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(54) **DEVICE FOR MICRODIALYSIS SAMPLING**

GERÄT ZUR ENTNAHME VON MIKRODIALYSEPROBEN

DISPOSITIF D'ECHANTILLONNAGE EN MICRODIALYSE

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(56) References cited:
WO-A1-01/24692
WO-A1-2007/126380
US-A- 5 191 900
US-A1- 2002 182 658
US-A1- 2008 086 112

- **HAMBERGER A ET AL: "Amino acids in the neuronal microenvironment of focal human epileptic lesions", EPILEPSY RESEARCH, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 9, no. 1, 1 May 1991 (1991-05-01), pages 32-43, XP023971785, ISSN: 0920-1211, DOI: 10.1016/0920-1211(91)90044-G [retrieved on 1991-05-01]**
- **"Surface Microdialysis", , 17 March 2014 (2014-03-17), XP055108301, Retrieved from the Internet: URL:http://www.ubi.se/project/surface-microdialysis [retrieved on 2014-03-17]**
- **'CMA Microdialysis, product catalog' CMA MICRODIALYSIS, [Online] 22 April 2008, pages 1 - 66, XP003026419 Retrieved from the Internet: <URL:http://www.microdialysis.se/basic-research/product-catalog> [retrieved on 2010-03-11]**
- **PEDERSEN M.E. ET AL: 'Mediastinal microdialysis: early diagnosis of anastomotic leakage after resection for esophageal cancer' ESOPHAGUS vol. 6, 2009, pages 63 - 66, XP019667545**
- **JANSSON K. ET AL: 'Results of intraperitoneal microdialysis depend on the location of the catheter' SCAND J CLIN LAB INVEST vol. 64, 2004, pages 63 - 70, XP003026420**

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Description

Technical Field

[0001] The present invention concerns a method and device for microdialysis sampling the wellbeing 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

[0002] Microdialysis is a means of sampling substances from the body to help clinicians assess wellbeing 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.

[0003] 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.

[0004] 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.

[0005] 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

[0006] 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.

[0007] 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.

[0008] 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.

[0009] 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. Hamberger et al (Anders Hamberger et al. Epilepsy Res., 9(1991) 32-43) describe a dialytrode used during electrocorticography for continuous sampling of extracellular fluid. The dialytrode is placed on the surface of the exposed cerebral cortex during epileptic surgery. However, the dialytrode is used in conjunction with and attached to the body surface through carbon electrodes thereby providing a complex, more invasive and less flexible means for attachment of the dialytrode.

Brief Description of the Invention Concept

[0010] 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 for microdialysis sampling. A further objective of the present invention is to achieve a stable device for measuring metabolic changes postoperatively.

Description of the Invention

[0011] 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 triangel) and on the surface of the epicardium (open square). Data are presented as mean +- 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 triangel) and on the surface of the epicardium (open square). Data are presented as mean +- 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 triangel) and on the surface of the epicardium (open square). Data are presented as mean +- 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 triangel) and on the surface of the epicardium (open square). Data are presented as mean +- 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 triangel) and on the surface of the epicardium (open square). Data are presented as mean +- 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 triangel) and on the surface of the epicardium (open square). Data are presented as mean +- 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 triangel) and on the surface of the epicardium (open square). Data are presented as mean +-_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 triangel) and on the surface of the epicardium (open square). Data are presented as mean +-_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.

[0012] The present invention concern a probe/catheter placed on the surface of a vital organ sampling 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. The microdialysis sampling catheter or probe according to the invention is configured to be temporarily attached to the outside surface of the vital organ to sample metabolic substances via a semipermeable membrane 9 attached to the catheter or probe 1 on the side facing the surface of the organ wherein the probe comprises an inlet 3 and an outlet 4 for the perfusate and 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 1 to a vital organ via at least one suture. The probe is not inserted into the substance of the vital organ. Further preferred embodiments of the catheter or probe are described in the dependent claims. According to another 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.

[0013] 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.

[0014] According to a 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.

[0015] 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 were 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.

[0016] 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 were 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 1 1 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.

[0017] 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 were 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.

[0018] 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.

[0019] 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.

[0020] 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.

[0021] 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.

[0022] 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. As an example, at least one of the metabolic substances sampled by a probe according to the invention may be glucose, lactate, pyruvate, glycerol. 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

[0023] The case study was approved by the Animal Experimental Ethics Committee at Umea 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.

[0024] After intramuscular premedication, with a mixture of ketamine 10mg/kg (Ketalar(R), 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 [mu]g/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 maintainenance of anaesthesia. The animals were tracheotomized (7.0 OP endotracheal tube, Rusch, kernen, Germany) and mechanically ventilated with air containing 30% oxygen (Evita 4, Drager, 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.

[0025] 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 midaxillary's level. Data was continuously recorded using a computer based multichannel signal acquisition and analysis system (Acknowledge, Biopac system Inc.,CA, USA).

[0026] 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.

[0027] The microdialysis probes were perfused with Ringers solution (a modified Krebs- Ringer phosphate buffer) at a flow rate of 2.0 [mu]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.

[0028] 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 4-6oC no longer than one day. All samples were centrifuged (Mini Galaxy, VWR, West Chester, PA, USA) for 30 seconds before analyses.

[0029] 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.

[0030] 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).

[0031] 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).

[0032] 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).

[0033] 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).

[0034] 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.

[0035] 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).

[0036] Pyruvate concentrations continuously increased during the experimental protocol as measured by both probes. The short ischemia periods were asso-

ciated 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.

[0037] 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.

[0038] 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

[0039] 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.

[0040] 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.

[0041] 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.

[0042] 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 catheter or probe (1) configured to be 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 and further configured to be temporarily attached to the outside surface of the vital organ to sample said metabolic substances via a semi-permeable membrane (9) attached to the catheter or probe (1) on the side facing the surface of the organ; wherein the probe comprises an inlet (3) and an outlet (4) for the perfusate; **characterised in 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.

2. Microdialysis sampling catheter or probe (1) according to 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).

3. Microdialysis sampling catheter or probe (1) according to any of claims 1 to 2 **characterized by** that the side of the permeable membrane (9) intended to be facing away from the organ is covered.

4. Microdialysis sampling catheter or probe (1) according to any of claims 1 to 3 essentially of an elliptical, rectangular or other for the purpose suitable shape.

5. Microdialysis sampling catheter or probe (1) according to any of claims 1 to 4 **characterized by** that the membrane (9) consists preferably of a polymer composition such as for example PAES (polyarylethersulfone).

6. Microdialysis sampling catheter or probe according to any of claims 1 to 5 **characterized by** that the outer casing (2) consists preferably of a polymer material as for example polyurethane, polyamide or polyimide.

Patentansprüche

1. Katheter oder Sonde (1) zur Entnahme von Mikrodialyseproben, der/die dazu konfiguriert ist, auf der Oberfläche eines lebenswichtigen menschlichen oder tierischen Organs platziert zu werden, um von der Oberfläche des Organs Proben von Stoffwechselsubstanzen zu entnehmen, die die Stoffwechselzustände des Organs anzeigen, und ferner dazu konfiguriert ist, temporär an der Außenfläche des lebenswichtigen Organs angebracht zu werden, um über eine an dem Katheter oder der Sonde (1) auf der der Oberfläche des Organs zugewandten Seite angebrachte halbdurchlässige Membran (9) Proben von den Stoffwechselsubstanzen zu entnehmen;
wobei die Sonde einen Einlass (3) und einen Auslass (4) für das Perfusat umfasst;
dadurch gekennzeichnet, dass an dem Ende oder der Spitze der Sonde (1) gegenüber dem Einlass (3) und dem Auslass (4) ein Ring (8) platziert ist, der zum temporären Befestigen der Sonde an dem lebenswichtigen Organ über mindestens eine Naht konzipiert ist.

2. Katheter oder Sonde (1) zur Entnahme von Mikrodialyseproben nach Anspruch 1, **dadurch gekennzeichnet, dass** ein Befestigungsgürtel (6), der zum Erleichtern der temporären Anbringung der Sonde (1) an dem Oberflächengewebe eines lebenswichtigen Organs über mindestens eine Öse (7) unter Verwendung mindestens einer Naht konzipiert ist, auf dem Außengehäuse (2) der Sonde (1) integriert ist.

3. Katheter oder Sonde (1) zur Entnahme von Mikrodialyseproben nach einem der Ansprüche 1 bis 2, **dadurch gekennzeichnet, dass** die Seite der durchlässigen Membran (9), die vom Organ abgewandt sein soll, abgedeckt ist.

4. Katheter oder Sonde (1) zur Entnahme von Mikrodialyseproben nach einem der Ansprüche 1 bis 3, der/die im Wesentlichen eine elliptische, rechtwinklige oder andere zweckmäßige Form aufweist.

5. Katheter oder Sonde (1) zur Entnahme von Mikrodialyseproben nach einem der Ansprüche 1 bis 4, **dadurch gekennzeichnet, dass** die Membran (9) vorzugsweise aus einer Polymerzusammensetzung wie beispielsweise PAES (Polyarylethersulfon) besteht.

6. Katheter oder Sonde zur Entnahme von Mikrodialyseproben nach einem der Ansprüche 1 bis 5, **dadurch gekennzeichnet, dass** das Außengehäuse (2) vorzugsweise aus einem Polymermaterial wie beispielsweise Polyurethan, Polyamid oder Polyimid besteht.

Revendications

1. Cathéter ou sonde d'échantillonnage en microdialyse (1) conçue pour être placée sur la surface d'un organe vital humain ou animal pour l'échantillonnage des substances métaboliques qui indiquent les conditions métaboliques de l'organe à partir de la surface de l'organe et en outre conçue pour être temporairement fixée à la surface externe de l'organe vital pour échantillonner lesdites substances métaboliques à travers une membrane semi-perméable (9) fixée au cathéter ou à la sonde (1) sur le côté faisant face à la surface de l'organe ;
dans lequel
la sonde comprend une entrée (3) et une sortie (4) pour le perfusat ; **caractérisé en ce que**
sur l'extrémité ou sur la pointe de la sonde (1) à l'opposé de l'entrée (3) et de la sortie (4) est placé un anneau (8) conçu pour fixer temporairement la sonde à un organe vital à travers au moins une suture.

2. Cathéter ou sonde d'échantillonnage en microdialyse (1) selon la revendication 1, **caractérisé en ce qu'**une ceinture de fixation (6), conçue pour faciliter la fixation temporaire de la sonde (1) au tissu de surface d'un organe vital à travers au moins un oeillet (7) utilisant au moins une suture, est intégrée sur le boîtier externe (2) de la sonde (1).

3. Cathéter ou sonde d'échantillonnage en microdialyse (1) selon l'une quelconque des revendications 1 à 2, **caractérisé par le fait que** le côté de la membrane perméable (9) qui doit être à l'opposé de l'or-

gane est couvert.

4. Cathéter ou sonde d'échantillonnage en microdialyse (1) selon l'une quelconque des revendications 1 à 3, essentiellement en forme elliptique, rectangulaire ou une autre forme appropriée à la fonction.

5. Cathéter ou sonde d'échantillonnage en microdialyse (1) selon l'une quelconque des revendications 1 à 4, **caractérisé par le fait que** la membrane (9) est préférablement composée d'une composition de polymère telle que par exemple le PAES (polyaryléthersulfone).

6. Cathéter ou sonde d'échantillonnage en microdialyse selon l'une quelconque des revendications 1 à 5, **caractérisé par le fait que** le boîtier externe (2) est préférablement composé d'un matériau de polymère tel que par exemple le polyuréthane, le polyamide ou le polyimide.

Figure 1

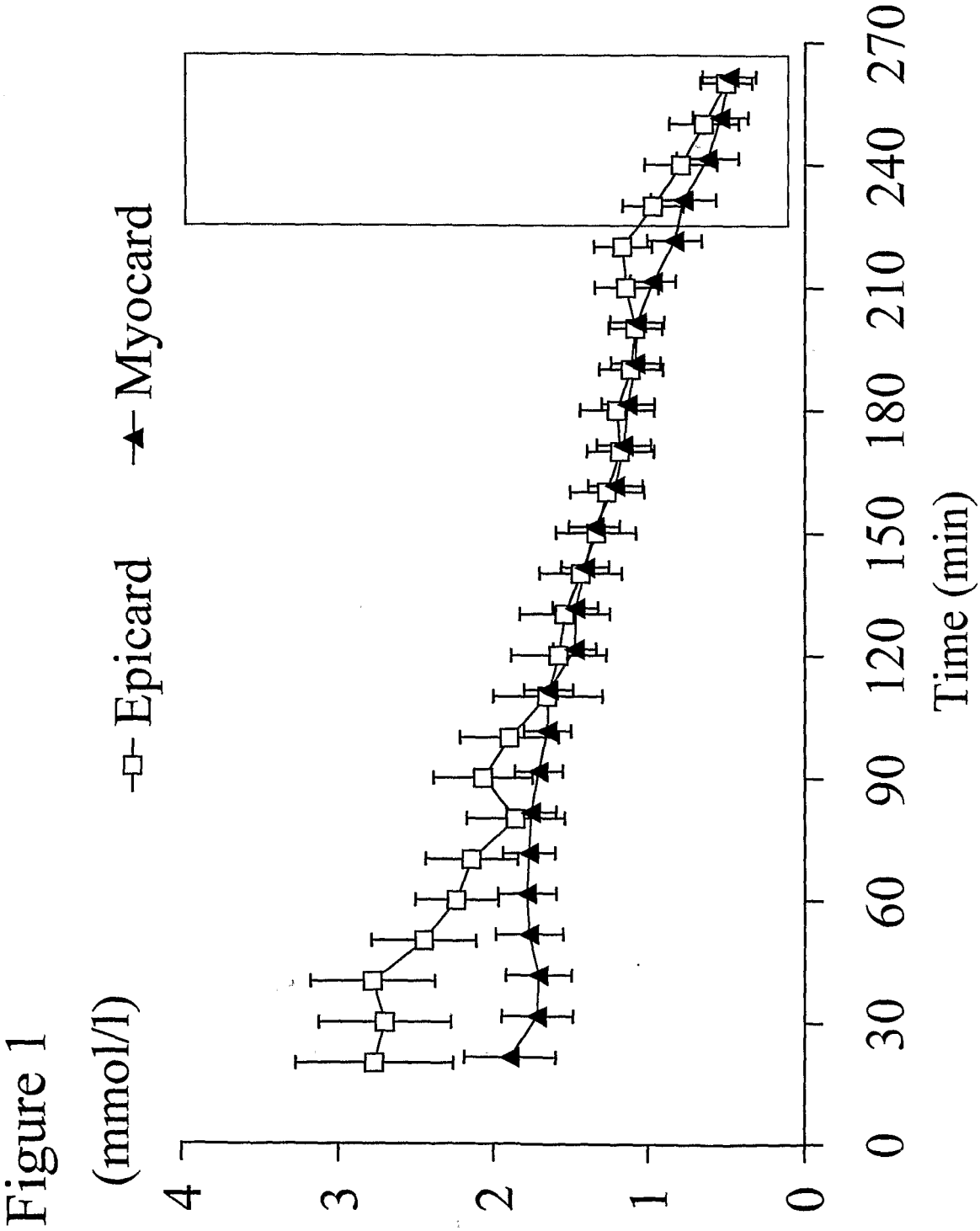
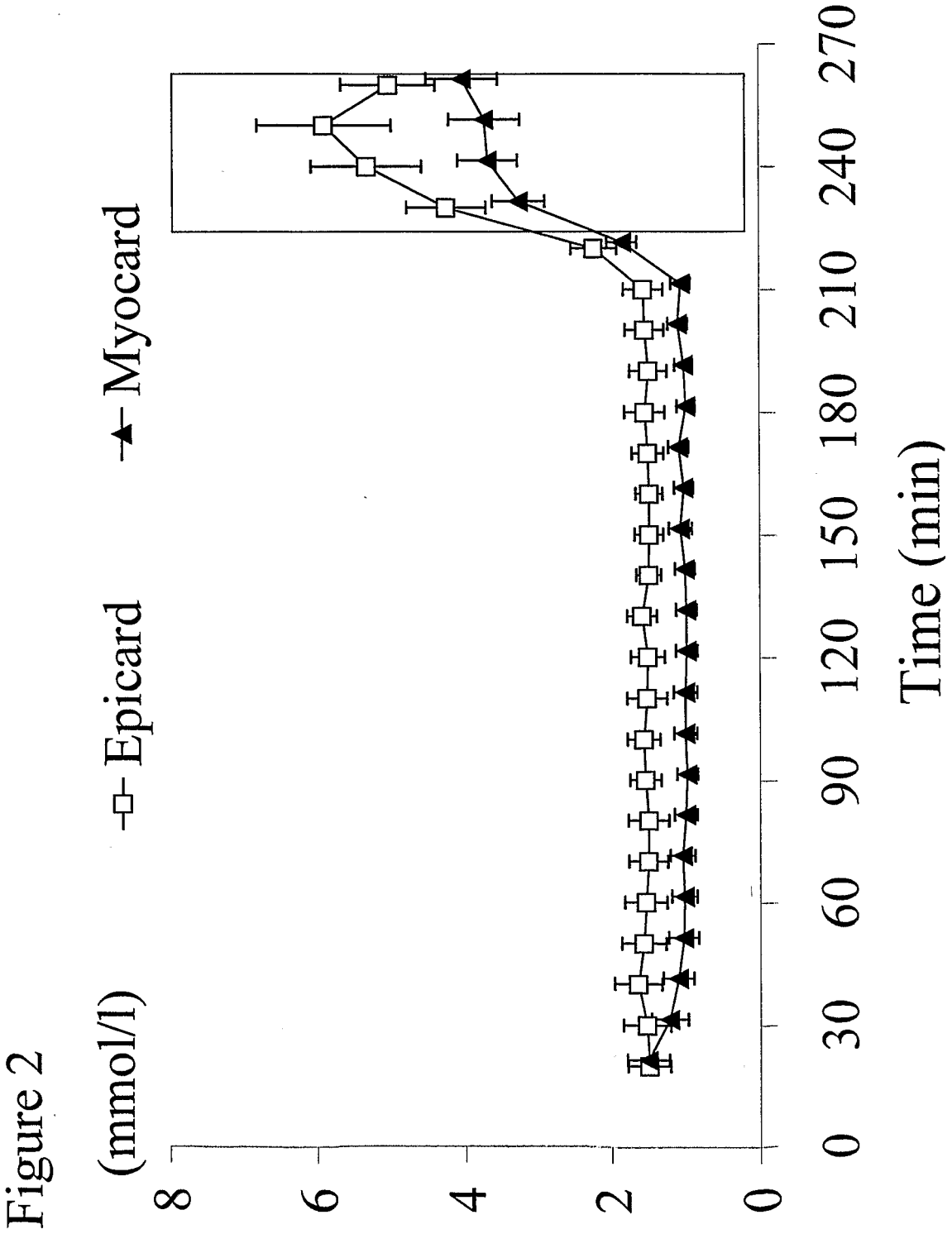

(mmol/l)
Epicard
Myocard
4
3
2
1
0
0
30
60
90
120
150
180
210
240
270
Time (min)

Figure 2


(mmol/l)
Epicard
Myocard
8
6
4
2
0
0
30
60
90
120
150
180
210
240
270
Time (min)

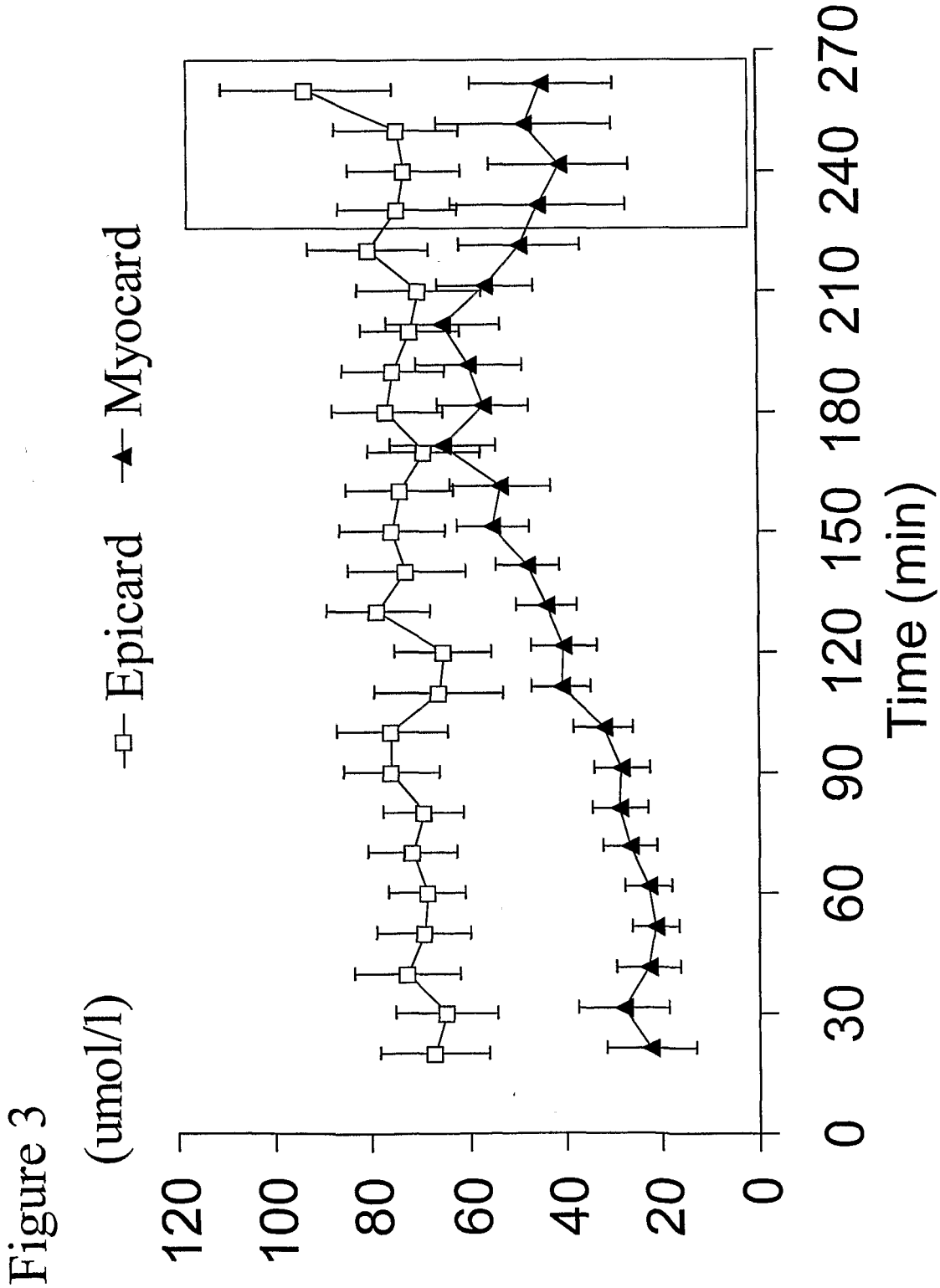

Epicard
Myocard
(umol/l)
120
100
80
60
40
20
0
0
30
60
90
120
150
180
210
240
270
Time (min)

Figure 3

Figure 4

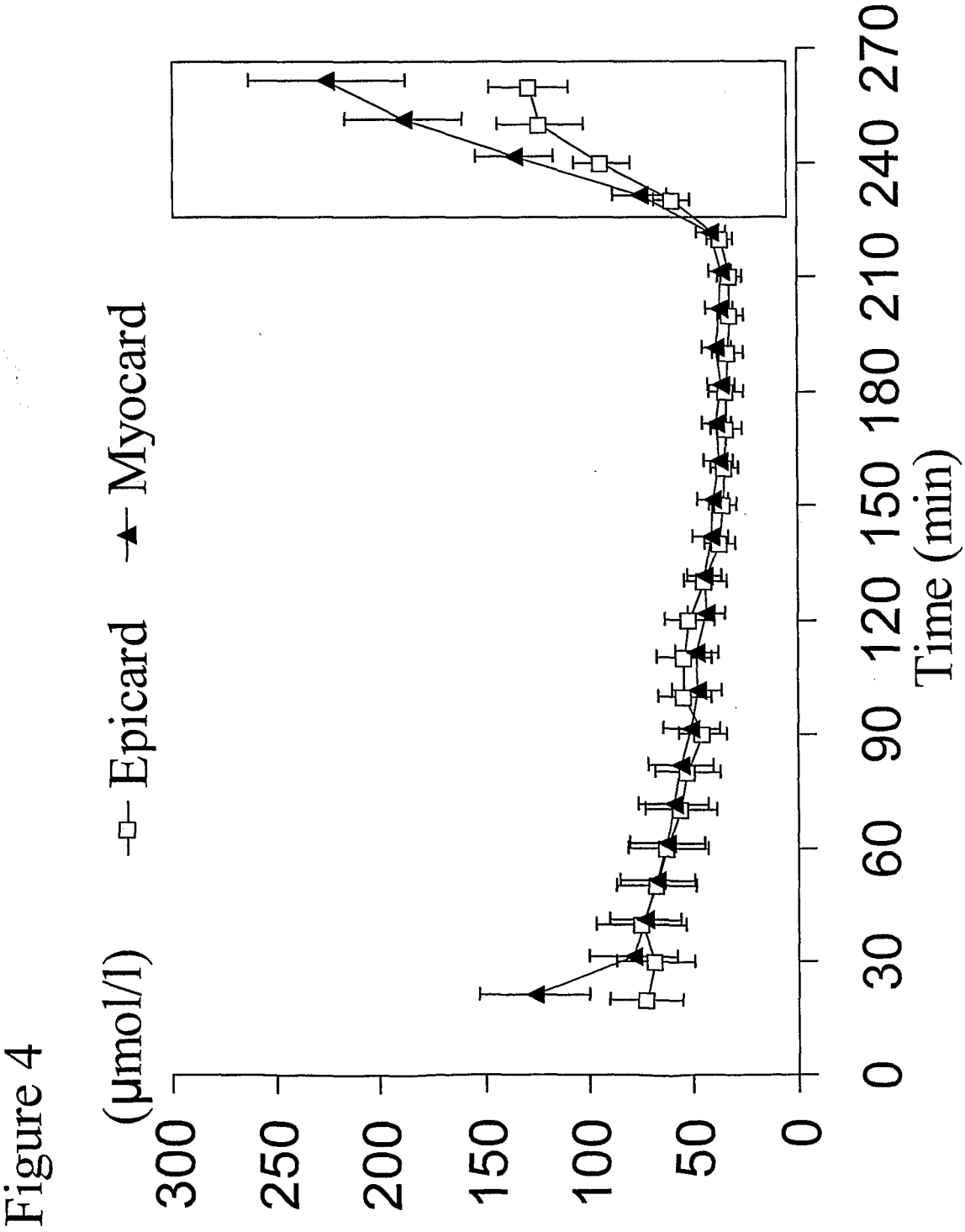

(µmol/l)
300
250
200
150
100
50
0
Epicard
Myocard
0
30
60
90
120
150
180
210
240
270
Time (min)

Figure 5

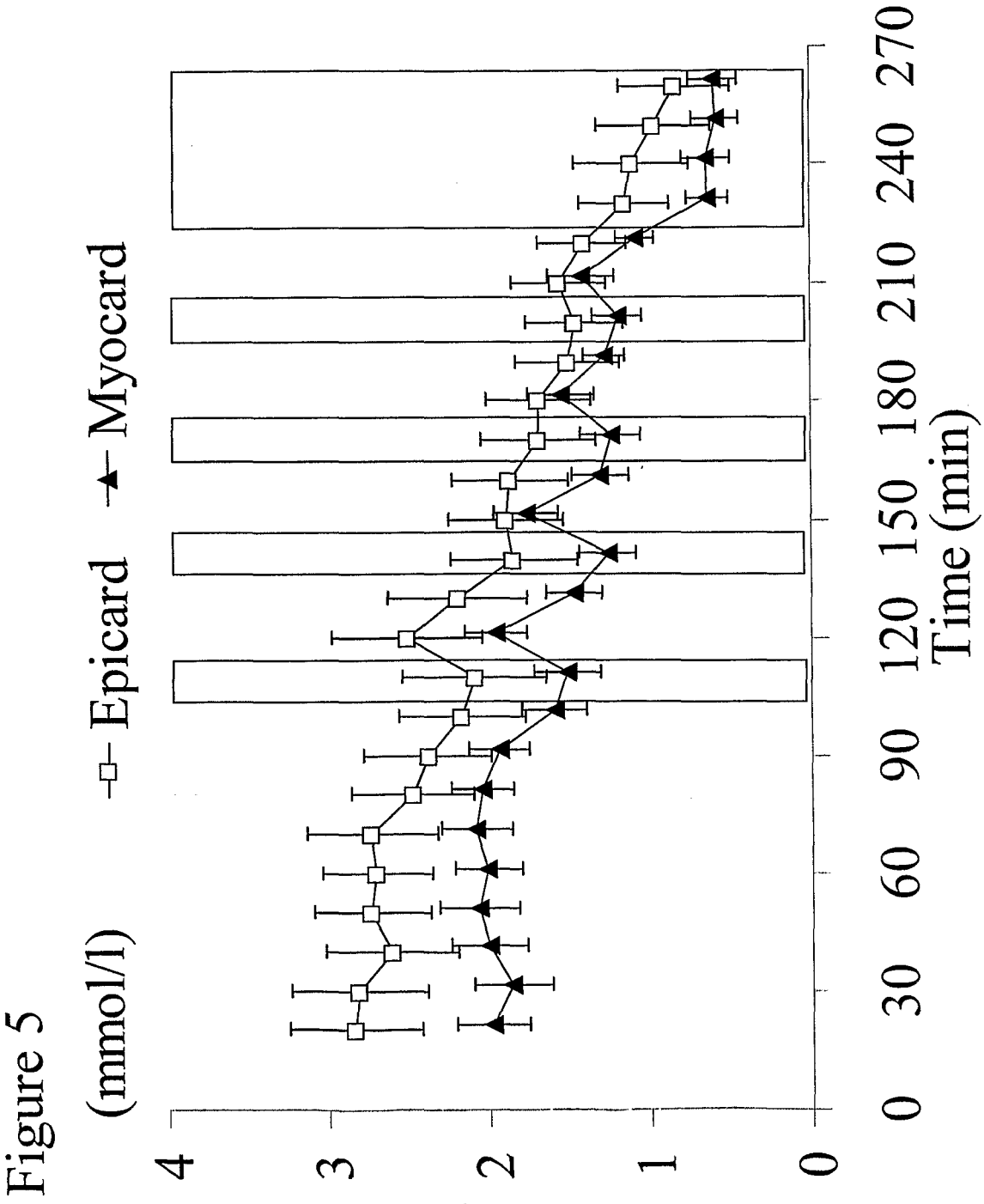

(mmol/l)
Epicard
Myocard
4
3
2
1
0
0
30
60
90
120
150
180
210
240
270
Time (min)

Figure 6

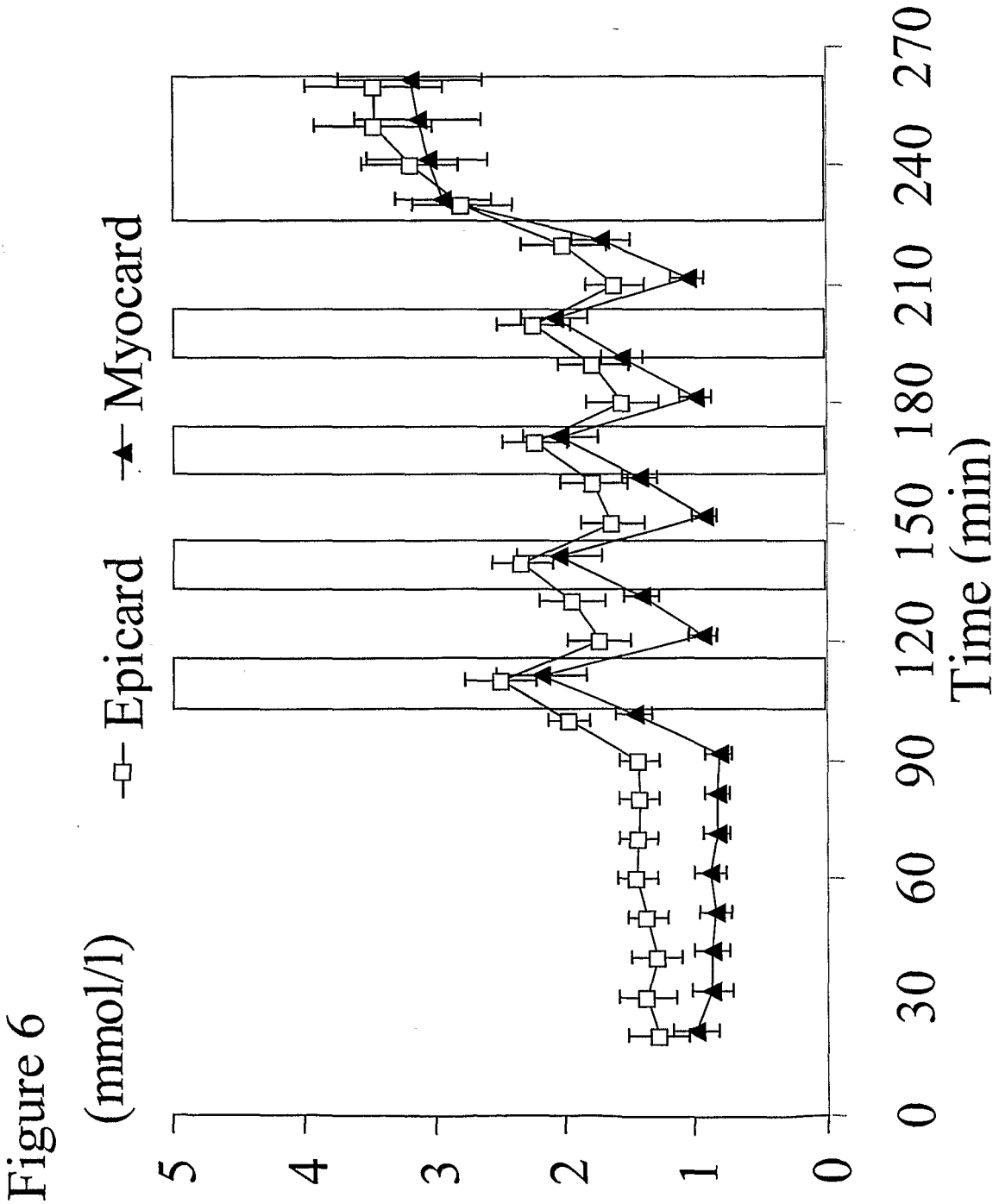

(mmol/l)
Epicard
Myocard
5
4
3
2
1
0
0
30
60
90
120
150
180
210
240
270
Time (min)

Figure 7

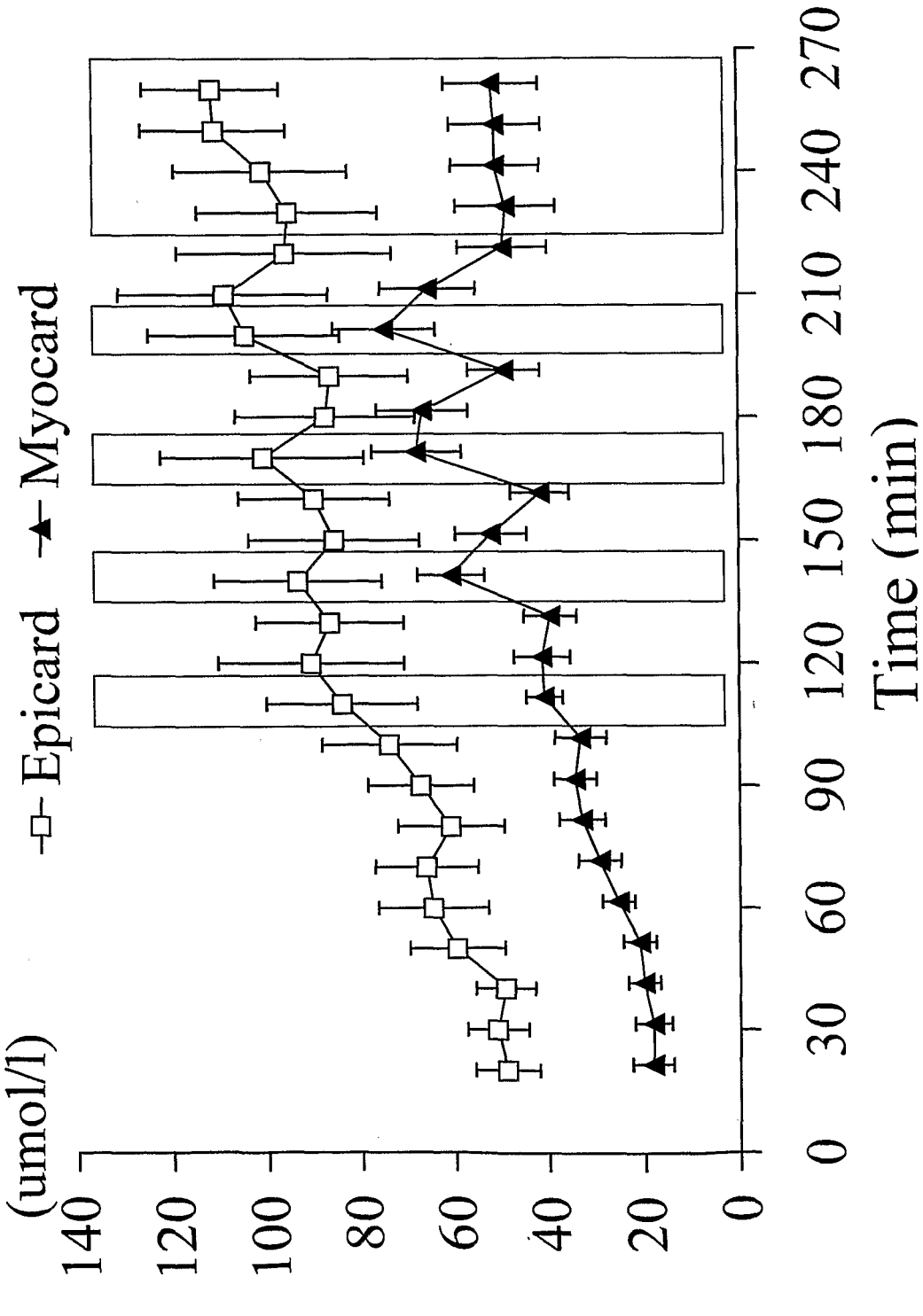
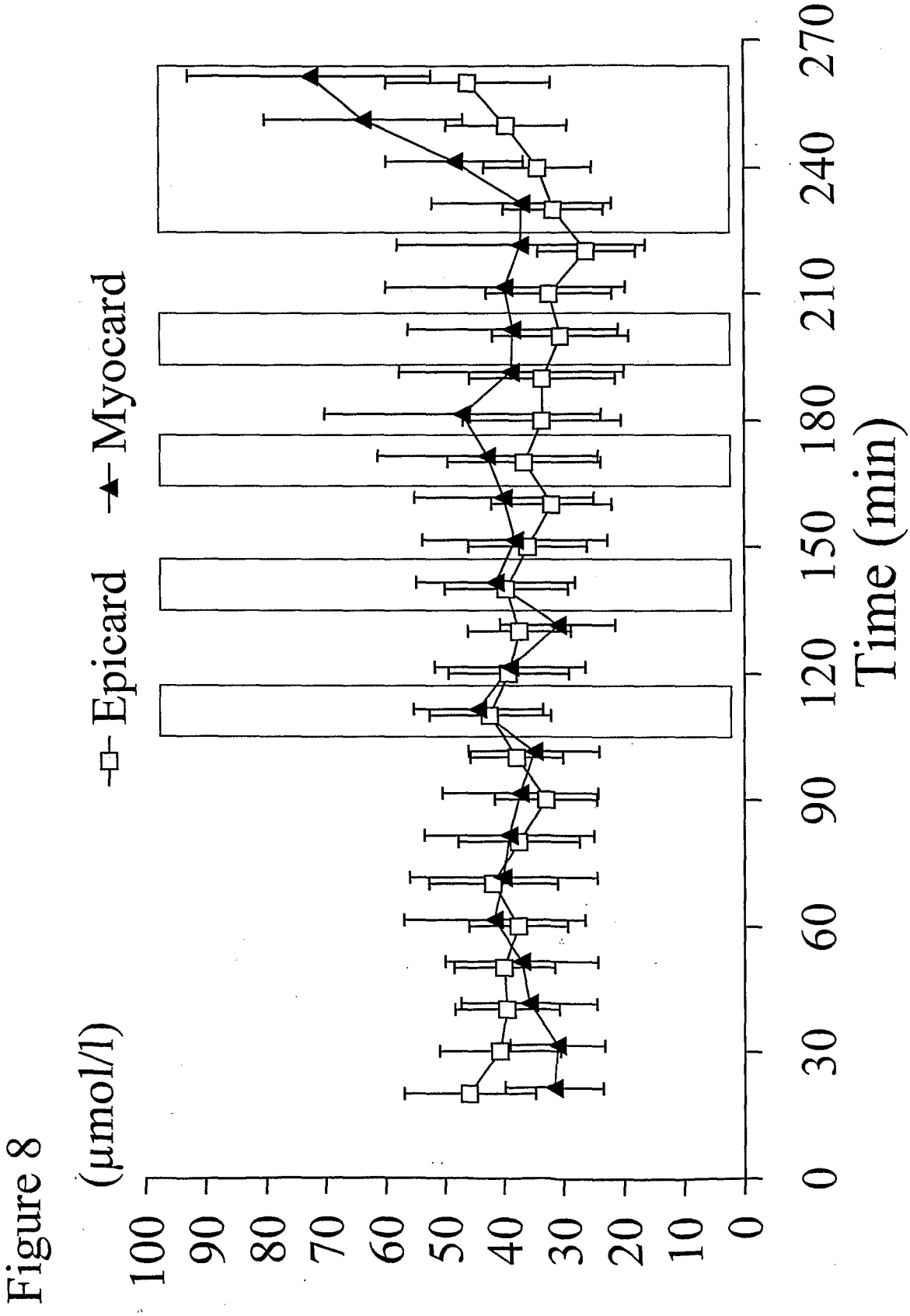

(umol/l)
140
120
100
80
60
40
20
0
Epicard
Myocard
0
30
60
90
120
150
180
210
240
270
Time (min)

Figure 8


(µmol/l)
100
90
80
70
60
50
40
30
20
10
0
Epicard
Myocard
0
30
60
90
120
150
180
210
240
270
Time (min)

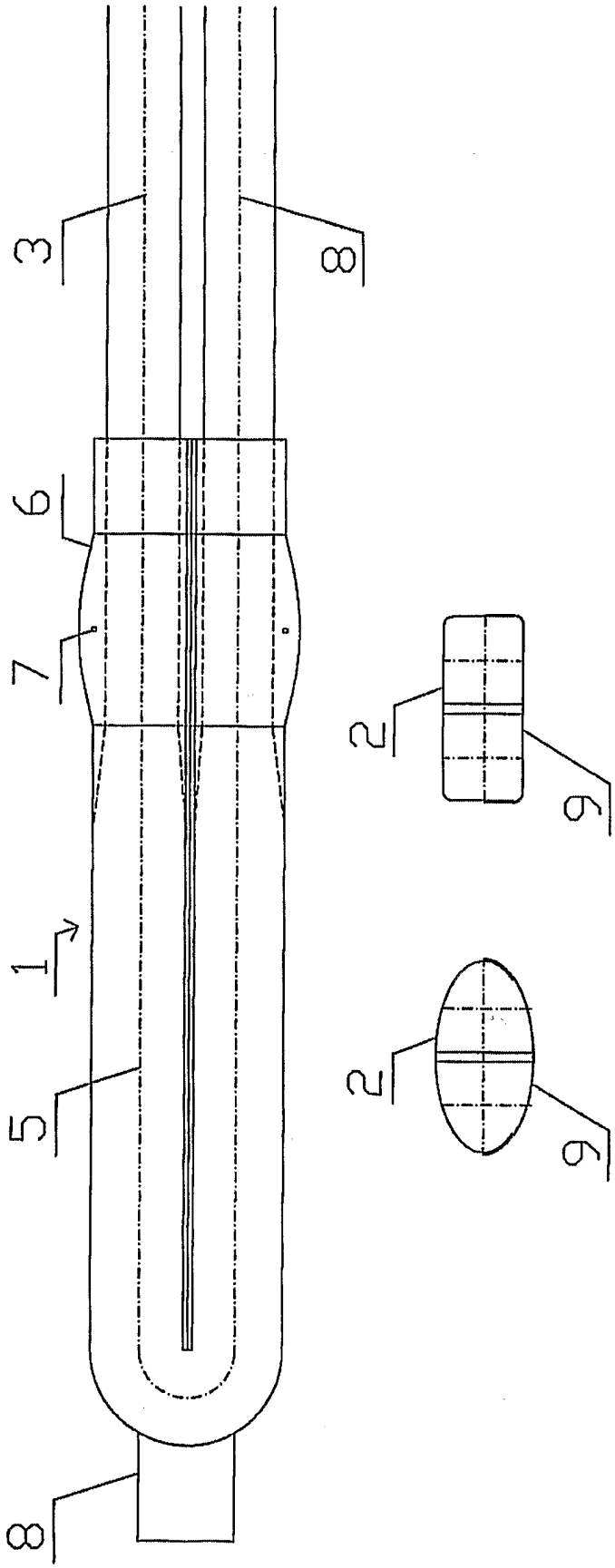


Figure 9

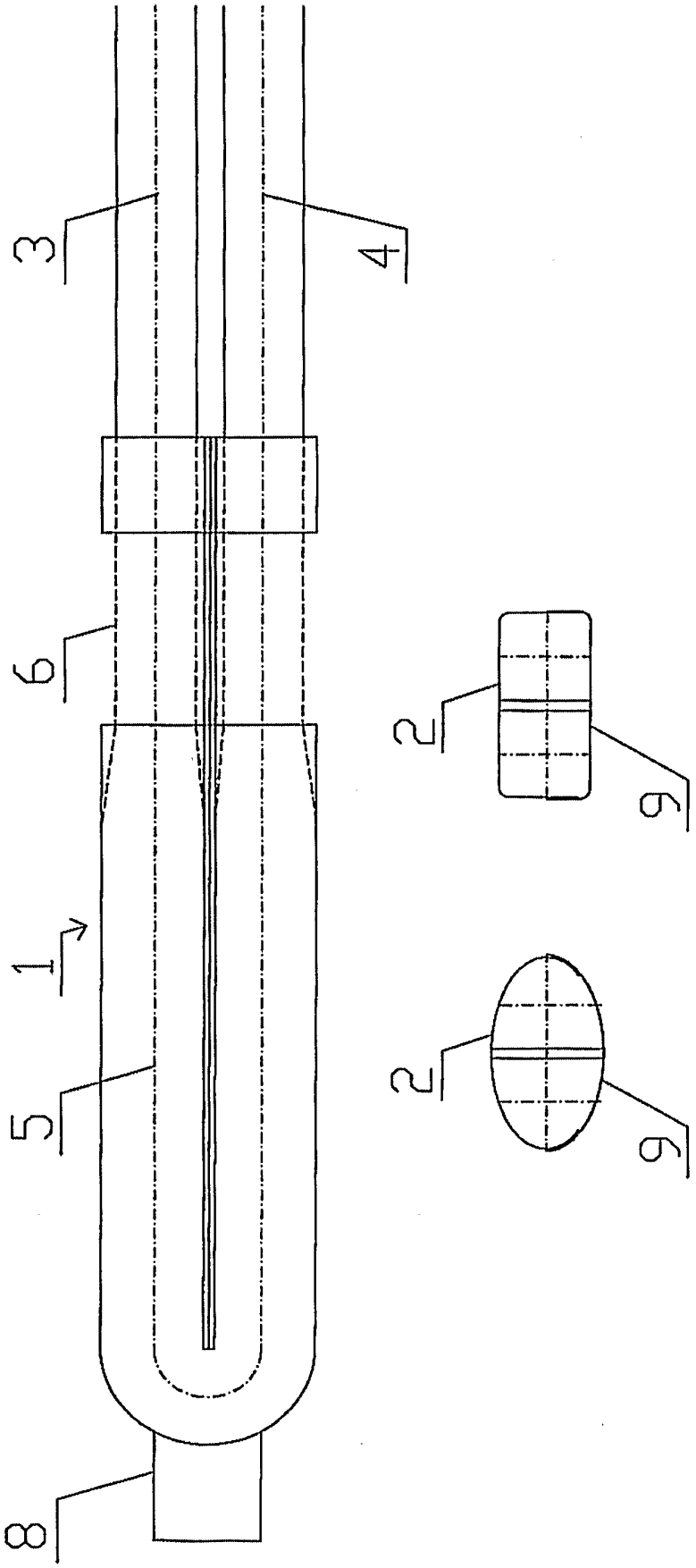


Figure 10

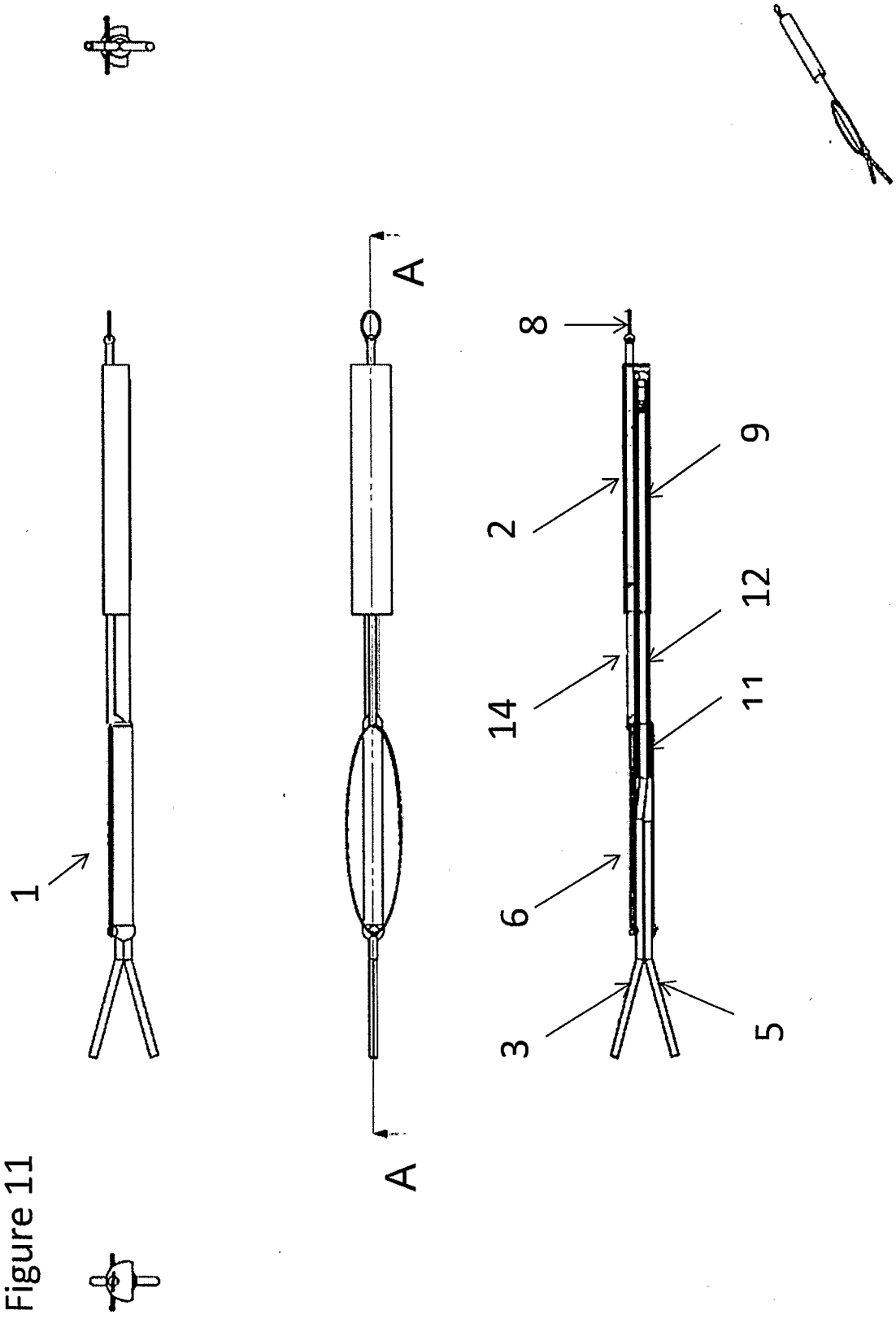


Figure 11

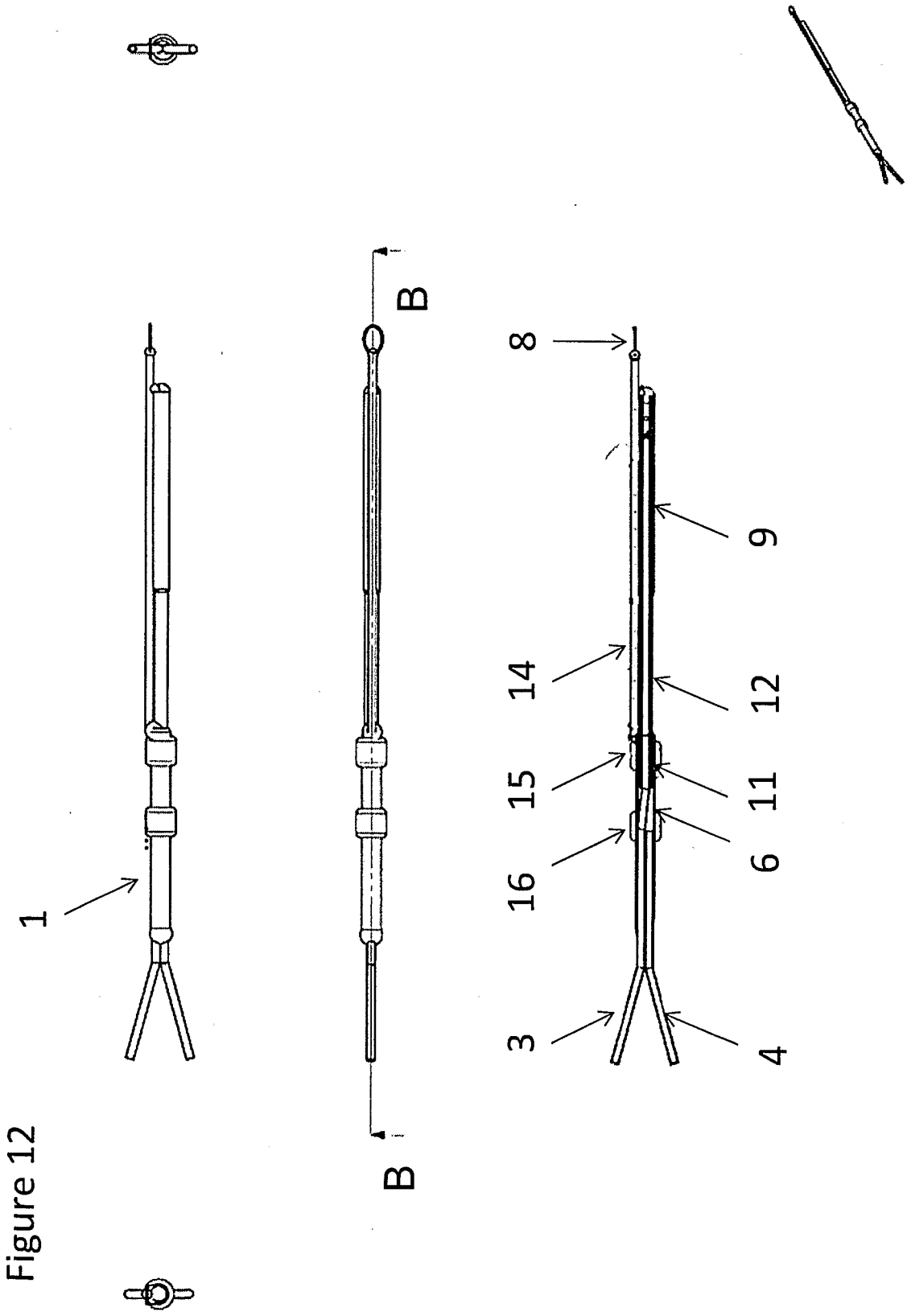


Figure 12

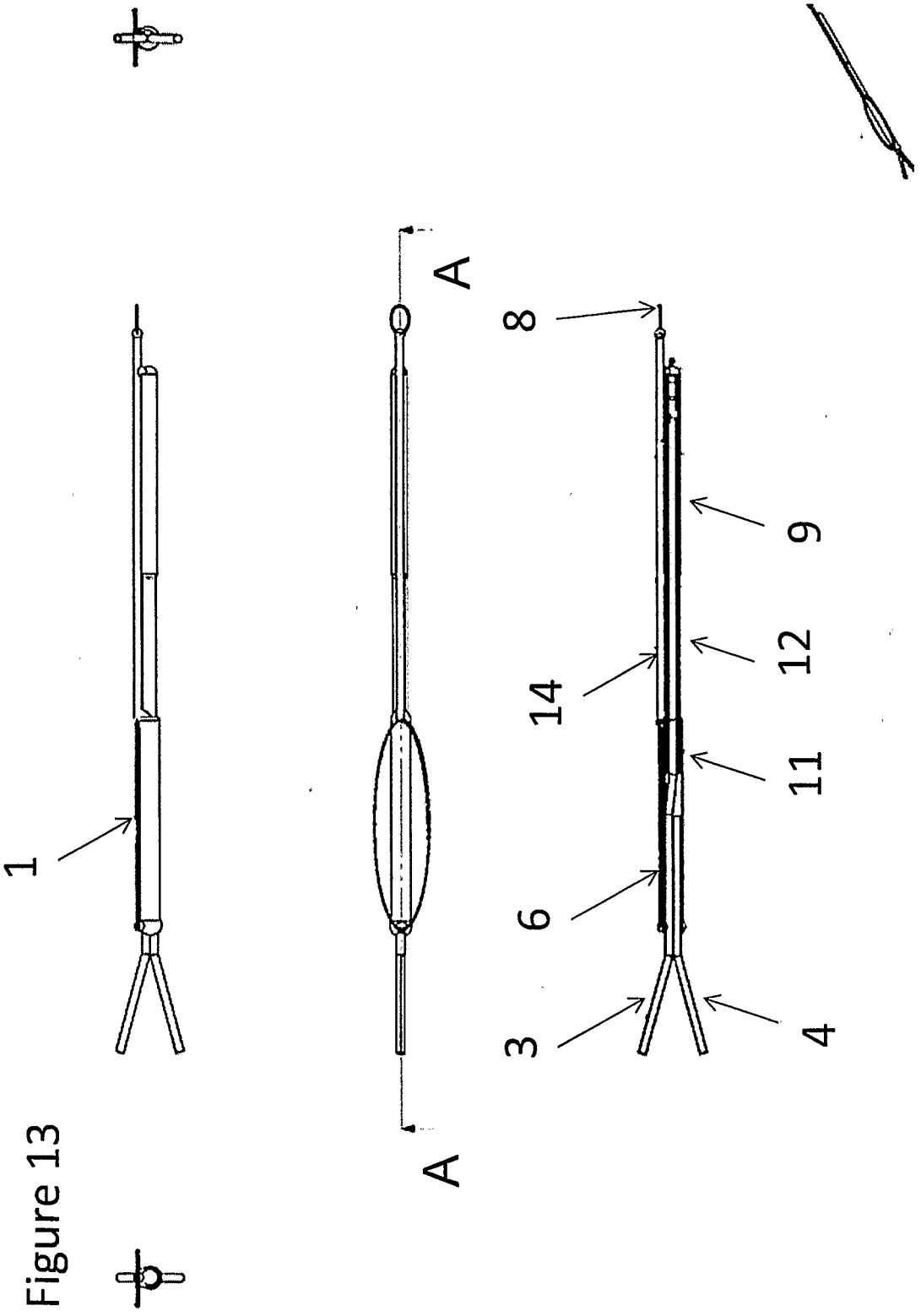


Figure 13

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- SE 434214 **[0007]**
- EP 0742725 B1 **[0008]**
- SE 511932 **[0009]**

Non-patent literature cited in the description

- **ANDERS HAMBERGER et al.** *Epilepsy Res.,* 1991, vol. 9, 32-43 **[0009]**

专利名称(译)	微透析取样的方法和装置		
公开(公告)号	EP2391275A4	公开(公告)日	2014-04-30
申请号	EP2009832196	申请日	2009-12-08
[标]申请(专利权)人(译)	ABRAHAMSSON佩妮拉		
申请(专利权)人(译)	ABRAHAMSSON，佩妮拉		
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发明人	ABRAHAMSSON, PERNILLA		
IPC分类号	A61B10/00 B01D61/24 A61B5/00 A61M1/16 A61M25/00		
CPC分类号	A61B5/14525 A61B5/14528 A61B10/0045 A61B2010/008 A61M25/00 A61M25/02 A61M2025/0286		
优先权	61/120849 2008-12-09 US		
其他公开文献	EP2391275A1 EP2391275B1		
外部链接	Espacenet		

摘要(译)

微透析取样方法利用至少一个微透析探针放置在重要的人或动物器官的表面上，用于取样代表从器官表面指示器官代谢状况的代谢物质。本发明还涉及用于对代谢物质进行取样的微透析取样探针，所述探针适于附着在重要的人或动物器官的表面上。