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Continuous metabolic monitoring techniques

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Chapter 4

An ultrafiltration catheter for monitoring of venous lactate and glucose around myocardial ischemia



Abstract

Introduction: Early detection of myocardial ischemia is of major importance in critical-care medicine. Changes of lactate or glucose levels in the cardiac venous efflux may be useful parameters.

Methods: We succeeded in integrating an ultrafiltration membrane in a cardiac catheter for continuous sampling. The ultrafiltrate was analyzed outside the body, resulting in a lag-time of about 24 minutes. Biosensors in a flow-injection analysis system were used for minute by minute sample analyses. The coronary sinus of pigs was catheterized to monitor the effects of 5, 15 or 45 minutes ischemia by coronary artery obstruction or myocardial stress by dobutamine infusion. A total of 27 hours was monitored.

Results: The intravascular response time was 1.33 ± 0.61 minutes (10-90%). Linear regression in vivo of blood and ultrafiltrate samples was 0.977 for lactate and 0.994 for glucose. Lactate levels rose 0.38 ± 0.10 mM above baseline within five minutes after ischemia. Reperfusion was clearly marked by a promptly peaking lactate release (max. 9.27mM). Myocardial stress by dobutamine increased glucose but not lactate levels. Once, a wall effect was noted at the catheter tip.

Conclusions: In vivo semi-continuous myocardial monitoring of absolute lactate and glucose concentrations was thus achieved by an ultrafiltration catheter. Ischemia and reperfusion can be detected very early by a lactate level rise. Further development of the ultrafiltration catheter will be focused on the diagnostic potential of lactate monitoring for patients.

Introduction

Insufficient myocardial perfusion is a major concern in critical-care medicine, because it often leads to irreversible myocardial damage. Before the damage becomes irreversible, poorly perfused tissue shifts from aerobic to anaerobic metabolism, the latter characterised among other by increased lactate production. Routinely used markers of myocardial ischemia, e.g. troponin and creatine kinase, are released only after cell death, so monitoring of these markers can not help to prevent infarction⁽¹⁾. Lactate monitoring, however, may offer an opportunity to detect tissue oxygen deficit in time for preventive intervention. Ischemic myocardium releases lactate in a quantitative relation to the extent of ischemia^(2;3). Indeed, major concentration shifts may occur in a matter of minutes both after the onset and at the end of myocardial ischemia⁽⁴⁾. So the occlusion and reperfusion of the myocardium could be monitored by measuring the lactate efflux into the common cardiac vein, the coronary sinus. This is however not practised in the clinic, because there are no logistics for frequent blood sampling and analysis. Further, the data are neither continuous, nor instantly available for making therapeutic decisions. Moreover, to justify catheterisation for intravascular measurement, the diagnostic value of continuous lactate monitoring has yet to be proven.

Biosensors are devices that have the potential to monitor analytes in vivo continuously. There are however many requirements for in vivo application which hinder the development of an intravascular lactate sensor⁽⁵⁾. These requirements may be met much more easily by application of microdialysis or ultrafiltration probes as an interface between the sensor and the blood. The analyte enters such probes through a membrane inside an organ, and is subsequently transported to the sensor, which can be kept outside the individual. This separation has many technical advantages, e.g. calibration of the biosensor (if necessary) can be done without interrupting in vivo measurements⁽⁶⁾.

Microdialysis probes directly inserted in the myocardium have been used to study myocardial metabolism in ischemia, reperfusion, and preconditioning⁽⁷⁻¹²⁾. Microdialysis however, has some limitations. In the first place, the precise calibration in vivo is difficult, because the diffusion inside tissue does not guarantee a constant analyte recovery⁽¹³⁾. If measurements are relative and instable, this precludes quantitative and reliable long-term monitoring. Secondly, the sampling time of microdialysis is usually long (5-60 minutes^(7;14-17)) which is not appropriate to detect acute events. A final limitation of myocardial microdialysis is the fact that the probes can only be placed during open thorax surgery.

Recently, we described an ultrafiltration technique allowing continuous sampling and monitoring of absolute glucose concentrations in the rat jugular vein⁽¹⁸⁾. Ultrafiltration excludes compounds with a molecular weight over 20 kD, but poses no barrier for small solutes like glucose and lactate⁽¹⁹⁾. Continuously sampled blood ultrafiltrate was analyzed in our method by a biosensor placed in a flow injection analysis system.

In the present study, an ultrafiltration catheter was placed in the coronary sinus allowing myocardial monitoring without cardiac surgery. An ultrafiltration probe was integrated to this end in the tip of a double lumen cardiac catheter, in order to take simultaneously ultrafiltrate and whole blood samples. The feasibility of monitoring with this probe was evaluated for several hours in pigs, during which ischemia was induced for various periods of time by inflating a balloon in the Left Anterior Descending coronary artery (LAD). The response time of this ultrafiltration catheter was determined before an attempt to detect any prompt and major changes in lactate and glucose levels, if present during myocardial ischemic events. Next, the possibility was explored to use the data for quantification of the lactate production during myocardial ischemia. The stress of heart rate acceleration on compromised myocardium was also tested in some experiments by dobutamine infusion.

Methods

Ultrafiltration catheter

A 5F (1.78mm o.d.) Nylon blend double lumen catheter of 120 cm length (shape: Modified Cordis Multipurpose, Cordis Europa N.V., Roden, The Netherlands) was designed to simultaneously withdraw blood and blood ultrafiltrate (Figure 1).

The large lumen, 0.98 mm i.d., was used as guidewire/flush/blood sample lumen. The proximal end of the large lumen was provided with a luer connector. Five side holes in the large lumen (i.d. 0.635 mm) were made in the last 4 cm of the catheter tip. The small lumen, oval with i.d. 0.83 mm x 0.35 mm, was provided with two closely adjoining fenestrations of 2 times 2 cm length at 2 mm from the distal tip, to place a hollow fiber membrane AN69HF, Hospal, Meyzieu, france; 340 μ m o.d.; 240 μ m i.d.). This hollow fiber has a MWCO of 20kD, but forms no diffusional barrier for small molecules like glucose and lactate⁽²⁰⁾. Two marker bands, gold 18 Kt, width 1.0mm, were placed at either end of the fenestration to locate the probe on the x-ray. A helical platinum wire was placed inside the hollow fiber to support the wall of the probe. The fiber was closed and fixed with two components

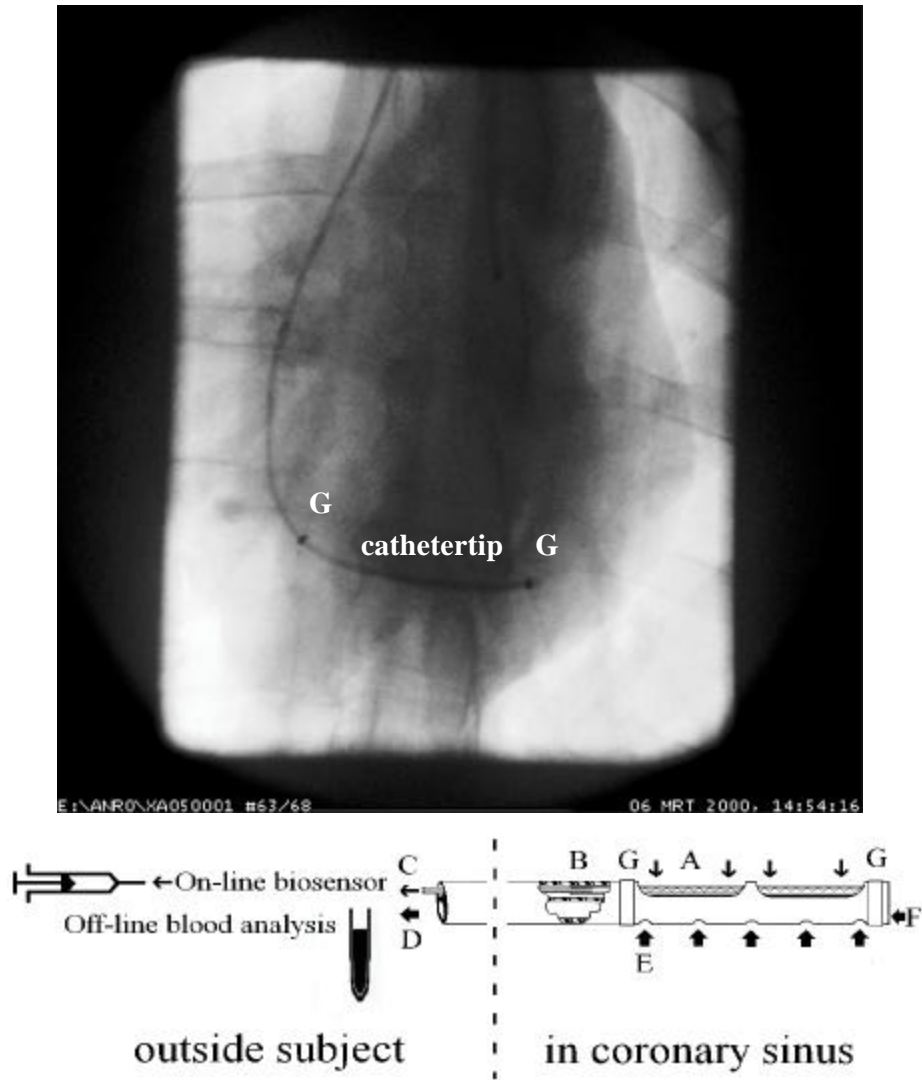


Figure 1 Schematic drawing of the ultrafiltration monitoring catheter (bottom), and x-ray of the ultrafiltration catheter in situ in the coronary sinus (top). The drawing is not to scale.

† flowdirection of continuous ultrafiltration, † flowdirection of whole blood samples
 A fenestration containing hollow fiber with helical spring inside, B connection of ultrafiltrate tube and fibre inside the small lumen of the catheter, C ultrafiltrate transport in polysulfon tube from catheter tip to on-line biosensor, D blood sampling via large lumen of the catheter for off-line analysis, E first of the five side holes of the large lumen, F end hole of the large lumen, G marker bands for positioning on x-ray

polyurethane adhesive (e.V. Roberts, Culver City, CA, USA) in the distal end of the catheter window. Proximal, the fiber was glued to a draining tube (polysulfon, 260 μ m o.d.; 42 μ m i.d., 145cm l.; Cordis Europa N.V., Roden, The Netherlands) which transported the sample fluid to the loop of the flow injection analysis system. The ultrafiltration flow rate was determined by the semi-vacuum of a syringe with a fixed piston (625 \pm 1 mbar \pm SD, 0.2 %CV, 1.2 ml s-monovette, Sarstedt, Nümbrecht, Germany) and the flowresistance of the system, as described previously⁽²¹⁾. The flowresistance consisted mainly of the very narrow draining tube which reduced the influence of the ultrafiltration probe membrane resistance on the flow rate. The lag-time between sampling and measurement varies with the length of the ultrafiltration draining tube. The ultrafiltrate flow generated was checked by continuously weighing the syringe.

A 9F introducer sheath (Avanti™, Cordis Europa, Roden, The Netherlands) was used to introduce the ultrafiltration catheter in the left jugular vein. To protect the tip membrane from damage while introducing, a tube was temporarily placed in the valve of the introducer. From the left jugular vein, the ultrafiltration catheter was advanced, and positioned at least 5 cm within the coronary sinus. The position of the catheter was checked by contrast injection (Figure 1(top)).

Lactate and glucose analysis

The ultrafiltration catheter was connected to a 20 nanolitre loop in a flow injection analysis system. Lactate and glucose were electrochemically detected every minute before, during, and after the experiments in the continuous ultrafiltrate flow as described by Tiessen et al⁽²²⁾. Calibration solutions were measured before and after each experiment by placing the catheter in standard solutions of glucose and lactate. The sensitivity in vitro of lactate and glucose sensors, respectively 8.09 and 1.66 nA/mM with both linearity $r > 0.99$, $p < 0.0001$, decreased over a period of days. The decrease before and after each experiment was negligible. Whole blood samples (2 ml) were withdrawn at the catheter tip every 10 minutes throughout the experiment, and every 2 or 5 minutes around anticipated quick concentration changes (Figure 1). The test tubes contained sodium fluoride and potassium oxalate to arrest coagulation and metabolism. The tubes were kept on ice until measurement on the same day. Concentrations of glucose and lactate were measured in whole blood and blood plasma after centrifugation with the Vitros 750 analyser (manufacturer: Ortho-Clinical Diagnostics, Illkirch Cedex, France) in the hospital routine laboratory. In order to make correct comparisons with whole blood glucose determinations, we adjusted the ultrafiltrate concentrations by -15% to unite with clinical practice of molarity measurement in whole blood (in accordance with the manufacturer's

report). Glucose molarity (mol/l blood) of whole blood is different from the molality (mol/kg water) as only about 80% of the blood volume consists of water⁽²³⁾. Lactate was determined in blood plasma. No correction for plasma protein volume was applied, because no corrective factor is known for lactate.

Experimental procedures

All procedures were reviewed and approved by the Animal Experiments Committee of the Groningen University. Experiments were performed on six Yorkshire swines (weighing 32, 33, 34, 53, 65 and 93 kg) because of the similarity with the human cardiac anatomy. The animals were maintained on a normal diet. All procedures were performed under anaesthesia. The swines were anaesthetised using a combination of ketamine (15 mg/kg;), acepromazine (0.2 mg/kg) and atropine (0.05 mg/kg) intramuscularly. An endotracheal tube was inserted for O₂/NO₂ ventilation. Ventilation with 2 % isoflurane (Forene®, Abbott, U.S.A.) was used to ensure adequate anaesthesia throughout the experiments. Levodromaron (2mg subcutaneously) was given as analgesic at the beginning of the procedure and supplemented if necessary. Lidocaine (50mg intravenously) was given prophylactically. Throughout the experiments, the condition of the animals was carefully monitored by means of continuous transcutaneous oximetry, intra-arterial blood pressure measurement, and electrocardiographic registration (ECG) of the limb leads and one modified precordial lead.

The pigs were administered initially 3mg/kg heparin intravenously, followed by 1.5mg/kg/h. The use of blood anticoagulant is known to be necessary in artificial kidneys to preserve the permeability of the membrane, which was here applied for the probe⁽²⁴⁾. The need to prevent blood clotting was confirmed in three preparatory experiments without heparin, which resulted in poor accuracy and a response time of about 20 minutes.

To measure the response time in vivo, 0.25g/kg of glucose 40% solution in water was injected intravenously in 2 minutes time once in every experiment. 0.1 g/kg of lactate 20% solution in 0.9% saline was added to the intravenous glucose injection in one experiment.

LAD coronary artery obstruction and reperfusion (n=3)

The myocardium of three pigs were subjected to partial ischemia. To this end, a 6F left Judkins coronary guiding catheter was advanced via an introducer sheath in the carotid artery to the ostium of the left coronary artery. Cine-angiograms (26 frames per second) were made from the 30° left anterior oblique position and filmed until the venous phase was reached. A balloon catheter was advanced

through the guiding into the left anterior descending coronary artery just past the first diagonal, where the balloon was inflated temporally for 5 minutes in one pig, and for 15 and 45 minutes in two pigs. The heart rate did not change significantly during inflation (95 ± 10 to 103 ± 9 min^{-1}), neither did the blood pressure (79 ± 8 to 68 ± 7 mmHg). In two instances ventricular tachycardia/fibrillation occurred at reperfusion. Electroconversion shocks were given for severe arrhythmias to re-establish sinus rhythm. The defibrillation at 10 J with surface electrodes did not interrupt the ultrafiltrate monitoring. These three experiments eventually ended with cardiac arrest after a total of 6.5, 6.5, and 8.5 hours continuous measurement.

Animal model myocardial dobutamine stress test (n=3)

Three pigs were evaluated 4 weeks after a nearly complete occlusion of the distal LAD by local injury and stent placement. The distal LAD showed at that time a strongly reduced flow (TIMI1). The angiogram of the left ventricle showed hypokinesia or akinesia in the distal part of the anterior wall with an overall good left ventricle rest function.

Dobutamine was infused with incremental doses from 2.5 $\mu\text{g}/\text{kg}/\text{min}$ to stress the myocardium by increasing the heart rate. After 3 minutes infusion of each dose, the heart rate and the blood pressure were measured, and a higher dose was started. Doses were increased until a clear drop in blood pressure was observed. The doses were increased up to 20 $\mu\text{g}/\text{kg}/\text{min}$ in the first pig, up to 30 $\mu\text{g}/\text{kg}/\text{min}$ in the second pig, and up to 22.5 $\mu\text{g}/\text{kg}/\text{min}$ in the third pig. On completion of each procedure, the animals were euthanised using a standard solution.

Data analysis and statistics

After a sudden change in concentration on the outside of the catheter tip, the equilibration on the inside took some time. This response followed a sigmoidal course from one level (0%) to the next level (100% equilibration). The time from 10 to 90% equilibration was calculated with sigmoidal fitting. The average (10-90%) equilibration time \pm standard deviation (SD) was calculated for the twelve im- and explantations. The lag-time (average \pm SD for all six experiments) was defined as the time interval from actual catheter implantation to measurement of 90% change of signal by the sensors. The response time in vivo was defined as the average time \pm SD for the amperometric signal to change from 10 % to 90% after an intravenous glucose injection (n=6).

The ultrafiltrate flow rates in vitro and in vivo were calculated with the pump

weight changes every five minutes in one hour before and during the implantation (averages \pm SD for n=6).

The ratio of the ultrafiltrate and blood measurements after the start of the experiments was compared to the ratio near the end as an indication of stability of glucose and lactate ultrafiltrate measurements.

The correlation between whole blood glucose and coronary ultrafiltrate measurements was determined with the samples around one i.v. glucose injection every experiment. Two baseline points before the injection and all points until return to baseline were used for linear regression (42 paired measurements from 6 injections). Samples taken within two minutes before and after the injection were omitted for reasons of response time limitation. The data were also compared using the Bland-Altman analysis on the relative differences of glucose concentrations between whole blood laboratory analysis and ultrafiltrate flowinjection analysis⁽²⁵⁾. The bias (the average difference), and the precision (the 95% confidence interval) were determined as a percentage of the reference values. The correlation between blood plasma lactate and coronary ultrafiltrate measurements was determined with paired samples around the concentration excursions from baseline after the i.v. lactate injection in one experiment (n=11) and after myocardial reperfusion in two experiments (n=35). To detect acute ischemic changes, the lactate baseline, taken as the last 5 minutes ultrafiltrate measurements before balloon inflation, was compared to the concentration during the first 5 minutes of ischemia. The concentration shifts expressed as the average \pm mM lactate and as a percentage of the baseline concentration before ischemia were compared with the Mann-Whitney Rank Sum Test. The same procedure was used for acute lactate/glucose rate changes.

Some assumptions were made in order to calculate estimations of the extracellular myocardial lactate build-up during ischemia. From the very quick lactate concentration rise after balloon deflation (see results) was deduced that this release can be considered as an intravenous lactate bolus injection with immediate distribution in the bloodplasma volume. Further, it was assumed that the body lactate clearance and production are not affected during reperfusion, and that the rate of lactate elimination from blood is linear⁽²⁶⁾. A one-compartment behavior was assumed for the first fifteen minutes, so from t= 0 to t=15.

Next, the equation for estimations $C_{t=x} = C_{t=0} * e^{-K*t=x}$ was found by least square regression (Gauss-Newton method). Thus, the differences between the measured data in the 15 minutes after balloon deflation (as far as within the response time and the precision of measurement) and the estimated data ($C_{t=x}$)

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were minimised. The γ lactate concentration at the site of origin at the time of balloon deflation ($\gamma C_{t=0}$) was calculated by loglinear extrapolation of the estimated γ lactate elimination course ($\gamma C_{t=x}$) for 2 or 3 minutes back to reperfusion onset at $t=0$. The variable K is the lactate elimination time constant with a half-life of $t_{1/2} = 0.693/K$.

The total lactate release after reperfusion was determined with the area under the curve, calculated by the trapezoid method when the γ lactate concentration is plotted against time from 0 to 8. The area under the curve (AUC) was expressed in $\text{mmol l}^{-1} \text{h}$ being the amount of lactate (mmol) divided by the bloodflow in the coronary sinus (l h^{-1}). No bloodflow measurements were available to further calculate this amount in Mols.

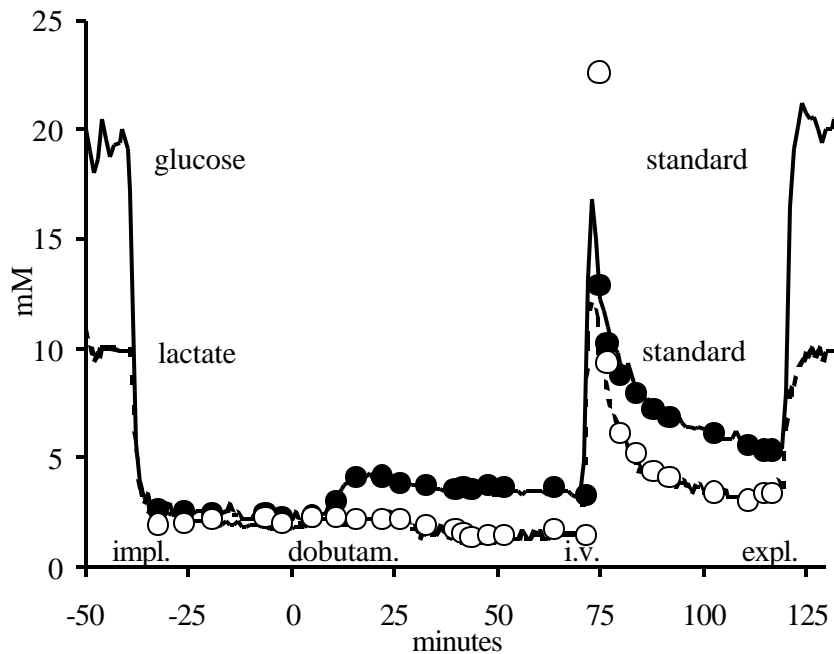


Figure 2 Typical example of an experiment. Lactate (\bullet) and glucose (\circ) blood sample and lactate ($---$) and glucose (\circ) ultrafiltrate measurements. Glucose and lactate standards before implantation and after explantation of the catheter from the blood circulation. Myocardial stress by dobutamine infusion from $t=0$ to $t=27$ minutes. I.v. injection with glucose and lactate solution.

Results

In vivo performance characteristics

In total 27 hours monitoring was performed in vivo with sixty ultrafiltrate measurements per hour. The equilibration time after im- and explantation was 1.33 ± 1.00 minutes (see typical experiment in Figure 2). The response time of ultrafiltration after i.v. injections was 1.33 ± 0.61 minutes. The lag-time was on

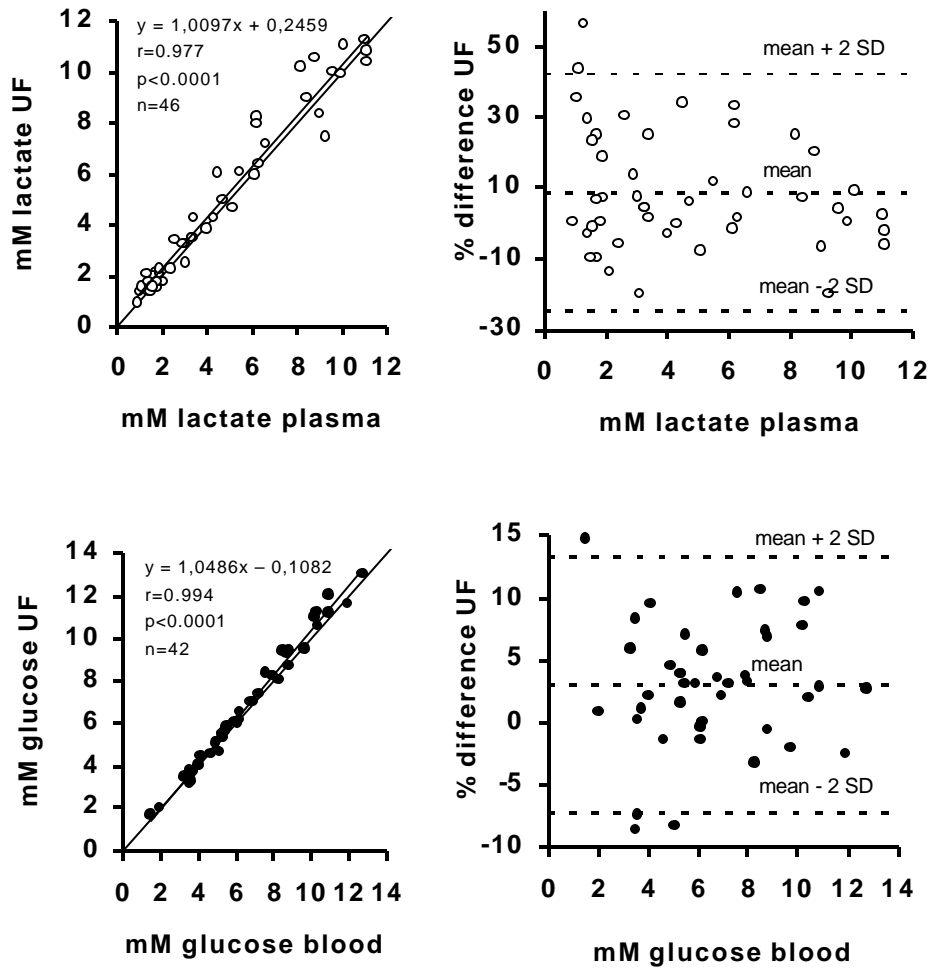


Figure 3 Regression and bias/precision plots for blood versus ultrafiltration samples. Upper panel: lactate, lower panel: glucose. The regression lines and the lines of identity are shown left. Mean (bias) and mean ± 2 SD (precision) lines are shown right.

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average 24.3 minutes (range 21-26 minutes). In five pigs, the catheter ultrafiltrate flow rate remained stable after introduction in the bloodstream with 85.1 ± 4.9 nl/min in vitro and 85.5 ± 8.2 nl/min in vivo. At the end of the experiments was the ultrafiltrate/blood concentration ratio for glucose $101 \pm 9\%$ and for lactate $88 \pm 14\%$ of the ratio at the start of the experiments ($p > 0.05$). No apparent effect was seen of the electrical defibrillations on ultrafiltrate flow or measurements.

Figure 3, upper panel left shows the linear regression for lactate in the ultrafiltrates (y) and blood samples (x) which was $y = 1,0097x + 0,2459$, $r = 0.977$, $p < 0.0001$, $n = 46$. The bias was 8.86%, the precision 33.42% (Figure 3, upper panel right). The linear regression for glucose was $y = 1,0486x - 0,1082$, $r = 0.994$, $p < 0.0001$, $n = 42$ (Figure 3, lower panel left). The bias was 3.03%, the precision 10.22% (Figure 3, lower panel right). The regression coefficient r rose for lactate during subsequent experiments as a result of improvement of the blood sampling procedure.

Only in the second experiment declined the flow rate from 90 nl/min to 56 nl/min in the second half of the experiment lasting 6.5 hours. Blood sampling became then almost impossible. The ultrafiltration response time after an i.v. injection at 30 minutes after start of the experiment was still 1.78 minutes, the lag-time 26 minutes. The ultrafiltration response time after an i.v. glucose injection at 450 minutes after start of the experiment was estimated 0.85 minutes, but the lag-time 43 minutes. The course of the lactate concentrations in ultrafiltrate did not change significantly during and after 15 minutes balloon inflation in the LAD. The ultrafiltrate lactate levels followed an irregular course and started to rise slowly after 45 minutes balloon inflation in the LAD, while the lactate in the blood samples remained low. The ultrafiltrate/blood lactate concentration ratio rose near the end of the experiment to 324% of the start. Ultrafiltrate glucose levels decreased slowly after 45 minutes balloon inflation in the LAD while the blood levels did not alter much. The ultrafiltrate/blood glucose concentration ratio descended near the end of the experiment to 60% of the rate at the start of the experiment. The ultrafiltrate flow was immediately restored to 92 nl/min after placing the catheter from the coronary sinus into a calibration solution. The data of this experiment were excluded from further data analysis.

Coronary sinus lactate and glucose levels after LAD coronary artery obstruction and reperfusion (n=3)

After balloon inflation in the LAD, lactate levels in the coronary sinus ultrafiltrate rose by 0.38 ± 0.10 mM above baseline during the first 5 minutes of ischemia ($p < 0.05$), see Figure 4. The lactate/glucose rate rose by $28 \pm 16\%$

Monitoring myocardial ischemia

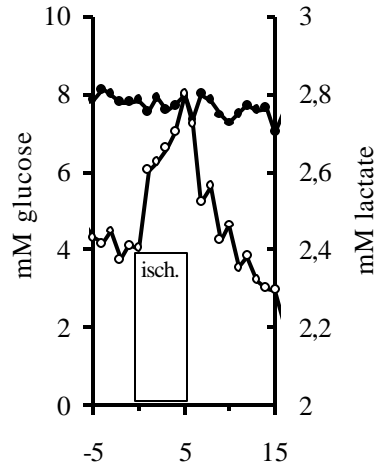
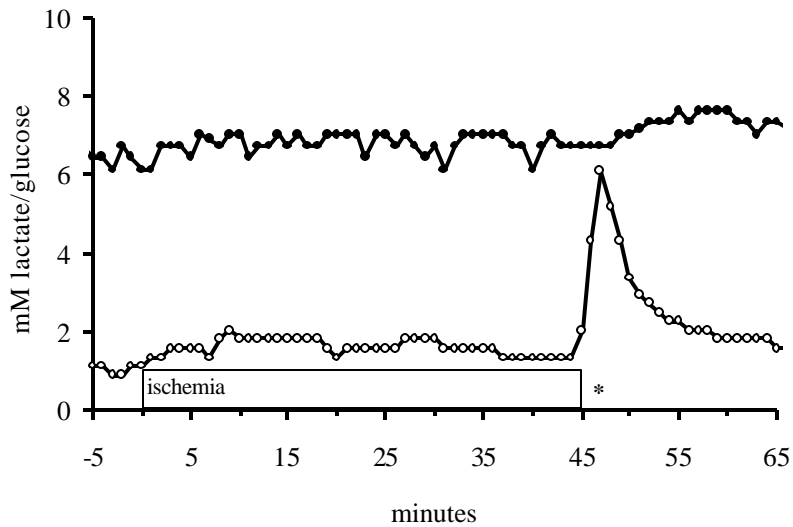
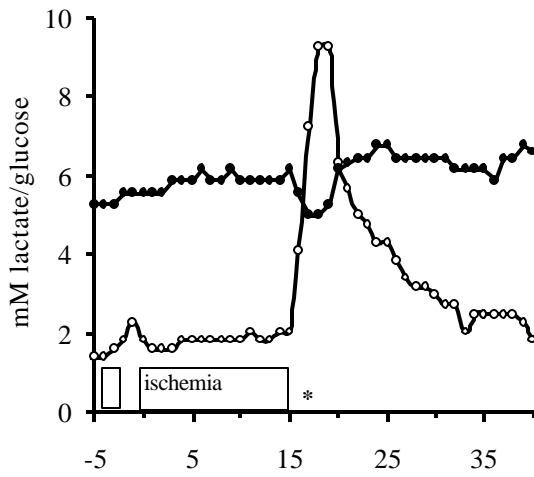


Figure 4
Lactate (-o-) and glucose (-?)
ultrafiltrate levels in mM in the coronary
sinus during myocardial ischemia of 5, 15
or 45 minutes respectively in upper,
middle and lower panel. In the upper
panel the left y-axis indicates mM
glucose, the right y-axis mM lactate. (?
) indicates a short accidental balloon
inflation. (*) indicates electric
defibrillation of ventricular fibrillation



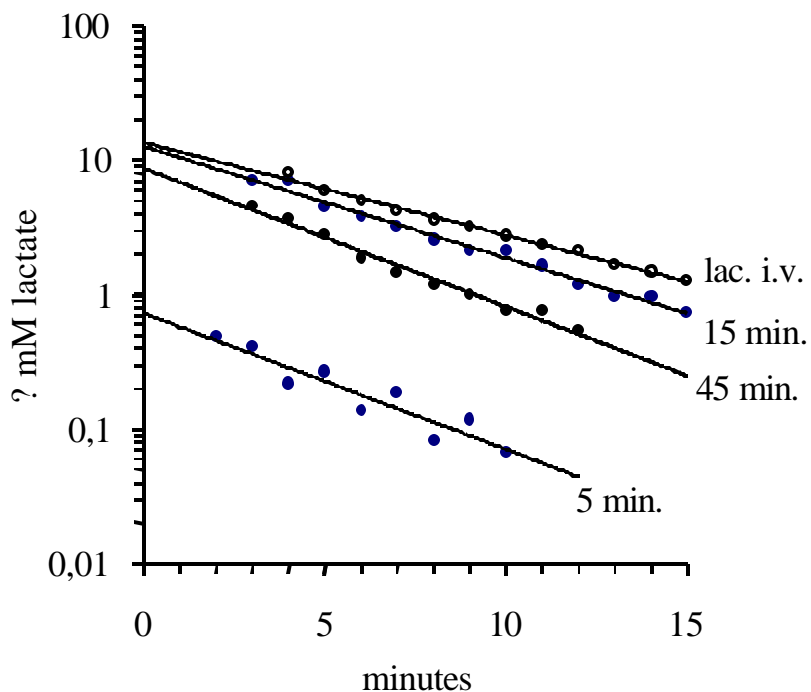


Figure 5

(?) Coronary sinus lactate concentrations (? mM above baseline) during reperfusion (onset at $t = 0$) after 5, 15, or 45 minutes ischemia.

(o) Coronary sinus lactate concentrations (? mM above baseline) after intravenous lactate injection. Extrapolations are shown for best fitting lines back to the ? lactate concentration at the start of reperfusion or injection at $t = 0$.

($p < 0.05$). Arterial plasma lactate levels were similar before and after the onset of ischemia (2.1 ± 0.4 mM, n.s.).

Immediately after balloon deflation, the lactate concentration rose sharply during reperfusion for a few minutes, reaching a maximum of 2.80 mM (116% of baseline) at 1 minute after 5 minutes ischemia, 9.27 mM (683% of baseline) at 3 minutes after 15 minutes ischemia and 6.11 mM (587% of baseline) at 3 minutes after 45 minutes ischemia (Figure 4). The total lactate releases at reperfusion were $3.77 \text{ mmol l}^{-1} \text{ h}$, $1.49 \text{ mmol l}^{-1} \text{ h}$, and $0.09 \text{ mmol l}^{-1} \text{ h}$, respectively. The lactate plasma concentration at the moment of the intravenous injection was estimated to be 13.80 mM ($R^2 = 0.99$, $t_{1/2} = 4.36$ min.) (Figure 5). The lactate concentrations at the onset of reperfusion were estimated to be 3.13 mM ($R^2 = 0.88$, $t_{1/2} = 2.97$ min.), 14.82 mM ($R^2 = 0.99$, $t_{1/2} = 3.63$ min.), and 10.20 mM

($R^2=0.98$, $t_{1/2}=2.93\text{min.}$), respectively. In some cases electrical cardioversion was necessary due to ventricle tachycardia/fibrillation at the onset of reperfusion (indicated in Figure 4 with *). Apart from the balloon manoeuvres, the lactate/glucose rate showed little change. The lactate/glucose rate rose again about 60 to 30 minutes before asystole, escorting a general deterioration of the circulation by a dying heart (diagnosed on ECG).

Lactate and glucose levels during myocardial dobutamine stress (n=3)

In the first pig, the heart rate increased from 82 to 191 at the highest dose (24 minutes after start of the dobutamine infusion). The maximal blood pressure was 123/104 mmHg at a dose of 20 $\mu\text{g/kg/min}$. Blood pressure at the highest dose was 102/77 mmHg. In the second pig, the heart rate increased from 123 to 208 /min at the highest dose (36 minutes after start of the dobutamine infusion), with a maximal blood pressure increase from 64/46 to 120/81 at a dobutamine dose of 20 $\mu\text{g/kg/min}$. Blood pressure at the highest dose was 105/50 mmHg. In the third pig (see Figure 2), the heart rate increased from 83 to 204 /min at the highest dose (27 minutes after start of the dobutamine infusion). Blood pressure increased from 95/84 to 128/108 at a dose of 20 $\mu\text{g/kg/min}$. Blood pressure at the highest dose was 106/66 mmHg. The ECG did not show any signs of ischemia during these three experiments.

The ultrafiltrate glucose levels in the three dobutamine experiments rose gradually from a baseline at 3.84, 3.06, and 1.70 mM to a maximum of 4.88, 5.12 and 4.23 mM, at 18, 36, and 19 minutes after start of the dobutamine infusion. A similar rise was observed in the arterial blood samples. The lactate levels demonstrated no significant alteration during the dobutamine infusion test. At macroscopic evaluation the infarct areas were small and located at the apex and distal part of the interventricular septum.

Conclusions

This report describes the first application of ultrafiltration on myocardial pathophysiology. It demonstrates that an ultrafiltration catheter can sample bloodultrafiltrate continuously for hours in the coronary sinus. The combination of an intravascular ultrafiltration catheter and biosensor technology allows stable measurement of absolute lactate and glucose concentrations on a minute to minute basis. The automated detection was in good correlation with reference values in manually sampled blood. This is possibly the first study on venous efflux monitoring with such short time intervals. A significant increase in the

myocardial lactate efflux was detected within minutes after the cardiac arterial flow interruptions and reperfusions performed. A quantitative estimate of the lactate efflux at reperfusion was possible. These observations suggest the existence of a tight link in time between cardiac pathologic events and metabolic shifts in the venous efflux, interesting for their potential diagnostic value.

In the present exploration, only a limited number of observations has been done, so most of our conclusions on cardiac ultrafiltration monitoring must be considered as preliminary. Once, in the second experiment described, the measurements appeared as being done outside the coronary bloodstream, an effect well known of intravascular sensors, referred to as the “wall effect”⁽⁵⁾. Extravasation of the catheter tip may create a diffusional barrier between the probe surface in tissue and the bloodstream. This can explain the worsened response time, the lower glucose and the increased lactate levels. Similar effects were previously noticed by us in human subcutaneous tissue⁽²²⁾, in intravascular rat⁽²⁷⁾ and chicken experiments, and in vitro experiments when blood cells were attached to a probe (unpublished data). The possibility of the wall effect and the need for heparinisation observed may of course limit the future application of ultrafiltration monitoring.

Various techniques, previously studied by others, have already demonstrated the feasibility of (semi-) continuous metabolic monitoring in peripheral blood. These studies applied frequent blood sampling and on-line analysis⁽²⁸⁾, microdialysis in venous shunts^(6;29), and microdialysis with probes placed in peripheral veins^(17;30). Microdialysis probes have also been placed directly in myocardial tissue^(7-10;15). The lactate levels in ischemic myocardium calculated here by extrapolation were in the same range as the elevations found with interstitial space microdialysis studies (300 and 775%^(9;10)). The lacking effect on lactate levels of a myocardial dobutamine challenge is also in line with the results of a previous microdialysis study⁽¹⁵⁾. There are however some important methodological differences between intravenous ultrafiltration and tissue microdialysis. Microdialysis measures in an area of tissue less than 5 mm around the probe⁽¹⁶⁾, where a downward concentration gradient exists in the tissue towards the probe, descending from 100% to between 7 and 74%. This percentage can change in time, but it must be determined for calibration of microdialysis measurements. Calibration of microdialysis in vivo is a well documented, but complicated issue. Microdialysis also requires a considerable equilibration time (e.g. 90 minutes) before measurement can be started. Further is exposure of the heart required for insertion of microdialysis probes, so the technique is restricted to the operation theatre. For comparison, the present ultrafiltration catheter only needs angiography to check the position of the tip. Equilibration of the ultrafiltration

probe takes about 2 minutes for concentrations of small molecules. There is no need for in vivo calibration of ultrafiltration, because it evacuates bloodplasma water together with 100% of its small solutes, and measurements remain stable, as shown for many hours.

The limitation of microdialysis measurement to a small area around a probe in pathologic or healthy tissue may be advantageous, because one can expect the concentration changes in the coronary sinus to be diluted compared to those at the site of origin, what may diminish the sensitivity of a coronary sinus probe. Some pathologic processes may even stay hidden behind the endothelium⁽³¹⁾. This is however not the case for myocardial ischemia^(2;3). We extrapolated here the diminishing coronary sinus concentrations back to the concentrations at the time of release. This may be the extracellular lactate level in the ischemic tissue. So a venous application of the catheter as chosen in the present study appears sensitive enough to measure local myocardial metabolism. Besides, the entire myocardial metabolism is more often of interest than local changes, as illustrated by the afore mentioned intravascular approaches for lactate^(2;3). This underscores the advantage of the position of the present probe in the coronary sinus, so in the cardiac common venous efflux.

Ultrafiltration offers new research opportunities in acute pathology through the shortening of the response time and the absolute measurements. Metabolic shifts in organs can be linked to pathologic events in time, e.g. the reopening of cardiac arteries by thrombolysis may thus be detected. Quick kinetic processes can also be studied using the absolute concentrations. Estimates can be made of the lactate concentration at the onset of reperfusion as well as the area under the curve using some assumptions on the lactate kinetic behavior. Although the datapoints showed a good fit, firm statements about onset concentrations and the area under the curve are not possible because of the limited number of experiments. In future, novel metabolic insights may be found in this way, e.g. insights in myocardial preconditioning and ventricular fibrillation mechanisms.

Future technical developments should be aimed at monitoring real-time, because a possible early detection of ischemia and reperfusion bears the potential for assisting therapeutic decision making. The lag-time of the present catheter is too long, and should be shortened by utilizing shorter catheters and by optimizing the dead volume/flow ratio or by insertion of small biosensors in the tip of the catheter. The current ultrafiltrate sampling method has indeed recently been coupled to such miniature biosensors with essentially the same results (Rhemrev et al., submitted).

The primary achievement of this study is the short response time obtained with absolute measurements with the ultrafiltration catheter and the first in vivo

observations of prompt myocardial lactate changes. Possible future benefits of such system for patients may be an early alert for acute ischemia by monitoring the moving average of lactate concentration, e.g. the reocclusion of a coronary artery. The success of therapy (e.g. of thrombolysis), defined as reperfusion of an obstructed coronary artery, may be recognizable as a sudden release of lactate from the myocardium. Metabolic monitoring may become supplementary to current ECG monitoring.

At present, there are to our knowledge as yet no intravascular sensors for monitoring metabolites available for use in patients, because this poses many demands, e.g. regarding specificity, accuracy, stability, miniaturisation, sterilisation, thrombogenicity, toxicity, biocompatibility, disposability and inexpensiveness. Some of these demands may be easier to meet in future by combining biosensors with ultrafiltration sampling. It appears worthwhile to explore cardiac lactate monitoring techniques further, because it eventually may prove to have diagnostic value for patients.

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