Microdialysis Detects Postoperative Perfusion Failure in Microvascular Flaps

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ABSTRACT

In microvascular tissue transfers, it is essential postoperatively to follow-up on the perfusion of the transferred flap because of the risk of anastomotic failure. The diagnosis of pedicle obstruction is usually made by clinical observation, but some techniques have been reported as more reliable than clinical observation in detecting perfusion failure. The authors used microdialysis (MD), a method developed to assess in situ tissue metabolism, in the follow-up of 80 consecutive microvascular flaps from October, 2001 to October, 2003. Of the 78 flaps with postoperative data, 58 flaps were uneventful clinically and using MD, and served as the reference material for normal postoperative metabolism. Twenty flaps showed some abnormality in the clinical course or with MD. Of these, 13 flaps were reoperated for anastomosis thrombosis (9 arterial, 4 venous). All thromboses were clearly recognized by MD via a decrease in the glucose concentration in the tissue (< 2.7 mmol/l) and an increase in the lactate concentrations (> 5.7 mmol/l). In some cases, MD indicated a pathological trend in glucose and lactate concentrations hours before there were any clinical signs. A system of alarm levels was developed for the staff: when the limits were reached, a critical evaluation of the situation was undertaken, and the need for reoperation was considered. In the series, the salvage rate of all thrombosed flaps was 77 percent, with a final success rate in microvascular reconstruction of 95 percent. No flap was lost due to a delay in the diagnosis of secondary ischemia, if on-line MD monitoring was available.

Microdialysis is a clinically feasible and sensitive monitoring method for all kinds of microvascular flaps, especially for those in which clinical observation is difficult or impossible. The performance of the analysis is easy and can be done by even less experienced nursing staff working in institutes with a low frequency of microsurgery.

KEYWORDS: Microdialysis, microvascular, monitoring

Flap loss due to thrombosis of the anastomosis is the most feared complication in microsurgical reconstructions. The risk for pedicle thrombosis varies from 0.9 to 16.7 percent, depending on flap type, the local circumstances in the reconstructed area, and the general condition of the patient.[1,2] The majority of thrombi (80 percent) occur during the first two postoperative days.[3] In most cases, perfusion failure can be corrected by a reoperation within the first 4 hr.[4]

The diagnosis of pedicle thrombosis is usually made by clinical observation, which sometimes is unreliable.[2,5–7] Several methods have been suggested to aid in

Journal of Reconstructive Microsurgery, Volume 22, Number 2, 2006; accepted for publication October 25, 2005. Address for correspondence and reprint requests: Leena Setälä, M.D., Ph.D., Department of Plastic Surgery 2214, Kuopio University Hospital, P.O. Box 1777, 70211 Kuopio, Finland. Departments of [1]Plastic Surgery and [2]Clinical Chemistry, Kuopio University Hospital, Kuopio, Finland. Tel: +1(212) 584-4662. 0743-684X,p;2006,22,02,087,096,ftx,en; jrm01165x.

the diagnosis of perfusion failure. The blood flow in the pedicle can be monitored by an ultrasound Doppler probe,[4] while the microcirculation in the flap can be monitored by laser Doppler flowmeter (LDF), a method preferred by many institutes.[5,8,9] Moreover, instruments have been developed to monitor flap tissue pH and oxygen partial pressure (TiO_2).[10–12] The use of these methods has been reported to be beneficial compared to clinical observation only, and it has been claimed that the flap salvage rate can be improved as a result of earlier diagnosis and revascularisation.[4] However, none of these methods has been shown to be superior to the others; in fact, all these methods have their own inherent limitations.

Microdialysis (MD) is a method used to investigate tissue metabolism via a mini-invasive probe implanted into the tissue. A multitude of different molecules can be detected in a sample of the microdialysate, but when tissue blood perfusion is to be assessed, familiar metabolites of the Krebs cycle, such as glucose, lactate, and pyruvate are analyzed.[13] Microdialysis has been used in small series for clinical free-flap surveillance.[14,15] We evaluated the feasibility of using microdialysis in the detection of postoperative perfusion failure in a clinical series with a variety of microsurgical flaps.

PATIENTS AND METHODS

From October, 2001 to October, 2003, 80 consecutive microvascular flaps (Table 1) were monitored with microdialysis. The series consists of 78 patients with an acute or chronic tissue deficit due to trauma or cancer surgery. There were 35 male patients and 43 females, and their mean age was 50 years (range: 16 to 79 years). After the operation, patients were followed-up in the recovery room for the first postoperative day, except those undergoing extensive head-and-neck reconstruction or those in a compromised general condition; these were monitored in the intensive care unit. The visible flaps were monitored for clinical signs such as color and turgor and, in flaps with a skin island, the speed of capillary refill (vital reaction) was assessed. Temperature was measured occasionally, but bleeding for needle puncture was tested only when a pedicle thrombosis was suspected. Patient status was registered hourly during the first postoperative day, every 2 hr throughout the second day, and every third hour on the following day.

Microdialysis The principles of MD have been previously presented in detail.[13] Briefly, a catheter inserted into the tissue is perfused with a physiologic fluid that makes contact with the extracellular fluid through a semipermeable membrane. Outcoming fluid with molecules from the tissue is collected and analyzed in a separate analyser. In our study, an MD catheter (CMA60 or CMA70, CMA Microdialysis Ab, Stockholm, Sweden) was inserted into the flap tissue using a commercial introducer or a large intravenous cannula (16G) at the end of the surgical procedure. The catheter was stabilized with deep or superficial sutures to ensure that the semipermeable part of the catheter was embedded within the monitored tissue. A battery-powered microinfusion pump (CMA 106 or 107, CMA Microdialysis Ab, Sweden) was connected to the catheter to perfuse the inner lumen with sterile isotonic Ringer's chloride solution (perfusion rate: 0.3 μl/min). The perfusate was collected to commercial microvials hourly for the first postoperative day, every 2 hr on the second day, and every 3 hr during the third postoperative day. The sample was analyzed by a nurse in the recovery room using a transportable CMA 600 Analyser (CMA Microdialysis, Stockholm). The data on glucose, lactate, and pyruvate concentrations in the microdialysate were usually available within 10 min after the sampling. When the patient was transferred to the regular ward, the samples were analyzed by the nursing staff or sent to the laboratory, in which case the results were available within 1 hr from sampling. The data on the first 20 patients were used to discriminate normal values from abnormal, and alarm levels were created for all MD parameters. Thus, glucose level < 2 mmol/l, lactate > 6 mmol/l, and lactate-to-pyruvate ratio (L/P) > 25 were used as indicators for alerting the attending microsurgeon. In the first patients, we also used a control catheter inserted to the subcutaneous fat outside the operated area. The samples were collected at the same intervals as those from the flap.

Table 1 Microvascular Flaps and the Area to be Reconstructed in the Series of 78 Patients

Flap Type	Breast	Head-neck	Lower Extremity	Upper Extremity	Trunk
TRAM rectus abdominis myocutaneous flap	28	—	—	—	—
ALT anterolateral thigh flap	—	10	2	1	—
RFA radial forearm flap	—	6	2	—	—
LD latissimus dorsi muscle flap	—	—	12	—	—
LD latissimus dorsi myocutaneous flap	—	1	10	—	1
RA rectus abdominis muscle flap	—	—	3	—	—
VRAM vertical rectus abdominis flap	—	2	—	—	—
Other	—	—	gracilis muscle	temporalis fascia	—

Statistical Analysis The data were analyzed with a commercially available software package (SPSS for Windows, Version 11.5, SPSS Inc, Chicago, IL). Substance concentrations were expressed in medians and interquartile ranges because of skewed distributions and lack of normality of the outcome values (Shapiro-Wilk's and Kolmogorov-Smirnov normality tests). The differences in repeated measures over time were tested applying Wilcoxon's test, and the differences between study groups were tested using Kruskal-Wallis and Mann-Whitney U tests. Bonferroni corrections were used in multiple comparisons in order to reduce the chance of type I errors. p-values less than 0.05 were considered statistically significant. ROC analysis was used to examine the sensitivity and specificity of MD.

RESULTS

Normal Flaps and Control Tissue Of an original 80 flaps, two were excluded, one because all of the samples were collected intraoperatively, and the other because the postoperative samples were accidentally stored at room temperature for 1 week before analysis, resulting in possible false results. Seventy-eight flaps remained for a more profound analysis of the MD results. The postoperative course of 58 flaps was uneventful clinically and this was reflected in stable metabolism in MD. The samples collected from these flaps during the first 52 hr (after the end of primary ischemia) represent the normal postoperative values of a well-perfused flap (Table 2). Glucose concentration remained higher than 2 mmol/l, lactate under 9 mmol/l, and the L/P ratio under 32 in 98 percent of the samples from flaps with normal perfusion.

In 17 patients, flap tissue was compared to the same person's control tissue, showing that the glucose level remained slightly lower and the lactate higher in the flap tissue postoperatively during the first 12 hr

Table 2 Postoperative MD Glucose and Lactate Concentrations and L/P Ratios in 58 Normally Perfused Flaps

MD-Variable		N = 1522
Glucose (mmol/1)	Median	5.7
	IQR	(4.5–6.8)
	95% over	2.9
	98% over	2.1
Lactate (mmol/1)	Median	2.4
	IQR	(1.5–3.3)
	95% less than	6.3
	98% less than	8.9
L/P ratio	Median	12
	IQR	(9–16)
	95% less than	24
	98% less than	32

IQR = interquartile range.
N = total number of samples collected from the 58 flaps.

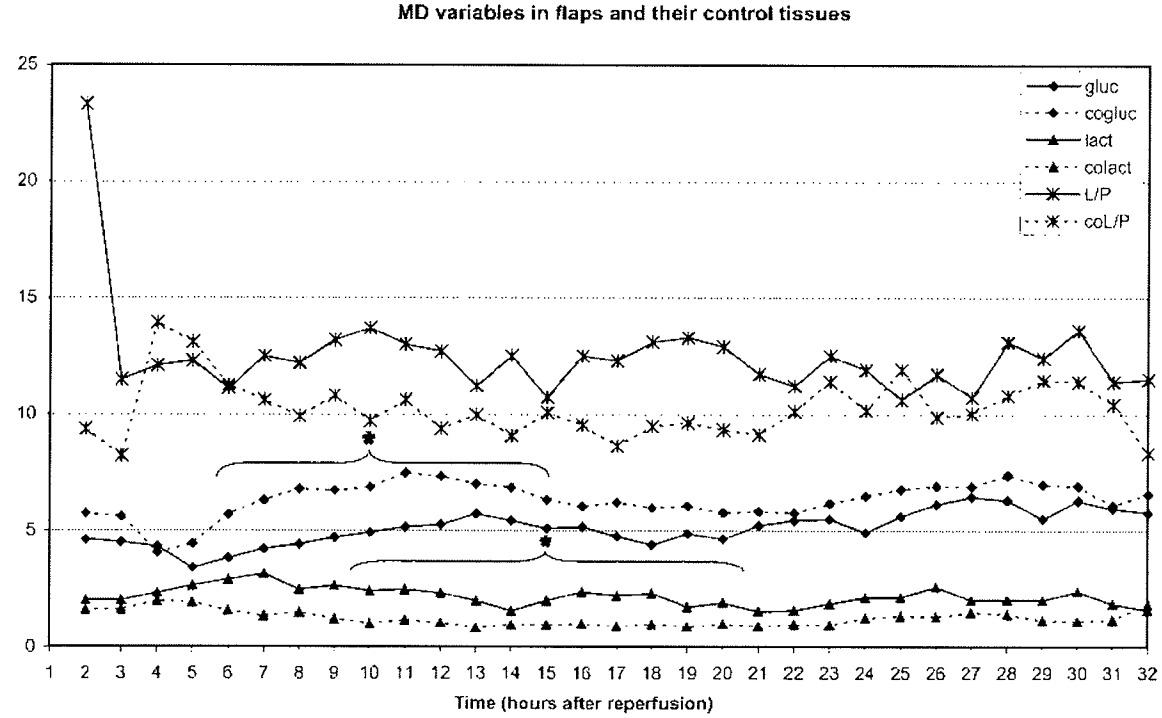

Figure 1 Differences in MD glucose (gluc, mmol/l) and lactate concentrations (lact, mmol/l) and lactate-to-pyruvate ratios (L/P) between the normally perfused microvascular flaps and control tissues (cogluc, colact, coL/P). (Values are expressed as medians, *$p < 0.05$, Wilcoxon.)

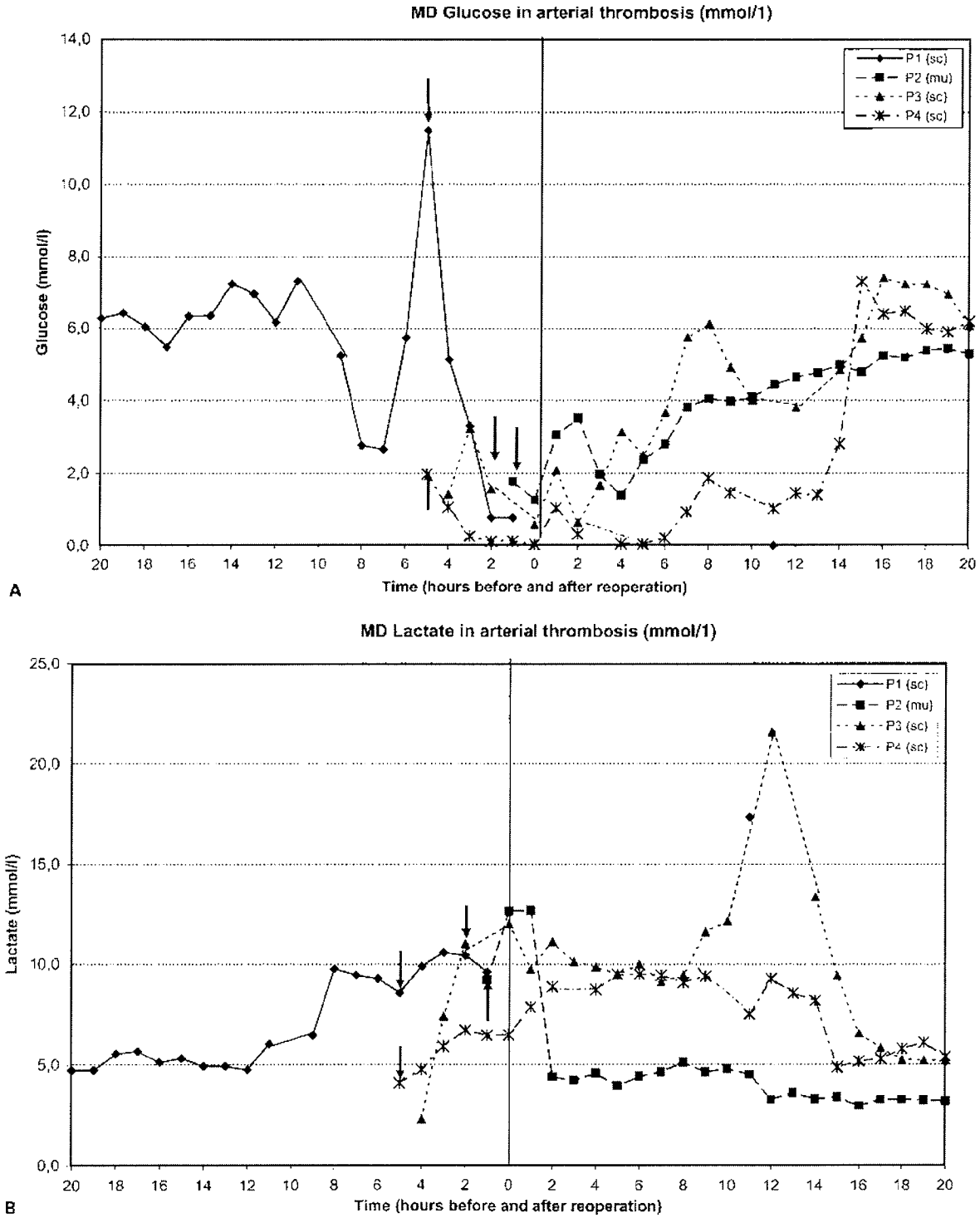

Figure 2 (A–C) Time course of four arterial thromboses (patients P1-4) in terms of the appearance of clinical signs (arrows) and MD values before and after reanastomosis (vertical line at time point zero). (A) Microdialysate glucose concentration (mmol/l). (B) Microdialysate lactate concentration (mmol/l).

(Fig. 1). The comparison of glucose concentrations in different tissue components of the flaps indicated no difference, while the lactate concentration and L/P ratio were slightly higher in the muscle than in the subcutaneous fat or dermis.

Abnormal Flaps The remaining 20 flaps with abnormal MD data are depicted in Table 3, including 14 flaps with a pedicle thrombosis (10 arterial, 4 venous). Other causes of vascular insufficiency were found in three cases, including an arterial spasm (patient 15), general

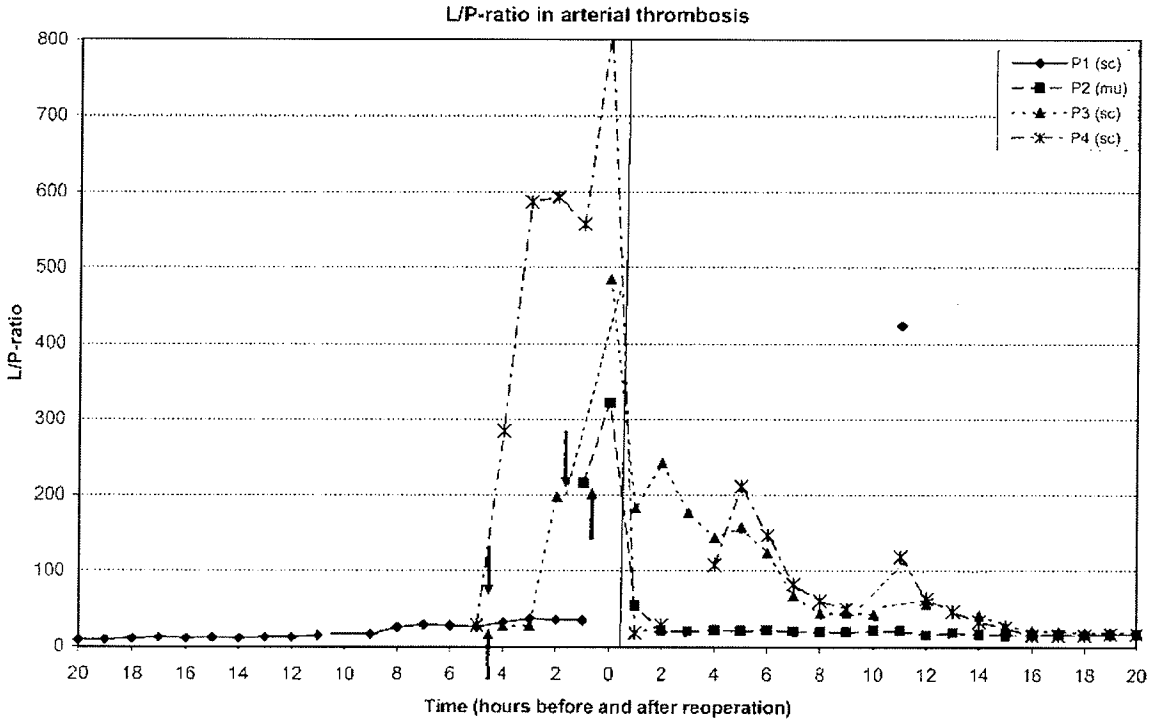

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Figure 2 *(continued)* (C) Microdialysate lactate-to-pyruvate ratio. (sc = measured from subcutis/dermis; mu = measured from muscle.)

hypotension (patient 16), and tight wound closure over a venous anastomosis (patient 17). In these cases, MD reported marginally elevated lactate or decreased glucose concentrations. In one patient (18) reoperated for a large hematoma around the pedicle, no disturbance was detected in flap perfusion clinically or in MD. One unnecessary reoperation (patient 19) was done due to false positive MD data. In this case, clinical follow-up

Table 3 Twenty Patients with Abnormal Clinical Course or Abnormal MD Results

	At the Incident				
Patient	**Lowest Glucose**	**Highest Lactate**	**Highest L/P**	**Reoperation**	**Findings**
1	0.8	10.6	37	yes	arterial thrombosis
2	1.3	12.6	321	yes	arterial thrombosis
3	0.6	12.0	486	yes	arterial thrombosis
4	0.0	6.5	809	yes	arterial thrombosis
5	0.0	9.5	130	yes	arterial thrombosis
6	0.5	11.9	267	yes	arterial thrombosis
7	0.0	17.8	746	not successful	late diagnosis of an arterial thrombosis
8	0.4	16.6	112	not successful	arterial thrombosis, resistant spasm
9	0.0	32.7	315	not successful	prolonged primary ischemia, no-reflow
10	0.9	60.2	5890	no	prolonged arterial ischemia and thrombosis, reanastomosis impossible
11	2.6	5.5	28	yes	venous thrombosis
12	0.2	10.2	39	yes	venous thrombosis
13	0.2	17.3	91	yes	venous thrombosis
14	0.8	13.6	81	yes	venous thrombosis
15	1.2	14.5	141	yes	arterial spasm, no clot
16	0.7	18.9	408	yes	hypotension (shock)
17	0.8	6.3	251	yes	venous occlusion, no clot
18	6.9	3.6	19	yes	hematoma, patent pedicle
19	0.7	7.6	38	yes	misplaced catheter
20	0.5	10.6	25	no	no obvious cause, clinical status normal

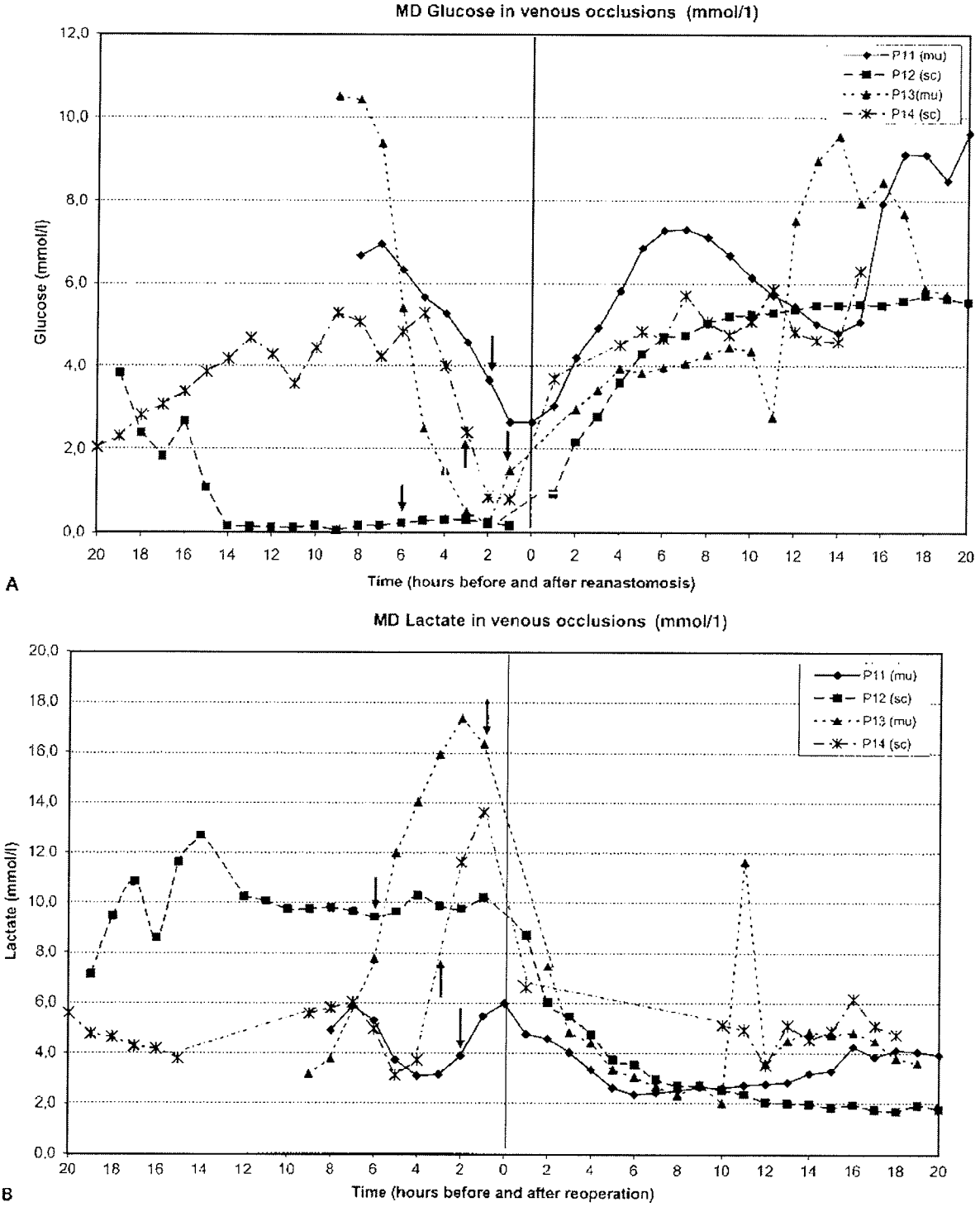

Figure 3 (A–C) Time course of four venous thromboses (patients P11-14) in terms of the appearance of clinical signs (arrows) and MD values before and after reanastomosis (vertical line at time point zero). (A) Microdialysate glucose concentration (mmol/l). (B) Microdialysate lactate concentration (mmol/l).

was not available, because the visible part of a TRAM flap was used for the reconstruction of a nipple-areola complex. The MD probe was inserted here under the de-epithelialized dermis. Suboptimal MD values resulted, probably from suboptimal local tissue perfusion in this manipulated area. In one case (patient 20 in Table 3), MD monitoring was discontinued because the MD indicated marginally low glucose and elevated lactate, while the appearance of the flap was normal. The reason for the discrepancy is not known.

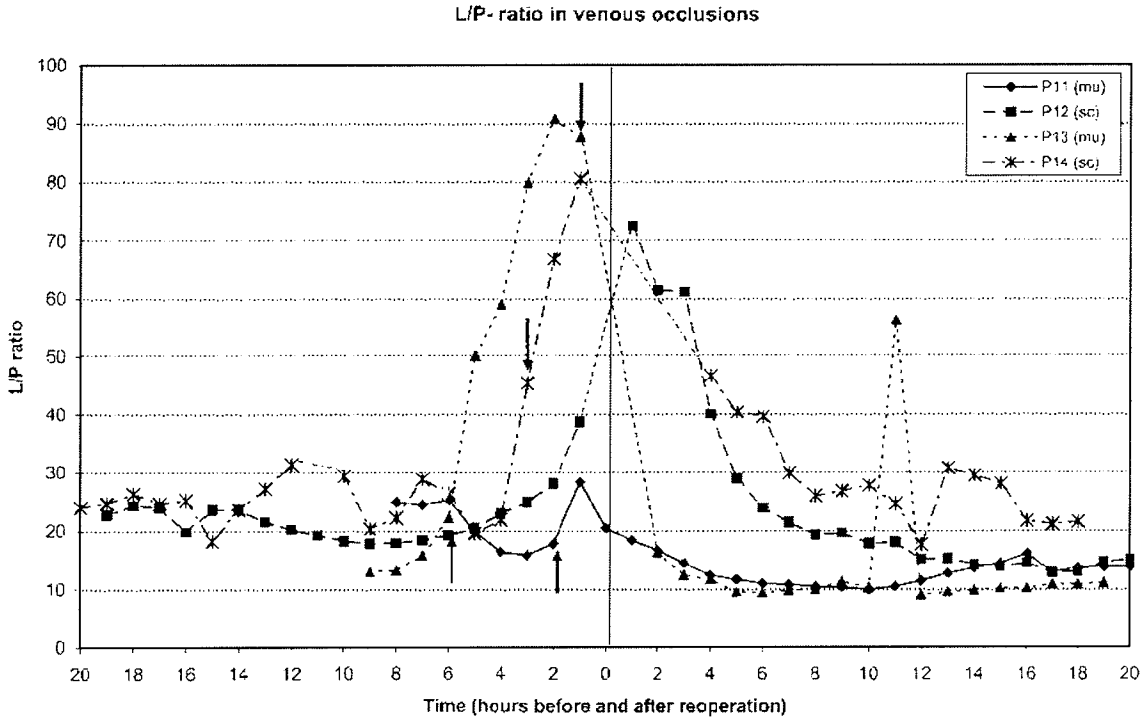

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Figure 3 *(continued)* (C) Microdialysate lactate-to-pyruvate ratio. (sc = measured from subcutis/dermis, mu = measured from muscle.)

Figures 2A–2C describe the development of four arterial thromboses in patients who were monitored by MD for a long period. Three of the thromboses had a rapid onset soon after the operation, while one flap became unstable after being stable for several hours. Clinical signs of vascular insufficiency (indicated by arrows) appeared when the glucose concentration had declined to the level of 1 to 2 mmol/l (see Fig. 2A). In Figure 2B we can see rapidly increasing lactate concentrations in two flaps, with arterial thrombosis at the same moment as clinical signs of perfusion failure are seen. In two cases, the increase in lactate concentration is visible 1 to 3 hr before clinical signs. The L/P ratio increased rapidly in flaps with arterial ischemia (see Fig. 3C, Table 3). In patient 3, the glucose level remained low and the lactate level was high after the reoperation, indicating poor flap perfusion and probably caused by general hypotension (mean arterial pressure: 55 mm Hg) and hypoksemia (blood hemoglobin: 70). Flap perfusion was corrected and the flap saved by general interactions such as invasive monitoring and infusion of fluid, blood, and vasoactive medications.

In the four cases with venous thrombosis (Fig. 3A–C), the decline of glucose concentration was seen as early as 2 to 8 hr before there were any clinical signs of venous congestion (Fig. 3A). The increase in lactate concentration was seen 1 to 12 hr before clinical signs (Fig. 3B). The clinical diagnosis of venous compromise could be confirmed within the same hour as the set alarm levels of MD were reached. The L/P ratio was increased to over 25, but always remained under 100 in venous thrombosis (Fig. 3C).

The glucose values < 0.4 mmol/l and lactate concentrations > 15 mmol/l were 100 percent specific for pedicle thrombosis (Table 4). No thrombosis was present if glucose was > 2.7 mmol/l or lactate < 5.7 mmol/l (100 percent sensitivity). The results of the ROC analysis are naturally affected by the fact that some patients were reoperated on before the minimum of glucose or maximum of lactate or the L/P ratio were reached.

Clinical Results The primary success rate in microsurgical tissue transfer was 74 percent (59/80) in our series. Reoperations were performed in 18 patients (22 percent), 13 of them for pedicle thrombosis. All but three of the reoperations were successful; in these latter cases, latter perfusion could not be established due to resistant arterial spasm (patient 8), prolonged primary ischemia (patient 9), or prolonged secondary ischemia (patient 7). In this last case, ischemia was not suspected in the clinical surveillance. Immediate analysis of MD samples was not available due to technical problems with the analyzer. Later sample analysis revealed that arterial insufficiency had developed soon after the end of the operation. For this patient, another flap was successfully transferred some days later. Consequently, salvage of the flap in reoperations for anastomotic thrombosis was possible for 10 patients (salvage rate: 77 percent). If flaps with prolonged primary ischemia or no on-line MD

Table 4 ROC Analysis of the Sensitivity and Specificity of MD in Detecting Pedicle Thrombosis

Variable	Threshold Level	Sensitivity	Specificity	AUC
Lowest glucose (mmol/1) below	0.4	53%	100%	
	0.9	87%	90%	0.934
	2.7	100%	61%	
Highest lactate (mmol/1) over	5.7	100%	67%	
	9.3	93%	91%	0.956
	15.5	53%	100%	
Highest L/P over	28	100%	72%	
	67	93%	90%	0.945
	259	60%	97%	

AUC = area under the curve.

monitoring were excluded, the salvage rate would have been 92 percent. We detected eight partial necroses involving the adipose tissue or skin margins—five in normally perfused flaps and three after arterial insufficiency. Most of the partial necroses were minor and partially due to flap design. None of the venous thromboses caused partial necrosis. Since four flaps were lost, the ultimate success rate was 95 percent.

DISCUSSION

The study indicates that MD efficiently detects a failing microvascular flap, in many cases well before there are any visible signs. The method produces objective data and visualizes trends that are easier to interpret than subjective evaluation. Thus, the use of MD alleviates the stress caused by insecurity of clinical assessment through lack of experience, or the lack of uniformity of communication among everyone participating in the postoperative treatment of microsurgical patients.

The efficacy of flap monitoring by clinical signs relies only on the experience of the personnel executing the follow-up. A high flap survival can be expected in clinics with a high frequency of microsurgical tissue transfers, where the personnel are well-trained and experienced.[2,6] However, this is not the situation in all institutes. In a study of 194 flaps with clinical follow-up only, the final flap success rate was only 85 percent,[7] which is not acceptable.[16] An experienced surgeon can achieve a high rate of primary success, but it is not possible to totally avoid postoperative perfusion failure. Restoring the flow within 4 hr after thrombosis can save the flap,[4] but 4 hr is too much time if used in waiting for a surgeon to arrive at the hospital to confirm the diagnosis; then to arrange to gain access to the operating theater; and finally to restore perfusion in the flap, sometimes with a new design and a venous graft. This is the reason why many institutes have chosen to use a technical device to alert the staff as early as possible, if there are signs of vascular insufficiency. It has been reported that the rate of successful salvage after pedicle thrombosis can be increased significantly, up to 100 percent, using an implantable Doppler probe[4] or to 88 percent using a laser Doppler flowmeter.[9] Using MD in our series, we could achieve a higher salvage rate than previously was the case in our institute.

The signs of arterial insufficiency in a skin island usually appear soon after pedicle occlusion. However, sometimes the skin island is too small, pale, or pigmented to be reliably assessed by visual inspection. Clinical signs of venous congestion are often easier to interpret, but they may appear only during the later phases of venous obstruction. For example, one musculocutaneous flap in our series showed constantly decreasing MD glucose concentration 5 hr before the capillary reaction changed from normal to rapid (Fig. 3A). The muscular surface of a flap is difficult to assess even with some experience. Furthermore, if a flap is buried deep, as in the skull base or in pharyngeal reconstructions, there can be no observation of the tissue. As shown by Disa et al.,[6] none of the buried flaps was salvaged in cases of pedicle thrombosis, if only clinical monitoring was used. Buried flaps can be evaluated by using a Doppler flowprobe over the outflowing vein, by exteriorizing a part of the flap for visual follow-up, or by the use of other monitoring methods. In our experience, a long MD catheter such as CMA70 can be reliably used in all kinds of buried flaps.

Another benefit of MD is that despite different tissue components, general alarm limits can be provided for all flaps. The small differences we found in the metabolism of the subcutaneous fat and the muscle do not affect the interpretation of MD results. This is not the case with laser Doppler flow signals[9] or tissue oxygen partial pressure values.[12] Perfusion failure can be diagnosed via the observed trend of LDF or TiO_2 values, and good results can be achieved as long as the limits of these methods are understood and controlled. Similarly, if an alarming trend is seen in MD, the medical staff can prepare for possible reoperation well in advance The final decision is made by the attending microsurgeon based on the alarm levels and/or any clinical data

available. Naturally, individuality of flap biology and variation in the perfusional status may result in abnormal MD values. For example, in flaps with transient ischemia, such as in those due to an arterial spasm, there was a shallow and temporary decline of glucose. We suggest that these situations should be treated conservatively and monitored, unless the criteria for true tissue ischemia are met, as indicated by the three alarm levels. Hypothermia, anemia, hypovolemia, and hypotension should be corrected before any reoperation. If the pedicle has remained patent, MD values should normalize soon after the restoration of optimal system perfusion.

It is obvious that an MD catheter must be inserted into a well-perfused part of the flap. Any component of the soft tissue is useful except the fascia. We have no experience with bony tissue, but osseous flaps often carry a soft-tissue component that can be used for catheter implantation. One should avoid the peripheral or manipulated part of the flap when inserting the probe. A dislocation of the probe out of the tissue may result in suboptimal MD values, since the probe will then not be in contact with the extracellular space. In superficial flaps, catheter dislocation is easily noted and corrected at the bedside by reinsertion, but in deep tissues, it is essential that the catheter is intraoperatively well secured to the tissue. Good values in MD provide an assurance of proper perfusion of the flap and of correct technique of the monitoring. The trauma induced by an MD catheter is comparable to that of a small intravenous cannula, and we did not observe any local complications in our study. However, the catheter is fragile and, in our experience, there is a learning curve in the insertion technique. A broken catheter will not provide any microdialysate samples, or the sample may be bloody, preventing its analysis. The catheter will not give samples before it is properly wet, which may take some hours. Repeated flushing of the system and immersion in perfusion fluid before insertion are helpful. We usually begin to prepare the catheter at the same time as we begin flap elevation.

The MD method does create some extra costs due to the catheter (about 200 €), reagents (120 €, useful for 5 days), and an analyzer (20,000 to 40,000 €). A set of reagents can be shared by several patients. The cost-effectiveness of the method depends on the number of flaps that can be saved with better monitoring: if the clinical diagnosis of perfusion failure is often delayed, and thus the salvage rate is poor, a method providing for early and reliable diagnoses would aid in early intervention and salvage of the compromised flaps. Consequently, this would lead to a decrease in the need for secondary flap reconstruction, fewer amputations, and lower patient morbidity, factors which cannot be measured in money.

In conclusion, we found microdialysis to be suitable for clinical use in any unit where flaps require monitoring. It is a sensitive and specific method for detecting perfusion failure, and we were able to ensure that the follow-up was simple and safe by setting easy rules and alarm limits. Despite some technical demands, we consider that MD represents a valuable aid in the postoperative monitoring of microsurgical flaps.

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