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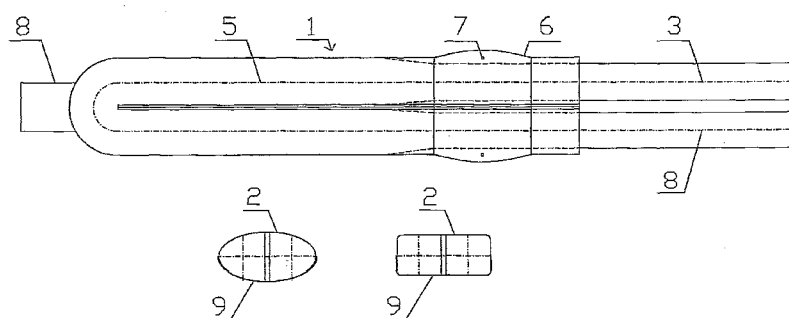
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Figure 9



(57) Abstract: The microdialysis technique and device of the present invention can be used to study metabolic aspects of human and animal organs. When a microdialysis catheter is for example placed into the substance of a beating heart, there is always concern for problems with the catheter position. Further, there is always a risk for damage to heart tissue as well as to the catheter. The present invention is designed to avoid such damages, and a study has confirmed that data obtained from the epicardial probe of the present invention reflects the state of the myocardial metabolism. In anesthetized normoventilated pigs (n=20), a sternotomy was performed and a Gore-tex suture snare was placed around a branch of the left anterior descending (LAD) artery. One microdialysis probe was inserted in the myocardial tissue supplied by the snared LAD branch. Another microdialysis probe was placed on the epicardial surface above the myocardial probe. The protocol included four, ten minute ischemic periods (intervention group) followed by a forty minute ischemic period. The control group was only exposed to a forty minute ischemic period. It was possible to place the microdialysis probes of the present invention on the epicardial surface, and to recover samples reflecting the myocardial metabolic state of the heart. It was also possible to measure rapid changes in concentrations especially for lactate, where ischemia periods as short as ten minutes resulted in detectable increases. A similar pattern was found when analysing glucose and glycerol concentrations in paired samples. Data obtained from the device and method of the present invention, placed on the epicardial surface showed a similar pattern compared to data from a standard probe placed in the myocardium. Thus, the epicardial application of the present invention is useful for perioperative monitoring during cardiac surgery.

METHOD AND DEVICE FOR MICRODIALYSIS SAMPLING

Technical Field

The present invention concerns a method and device for microdialysis sampling the well-being or metabolic conditions of vital organs within humans and animals. More specifically the present invention regards the measurement of substance concentrations (molecules) on the surface of vital organs in accordance with the claims.

Background of the Invention

Microdialysis is a means of sampling substances from the body to help clinicians assess well-being or metabolic conditions by providing serial biochemical samples from a catheter which lies within the substance of an organ. Current commercial microdialysis systems are equipped for sample collection, handling, and analysis of small molecules including glucose, lactate, pyruvate and glycerol as markers of cell injury. Sample collection is based on passive diffusion through a semi-permeable membrane placed at the end of a catheter.

Microdialysis sampling can be performed on organs which move. For example microdialysis sampling can be used to study metabolic aspects of the beating heart. When a microdialysis probe is placed into the substance of a beating heart, there is always concern that the catheter position can be disturbed by the heart's contractions as well as risk for damage to heart tissue as well as the catheter when inserting the microdialysis probe. These risks are taken because it has been shown that the microdialysis technique gives a more rapid response compared to ECG monitoring, catecholamine analyses or other clinical signs of cardiac ischemia.

When a microdialysis catheter is placed in a tissue or organ, there will unavoidably be some tissue damage. If the microdialysis method is used clinically to monitor for example a myocardial metabolic state, it is important to minimize the damage associated with probe insertion. The tissue damage caused by probe placement makes it necessary to allow an equilibration period of 60 to 90 minutes before reliable data can be obtained and this is done in order to allow local resorption or redistribution of fluid that may have initially accumulated surrounding the catheter at the time of insertion. If the time needed for this equilibration period could be shortened or eliminated altogether, this would allow for a more efficacious clinical application of microdialysis sampling.

There is a clear need for a device and method that can sample changes in interstitial fluid concentrations of small molecules which agree strongly with microdialysis sampling direct from the interstitium which alleviates the above mentioned problems associated with microdialysis sampling from a probe placed in the substance of an organ, for example the heart wall.

Prior Art

Langemann introduced the microdialysis technique for studies in association with human cardiac surgery in 1996. He placed the catheter in the left ventricular wall and showed that it was possible to measure serial changes in glucose and lactate in the myocardium.

The Swedish patent document SE434214 titled, "Dialysis Probe for Insertion in Living Tissue - has Membrane Surrounded by Stiffening Casing" describes a dialysis probe, primarily intended for insertion in biological tissues, for example brain tissue, which is comprised of a dialysis membrane and ducts for flow of the perfusion fluid over the membrane. The dialysis membrane in such a probe can be surrounded by a mounting which supports and partially reveals the membrane, and which is more rigid than the membrane. This design has a clear disadvantage compared with the present invention because it does not incorporate a method that allows for microdialysis sampling by the placement of the catheter and/or probe on the surface of the organ to be sampled. Furthermore the design is not intended for organs that contract, expand or in some way move.

The patent document EP0742725B1 applied for by MICRODIALYSIS HOLDING AB titled, "Microdialysis Probe having Reinforced Tube - Comprises a Dialysis Tube over Centre Tube having Enlarged Distal End to Remove Probe Intact" describes a microdialysis probe having a center tube surrounded by a thin dialysis tube, which is located between two tubular fitting parts. The purpose of which is to reinforce the probe and facilitate its withdrawal without any part of the probe remaining. Despite the fragility of the dialysis tube, the distal end of the center tube from within is fixedly joined to the distal fitting part, which also has a larger diameter than the dialysis tube. The design is essentially different from the present invention because it does not incorporate a method that allows for microdialysis sampling by the placement of the catheter and/or probe on the surface of the organ to be sampled.

The Swedish patent document SE511932 titled, "Catheter for Insertion into Blood Vessel to Detect Substances in Coronary Sinus Related to Metabolic Changes in Heart" describes a catheter that is to be inserted into a blood vessel and guided by said blood vessel. The catheter

is comprised of an essentially cylindrical wall structure which defines an elongated catheter body having a proximal end and a distal end, an opening formed in said cylindrical wall structure which extends into said catheter body forming a microdialysis chamber therein having a proximal and distal end. The microdialysis membrane covering said opening such that said microdialysis chamber has at least a portion of said microdialysis membrane as part of its wall, first and second channels extending through at least a portion of said catheter body and having proximal and distal ends, a cross channel connecting one of said first or second channels to the more distal side of said microdialysis chamber and the other of said first or second channels connected to the more proximal side of said microdialysis chamber. The said proximal ends of said first and second channels are connected to an external means for circulating, monitoring and analyzing a microdialysis solution passing there through. The design differs greatly from the present invention because it is intended to be inserted into a body part does not incorporate a method that allows for microdialysis sampling by the placement of the catheter and/or probe on the surface of the body part to be sampled.

Brief Description of the Invention Concept

The main objective of the present invention is to achieve a considerable improvement in the above mentioned drawbacks with current techniques. This is achieved by using a device in accordance with the patent claims' characteristic parts. Another aim of the present invention is to create a reliable, safe and efficient device and method for microdialysis sampling. A further objective of the present invention is to achieve a stable method for measuring metabolic changes postoperatively.

Description of the Invention

The invention will be described in detail in the following text with reference to the enclosed tables and drawings that in an exemplifying purpose show the current preferred embodiments of the invention.

Figure 1 shows the glucose concentrations during a control period followed by an ischemic period (time 220-270 minutes). Microdialysis probes were placed in the myocardium (filled triangle) and on the surface of the epicardium (open square). Data are presented as mean $\pm$ SEM. n=10.

Figure 2 shows lactate concentrations during a control period followed by an ischemic period (sample 220-270 minutes). Microdialysis probes were placed in the myocardium

(filled triangle) and on the surface of the epicardium (open square). Data are presented as mean $\pm$ SEM, n=10.

Figure 3 shows the pyruvate concentrations during a baseline period followed by an ischemic period (sample 220-270 minutes). Microdialysis probes were placed in the myocardium (filled triangle) and on the surface of the epicardium (open square). Data are presented as mean $\pm$ SEM, n=10.

Figure 4 shows glycerol concentrations during a baseline period followed by an ischemic period (sample 220-270 minutes). Microdialysis probes were placed in the myocardium (filled triangle) and on the surface of the epicardium (open square). Data are presented as mean $\pm$ SEM, n=9.

Figure 5 shows the glucose concentrations during a short ischemic period followed by a longer ischemic period (sample 220-270 minutes). Microdialysis probes were placed in the myocardium (filled triangle) and on the surface of the epicardium (open square). Data are presented as mean $\pm$ SEM, n=9.

Figure 6 shows the lactate concentrations during a short ischemic period followed by a longer ischemic period (sample 220-270 minutes). Microdialysis probes were placed in the myocardium (filled triangle) and on the surface of the epicardium (open square). Data are presented as mean $\pm$ SEM, n=9.

Figure 7 shows pyruvate concentrations during a short ischemic period followed by a longer ischemic period (sample 220-270 minutes). Microdialysis probes were placed in the myocardium (filled triangle) and on the surface of the epicardium (open square). Data are presented as mean $\pm$ SEM, n=9.

Figure 8 shows glycerol concentrations during a short ischemic period followed by a longer ischemic period (sample 220-270 minutes). Microdialysis probes were placed in the myocardium (filled triangle) and on the surface of the epicardium (open square). Data are presented as mean $\pm$ SEM, n=9.

Figure 9 shows a first preferred embodiment of the present invention.

Figure 10 shows a second preferred embodiment of the present invention.

Figure 11 shows a third preferred embodiment of the present invention.

Figure 12 shows a fourth preferred embodiment of the present invention.

Figure 13 shows a fifth preferred embodiment of the present invention.

By utilizing the method of the present invention a probe/catheter is placed on the surface of a vital organ and it samples substances that follow relatively rapid metabolic changes in the organ which previously required that a catheter be placed in the substance of the organ to collect the samples. According to the first preferred embodiment of the present invention as shown in figure 9, a probe/catheter 1, of an elliptical, rectangular or other for the purpose suitable shape, is comprised of an outer casing 2 with an inlet 3 and an outlet 4 that are intended to be connected to a pump by tubing. The pump and tubing suitable for the purpose are of current designs and are therefore not shown in the figures or discussed further in detail.

The pump and tubing are intended for providing a flow of suitable fluid such as perfusion fluid (perfusate) or similar through the probe 1. Within the probe 1 is a U-shaped channel 5 that connects the inlet 3 with the outlet 4. The channel 5 is designed to allow perfusion fluid (perfusate) or similar to flow through the probe 1. The channel 5 may consist of a tube or other suitable for the purpose hollow design. According to the first preferred embodiment of the present invention as shown in figure 9 an attachment girdle 6 designed to facilitate the attachment of the probe 1 to the tissue surface of an organ using at least one suture via at least one lateral hole or eyelet 7 is integrated onto the outer casing 2 of the probe 1. On the end of the probe 1 opposite the inlet 3 and outlet 4 is placed a ring 8 also designed for securing the probe 1 to an organ via at least one suture. A semi-permeable membrane 9 is attached to the underside of the probe 1, the side facing the organ.

According to the second preferred embodiment of the present invention as shown in figure 10, a probe/catheter 1, of an elliptical, rectangular or other for the purpose suitable shape, is comprised of an outer casing 2 with an inlet 3 and an outlet 4 that are intended to be connected to a pump by tubing. Within the probe 1 is a U-shaped channel 5 that connects the inlet 3 with the outlet 4. In all the preferred embodiments except the embodiment shown in figure 9 the attachment girdle 6 is essentially in the form of a recess in the outer casing 2 and does not contain eyelets 7. Attachment of the probe 1 to the tissue surface of an organ is accomplished by using at least one suture placed in the recess of the attachment girdle 6. In this way the suture may contain several millimeters of slack, preferably within an interval of three to eight millimeters, so that the probe/catheter 1 is not subjected to large mechanical forces relating to a beating or moving organ such as the heart. On the end of the probe 1 opposite the inlet 3 and outlet 4 is placed a ring 8 also designed for securing the probe to an organ via at least one suture. A semi-permeable membrane 9 is attached to the underside of

the probe 1, the side facing the organ. It is conceivable that several other embodiments of the catheter/probe 1 which are suitable for the method can be used.

A third preferred embodiment of the present invention is shown in figure 11. Figure 11 shows a probe/catheter 1 with a tube in the inlet 3 that is intended to be connected to a pump (not shown). Via a preferably concentric tube the perfusion fluid flows into the inlet 3 to the probes 1 distal end allowing the fluid to come into contact with the semi-permeable membrane 9. At the crossover point 11 the fluid then passes through to the outlet 4 into tubing leading to a vial where the liquid is intended to be collected. The tubes leading to and from the inlet 3 and outlet 4 are inserted in the first shaft 12 and secured by suitable means for example gluing to the liquid crossover point 11 and an attachment girdle 6. A second shaft 14 is fixed upon the membrane 9 and also attached to the liquid crossover point 11 and the attachment girdle 6. On the end of the second shaft 14 a ring 8 is placed for temporarily securing the probe 1 to an organ via at least one suture. An attachment girdle 6 is designed to facilitate the temporary attachment of the probe 1 to the tissue surface of an organ using at least one suture around the attachment girdle 6. The suture or sutures may be placed so it/they will be able to move along the attachment girdle 6 to avoid damage to the probe and/or tissue. To reduce evaporation and possible interface with other organs an outer casing 2 covers the probe 1.

A fourth preferred embodiment of the present invention is shown in figure 12. Figure 12 shows a probe/catheter 1 with a tube in the inlet 3 that is intended to be connected to a pump (not shown). Via a preferably concentric tube the perfusion fluid flows into the inlet 3 to the probes 1 distal end allowing the fluid to come into contact with the semi-permeable membrane 9. At the crossover point 11 the fluid then passes through to the outlet 4 into tubing leading to a vial where the liquid is intended to be collected. The tubes in the inlet 3 and outlet 4 are inserted in the first shaft 12 and secured by suitable means to the liquid crossover point 11 for example by being glued to the attachment elements 15 and 16. The second shaft 14 is fixed upon the membrane 9 and into the liquid crossover point 11 and attachment elements 15 and 16. On the end of the second shaft 14 a ring 8 is placed for temporarily securing the probe to an organ via at least one suture. An attachment girdle 6 between attachment element 15 and 16 is designed to facilitate the temporary attachment of the probe to the tissue surface of an organ using at least one suture around the attachment girdle 6. The suture or sutures may be placed so it/they will be able to move between the attachment elements 15 and 16 to avoid damage of the probe and/or organ tissue.

A fifth preferred embodiment of the present invention is shown in figure 13. Figure 13 shows

a probe/catheter 1 with a tube in the inlet 3 that is intended to be connected to a pump (not shown). Via a preferably concentric tube the perfusion fluid flows into the inlet 3 to the probes 1 distal end allowing the fluid to come into contact with the semi-permeable membrane 9. At the crossover point 11 the fluid then passes through to the outlet 4 into tubing leading to a vial where the liquid is intended to be collected. The tubes leading to and from the inlet 3 and outlet 4 are inserted in the first shaft 12 and secured by suitable means to the liquid crossover point 11 and an attachment girdle 6 for example by being glued to the second shaft 14. On the end of the second shaft 14 a ring 8 is placed for temporarily securing the probe 1 to an organ via at least one suture. An attachment girdle 6 is designed to facilitate the temporary attachment of the probe 1 to the tissue surface of an organ using at least one suture around the attachment girdle 6. The suture or sutures may be placed so it/they will be able to move along the attachment girdle 6 to avoid damage to the probe 1 and/or organ tissue.

The idea for this unconventional site of microdialysis sampling came about after a serendipitous collection of microdialysis samples from a probe which relocated itself from an intestinal placement to an epicardial position accidentally, and, unexpectedly, analysis of samples from the epicardial catheter were similar to the other catheters which were attached by current techniques in the substance of the organ.

Testing shows that it is possible to place the microdialysis probe 1 of the present invention on the epicardial surface and recover samples reflecting the myocardial metabolic state of the organ. Testing has also shown that it is possible to measure rapid changes in concentrations especially for lactate where an ischemia period as short as ten minutes resulted in detectable increases in lactate concentrations. There was a similar pattern in lactate concentrations between samples analyzed from the myocardial and epicardial probes. A similar pattern was found when analyzing glucose and glycerol concentrations in paired samples.

The microdialysis catheter 1 of the present invention is configured with a catheter which lies relatively flat against the organ's surface, in order to have a larger contact area between the catheter 1 and the organ. In the preferred embodiments shown in figures 9 and 10 the membrane 9 lies essentially on the underside (the side facing the organ) of the catheter 1, in order to avoid evaporation of microdialysate which can lead to artifactual concentration increases. This preferred design also provides more reliability in sampling because a steady state between the catheter 1 and the organ surface is reached more quickly. In the preferred embodiments shown in figures 11, 12 and 13, the membrane's 9 side, the side facing away from the organ being sampled is covered so as not to come into contact with surrounding

organs. The establishment of a steady state for sampling, during for example a heart operation, is necessary if the technique is to be used during the rest of the operation.

In the preferred embodiments in figures 10, 11 and 12 the catheter's membrane 9 is glued to the outer casing 2 which will be constructed of a less elastic/flexible material so that the catheter 1 will resist folding or bending during placement and sampling periods. The probe/catheter 1 is temporarily attached to an organ surface, by at least one suture to the attachment girdle 6 in a manner that allows for several millimeters of slack so that the catheter 1 is not subjected to large mechanical forces relating to a beating or moving organ. At the catheter's tip/end, a small ring 8 is used to temporarily attach the catheter's tip/end to an organ surface with at least one suture, so that the catheter's membrane 9 is held stationary on the organ surface. The catheter 1 is designed with no structures which can catch or fasten themselves to tissue so that it can be easily removed through an operative incision in the post operative period without causing any tissue injury. The catheter 1 is coupled to a pump which generates a constant flow of fluid or perfusate over the membrane 9 area. The fluid is pumped in through the tubes into the inlet 3, flows through the entire catheter 1, and then flows out through the tubes from the outlet 4.

The membrane 9 of the present invention consists preferably of a polymer composition such as for example PAES (polyarylethersulfone). The tubes from and to the inlet 3 and outlet 4 consist preferably of a polymer material, for example PUR (polyurethane). The outer casing 2 consists preferably of a polymer material as for example polyurethane, polyamide or polyimide. Other materials than the ones mentioned, that are suitable for the purpose, may of course also be used for the probe and its parts.

Test Case

The case study was approved by the Animal Experimental Ethics Committee at Umeå University Sweden, and was conducted in accordance with the (Guide for the Care and Use of Laboratory Animals, National Research Council, Washington, USA, 1996) NIH Institutional animal care and use committee guidebook. A total of 19 female pigs were used.

After intramuscular premedication, with a mixture of ketamine 10mg/kg (Ketalar®, Pfizer, Morris Plains, New Jersey, USA), Rompum (Xylazine) and atropine sulphate 0.05 mg/kg (Atropin, NM, Pharma, Stockholm, Sweden) anaesthesia was introduced by an intravenous bolus dose of 10 mg/kg sodium pentobarbital (Pentobarbitalnatrium, Apoteksbolaget, Stockholm, Sweden). Infusion of Fentanyl 20 µg/kg/h (Fentanyl, Braun, Melsungen,

Germany), Midazolam 0.3 mg/kg/h (Dormicum, Roche, Basel, Switzerland) and sodium pentobarbital 5 mg/kg/h was used for maintenance of anaesthesia. The animals were tracheotomized (7.0 OP endotracheal tube, Rusch, kernen, Germany) and mechanically ventilated with air containing 30% oxygen (Evita 4, Dräger, Germany) and adjusted to normoventilation as measured with intermittent arterial blood gas analyses (ABL 5 autoanalyzer, Radiometer, Copenhagen, Denmark). One litre of Ringer's acetate (Pharmacia-Upjohn, Sweden) was given to the animals during the first hour followed by an infusion that started at 15 ml/kg/h. The infusion was increased during the day to maintain normovolemia, as determined by the goal to achieve a CVP between 5 and 10 mmHg.

In brief, an arterial catheter was placed in a small neck artery and a central venous catheter was inserted in the external jugular vein. Basal registration included measurement of heart rate (HR), mean arterial pressure (MAP) and central venous pressure (CVP). All pressures were measured using fluid filled catheters and pressure transducers (Ohmeda Inc., USA) at the mid-axillary's level. Data was continuously recorded using a computer based multi-channel signal acquisition and analysis system (Acknowledge, Biopac system Inc., CA, USA).

A medial sternotomy was then performed and a diagonal branch of the left anterior descending (LAD) artery was identified. A Gore-tex suture snare was placed around the proximal aspect of the branch. One microdialysis probe (CMA 20 PEAS Elite, CMA Microdialysis, Solna, Sweden) was placed in the myocardial tissue supplied by the snared LAD branch using a modified Seldinger technique was used in order to minimise mechanical injury to the microdialysis probe and to the myocardium. Another microdialysis probe (CMA 20 PEAS Elite, CMA Microdialysis, Solna, Sweden) was placed on the epicardial surface above the first myocardial probe. The epicardial probe was secured with sutures at the suture point and over the membrane.

The microdialysis probes were perfused with Ringers solution (a modified Krebs- Ringer phosphate buffer) at a flow rate of 2.0 μ l/min. Samples were collected every 10th minute during the equilibration period and throughout the study protocol. Animals were randomized in two groups for a protocol involving another study (for which microdialysis was employed here as a sampling method). One group had a 150 minutes period without any intervention before 40 minutes of ischemia induced by tightening the Gore-tex suture. The second group had four 10 minute periods of snare occlusion followed by 20 minutes of reperfusion before the 40 minutes ischemic period.

52 samples were collected for each animal, 26 from each probe. Glucose, lactate, pyruvate

and glycerol were analysed in a CMA 600 analyser (CMA, Solna, Sweden). The analyser is a clinical chemical analyser that uses enzymatic reagents and colorimetric measurements of the microdialysis samples. All samples were collected in glass vials and sealed with a crimp cap directly after sampling. The samples were stored in 4-6°C no longer than one day. All samples were centrifuged (Mini Galaxy, VWR, West Chester, PA, USA) for 30 seconds before analyses.

Microdialysis analysis was performed on sample from the area affected by the coronary artery occlusion for detection of metabolic by products related to myocardial ischemia and reperfusion. All results were paired, one from the microdialysis probe in the substance of the heart wall, and the other result from the probe lying on the surface of the ventricular wall adjacent to the first probe.

Glucose concentrations measured from the epicardial surface showed more variation during the equilibration period (time 20-50 minutes) than concentrations measured in the myocardium. After the equilibration period (60 minutes), glucose levels were similar in both probes and showed also a similar pattern, with decreasing glucose concentration during the resting period, and then also during ischemia (Figure 1).

Also lactate concentrations followed the same pattern in both probes. However, concentrations were higher in the epicardial probe than in the myocardial probe during the 40 minutes final ischemia period (Figure 2).

There was a discrepancy in pyruvate concentrations as measured by the two different probes. Thus, pyruvate concentrations measured by the epicardial probe were similar throughout the study period, while pyruvate concentrations measured in the myocardium showed a dual pattern, with a gradual increase until a final decrease during the index ischemia period (Figure 3).

Glycerol concentrations were stable during the equilibration and baseline periods with an increase during the 40 minutes ischemia period. The epicardial and myocardial probes followed a similar pattern (Figure 4).

Glucose concentrations measured from the epicardial surface during equilibration and baseline periods were less stable in this group of animals with several ischemic periods compared with the concentrations in the myocardial probe. Glucose decreased similarly in both probes during the study protocol (Figure 5). Rapid changes in glucose concentrations were difficult to detect in samples from the epicardial probe compared to the myocardial

probe.

Lactate concentrations were stable during the initial equilibration period as measured by both probes. In both probes, lactate concentrations increased in association with ischemia period and decreased during reperfusion (Figure 6).

Pyruvate concentrations continuously increased during the experimental protocol as measured by both probes. The short ischemia periods were associated with increased pyruvate concentrations detected with the myocardial probe but not with the epicardial probe (Figure 7). Concentrations of glycerol were rather unchanged in both probes during the protocol (Figure 8). A small increase was observed during the final longer ischemia period.

Even if the preferred embodiment has been described in detail, variations and modifications within the scope of the invention can become apparent for professionals in the field and all these variations are considered to fall under the subsequent claims. Alternatively, different materials with suitable qualities can be applied to the entire, or a partial part of, the present invention. Alternatively, the shapes, dimensions and sizes of the described preferred embodiments may vary substantially. For example the size and shape of the attachment girdle 6, the attachment elements 15 and 16 and the ring 8 of the probe 1 may vary substantially and still be suitable for the purpose. Several alternative embodiments, for example of the catheter/probe's 1 shape or number of points of attachment to the organ as well as placement of the membrane 9 and so on are conceivable.

In alternative embodiments the membrane 9 may for example be designed in the form of a cylinder, and constructed using previously established methods. The aspect which distinguishes the present invention from previous designs is the zone in the catheter where the membrane 9 is placed on the catheter 1 (see above). In order to minimize evaporative microdialysate loss, and in order to more rapidly achieve a steady state of physiological substance concentrations across the catheter's membrane 9, it is conceivable that a protective (cover) which lies approximately 0.5 mm above the membrane 9 will sit and protect the membrane.

Advantages of the Invention

The present invention eliminates or greatly reduces problems with existing designs that were previously described in this patent application. The main advantage of locating the microdialysis probe on the epicardial surface is the minimal damage to the tissue or organ.

This application lowers the risk for complications compared to when catheters are placed and removed from for example the myocardium. Although some clinical studies have shown that microdialysis catheters can be placed and removed from the myocardium without complications, the placement of a microdialysis catheter on the epicardium is safer especially for patients with myocardial injuries. Further, the epicardial approach of the present invention enables the catheter to be placed on for example the atria. The intramyocardial approach does not allow for sampling in the thin walled atriums. Another advantage aspect of probe location in the experimental settings is that it is easier to obtain an adequate and certain location on the epicardial surface than in the myocardium. Thus, the epicardial approach of the present invention reduces the risk of inadequate probe placement in conjunction with experimentally induced myocardial ischemia.

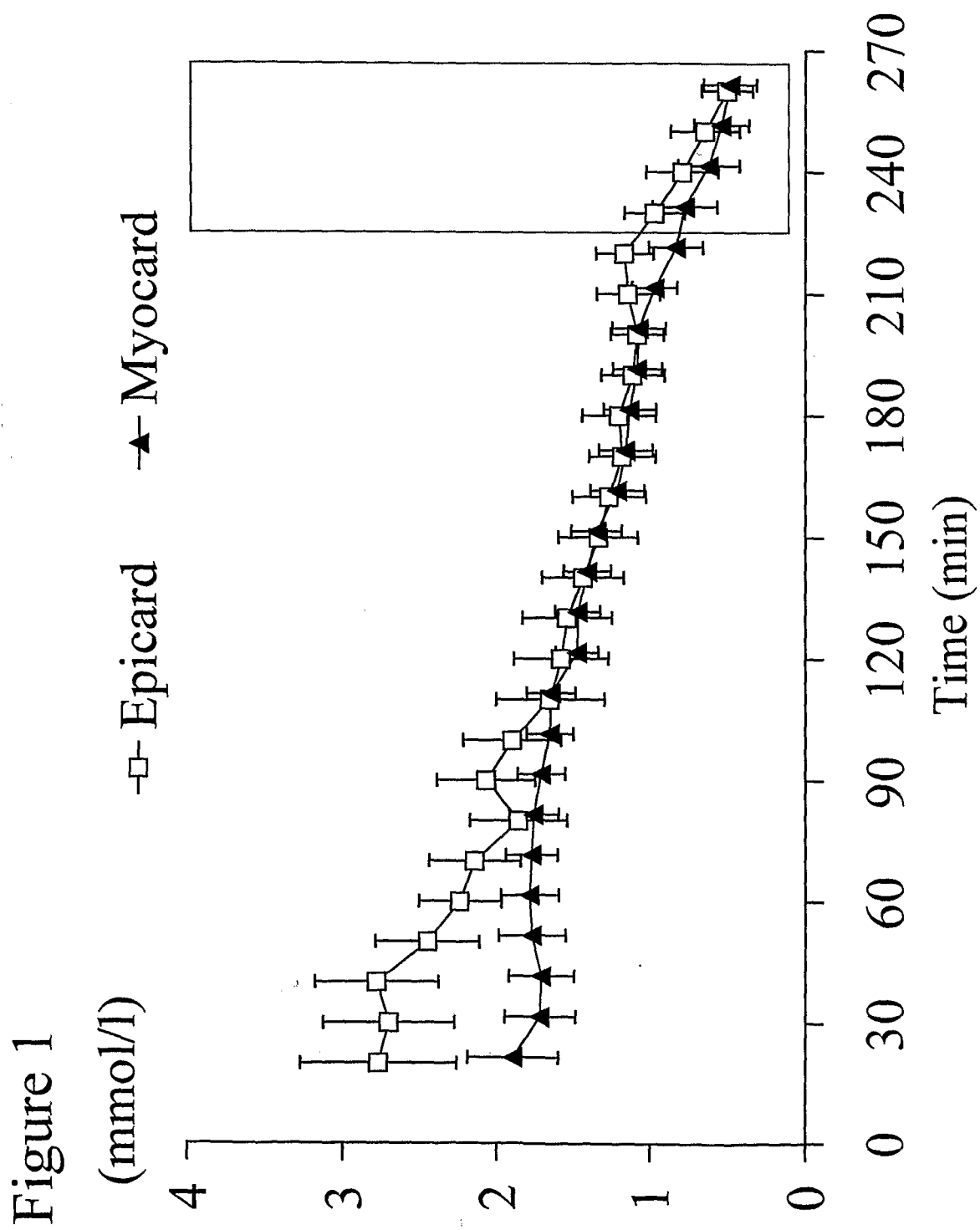
An additional advantage of the present invention is that there is virtually no need for equilibration time. Previous studies have shown equilibration times for known clinically-used microdialysis monitoring systems that vary from 60 to 90 minutes. Equilibration time depends on which substances that were analyzed and from which tissue the samples were collected. Clinical studies have shown that the equilibration time for glutamate was 30 minutes longer in injured patients than in healthy patients. With this in mind it is very advantageous to reduce or eliminate equilibration times both in healthy and injured patients.

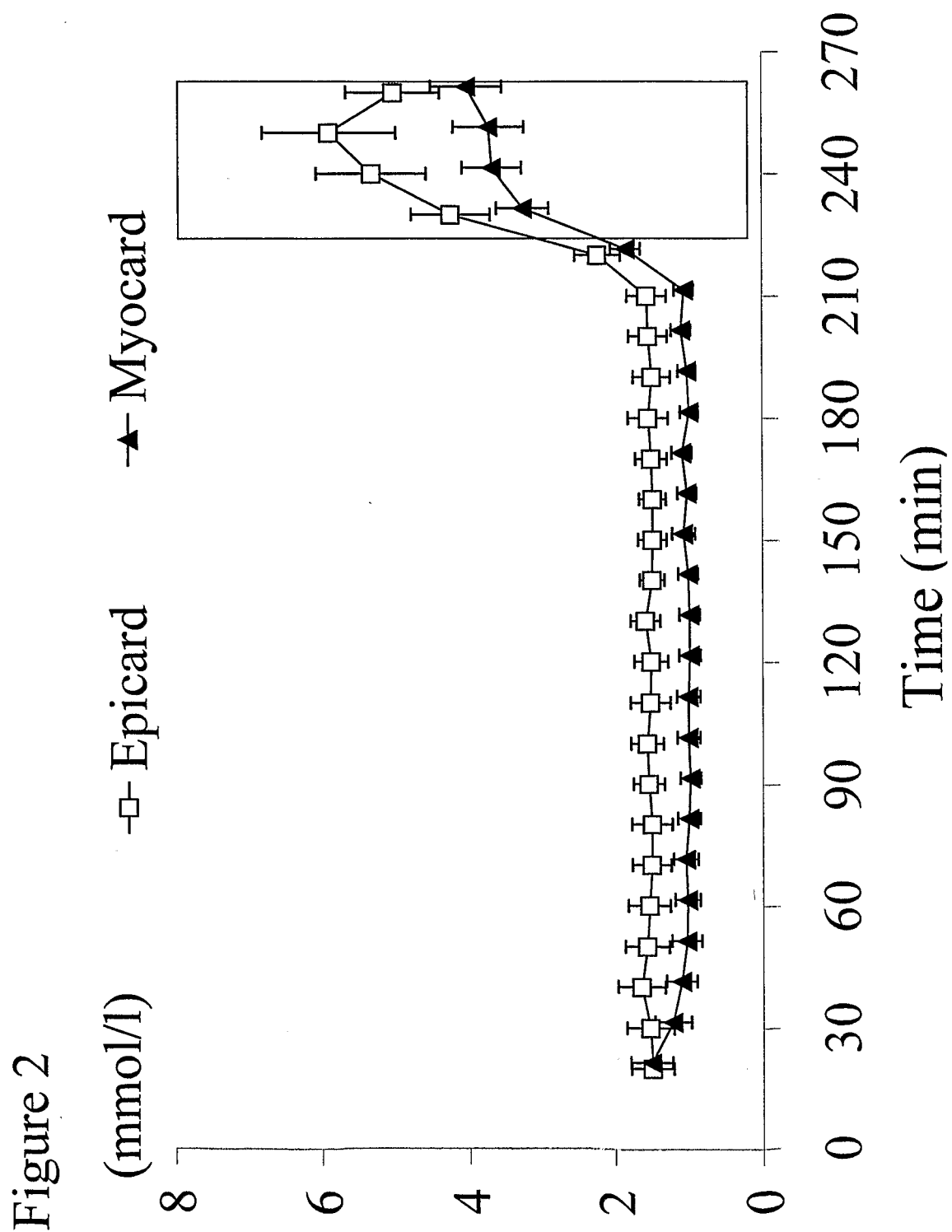
Another advantage of the present invention is the virtual elimination of organ damage or bleeding related to the placement of microdialysis probes within solid organs using needles. Local bleeding at the insertion site adds to the equilibration time. Yet another advantage with microdialysis measurement on the heart surface which is made possible by the present invention is the possibility to continuously follow the metabolic state postoperatively. It has been shown that the microdialysis technique of the present invention provides a more rapid response compared to ECG monitoring, catecholamine analyses or other clinical signs of cardiac ischemia. This will lead to faster diagnostics and greatly minimize complications for patients during and after cardiac surgery. Furthermore the present invention allows for use of a very advantageous microdialysis technique for perioperative monitoring during cardiac surgery.

Claims

1. Microdialysis sampling method utilizing at least one microdialysis catheter or probe (1) placed on the surface of a vital human or animal organ for sampling metabolic substances that indicate the metabolic conditions of the organ from the surface of the organ **characterized by** that the catheter or probe (1), temporarily attached to the outside surface of the vital organ and not inserted into the substance of the vital organ, samples said metabolic substances via a semi-permeable membrane (9) attached to the catheter or probe (1), the side facing the surface of the organ.
2. Microdialysis sampling method according to claim 1 utilizing at least one microdialysis catheter or probe (1) placed on the surface of a vital human or animal organ for sampling metabolic substances that indicate the metabolic conditions of the organ from the surface of the organ **characterized by** that the catheter or probe (1) is temporarily attached to the vital organ by at least one suture.
3. Microdialysis sampling method according to claim 2 utilizing at least one microdialysis catheter or probe (1) placed on the surface of a vital human or animal organ for sampling metabolic substances that indicate the metabolic conditions of the organ from the surface of the organ **characterized by** that the catheter or probe (1) is temporarily attached to the vital organ by at least one suture with several millimeters of slack, preferably within an interval of 3 to 8 millimeters, in a recess in the attachment girdle 6 on the probe (1) so that the catheter (1) is not subjected to large mechanical forces relating to a beating or moving organ.
4. Microdialysis sampling catheter or probe (1) according to the method of claim 1 **characterized by** that the probe/catheter (1), essentially of an elliptical, rectangular or other for the purpose suitable shape, is comprised of an outer casing (2) with an inlet (3) and an outlet (4) connected by a U-shaped channel (5) that allows perfusion fluid (perfusate) or similar to flow through the probe (1).
5. Microdialysis sampling catheter or probe (1) according to the method of claim 1 **characterized by** that an attachment girdle (6), designed to facilitate the temporary attachment of the probe (1) to the surface tissue of a vital organ via at least one eyelet (7) using at least one suture, is integrated onto the outer casing (2) of the probe (1).
6. Microdialysis sampling catheter or probe (1) according to the method of claim 1 **characterized by** that on the end or tip of the probe (1) opposite the inlet (3) and outlet

- (4) is placed a ring (8) designed for temporarily securing the probe to a vital organ via at least one suture.
7. Microdialysis sampling catheter or probe (1) according to the method of claim 1 **characterized by** that a membrane (9) consists preferably of a polymer composition such as for example PAES (polyarylethersulfone).
 8. Microdialysis sampling catheter or probe according to the method of claim 1 **characterized by** that the outer casing (2) consists preferably of a polymer material as for example polyurethane, polyamide or polyimide.
 9. Microdialysis sampling method according to claim 1 utilizing at least one microdialysis catheter or probe (1) placed on the surface of a vital human or animal organ for sampling metabolic substances that indicate the metabolic conditions of the organ from the surface of the organ **characterized by** that at least one of the metabolic substances sampled is glucose.
 10. Microdialysis sampling method according to claim 1 utilizing at least one microdialysis catheter or probe (1) placed on the surface of a vital human or animal organ for sampling metabolic substances that indicate the metabolic conditions of the organ from the surface of the organ **characterized by** that at least one of the metabolic substances sampled is lactate.
 11. Microdialysis sampling method according to claim 1 utilizing at least one microdialysis catheter or probe (1) placed on the surface of a vital human or animal organ for sampling metabolic substances that indicate the metabolic conditions of the organ from the surface of the organ **characterized by** that at least one of the metabolic substances sampled is pyruvate.
 12. Microdialysis sampling method according to claim 1 utilizing at least one microdialysis catheter or probe (1) placed on the surface of a vital human or animal organ for sampling metabolic substances that indicate the metabolic conditions of the organ from the surface of the organ **characterized by** that at least one of the metabolic substances sampled is glycerol.





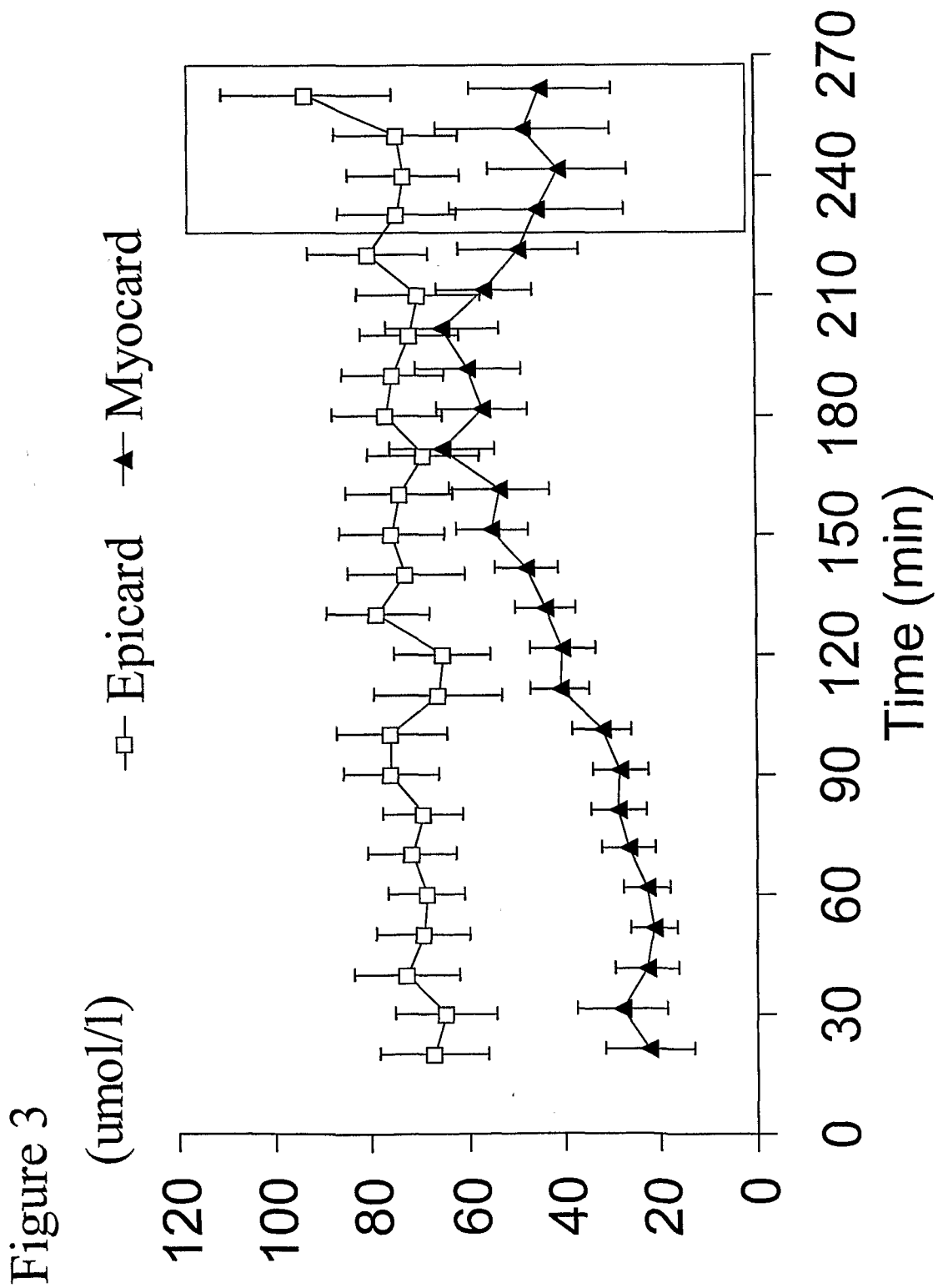
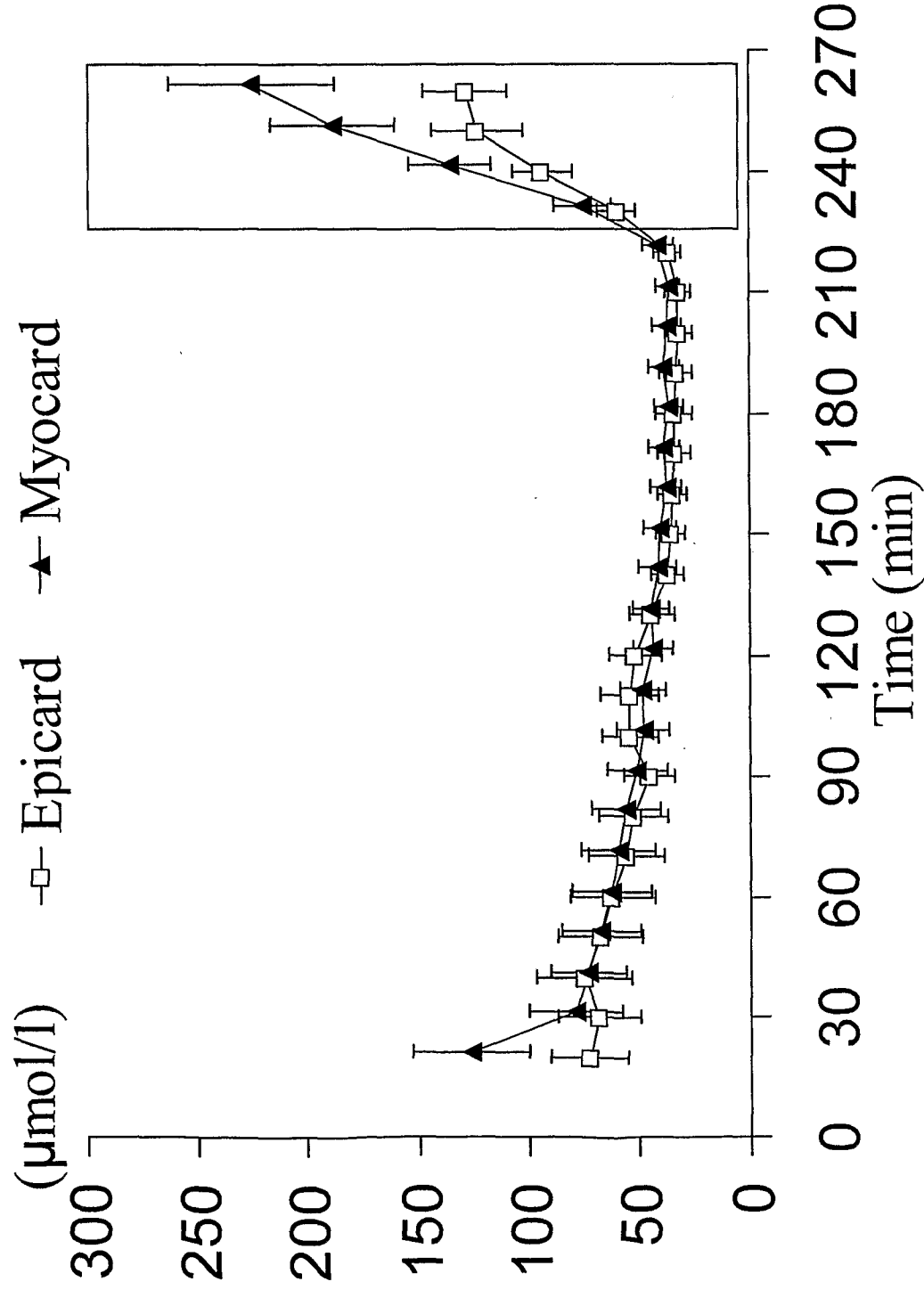


Figure 4



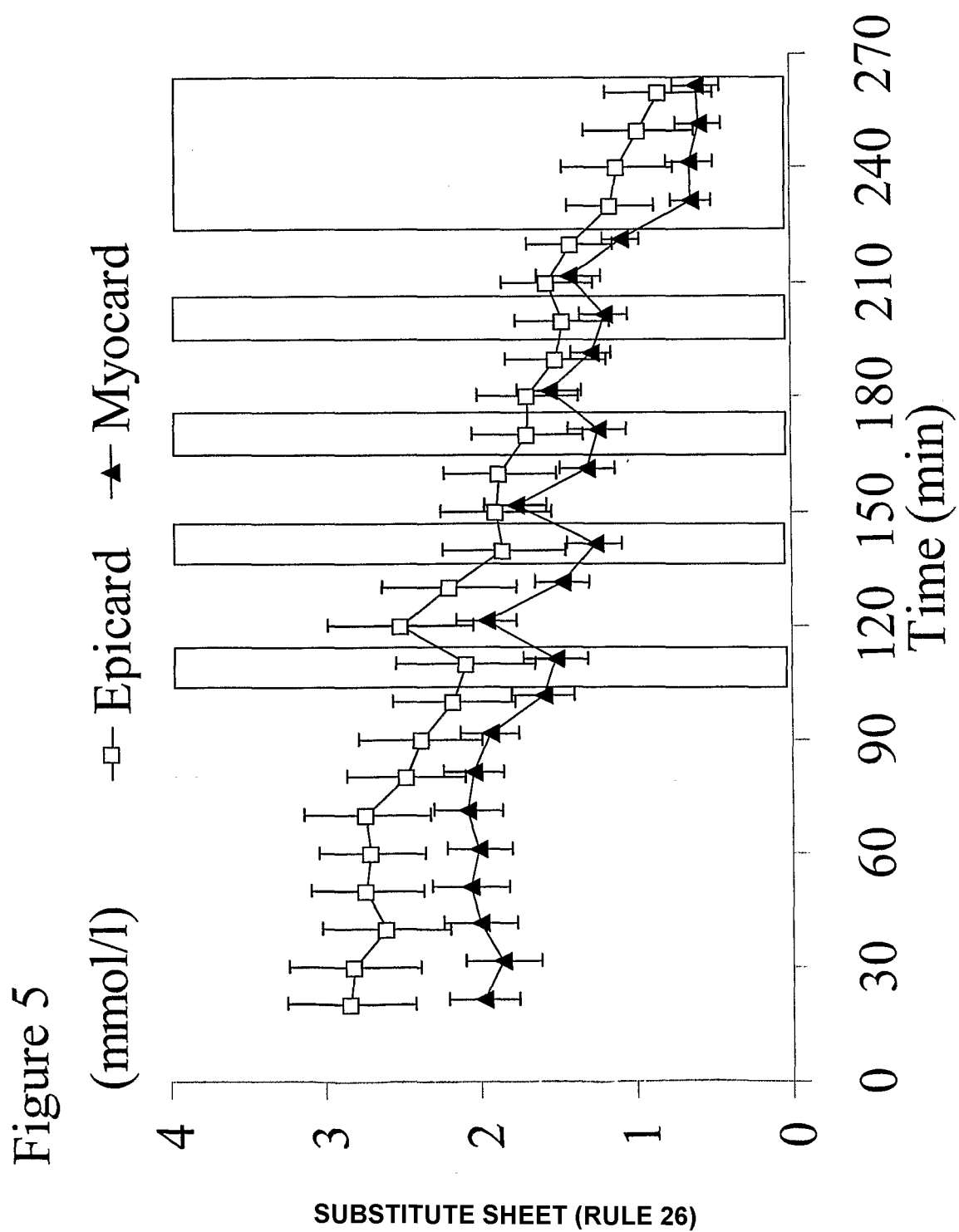


Figure 6

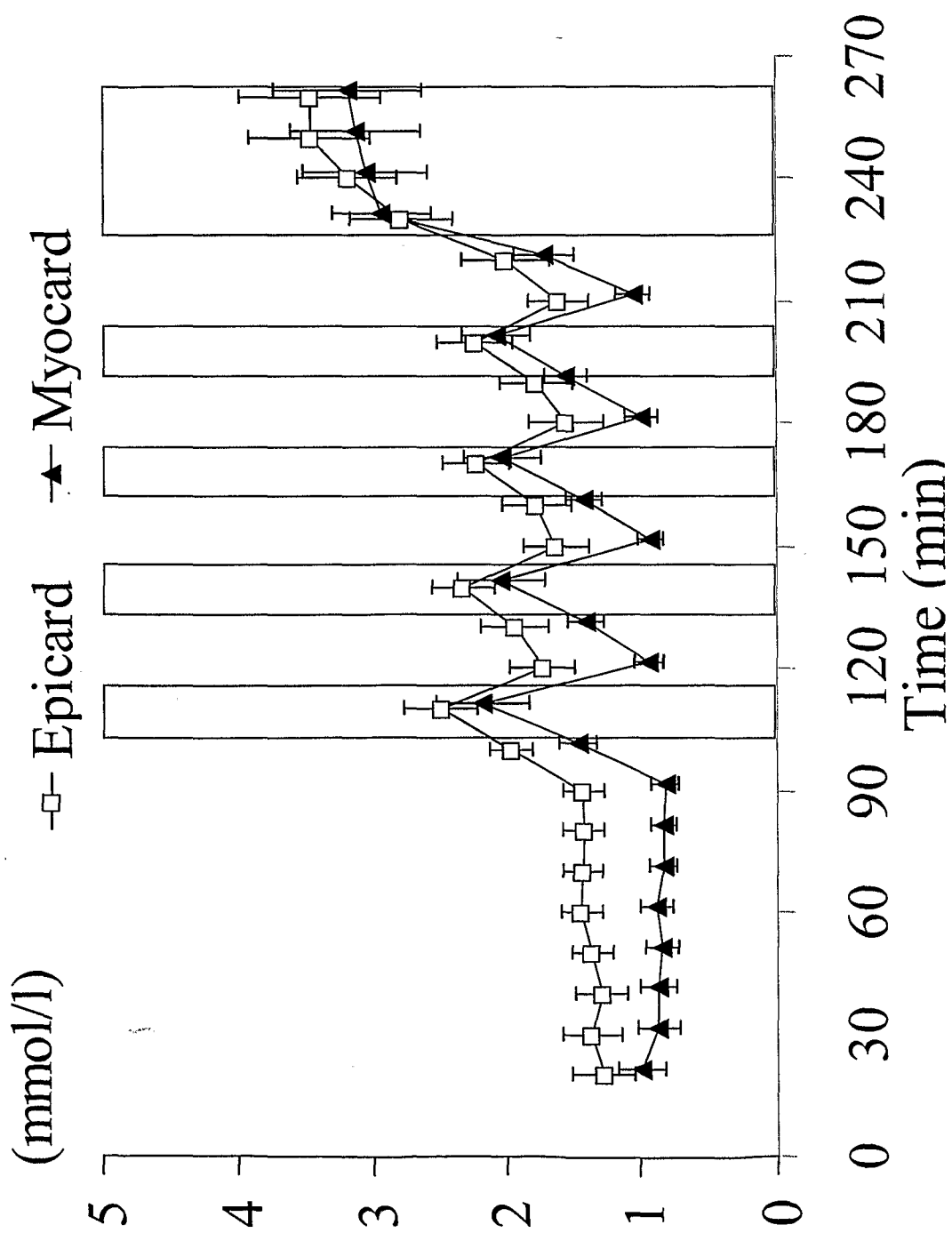
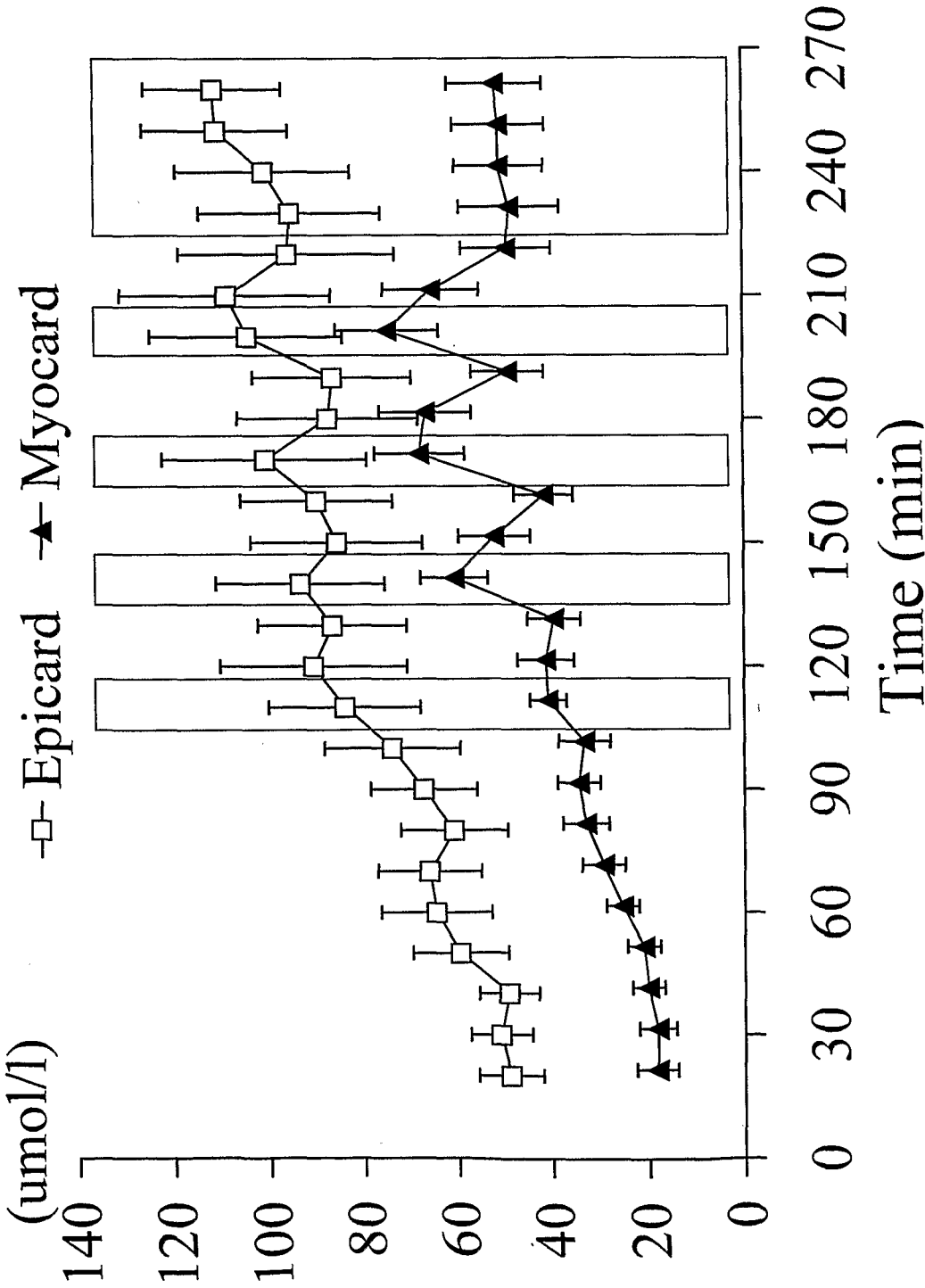


Figure 7



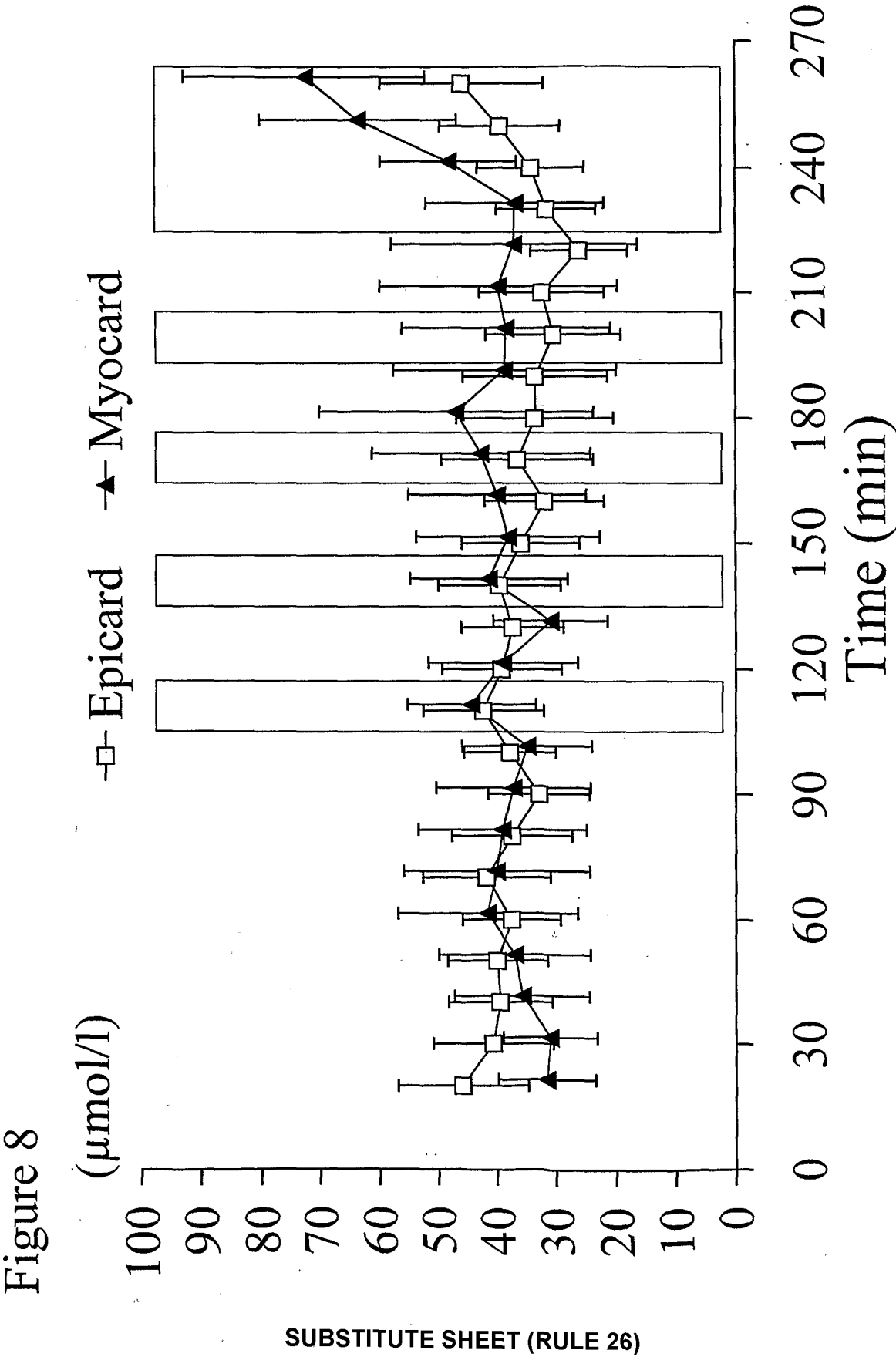
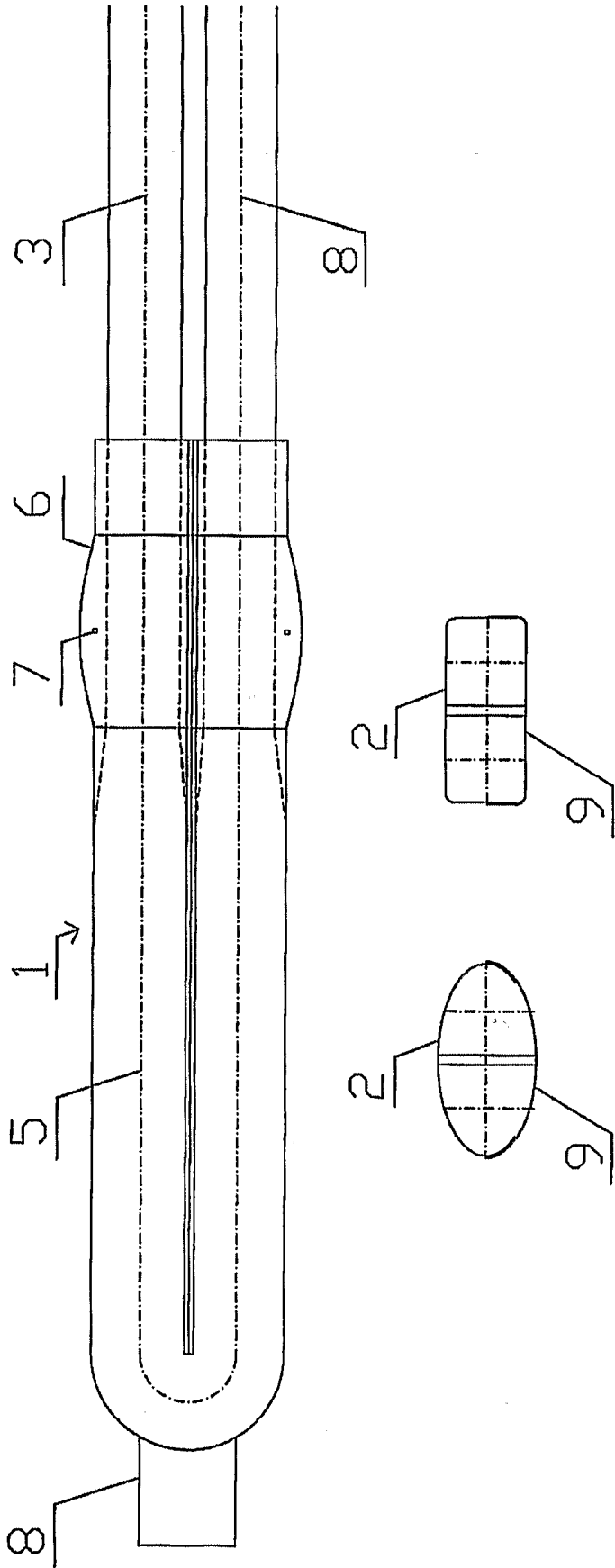
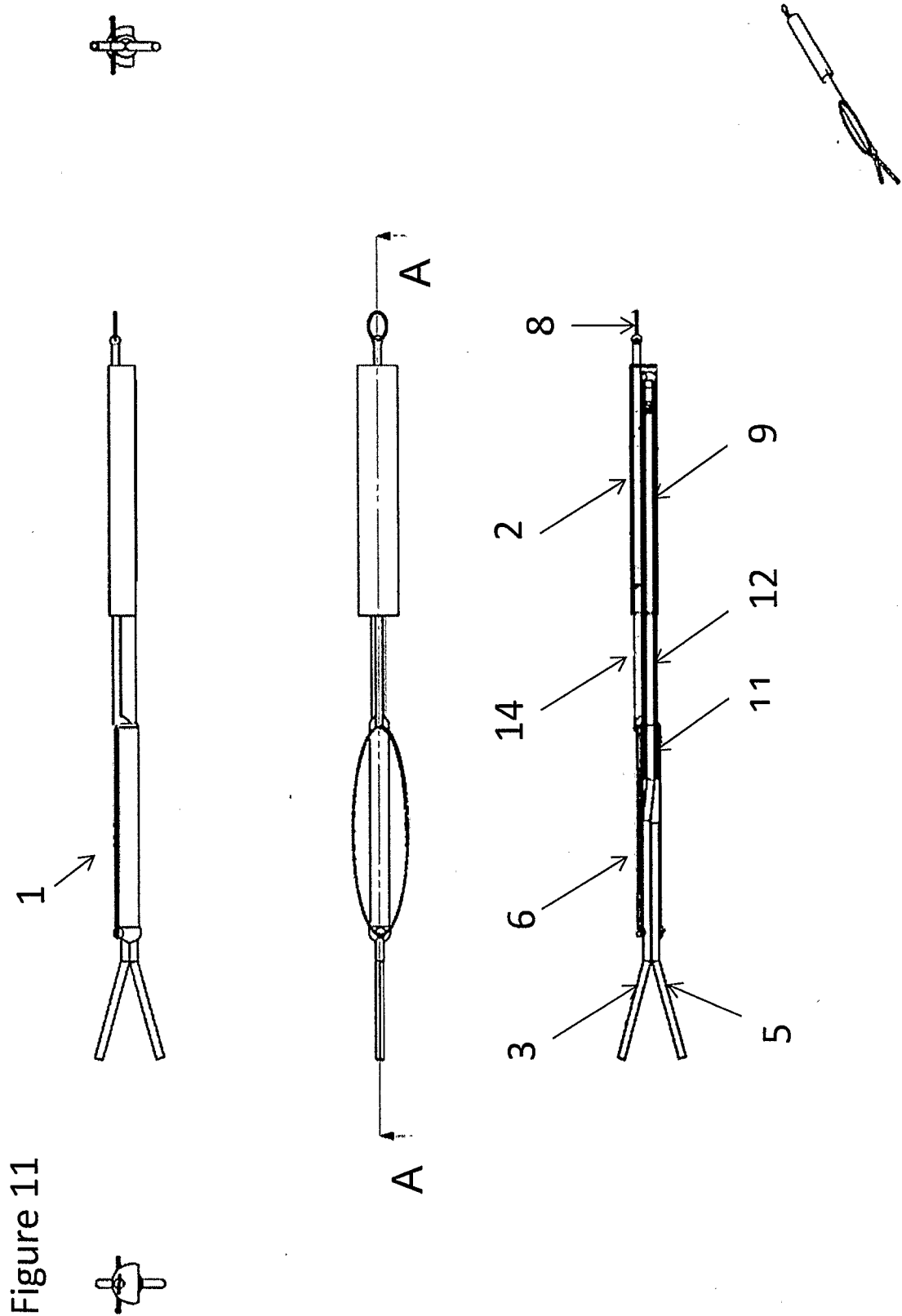
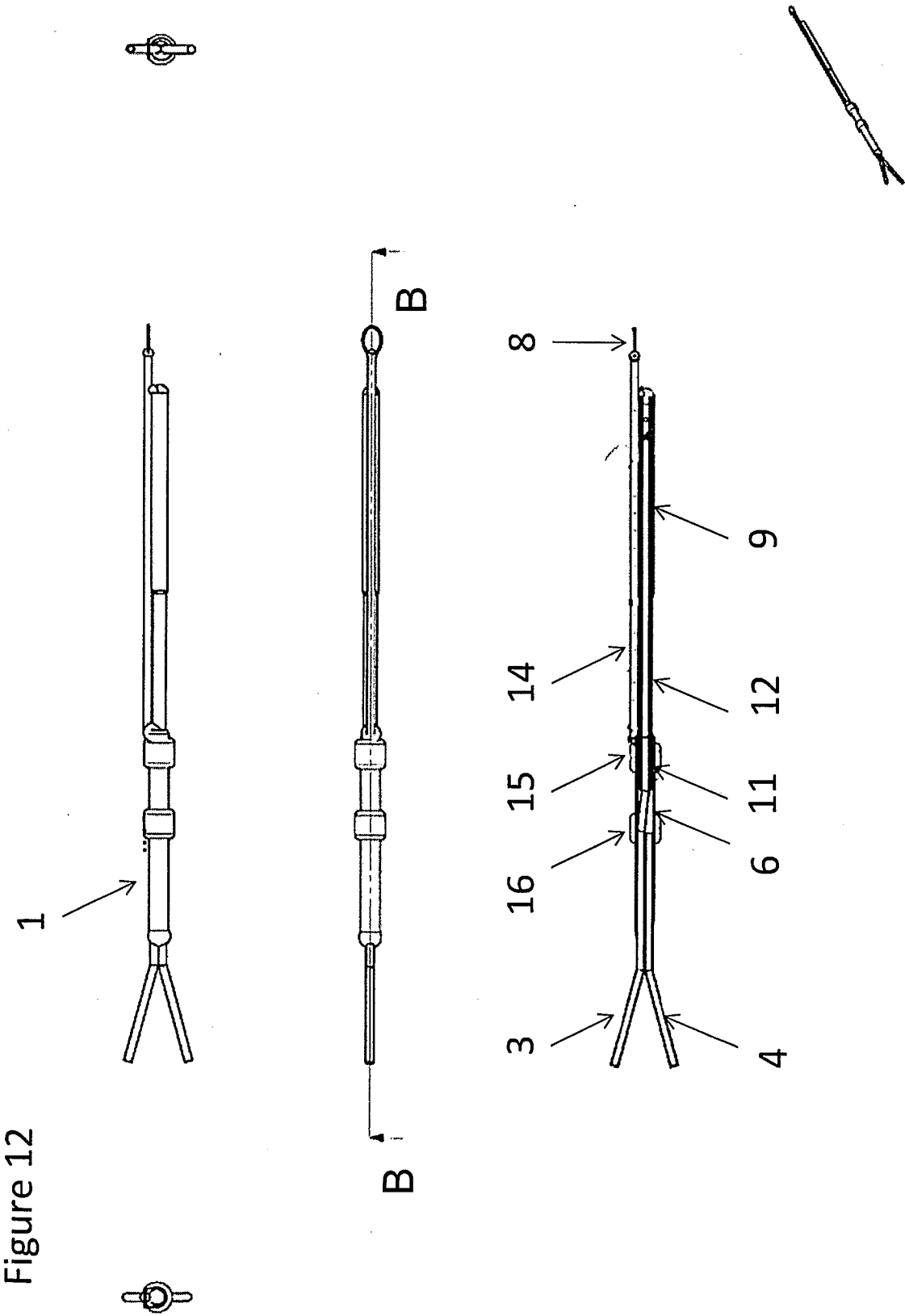
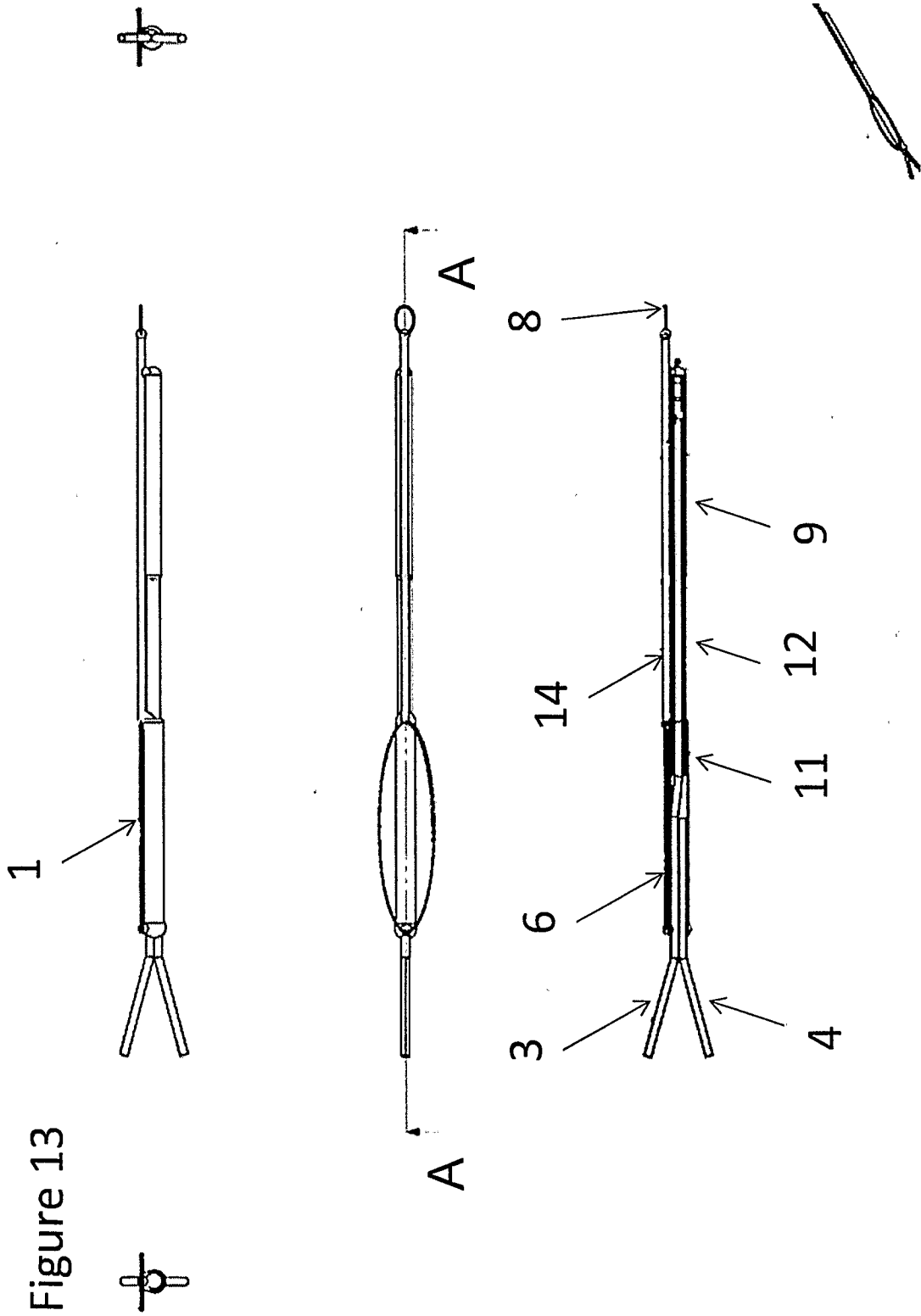


Figure 9









INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2009/000511

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61B, B01D, A61M

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ, MEDLINE, EMBASE, BIOSIS, INSPEC, COMPDX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20020182658 A1 (POLAK, ANTHONY J.), 5 December 2002 (05.12.2002), see paragraph [0007], lines 9-12, and paragraph [0023] --	1-3,9-12
X	US 5191900 A (MISHRA, PRAVIN K.), 9 March 1993 (09.03.1993), figures 1-3 --	4,7-8
X	CMA Microdialysis, product catalog, [online], CMA Microdialysis, 22 April, 2008, [retrieved on 2010-03-11] Retrieved from the internet: <URL:http://www.microdialysis.se/basic-research /product-catalog, page 14 --	7-8

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

25 March 2010

Date of mailing of the international search report

31-03-2010

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2009/000511

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Pedersen, ME et al, Mediastinal microdialysis: early diagnosis of anastomotic leakage after resection for esophageal cancer. Esophagus, 2009, vol. 6, pages 63-66, see abstract, lines 6-8 --	1-12
A	Jansson K et al, Results of intraperitoneal microdialysis depend on the location of the catheter. Scand J Clin Lab Invest, 2004, vol 64, pages 63-70, abstract --	1-12
A	US 20080086112 A1 (LO, LEU-WEI ET AL), 10 April 2008 (10.04.2008), see paragraph [0043] --	1-12
A	WO 0124692 A1 (DAMGAARD, LARS, RIIS), 12 April 2001 (12.04.2001), page 8, line 16 - line 23 --	1-3,9-12
A	WO 2007126380 A1 (CMA/MICRODIALYSIS AB), 8 November 2007 (08.11.2007), page 2, line 16 - line 19; page 4, line 12 - line 15; page 5, line 4 - line 8 -- -----	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2009/000511

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. ☒ Claims Nos.: 1-3 and 9-12
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-3 and 9-12 relate to a method for treatment of the human or animal body by surgery, see PCT rule 39.1(iv).
.../...
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 any 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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2009/000511

Box II.1

The claims include attaching a device with a suture. Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.

International patent classification (IPC)**A61B 10/00** (2006.01)**B01D 61/24** (2006.01)**A61B 5/00** (2006.01)**A61M 1/16** (2006.01)**A61M 25/00** (2006.01)**Download your patent documents at www.prv.se**

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Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE2009/000511

US	20020182658	A1	05/12/2002	NONE		

US	5191900	A	09/03/1993	WO	9218191 A	29/10/1992

US	20080086112	A1	10/04/2008	NONE		

WO	0124692	A1	12/04/2001	AT	313293 T	15/01/2006
				AU	5968599 A	10/05/2001
				CA	2385850 A	12/04/2001
				DE	69929092 D,T	06/07/2006
				EP	1217944 A,B	21/12/2005
				JP	2003510153 T	18/03/2003
				US	7215988 B	08/05/2007

WO	2007126380	A1	08/11/2007	NONE		
