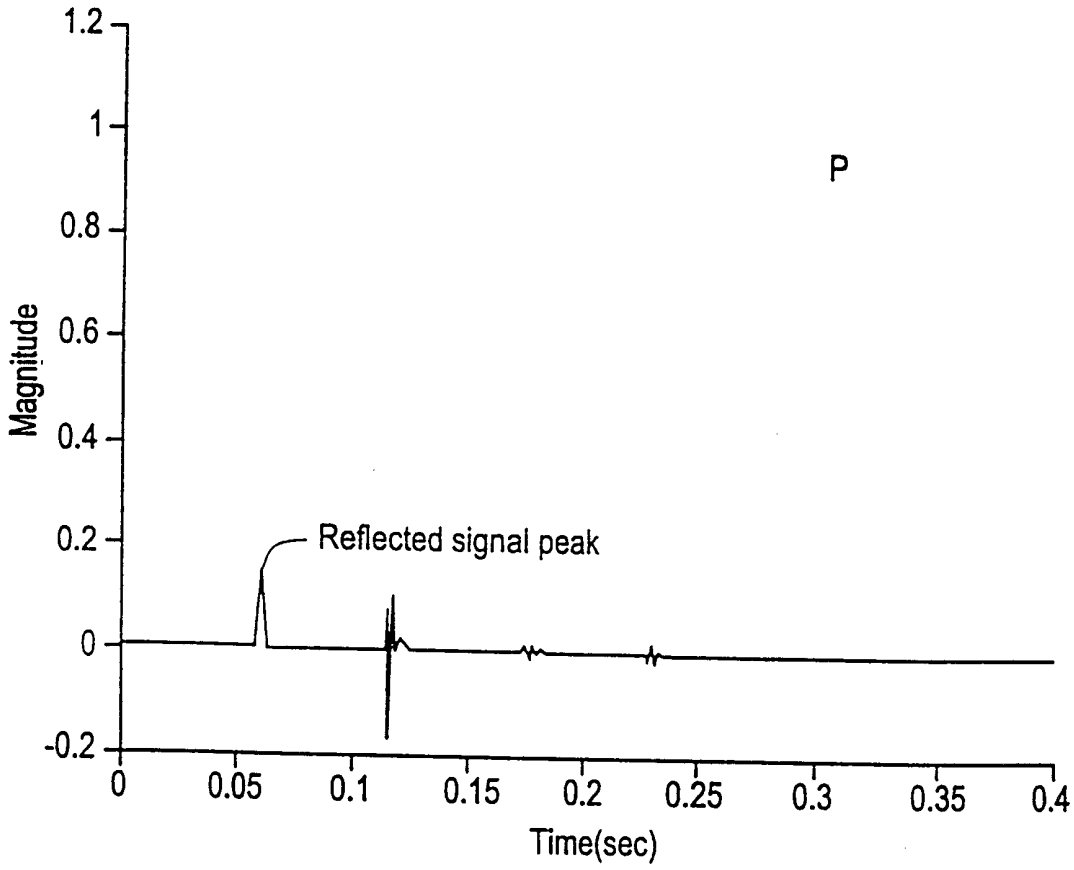
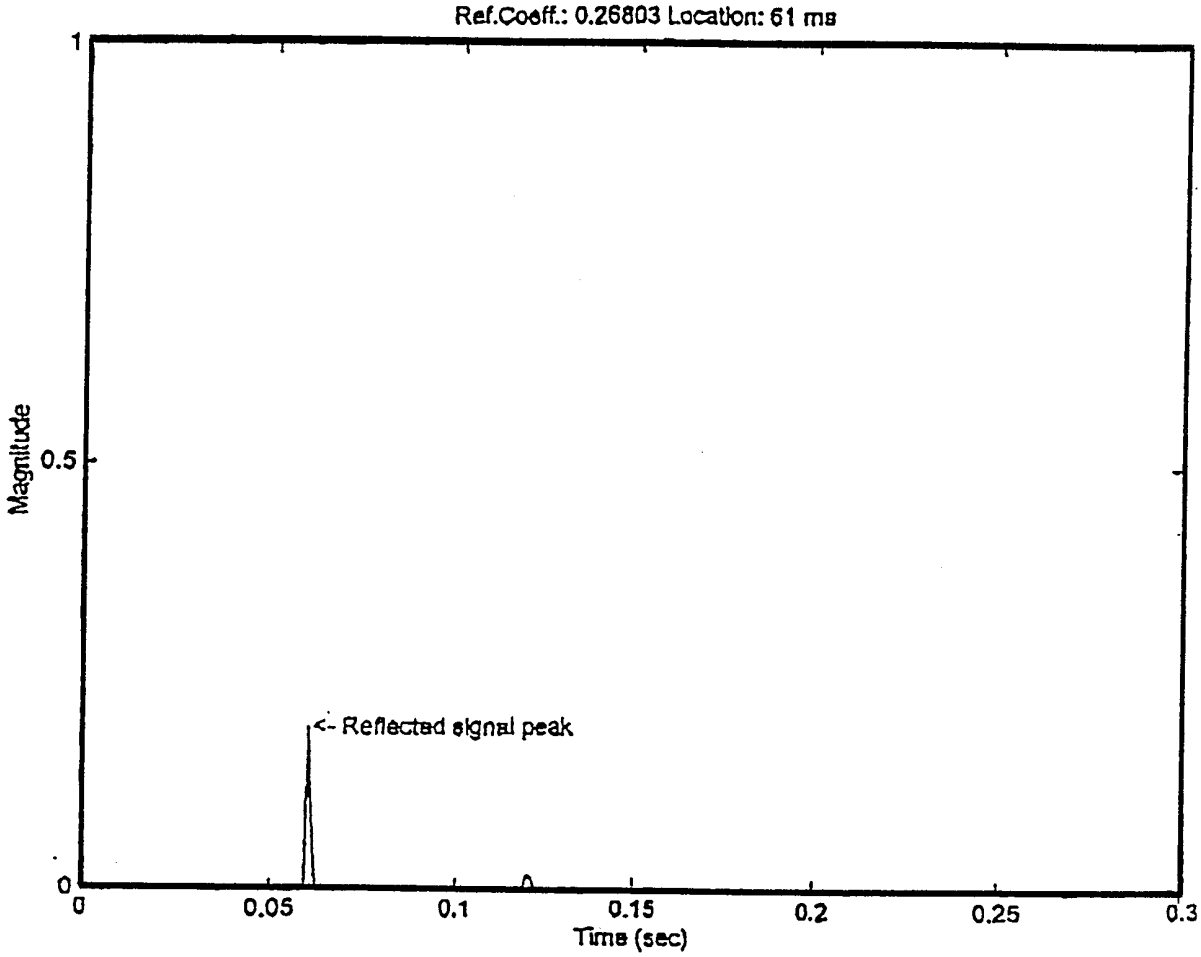

P
Magnitude
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
Reflected signal peak
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
Time(sec)

FIG. 44


Ref.Coeff.: 0.26803 Location: 61 ms
Magnitude
1
0.5
0
<- Reflected signal peak
0
0.05
0.1
0.15
0.2
0.25
0.3
Time (sec)