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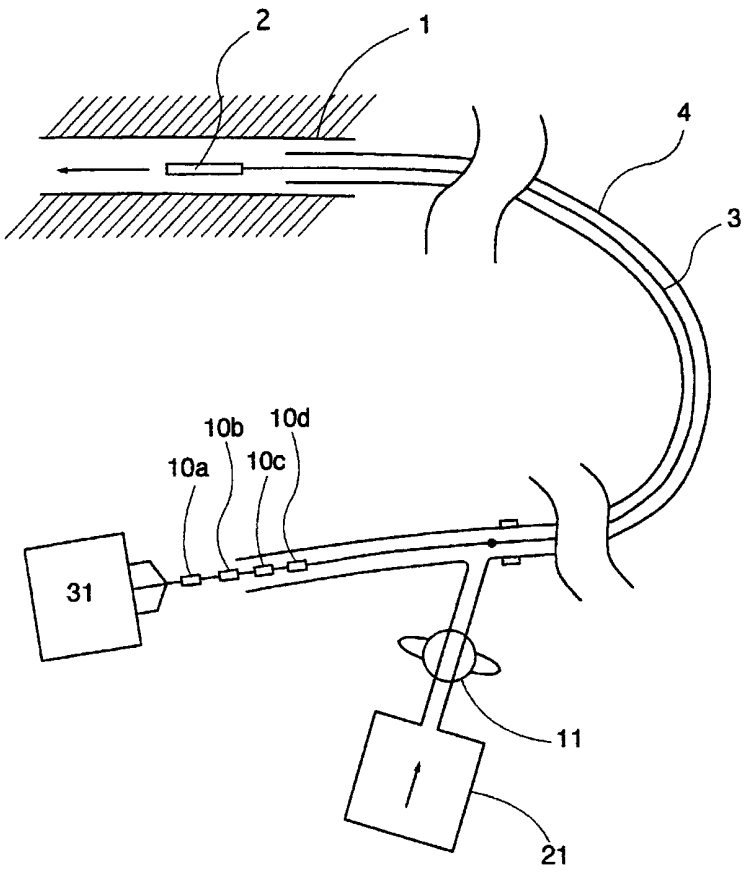
(54) Title: SYSTEM FOR MEASURING PRESSURE AND FLOW IN A BLOOD VESSEL



(57) Abstract: A system for the measurement of pressure and flow within a blood vessel (1) is disclosed. It comprises at least one sensor element (2) providing signals corresponding to the instantaneous pressure and temperature, said sensor element (2) being an integral part of a guide wire (3). The guide wire is insertable into the lumen of at least one catheter (4). The catheter (4) is in its turn insertable into said blood vessel (1). There is provided fluid injection means (21) for delivering a controllable fluid volume flow into said blood vessel (1) via said catheter (4). A means (26) for controlling or measuring the temperature of said fluid (22) is also provided. There is also at least one electronic signal analyzer (31), the input signals of which correspond to instantaneous pressure and temperature at said integrated sensor (2), and providing at least one signal corresponding to the flow in said blood vessel (1).

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SYSTEM FOR MEASURING PRESSURE AND FLOW IN A BLOOD VESSEL

The present invention relates to pressure and flow measurements within blood vessels, in particular the coronary arteries of the heart.

Background of the Invention

A well-known disease, often associated with cardiac infarction, is caused by constrictions of the coronary arteries. These constrictions, in turn caused by deposited material on the arterial walls, may hinder blood flow to an extent that the cardiac muscle is not supplied properly with arterial blood for oxygenation.

In order to determine the ability of a specific coronary vessel to supply oxygenated blood to the heart muscle, i e the myocardium, there is known a method by which the intracoronary pressure distal to a stricture in combination with the proximal pressure is measured. The method concerns a determination of the Fractional Flow Reserve (FFR, see N.H.J. Pijls, D.B. De Bruyne: Coronary Pressure, Kluwer Academic Publishers, Dordrecht, The Netherlands, 1997, pp 16ff). FFR is defined as the ratio between the nominal and the actual values of blood flow, and can be determined by measuring the pressures at positions proximal and distal to a constriction, i e $FFR=P_{dist}/P_{prox}$. The distal pressure is measured in the vessel using a microtransducer, and the proximal pressure is the systemic arterial pressure, which can be measured using a fluid-filled catheter connected to an external transducer.

Major technological difficulties are related to the location and the small dimensions of the coronary arteries, which can only be accessed
with extremely thin wires and catheters guided by fluoroscopy. The guide wires typically have outside diameters of 0.35 mm, and sensor elements must be considerably smaller and adequately secured in order not to impose any hazards on the patient.

Clinically, FFR has proven to be a powerful variable to distinguish between healthy and constricted coronary arteries. A reliable decision rule for treatment is $FFR<0.75$. The treatment could either be dilatation of the artery by e g balloon angioplasty, or bypass surgery.

If FFR>0.75 there are two possibilities:
a) either the patient is healthy with respect to the actual coronary artery vessel (most probable), or
b) there is an additional constriction distal to the suspected one, or some other distally located limitation to the blood flow, e g a non-functional myocardium.

To distinguish between the possibilities a) and b), it is necessary to determine whether the artery blood flow is adequate or not. Ideally, one wishes to determine the absolute coronary flow reserve (CFR), defined as the ratio between the hyperemic volume flow and the resting volume flow. By hyperemic flow is meant the maximum obtainable flow, during extreme cardiac loads. In clinical practice, the hyperemic condition can be developed by infusing vasodilatory drugs, such as adenosine, or papaverine. For determining CFR, it is necessary to measure volume blood flow, but the requirement on absolute measurement is alleviated by the fact that CFR involves a ratio between two values of volume flow. Therefore, factors that are constant between the two measurements need not be determined independently.

Methods for relative blood flow measurement include the use of miniature ultrasonic probes has been tested. With these probes, it is possible to determine local blood flow velocity. Thus it is possible to determine CFVR, coronary flow velocity reserve, which is closely related to CFR. The clinical value of this variable alone is limited, since it is dependent on several hemodynamic parameters that must be determined independently. In fact, the combined use of FFR and CFR is desired.

Summary of the Invention

It is the object of this invention to make possible simultaneous measurements of both pressure and flow in small blood vessels, thereby making possible the simultaneous determination of both FFR and CFR. In fact, a synergistic feature of the present invention is that both measurements can be performed with one single ultraminiature sensor, requiring no further intervention or provocation to the patient than that required for dilatation of the diseased artery by balloon angioplasty, using catheter intervention. A further significant feature of the present invention is that the determination of the coronary artery functionality is

repeatable, and can be performed before and after therapy, thereby providing an objective assessment of the therapeutical result.

The present invention builds around a number of well-known physical principles, combined with recent advances in microsensor fabrication technology and signal processing techniques. The specific characteristics of the present invention will become evident from the study of the enclosed drawings, together with a description of the functionality with reference to the drawings.

The inventive system is defined in claim 1.

Brief Description of the Drawings

Figure 1 depicts the basic outline of the system according to the invention.

Figure 2 depicts in some detail one embodiment of the fluid injection means, being one part of the system according to the invention.

Figure 3 depicts the physical outline of one sensor element, being also part of the system according to the invention.

Figure 4 depicts a schematic view of an electronic signal analyzer and associated electronic circuitry, being also part of the system according to the invention.

Figures 5 and 6 depict in schematic form typical signals occurring within the system according to the invention using two different signal schemes.

Detailed Description of the Invention

The functional principle and physical outline of the system according to the invention can be understood from a discussion with reference to Figure 1. A guide wire 3 is inserted into the blood vessel or artery 1, using the wellknown Seldinger technique. In the case of a coronary artery, introduction takes place by way of the left ventricle, and the guide wire is then

advanced downstream into the coronary artery tree. A catheter 4 is also inserted and advanced to a position, slightly proximal to the tip of the guide wire3. Closer to this tip, the guide wire 3 contains one integrated sensor element 2, consisting of one or several resistors, the resistance of which is a monotonous function of pressure, or temperature, or both. By electrical connections along the guide wire 3, the resistance may be measured and analyzed by an electronic analyzer 31, connected to the proximal end of the guide wire 3.

The guide wire 3 typically consists of a monolithic metal wire, being sectioned in order to obtain different bending flexibility of the different sections. Most important is to have maximal bending flexibility close to the distal tip, in order to prevent the tip from perforating soft tissue.

The axial position of the sensor element 2 with respect to the catheter tip is controlled by positioning means 10a,b,c,d. This could for example consist of inscribed position marks on the guide wire, indicating its axial position in relation to the catheter. In the case of absolute volume flow measurements, it may be important to measure the position with an accuracy of ±1 mm or better. Measurement and control of the axial position can be maintained by mechanical means, but electronic sensor devices could also be used. On the other hand, if only relative measurments are required, the required accuracy is much less. In fact, it may be reduced to ensuring that the sensor position is kept at a constant distance, distal to the catheter tip. In this case, the positioning may be performed by fluoroscopy, eliminating any need for mechanical arrangements on the guide wire 3, or the catheter 4.

Fluid injection means 21 is connected to the catheter via a valve 11. The injected fluid is maintained at a temperature differing from that of the blood flowing in the artery 1. By using the combined pressure and temperature sensor element 2, the temporal variations of pressure and temperature can, in principle, be transformed into absolute continuous measurements of both pressure and flow. More detailed description of both the sensor function and the required electronic signal processing will follow below.

Figure 2 shows in more detail the outline of the fluid injection means 21, connected via the valve 11 to the catheter 4. The fluid 22 is contained in a bottle 25 with flexible walls. When mechanical pressure is acting on the walls, e g via a cuff, or the like, the fluid 22 will be

subjected to an elevated pressure. If this pressure is significantly higher than the pressure within the blood vessel, a constant volume flow of the fluid 22 will be injected into the blood vessel 1 from the tip of the catheter 4. The magnitude of the flow will be uniquely determined by the pressure difference between the bottle and the artery, and the flow resistance along that fluid line. Since all these parameters may be known and controlled, the magnitude of the flow will be likewise known and controlled. The fluid 22 preferably consists of physiological saline solution or some other biocompatible fluid, kept at room temperature or lower. The temperature is measured by a temperature sensor 23, and this information is transferred to the electronic analyzer 31 via a signal converter 24.

As described above concerning the accuracy of the positioning means 10a,b,c,d, the degree of accuracy of the fluid injection means 21 may vary from one embodiment of the presen invention to another. If it is required to measure absolute volume flow at high precision, it is necessary to control the volume flow of the injected fluid, and its temperature with high precision, since all errors are additive to the final measurement error. Also, it is necessary to compensate for thermal loss occurring during passage from the bottle 25 to the point of injection into the blood vessel, i e at the tip of the catheter 4. On the other hand, if only relative measurements are to be performed, it may be sufficient to ensure that the experimental conditions are stable, i e that fluid is injected at a constant rate. A necessary condition is also that there is a significant difference between the temperature of the injected fluid and that of blood.

The sensor element 2 is depicted in Figure 3. It is basically a monolithic silicon die, with integrated microsensor elements located on one of its surfaces, and fabricated by the technique known as surface micromachining whic involves deposition and etching techniques combined with photolithography to define several aligned patterns on the surface. By using a sacrificial layer, an evacuated cavity 64 under an elastic diaphragm 61 has been formed. One or several piezoresistors 62, 63 are located on the diaphragm. The deflection of the diaphragm is linearly depending on the pressure difference between the ambient and the cavity, and if one piezoresistor 62 is located on a part of the diaphragm 61 being subjected to positive strain when pressure is applied, its resistance will increase, approximately linearly. On the other hand, the resistor 63 is located on a part of the diaphragm being subjected to negative strain, and its resistance will decrease in a corresponding fashion. Thus each one of the

piezoresistors is pressure dependent, whereas the sum of their resistance is not, since the two contributing variations will cancel. On the other hand, the response to temperature variations of the two piezoresistors 62, 63 is equal both in sign and magnitude.

Figure 4 shows how the piezoresistors 62, 63, included in the sensor 2 are combined in an electronic signal analyzer circuit to provide output signals corresponding to pressure (P) and temperature (T). The piezoresistors 62,63 form a resistive bridge together with two resistors 70, 71, the resistance of which are essentially independent of both pressure and temperature. A voltage supply 72 is applied to the bridge via another resistor 73. Two amplifiers 75, 76 with differential inputs are connected to the bridge output, and the division point between resistor 73 and the bridge. A potentiometer 74 provides an adjustable reference for the amplifier 75. The sensor element 2 with the piezoresistors 62, 63, are connected to the electronic analyzer by electrical leads or conductors 78, 79 80. Physically, these conductors 78,79, 80 are insulated wires contained within the guide wire 3. When two piezoresistors 63, 63 are used as in the embodiment of Figure 3 and 4, three separate conductors are required. However, a minimal embodiment would require only one piezoresistor, and one insulated conductors. A second terminal to the piezoresitor could be provided by using the conductivity of human tissue.

Applied pressure to the sensor element 2 will influence the piezoresistors 62, 63 in such a way that a differential output of the bridge will be transferred to the amplifier 76, giving rise to an output signal (P) corresponding to pressure. The differential input to amplifier 75, on the other hand, will correspond to variations of the sum of the resistance values, being connected in series via the resistor 73. Thus amplifier 75 provides an output signal corresponding to temperature (T).

The signals corresponding to pressure and temperature (P) and (T) are inputs to a cross correlation unit 77, the function of which will be described in relation to the signal diagrams of Figure 5. The diagram at top shows the typical variations of coronary artery pressure, measured with the sensor element 2, in units of mm Hg, with time. The pressure exhibits typical cyclic variations, in which each heart beat gives rise to identical variations. With a mean value of about 100 mm Hg, the maximum (systolic) pressure is typically 130 mm Hg, and a minimum (diastolic) value of 70 mm Hg. The variations are caused by the repetitive

pumping action of the cardiac muscles, in combination with the synchronous openings and closures of the valves. The corresponding volume flow variations are depicted in the middle part of the diagram. Flow velocity is plotted against time, using identical time scale as that of the upper part of Figure 5. The flow velocity waveform exhibits peaks during the diastolic phase, the beginning of which corresponds to the so called dichrotic notch of the pressure waveform, indicating the closure of the aortic valve. The end of diastole is indicated by the rise of the pressure.

The lowest part of the diagram in Fig 5 shows schematically the temperature variations measured with the sensor element 2 when cooled saline solution is injected at a constant rate through the catheter 4. Note that the temporal variations of T correspond to that of flow velocity shown in the middle part of Figure 5, with a displacement corresponding to a phase delay θ. This delay is depending on the flow velocity of the blood but also the axial location of the sensor element 2 with respect to the point of mixing between the injected fluid and the blood, and the time response of the sensor element 2 with respect to temperature variations. For a given individual sensor element 2 and a given position, θ will be uniquely determined by the flow velocity. θ may be determined as the time lapse between the onset of the systole of the P and T curves as depicted in Figure 5. Another possibility to determine θ is to compute the cross correlation function between the P and T signals. This is depicted in Figure 4 by the cross correlation unit 77, performing this computation according to well-known digital signal processing techniques.

By various means of controlling the injection of cooling fluid, it is also possible to determine volume flow in absolute terms. This is indicated in Figure 5 by a point in time, t_{off}, when injection is stopped completely by closing the valve 11. Then T will resume a constant value corresponding to the actual blood temperature. Determination of this value in relation to the mean value and pulsatile variations will provide information in absolute terms as defined by the approximate relation

$$VF=\Delta T_0 \times IF/\Delta T \quad \text{..... (1)}$$

where ΔT_0 is the difference between the injected fluid temperature and the blood temperature, ΔT is the measured temperature relative to the blood temperature and IF is the injected fluid

volume flow rate. The approximation is based on the assumption that VF>>IF, and that Equation (1) indicates the possibility to determine absolute volume flow from variables obtainable from temperature measurements alone, provided that the fluid injection is controlled according to the description above. A necessary and sufficient condition for determination of absolute volume flow is adequate control of the fluid injection. First, the temperature of the injected fluid must be known, as well as its possible change during the transport from the bottle 25 to the point of injection. Second, the actual magnitude of the injected flow must be accurately controlled. Third, the development over time of the injected flow must be accurately controlled, either as indicated above, by keeping it constant over one period of time, then closed to zero in order to define the reference temperature.

In fig 6 a second possibility to perform flow determinations is indicated. In this embodiment, the fluid injection means 21 provides a pulsating volume flow. The pulsating frequency is chosen to be considerably higher than the heart rate frequency. A typical pulsating frequency is 10 Hz. In fig 6, the resulting waveforms are depicted. The top and middle waveforms are the pressure and flow velocity waveforms, like those of Fig 5. The lower waveform is the temperature variations as a function of time. The pulsations have an amplitude and phase relationship with that of the generated injection flow waveform that may be used to determine the actual blood flow of the coronary artery. In this case, the electronic signal analyzer 31 will include circuitry to determine amplitude or phase relationships between the generated fluid injection and the measured temperature waveform.

A pulsating flow may be generated by fast switching of the flow by means of the valve 11, which then consists of an electromagnetic valve, having small dead volume in order to operate at the necessary high speed. An additional advantage of this embodiment is that it eliminates the requirement of separate positioning means. Incorrect positioning of the sensor 2 with respect to the catheter tip can be deducted from the analysis of the temperature waveform, from the simple fact that no pulsations synchronous with the pulsatile flow will be detected.

The exact design and construction of the method and system according to the invention can be varied substantially within the framework of the enclosed claims.

CLAIMS:

1. A system for the measurement of pressure and flow within a blood vessel (1), **characterized by**:

-at least one sensor element (2) providing signals corresponding to the instantaneous pressure and temperature;

-said sensor element (2) being an integral part of a guide wire (3);

-said guide wire being insertable into the lumen of at least one catheter (4);

-said catheter (4) being insertable into said blood vessel (1);

-fluid injection means (21) for delivering a controllable fluid volume flow into said blood vessel (1) via said catheter (4);

-means (26) for controlling or measuring the temperature of said fluid (22);

-at least one electronic signal analyzer (31), the input signals of which correspond to instantaneous pressure and temperature at said integrated sensor (2), and providing at least one signal corresponding to the flow in said blood vessel (1).

2. A system according to claim 1, **characterized** by at least one positioning means (10a-d) for defining the axial position of said guide wire (3) with respect to said catheter (4).

3. A system according to claim 1 or 2, **characterized in that** said fluid (22) being an aqueous solution of sodium chloride, having a temperature siginificantly differing from that of said blood vessel (1).

4. A system according to any preceding claim, **characterized in that** said temperature control means (26) includes at least one temperature sensor (25).

5. A system according to any preceding claim, **characterized in that** said sensor element (2) is made from silicon, includes at least one diaphragm (61), piezoresistor (62, 63), and cavity (64), whereby the resistance of at least one of said piezoresistors (62, 63) is a monotonous function of hydrostatic pressure and/or temperature.

6. A system according to any preceding claim, **characterized in that** said analyzer (31) includes at least one unit (77) for the computation of the cross correlation function between said input signals corresponding to pressure and temperature.

7. A system according to any preceding claim, **characterized in that** said sensor element (2) is located at one point on said guide wire (3) no less than 5 mm and no more than 50 mm from its distal end.

8. A system according to any preceding claim, **characterized in that** said guide wire (3) includes at least one insulated electrical conductor (78, 79, 80) providing electrical connection between said sensor element (2) and said analyzer (31).

9. A system according to any preceding claim, **characterized in that** said analyzer (31) includes means for determining the time delay between the onset of systole as determined by said signal corresponding to pressure and corresponding onset as determined by said signal signal corresponding to temperature.

10. A system according to any preceding claim, **characterized in at** least one valve (11) for control of injection of said fluid.

11. A system according to any preceding claim, **characterized in that** said fluid injection means (21) includes at least one pressurized bottle (25) containing said fluid (22).

12. A system according to any preceding claim, **characterized in that** said fluid injection means (21) provides a pulsating flow, the pulse frequency of which considerably exceeds the heart rate.

13. A system according to any preceding claim, **characterized in at** least one valve (11), providing a pulsating volume flow of fluid (22), having a pulse frequency considerably higher than the heart rate.

14. A system according to claim 1 and 12 characterized in that said electronic signal analyzer (31) includes means for the determination of the amplitude and phase of said signal corresponding to temperature in relation to said pulsations of fluid flow.

15. A system according to claim 1 characterized in that said guide wire (3) includes a monolithic metal wire having a plurality of sections each having different bending flexibility.

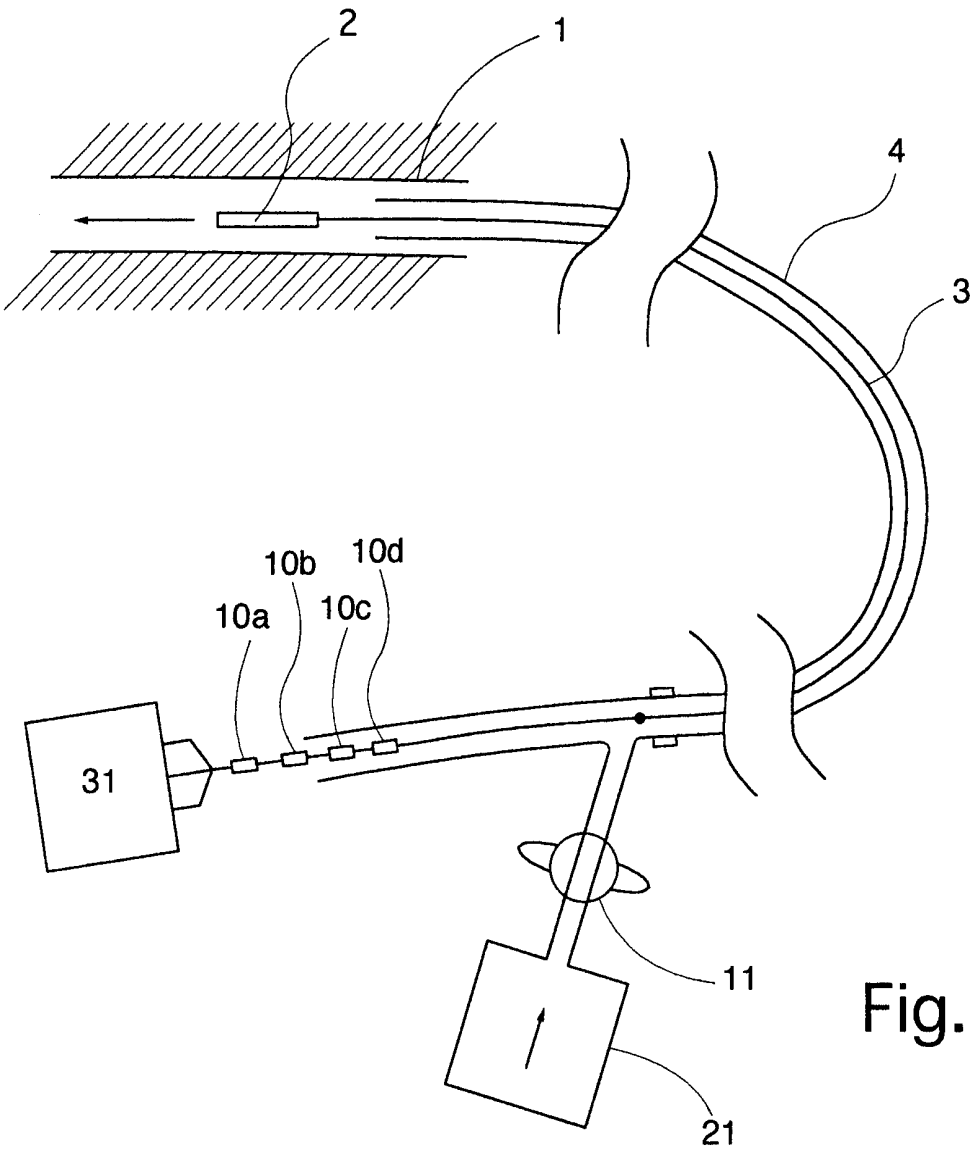


Fig. 1

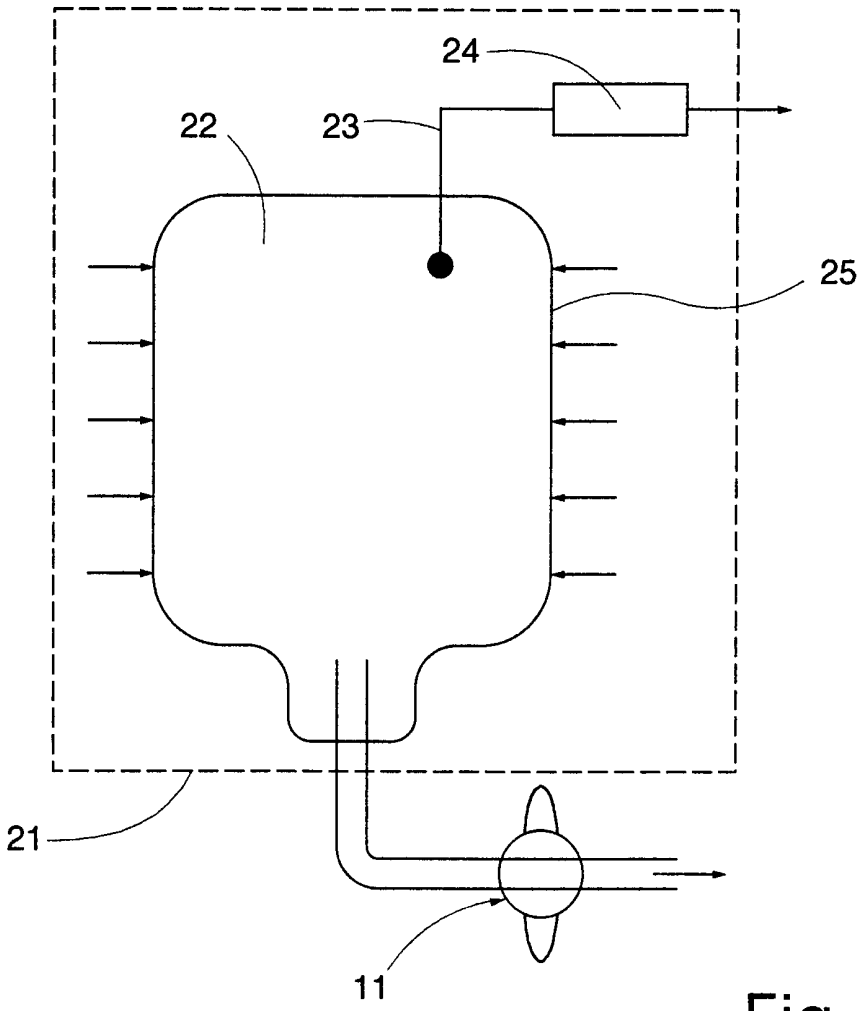


Fig. 2

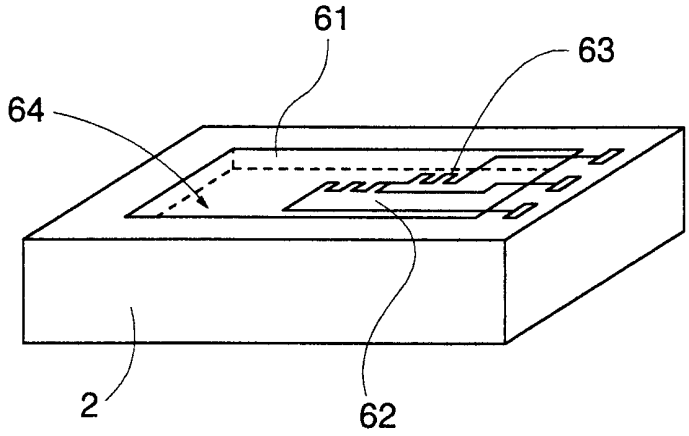


Fig. 3

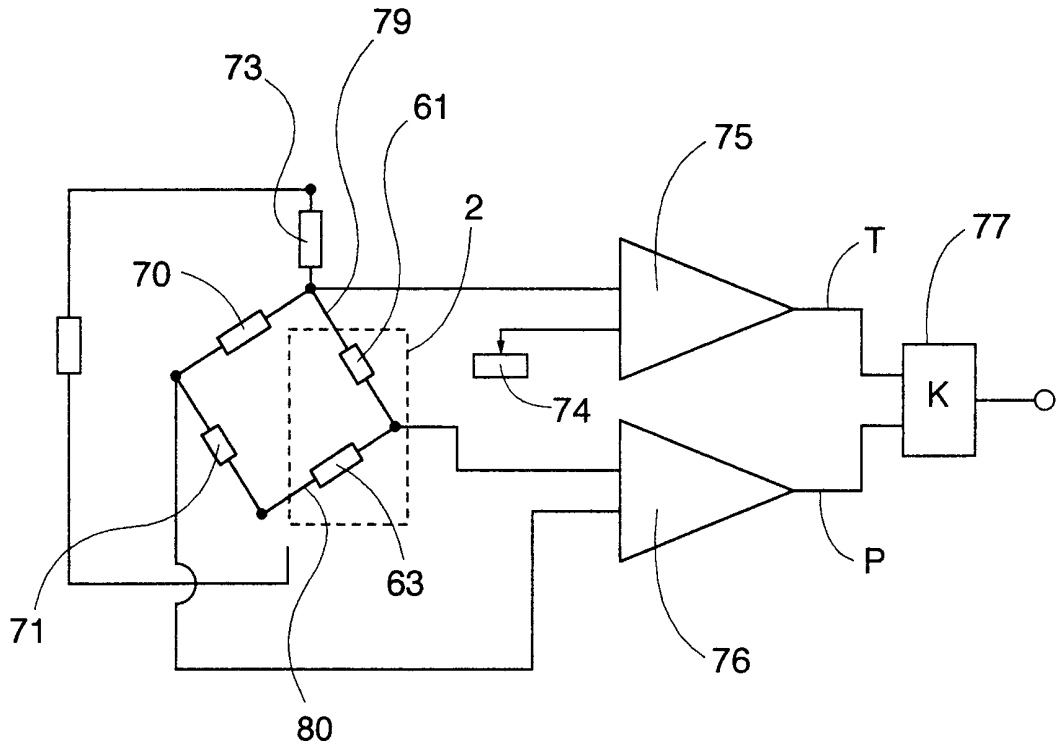
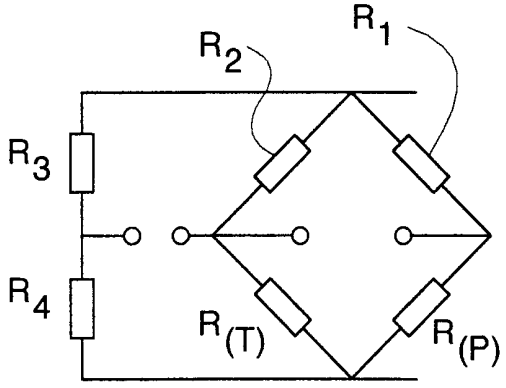
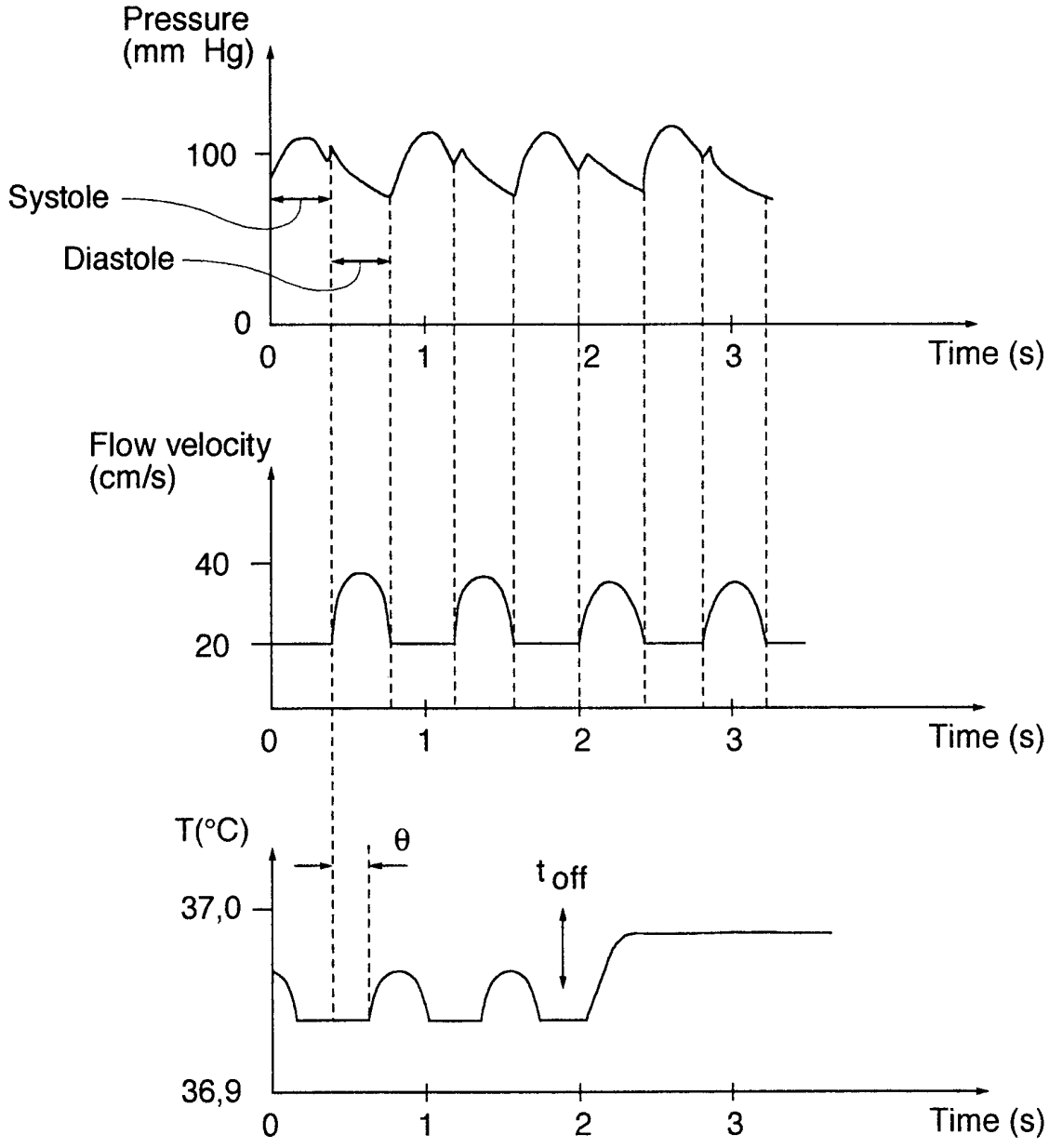


Fig. 4

or




Pressure
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Systole
Diastole
0
0
1
2
3
Time (s)
Flow velocity
(cm/s)
40
20
0
1
2
3
Time (s)
T(°C)
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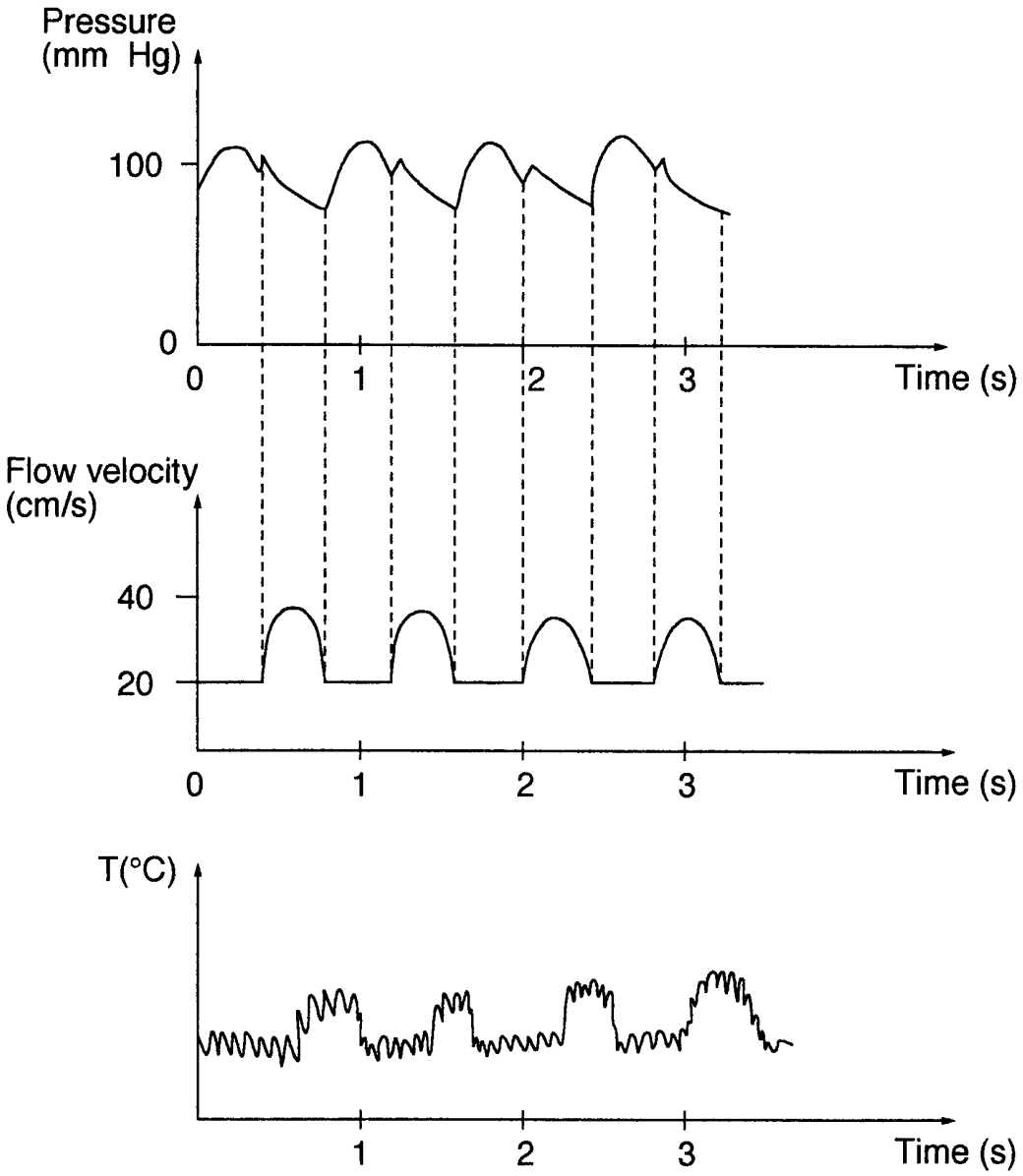
t off
37,0
36,9
0
1
2
3
Time (s)

Fig. 5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3
Time (s)
Flow velocity
(cm/s)
40
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0
1
2
3
Time (s)
T(°C)
1
2
3
Time (s)

Fig. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00175

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61B 5/028, G01L 9/06, G01F 1/69 // A61B 5/02, A61M 25/01
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61B, A61M, G01L, G01F

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

SE,DK,FI,NO classes as above

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9956617 A1 (RADI MEDICAL SYSTEMS AB), 11 November 1999 (11.11.99), page 6, line 25 - page 8, line 21, abstract	1,3-4,6-9
Y	--	2,5,10-15
Y	US 5114401 A (STUART ET AL), 19 May 1992 (19.05.92), abstract	2
	--	
Y	US 4554927 A (FUSSELL), 26 November 1985 (26.11.85), column 3, line 64 - column 4, line 21, abstract	5
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 May 2001	14 -05- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Frida Plym Forshell /OGU Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00175

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 9321822 A1 (PFEIFFER, ULRICH), 11 November 1993 (11.11.93), abstract ---	10-14
Y	WO 9700641 A1 (RADI MEDICAL SYSTEMS AB), 9 January 1997 (09.01.97), page 7, line 13 - page 8, line 6 ---	15
P,A	WO 0038775 A2 (RADI MEDICAL SYSTEMS AB), 6 July 2000 (06.07.00), abstract --- --------	15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/00175

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

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Continuation of box II

According to Article 34 (3) (a-c) and Rule 13.2, an international application shall relate to one invention only or to a group of inventions linked by one or more of the same or corresponding "special technical features", i.e. features that define a contribution which each of the inventions makes over the prior art.

Since the prior art found in the search covers the subject matter in independent claim 1, there is no common special technical feature linking the inventions in the dependent claims 2-15. Therefore, these claims do not, à posteriori, satisfy the requirement of unity of invention.

Five different inventions have been identified, namely:

1. Claims 2-3 relating to a guide wire with positioning means.

2. Claims 4-5, and 7-8 relating to a sensor element for temperature and pressure measurements.

3. Claims 6 and 9 relating to an analyzer for computation of blood flow based on pressure and temperature values.

4. Claims 10-14 relating to fluid injection into a vessel through a catheter for measurement of blood flow.

5. Claim 15 relating to a guide wire with sections having different flexibility.

These inventions lack a common technical feature that defines a contribution over the prior art.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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