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(54) **Title**: COMBINED FLOW DIRECTED INTRAARTERIAL MICROCATHETER FOR THE INFUSION OF HYPEREMIC AGENT AND CONCOMITANT PRESSURE MEASUREMENTS FOR DIAGNOSTIC PURPOSES

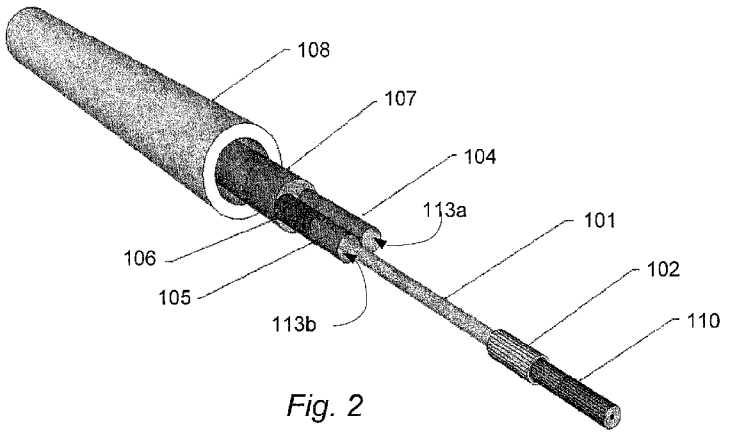

Fig. 2

(57) **Abstract**: The invention relates to a method and an infusion system for determining the blood flow and pressure in an individual artery of a patient, wherein the method comprises the steps of positioning a combined infusion catheter and pressure sensor mounted at a distal portion of a guide wire at a distal position in the investigated artery, positioning the combined catheter in an artery in such a way that the distal end of the infusion catheter is proximal to the distal pressure sensor, measuring the pressure with the sensor at rest, infusing hyperemic agent with a known infusion rate and known concentration into an artery by the infusion catheter, measuring the pressure by the pressure sensor during infusion into the blood stream by a hyperemic agent, and calculating the arterial blood flow by a formula based on the known and measured quantities. In an extended version, the method comprises of steps for relating the calculated blood flow value to related normal flow values, or related FFR values, or a related flow resistance.

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Combined flow directed intraarterial microcatheter for the infusion of hyperemic agent and concomitant pressure measurements for diagnostic purposes.

Field of the invention

The present invention relates to a microcatheter and to a diagnostic method for in vivo measurements of blood pressure in vessels, and in particular to blood pressure measurements in individual arteries by means of a pressure sensitive sensor mounted on a guide wire while simultenously using an infusion catheter for continuous infusion of a vasodilator agent in the form of diagnostic fluid with a specific infusion range.

Background

Coronary pressure measurements have recently received renewed interest, partly due to technical innovations (such as the development of pressure-measuring angioplasty guidewire) and theoretical progress (such as the concept of pressure derived fractional flow reserve).

Fractional flow reserve (FFR) is the ratio of maximal flow in the myocardial region affected by a stenosis to maximal flow in that same region if the stenosis were absent. With the development of pressure guidewires, fractional flow reserve can be calculated rapidly and safely in the diagnostic and interventional setting. It has been shown that pressure derived FFR can be used as a surrogate for a stress test for on-line clinical decision making in the catheterization laboratory. In the heart, values < 0.75 are most often associated with exercise-inducible myocardial ischemia, while values > 0.75 exclude objective signs of ischemia during exercise. The accuracy of FFR for that purpose is approximately 95% which is higher than that of any single non-invasive test taken alone. It is further interesting to note that it has been shown that the prognosis is favourable in patients in whom a planned angioplasty was deferred on the basis of a myocardial fractional flow reserve

> 0.75. After regular balloon angioplasty, the combination of a good angiographic result and a FFR > 0.90 is associated with an event rate during a 2-year follow-up, which is similar to that after stenting. After stent implantation, FFR should normalize. A FFR < 0.94 after stent implantation appears to be as accurate as intravascular ultrasound (IVUS) to detect stent malposition. Furthermore, a multicentre registry study has also recently shown that in patients with multivessel coronary artery disease FFR can be used as a reliable and lesion-specific index of stenosis severity (FAME study) [1]. Thus, pressure derived FFR is a well-validated index of stenosis severity that has evolved from a physiological index to a clinical tool.

Maximal coronary hyperaemia is beneficial in producing accurate, reproducible measurements. In a normal artery there should be no pressure gradient between the aorta and the distal artery resulting in a FFR value of 1. Pullback of the pressure wire can be used to determine which of two or more serial stenoses is more functionally significant. As stated, the achievement of maximal hyperaemia is beneficial for the accurate determination of FFR. Otherwise the pressure gradient across a stenosis will be underestimated. As may be appreciated, maximum distal pressure (DPmax) and the distal coronary pressure (Pd) are directly proportional to the arterial pressure (Pa) but only in conditions where maximal hyperemia has been secured. Therefore, changes in systemic blood pressure during maximum hyperemia are accompanied by proportional changes in DPmax. If maximum hyperemia is not completely achieved, patients may be undertreated.

The available pharmacological agents for inducing maximal coronary hyperaemia (e.g. papaverine, intracoronary adenosine, intravenous adenosine, intracoronary ATP, and intravenous ATP) can be given by intracoronary injection (ic) or intravenous infusion (iv). When using intracoronary adenosine, some specific pitfalls are present which may lead to

underestimation of the maximum gradient and overestimation of FFR. These have been mentioned in WO11018468

The available pharmacological agents for inducing maximal renal hyperaemia are papaverine [2] whereas adenosine induces vasoconstriction and UTP induces vasodilation[3]

As stated there is no definite difference in the achievement of hyperemia of using currently employed used drugs (adenosine, NO, ATP) via IV, IC or bolus infusion. For adenosine, however, the iv infusion can cause more systemic side effects and also take longer in order to achieve steady state which is required in order to make a correct FFR measurement thus prolonging procedure time. Also the concentration of the individual drugs required to produce close to maximal hyperemia has to be higher with systemic infusion in comparison to local infusion.

Optimizing delivery of a diagnostic hyperemic agent to a site of artery stenosis while reducing or even avoiding severe systemic side effects and simultaneously measure fractional flow reserve (FFR) would be an advantage in every FFR investigation and also improve ease of use.

U.S. Patent Application No. US 20070078352 is directed to a system for measuring coronary flow reserve (CFR), wherein a known amount of saline is injected as a bolus and is this bolus is used for measurements of blood flow (CFR) by continuous thermodilution. This document describes a catheter that has side holes which are not optimal for drug delivery and can only be used for iv hyperemic agent infusion in order to perform both FFR and CFR measurements. The infusion rate range by which this catheter allows for IC infusion of saline is not disclosed.

The use of short-acting intracoronary vasodilators like papaverine or adenosine is attractive because no venous line or sheath is necessary and the measurements can be performed quickly and repeated in short intervals if desired as long as the infusion catheter is placed below the proximal pressure sensor. This bypasses the problem of not being able to perform a pullback manoeuvre of the distal pressure wire in cases of multiple stenoses in the same artery.

The industrial development of catheters have tended toward smaller-diameter, yet more flexible catheters and have shown that use of these catheters is relatively safe, allowing angiography to be performed on an outpatient basis. Five-French catheters can tolerate pressures up to and above 1000 psi and deliver at 20-25 ml/sec., however it has previously been established that tapering end holes and having variably-sized side holes produces a "cloud effect" in comparison to the near laminar flow produced in catheters without side holes. Also, for all pressure wire studies, it is important not to use a guide catheter that is too large for the ostium of the artery as this may cause pressure damping to occur. This can be recognized by the presence of a "ventricularized" aortic pressure tracing. Thus, it remains a problem to optimize the flow, effect accurate delivery of diagnostic hyperemic agents to a site of coronary artery stenosis and to simultaneously measure coronary fractional flow reserve (FFR) without causing severe side effects and without having to switch off the infusion temporarily in every FFR investigation resulting in FFR in only a suboptimal hyperemic plateau time in some patients because optimal hyperemic plateau time may vary from patient to patient after stopping the infusion through the guiding catheter
The diagnostic tool fractional Flow Reserve (FFR) helps physicians to decide whether to intervene on a stenosis or not. This stenosis may e.g. be a coronary, aortic,pulmonary, renal, or leg artery stenosis.

For example, when a renal arterial stenosis is identified on an arteriogram, the intraarterial systemic pressure can be measured continuously with a transducer and a miniaturized pressure-gradient wire system (PressureWire; St. Jude Medical or Volcano combo wire). Pressures can be recorded using a fiber-optic pressure sensor located laterally and 3 cm from the distal end. The basic principle is that the element modulates an optical reflection with pressure-induced elastic movements. This pressure wire thus replaces a standard 0.018-inch guide wire. After advancing a 4 to 7-F guiding catheter from the femoral artery to the ostium of the renal artery, there is an introduction of the "coronary" 0.014-inch wire into the guiding catheter and then it is moved to the ostium of the stenosis. Also, dilation equipment can then be inserted through the guiding catheter and across the stenosis, leaving the wire in place. The pressure gradient is thus measured with the wire at rest.

However, it would desirable to use an infusion of a suitable agent in order to perfuse the kidney tissue.

Also, in the context of other types of stenosis, it would be desirable to perform a local intraarterial infusion to the specific artery under investigation, resulting in less side effects.

Summary

Disclosed herein is a method for using intraarterial (e.g coronary, renal, leg, etc.) infusion of a hyperemic agent which elevates arterial blood flow in individual arteries and therefore lowers local artery pressure distally in the artery in comparison to proximal pressure in the aorta (FFR). The induction of a pressure difference (index) is achieved by intraarterial infusion of a vasodilator agent such as adenosine, papaverine, adenosine-tri-phosphate, dopamine, nitric oxide or uridine triphosphate(UTP).

To this end, disclosed herein is a catheter system, e.g. a flow-directed catheter system, for carrying out such an FFR method, where the catheter comprises a intraarterial artery Infusion catheter for hyperemic agent and an FFR catheter in the same catheter. In some embodiments, the infusion catheter comprises a tubular member having a circumferential side wall and an opening at its distal end so for discharging a vasodilator agent. In some embodiments, the circumferential side wall is impermeable to the vasodilator agent and, in particular, does not comprise any openings or other outlets that would allow the vasodilator agent to be discharged. Hence, in some embodiments, the only opening for discharging the vasodilator agent is adapted to discharge the vasodilator agent in a longitudinal direction of the tubular member, thereby improving the drug delivery.

In some embodiments the aortic pressure signal is recorded proximal to the infusion catheter so pressure measurements do not have to be interrupted for administration of the drug. Therefore, the drug could then be administered continuously without using the stopcock to register Pa again, avoiding care should be taken to be sure that the correct value is taken for Pa at the correct moment (peak hyperemia, minimal distal pressure) by checking the FFR screen for the lowest possible FFR and highest possible CFR.
Also a pullback curve is possible with this invention.

In some embodiments, the catheter comprises a first lumen for infusing the vasodilator agent, and a second lumen for advancing a wire-mounted pressure sensor. For example, the catheter may be embodied as a double-lumen catheter. The separate lumen allow maximal drug delivery to the coronary artery and permit accurate measurements of the aortic pressure.. If a guiding catheter with side holes is used, an unpredictable part of the hyperemic drug will be spilled in the ascending aorta. As a consequence, the measurements may be unreliable, as mean arterial pressure may be underestimated and intracoronary FFR overestimated.

According to one aspect, disclosed herein is a kit comprising an intracoronary infusion and FFR catheter disclosed herein and a pre-specified amount of uridine triphosphate (with or without Nitric oxide and/or in combination with one or more other medicaments) or another vasodilator agent.

Embodiments of the method described herein enhance the medical usefulness of blood flow measurements, and in particular provide absolute values of blood flow and pressure measured through application of the continuous intracoronary infusion of UTP in a patient who suffers from a coronary disease that can be related to normal blood flow values for this particular patient.

According to one aspect, disclosed herein is a method of measuring coronary blood flow, the method comprising the following steps: positioning of a guide-wire mounted infusion lumen and pressure sensor at a distal position in a coronary artery of a patient, in such a way that the positioning of an infusion catheter in the coronary artery is proximally (upstream) of the distal pressure sensor, but distal to the proximal pressure sensor, measurement of resting pressure by both a proximal and a distal pressure sensor to get a baseline FFR value of 1, hereafter initiate a continuous infusion of a hyperemic diagnostic agent such as UTP with known infusion rates through the infusion catheter, and calculation of absolute coronary proximal and distal pressure according to a calculated index on the known and measured quantities. Embodiments of the method comprises the preferred induction of a steady state hyperemia with hyperemic agents in the patient, such that the obtained absolute coronary flow is the maximum absolute coronary flow (post occlusion hyperemia).

In one embodiment, the blood flow increase due to the infusion of a hyperemic agent is measured by the same combined guide wire mounted

pressure sensor as is used for infusing the hyperemic agent. The actual guide wire is placed in the pressure sensor lumen. The positioning of the pressure sensor guide wire and infusion catheter is usually accomplished through a guide catheter that has been inserted into the patient's aorta, and the method can be supplemented with a corresponding step.

In some embodiments, the method comprises the following steps: positioning of a guide wire mounted pressure sensor at a distal position in a coronary artery of a patient, positioning the infusion lumen in the coronary artery such that the distal end of the infusion catheter is located proximally (upstream) of the pressure sensor, inducting steady state hyperemia by intracoronary infusion of hyperemic agent through the intracoronary mounted catheter in the patient, measuring the blood pressure difference by the two pressure sensors, calculation of FFR index according to a formula based on the known and measured quantities, valued as a ratio of the measured hyperemic aortic pressure and the measured distal coronary pressure, and calculating a related FFR value. The method for calculating FFR values is disclosed in e.g. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJJ, Koolen JJ: Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. The New England Journal of Medicine 1996;334:1703-1708

In some embodiments, the method further comprises inducing a steady state hyperemia in the patient before and after hyperemia, and measurement is calculated so that the coronary blood flow is the maximum coronary blood flow. This may occur by infusing a hyperaemic agent in increasing concentration until the largest possible pressure drop across a stenotic vessel is observed in either the renal or coronary artery. The infusion can be in either continuous or bolus fashion.

In one embodiment, the sensor guide wire as well as the infusion catheter is introduced into the coronary artery via a guide catheter inserted into the patient's aorta, and the hyperemic aortic pressure is measured by a pressure transducer e.g. a pressure transducer connected to the guide catheter or a second pressure transducer connected to the sensor guide wire or to the infusion catheter. Optionally, the method can further include the following steps: positioning of a balloon arranged on a catheter in the coronary artery such that the balloon is positioned proximally (upstream) of the guide wire moulted pressure sensor, inflating the balloon to create total occlusion of the coronary artery, and measuring the coronary wedge pressure by the pressure sensor. The balloon is then deflated, and - like in the previous method - the FFR can be measured by the same guide wire after the angioplasty by the mounted sensors as is used for measurements prior to the angioplasty.

In some embodiments the method further comprises the step of retracting the first pressure sensor along a vessel in case of either uni- and/or multi-vessel artery disease; and measuring the pressure at at least three locations. This operation may be referred to as a pull back maneuver and performed e.g. as described in Pressure-Derived Fractional Flow Reserve to Assess Serial Epicardial Stenoses theoretical Basis and Animal Validation by Bernard De Bruyne et al,circulation,2000. For two stenoses in series, equations are known in the art to predict FFR (FFRpred) of each stenosis separately (ie, as if the other one were removed) from arterial pressure (Pa), pressure between the 2 stenoses (Pm), distal coronary pressure (Pd), and coronary occlusive pressure (Pw). The interaction between 2 stenoses is such that FFR of each lesion separately cannot be calculated by the equation for isolated stenoses (Pd/Pa during hyperemia) applied to each separately but can be predicted by more complete equations taking into account Pa, and Pd.

Advantages of using a micro catheter for the FFR diagnostic method in patients with coronary artery disease include

- in some subsets of patients (left ventricular hypertrophy, post-infarction) or with arrhythmia, this particular pharmacological stimulus and route of administration exhaust myocardial resistance rendering the method proper for many different kinds of cardiac problems
- outpatient catheterization is possible via the radial route enabling local coronary arteriography labs to do the procedure;
- the microcatheter secures ostial infusion instead of infusion into aorta which results in less systemic spill over;
- One catheter instead of two which reduces procedure time;
- Reduces risk of procedural problems, such as vasospasm and kinking that may prolong procedure time;
- Enables access through distal tortuous vessels and enhances crossability of the stenosis because infusion lumen is proximal to pressure transducer;
- Improvement in FFR which is easy to use and presents no side effects; this will help to establish FFR measurement as a standard and routine of care across a broader range of patients.

Use of adenosine versus UTP: The preferred hyperemic agent used today for inducing coronary hyperemia is the naturally occurring nucleoside adenosine. Although multiple studies have used intracoronary (IC) adenosine for the determination of FFR or coronary flow reserve (CFR), this method is now shown to be suboptimal for inducing maximal hyperemia. Also, adenosine cannot provide sufficient stable steady state hyperemia duration for the FFR measurements in diffuse or tandem lesions with the pullback method or CFR and index of microvascular resistance measurements with thermodilution[4]. Intravenous (IV) continuous adenosine infusion has also been validated as a standard method for the induction of coronary hyperemia for FFR measurements [5]. However, compared with the IC method, the IV method

takes longer, and it is associated with more systemic adverse effects. Furthermore, it is difficult to perform it with outpatient catheterization via the radial route because it requires additional central vascular access. Earlier studies have also established that in the coronary circulation of humans with coronary artery disease ATP=adenosine=papaverine for inducing maximal hyperemia [4] . An intracoronary bolus of ATP or adenosine (20 to 40 µg) induced a similar degree of hyperemia as in intracoronary bolus of 20 mg papaverine in humans. However, intracoronary ATP and adenosine often fail to induce true steady-state hyperemia. Also Jeremias et al [6] found a strong linear correlation between FFR measurements by IC and IV adenosine infusion methods and a high agreement between the 2 methods. However, in 8.3% of the patients, the FFR obtained by the IC adenosine bolus injection was higher than that obtained by the IV infusion method, which suggests a submaximal response in these patients to intravenous infusion. Although Casella et al.[7] have demonstrated previously that FFR decreased with increasing doses of IC adenosine bolus a recent method study by the inventor shows that blood flow during adenosine was not resembling post occlusion hyperemia as well as UTP, se e.g. co-pending US application no. 61/232518.

In conclusion, the IC continuous UTP infusion method by using either a guide wire or an IC microcatheter is safe and useful for inducing optimal coronary hyperemia without any additional procedure. There are no obvious contraindications or cautions to consider since it carries no side effects, is more receptor selective and has a faster and slightly longer steady state. It produces maximal hypermia which is close to post occlusion hyperemia thus more accurately estimating maximal coronary blood flow rendering a more precise FFR calculation. UTP can therefore be used in all patients following normal guidelines for FFR use.

The present invention relates to different aspects including the device described above and in the following, and corresponding methods, uses and/or product means, each yielding one or more of the benefits and advantages described in connection with one or more of the above-mentioned aspects, and each having one or more embodiments corresponding to the embodiments described in connection with one or more of the above-mentioned aspects and/or disclosed in the appended claims.

Brief description of the drawings

The above and/or additional objects, features and advantages of the present invention, will be further elucidated by the following illustrative and non-limiting detailed description of embodiments of the present invention, with reference to the appended drawings, wherein:

FIG. 1 schematically illustrates an example of a combined catheter with a single infusion and pressure wire lumina.

FIG. 2 schematically illustrates an example of a combined catheter with two different lumina, one for infusion and one for a pressure wire.

FIG. 3 schematically illustrates a kit comprising a hyperemic agent (e.g. UTP optionally with NO), a combined catheter and an infusion pump. FIG. 4 is a schematic illustration of a human with coronary artery disease in which there is inserted a combined catheter positioned in order to perform the steps included in the method described herein.

FIG 5.is a graph showing IC UTP versus IC adenosine in an equimolar concentration comparison during FFR measurements, illustrating the difference in maximal hyperemia by use of UTP in comparison to adenosine. As shown in Fig 5, UTP is more effective than adenosine with regard to lowing FFR in comparison to adenosine during continuous intracoronary infusion using a microcatheter.

Detailed description

In the following description, reference is made to the accompanying figures, which show by way of illustration how the invention may be practiced.

The maximal coronary blood flow in a coronary artery of a patient, who is in a state of maximal hyperemia with UTP infusion can be calculated from previously described equations, e.g. as mentioned in detail in US 2007/0078352. It is applicable in a situation where a patient is set in a state of hyperemia such that the incoming blood flow cannot be increased further pharmacologically.

The concept of fractional flow reserve (FFR) is thoroughly explained in several medical review articles. Therefore, the theoretical framework on which the methods described herein are based will not be described in detail. Nevertheless, how the different parameters actually are obtained will be thoroughly explained below.

The concept of inducing maximal hyperemia is desirable in order to get an accurate FFR because only at maximal hyperemia are pressure and flow comparative which is the basis for the calculations. The true maximal hyperemic response in a human subject can be achieved during post occlusion episodes, where several compound/metabolites that are discharged from the endothelial cells and myocardial cells participate in the response. Although pharmacological agents are used to simulate this response it is not the true maximum, as shown in FIG. 5 where it is clear that UTP is superior to adenosine for resembling post occlusion hyperemia as much as possible. For a pharmacological agent to be used for intracoronary infusion it needs to be: a powerful endogenous molecule with high receptor selectivity. It should also produce close to max. perfusion, have a rapid action but also a short duration and preferably lack side effects.

Having established the theoretical basis for the present invention, the practical details of a medical procedure and embodiments of a device for measuring blood flow in an individual coronary by application of the pressure sensor principle with continuous infusion of a hyperemic agent are now to be described with reference to figures 1-4.

FIG. 1 schematically illustrates an example of a combined catheter with a single infusion and pressure wire lumen. The catheter comprises an infusion catheter 100 having a single lumen with an open distal end 113 through which a hyperemic agent may be infused into a coronary. Hence, sufficient amounts of hyperaemic agent may be infused directly into the coronary; furthermore as the opening 113 is provided at the distal end face of the infusion catheter, and as the infusion catheter does not have any lateral openings, the hyperemic agent is infused in the longitudinal direction of the infusion catheter, thus allowing a more efficient infusion of hyperaemic agent. Furthermore, the catheter comprises a wire 101 movably arranged inside the infusion catheter 100 such that the wire can be caused to slide in its longitudinal direction in and out of the distal opening 113 of the infusion catheter. The wire 101 comprises a pressure sensor 102 at its distal end. Hence, advancing and/or retracting the wire 101 in and out of the infusion catheter allows a user to position the pressure sensor at different distances from the opening 113 of the infusion catheter, thus allowing pressure measurements at different distances from the position of infusion. This affords more sensitivity for the diagnostic technique.

The infusion catheter 100 may have a diameter sufficiently small to allow insertion into a coronary, e.g. no larger than 4 Fr or 1.35 mm in diameter. The infusion catheter may be sufficiently long to allow advancement of the catheter from a patient's groin to a patient's heart, e.g. the catheter may be 175 cm long.

The pressure sensor 102 may have a pressure range of -30 to +300 mmHg and a pressure accuracy of +/-1 mmHg plus +/-1% (<50 mmHg)+/-3% (>50 mmHg) and a frequency response of DC to 25 Hz

In use, the catheter is inserted into the coronary artery to be investigated, e.g. as illustrated in fig. 4. For example, the catheter may be introduced via a guide catheter inserted into either the radial or femoral artery. Once inserted, pressure measurements are performed with the guide-wire mounted sensor 102. A suitable guide wire mounted sensor is, for example, manufactured and sold by Volcano Corporation under the registered trademark Combowire® or the St. Jude Medical produced PressureWire® Sensor, and is described in the U.S. Pat. No. 6,343,514 and Re 35,648. The sensor signals representing the measured pressures may be processed in a device for monitoring, calculating and displaying the measured variables. For example, such a device is sold under the registered trademark RadiAnalyzer® by Radi Medical Systems AB, and is described in U.S. Pat. No. 6,565,514.

FIG. 2 schematically illustrates an example of a combined catheter with two different lumina, one for infusion and one for a pressure wire. The catheter comprises a double lumen microcatheter 107 providing two separate lumina 104 and 105, respectively. The two lumina function as an infusion lumen 104 and a pressure wire lumen 105, respectively, and have respective open ends 113a and 113b. The pressure wire lumen which may be made from a flexible material; in some embodiments it may be pre-shaped in a J-form so as to facilitate insertion.

The infusion lumen 104 has an open distal end 113a through which a hyperemic agent may be infused into a coronary artery as described in connection with fig. 1; furthermore the opening 113a is provided at the distal

end face of the infusion catheter, and the infusion catheter does not have any lateral openings.

Furthermore, the catheter comprises a wire 101 movably arranged inside the pressure wire lumen 105 such that the wire can be caused to slide in its longitudinal direction in an out the distal opening 113b of the pressure wire lumen 105. The wire 101 comprises a pressure sensor 102 at or proximal to its distal end, e.g. a pressure sensor as described in connection with fig. 1. Hence, advancing and/or retracting the wire 101 in and out of the pressure wire lumen 105 allows a user to position the pressure sensor at different distances from the opening 113b, thus allowing pressure measurements at different distances from the position of infusion. The pressure sensor 102 may be located close the distal end of the pressure wire thus leaving a dead end pressure wire 100. The end of the pressure wire may be made of and/or coated with an x-ray sensitive material so as to facilitate identification of the tip in x-ray images. It will be appreciated, however, that the pressure sensor may alternatively be positioned directly at the end of the wire. Hence, the distal pressure sensor is capable of being repositioned along the artery whereas the infusion catheter is a "dead end" on the combined catheter.

The catheter 107 may have a diameter sufficiently small to allow insertion into a coronary, e.g. no larger than 4 Fr or 1.35 mm in diameter. The infusion catheter may be sufficiently long to allow advancement of the catheter from a patient's groin to a patient's heart, e.g. the catheter may be 175 cm long. The pressure wire and infusion lumina may have the same or different diameter.

The catheter may comprise a second pressure sensor 106 positioned upstream of the opening 113a of the infusion lumen. The pressure sensor 105 may be of the same or a similar type of the distal pressure sensor 102. The pressure sensor 106 may be positioned on the pressure wire lumen as

shown in fig. 2, and/or on the infusion lumen and/or the combined catheter 107.

The catheter may further comprise or be used in combination with a guide catheter 108 facilitating insertion of the combined microcatheter 107.

Hence, fig. 2 shows an example of a combined catheter with two different lumina one for infusion and one for a pressure wire. The catheter is constructed in such a way that it consists of two separate lumina: a fixed infusion catheter lumen and a lumen with a movable pressure wire where the guide wire can pass through. This is created in such a way that one can slide the pressure wire in and out whereas the infusion catheter is stable.

Examples of catheters described herein do not have side holes. In the case of multiple stenosis in the same vessel, the sliding pressure wire will thus be able to extend itself across several lesion without affecting the infusion lumen. The guide wire is applied trough the pressure lumen.

Fig. 3 schematically shows a system for determining a blood flow/pressure index (FFR) using intracoronary infusion of a hyperemic agent into an individual artery of a patient, e.g. a human or mammal. The system comprises a combined catheter 301, e.g. as described in connection with fig. 1 or 2, an infusion pump 302 for injecting a hyperaemic agent such as UTP, NO or a combination thereof, and a signal processing device 303. As described above, the combined catheter comprises one or two pressure sensors (not explicitly shown). The measured pressure signals by the pressure sensor(s) are fed into the signal processing device for signal processing and calculation of the FFR and output and/or recording of the calculated FFR. To this end, the pressure wire and/or a sensor lumen 305 of the combined catheter is connected to the signal processing device. The

infusion pump is connected to an infusion catheter 304 of the combined catheter.

Use of the catheter of fig. 2 is illustrated in fig. 4 and will now be described in more detail. It will be understood that the method described in the following may also be performed with the catheter shown in fig. 1 and/r the system shown in fig. 3.

In use, when access to the artery of a patient has been obtained, an embodiment of the method described herein may begin with the introduction of a guide catheter 108 into the patient's aorta, as is well-known in the field. If needed, a conventional guide wire can be employed to facilitate the introduction of the guide catheter, as also is well-known in the field. The combined catheter 107 including the guide-wire mounted pressure sensor 102 is subsequently introduced into the guide catheter, and is then advanced out of the end of the guide catheter and into a specific coronary artery until the openings 113a,b and the proximal pressure sensor 106 are positioned at a proximal position in the coronary artery. The pressure wire 101 may then be further advanced into the coronary artery until the distal pressure sensor 102 is located at a distal position in the coronary artery.

The specially designed infusion lumen 104 is parallel to the pressure lumen 105 but positioned next to the sensor lumen but in such a way that the infusion is released out of the opening 113a distal to the proximal pressure sensor 106 but proximal to the distal pressure sensor 102. The guide wire runs in the sensor lumen 105, and is advanced in this lumen distal to a stenosis. The open end of the infusion catheter 113a is thus outside the end of the guide catheter and is located proximally (upstream) of the distal pressure sensor 102 in the specific coronary artery. Furthermore, although a guide catheter is usually used in coronary interventions, it is not an absolute necessity for practicing the present invention, and the invention, as defined

by the claims, comprises embodiments wherein a guide catheter has been dispensed with. In such a case, a guide wire, with or without a sensor mounted thereon, an infusion catheter, or a combination of both, may be utilized to locate a specific coronary artery without the assistance of a guide catheter; or a guide catheter could be removed before the FFR measurements begins.

Practical experiments have shown that a special infusion catheter is usually needed to achieve the highest flow rates possible of the hyperemic agent. As will be described below, in a preferred embodiment of the invention, the effects of hyperemic agent fluid is measured at the downstream pressure sensor 102. The infusion catheter without side holes ensures a coaxial flow even in the case of high infusion rates.

If the steps of the above method are conducted in a patient suffering from a flow restricting disease, such as a stenosis, the measured coronary flow will apparently be the momentary flow, which consequently depends on the present state of the stenosis. To be able to relate the measured flow to a normal flow for this particular patient, and to thereby enhance the medical usefulness of the flow measurement, a medical intervention such as a PTCA is usually undertaken, and such operation involves the creation of total occlusion and the FFR can then simultaneously be measured without any extra efforts.

Embodiments of the method described herein may be summarized as comprising at least the steps of: (l) positioning a pressure sensor combined with an infusion catheter mounted at a distal portion of a guide wire or other member at a distal position in a coronary artery of a patient, (2) positioning the combined catheter in the coronary artery such that the distal end of the infusion catheter is located proximally (upstream) of the distal pressure sensor, (3) measuring the blood pressure at proximal and distal locations in

the individual coronary artery, (4) infusing a hyperemic agent such as adenosine , nitric oxide or UTP with a known rate into the coronary artery by the infusion catheter, (5) measuring the pressure at the distal and proximal location (6) calculating the FFR by an equation based on the known and measured quantities.

The method may also comprise the step of inducting steady state hyperaemia in the patient before the pressure measurements are done, such that the calculated blood flow is the maximum coronary blood flow, which is the clinically most relevant type of coronary blood flow. In practise, the method may often start with the introduction of a guide catheter into the aorta of the patient, and the infusion catheter and the sensor guide is then introduced via this guide catheter.

The calculation of some FFR values may require knowledge of the so-called wedge pressure, which, by definition, can only be obtained at total occlusion of the coronary artery. Total occlusion can be artificially induced by inflating a balloon provided at a balloon catheter introduced into the coronary artery, for example via the above-mentioned guide catheter. The method above can therefore be supplemented with the steps of inducing total occlusion and measuring the wedge pressure. In many cases, e.g. for an insignificant stenosis, the distal coronary pressure is equal, or almost equal, to the aortic pressure, and the wedge pressure can be neglected in the different calculations.

Although some embodiments have been described and shown in detail, the invention is not restricted to them, but may also be embodied in other ways within the scope of the subject matter defined in the following claims. In particular, it is to be understood that other embodiments may be utilised and structural and functional modifications may be made without departing from the scope of the present invention.

In device claims enumerating several means, several of these means can be embodied by one and the same item of hardware. The mere fact that certain measures are recited in mutually different dependent claims or described in different embodiments does not indicate that a combination of these measures cannot be used to advantage.

It should be emphasized that the term "comprises/comprising" when used in this specification is taken to specify the presence of stated features, integers, steps or components but does not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

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Claims:

1. A method for determining a blood flow/pressure index (FFR) using intraarterial infusion of a hyperemic agent into an individual artery of a patient, the method comprising at least the following steps:
- introducing a combined catheter into the artery, the combined catheter comprising one or more lumina including an infusion lumen having an opening at its distal end for discharging the hyperaemic agent; and a guide wire having a distal end and a first pressure sensor mounted at the distal end of the guide wire; the guide wire being movabely inserted in one of the one or more lumina, wherein introducing comprises introducing the combined catheter such that the first pressure sensor is located at a distal position in the artery and that the open distal end of the infusion lumen is proximal of the first pressure sensor;
- Infusing a hyperemic agent with a known infusion rate and known concentration into the artery through the infusion lumen;
- measuring the pressure at a proximal and distal position at rest and during maximal hyperemia resulting from hyperemic agent infusion; and
- calculating the arterial blood pressure difference based on at least the measured pressures.

2. A method according to claim 1 wherein the hyperaemic agent includes UTP.

3. The method according to claim 1 or 2, further comprising the step of retracting or advancing the first pressure sensor along a vessel with a uni- and/or multi-vessel artery disease; and measuring the pressure at at least three locations.

4. The method according to any one of the preceding claims, wherein the combined catheter comprises at least two lumina arranged next to each

other, and wherein the wire comprising the pressure sensor is located in a lumen different from the infusion lumen, and wherein measuring the pressure comprises measuring the pressure distal of the infusion catheter.

5. The method according to any of the preceding claims, further comprising the step of inducing a steady state hyperemia in the patient before and after hyperemia and wherein measurement is calculated so that the coronary blood flow is the maximum coronary blood flow.

6. The method according to any of the preceding claims wherein the artery is a coronary artery.

7. The method according to any of the preceding claims wherein the artery is a renal artery.

8. The method according to any of the preceding claims, wherein the infusing is continuous.

9. A method for determining the blood flow in an individual coronary artery of a patient and for relating this blood flow to at least one related flow value or to at least one related FFR value, comprising at least the following steps:
- positioning a first pressure sensor mounted at a distal portion of a guide wire at a distal position in the coronary artery;
-positioning an infusion catheter in the coronary artery such that the distal end of the infusion catheter is proximally of the first pressure sensor;
- inducing steady state hyperemia in the patient;
- measuring a distal pressure by the first pressure sensor;
- measuring the aortic pressure;
- calculating a first FFR value based on the measured aortic and distal pressures; and

- calculating a related flow value, or a related FFR value, based on the calculated maximum coronary blood flow and the first FFR value, or a related flow resistance based on the measured pressures and a calculated flow value.

10. The method according to claim 9, wherein the measurement of the aortic pressure is executed with a second pressure sensor connected to a guide catheter inserted into the patient's aorta.

11. The method according to claim 9, wherein the measurement of the aortic pressure is executed with a second pressure sensor positioned at a proximal position of the guide wire.

12. The method according to claim 9, further comprising the step of positioning a balloon arranged at a catheter to a position proximal of the pressure sensor, inflating the balloon to completely occlude the coronary artery, and measuring the coronary wedge pressure using the pressure sensors.

13. An apparatus for determining the FFR in an individual artery of a patient, the system comprising: a sensor guide wire having a distal portion provided with a first pressure sensor and being adapted for positioning in the individual artery; an infusion catheter adapted for positioning in an artery and adapted for injecting a hyperemic agent into the individual artery.

14. An apparatus according to claim 13; wherein the infusion catheter is configured to inject the hyperaemic agent in a longitudinal direction of the catheter.

15. An apparatus according to claim 13 or 14, wherein the infusion catheter comprises an infusion lumen adapted for positioning in an artery and adapted

for injecting a hyperemic agent into the individual artery; and a separate sensor lumen; and wherein the sensor guide wire is movably arranged in the sensor lumen.

16. An apparatus according to any one of claims 13 through 15; comprising a second pressure sensor arranged at a position proximal to an outlet opening of the infusion catheter.

17. A kit comprising an apparatus according to any one of claims 13-16; and a predetermined amount of a hyperaemic agent.

18. The kit according to claim 17, further comprising an infusion pump.

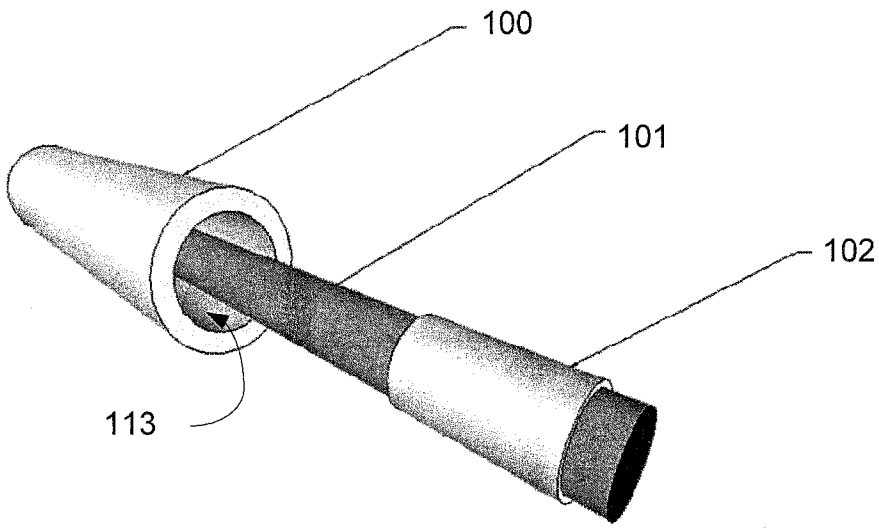

Fig. 1

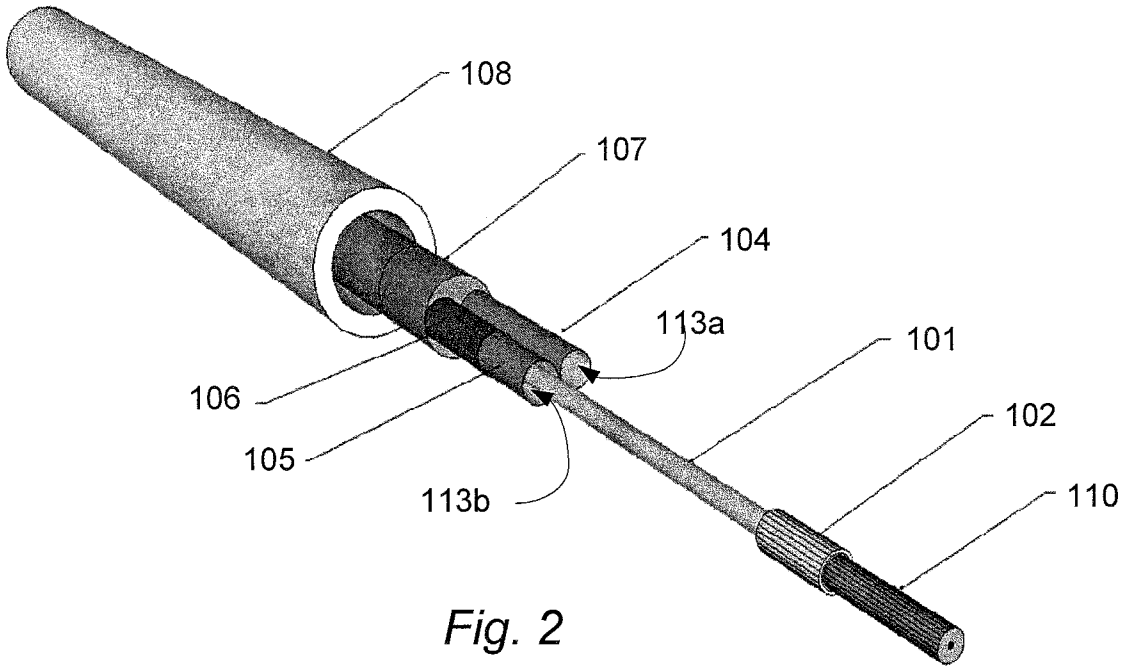

Fig. 2

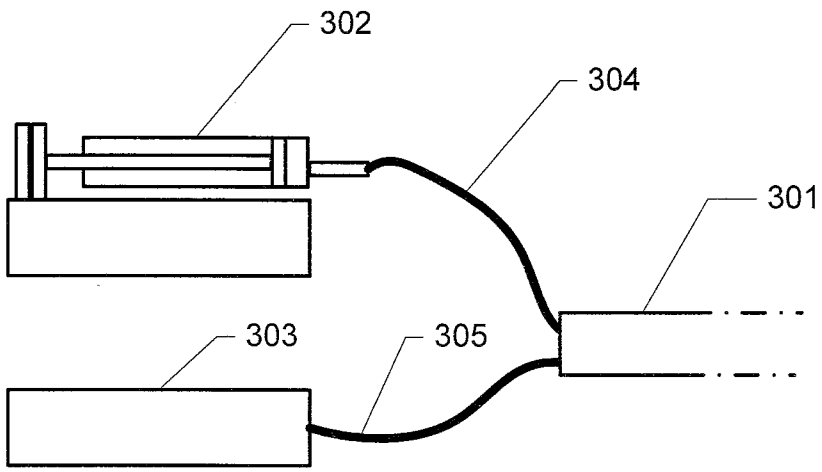

Fig. 3

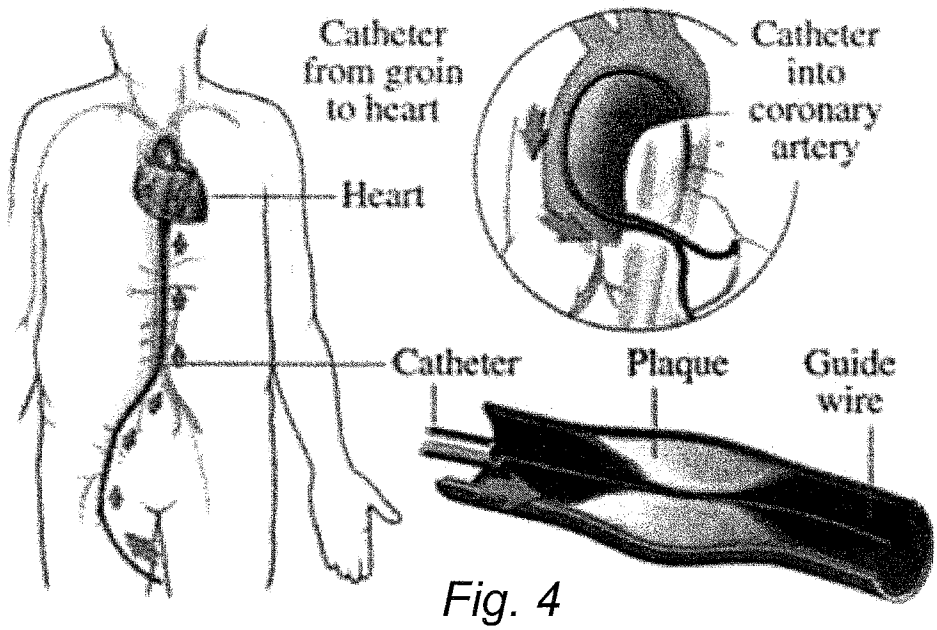
Catheter from groin to heart
Heart
Catheter into coronary artery
Catheter
Plaque
Guide wire

Fig. 4

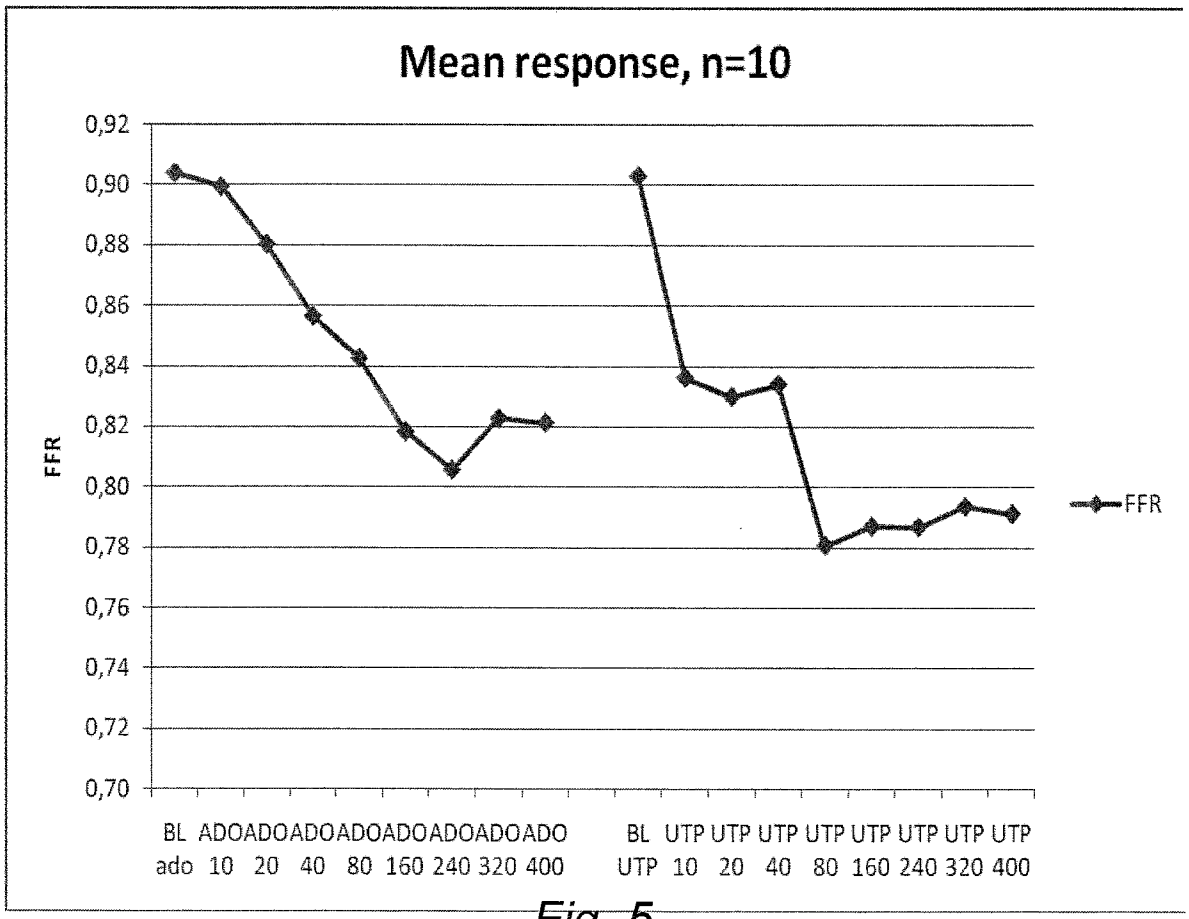
Mean response, n=10
FFR
0,92
0,90
0,88
0,86
0,84
0,82
0,80
0,78
0,76
0,74
0,72
0,70
BL ADOADOADOADOADOADOADOADO
ado 10 20 40 80 160 240 320 400
BL UTP UTP UTP UTP UTP UTP UTP UTP
UTP 10 20 40 80 160 240 320 400
FFR

Fig. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/060548

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/0215 A61B5/026
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/078352 A1 (PIJLS NICO H [NL] PIJLS NICO H J [NL]) 5 April 2007 (2007-04-05) paragraph [0032] figure 3	13-15, 17,18
X	WO 2010/030882 A1 (ACIST MEDICAL SYS INC [US]; MANSTROM DALE R [US]; RAATIKKA AMY R [US];) 18 March 2010 (2010-03-18) figures 7b,12,16	13,14, 16-18
X	WO 2009/111528 A2 (HOCH ROBERT [US]; WELTNER THOMAS [US]; HANNULA DONALD [US]) 11 September 2009 (2009-09-11) page 6, lines 25-32 figures 1,2	13,14,17
A	US 2006/004286 A1 (CHANG JOHN Y [US] ET AL) 5 January 2006 (2006-01-05) figures 4E,4G	15

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

☒ See patent family annex.

* Special categories of cited documents :

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

"E" earlier 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
8 September 2011	16/09/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Worms, Georg

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2011/060548

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. [X] Claims Nos.: 1-12
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

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

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 1-12

The present application does not meet the criteria of Article 17(2)(a)(i) and Rule 39.1(iv) PCT, because the subject-matter of independent claims 1 and 9 discloses a surgical method (see also PCT Guidelines 9.10) for the following reasons: As a catheter is introduced into a human and advanced to a coronary artery a surgical step would be necessary to carry out this step. Hence, the methods of claims 1 and 9 entail an implicit surgical step and are therefore not allowable.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/060548

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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