(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 June 2004 (24.06.2004)

PCT

(10) International Publication Number
WO 2004/052431 A1

(51) International Patent Classification[7]: A61M 5/168

(21) International Application Number:
PCT/GB2003/005269

(22) International Filing Date: 4 December 2003 (04.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0228770.4 10 December 2002 (10.12.2002) GB

(71) Applicant: **NEORAD AS** [NO/NO]; Parkveien 55, N-0256 Oslo (NO).

(71) Applicant *(for MG only)*: **JACKSON, Robert, Patrick** [GB/GB]; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).

(72) Inventor: **BRABRAND, Knut**; Haukeveien 14b, N-1476 Rasta (NO).

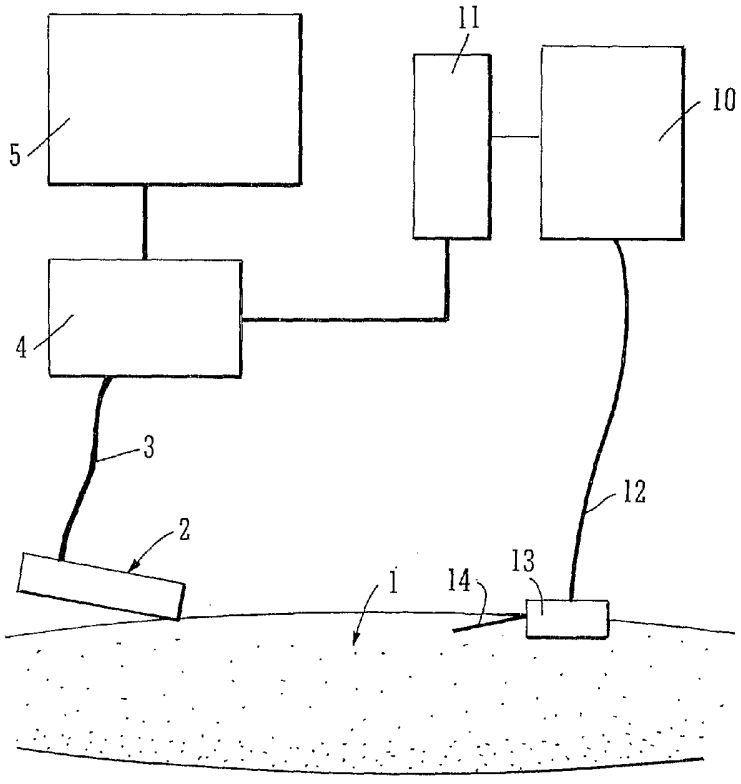
(74) Agent: **FRANK B. Dehn & Co.**; 179 Queen Victoria Street, London EC4V 4EL (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, EG, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO utility model (BW), ARIPO patent (BW), ARIPO utility model (GH), ARIPO patent (GH), ARIPO utility model (GM), ARIPO patent

[Continued on next page]

(54) Title: EXTRAVASATION DETECTOR



(57) Abstract: Ultrasound Doppler probe (2) is placed above the vein downstream of the infusion site. Processor (4) converts the output from the probe (2) into a form that may be displayed as an image on display unit (5). It also determines whether the velocity corresponds to a flow of contrast medium along the vein. If the cannula (13) is properly sited and the contrast medium flows as desired along the vein, this will lead to an increased flow velocity in the vein. This is detected by ultrasound probe (2) and, as described above, the processor unit (4) will therefore determine that no extravasation has occurred. However, where extravasation of contrast medium occurs this results in a low or zero velocity output from the probe (2) from which the processor unit (4) determines that extravasation has occurred. It therefore immediately sends a "stop" signal to pump controller (11) which stops pump (10).

WO 2004/052431 A1

(GM), ARIPO utility model (KE), ARIPO patent (KE), ARIPO utility model (LS), ARIPO patent (LS), ARIPO utility model (MW), ARIPO patent (MW), ARIPO utility model (MZ), ARIPO patent (MZ), ARIPO utility model (SD), ARIPO patent (SD), ARIPO utility model (SL), ARIPO patent (SL), ARIPO utility model (SZ), ARIPO patent (SZ), ARIPO utility model (TZ), ARIPO patent (TZ), ARIPO utility model (UG), ARIPO patent (UG), ARIPO utility model (ZM), ARIPO patent (ZM), ARIPO utility model (ZW), ARIPO patent (ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

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

Extravasation Detector

The present invention relates to an apparatus and method for detecting extravasation.

There are numerous medical procedures in which it is necessary to infuse a substance into a blood vessel. Typically a cannula is inserted into a vein and the substance is fed to this via a flexible tube. The substance may be blood, saline, a drug, a contrast medium, etc. In many cases it is desirable that the infusion occurs slowly and so the substance is simply gravity fed. However, there are circumstances in which it is necessary to force the substance into the blood vessel.

One example is the infusion of a contrast medium used in conjunction with an imaging system such as angiography, computed tomography (CT), ultrasound or MRI. In many applications of these procedures it is necessary to infuse a contrast medium into the part of the body that is to be imaged. The medium must often be infused at a comparatively high rate for effective results to be achieved. As a consequence, in recent years, a number of injector-actuated syringes and power injectors for pressurized injection of contrast medium have been developed.

However, whilst such devices are valuable and effective, they do create a risk of extravasation. Extravasation is the accidental infusion of fluid such as contrast media into tissue surrounding a blood vessel, rather than into the blood vessel itself. The causes for extravasation vary. Fragile vasculature or valve disease may cause physiological limitations to the ability of the blood vessel to tolerate the high rate of fluid administration used in some procedures. In computed tomography, for example, contrast injection flow rates can be in the range of 0.1 to 10 ml/s. and so

a failure of the vessel may occur. Alternatively, operator error may lead to inappropriate needle placement and patient movement may cause the infusing needle to be pulled from the intended vessel or cause the needle to be pushed through the wall of the vessel.

Extravasation of contrast media during intravenous injection is a potential serious complication that might necessitate surgical drainage of the affected region. Even though the incidence rate is low, it is considered to be a major concern and is associated with local pain and possibly necrosis of the tissue. If it occurs during an imaging procedure it is often necessary for the examination to be aborted and repeated at a later stage. It is therefore important to be able to detect extravasation quickly and reliably so that infusion may then be stopped. Other substances may have more serious effects. Chemotherapy drugs can be toxic to tissue if not diluted by blood flow.

Several extravasation detection techniques are known in the art. Two simple and very useful techniques for detecting extravasation are palpation of the patient in the vicinity of the injection site and simple visual observation of the vicinity of the injection site by a trained health care provider.

In the palpation technique, the health care provider manually senses swelling of tissue near the injection resulting from extravasation. By visual observation, it is also sometimes possible to observe directly any swelling of the skin in the vicinity of an injection site resulting from extravasation.

There have been a number of attempts to improve the detection of extravasation. For example, mercury strain gauge plethysmographs measure the volume change resulting from venous blood flow in a cross sectional area of a limb of a patient in order to detect a change in volume of a limb or digit as a result of extravasation.

Photo-plethysmographs measure the optical scattering properties of capillary blood to detect the presence of extravasated fluids in tissue. WO 99/15074 provides a sensor pad having a surface that is placed against a patient. A light source is also provided and a detector on the pad optically detects extravasation by detecting light that is reflected, scattered, etc.

U.S. Patent No. 4,647,281 discloses subcutaneous temperature sensing of extravasation using a microwave radiometer. The temperature of the subcutaneous tissue where the fluid is injected is compared to that of the injected fluid.

It is also known to detect extravasation by measuring changes in the electrical impedance. Injection fluid in the tissue of the patient also changes the electrical impedance properties of the tissue. Thus, an impedance change of a certain level in the vicinity of the injection site is interpreted as being due to extravasation. WO 99/26686 discloses an electrode patch for attachment to the skin of a patient. It has elongate pick-up electrodes and energizing electrodes. The patch is used to monitor tissue impedance during the procedure and this is compared to a baseline level.

A disadvantage of such devices is that it can be difficult to maintain good electrical contact with the skin of the patient. Also, the location of the patch makes it more difficult to carry out palpation or visual inspection. A similar problem arises with the other prior art detectors. In order to address this problem, United States Patent No. 6,408,204 proposes an apparatus that may be positioned so as not to interfere with palpation or visual inspection. An energy source and a receiver are positioned between a first layer of high dielectric material and a second layer of low dielectric material. If extravasation occurs, as noted above, there is a change in the bulk electrical properties of the tissue. The receiver measures a signal resulting from

changes in the energy supplied to the tissue by the energy source.

According to the present invention there is provided a method of detecting extravasation during the infusion of a substance into a blood vessel comprising the step of detecting a change in the flow velocity within the blood vessel downstream of the point of infusion.

Thus, unlike the prior art techniques the present invention is not based on volume changes of tissue induced by extravasation, but on direct monitoring of the increased flow velocity within the blood vessel induced by the infusion. The lack of a velocity increase indicates that extravasation has occurred. Since the increase in flow velocity should occur almost immediately infusion commences, this method gives the operator an early warning if a problem occurs.

It can be difficult to precisely locate the blood vessel downstream of the point of infusion. Therefore in a preferred embodiment of the invention, an array of detector elements is arranged substantially transverse to the direction of flow of the blood vessel so that at least one element of the array will be located over the vessel. The signal from each detector element varies depending on whether the detector element is located over the blood vessel or over ordinary tissue. This has the advantage that the accuracy with which the detector must be placed is reduced. At least one element of the array will be located over the vessel, and so it is not necessary to precisely locate the blood vessel at the point of measurement prior to commencing the measurement. Instead, a change in flow velocity will be detected by whichever element or elements of the array are located over the blood vessel.

The change in flow velocity could be detected by measuring the flow velocity at a single point downstream of the point of infusion. In one preferred embodiment

however, the flow velocity within the blood vessel is measured at a plurality of points spaced apart along the extent of the vessel and positioned downstream of the point of infusion. This has the advantage of enabling a user to determine the approximate position within the vessel at which extravasation has occurred.

Although the method of the invention is applicable to any infusion of a substance that causes a detectable increase in blood flow velocity, it is of particular use where the infusion is at a high rate where the greatest risk of extravasation occurs. The rates of infusion may be over 5ml/s and sometimes over 10ml/s. Thus, the invention is of particular application to venous infusions such as contrast agents. The invention may therefore be incorporated as part of a process of generating a medical image.

The invention could just be applied when the infusion is commenced, or when the rate of infusion is increased, these being times when a problem is most likely to occur. However, as noted above, extravasation may be caused by patient movement and so preferably blood flow velocity changes are continuously or repeatedly monitored during the procedure.

In a simple form of the invention, a change in velocity may be noted by an operator who can then stop the infusion. However, it is preferable that the method further comprises the provision of a notification that extravasation has occurred and most preferably there may be automatic shutdown of the infusion in response to the detection of extravasation.

The invention also extends to an apparatus for detecting extravasation during the infusion of a substance into a blood vessel comprising a detector for detecting a change in the flow velocity within the blood vessel downstream of the point of infusion, the apparatus being arranged to provide an output signal when extravasation occurs.

The output signal may be a notification such as an alarm. More preferably it comprises a control signal to control the infusion. The output signal need not be "high" to indicate extravasation. Indeed, it may be preferable to use a fail-safe system in which a "high" output indicates an increased velocity and therefore that extravasation has not occurred. Thus, if the "high" signal is lost, either due to extravasation or equipment failure, the infusion can be stopped.

Any suitable method of detecting flow velocity may be applied, but it is believed that the most effective technique is ultrasound Doppler. Thus, the detector is preferably an ultrasound Doppler probe which may consist of a single transducer element and more preferably consists of an array of individual transducer elements adapted to be arranged substantially transverse to the direction of flow of the blood vessel so that the position of the blood vessel can be detected and/or the change in flow velocity in the blood vessel can be detected without first knowing the precise location of the blood vessel. In another embodiment of the invention, a plurality of individual transducer elements (or arrays of transducer elements) are spaced apart along the direction of flow of the blood vessel to form an array (or a two dimensional array) of transducer elements which can track the direction of a blood vessel in use. The probe may be located against the skin of a patient proximate to a vein into which the infusion is being made and downstream of the infusion site. The probe is preferably fixed to the patient's skin using an adhesive. In accordance with standard practice, a coupling medium (ultrasound gel) should preferably be applied to the patient's skin under the transducer elements.

The probe may be connected to a display unit in the conventional manner in which case increases in flow velocity will be visible conventionally as bright

patches on the display. These may be detected using conventional techniques, for example by comparing pixel brightness in a preselected region on the display. Alternatively, the display can be dispensed with and a direct indication of velocity produced. Normally the velocity of the infusion will be significantly higher than any other velocity of flow in the region concerned and so precise measurement is not required.

An analogue signal voltage which is generally proportional to the detected flow velocity may be provided as the output from the detector. This could be used to drive a simply calibrated meter. Additionally or alternatively the voltage may be compared to a threshold voltage such that when this is exceeded an indication is provided that extravasation has (or has not) occurred.

In many applications it may be preferable to use a digital system. If the output from the detector is not in digital form then it may be converted using a conventional analogue-digital converter. The output may then be fed to a processor such as a personal computer or a custom processor incorporated into the apparatus.

Regardless of the system used, an output control signal may then be provided to control the infusion pump. In a simple form this may operate a relay to cut the power to the pump, or if the pump is computer controlled it may be a digital control signal. Alternatively, a valve arrangement may be used to prevent flow to the vein.

It will be appreciated that the invention extends to a system for giving an infusion comprising an infusion pump arranged to infuse a substance into a blood vessel and an extravasation detector according to the apparatus defined above wherein the detector apparatus is arranged to control the infusion pump. The invention also extends to a method of giving such an infusion comprising the use of such apparatus.

Certain embodiments of the invention will now be

described, by way of example only, and with reference to the accompanying drawings in which:-

Figure 1 is a schematic view of a first embodiment of the invention;

Figure 2 is a schematic view of a modified version of the Figure 1 embodiment;

Figure 3 is a schematic view of an alternative embodiment of the invention;

Figure 4 is a diagram illustrating the use of the embodiment of Figure 1 where no extravasation has occurred; and

Figure 5 is a diagram illustrating the use of the embodiment of Figure 1 where extravasation has occurred.

In Figure 1 a patient's arm is illustrated at 1. A contrast medium is being infused into the patient from a pump 10. The pump is controlled by an electronic pump controller 11, which varies the pump speed as required and starts and stops it.

The contrast medium flows via flexible tube 12 to cannula arrangement 13, which comprises a connector for connection to the flexible tube, and a fine bore tube 14 which has been inserted into a vein in the known manner.

Ultrasound Doppler probe 2 is placed above the same vein and a convenient distance downstream so as to be clear of the infusion site. The Doppler probe consists of a single transducer element 2 which in use is placed at an angle to the vein to create and detect a Doppler shift from the flow. The probe 2 is connected via a flexible lead 3 to a processor unit 4. This converts the output from the probe 2 into a form that may be displayed as an image on display unit 5 in the conventional manner. In addition it provides a digital signal proportional to the flow velocity detected by the probe 2. This value is then also displayed on display 5. In addition, the unit 4 determines whether the velocity corresponds to a flow of contrast medium along the vein.

When the infusion is to commence, the operator sets

the desired infusion rate by inputting it into the pump controller 11 and then inputs a start signal into unit 4 by pressing a key (not shown). This in turn transmits a start signal to the pump controller 11 which energises the pump and causes it to run at the desired speed.

The processor unit 4 then checks the flow velocity as described above. If it is not satisfactory within a pre-determined short period of time the infusion will be stopped.

As may be seen from Figure 4, if the cannula is properly sited and the contrast medium flows as desired along the vein, this will lead to an increased flow velocity in the vein. This is detected by ultrasound probe 2 and, as described above, the processor unit 4 will therefore determine that no extravasation has occurred. It will therefore continue to send a "pump" signal to pump controller 11.

Figure 5 shows the situation that might occur when there is extravasation of contrast medium and consequently no flow in the vein. This results in a low or zero velocity output from the probe 2 from which the processor unit 4 determines that extravasation has occurred. It therefore immediately sends a "stop" signal to pump controller 11 which stops pump 10. In this way, the infusion may be stopped almost as soon as the problem occurs with the result that only a small amount of contrast medium enters the tissue surrounding the vein.

Although the situation illustrated in Fig 5 is most likely to occur when the infusion commences, the processor unit constantly monitors the output from the probe 2 throughout the infusion procedure and can stop the pump at any time.

Figure 2 shows a modified version of the embodiment of Figure 1 in which an array of individual transducer elements is provided and in use is arranged on the patient's arm substantially transverse to the direction

of flow of the vein (i.e. normal to the plane of Figure 1). Thus, the precise location of the vein need not be known prior to measurement. The signal from each transducer varies depending upon whether it is situated above tissue or above a vein (a Doppler shift will be detected if the transducer is directed towards moving fluid such as blood flowing in a vein). By monitoring the signals received by each transducer element in the array, the location of the vein can be detected. Once it has been determined which transducer elements are situated over the vein, those transducer elements can be monitored for changes in the flow velocity within the vein and hence it can be determined whether or not extravasation has occurred.

Figure 3 shows an alternative embodiment of the invention in which the Doppler probe 2 consists of a number of individual transducer elements 2a-2f. These transducer elements are spaced at regular intervals to form an array which can be placed on a patient's arm downstream of cannula arrangement 13 to extend along the vein in the flow direction.

In a modified version of the embodiment of Figure 3 (not illustrated), a two dimensional array of individual transducer elements is provided such that the elements extend both substantially transverse and substantially parallel to the direction of flow of the vein. In this way, the precise location of the vein need not be known at each measurement point before commencing measurement. Instead, as previously described, it is determined which elements of the array are situated over the vein and those elements are monitored for changes in the flow velocity within the vein. Each such transducer element measures the flow rate at a respective point in the vein and this information is provided to the processor unit 4. The processor can therefore determine the approximate position along the vein at which extravasation has occurred. Thus for example, if the

flow velocity measured at elements 2a to 2c corresponds to the flow velocity of the contrast medium within the vein but the velocity measured at element 2d does not, the processor determines that extravasation has occurred in the region of transducer element 2d. The remaining parts shown in Figure 3 correspond to those shown in Figure 1 and so are not described again here.

Claims

1. A method of detecting extravasation during the infusion of a substance into a blood vessel comprising the step of detecting a change in the flow velocity within the blood vessel downstream of the point of infusion.

2. A method as claimed in claim 1, wherein an array of detector elements is arranged substantially transverse to the direction of flow of the blood vessel downstream of the point of infusion so as to locate at least one said detector element over the vessel.

3. A method as claimed in claim 1 or 2, wherein the flow velocity within the blood vessel is measured at a plurality of points spaced apart along the vessel and downstream of the point of infusion.

4. A method as claimed in claim 1, 2 or 3, wherein the infusion is a venous infusion of a contrast agent.

5. A method as claimed in any preceding claim, wherein flow velocity changes are continuously or repeatedly monitored during the procedure.

6. A method as claimed in any preceding claim, further comprising the provision of a notification that extravasation has occurred.

7. A method as claimed in any preceding claim, further comprising the automatic shutdown of the infusion in response to the detection of extravasation.

8. An apparatus for detecting extravasation during the infusion of a substance into a blood vessel

comprising a detector for detecting a change in the flow velocity within the blood vessel downstream of the point of infusion, the apparatus being arranged to provide an output signal when extravasation occurs.

9. An apparatus as claimed in claim 8, wherein the detector comprises an array of detector elements that may be arranged substantially transverse to the direction of flow of the blood vessel so as to locate at least one said detector element over the vessel.

10. An apparatus as claimed in claim 8 or 9, the detector being adapted to measure the flow velocity within the blood vessel at a plurality of points spaced apart along the vessel and downstream of the point of infusion.

11. An apparatus as claimed in claim 8, 9 or 10, wherein the output signal is a notification, alarm or the like.

12. An apparatus as claimed in any of claims 8 to 11, wherein the output signal is a control signal to control the infusion.

13. An apparatus as claimed in any of claims 8 to 12, or a method as claimed in any of claims 1 to 7, wherein the detector is an ultrasound Doppler probe.

14. An apparatus or method as claimed in claim 2 or 9, wherein the detector elements are ultrasound transducer elements.

15. A system for giving an infusion comprising an infusion pump arranged to infuse a substance into a blood vessel and an extravasation detector according to

any of claims 8 to 14, wherein the detector apparatus is arranged to control the infusion pump.

16. A method of detecting extravasation substantially as herein described with reference to Figures 1, 4 and 5 of the accompanying drawings.

17. A method of detecting extravasation substantially as herein described with reference to Figures 2, 4 and 5 of the accompanying drawings.

18. A method of detecting extravasation substantially as herein described with reference to Figures 3 to 5 of the accompanying drawings.

19. An apparatus for detecting extravasation substantially as herein described with reference to Figures 1, 4 and 5 of the accompanying drawings.

20. An apparatus for detecting extravasation substantially as herein described with reference to Figures 2, 4 and 5 of the accompanying drawings.

21. An apparatus for detecting extravasation substantially as herein described with reference to Figures 3 to 5 of the accompanying drawings.

22. A system for giving an infusion substantially as herein described with reference to Figures 1, 4 and 5 of the accompanying drawings.

23. A system for giving an infusion substantially as herein described with reference to Figures 2, 4 and 5 of the accompanying drawings.

24. A system for giving an infusion substantially as herein described with reference to Figures 3 to 5 of

the accompanying drawings.

5

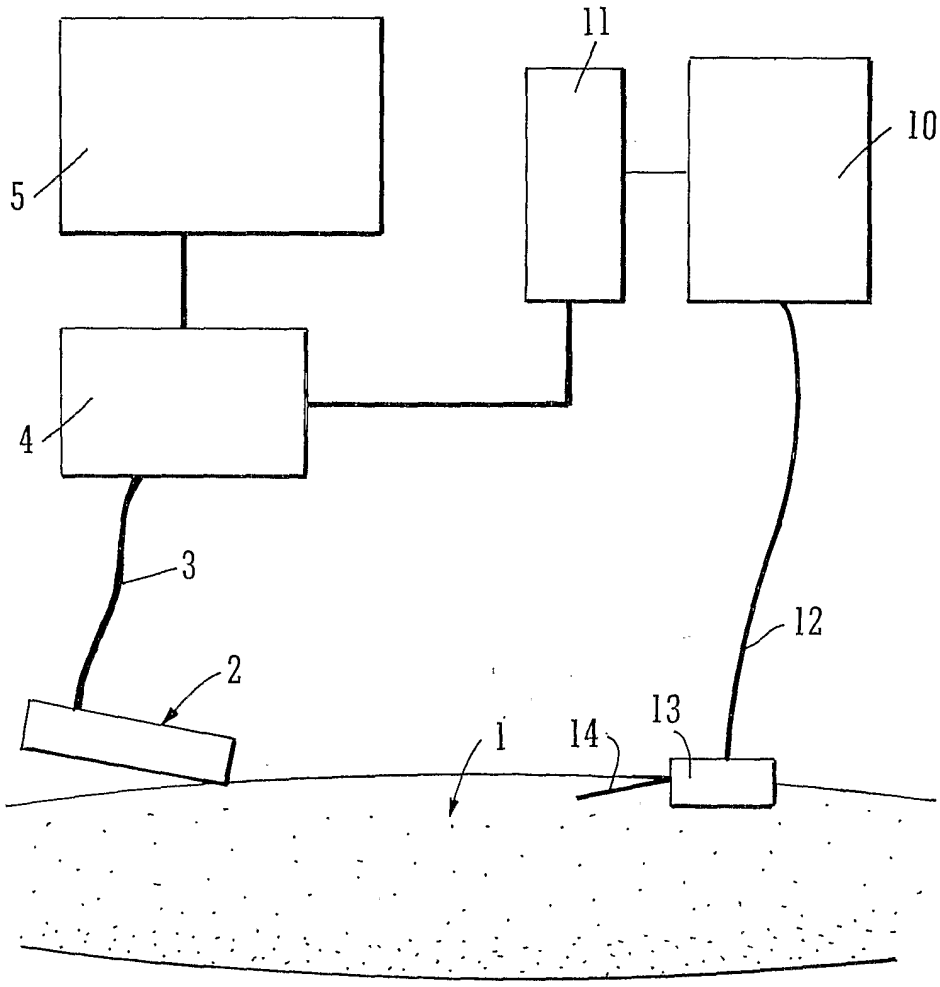


FIG. 1

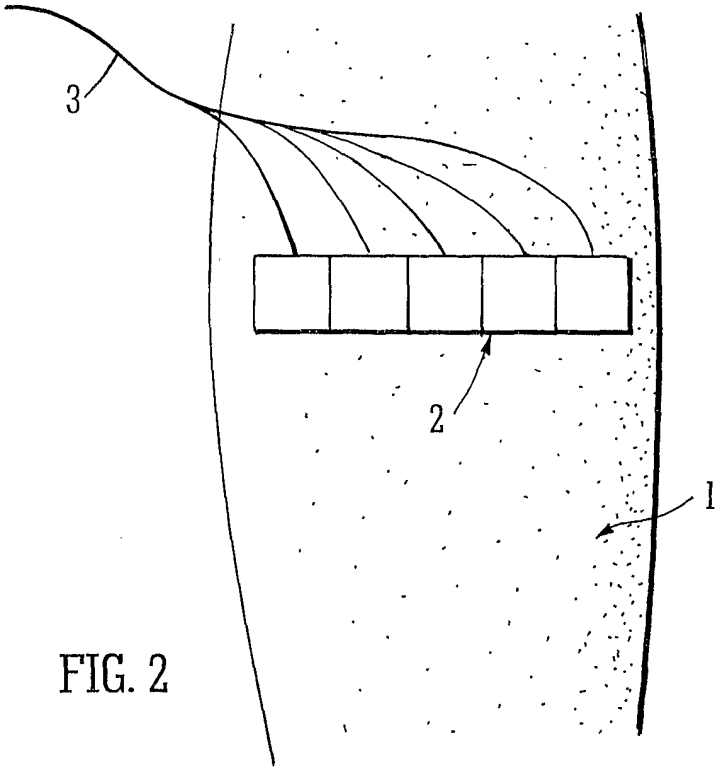


FIG. 2

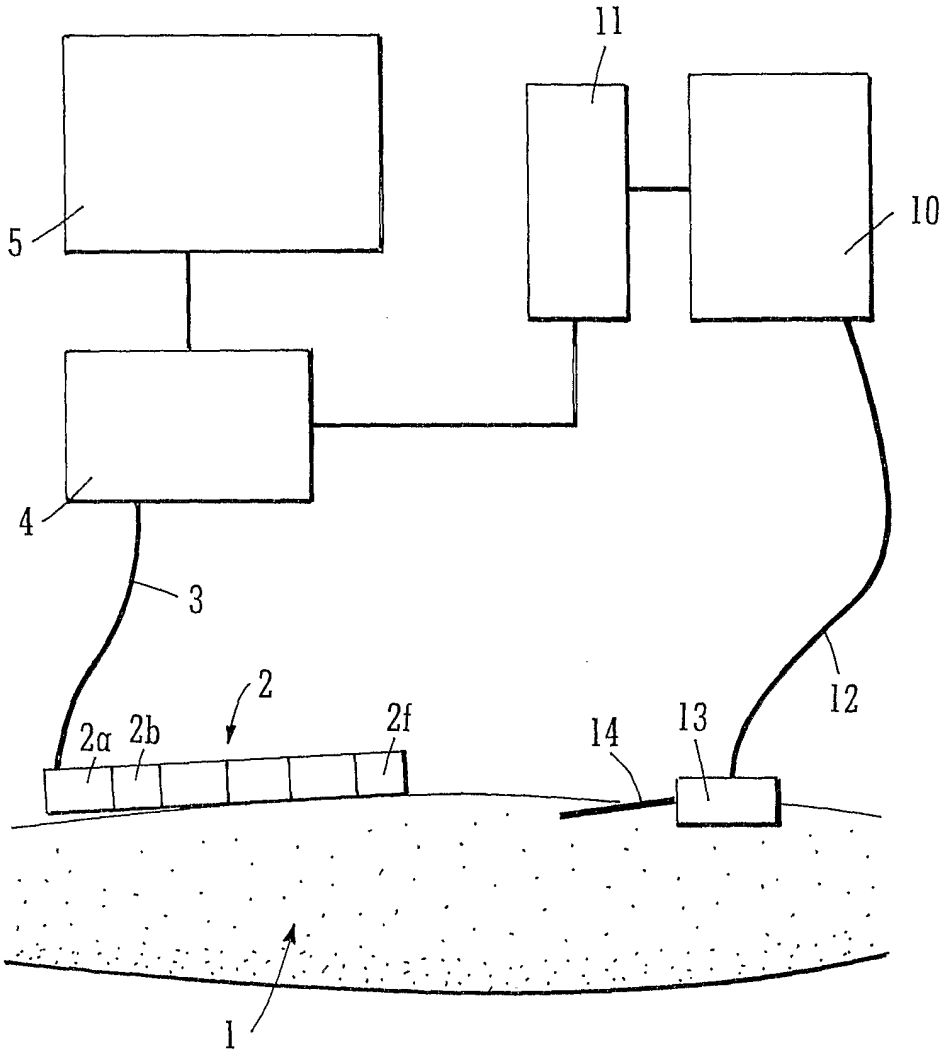


FIG. 3

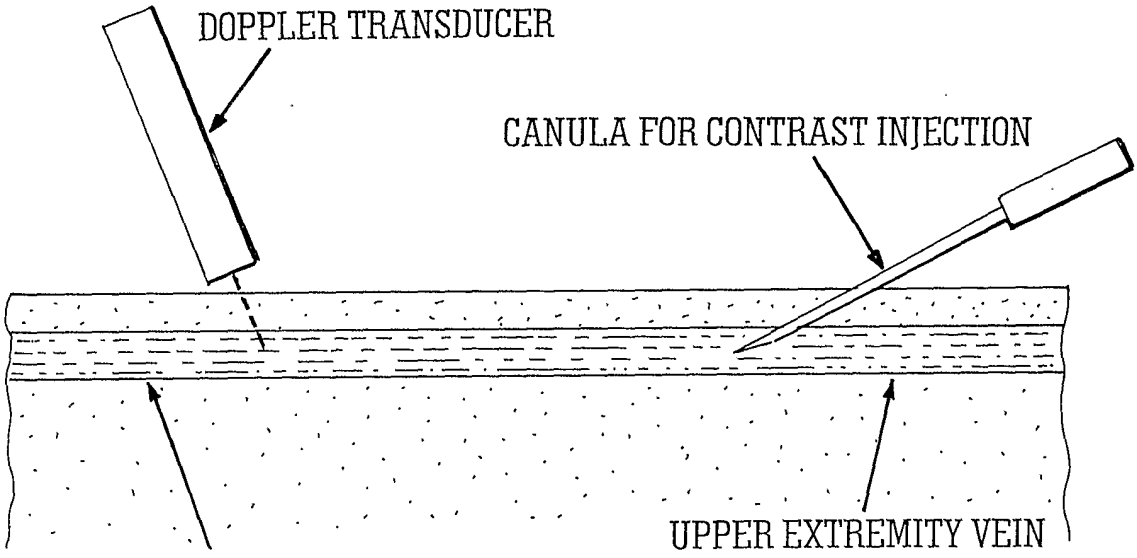

DOPPLER TRANSDUCER
CANULA FOR CONTRAST INJECTION
UPPER EXTREMITY VEIN
INCREASED FLOW IN THE VEIN DURING NORMAL CONTRAST INJECTION DETECTED BY DOPPLER TRANSDUCER

FIG. 4

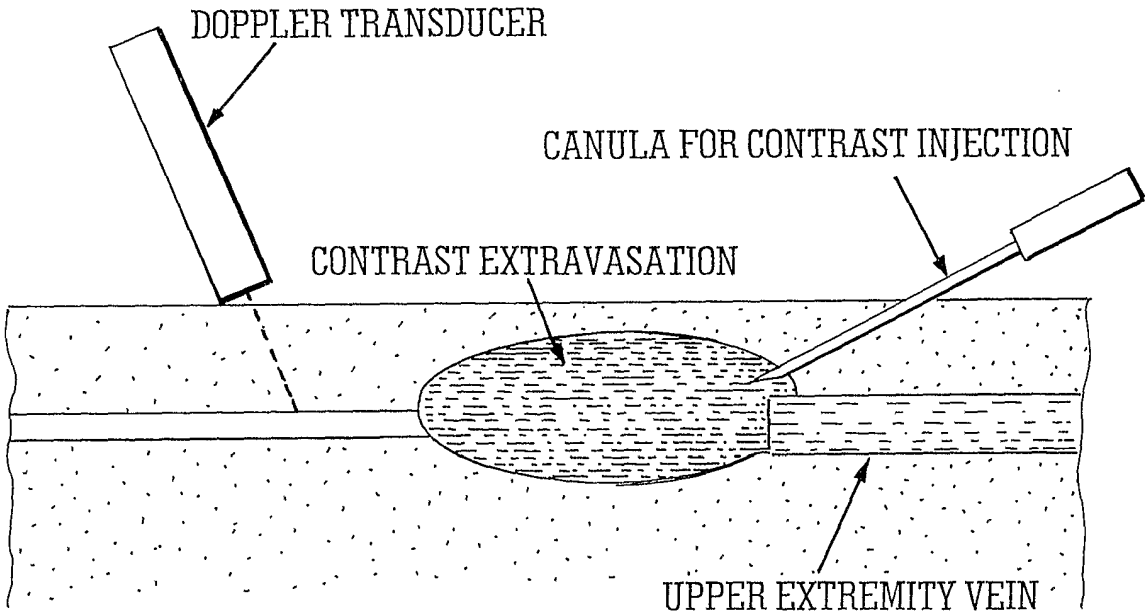

DOPPLER TRANSDUCER
CANULA FOR CONTRAST INJECTION
CONTRAST EXTRAVASATION
UPPER EXTREMITY VEIN
NO FLOW IN THE VEIN DUE TO EXTRA-VASATION DETECTED BY DOPPLER TRANSDUCER. INFUSION THEN ABORTED BY OPERATOR

FIG. 5

INTERNATIONAL SEARCH REPORT

PCT/GB 03/05269

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61M5/168

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61M A61B

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

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

EPO-Internal, PAJ, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2002/173725 A1 (ROCK JOSEPH E ET AL) 21 November 2002 (2002-11-21) paragraph '0020! - paragraph '0021! paragraph '0024! paragraph '0026! - paragraph '0027! paragraph '0031! - paragraph '0033!; figures 1,4,5A-6	8-10,13, 14 11,12,15
Y	US 6 425 878 B1 (SHEKALIM AVRAHARN) 30 July 2002 (2002-07-30) paragraph '0030! - paragraph '0032! paragraph '0038!; figures 1,5,6	11,12,15
A	US 2002/016547 A1 (BANG JI HOON ET AL) 7 February 2002 (2002-02-07)	

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 March 2004	11/03/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Michels, N

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/GB 03/05269

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 15074 A (RALSTON WILLIAM H ;MALLINCKRODT INC (US)) 1 April 1999 (1999-04-01)	
A	US 5 233 994 A (SHMULEWITZ ASCHER) 10 August 1993 (1993-08-10)	

INTERNATIONAL SEARCH REPORT

PCT/GB 03/05269

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. [X] Claims Nos.: 1-7, 16-24
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 1-7: Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy;
Claims 16-24: Rule 6.2(a) PCT - Reference to drawings

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

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

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/GB 03/05269

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002173725 A1	21-11-2002	CN 1463194 T	24-12-2003
		WO 02094373 A1	28-11-2002
US 6425878 B1	30-07-2002	WO 02070044 A1	12-09-2002
US 2002016547 A1	07-02-2002	KR 2002005110 A	17-01-2002
		JP 2002065674 A	05-03-2002
WO 9915074 A	01-04-1999	AU 9569898 A	12-04-1999
		CA 2301209 A1	01-04-1999
		EP 1017311 A1	12-07-2000
		JP 2001517469 T	09-10-2001
		WO 9915074 A1	01-04-1999
US 5233994 A	10-08-1993	NONE	