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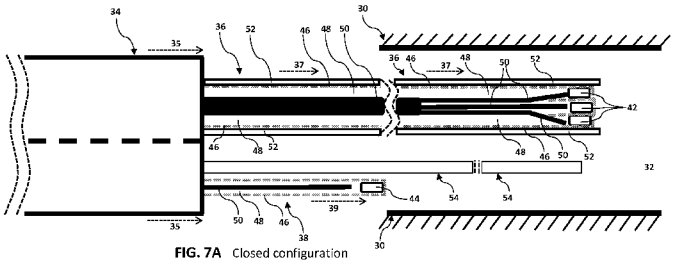

FIG. 7A Closed configuration

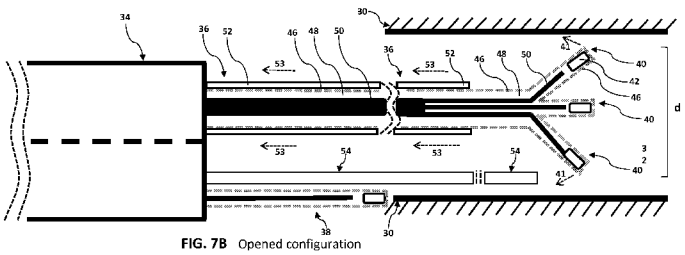

FIG. 7B Opened configuration

(57) **Abstract**: Identification, measurement, and/or estimation of temperatures of vessel walls and/or near-wall temperatures, including: cooling a first portion of vessel fluid flow; and measuring a temperature of a second portion of the flow, which second portion includes fluid cooled by the cooling, and which second portion is associated with a location at the wall. Identifying vulnerable plaque. Catheter temperature sensor, including an elongate body adapted for insertion into a blood vessel, a first temperature sensor at a first location along the catheter, a second temperature sensor at a location distanced at least 1 cm from the first location, and a mechanism for axially moving second sensor relative to the first sensor, along the catheter; and a system, for performing (blood) vessel wall temperature measurements. Heat treating a blood vessel wall (e.g., including [vulnerable] plaque) of a blood vessel.

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MEASUREMENT AND ESTIMATION OF TEMPERATURES IN VESSELS

RELATED APPLICATIONS

This application claims the benefit of priority under 35 USC 119(e) of U.S. Provisional Patent Application No. 61/348,282 filed 26 May 2010 the content of which is incorporated herein by reference in its entirety.

FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to measurement of temperatures of vessel walls and, more particularly, but not exclusively, to identifying vulnerable plaque by such measurements. The present invention, in some embodiments thereof, also particularly relates to a catheter temperature sensor, and a system, for (blood) vessel wall and/or near-wall temperature identification, measurement, and/or estimation. The present invention, in some embodiments thereof, also relates to a method of heat treating a blood vessel wall (for example, including plaque) of a blood vessel.

Atherosclerosis is an inflammatory disease. It is generally assumed that macrophages play an important role in atherosclerotic plaque inflammation, by secreting cytokines, growth factors, and matrix metalloproteinases (MMPs), which destabilize the plaque and promote its rupture. During the past decade, several studies aimed to assess thermal heterogeneity over plaque surfaces, to demonstrate that inflamed lesions are hotter. One of the first studies [1] targeted in predicting thrombotic events by heat released from activated macrophages on the plaque surface or under its thin cap. By measuring intimal surface temperatures at different sites of ex-vivo human carotid artery plaques, temperature differences of 0.2 to 2.2°C have been measured. Temperature differences also correlated positively with the density of the underlying cells (mostly macrophages), and inversely with cap thickness.

To further investigate the subject, a thermography catheter was designed and developed for in vivo measurements of thermal heterogeneity in the human arterial system [2]. The distal tip of the intravascular catheter was equipped with accurate thermistor temperature microsensors, enabling measurement of temperature when in close contact with the vascular wall. This research included patients with unstable

angina and with acute myocardial infarction, and found that median temperature differences at the site of the lesion were increased by 1.025°C and by 2.15°C, respectively, from the core temperature. It has also been found that systemic markers of inflammation such as CRP (C-reactive protein) and SAA (Serum amyloid A) correlated with temperature differences, hence implying that increased local heat production of coronary atherosclerotic lesions may be due to inflammatory response. In another research conducted by this group [3], it was demonstrated that the difference in atheromatous plaque temperature from background temperature was a strong predictor of cardiac events in patients after a successful percutaneous intervention. Moreover, a threshold of 0.5°C has been found, above which the rate of these adverse cardiac events has significantly increased. These findings were followed by an in vivo animal study [4], which demonstrated the presence of temperature heterogeneity in hypercholestrolemic rabbits and its absence in normocholestrolemic rabbits. Another animal model showed a thermal heterogeneity of 1.5 to 2.0°C inside hypercholestrolemic rabbits' aorta [5].

Following the aforementioned pioneering human thermography studies, smaller scale ones [6] measured more modest temperature increase in the range of 0.1 to 0.36°C in patients with stable angina, unstable angina, and acute myocardial infarction, yet such increase was not found in all of the subjects.

Consequently, analytic and numerical studies, modeling inflamed coronary artery plaques, and their relevance to temperature heterogeneity, have been initiated, taking advantage of the fact that such models can easily change various meaningful model parameters. Mathematical simulation of a coronary artery model with heat source confirmed that measured temperature is strongly influenced by blood flow and also by cap thickness and source geometry [7]. Cases in which the heat source was located in the proximal or distal shoulder of the plaque were further studied [8], as well as the implications of blood temperature profile in multifocal coronary artery disease and the design of the thermography catheter. Another numerical study [9] shows that the presence of the thermography catheter in the artery, and its effect on measurement, which was previously demonstrated to be meaningful. Another significant result of a numerical model was the prediction of temperature increase (due to metabolism) in the

center of the plaque to be less than 0.1°C, thereby claiming that higher reported values should be attributed to other factors [10].

Recently, a contra-hypothesis, claiming that previous measurements of lesion wall temperature increase were attributed to blood pressure effects rather than heat release from the unstable plaque wall was presented in-vitro and in-vivo [11]. This hypothesis was based on pressure and temperature recordings acquired while inflating a balloon proximal and distal to the plaque.

Exemplary teachings relating to vascular catheter apparatuses and methods for temperature measurement of vascular tissue, specifically 'at' a vascular wall, are provided in the patent literature [12 - 14].

Exemplary teachings relating to intravascular thermography devices and methods for treating vulnerable plaque or/and diseased tissue, are also provided in the patent literature [15 - 19].

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Some exemplary devices for wall temperature measurement in blood vessels.

1. **PressureWire™ Certus**

Manufacturer: Radi Medical Systems (acquired by St. Jude Medical™).

The PressureWire™ catheter includes an angioplasty guidewire with a pressure and temperature sensor located about 3 cm from the tip. In the sensor, the temperature is measured by means of a thermistor. The sensor utilizes the peizo-resistive effect and consists of two resistances, of which one is placed on a pressure-sensitive membrane and one at its vicinity. These two resistances are connected by small electrical wires to the proximal end of the guidewire, where they are coupled into an instrument forming a Wheatstone bridge. Since these resistors are also sensitive to temperature, the sensor is able to measure both pressure and temperature. It should be emphasized that this catheter measures the blood temperature rather than the artery wall temperature.

2. **Epiphany™**

Manufacturer: Medispes™.

A coronary thermography catheter with a thermistor positioned at its distal part. The catheter contains two lumens. The first lumen runs through the distal part of the device and is used for the insertion of a guidewire. In the second lumen, the thermistor leads are inserted. The catheter comprises a special hydrodynamic geometry that forces the temperature sensor to be in contact with the artery wall.

3. **Volcano Intravascular Thermography Catheter**

Manufacturer: Volcano Therapeutics Inc.

A thermography basket catheter consisting of an expandable catheter made of a nitinol system loaded with small and flexible thermocouples. Measures the artery wall temperature using five temperature sensors that are deployed circumferentially on a self-expanding basket. An additional reference temperature sensor is deployed in the center of the basket (and measures the blood temperature).

4. **ThermoSense™**

Manufactuerer: Thermocore Medical Systems NV.

An over-the-wire system consisting of a functional end that can be engaged by retracting a covering sheath. The distal part has four dedicated thermistors, each at 90 degrees, which, after engagement, ensure endoluminal surface contact with the artery wall. Each thermistor is located on the distal tip of a flexible nitinol strip.

SUMMARY OF THE INVENTION

An aspect of some embodiments of the present invention relates to vessel wall assessment by using relative temperature measurements and/or pre-cooling of a fluid such a blood that flows in the vessel.

There is provided in accordance with an exemplary embodiment of the invention, a method of identifying temperature differences related to temperature differences in the wall of a vessel with flow of fluid therethrough, comprising:

cooling a first portion of said flow; and

measuring a temperature of a second portion of said flow, which second portion includes fluid cooled by said cooling, and which second portion is associated with a location at said wall. Optionally, said fluid is blood. Optionally or alternatively, said vessel is a blood vessel.

In an exemplary embodiment of the invention, cooling comprises injecting a cold fluid into said vessel. Optionally or alternatively, cooling comprises cooling said fluid using a cooling element. Optionally or alternatively, cooling comprises cooling said fluid to have a temperature difference of at least 5 degrees Celsius from said wall location, at said first portion. Optionally or alternatively, cooling comprises cooling said fluid to have a temperature difference of at least 10 degrees Celsius from said wall location, at said first portion. Optionally or alternatively, cooling comprises cooling said

fluid to have a temperature difference of at least 15 degrees Celsius from said wall location, at said first portion. Optionally or alternatively, cooling comprises cooling said fluid to have a temperature difference of at least 3 degrees Celsius from said wall location, at said second portion. Optionally or alternatively, cooling comprises cooling said fluid to have a temperature difference of at least 5 degrees Celsius from said wall location, at said second portion.

In an exemplary embodiment of the invention, said measuring comprises measuring using a temperature sensor and comprising reducing a fluid exchange rate at said sensor. Optionally or alternatively, said measuring comprises measuring using a temperature sensor and comprising reducing a fluid exchange rate at said wall location. Optionally or alternatively, said measuring comprises measuring using a temperature sensor and comprising reducing a fluid flow rate in said vessel.

Optionally, said reducing comprises reducing by extending one or more flow-interference objects into said flow. Optionally or alternatively, said reducing comprises reducing by at least 50%.

In an exemplary embodiment of the invention, said measuring comprises measuring using a temperature sensor and said temperature sensor is configured to not contact said wall. Optionally or alternatively, said measuring comprises measuring using a temperature sensor and said temperature sensor is configured to not be urged against said wall. Optionally or alternatively, said measuring comprises measuring using a temperature sensor and said temperature sensor is recessed in a delivery system thereof. Optionally or alternatively, said measuring comprises measuring using a temperature sensor and said temperature sensor is not on an outer surface of a delivery system thereof.

In an exemplary embodiment of the invention, the method comprises measuring a reference temperature of said flow at a reference location upflow from said second portion.

In an exemplary embodiment of the invention, the method comprises measuring a reference temperature of said flow at a reference location upflow from said first portion.

In an exemplary embodiment of the invention, the method comprises changing said reference location.

In an exemplary embodiment of the invention, the method comprises changing a location of said second portion.

In an exemplary embodiment of the invention, measuring comprises acquiring a plurality of measurements at different axial locations along said wall.

In an exemplary embodiment of the invention, the method comprises identifying an axial gradient from said measurements.

In an exemplary embodiment of the invention, measuring comprises acquiring a plurality of measurements at different radial distances from said wall.

In an exemplary embodiment of the invention, the method comprises identifying a radial gradient from said measurements.

In an exemplary embodiment of the invention, measuring comprises acquiring a plurality of measurements at different circumferential locations on said wall.

In an exemplary embodiment of the invention, the method comprises identifying a circumferential gradient from said measurements.

In an exemplary embodiment of the invention, said plurality of measurements are acquired using a plurality of temperature sensors. Optionally or alternatively, said plurality of measurements are acquired by moving one or more temperature sensors.

In an exemplary embodiment of the invention, the method comprises displaying a rate of temperature change as a function of space and/or time, to a user.

In an exemplary embodiment of the invention, the method comprises identifying suspicious plaque in a blood vessel based on a rate of temperature change as a function of space and/or time.

In an exemplary embodiment of the invention, the method comprises identifying suspicious plaque in a blood vessel based on a difference between said measured temperature of said second portion and at least an estimated temperature of said flow.

In an exemplary embodiment of the invention, the method comprises mapping the axial and/or radial extent of suspicious plaque in a blood vessel based on said measured temperature of said second portion.

In an exemplary embodiment of the invention, the method comprises also measuring a temperature of a third portion of said flow, which third portion is in or past a vessel bifurcation, downflow from said first portion and using this measurement for

identifying suspicious plaque associated with any of the vessels comprising said bifurcation or the bifurcation itself.

There is provided in accordance with an exemplary embodiment of the invention, a method of identifying temperature differences in the wall of a vessel with flow of fluid therethrough, comprising:

measuring a reference temperature of said flow at a reference portion of said flow; and

measuring a temperature of a second portion of said flow, which second portion is associated with a location at said wall and at least 1 cm downflow from said first portion, such that a temperature of said flow at said reference portion is not affected by a temperature of said wall location.

There is provided in accordance with an exemplary embodiment of the invention, a method of plaque identification comprising mapping a temperature profile of a wall of a blood vessel where no stenosis is visible on an angiography image and identifying vulnerable plaque or other plaque on said wall from changes in temperature thereat.

There is provided in accordance with an exemplary embodiment of the invention, a catheter temperature sensor, comprising:

(a) an elongate body adapted for insertion into a blood vessel;

(b) a first temperature sensor at a first location along said catheter;

(c) a second temperature sensor at a location distanced at least 1 cm from said first location, along said catheter; and

(d) a mechanism for axially moving said second sensor relative to said first sensor, along said catheter.

There is provided in accordance with an exemplary embodiment of the invention, a system for at least estimating blood vessel wall temperature, comprising:

(a) a first input for a first temperature indicating signal, corresponding to a blood vessel wall temperature; and

(b) a processor configured to process said signal as indicating a temperature corresponding to a normal wall temperature or as indicating a temperature corresponding to a inflamed wall, wherein said processor includes a classifier configured to classify temperatures under, for example, 37 degrees Celsius, and

optionally, under 35 degrees Celsius, as vulnerable plaque and as non-plaque. Optionally, the system comprises a display adapted to display blood or wall temperatures over a range of at least 5 degrees Celsius. Optionally or alternatively, the system comprises a gradient calculator configured to calculate a temperature gradient, for example, of at least 0.01 degree Celsius, optionally, of at least 0.1 degree Celsius, and optionally, of at least 1 degree Celsius, between two locations in said vessel. Optionally, said gradient is a gradient along a blood vessel. Optionally or alternatively, said gradient is a gradient perpendicular to an axis of said vessel.

In an exemplary embodiment of the invention, the system comprises a display generator configured to generate a temperature map of a wall of a blood vessel, using said processed signal. Optionally, said display includes an indication of vulnerable plaque.

In an exemplary embodiment of the invention, the system comprises an actuator which controls a cooling function of a temperature measurement catheter.

In an exemplary embodiment of the invention, the system comprises an input for the actuation of a cooling function of a temperature measurement catheter.

In an exemplary embodiment of the invention, the system comprises an actuator which controls a flow modification function of a temperature measurement catheter.

In an exemplary embodiment of the invention, the system comprises an input for a flow modification function of a temperature measurement catheter.

In an exemplary embodiment of the invention, the system comprises a temperature measurement catheter.

In an exemplary embodiment of the invention, the system comprises a blood cooling system.

There is provided in accordance with an exemplary embodiment of the invention, a catheter temperature sensor, comprising:

(a) an elongate body adapted for insertion into a blood vessel;

(b) a first temperature sensor at a first location along said catheter and adapted for measurement in blood vessels of less than 20 mm in diameter; and

(c) a blood cooling system upstream of said first temperature sensor. Optionally, said cooling system comprises a bulk of cold fluid.

There is provided in accordance with an exemplary embodiment of the invention, a catheter temperature sensor, comprising:

(a) an elongate body adapted for insertion into a blood vessel;

(b) a plurality of temperature sensors configured to not forcefully contact a wall of said blood vessel. Optionally, said plurality of temperature sensors are recessed in a body of said catheter. Optionally or alternatively, said plurality of temperature sensors are located at parts of said catheter with diameter of less than half a diameter of said blood vessel and less than 10 mm. Optionally or alternatively, said plurality of temperature sensors are prevented from contacting said vessel wall by one or more protrusions extending from said catheter. Optionally, said one or more protrusions are selectively extendable. Optionally, said one or more protrusions are selectively extendable using an overtube.

In an exemplary embodiment of the invention, said one or more protrusions are configured to lean on the vessel wall and provide stabilization during a temperature sensor measurement session.

In an exemplary embodiment of the invention, said plurality of temperature sensors are located in portions of said catheter where average fluid exchange rate is less than 50% of that in unobstructed parts of said vessel. Optionally or alternatively, at least two of said plurality of temperature sensors are circumferentially spaced apart. Optionally or alternatively, at least two of said plurality of temperature sensors are axially spaced apart. Optionally or alternatively, at least two of said plurality of temperature sensors are radially spaced apart. Optionally or alternatively, said catheter comprises a sheath with a lumen therein suitable for delivery of cooling fluid therethrough.

There is provided in accordance with an exemplary embodiment of the invention, a method of heat treating a blood vessel wall, the method comprising:

providing a temperature sensor assembly, including at least one temperature sensor each configured and operative as a thermistor;

positioning the temperature sensor assembly inside the blood vessel;

activating the thermistor of the temperature sensor assembly, by supplying current to each of the at least one thermistor;

opening the temperature sensor assembly to a fully-opened configuration, such that there is contact of a tip of at least one of the thermistors with the blood vessel wall;

increasing the current supplied to at least one of the thermistors, whereby temperature of the at least one thermistors increases to higher than 40 ^{o}C;

axially or/and circumferentially moving the temperature sensor assembly in the blood vessel, for effecting thermal damage to the blood vessel wall; and

removing the temperature sensor assembly to outside of the blood vessel.

In an exemplary embodiment of the invention, the blood vessel wall includes plaque.

In an exemplary embodiment of the invention, the plaque is vulnerable plaque.

In an exemplary embodiment of the invention, increasing the current to the thermistors is repeated until obtaining an indication of the effecting thermal damage to the blood vessel wall.

In an exemplary embodiment of the invention, effecting thermal damage to the blood vessel wall stabilizes the blood vessel wall.

In an exemplary embodiment of the invention, the temperature of the at least one thermistor increases to higher than 50 degrees Celsius.

In an exemplary embodiment of the invention, the blood vessel wall includes plaque, and is applicable for treating a subject with atherosclerosis.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

Implementation of the method and/or system of embodiments of the invention can involve performing or completing selected tasks manually, automatically, or a combination thereof. Moreover, according to actual instrumentation and equipment of

embodiments of the method and/or system of the invention, several selected tasks could be implemented by hardware, by software or by firmware or by a combination thereof using an operating system.

For example, hardware for performing selected tasks according to embodiments of the invention could be implemented as a chip or a circuit. As software, selected tasks according to embodiments of the invention could be implemented as a plurality of software instructions being executed by a computer using any suitable operating system. In an exemplary embodiment of the invention, one or more tasks according to exemplary embodiments of method and/or system as described herein are performed by a data processor, such as a computing platform for executing a plurality of instructions. Optionally, the data processor includes a volatile memory for storing instructions and/or data and/or a non-volatile storage, for example, a magnetic hard-disk and/or removable media, for storing instructions and/or data. Optionally, a network connection is provided as well. A display and/or a user input device such as a keyboard or mouse are optionally provided as well.

BRIEF DESCRIPTION OF THE DRAWINGS

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

FIG. 1 is an illustration of the catheter delivery system and the temperature sensors in the coronary artery tree during an ICT (intracoronary thermography) procedure, in accordance with an exemplary embodiment of the invention; the bold rectangles are the temperature sensors and cold saline indwells the catheter delivery system;

FIGs. 2A-D are illustrations of the possible arrangements of the distal temperature sensors included in the catheter delivery system, in accordance with exemplary embodiments of the invention, including, for example, longitudinally

positioned configurations (A [parallel electrical wiring configuration], D [series electrical wiring configuration]), circumferentially positioned configurations (B [parallel electrical wiring configuration], C [series electrical wiring configuration]), or combined (not illustrated); Another possibility being that only one distal temperature sensor is placed (not illustrated);

FIGs. 3A-E are illustrations of a gate feature of the temperature measurement catheter, in accordance with various different exemplary embodiments of the invention, where, in A is shown, the catheter with the gates closed due to an optional cover sheath that covers the catheter; axial movement of the sheath enables the gates to get opened; and in B, C, and D, the catheter is shown with the gates opened, however with different deployment of temperature sensors; and in E is shown a zoom in on one of the gates and the expected flow streamlines; it is noted that the number of gates may be 1 or more and that they may be, for example, associated each with one or more temperature sensors, arranged according to longitudinally (axially) and/or circumferentially positioned configurations, and/or not in a direct association or contact with the temperature sensors;

FIG. 4 is an illustration of the cold saline injection during an ICT procedure, in accordance with an exemplary embodiment of the invention, where during the procedure the blood flow is optionally maintained, and/or cooled by the cold saline or by other means such as a cooling element;

FIG. 5 is an illustration of another exemplary embodiment of the invention, optionally used for identifying vulnerable plaque in a bifurcation anatomy; as shown, distinct temperature sensors are optionally designated for one or both of the main-branch and the side-branch of the bifurcation, which may be read simultaneously or serially, possibly improving the vulnerable plaque detection capability at or near the bifurcation;

FIG. 6 is an illustration of an exemplary blood temperature [°C] vs. time [seconds] profile, obtained by employing a blood flow cooling procedure (e.g., via an intermittent injection of cold saline), in accordance with another exemplary embodiment of the invention;

FIGs. 7A-B are schematic diagrams illustrating exemplary embodiments of the multi-lumen delivery catheter, and main components / elements (including exemplary retractable temperature measurement catheter and intracoronary catheter temperature sensors), thereof, in closed (7A) and opened (7B) configurations, particularly

highlighting retractable temperature measurement catheter (36), (proximal) reference insulated temperature sensor assembly (38), and guidewire (54), having separate lumens inside the multi-lumen delivery catheter (34), for example, as relating to identifying and measuring temperature differences in the wall of a vessel, in accordance with some exemplary embodiments of the invention;

FIGs. 8A-B are schematic diagrams illustrating additional exemplary embodiments of the multi-lumen delivery catheter, and main components / elements (including exemplary retractable temperature measurement catheter and intracoronary catheter temperature sensors), thereof, in closed (8A) and opened (8B) configurations, particularly highlighting retractable temperature measurement catheter (36) and guidewire (54) having separate lumens inside the multi-lumen delivery catheter (34), and further highlighting the (proximal) stationary reference temperature (measuring) sensor (44) deployed on the (distal) retractable sheath (shaft) (52) of the retractable temperature measurement catheter (36), for example, as relating to identifying and measuring temperature differences in the wall of a vessel, in accordance with some exemplary embodiments of the invention;

FIGs. 9A-B are schematic diagrams illustrating additional exemplary embodiments of the multi-lumen delivery catheter, and main components / elements (including exemplary retractable temperature measurement catheter and intracoronary catheter temperature sensors), thereof, in closed (9A) and opened (9B) configurations, particularly highlighting retractable temperature measurement catheter (36) and guidewire (54) generally sharing the same lumen inside the multi-lumen delivery catheter (34), with guidewire (54) inside a separate lumen of catheter (36), and further highlighting the (proximal) stationary reference temperature (measuring) sensor (44) deployed on the (distal) retractable sheath (shaft) (52) of the retractable temperature measurement catheter (36), for example, as relating to identifying and measuring temperature differences in the wall of a vessel, in accordance with some exemplary embodiments of the invention;

FIGs. 10A-B are schematic diagrams illustrating additional exemplary embodiments of the multi-lumen delivery catheter, and main components / elements (including exemplary retractable temperature measurement catheter and intracoronary catheter temperature sensor), thereof, in closed (10A) and opened (10B) configurations,

particularly highlighting retractable temperature measurement catheter (36) includes a single (distal) temperature (measuring) sensor (42), and the (proximal) stationary reference temperature (measuring) sensor (44) is deployed on the (distal) retractable sheath (shaft) (52) of the retractable temperature measurement catheter (36), and further highlighting guidewire (54) and catheter (36) located inside a separate lumen of the multi-lumen delivery catheter (34), for example, as relating to identifying and measuring temperature differences in the wall of a vessel, in accordance with some exemplary embodiments of the invention;

FIG. 11A is a schematic diagram illustrating a front view of an exemplary embodiment of a multi-lumen (four lumen) delivery catheter retractable temperature measurement catheter (34), and selected main components / elements thereof, particularly highlighting equally sized lumens (56), with the retractable temperature measurement catheter (36) and the (distal) insulated temperature sensor assembly (40) in their closed configurations; in accordance with some exemplary embodiments of the invention;

FIG. 11B is a schematic diagram illustrating a front view of an exemplary embodiment of a multi-lumen (four lumen) delivery catheter retractable temperature measurement catheter (34), particularly highlighting unequally sized lumens (56), in accordance with some exemplary embodiments of the invention;

FIG. 11C is a schematic diagram illustrating a front view of an exemplary embodiment of a double lumen delivery catheter retractable temperature measurement catheter (34), and selected main components / elements thereof, particularly highlighting one lumen configured and operative for the temperature measurement catheter (36), and another lumen configured and operative for injecting cooling (e.g., cold saline) fluid, with the guidewire lumen inside the temperature measurement catheter (36), with the retractable temperature measurement catheter (36) and the (distal) insulated temperature sensor assembly (40) in their closed configurations; in accordance with some exemplary embodiments of the invention;

FIG. 11D is a schematic diagram illustrating a front view of an exemplary embodiment of a multi-lumen (four lumen) delivery catheter retractable temperature measurement catheter (34), and selected main components / elements thereof, particularly highlighting unequally sized and separated lumens (56) configured and

shaped according to configurations and dimensions of the retractable temperature measurement catheter (36), the (proximal) reference insulated temperature sensor assembly (38), and the guidewire (54), with the retractable temperature measurement catheter (36) and the (distal) insulated temperature sensor assembly (40) in their closed configurations, wherein the (proximal) stationary reference temperature (measuring) sensor (44) is variably positionable inside the polymeric sleeve lumen (48); in accordance with some exemplary embodiments of the invention;

FIG. 12 is a (block-type) flow diagram of an exemplary embodiment of the method of heat treating a blood vessel wall (e.g., including plaque) of a blood vessel, in accordance with some exemplary embodiments of the invention;

FIGs. 13A-B are schematic diagrams illustrating exemplary embodiments of the multi-lumen delivery catheter, and main components / elements (including exemplary retractable temperature measurement catheter and intracoronary catheter temperature sensors), thereof, in closed (13A) and semi-opened (13B) configurations, particularly relating to heat treating a blood vessel wall (e.g., including plaque) of a blood vessel, in accordance with some exemplary embodiments of the invention;

FIG. 13C is a schematic diagram illustrating an additional exemplary embodiment of the multi-lumen delivery catheter, and main components / elements (including exemplary retractable temperature measurement catheter and intracoronary catheter temperature sensors), thereof, in a fully-opened configuration, particularly highlighting the extent or degree (β) of opening of the (distal) insulated temperature sensor assembly (40) from the catheter axis, particularly relating to heat treating a blood vessel wall (e.g., including plaque) of a blood vessel, in accordance with some exemplary embodiments of the invention;

FIG. 13D is a schematic diagram illustrating an additional exemplary embodiment of the multi-lumen delivery catheter, and main components / elements (including exemplary retractable temperature measurement catheter and intracoronary catheter temperature sensors), thereof, in a fully-opened configuration, particularly highlighting rotation of the (distal) insulated temperature sensor assembly (40), in order to make a circumferential thermal effect, particularly relating to heat treating a blood vessel wall (e.g., including plaque) of a blood vessel, in accordance with some exemplary embodiments of the invention;

FIG. 13E is a schematic diagram illustrating an additional exemplary embodiment of the multi-lumen delivery catheter, and main components / elements (including exemplary retractable temperature measurement catheter and intracoronary catheter temperature sensors), thereof, in a fully-opened configuration, particularly highlighting rotation of the (distal) insulated temperature sensor assembly (40), in order to make a circumferential thermal effect, and further highlighting the tip of the temperature sensor assembly (40) configured as a flexible (bendable) joint for flexibly contacting a blood vessel wall, particularly relating to heat treating a blood vessel wall (e.g., including plaque) of a blood vessel, in accordance with some exemplary embodiments of the invention;

FIG. 14A is a schematic diagram illustrating a front view of an exemplary embodiment of the retractable temperature measurement catheter, and main components / elements (including exemplary intracoronary catheter temperature sensors), thereof, in a closed configuration, for example, as relating to heat treating a blood vessel wall (e.g., including plaque) of a blood vessel, in accordance with some exemplary embodiments of the invention;

FIG. 14B is a schematic diagram illustrating a front view of an exemplary embodiment of the retractable temperature measurement catheter, and main components / elements (including exemplary intracoronary catheter temperature sensors), thereof, in a semi-opened configuration, particularly relating to identifying and measuring temperature differences in the wall of a vessel, as part of a procedure for heat treating a blood vessel wall (e.g., including plaque) of a blood vessel, in accordance with some exemplary embodiments of the invention;

FIG. 14C is a schematic diagram illustrating a front view of an exemplary embodiment of the retractable temperature measurement catheter, and main components/ elements (including exemplary intracoronary catheter temperature sensors), thereof, in a fully-opened configuration, enabled for optional rotational movement, particularly relating to heat treating a blood vessel wall (e.g., including plaque) of a blood vessel, in accordance with some exemplary embodiments of the invention;

FIGs. 15A-B are illustrations of, in A, the geometry of a simulated lumen of an artery; and in B, a longitudinal cross-section of the artery, including the media (brown),

adventitia (green), eccentric plaque (purple) at the bottom, and necrotic tissue (blue) within the plaque;

FIGs. 16A-B show, in A, velocity vectors; and in B, temperature distribution of case I (blood core temperature at 37°C), warm plaque wall is located at the bottom; points I and II indicate temperature measurement points; and

FIGs. 17A-B show temperature measured at points I and II, in A for case 1 (blood core temperature at 37°C), and in B for case 2 (blood core temperature cooled down to 17°C, in accordance with exemplary embodiments of the invention), with temperature values shown in °K.

DESCRIPTION OF EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to identification, measurement, and/or estimation of temperatures of vessel walls and/or near-wall temperatures and, more particularly, but not exclusively, to identifying vulnerable plaque by such vessel wall and/or near-wall temperature identification, measurement, and/or estimation. The present invention, in some embodiments thereof, also particularly relates to a catheter temperature sensor, and a system, for performing such (blood) vessel wall and/or near-wall temperature identification, measurement, and/or estimation. The present invention, in some embodiments thereof, also relates to a method of heat treating a blood vessel wall (e.g., including plaque) of a blood vessel.

Thermography is a method used mainly for the detection of warmer arterial wall regions, as an indication for the presence of inflamed atherosclerotic plaques. As described herein, injection of cold saline to the bloodstream (or otherwise cooling the blood flow) and measuring temperature gradients within the flow instead of or in addition to in contact with the wall, is numerically investigated. Results show an almost 12-fold increase in expected temperature gradients, emphasizing the potential usefulness of such method for novel catheter design.

The prior methods have some limitations, some of which are optionally overcome using methods and apparatus in accordance with exemplary embodiments of the invention.

1. **Sensitivity to temperature values:**

Atherosclerotic plaques are inflamed lesions, thus exhibit a warmer temperature than body core temperature (37°C). However, heat convection resulting from the blood flow reduces the measured temperatures substantially, making it harder to identify the expected temperature differences of warm lesions. Since temperature measurement in all heat-measurement devices is based on catheters inserted into the lumen of blood vessels, heat convection is a major problem induced by the pulsatile flow of blood. The result is that in many cases, the measured temperature difference, between diseased and healthy vessel wall, is less than 1°C, and much less when the measurement is from the blood stream, though the actual difference between the inflamed lesions and core temperature can be larger.

In accordance with an exemplary embodiment of the invention, blood flow is cooled, for example, by injection of cold saline proximal to a hot and inflamed lesion is expected not only to diminish the phenomena of temperature difference reduction due to flow convection, but actually amplify it in proportion to the temperature of the saline, utilizing the same flow convection phenomena. The convection principle is such that when a fluid at one temperature flows over a surface of a different temperature, the temperature difference tends to get smaller, in an attempt to reach equilibrium between the surface and fluid temperatures. When cold saline flows over a warmer surface, its temperature rises in proportion to the temperature difference. Thus, the higher is the temperature difference between the surface temperature and the saline, the greater will be the heating process such that the temperature difference measured in the vicinity of the warmer lesion and the core temperature gets 'amplified'. Initial numerical simulations show that injection of a saline at 17°C might reach a temperature difference of more than 5°C between a region in the vicinity of the warm lesion itself and the centerline of the lumen, compared to less than 0.5°C under normal blood flow (an 11-fold amplification). If the temperature at the center of the blood vessel in the plaque region is compared to the injection temperature, the difference may reach up to 7°C. Other temperature differences and amplifications may be provided. For example, a difference of 5°C, 10°C, 20°C, 25°C, 30°C or smaller or intermediate or larger differences may be provided between blood flow and vessel wall. Similarly, flow and flow temperature

may be controlled so a gradient of at least 1°C, 2°C, 3°C, 5°C, 7°C or smaller, intermediate or greater is provided between a wall area and a non-heated area. Similarly, flow and flow temperature may be controlled so an expected difference of at least 1°C, 2°C, 3°C, 5°C, 7°C or smaller, intermediate or greater is provided at points at a same distance from either diseased wall or healthy wall.

In an exemplary embodiment of the invention, there are provided gates (movable obstructions) or fixed obstructions, such as recessing, which partially block the stream of flow over the temperature sensor (and/or wall and/or in vessel) and may cause a region of flow stagnation or recirculation, thus possibly diminishing substantially the temperature reduction due to heat convection over the sensor itself. Optionally, by opening and closing the gates and/or by pulsating the cooling effect, a rate of heat transfer through a cap of the plaque is estimated. Optionally or alternatively to gate opening, a temperature sensor may be retracted into the body of the catheter.

In an exemplary embodiment of the invention, the gates are used to cover the sensors (e.g., thermocouples or thermistors or other temperature sensors, such as known in the art) when not in use.

2. <u>Blood vessel's wall contact</u>:

Most of the current thermography catheters require a physical contact between the temperature sensor and the arterial wall. Some catheters include a variable number of flexible arms with thermistors or thermocouples at their tips, as these tips are in full contact with the artery wall. Others may be shaped as a basket with several arms curved in a manner that the highest curvature once again comes in touch with the blood vessel's wall.

Thermography catheters are mainly used for detecting vulnerable atherosclerotic plaques. The nature of these plaques is that they are composed of a very soft lipid core, with a thin fibrous cap (often less than 65 μm) separating it from the blood flow in the lumen. The risk of rupture of this thin cap is worrying to many physicians. Once the cap is ruptured and the blood flow is exposed to the internal lipid core, a thrombus may be formed, with the risk of occluding the blood vessel, thus leading either to a myocardial infarction or a stroke. In fact, the whole point of

detecting vulnerable plaques is for appropriate treatment prior to rupture, to prevent such events from occurring. The problem with current thermography catheters is that having metal or plastic arms which touch and possibly 'scratch' the vessel wall, may, by itself, contribute, by applying a mechanical pressure, to the rupture of such thin fibrous caps once it comes in contact with them, essentially triggering the onset of the same phenomena they initially are designed to detect in order to prevent from happening.

In an exemplary embodiment of the invention, the higher temperature gradients expected in the current method of cold-saline injection allows the measurement of large temperature differences, due to the saline's heating as it comes in contact with a warmer lesion, to be measured not only on the arterial wall itself, but in its vicinity, e.g., in comparison to the centerline of the blood vessel, or even to a core temperature measured proximal to the injection site. In an exemplary embodiment of the invention, the sensor is at least 0.1 mm, 0.5 mm, 1 mm, 2 mm, or more away from the vessel wall or at least vulnerable plaque and or is pressed against such plaque with a force of less than, for example, 20 grams, 10 grams, 5 grams or 3 grams (e.g., to avoid damaging the vessel wall or plaque cap). In an exemplary embodiment of the invention, the sensor is embedded in a section with a large surface area, for example, having a contact surface with the wall with a minimal dimension of 0.5 mm or 1 mm.

In an exemplary embodiment of the invention, imaging (e.g., IVUS [intravascular ultra-sound], OCT [optical coherence tomography]) is applied during measurement, optionally using a same catheter, to determine a distance of sensors form the wall. Optionally or alternatively, the gates, described below may be used instead or in addition for catheter anchoring and positioning.

Moreover, numerical simulations show that such differences can be measured not only radially but also in the longitudinal direction of the artery, keeping the sensors at a fair distance from the blood vessel's wall.

Avoiding the risk of triggering a plaque rupture due to a contact between the thermography sensors and the arterial wall can have substantial impact regarding the regulatory approval for the usage of such devices (i.e. FDA and CE approvals).

3. **Small difference between absolute temperature values:**

Current Thermography catheters measure only the absolute values of temperature at different sites, in an attempt to compare between the absolute value of the core temperature (which is usually 37°C) and the inflamed lesion, leading in some occasions to a difficult comparison of value-differences on the order of 0.1-0.3°C.

Since the measured absolute values of the temperatures both of the blood and the vessel wall are so close to each other, such comparisons require both high sensitivity from the sensors, and a very reliable post-processing ability to avoid misinterpretation of the results.

In an exemplary embodiment of the invention, in addition to the fact that the difference between the absolute values themselves, while applying cold saline in the current suggested method, is much higher, initial numerical simulations also show that measuring the flow-heating rate (measured as degrees per a unit of length along the longitudinal axis of the artery) can possess additional value, as sites with warmer lesions exhibit a much higher slope of temperature-rising (from the region proximal to the lesion to a region distal to it). Combining the data of the temperature slope to the temperature values can exhibit results with a much higher reliability than the absolute temperature values alone.

An aspect of some embodiments of the invention relates to improving a dynamic range of blood temperature measurements by pre-cooling blood and allowing the blood to be heated by vessel walls, for example, in veins and/or arteries. Optionally, differences in heating caused by different types of wall situations are reflected in different amounts of heating of blood. In an exemplary embodiment of the invention, the measurement is provided without contact or without forceful contact with a blood vessel wall, Optionally, the contact is allowed or enforced, but the temperature senor used is positioned in the blood flow, rather than against the wall.

In an exemplary embodiment of the invention, one or more flow retarding elements are used in conjunction with temperature sensors.

An aspect of some embodiments of the invention relates to a method of plaque identification and classification which utilizes one or more gradients in blood

temperature measurements and/or in wall measurements. Optionally, the gradients include a radial gradient. Optionally or alternatively, the gradients include an axial gradient. Optionally or alternatively, the gradients include a circumferential gradient.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details of construction and the arrangement of the components and/or methods set forth in the following description and/or illustrated in the drawings and/or the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

Available ICT (intracoronary thermography) catheters can be classified, generally, into two types: catheters that measure the artery wall temperature directly (by attaching temperature sensors to the artery wall), and catheters that measure the wall temperature indirectly by measuring the blood stream temperature. The main problem of measuring the blood stream temperature is that temperature gradients, originating from the artery wall, are significantly reduced by the blood stream, and therefore practically undetectable by the sensors.

In an exemplary embodiment of the invention, one or more of the following three parts of an ICT system are modified, e.g., as compared to current ICT systems:

1. **Exemplary Technical modifications for the catheter:**
   a. Temperature Sensor Arrangement.

      In an exemplary embodiment of the invention, there is provided a new arrangement of the temperature sensors (e.g., thermistors or thermocouples) on the catheter body: for example, a proximal temperature sensor that will act as a reference sensor can be located on the catheter approximately at the entrance to the coronary arteries (see FIG. 1). Optionally, the distal temperature sensor(s) are slowly pulled along the coronary artery tree to map its temperature, with the reference sensor fixed in its position; e.g. it may be attached to the introducer catheter. The proximal temperature sensor optionally measures the blood true core temperature, for example, before or after cooling. Alternatively or additionally, the reference sensor is moved.

b. Temperature Sensor Deployment

In exemplary embodiments of the invention, there are provided several options of deployment of the distal temperature sensors within a retractable temperature measurement catheter of a multi-lumen delivery catheter. Namely, according to a longitudinally positioned configuration, a circumferentially positioned configuration, or a combination of both types of positioned configurations, wherein, for example, 3, 5, 7, 10 or smaller, intermediate, or larger, numbers of temperature sensors may be deployed, having a parallel, series, or series/parallel, electrical wiring configuration, for example, as shown in FIG. 2 (A-D). Another possibility being that only one distal temperature sensor is deployed (not illustrated).

FIG. 2-A illustrates an exemplary embodiment of an arrangement of the (distal) temperature (measuring) sensors (e.g. thermistor or thermocouple) **42**, positioned within the retractable temperature measurement catheter **36** of a multi-lumen delivery catheter **34** (FIGS. 7 - 11), according to a *longitudinally* positioned configuration having a *parallel* electrical wiring configuration. FIG. 2-B illustrates an exemplary embodiment of an arrangement of the distal temperature sensors **42**, positioned within the retractable temperature measurement catheter **36** of the multi-lumen delivery catheter **34**, according to a *circumferentially* positioned configuration having a *parallel* electrical wiring configuration. FIG. 2-C illustrates an exemplary embodiment of an arrangement of the distal temperature sensors **42**, positioned within the retractable temperature measurement catheter **36** of the multi-lumen delivery catheter **34**, according to a *circumferentially* positioned configuration having a *series* electrical wiring configuration. FIG. 2-D illustrates an exemplary embodiment of an arrangement of the distal temperature sensors **42**, positioned within the retractable temperature measurement catheter **36** of the multi-lumen delivery catheter **34**, according to a *longitudinally* positioned configuration having a *series* electrical wiring configuration. The exemplary embodiments of the distal temperature sensors **42** shown in FIG. 2-C and -D, featuring a *series* electrical wiring configuration, may improve sensitivity of the distal temperature sensors **42** for measuring temperature differences (relative to each other), particularly, wherein the distal temperature sensors **42** are thermocouples.

c. Blood Flow Disturbance Mechanism

In an exemplary embodiment of the invention, the catheter is designed to modify flow so as to enhance desired heat conduction situations, for example, as shown in FIG. 3. The presence of the temperature sensors acts as a local disturbance for blood flow, which can be advantageously exploited for 'capturing' low temperature changes. The tips of the temperature sensors may have various different shapes and geometries for the objective of enhancing their sensitivity for 'capturing' local changes in the blood flow temperature. It is noted that, by contrast, known ICT catheters, and temperature sensors thereof, are configured and operated utilizing specific hydrodynamic designs for the objective of *preventing* or/and *minimizing* such blood flow disturbances.

FIG. 3 (A-E) illustrates an exemplary embodiment of a retractable temperature measurement catheter **36**, including an exemplary distal retractable sheath (shaft) **52**, exemplary temperature sensors (e.g. thermistor or thermocouple) **42** [arranged according to longitudinally (axially) or/and circumferentially positioned configurations], and exemplary gates '**g**' which function as another type of blood flow disturbance mechanism. Proximal retraction (indicated via dashed arrows **53**) of sheath (shaft) **52** exposes inner insulated temperature sensors **42**, and gates **g**. Alternatively, while sheath (shaft) **52** remains stationary along catheter 36, the inner insulated temperature sensors **42**, and gates **g**, are pushed forward to be exposed. As shown, temperature sensors **42** may be located or positioned at various different possible locations or positions within catheter **36**. For example, separate from (i.e., not in direct association or contact with) gates **g**, as shown in FIG. 3-B and -E; or, connected or attached to (i.e., in direct association or contact with) gates **g**, as shown in FIG. 3-C, -D, and -E. Gates **g** may be in a form of, for example, a flexible metal, such as nitonol. Opening or closing gates **g** may be achieved via movement of retractable sheath (shaft) **52**.

FIG. 3-E qualitatively illustrates an exemplary blood recirculation region featuring exemplary blood flow streamlines '**sls**' formed by an exemplary blood flow disturbance mechanism including both temperature sensors **42** and a gate **g**. The recirculation region, via blood flow streamlines '**sls**', 'traps' heat, and therefore, enhance sensitivity of temperature sensors **42** to sense (detect) intravascular

temperature gradients. Streamlines ' sls ' may remove heat from the vessel wall via convection, for enhancing sensing (detecting) of low changes of vessel wall temperatures.

d. Blood Cooling Mechanism

Optionally, the catheter itself includes a blood cooling mechanism, such as a cooling unit or includes a lumen for provision of cool saline or other acceptable fluid from an external source, such as syringe. Optionally, a pump for controlling the flow rate of the coolant, is provided. In an exemplary embodiment of the invention, the system described in "Cardiac output by thermodilution technique. Effect of injectate's volume and temperature on accuracy and reproducibility in the critically Ill patient", 1983; 84; 418-422, U. Elkayam, R Berkley, S Azen, L Weber, B Geva and W L Henry, is used. Optionally, the catheter includes a lumen for cooling fluid with an exit. Optionally, the exit is between the two sensors, so the reference sensor can measure the normal temperature of blood. Alternatively, the proximal sensor is positioned to measure flow in blood after the cooled blood has mixed. Optionally, the catheter includes one or more shaped element adjacent the lumen opening to assist in mixing the blood flow. Optionally, the lumen for the cooling fluid is insulated (e.g., with an insulation layer), at least adjacent the reference sensor.

e. Axial Movement Mechanism

In an exemplary embodiment of the invention, the catheter includes a movement mechanism to allow axial movement of a measurement senor relative to a reference sensor. Optionally, the two sensors are mounted of tubes or extensions which can be separately moved (e.g., with the catheter acting as a sheath). Optionally or alternatively, one senor is mounted on the catheter and another is mounted on an extension that rides in a lumen within the catheter. Optionally, both sensors sit on a same extension which is moved relative to an exit of cooling fluid, which cooling fluid may be provided via a lumen also used to carry an extension which carries one or both sensors. In an exemplary embodiment of the invention, the sensors are configured to be moved, for example, to have a distance between them of between 1 and 12 cm, or a greater distance or a smaller or intermediate distance. Optionally, one or more stops are provided, for example, outside the body, to allow easy

identification of the relative positions of the sensors. Optionally or alternatively, movement is provided by a motor or other actuator located outside the body.

f. Small Blood Vessel Design

In an exemplary embodiment of the invention, the catheter is designed for small blood vessels, such as coronary vessel or brain vessels. Optionally, the catheter has a maximal diameter in its last 15 cm of less than 20 mm, 10 mm, 7mm, 5mm, 3mm or intermediate sizes.

g. Additional Design / Construction / Functional (operational) Features

In an exemplary embodiment of the invention, the catheter includes one or more temperate sensors connected by a wire or other signal conduction means to a processor and optional display. Optionally, the catheter design is otherwise standard and/or may include a fluid injection lumen, optionally insulated.

2. **Exemplary Modification of the intracoronary thermography (ICT) procedure:**

In an exemplary embodiment of the invention, there is provided injection of cold saline (or other cooling fluid for cooling of vessel flow) to the coronary artery during the procedure (see FIG. 4). As shown in FIG. 4, during an intracoronary thermography procedure, a catheter delivery system **34**, positioned within the coronary artery **25** having vessel wall **30**, while blood flow is maintained, releases (e.g., via injection) cold saline **27** into the coronary artery **25**. The catheter delivery system **34** includes a (proximal) stationary reference temperature (measuring) sensor **44**, and a plurality of (for example, four) (distal) temperature (measuring) sensors (e.g. thermistors or/and thermocouple) **42**, for measuring temperatures at different locations within the coronary artery **25**. One potential objective of this injection in some embodiments of the invention is to increase the temperature gradients in the blood stream so that it may be detectable by the sensors.

Moreover, such injection may also be used in the investigation of complex anatomical cases, such as locating vulnerable plaque in a coronary artery bifurcation, where more than one plaque usually exists.

In an exemplary embodiment of the invention, as shown in FIG. 5, the retractable temperature measurement catheter **36** will have longitudinal arrangement of the temperature sensors, for example, (distal) temperature (measuring) sensors (e.g. thermistors or/and thermocouple) **42**, and a (proximal) stationary reference

temperature (measuring) sensor **44**, the distal of which will be designated at the side-branch **28** of the bifurcation, and the proximal of which will be designated at the main-branch **29**. By that, simultaneous readings of the temperature at both the main **29** branch and the side branch **28**, it may be possible to spot a vulnerable plaque in either branches of the bifurcation, among other possible stable plaques. Optionally, the catheter **36** itself forks, for example, including an extending temperature probe, for measuring the downstream part of the main vessel as well (or for measuring two branch vessels). Other possible applications of such embodiment can possibly be locating a vulnerable plaque in the case of multi-focal coronary artery disease, a case in which not all the plaques can be angiographically detected, nor can the most vulnerable of which be easily identified. By applying the suggested embodiment, it expected to locate the currently hidden vulnerable plaque among a series of multi-focal inflammation sites.

An additional optional technique for identifying underlying vulnerable plaque is to expose its elevated heat source relative to the surrounding non-inflamed regions. While lowering blood flow temperature through cold saline injection, the vessel wall loses more heat to the blood stream, and therefore its temperature decreases as well. Since vulnerable plaque heat generation is relatively higher than its surroundings, its temperature profile as a function of time (via changing blood temperature) should act differently, namely, by cooling slower/faster then a non-inflamed vessel wall section. Therefore, the procedure may include intermittent injections of cold saline, for intermittently cooling and then thawing the measured area.

Accordingly, retraction speed of the temperature sensors is coordinated with the cold saline injection dynamics (for example, intermittent). An exemplary blood temperature [°C] vs. time [seconds] profile by using such a procedure is qualitatively seen as a graphical plot **23** in FIG. 6, where blood temperature decreases and then increases due to intermittent cold saline injections. By identifying unique features of temperature profiles as a function of time (due to cooling/thawing of blood flow), an underlying hidden heat source (e.g., inflamed plaque) may be identified.

3. **Exemplary Modification of the post processing procedure:**

All the available ICT catheters use only the absolute temperature measured. In an exemplary embodiment of the invention, data from the slope of temperature along the artery axis is utilized. This is enabled by the increase in temperature gradients achieved by the cold saline injection and may more accurately reveal the locations of dangerous plaque. In particular, plaque which is not visible when imaging (e.g., using angiography) may be visible based on its functionality. Mapping a surface area allows to detect such plaque and/or distinguish such plaque form regular wall surfaces and/or sclerosed wall surfaces.

In an exemplary embodiment of the invention, such classification is performed automatically by software.

In an exemplary embodiment of the invention, classification, manual or automatic, may also use data from other sources, such as IVUS and/or may be used to classify plaque according to, for example, size, gradients within or outside of plaque, shape and/or cap thickness. Optionally, a function or table or rules or a neural network or a case based system or other classifying means are provided to link such characteristics and an indication of danger or class.

While in some embodiments, the raw measured temperature, temperature gradients or temperature differences (optionally corrected for vessel type or coolant temperature) are used for classification and/or diagnosis, in some embodiments of the invention the plaque temperature may be reconstructed.

In an exemplary embodiment of the invention, such reconstruction is based on a calibration and/or a series of corrections or parameters or examples, for example, in a database or form of a table or function, which relate to, for example, one or more of vessel size or geometry, stenosis location(s), flow rate, sensor positions and catheter design. In an exemplary embodiment of the invention, the various parameters are used to look up one or more parameters to be used with a function for converting measured temperatures into a wall temperature estimate. In another example, an interpolation or extrapolation from one or more previously measured or calculated examples, is used. In another example, a model of the blood vessel is used and the temperatures calculated by solving the model using the measured readings as some or all of the boundary conditions.

In an exemplary embodiment of the invention, a complete ICT procedure, according to an exemplary embodiment of the invention, is as follows:

1. An introducer catheter reaches the entrance of the coronary arteries through the aorta, or by any other vessel usually used in regular angiography procedure. Alternatively, the introducer is used for any other vessel in the body.
2. A thermography catheter is then introduced through the introducer catheter into the target vessel (e.g., coronary artery). The ICT procedure may be conjugated with any other common procedures such as IVUS, IVUS-VH [intravascular ultrasound - virtual histology], etc.
3. The thermography catheter is positioned such that the distal temperature sensor(s) are at the most distal end of the vessel section, of which temperature should be measured.
4. A reference proximal temperature sensor, which is located, for example, on the thermography catheter, or on the introducer catheter, or on a third catheter, is positioned a few centimeters proximal to the vessel section to be measured. Optionally, the position of the reference proximal sensor is fixed during the procedure, however may be changed from time to tome according to the physician's decision.
5. Optionally, any gates which cover or are adjacent measurement sensor, are extended and/or used for anchoring.
6. Before the temperature measurement process begins, cooling of the blood flow that enters into the examined vessels takes place, for example, by using cold saline injection, or by any other means. This cooling of blood may continue along the whole temperature measurement process.
7. After the blood flow cooling in the vessel is achieved, the temperature measurements from all the temperature sensors (distal and proximal) are recorded.
8. During the temperature measurement, the thermography catheter and the distal temperature sensors located on it may stay fixed in place or may be dragged backward into the introducer catheter in a way that the distal sensor(s) 'scan'/ sample the temperatures along the vessel.

9. Analysis of the temperature records is optionally made using dedicated software to yield information from the temperature records, temperature differences, slopes etc. to produce risk analysis for the vessel segments measured. As mentioned herein, this information may be conjugated with data obtained by other methods (such as IVUS etc.) to estimate the risk and or the vulnerability of the plaques and stenoses in the vessel.
10. Stents placement or any other manipulation on the vessel can be done before or after the thermography procedure, for example, similar to done in a IVUS or a IVUS-VH procedure.

Additional Technical Features, Characteristics, Properties, and Aspects, of Exemplary Embodiments of the Invention

Reference is made to FIGS. 7 (a, b); 8 (a, b); 9 (a, b); 10 (a, b); 11 (a, b, c, d); 13 (a, b, c, d, e); and 14 (a, b, c). Immediately following is a brief descriptive listing of main components or/and elements of some embodiments of the invention illustrated in the figures:

30 = blood vessel wall.

32 = blood vessel lumen.

34 = multi-lumen delivery catheter (proximal shaft). Multi-lumen delivery catheter **34** optionally includes a lumen dedicated for delivering cooling fluid to the (blood) vessel

36 = retractable temperature measurement catheter (retractable into multi-lumen delivery catheter **34**). Optionally, may include a (distal) retractable sheath (shaft).

38 = (proximal) reference insulated temperature sensor assembly.

40 = (distal) insulated temperature sensor assembly (at least one temperature sensor assembly), configured for scanning / measuring temperature along the target vessel (artery), wherein each temperature sensor assembly includes the temperature (measuring) sensor **42**, the flexible metallic arm **50**, the polymeric insulation sleeve **46**, the polymeric sleeve lumen **48**, and the sensor electrical wiring.

42 = (distal) temperature (measuring) sensor (e.g. thermistor or thermocouple). For exemplary embodiments of the invention relating to temperature measuring procedures **42** is, for example, either a thermistor or a thermocouple. For exemplary embodiments of the invention relating to therapeutic (heat treatment) procedures, **42** is a thermistor.

44 = (proximal) stationary reference temperature (measuring) sensor.

46 = polymeric insulation (water resistant and electrically isolated) sleeve, which encapsulates the temperature (measuring) sensor **42**, the electrical wiring, and the flexible metallic arm **50**, and may be of hydrophilic or/and hydrophobic material.

48 = polymeric sleeve lumen.

50 = flexible metallic (e.g. nitinol - NiTi) arm, which supports the (distal) insulated temperature sensor assembly **40** and the (proximal) reference insulated temperature sensor assembly **38**.

52 = (distal) retractable sheath (shaft) of the retractable temperature measurement catheter **36**. Retraction of the sheath (shaft) exposes the inner insulated temperature sensor assemblies **40**. Alternatively, the inner insulated temperature sensor assemblies **40** may be pushed forward to be exposed, while the (distal) retractable sheath (shaft) **52** remains stationary.

54 = guidewire (standard commercially available).

56 = lumen of multi-lumen delivery catheter (proximal shaft).

Immediately following is a brief descriptive listing of main relative movements, and relevant diameters, of above listed main components or/and elements of some embodiments of the invention illustrated in the figures:

35 = relative axial movement between the multi-lumen delivery catheter (proximal shaft) **34** and the guidewire **54**. The multi-lumen delivery catheter **34** is pushed forward to the target vessel on the guidewire **54**.

37 = relative axial movement between the retractable temperature measurement catheter **36** and the multi-lumen delivery catheter **34**. The retractable temperature measurement catheter **36** is pushed outward (distally) from the multi-lumen delivery catheter **34**. If the guidewire lumen is inside the temperature measurement catheter **36**, then the axial movement of the temperature measurement catheter **36** is also relative to the guidewire **54**.

39 = relative axial movement between the reference (proximal) insulated temperature sensor element assembly **38** and the multi-lumen delivery catheter **34**. The reference (proximal) insulated temperature sensor element assembly **38** is pushed outward (distally) from the multi-lumen delivery catheter **34**.

41 = relative movement of the main (distal) insulated sensor element assembly **40** and the temperature measurement catheter **36**. The arms move away from the axis of the temperature measurement catheter **36**.

43 = rotational movement of the temperature measurement catheter **36**, with/without the distal retractable sheath (shaft) **52**, or, alternatively, of only the main (distal) insulated sensor element assembly **40**.

53 = relative axial movement between the distal retractable sheath (shaft) **52** and the multi-lumen delivery catheter **34** and the temperature measurement catheter **36**; meaning that only the distal retractable sheath (shaft) **52** is (proximally) pulled backwards.

d = maximum diameter of the temperature measurement catheter **36**. For a temperature measurement procedure, **d** corresponds to a fully-opened configuration. In an exemplary embodiment wherein the distal retractable sheath (shaft) **52** has several axial positions of expansion / retraction, then **d** corresponds to a semi-opened configuration. Such an exemplary embodiment is applicable to either temperature measuring procedures or therapeutic (heat treatment) procedures. For either temperature measurement procedures or therapeutic (heat treatment) procedures, the temperature measurement catheter **36** maximum diameter **d** has a magnitude less than the diameter of the examined vessel.

$\mathbf{d_2}$ = maximum diameter of the temperature measurement catheter **36** in a fully-opened configuration, being equal to inner diameter of a treated vessel, where $\mathbf{d_2}$ is equal to, or larger than **d**. The temperature measurement catheter **36** maximum diameter $\mathbf{d_2}$ is applicable to exemplary embodiments of therapeutic (heat treatment) procedures.

The following technical features, characteristics, properties, and aspects, are applicable to the exemplary embodiments illustratively described herein.

> The relative proportions of any of the above listed main components or/and elements of embodiments of the invention illustrated in the figures are not limited to those shown in the figures.

> When retractable temperature measurement catheter **36** includes only one temperature sensor **42**, the (distal) retractable sheath (shaft) **52** thereof may be omitted.

> When the (distal) temperature sensor assemblies **40** are exposed into the blood stream, and tend toward the vessel wall **30**, no contact with the vessel wall **30** is required or enforced. In addition, the maximal outer diameter (**d**) of the retractable temperature measurement catheter **36** in its fully open state is less than the typical diameter of the vessel (e.g. human coronary arteries, less than 3mm), such that no radial pressure is applied to the vessel wall **30**.

> The temperature (measuring) sensors can be thermistors, thermocouples, or any other temperature sensing technology that can be used on a catheter.

> The multi-lumen delivery catheter **34** may not be genuine, but may be used during the procedure. Such catheters exists commercially (e.g. such as those shown in FIGS. 7 - 11), however might be manufactured exactly to meet the needs of the described system. Commercially available multi-lumen catheters might not fit (length, connectors of the different ports, sizes and numbers of the orifices/lumens, etc.) and may need adjustments.

> As shown in FIGS. 9 and 11b, the guidewire lumen may pass axially through multi-lumen delivery catheter **34** and retractable temperature measurement catheter **36**. In such case the multi-lumen delivery catheter **34** can have two lumens only.

> The lumens of the multi-lumen delivery catheter **34** are not restricted to the shapes described in FIG. 11. The shape of the lumens may fit exactly the shapes of the guidewire **54**, and temperature (measuring) sensors **42**, polymeric water resistant and electrically isolated sleeve **46**, and polymeric sleeve lumen **48**.

> One of the lumens of the multi-lumen delivery catheter **34** is dedicated for the cold-saline injection.

> As shown in FIG. 13, the (proximal) stationary reference temperature (measuring) sensor **44** may be located on the distal retractable sheath (shaft) **52** of retractable temperature measurement catheter **36**, and therefore may not need the (proximal) reference insulated temperature sensor assembly **38**. In addition, in such case, the stationary reference temperature (measuring) sensor **44** will not need a separate lumen in the multi-lumen delivery catheter **34**.

Manipulation of the multi-lumen delivery catheter (proximal shaft) 34 and the retractable temperature measurement catheter 36

After the guidewire **54** is placed in the target vessel (e.g., coronary artery), the multi-lumen delivery catheter **34** (including the retractable temperature measurement catheter **36** and the reference (proximal) insulated temperature sensor assembly **38** therein) is introduced and guided into the target vessel, with the tip of the multi-lumen delivery catheter **34** a few centimeters proximally (upstream) to the desired measurement area. Then, retractable temperature measurement catheter **36** is pushed distally (downstream) into the vessel to the measurement area, while the multi-lumen delivery catheter **34** remains stationary. In case that the guidewire lumen crosses the retractable temperature measurement catheter **36**, then retractable temperature measurement catheter **36** is guided along the guidewire **54**. If the reference temperature (measuring) sensor **44** is not deployed on the (distal) retractable sheath (shaft) **52**, then the (proximal) reference insulated temperature sensor assembly **38** is pushed distally (downstream) into the vessel, up to several centimeters from the tip of the multi-lumen delivery catheter **34**. Then, the distal retractable sheath (shaft) **52** is retracted in order to expose the (one or more) (distal) insulated temperature sensor assemblies **40**. In case the insulated temperature sensor assemblies **40** include flexible metallic arms **50**, then the retraction of (distal) retractable sheath (shaft) **52** enables the insulated temperature sensor assemblies **40** to radially spread and get close to the vessel wall **30**, without applying pressure thereto. Alternatively, distal retractable sheath (shaft) **52** may remain stationary while the inner main (distal) insulated temperature sensor assemblies **40** are pushed forward to become exposed. Then, coolant liquid (e.g., cold saline) may be injected through a dedicated lumen in the multi-lumen delivery catheter **34**. Then the retractable temperature measurement catheter **36** is retracted backwards in order to measure temperatures along the vessel lumen. During this procedure, all the (distal) temperature (measuring) sensor **42** and the proximal) stationary reference temperature (measuring) sensor **44** measure temperatures, which are simultaneously recorded, processed, and analyzed. After the temperature measurements are done, all the components are retracted to a closed configuration (as at the beginning of the temperature measurement procedure) and retracted out of the vessel.

Therapeutic (Heat Treatment) Procedure (FIGS. 12 , 13, and 14)

Some additional exemplary embodiments of the invention relate to a method of heat treating a blood vessel wall (e.g., including plaque) of a blood vessel. FIG. 12 is a (block-type) flow diagram of an exemplary embodiment of the method of heat treating a blood vessel wall (e.g., including plaque) of a blood vessel. Reference is also made to FIGS. 13 and 14. In an exemplary embodiment of the invention, the method includes:

> providing a temperature sensor assembly **40**, including at least one temperature sensor **42** each configured and operative as a thermistor.

> positioning the temperature sensor assembly **40** inside the blood vessel, for example, at a location associated with plaque.

> activating the thermistor of the temperature sensor assembly **40**, by supplying current to each of the at least one thermistor **42**.

> opening the temperature sensor assembly **40** to a fully-opened configuration, such that there is contact of a tip of at least one of the thermistors **42** with the blood vessel wall (e.g., including plaque).

> increasing the current supplied to at least one of the thermistors **42**, whereby temperature of the at least one thermistors increases to higher than 50 ^{o}C.

> axially or/and circumferentially moving the temperature sensor assembly **40** in the blood vessel, for effecting thermal damage to the blood vessel wall, including, for example, for effecting thermal damage to plaque therein.

> removing the temperature sensor assembly **40** to outside of the blood vessel.

In an exemplary embodiment, increasing of the current supplied to the at least one of the thermistors is repeated until there is an indication of sufficiently effecting the thermal damage to the blood vessel wall (e.g., to plaque). Ordinarily, this requires increasing the temperature of the at least one thermistor to higher than 50 ^{o}C. In another exemplary embodiment, the thermistor temperature may be increased to less than 50 ^{o}C, for example, to within a range of between 42 ^{o}C and 50 ^{o}C.

Effecting thermal damage to the blood vessel wall (e.g., including plaque) results in stabilizing the blood vessel wall, for example, stabilizing plaque located inside the blood vessel wall of the blood vessel.

In exemplary embodiments of the method of heat treating a blood vessel wall, for example, including plaque, of a blood vessel, the plaque is vulnerable plaque.

The exemplary embodiment of the method of heat treating a blood vessel wall, for example, including plaque, of a blood vessel, is particularly applicable to treating a subject with atherosclerosis.

In an exemplary embodiment of the invention, the above exemplary embodiment of the method of heat treating a blood vessel wall (e.g., including plaque) of a blood vessel is performed for thermally treating the blood vessel wall (plaque) only, namely, without using the multi-lumen delivery catheter, and main components / elements (including exemplary retractable temperature measurement catheter and intracoronary catheter temperature sensors), thereof, for identifying and measuring temperature differences in the blood vessel wall.

In another exemplary embodiment of the invention, before performing the above exemplary embodiment of the method of heat treating a blood vessel wall of a blood vessel, there is first using the multi-lumen delivery catheter, and main components / elements (including exemplary retractable temperature measurement catheter and intracoronary catheter temperature sensors), thereof, for identifying and measuring temperature differences in the wall of a vessel.

Various features, characteristics, and aspects, of exemplary embodiments of the invention particularly relating to the method of heat treating a blood vessel wall (e.g., including plaque) of a blood vessel follow herein below.

Inside a blood vessel wall (such as blood vessel wall **30** illustrated in the figures), plaque, for example, vulnerable plaque, develops and consists of an active inflammatory biological process within its core, as low-density-lipoproteins (LDL) infiltrate from the circulating blood through the endothelia layer. Once inside, the LDL is oxidized, and the oxidized LDL recruits macrophages, which in turn absorb the oxidized LDL and turn into necrotic foam-cells. The macrophages also release proteolytic enzymes (MMPs), which in turn decompose the collagen that is the main component of the fibrous cap of the plaque, thus thinning the cap that separates the inner soft core of the plaque from the lumen. The ruptures are believed to be influenced by biomechanical forces which cause high stress concentration due to the very soft lipid core of the plaque, combined with a very thin fibrous cap. One of the following two factors: (i) increasing the thickness of the fibrous cap, or/and (ii) increasing the stiffness of the inner core, of the plaque, can have a positive influence on the stability of the

plaque, and protect it from a rupture, which can lead to severe consequences, including myocardial infarctions and strokes.

Heating tissue and increasing tissue temperature to more than 55 °C results in cell death and creation of a coagulative necrosis lesion.

Thermistors are electrical resistors, whose resistance is a function of its surrounding temperature. Therefore, supplying a constant electrical current to a thermistor enable measuring the voltage on the thermistor and deducing the temperature in the thermistor environment. A thermistor, being a resistor, has the characteristic of producing and dissipating heat, which causes bias to the temperature in the thermistor environment. The thermistor temperature reading is still the average temperature on the thermistor volume, however, higher than the temperature of the thermistor environment. The amount of heat produced by the thermistor is affected by the power applied (provided) thereto, according to the applied current, and the resistance of the thermistor, in accordance with the following well known relation of electricity:

$$Power\ [\text{watt}] = I^2R,$$

wherein I is the electrical current [amperes or amps], and R is the thermistor resistance [ohms].

The amount of heat dissipated from a thermistor is controlled according to: (a) its operative parameters which characterize operation of the thermistor, and (b) the amount of current supplied to the thermistor. Operation of a thermistor is characterized by 'at least' the following three operative parameters: (1) **Dissipation Coefficient**, which determines how many degrees its temperature changes as a function of the power supplied thereto; (2) **Nominal Resistance**, being the thermistor resistance at a standard reference temperature, for example, 25 °C, and (3) **Maximum Power**, being the maximum power which can be supplied (provided) to the thermistor during operation.

Therefore, this inherent property of thermistors can be used for both measuring temperatures of blood vessel walls, and diagnosing presence of plaque (for example, vulnerable plaque) located inside a blood vessel wall, and then to therapeutically (heat) treat the plaque (vulnerable plaque) by locally increasing the temperature of the plaque, in general, and specifically, of the fibrous cap thereof, to higher than about 50 °C, and more particularly, higher than about 55 °C, with all procedures performed using the same thermistors.

By changing the current supplies to the thermistors, one can control the heat dissipating therefrom. Therefore, one can set a minimal current for the diagnostic procedure, in order to minimize heat produced by the thermistor, which in turn minimizes the bias of the thermistor measurements of the surrounding temperature. For performing a therapeutic (heat treatment) procedure, one can increase the current supplied to the thermistors, thereby causing thermistor temperature to increase, in order to heat the blood vessel wall, for the objective of causing a thermal type of damage to the plaque, resulting in stabilizing the plaque. During the therapeutic (heat treatment) procedure, the current supplied to each thermistors can be changed, in accordance with a pre-determined calibration profile associated with each respective thermistor. During the therapeutic (heat treatment) the thermistor temperature measurement is continuously monitored and measured, in order to control heating of the plaque. The therapeutic (heat treatment) procedure may be performed by using multiple cycles of heating the plaque. In addition, between such heating cycles, the heat generated by the thermistors is dissipated by conduction and perfusion cooling effects, or even by coolant fluid (e.g., cold saline) flushes, thereby preventing or minimizing the possibility of over heating the blood vessel wall.

In order to localize the thermal damage to the plaque, the thermistors need to contact the blood vessel wall **30**. In such a case, retractable temperature measurement catheter **36** has the ability to retract the (distal) retractable sheath (shaft) **52** at several axial positions thereof, to enable opening of the (distal) insulated temperature sensor assembly **40**. In the fully-opened configuration (FIG. 13c, d, and e) the thermistors **42** at the tip of the (distal) insulated temperature sensor assembly **40** should be sufficiently open to achieve full contact with the blood vessel wall **30**.

In order to effect the thermal effect in a circumferential manner or configuration, the retractable temperature measurement catheter **36**, or (distal) insulated temperature sensor assembly **40** only, includes a torque mechanism, to allow the catheter **36**, or temperature sensor assembly **40** only, from rotating around its axis up to 360 ^{o} in either a (clockwise or counter-clockwise) direction. Since the catheter **40** can be retracted, there can be a simultaneous axial and circumferential movement of the catheter **36**, or temperature sensor assembly **40** only. Additionally, the tip of the temperature sensor assembly **40**, which includes the thermistor **42**, may be configured as a flexible joint, so

that the tip is bendable to fit the shape of the blood vessel wall **30**, in addition to increase the contact area between the thermistor **42** and the blood vessel wall **30**. Therefore, enabling more efficient local heating of the blood vessel wall **30**.

The hereinabove illustratively described exemplary embodiments of the invention, particularly, as shown in FIGS. 13 and 14, are not limited, and can be combined with any of the configurations shown in FIGS. 7 - 11 (e.g. different lumen for the guidewire, different number of temperature sensor elements, etc., etc.)

It is expected that during the life of a patent maturing from this application many relevant temperature sensing technologies will be developed and the scope of the term "temperature sensor" is intended to include all such new technologies *a priori*.

As used herein the term "about" refers to ± 10 %.

The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to". This term encompasses the terms "consisting of" and "consisting essentially of".

The phrase "consisting essentially of" means that the composition or method may include additional ingredients and/or steps, but only if the additional ingredients and/or steps do not materially alter the basic and novel characteristics of the claimed composition or method.

As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

The word "exemplary" is used herein to mean "serving as an example, instance or illustration". Any embodiment described as "exemplary" is not necessarily to be construed as preferred or advantageous over other embodiments and/or to exclude the incorporation of features from other embodiments.

The word "optionally" is used herein to mean "is provided in some embodiments and not provided in other embodiments". Any particular embodiment of the invention may include a plurality of "optional" features unless such features conflict.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range

format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

As used herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find experimental support in the following examples.

EXAMPLES

Reference is now made to the following example, which together with the above description, illustrate some embodiments of the invention in a non limiting fashion.

Example I: Numerical analysis of an intracoronary thermography catheter and method for temperature gradient measurement in the vicinity of warm inflamed atherosclerotic plaques

This example tries to estimate temperature differences of the blood flow in the vicinity of warmer arterial wall-regions, compared to the core temperature, both in a baseline condition of physiologic blood temperature measurement, and also while injecting the bloodstream with cold saline in order to amplify the temperature gradients. Varying flow conditions in both situations is conducted next, in order to map flow or pressure influences on the measured temperature gradients.

METHODS

A 3-D parametric model of an LAD coronary artery with a plaque has been designed in a CAD software (Solidworks Corporation©, Concord, Massachusetts, USA) and imported into a numerical Fluid-Structure-Interaction (FSI) software (ADINA R & D, Inc., MA, USA). The outer dimensions for the media and lumen were taken from a sequence of IVUS-VH LAD artery images, and incorporated into the CAD software only as the circular outer dimensions of these tissues. The LAD was chosen for this simulation due its significance in the left ventricle perfusion, and also as one third of coronary stenosis tend to occur in this artery [20].

The model consisted of a 3-D stenosed vessel section (see FIGs. 15A-B), wherein A shows the geometry of an exemplary simulated lumen of an artery, and B shows a longitudinal cross-section of the artery, including the media, adventitia, eccentric plaque at the bottom, and necrotic tissue within the plaque. The vessel section had a length and average diameter of 35 mm and 3.5 mm, respectively. A 36 mm long

extension of the vessel was added to its proximal part in order to allow the fluid to fully develop as it enters the arterial section. The stenosed LAD model was investigated under a typical physiological LAD flow profile. The flow inside the vessel was pulsating. It is generally agreed that under physiological conditions, the Newtonian model for blood rheology can be considered acceptable for a first level approximation. For this reason, the simulations considered blood as an incompressible and Newtonian fluid. The flow was assumed to be laminar, as the mean Reynolds number in the coronary arteries is about 120 under resting conditions [21]. Blood and arterial wall properties were taken from the literature [7].

The parametric model allows a variety of geometrical factors to be altered, including the luminal and medial dimensions, the depth and width of a plaque or necrotic volume, and the location, size and distribution of microcalcifications (FIG. 15B). Altering these parameters allows for a better comprehension of the effect of each structural factor on the temperature distribution in the vessel wall and the blood flow and/or on the mechanical stress distribution resulting from the fluid-structure coupling. The simulations presented in the current work include only the Adina-CFD module, presenting temperature distribution of the blood flow in the luminal space (FIG. 15A) where the region of the eccentric plaque coming in contact with the lumen was set with a uniform temperature boundary condition of 39°C, which was warmer than the core temperature set at 37°C.

In a second case the core temperature was set at 17°C, which is well in the range of temperatures used for similar procedures, such as Thermodilution. The temperature of the plaque was maintained at 39°C, increasing the initial temperature difference by 20°C compared to the first case. Next, the blood flow velocity was reduced by half for both cases to check its influence on temperature distribution.

The flow, pressure and temperature fields in the models were calculated by solving the governing equations in the fluid domain, using finite volume methods. The governing equations of the fluid are the continuity, momentum and energy equations. The continuity equation is derived from mass conservation considerations, and may be represented per unit volume as:

$$\nabla \cdot \vec{v} = 0 \qquad (1)$$

where $\vec{v}$ is the velocity vector.

The momentum equations are derived from Newton's second law. Assuming the blood is Newtonian, incompressible and with constant viscosity, the Navier-Stokes equations are:

$$\rho\left[\frac{\partial \vec{v}}{\partial t}+(\vec{v}\cdot\nabla)\vec{v}\right]=-\nabla p+\mu\nabla^2\vec{v} \quad (2)$$

where p is the static pressure, t is time, ρ is density, and μ is the dynamic viscosity. The energy equation is:

$$\rho C_p\frac{DT}{Dt}=k\nabla^2 T \quad (3)$$

where ρ is density, Cp is the heat capacity, T is the temperature and k is the thermal conductivity.

The model was meshed by 352,470 tetrahedral elements. The governing equations were solved for the domain, by discretization of the equations on the computational grid, the formulation of a set of algebraic equations, and their solution.

RESULTS

The released heat from the arterial wall is transferred by conduction and convection to the surrounding neighborhood. Regions in which the velocity is higher contribute to faster cooling of the blood, while regions in which velocity is lower are characterized with higher blood temperature. Peak velocity of the flow reached 59 cm/sec at the center of the narrowest area of the lumen (FIG. 16A). The temperature distribution is presented in FIG. 16B, as a warm region of blood flow develops in the vicinity of the hot plaque, and cools down towards the opposite wall, which is closer to the core temperature. As noted above, blood velocity may be reduced at the wall, sensor and/or vessel in general, to control blood temperature change rate at any given location. Optionally, this velocity modification is used to compensate for changes in vessel diameter that affect the correlation between measured temperature and plaque temperature.

Two points were selected on the same length of the artery (FIGs. 17A-B) – Point I at a distance of 0.9 mm from the border of the warm plaque with the lumen, representing a heated area of the flow which is in the vicinity of the plaque, but located midway between the plaque wall and the center of the flow, and Point II at a distance of

0.3 mm from the counter wall, representing a cooler region with temperature closer to the core temperature, which can typically be measured almost anywhere in the artery, as long as it is not in the proximity of the plaque. The difference between the measured values at Points I and II in both cases is depicted in FIGs. 17A-B.

When temperature is measured, at peak velocity, in measurement points I and II, the values are 37.49°C and 37.02°C, respectively, for case 1 in which the blood core temperature is kept at a physiological value of 37°C (FIG. 17A). However, if the blood is cooled down to 17°C, as in case 2, the temperatures measured in Points I and II are 22.46°C and 17.2°C, respectively. Thus, cooling the blood by 20°C for the period of temperature acquirement may increase the temperature gradient between a region in the vicinity of the warm plaque, and a region representing the core temperature, almost 12-fold from 0.47°C to 5.26°C. Lower or higher amounts of cooling of the blood may be employed. Optionally, the cooling is controlled so as to achieve a desired temperature gradient, and amount of cooling is used as measured variable.

Reducing the blood flow by half (thus, reaching a maximal peak velocity value of 0.29 cm/sec) did not affect the temperature gradients in case 1 (FIG. 17B). In case 2 reducing the flow had a minor effect, as the temperature measured at Points I and II was 22.42°C and 17.18°C respectively, reducing the temperature gradient by a mere 0.38% from 5.26°C to 5.24°C.

DISCUSSION

Current thermography studies focus on arterial wall temperature as a marker of atherosclerosis. Different kinds of catheters were developed in order to map temperature distributions along blood vessels in-vivo, most of which equipped with termistors or thermocouples that come in contact with the blood vessel wall to follow its contour while pulled backwards along a guidewire.

The results of the example demonstrate that searching for blood temperature variations in the coronary arteries, and in particular the temperature levels distal to inflammatory-suspicious areas, may benefit in locating vulnerable plaques. This may be done with or without blood cooling.

When measurements of wall temperature are compared in-vivo to blood core temperature, the variations are mostly in the range of less than 1°C, and only in severe cases, such as MI, may reach 2°C [5,6]. The current results suggest a potential benefit by applying a method in which a cold saline is injected to the area of measurement prior to acquirement of temperatures. Such method doesn't require the catheter to be in touch with the wall, which may have the risk of injuring the already vulnerable thin-capped plaques. Even by measuring the temperature in the lumen, at a distance of 0.9 mm from the plaque, and comparing it with a reference temperature measured at any other region (e.g. at the vicinity of the opposing wall, or at any region which is proximal or distal to the inflamed region), an almost 12-fold increase in temperature gradients can be reached, rendering this method potentially easier (and safer) for detecting regions suspected as being biologically and actively inflamed.

Reducing the blood flow did not have a significant effect on the temperature gradients. Nevertheless, only two flow waveforms were currently inspected. In an exemplary embodiment of the invention, a table or function is used which correlates the effect of flow or pressure on temperature distribution within the lumen.

The results of this example illustrate a potential benefit of using thermography catheters having spatial thermistor configuration, enabling measurement of temperature variations in various cross sections of the artery, and/or of utilizing injection of cold saline for the period of measurement.

In an exemplary embodiment of the invention, the calculation of a temperature also takes into account a model of heat conduction through the thin fibrotic cap of vulnerable plaques.

The present example demonstrates the potential contribution of applying cold saline injection to the temperature gradients measured for the detection of active inflamed regions of the artery. These high temperature gradients can indicate the location and/or severity of the inflammation of atherosclerotic coronary vulnerable plaques, possibly by relaying on its cellular activity and its consequences.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all

such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

CLAIMS

1. A method of identifying temperature differences related to temperature differences in the wall of a vessel with flow of fluid therethrough, comprising:

cooling a first portion of said flow; and

measuring a temperature of a second portion of said flow, which second portion includes fluid cooled by said cooling, and which second portion is associated with a location at said wall.

2. A method according to claim 1, wherein said fluid is blood.

3. A method according to claim 1 or claim 2, wherein said vessel is a blood vessel.

4. A method according to any of the preceding claims, wherein cooling comprises injecting a cold fluid into said vessel, or/and using a cooling element.

5. A method according to any of the preceding claims, wherein cooling comprises cooling said fluid to have a temperature difference of at least 5 degrees Celsius from said wall location, at said first portion, or of at least 3 degrees Celsius from said wall location, at said second portion.

6. A method according to any of the preceding claims, wherein said measuring comprises measuring using a temperature sensor and comprising reducing a fluid exchange rate at said sensor, at said wall location, or in said vessel.

7. A method according to claim 6, wherein said reducing comprises reducing by extending one or more flow-interference objects into said flow.

8. A method according to any of claims 6-7, wherein said reducing comprises reducing by at least 50%.

9. A method according to any of the preceding claims, wherein said measuring comprises measuring using a temperature sensor and said temperature sensor is configured to not contact said wall.

10. A method according to any of the preceding claims, wherein said measuring comprises measuring using a temperature sensor and said temperature sensor is configured to not be urged against said wall.

11. A method according to any of the preceding claims, comprising measuring a reference temperature of said flow at a reference location upflow from said second portion and downflow from said first portion.

12. A method according to any of the preceding claims, comprising changing a location of said second portion.

13. A method according to any of the preceding claims, wherein measuring comprises acquiring a plurality of measurements at different axial locations along said wall.

14. A method according to claim 13, comprising identifying an axial gradient from said measurements.

15. A method according to any of the preceding claims, wherein measuring comprises acquiring a plurality of measurements at different radial distances from said wall, or/and at different circumferential locations on said wall.

16. A method according to claim 15, comprising identifying a radial gradient, or/and a circumferential gradient, from said measurements.

17. A method according to any of claims 13-16, wherein said plurality of measurements are acquired using a plurality of temperature sensors.

18. A method according to any of claims 13-17, comprising identifying suspicious plaque in a blood vessel based on a rate of temperature change as a function of space and/or time.

19. A method according to any of the preceding claims, comprising identifying suspicious plaque in a blood vessel based on a difference between said measured temperature of said second portion and at least an estimated temperature of said flow.

20. A method according to any of the preceding claims, comprising mapping the axial and/or radial extent of suspicious plaque in a blood vessel based on said measured temperature of said second portion.

21. A method of identifying temperature differences in the wall of a vessel with flow of fluid therethrough, comprising:

measuring a reference temperature of said flow at a reference portion of said flow; and

measuring a temperature of a second portion of said flow, which second portion is associated with a location at said wall and at least 1 cm downflow from said first portion, such that a temperature of said flow at said reference portion is not affected by a temperature of said wall location.

22. A method of plaque identification comprising mapping a temperature profile of a wall of a blood vessel where no stenosis is visible on an angiography image and identifying vulnerable plaque or other plaque on said wall from changes in temperature thereat.

23. A catheter temperature sensor, comprising:

(a) an elongate body adapted for insertion into a blood vessel;

(b) a first temperature sensor at a first location along said catheter;

(c) a second temperature sensor at a location distanced at least 1 cm from said first location, along said catheter; and

(d) a mechanism for axially moving said second sensor relative to said first sensor, along said catheter.

24. A system for at least estimating blood vessel wall temperature, comprising:

(a) a first input for a first temperature indicating signal, corresponding to a blood vessel wall temperature; and

(b) a processor configured to process said signal as indicating a temperature corresponding to a normal wall temperature or as indicating a temperature corresponding to a inflamed wall, wherein said processor includes a classifier configured to classify temperatures under 37 degrees Celsius as vulnerable plaque and as non-plaque.

25. A system according to claim 24, comprising a display adapted to display blood or wall temperatures over a range of at least 5 degrees Celsius.

26. A system according to claim 24 or claim 25, comprising a gradient calculator configured to calculate a temperature gradient of at least 0.01 degree Celsius between two locations in said vessel.

27. A system according to claim 26, wherein said gradient is a gradient along a blood vessel or a gradient perpendicular to an axis of said vessel.

28. A system according to any of claims 24-27, comprising a display generator configured to generate a temperature map of a wall of a blood vessel, using said processed signal.

29. A system according to claim 26, wherein said display includes an indication of vulnerable plaque.

30. A system according to any of claims 24-25, comprising an actuator which controls a cooling function of a temperature measurement catheter.

31. A system according to any of claims 24-25, comprising an input for the actuation of a cooling function of a temperature measurement catheter.

32. A system according to any of claims 24-31, comprising a temperature measurement catheter.

33. A system according to any of claims 24-32, comprising a blood cooling system.

34. A catheter temperature sensor, comprising:

(a) an elongate body adapted for insertion into a blood vessel;

(b) a first temperature sensor at a first location along said catheter and adapted for measurement in blood vessels of less than 20 mm in diameter; and

(c) a blood cooling system upstream of said first temperature sensor.

35. A catheter according to claim 34, wherein said cooling system comprises a bulk of cold fluid.

36. A catheter temperature sensor, comprising:

(a) an elongate body adapted for insertion into a blood vessel;

(b) a plurality of temperature sensors configured to not forcefully contact a wall of said blood vessel.

37. A catheter according to claim 34, wherein said plurality of temperature sensors are recessed in a body of said catheter.

38. A catheter according to claim 36, wherein said plurality of temperature sensors are located at parts of said catheter with diameter of less than half a diameter of said blood vessel and less than 10 mm.

39. A catheter according to claim 36, wherein said plurality of temperature sensors are prevented from contacting said vessel wall by one or more protrusions extending from said catheter.

40. A catheter according to claim 39, wherein said one or more protrusions are selectively extendable.

41. A catheter according to claim 39 or claim 40, wherein said one or more protrusions are selectively extendable using an overtube.

42. A catheter according to any of claims 39-41, wherein said one or more protrusions are configured to lean on the vessel wall and provide stabilization during a temperature sensor measurement session.

43. A catheter according to any of claims 36-41, wherein said plurality of temperature sensors are located in portions of said catheter where average fluid exchange rate is less than 50% of that in unobstructed parts of said vessel.

44. A catheter according to any of claims 36-43, wherein at least two of said plurality of temperature sensors are circumferentially, or axially, or radially, spaced apart.

45. A catheter according to claim 36, wherein said catheter comprises a sheath with a lumen therein suitable for delivery of cooling fluid therethrough.

46. A method of heat treating a blood vessel wall, the method comprising:

providing a temperature sensor assembly, including at least one temperature sensor each configured and operative as a thermistor;

positioning said temperature sensor assembly inside the blood vessel;

activating said thermistor of said temperature sensor assembly, by supplying current to each of said at least one thermistor;

opening said temperature sensor assembly to a fully-opened configuration, such that there is contact of a tip of at least one of said thermistors with the blood vessel wall;

increasing said current supplied to at least one of said thermistors, whereby temperature of said at least one thermistors increases to higher than 40 ^{o}C;

axially or/and circumferentially moving said temperature sensor assembly in the blood vessel, for effecting thermal damage to the blood vessel wall; and

removing said temperature sensor assembly to outside of the blood vessel.

47. The method of claim 46, wherein the blood vessel wall includes plaque.

48. The method of claim 47, wherein said plaque is vulnerable plaque.

49. The method of claim 46, wherein said increasing said current to said thermistors is repeated until obtaining an indication of said effecting thermal damage to the blood vessel wall.

50. The method of claim 46, wherein said effecting thermal damage to the blood vessel wall stabilizes the blood vessel wall.

51. The method of claim 46, wherein said temperature of said at least one thermistor increases to higher than 50 degrees Celsius.

52. The method of claim 46, wherein the blood vessel wall includes plaque, and is applicable for treating a subject with atherosclerosis.

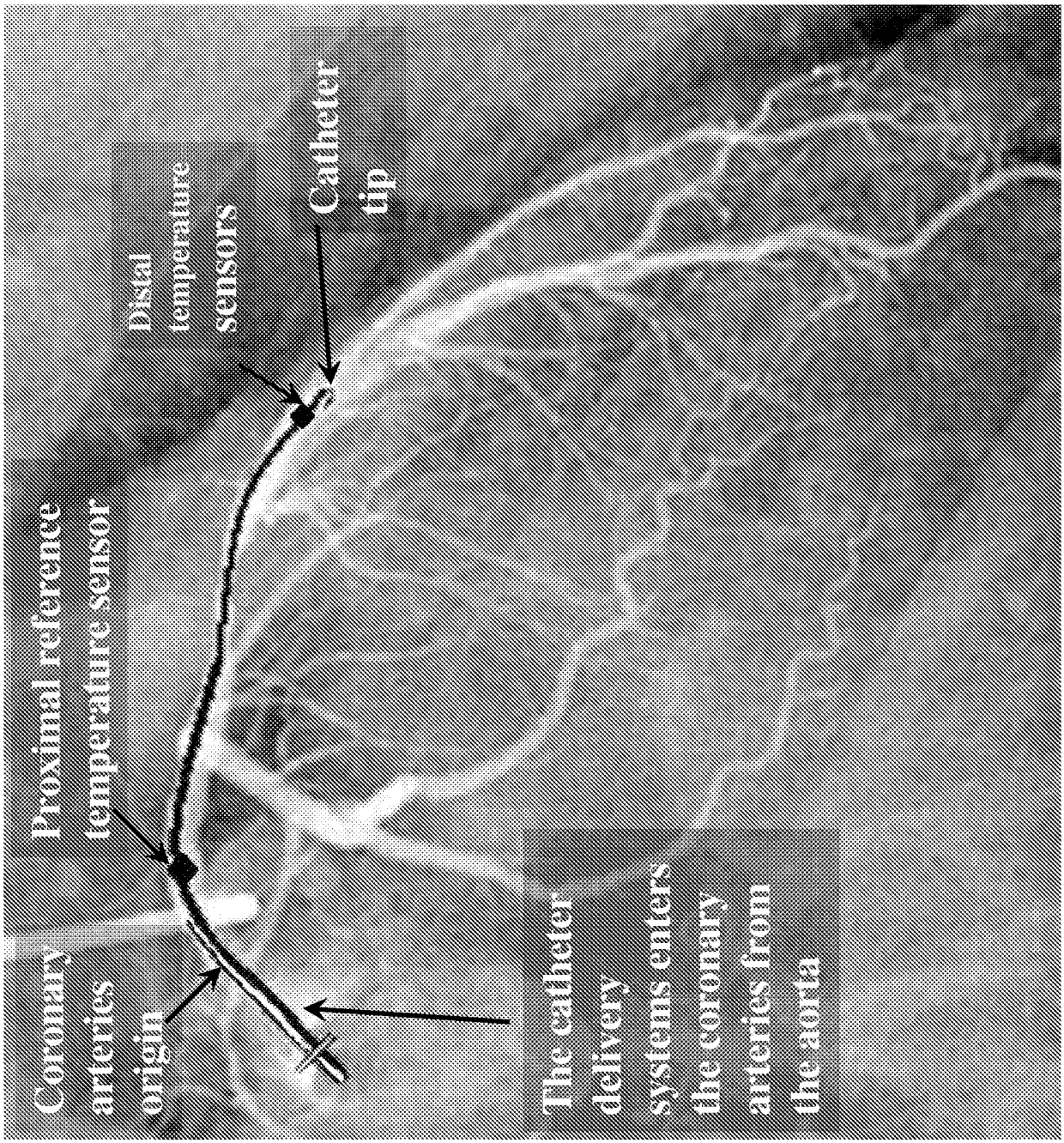
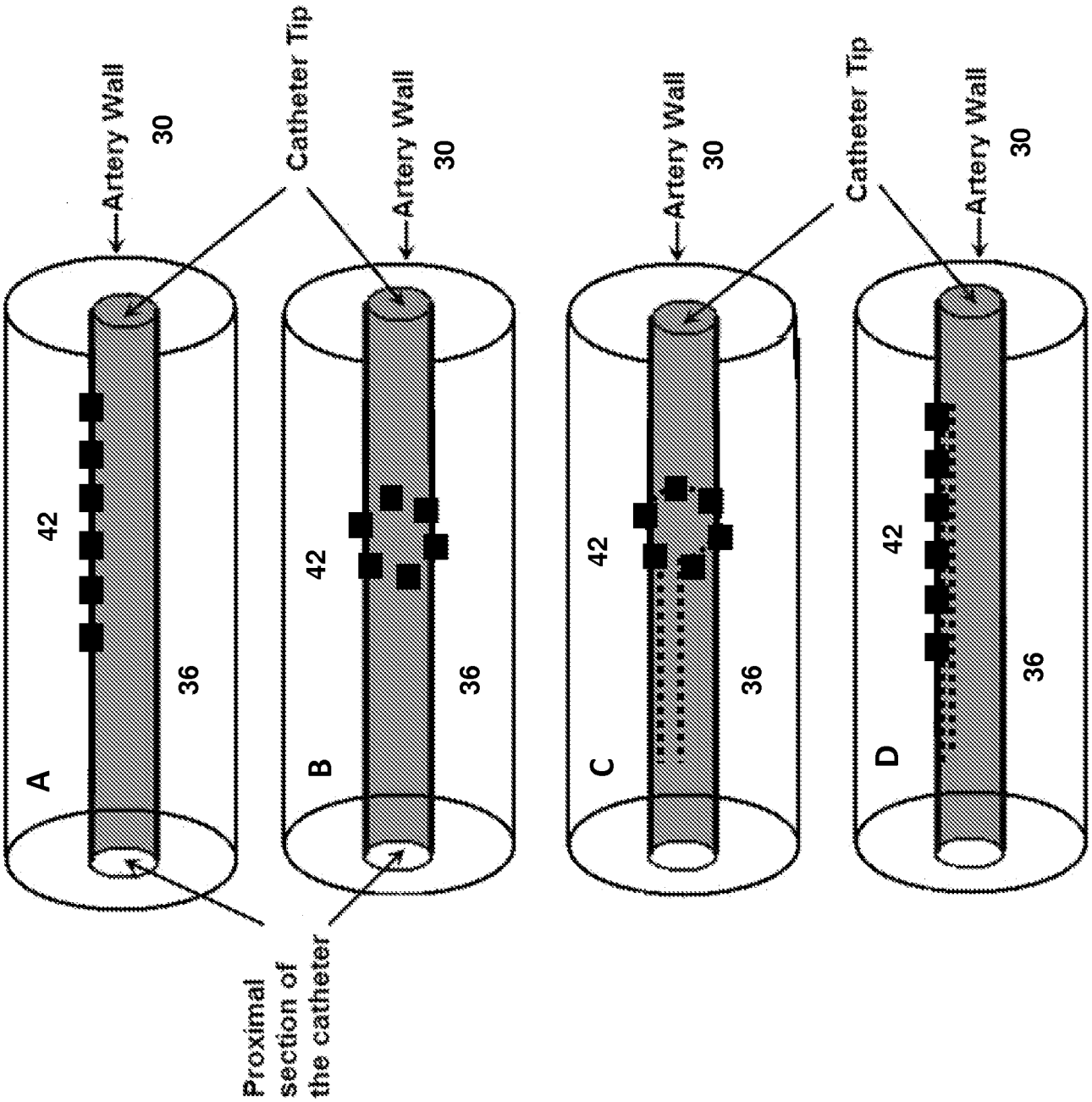
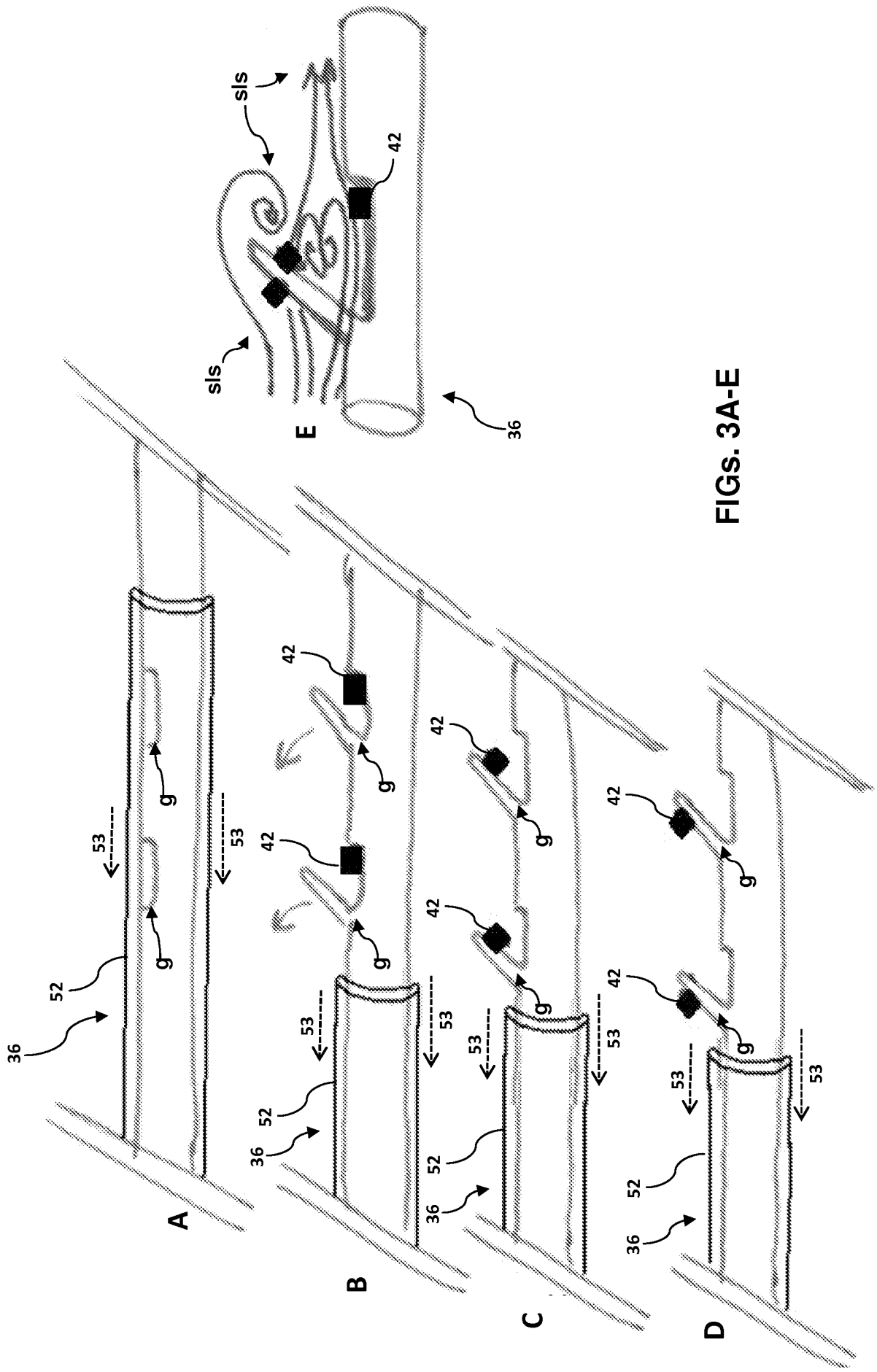

Coronary arteries origin
Proximal reference temperature sensor
Distal temperature sensors
Catheter tip
The catheter delivery systems enters the coronary arteries from the aorta

FIG. 1

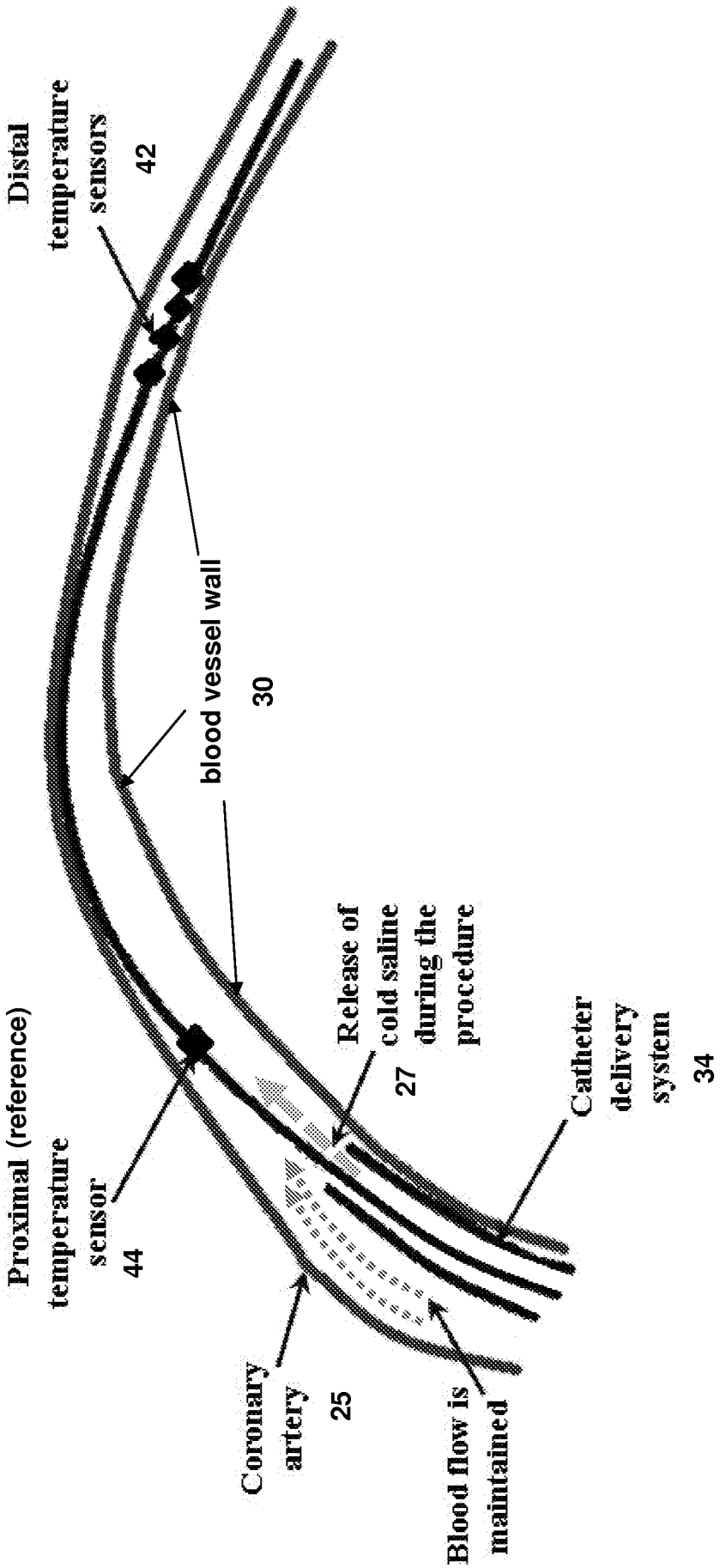

Artery Wall
30
Catheter Tip
Artery Wall
30
Artery Wall
30
Catheter Tip
Artery Wall
30
42
36
A
42
36
B
42
36
C
42
36
D
Proximal section of the catheter

FIGs. 2A-D



FIGs. 3A-E

FIG. 4


Distal temperature sensors 42
blood vessel wall 30
Release of cold saline during the procedure 27
Catheter delivery system 34
Proximal (reference) temperature sensor 44
Coronary artery 25
Blood flow is maintained

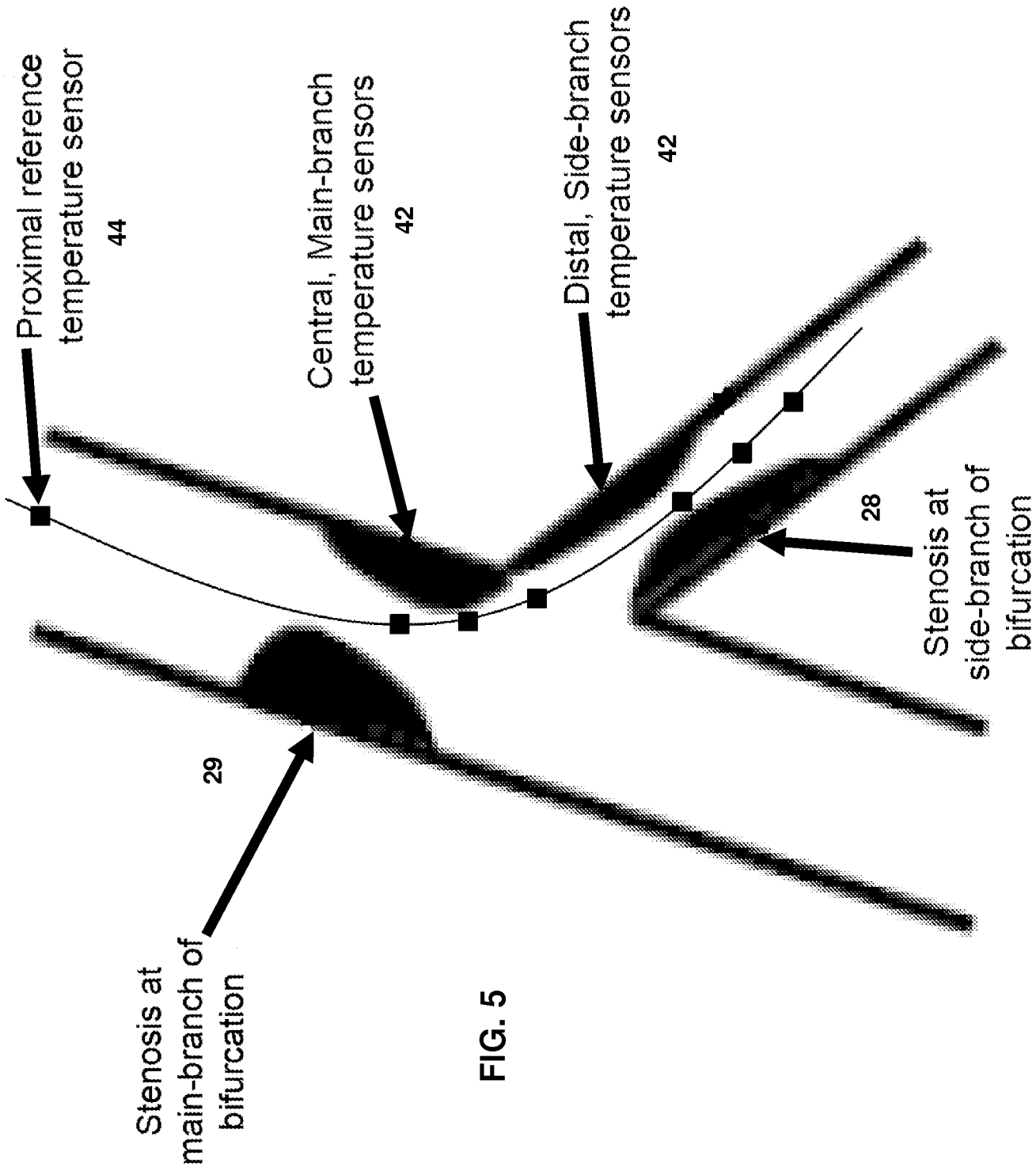

Proximal reference temperature sensor
44
Central, Main-branch temperature sensors
42
Distal, Side-branch temperature sensors
42
28
Stenosis at side-branch of bifurcation
29
Stenosis at main-branch of bifurcation

FIG. 5

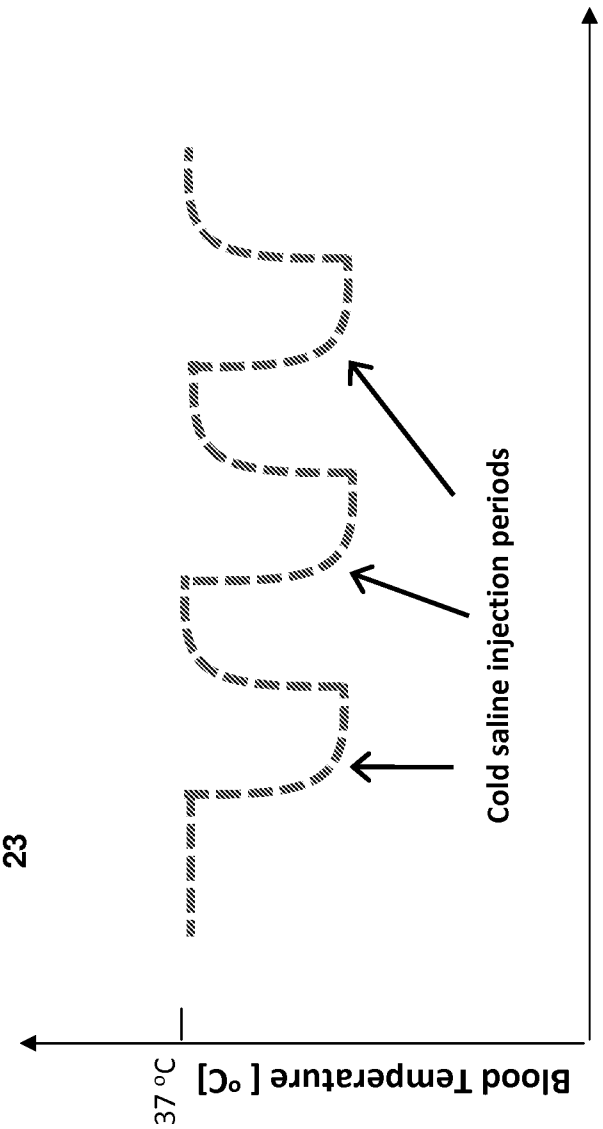

23
37 °C
Blood Temperature [°C]
Cold saline injection periods
Time [seconds]

FIG. 6

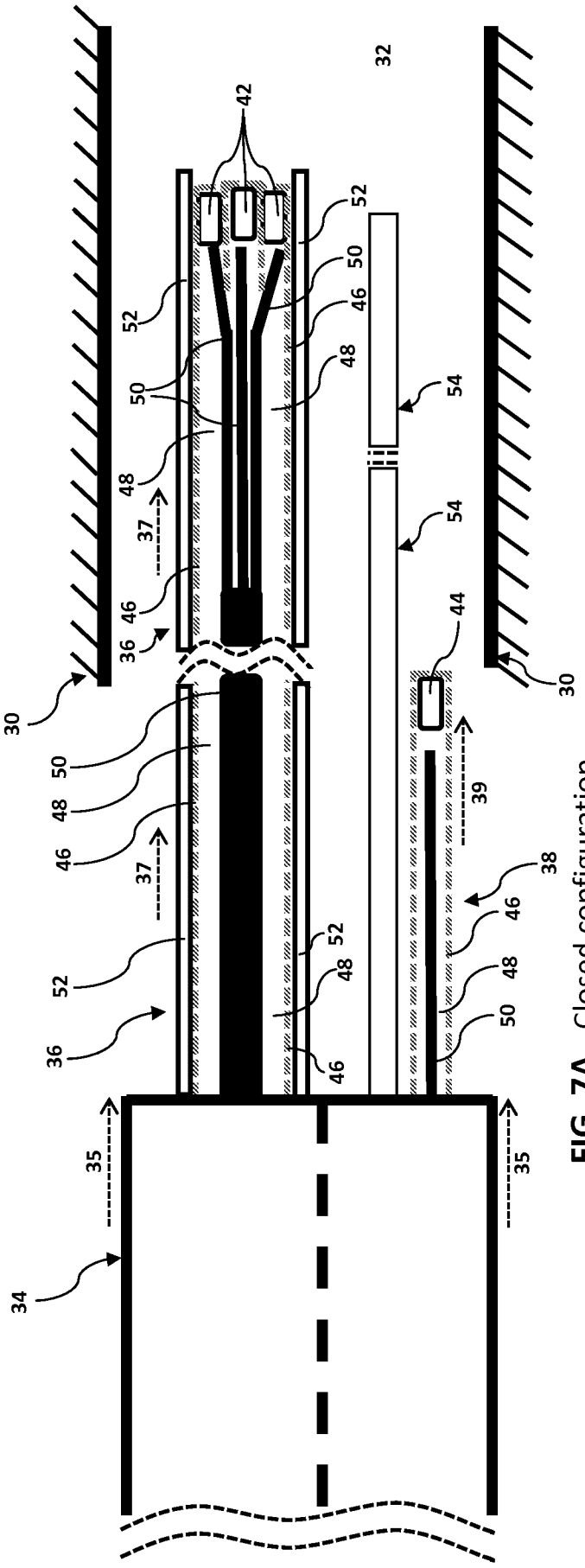


FIG. 7A Closed configuration

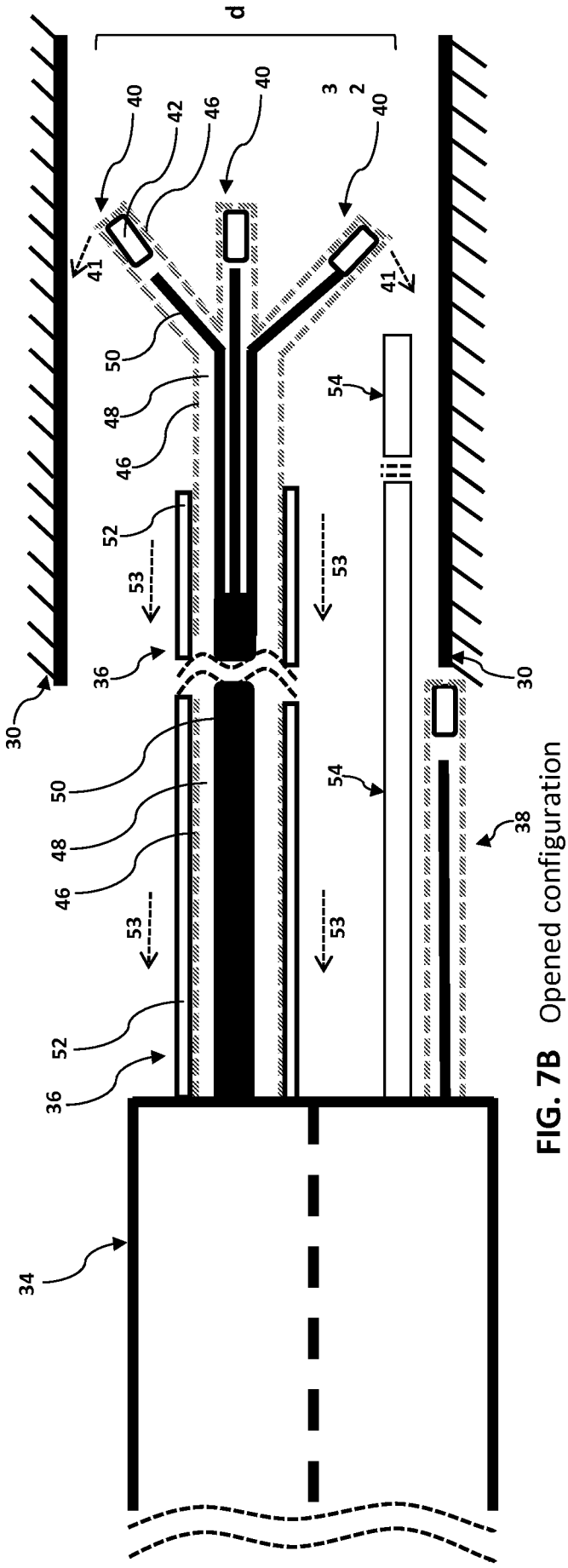


FIG. 7B Opened configuration

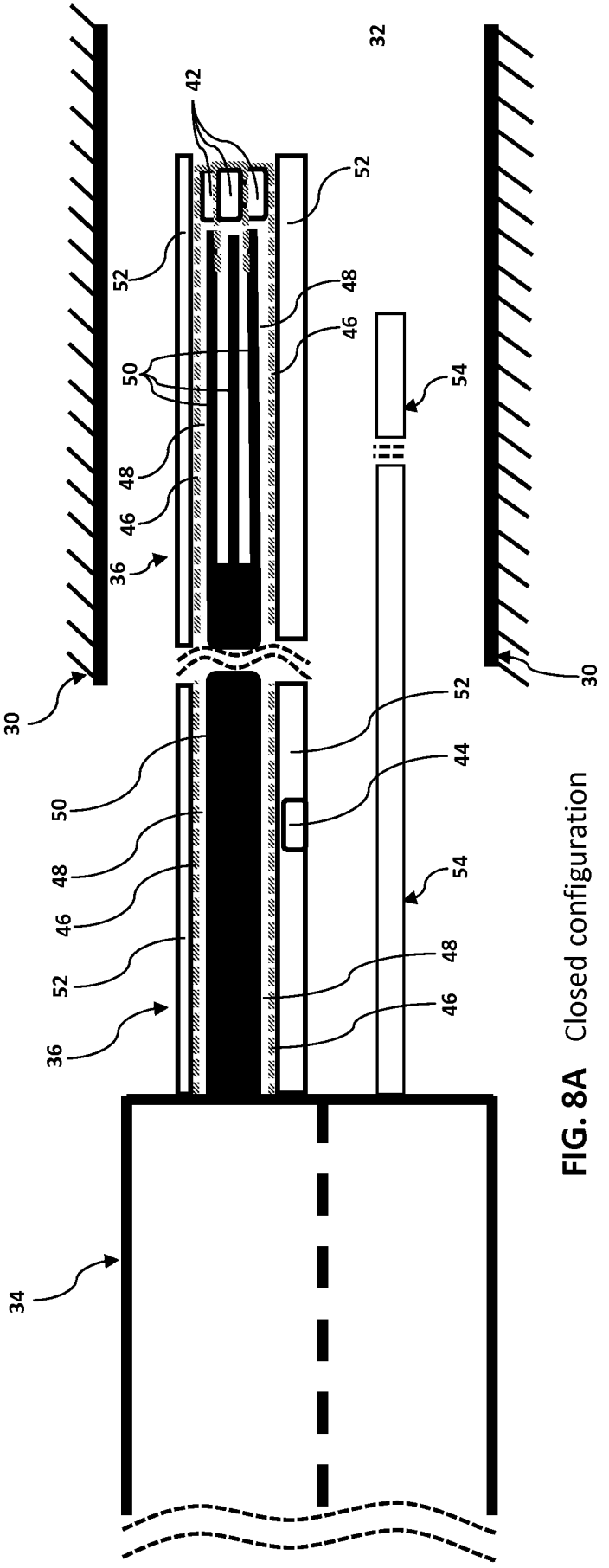


FIG. 8A Closed configuration

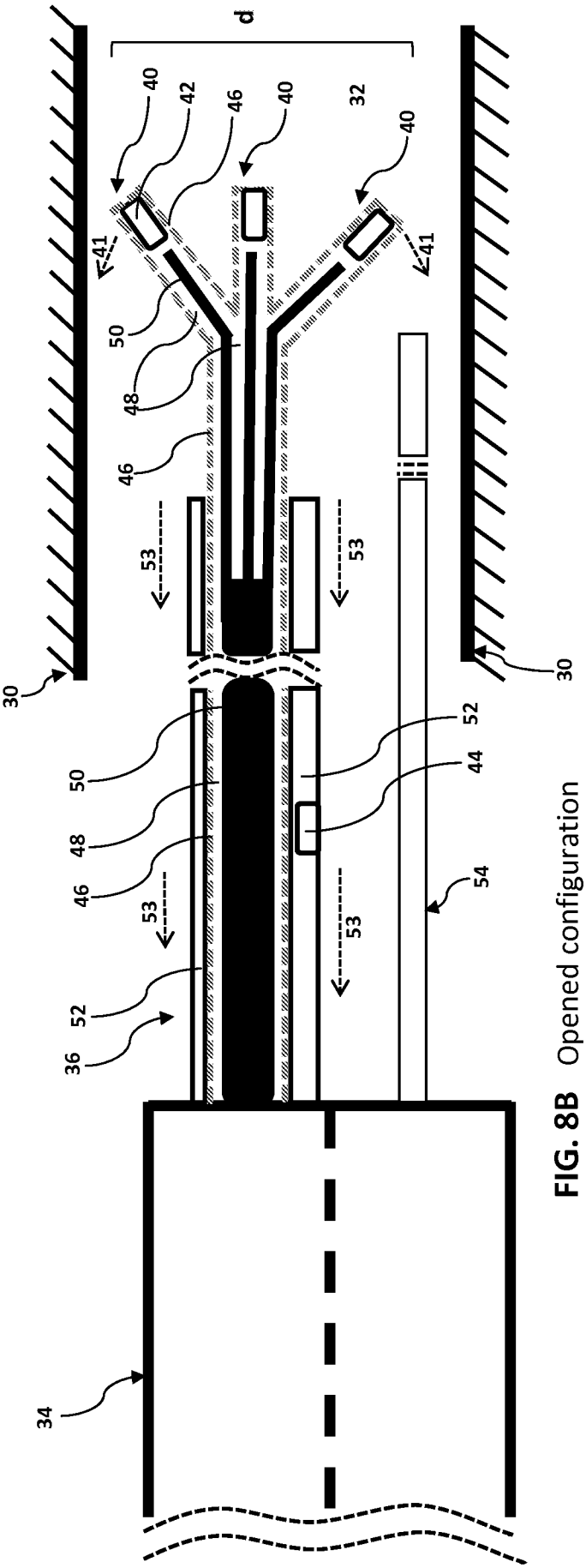


FIG. 8B Opened configuration

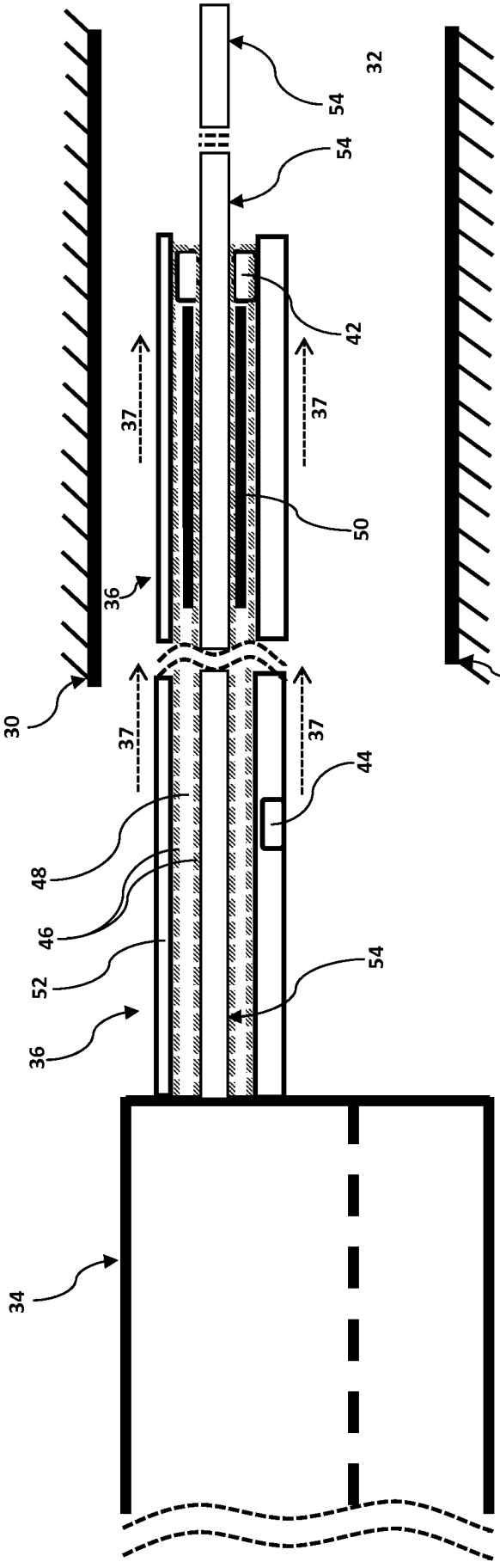


FIG. 9A Closed configuration

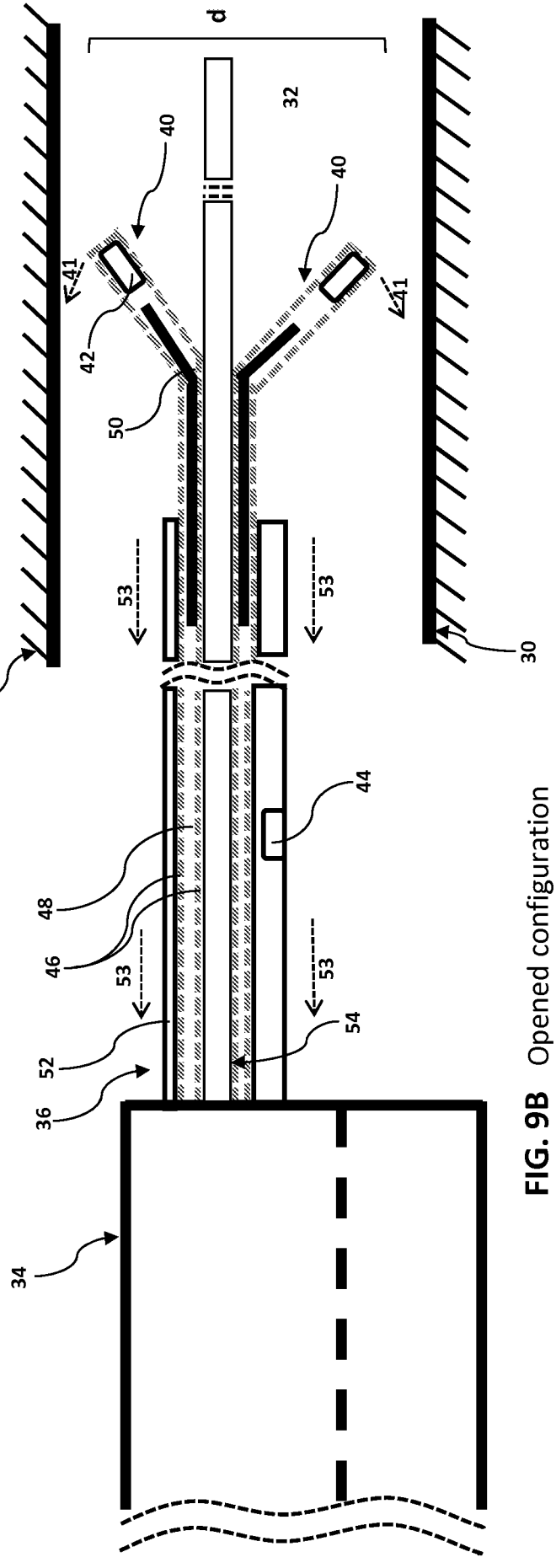


FIG. 9B Opened configuration

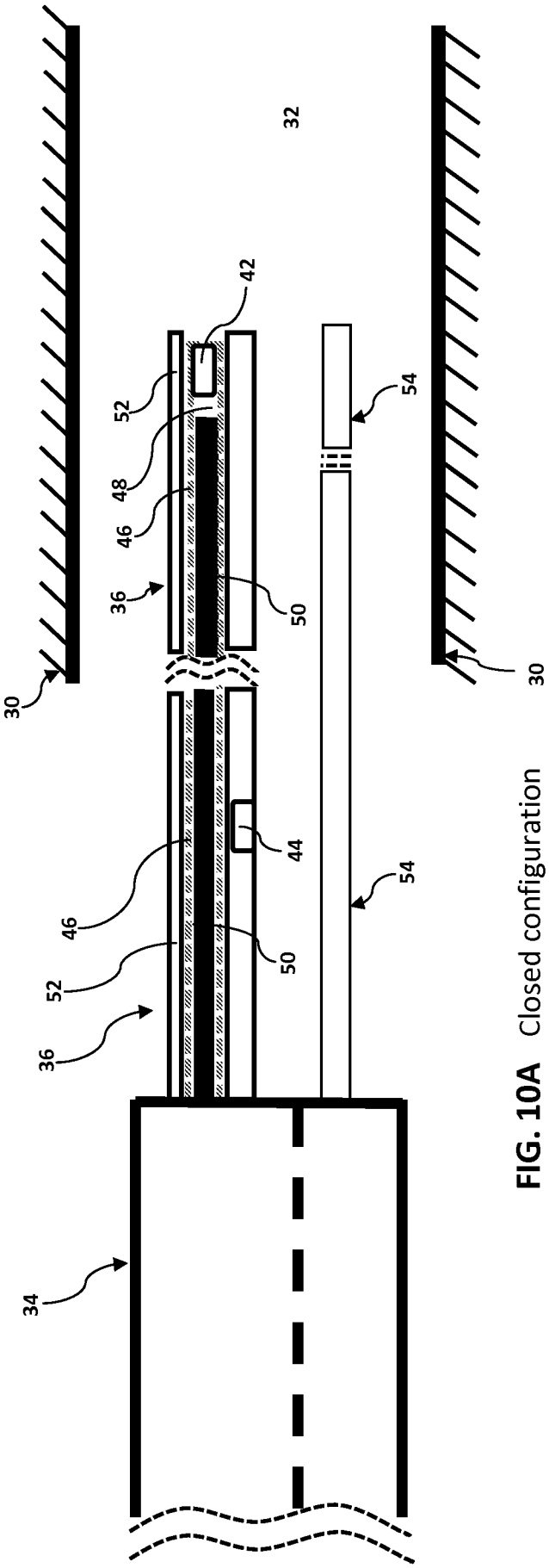


FIG. 10A Closed configuration

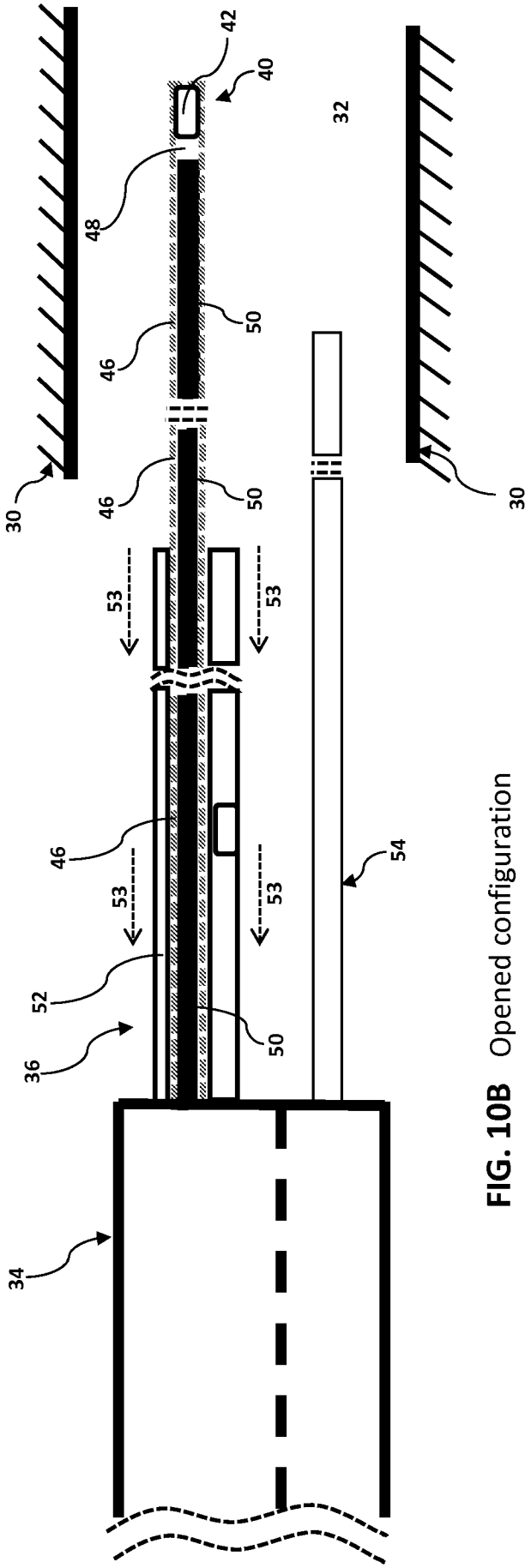


FIG. 10B Opened configuration

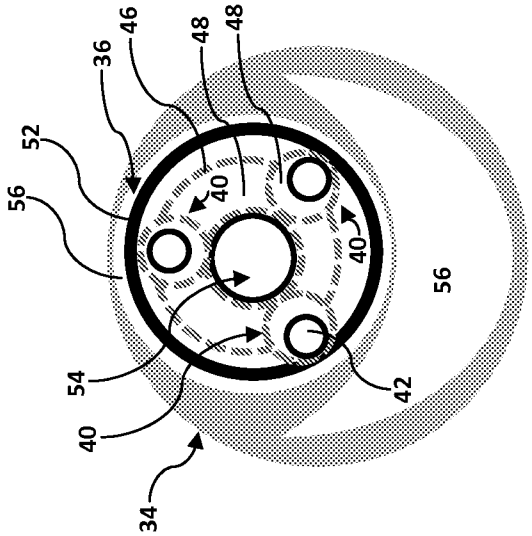


FIG. 11C

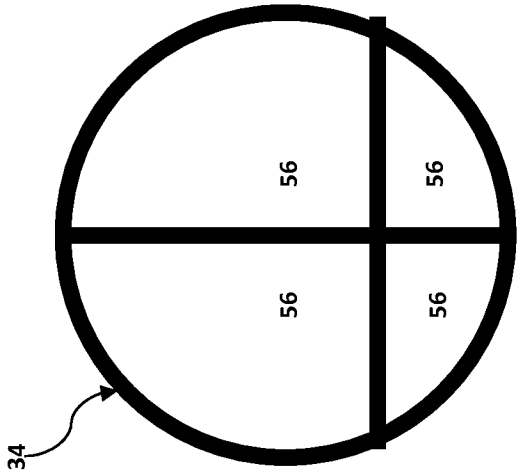


FIG. 11B

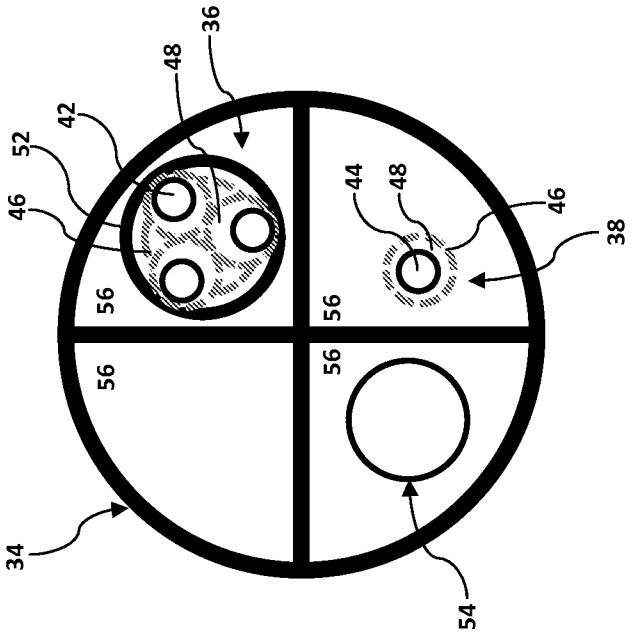


FIG. 11A

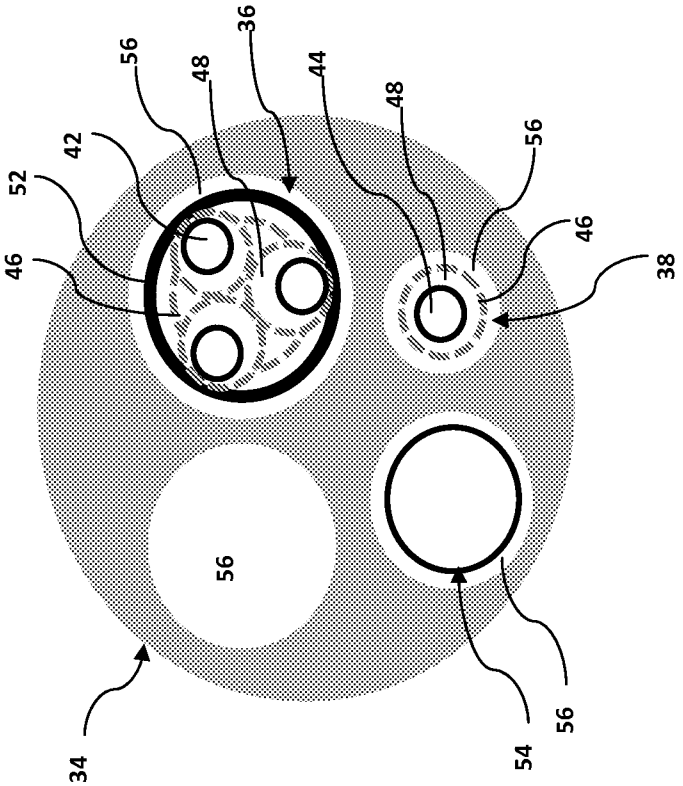


FIG. 11D

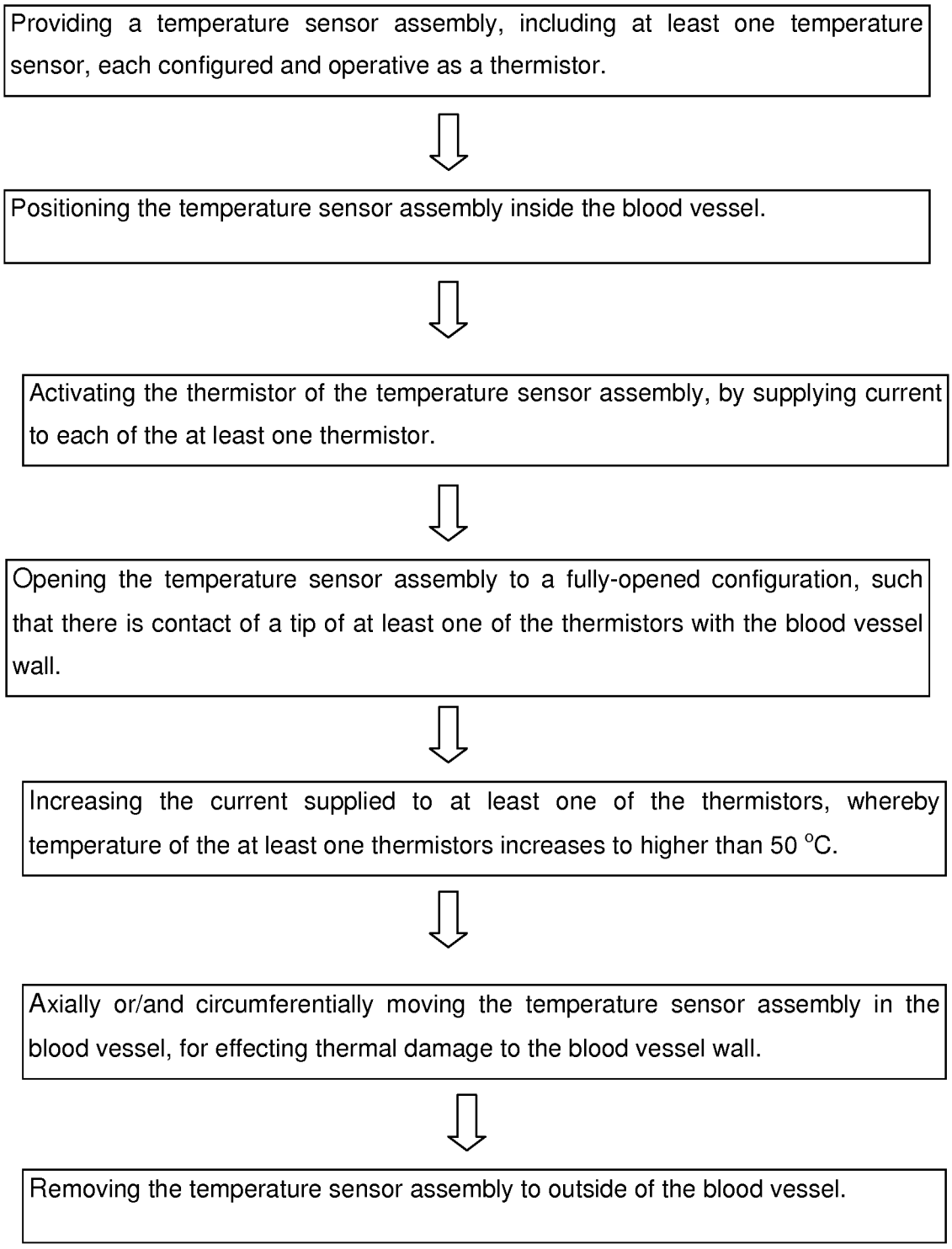

Providing a temperature sensor assembly, including at least one temperature sensor, each configured and operative as a thermistor.
Positioning the temperature sensor assembly inside the blood vessel.
Activating the thermistor of the temperature sensor assembly, by supplying current to each of the at least one thermistor.
Opening the temperature sensor assembly to a fully-opened configuration, such that there is contact of a tip of at least one of the thermistors with the blood vessel wall.
Increasing the current supplied to at least one of the thermistors, whereby temperature of the at least one thermistors increases to higher than 50 °C.
Axially or/and circumferentially moving the temperature sensor assembly in the blood vessel, for effecting thermal damage to the blood vessel wall.
Removing the temperature sensor assembly to outside of the blood vessel.

FIG. 12

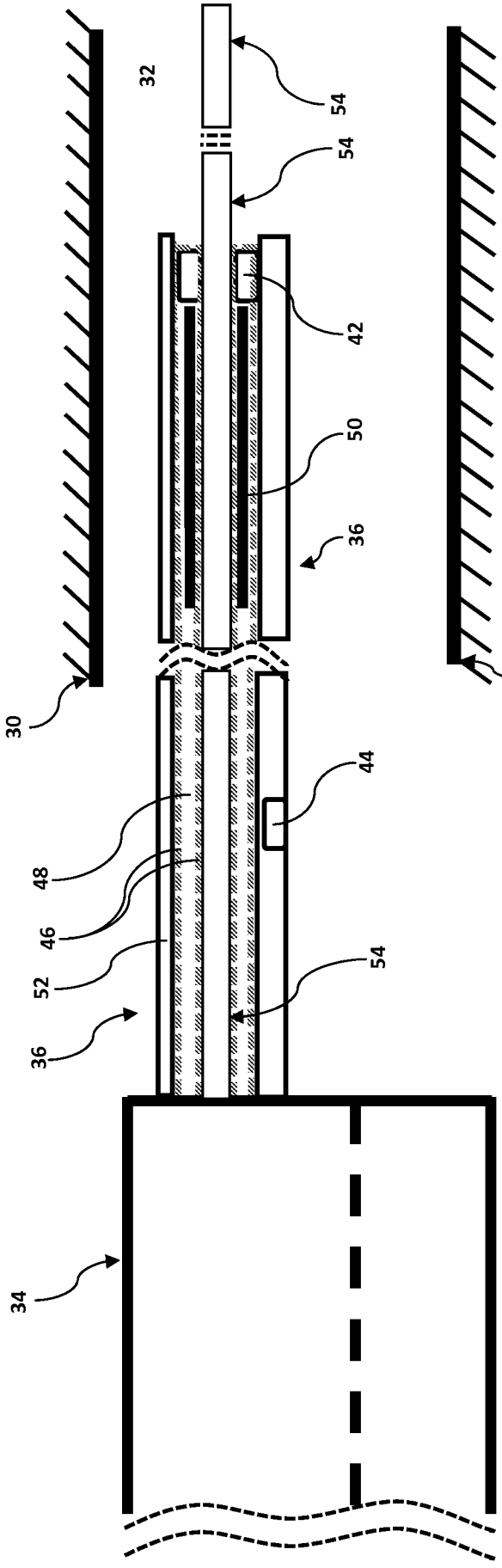


FIG. 13A Closed configuration

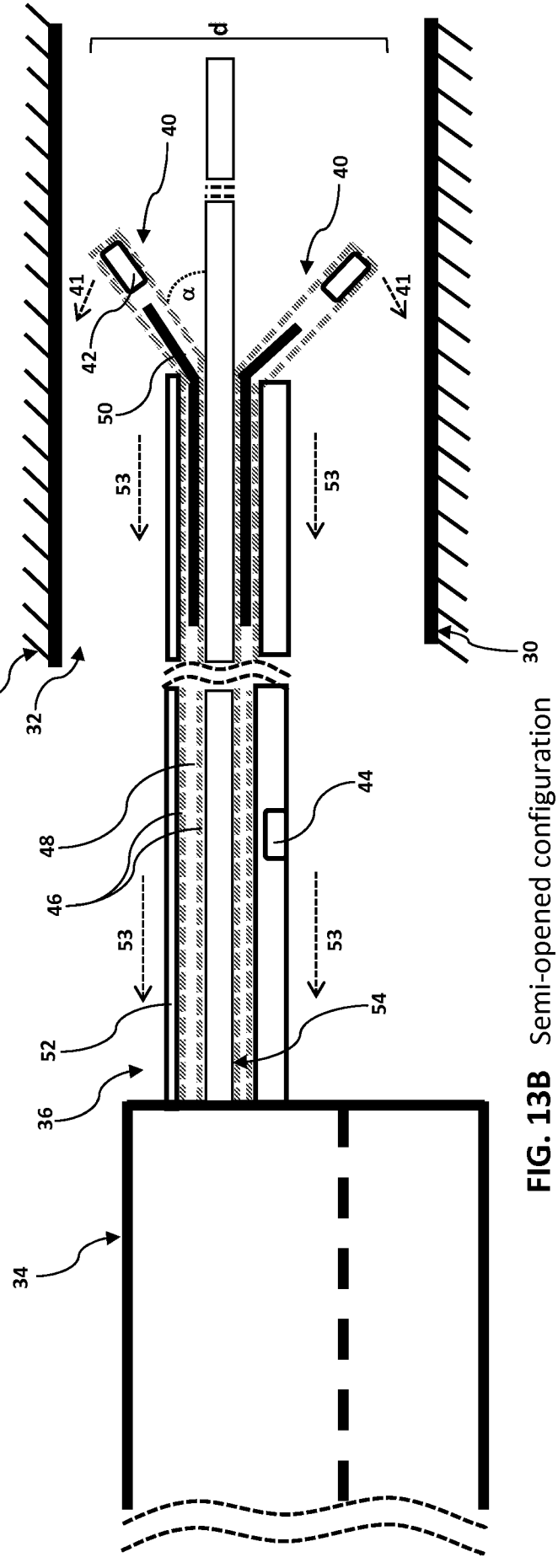


FIG. 13B Semi-opened configuration

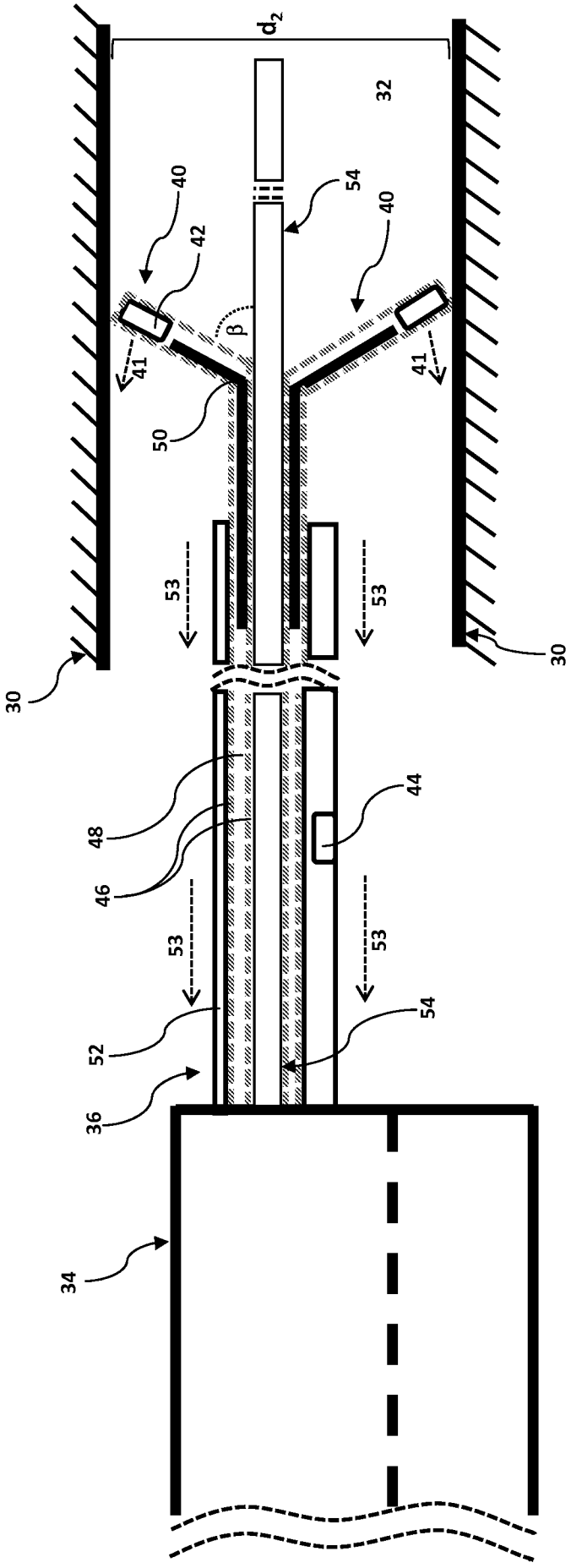


FIG. 13C Fully-opened configuration

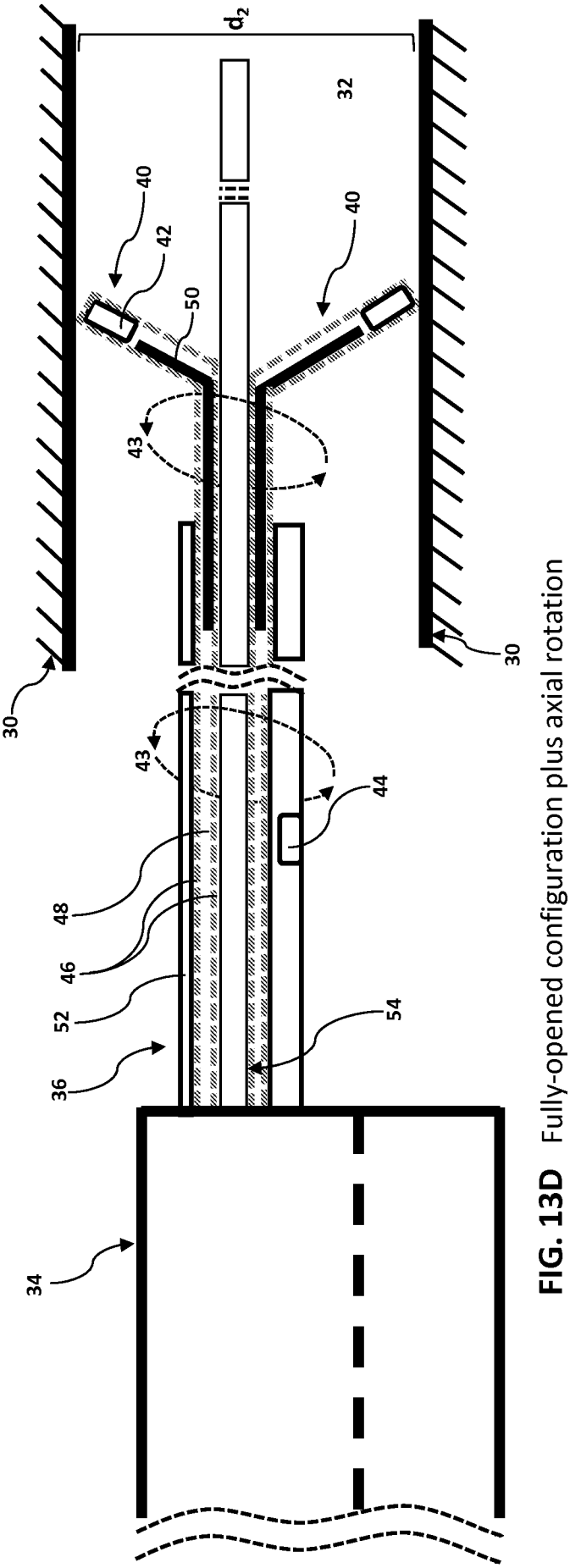


FIG. 13D Fully-opened configuration plus axial rotation

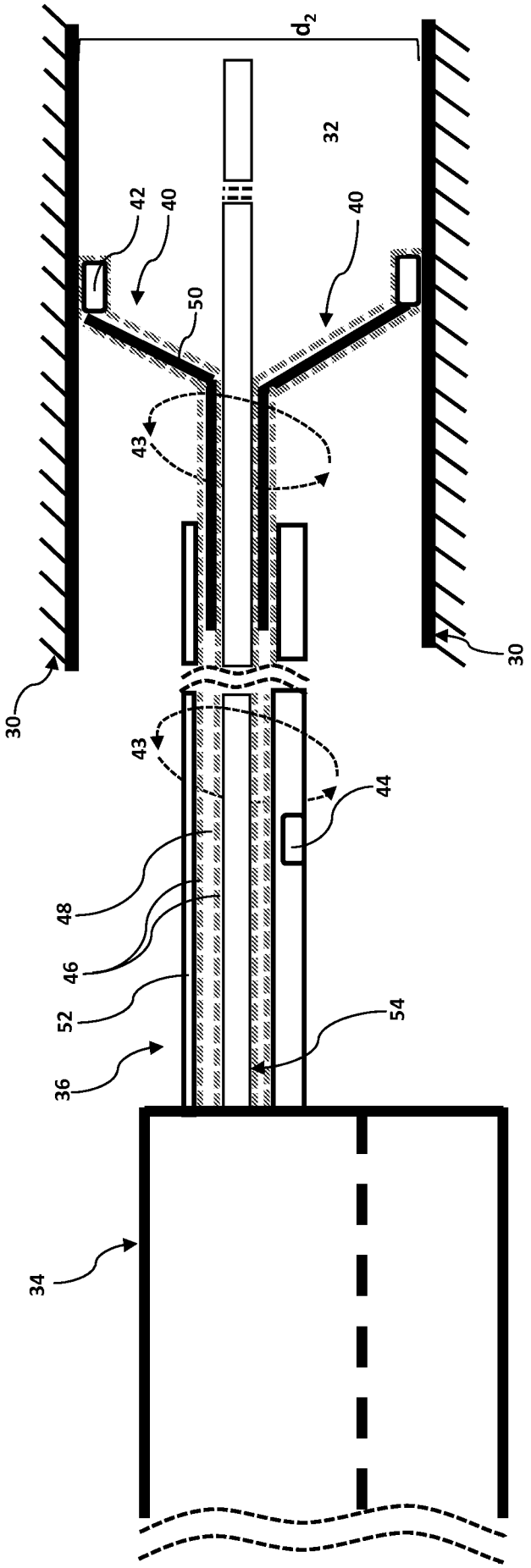


FIG. 13E Fully-opened configuration with flexible arm tip plus axial rotation

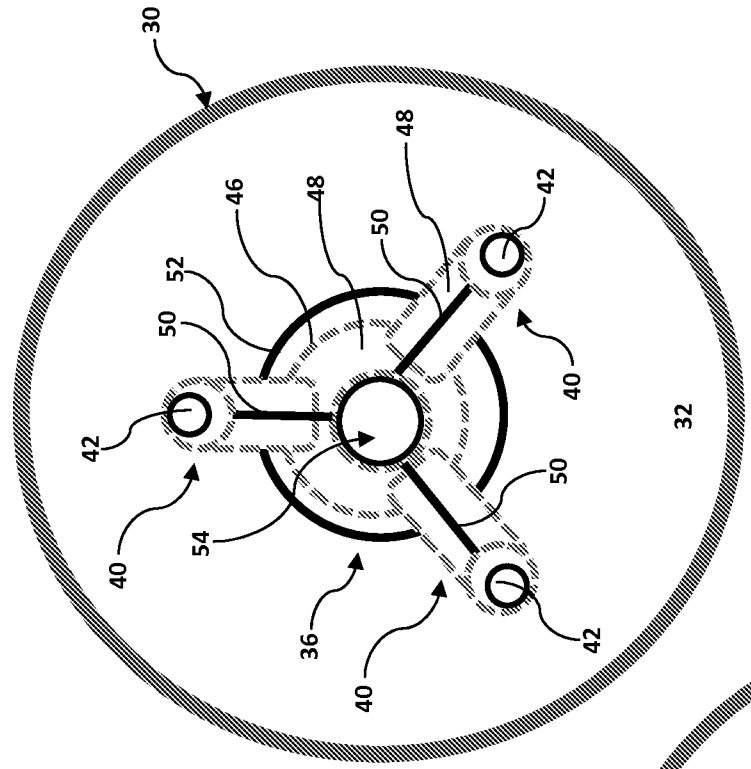


FIG. 14B

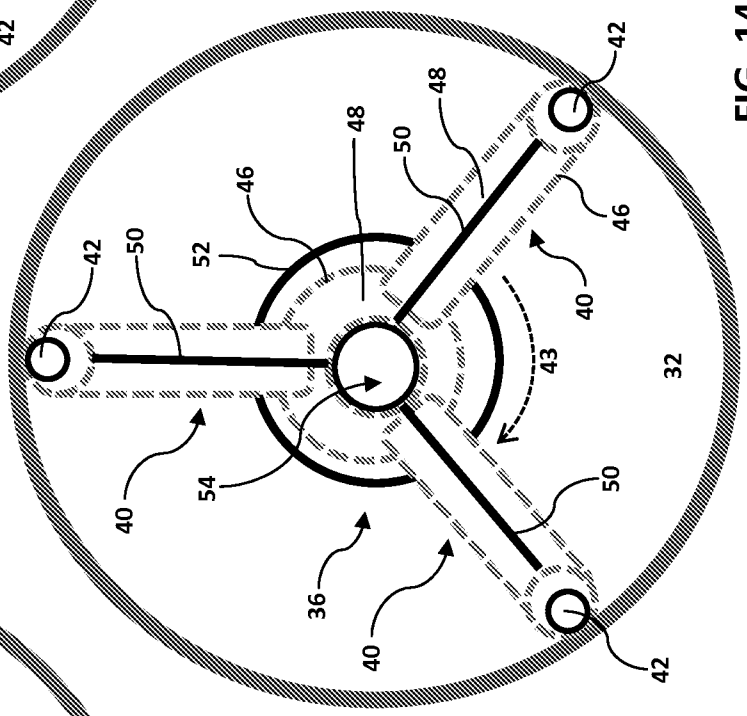


FIG. 14C

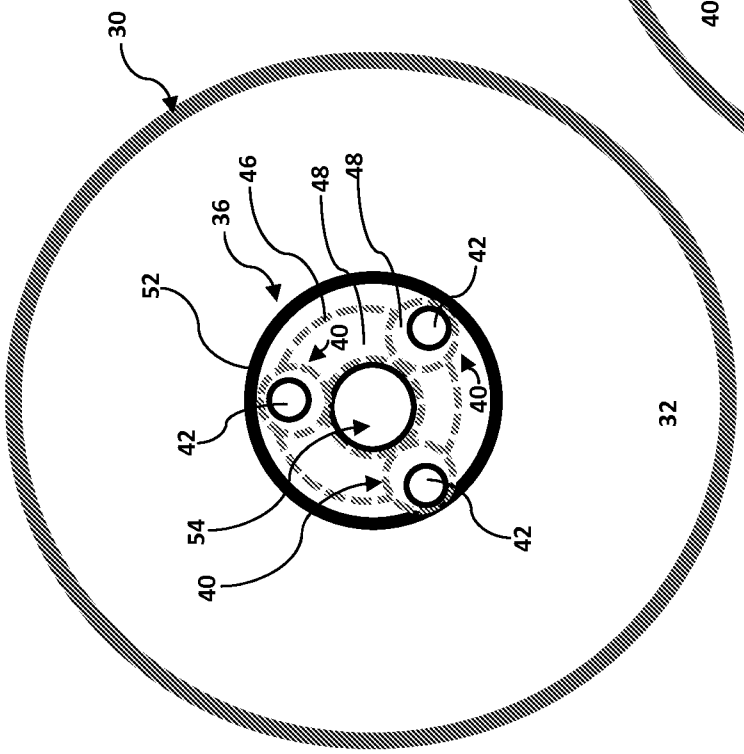


FIG. 14A

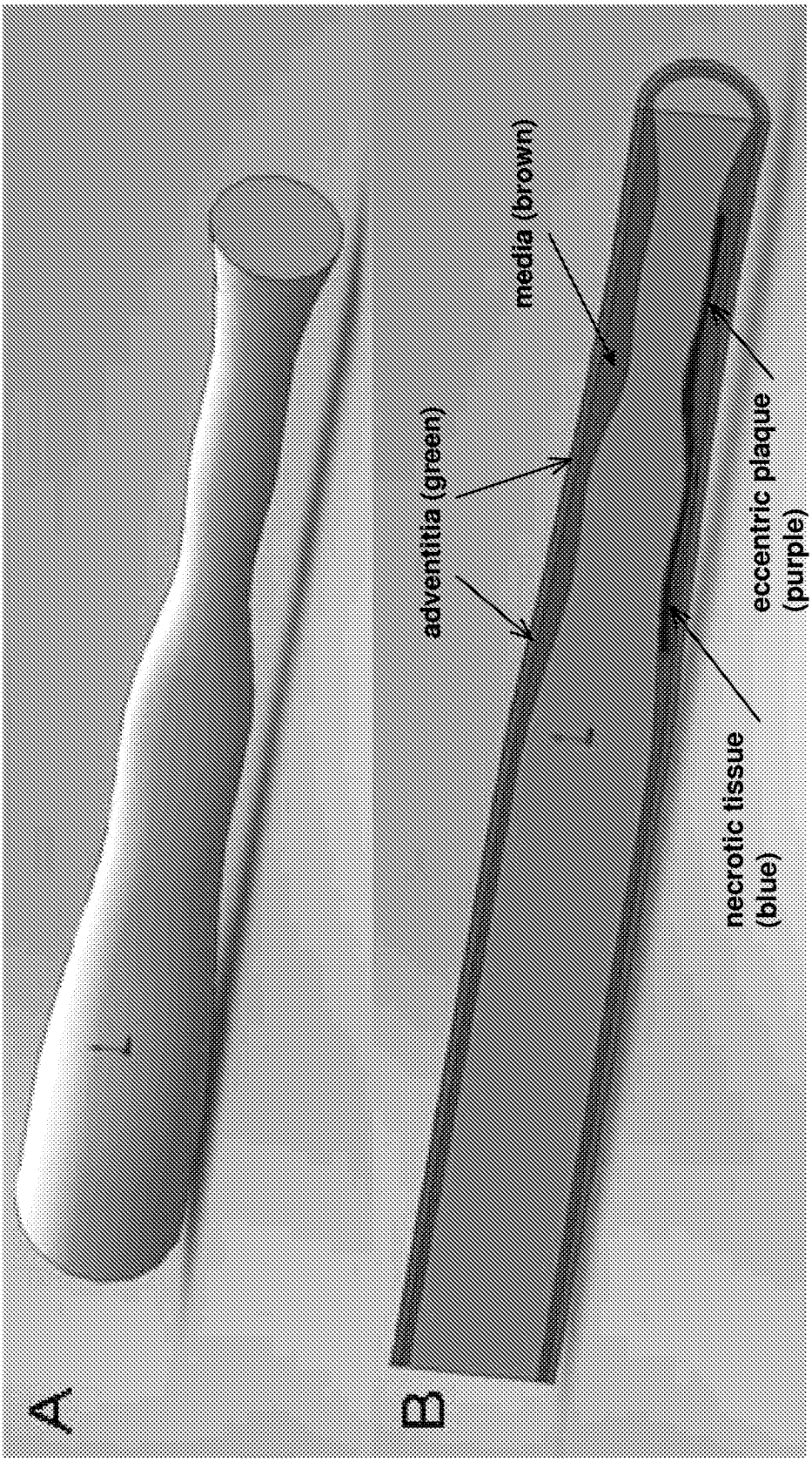


FIG. 15A

FIG. 15B

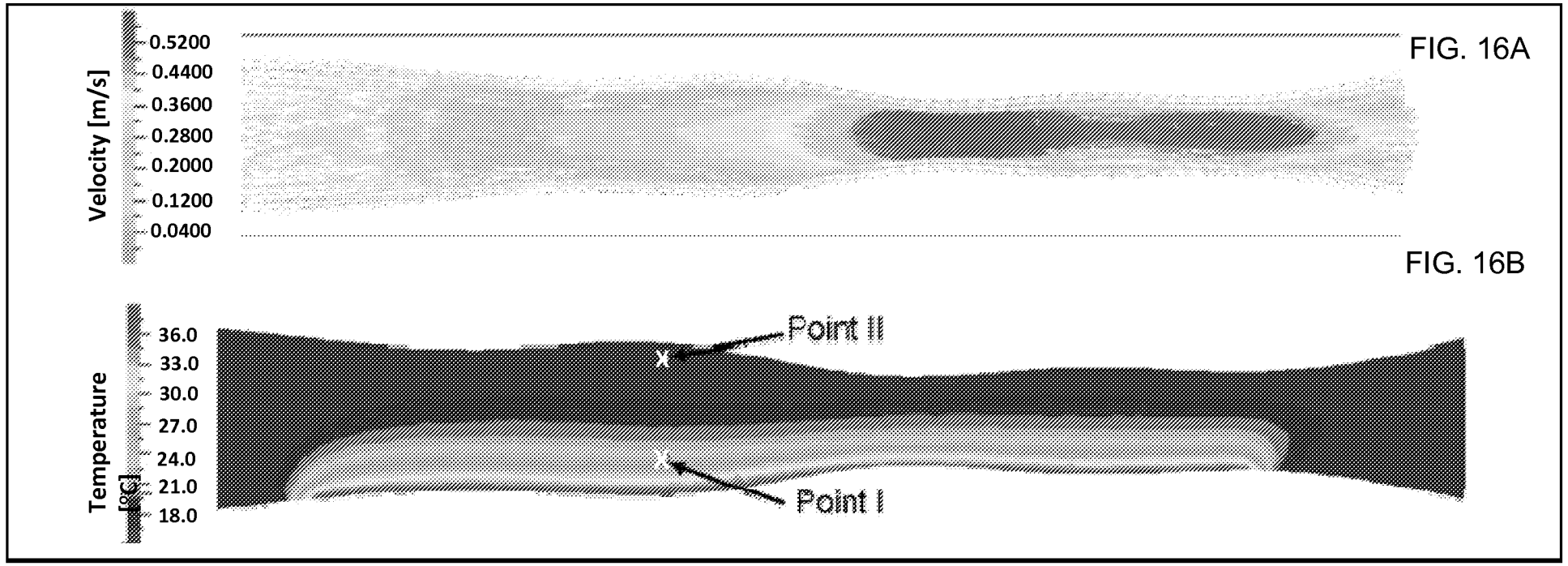
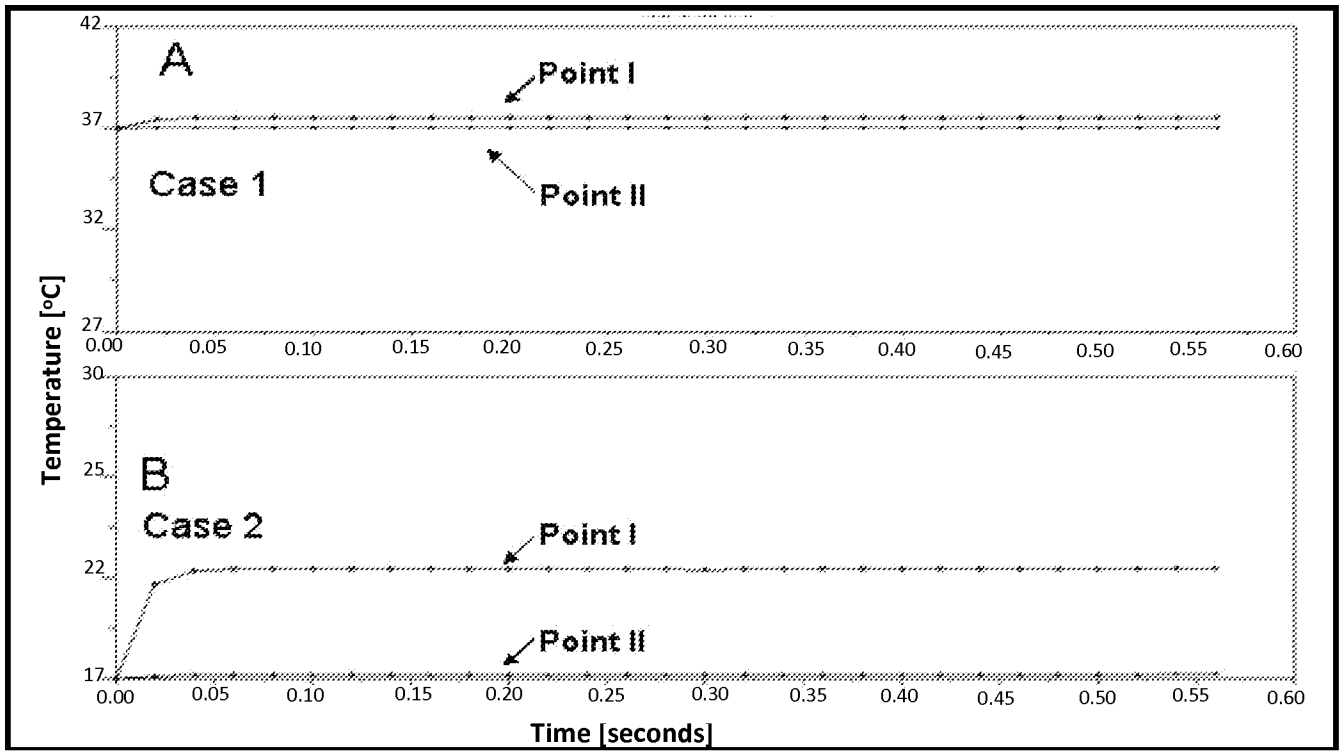


FIG. 16A

FIG. 16B

FIG. 17A

FIG. 17B



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/052306

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00 A61B5/01 A61F7/12 A61M25/00
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 A61F A61M

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 2005/090761 A1 (CARNEY JAMES K [US] CARNEY JAMES KEVIN [US]) 28 April 2005 (2005-04-28) paragraphs [0031], [0051], [0056] - [0059] figures 3,8	21,24-45
X	US 2004/260197 A1 (FOX STEWART M [GB] ET AL) 23 December 2004 (2004-12-23) paragraphs [0038], [0064], [0071]	22
X	US 2001/053882 A1 (HADDOCK THOMAS F [US] ET AL) 20 December 2001 (2001-12-20) paragraph [0047] figures 2A,B	23

-/--

[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 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
23 September 2011	05/10/2011

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	Bengtsson, Johan

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/052306

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/030259 A1 (DAE MICHAEL W [US] ET AL) 12 February 2004 (2004-02-12) the whole document	21-45
A	WO 01/06919 A1 (BARD INC C R [US]) 1 February 2001 (2001-02-01) the whole document	21-45
A	US 2010/049011 A1 (BOESE JAN [DE] ET AL) 25 February 2010 (2010-02-25) the whole document	21-45

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2011/052306

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.: 1-20, 46-52
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.: 1-20, 46-52

1. In accordance with Articles 17(2)(a)(i) and 17(2)(b) PCT, no International Search Report has been established for claims 1-20, since the claims involve a method of treatment on the human or animal body by surgery in the sense of Rule 39.1 (iv) PCT. 1.1 In particular, claim 1 includes the step of "cooling a first portion of said flow". In view of the disclosure of the description, see in particular pages 1-3, "FIELD AND BACKGROUND OF THE INVENTION" and pages 19-42, claim 1 implicitly discloses the step of in-vivo cooling of the human or animal blood. This step is considered to involve a method of treatment on the human or animal body by surgery in the sense of Rule 39.1 (iv) PCT. 2. Further, in accordance with Articles 17(2)(a)(i) and 17(2)(b) PCT, claims 46-52 have not been searched since the claims involve a method of treatment on the human or animal body by therapy in the sense of Rule 39.1 (iv) PCT. 2.1 In particular, claim 46 includes the steps of "...activating said thermistor of said temperature sensor assembly, by supplying current to each of said at least one thermistor; opening said temperature sensor assembly to a fully-opened configuration, such that there is contact of a tip of at least one of said thermistors with the blood vessel wall; increasing said current supplied to at least one of said thermistors, whereby temperature of said at least one thermistors increases to higher than 40 °C; axially or/and circumferentially moving said temperature sensor assembly in the blood vessel, for effecting thermal damage to the blood vessel wall...". These steps are considered to involve a method of treatment on the human or animal body by therapy in the sense of Rule 39.1 (iv) PCT. Further, for the sake of completeness it should be noted that these steps also involve a method of treatment on the human or animal body by surgery in the sense of Rule 39.1 (iv) PCT.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/052306

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