

Skeletal muscle P_{O_2} during imminent shock

G. I. J. M. BEERTHUIZEN¹, R. J. A. GORIS¹, & F. J. A. KREUZER²

¹*Department of General Surgery, University Hospital and* ²*Department of Physiology, Medical School, Nijmegen, The Netherlands*

INTRODUCTION

Circulatory shock remains a frequent, acute life-threatening condition with a high mortality, despite intensive treatment. Shock is often detected late, because circulatory disturbances in shock are clinically visible only to a limited extent. Clinical features, such as pallor, an increased pulse rate and, when detected, oliguria or anuria are barely specific. The diagnosis is usually made when there is a significant and persistent fall in the arterial blood pressure along with evidence of decreased tissue perfusion.

The aim of the circulation is to deliver an adequate volume of oxygen at an adequate partial pressure to replace the oxygen used at the terminal oxidase of the respiratory chain in the mitochondria. This oxygen supply is vital, as 95% of the energy generated by the body normally originates from aerobic pathways, and as the entire oxygen store of the body would support resting needs for maximally 5 min (Kreuzer & Cain, 1985). Thus, inadequate tissue perfusion and impaired tissue oxygenation, possibly from maldistribution of the blood flow, are the common denominators of shock (Hardaway, 1969; Shoemaker, 1971, 1973; Shoemaker *et al.*, 1971a,b, 1973; Bryan-Brown, 1978; Wilson, 1980; Hardaquay, 1981). However, direct measurement of tissue perfusion and/or oxygenation is still difficult.

Until now only systemic parameters such as arterial blood pressure, central venous pressure, pulmonary arterial blood pressure and cardiac output have been monitored. In shock these parameters are corrected meticulously, but the therapeutic interventions may actually impair tissue perfusion and tissue oxygenation. Attaining normal haemodynamic values may thus not be the optimal goal of treatment, since the compensatory bodily responses to stress also produce departures from the normal haemodynamic values (Shoemaker & Czer, 1979).

Direct monitoring of tissue perfusion and/or tissue oxygenation may thus provide a more sensitive method for the early detection of shock and for guiding treatment. But at the present time no clinically applicable method is available to measure tissue oxygena-

tion directly. Experimental and clinical studies were performed to establish the validity of skeletal muscle PO_2 assessment as a parameter of tissue oxygenation.

Skeletal muscle PO_2

Skeletal muscle PO_2 depends upon the balance between the rate of oxygen delivery to tissue and rate of oxygen consumption by tissue (Snyder & Carroll, 1982). Each of these in turn depends upon a complex series of interrelated factors. Oxygen delivery to muscle depends on blood flow to the muscle, which in turn depends on cardiac output and its distribution to different organs, and on the oxygen content of the blood. Oxygen content of the blood depends on arterial PO_2 , arterial SO_2 and haemoglobin concentration. The arterial PO_2 depends on the alveolar PO_2 , ventilation/perfusion ratio and pulmonary diffusing capacity. The alveolar PO_2 depends on FIO_2 and alveolar ventilation. Oxygen delivery within the muscle depends on the condition of the microcirculation. Significant elements of capillary behaviour are the number of open capillaries, the presence of non-capillary pathways from artery to vein (shunts) and the range of variation in type, length and flow pattern of the capillary bed (heterogeneity) (Duling, 1980). Perfusion heterogeneity may be present even under physiological conditions (Duling, 1980). Greater than normal heterogeneity in flow or its distribution in the peripheral microcirculation has the inevitable consequence of making tissue hypoxic (Shoemaker & Reinhard, 1973). The final determinant of skeletal muscle oxygen tension is the rate at which oxygen leaves the capillary blood and the diffusion of oxygen through the tissue (Grunewald, 1968). The rate at which oxygen leaves the blood is a function of oxyhaemoglobin dissociation curve (related to temperature, pH, carbon dioxide tension and 2, 3-DPG concentration), the time required by the haemoglobin to release the oxygen (Gutierrez, 1986) and the oxygen solubility in the plasma. Skeletal muscle oxygen tension is not solely dependent upon the rate of oxygen delivery to the tissue, but also depends upon the rate of oxygen consumption by the tissue. If oxygen delivery increases but oxygen consumption increases even more, then tissue oxygen tension decreases (Table 1).

Skeletal muscle PO_2 and shock

Correction of cardiac output and arterial oxygen tension in haemorrhagic shock does not necessarily ensure normal tissue oxygenation (Niinikoski & Halkola, 1978). Adequacy of tissue oxygenation cannot be predicted solely from measurement of arterial PO_2 since normal values may be associated with inadequate tissue oxygen supply (Kessler *et al.*, 1976). Measurement of mixed venous PO_2 also does not reliably reflect adequacy of tissue perfusion, as in sepsis mixed venous PO_2 and SO_2 may be elevated due to inadequate oxygen extraction in the microcirculation (Miller, 1982; Orlando 1986). In this situation oxygen consumption is subnormal and, despite increased arterial oxygen transport, signs of anaerobic metabolism and tissue hypoxia may be present (Danek *et al.*, 1980).

Monitoring PO_2 in the tissue may allow early detection of a disturbance in tissue oxygenation and may indicate how far the various compensatory mechanisms have been mobilized. Experience with techniques for measuring tissue PO_2 and PCO_2 levels suggests that the measurement of skeletal muscle gas tensions may provide an index of

Table 1 Determinants of tissue oxygen pressure*Rate of delivery of oxygen to tissue:*

- (1) Amount of oxygen in arterial blood:
 - Oxygen tension in inspired air
 - Alveolar ventilation
 - Alveolar oxygen partial pressure
 - Ventilation/perfusion ratio
 - Pulmonary diffusing capacity
 - Solubility of oxygen in plasma
 - Amount of hemoglobin
 - Arterial oxygen saturation
 - Arterial oxygen partial pressure
- (2) Delivery of arterial blood to tissues:
 - Cardiac output
 - Arterial blood pressure
- (3) The microcirculation:
 - Blood viscosity
 - Red blood cell size
 - Adherence of cellular blood components
 - Arterio-venous shunts
 - Number of open capillaries
 - Capillary radius
 - Capillary flow
 - Capillary oxygen content
 - Intercapillary distance
- (4) Rate at which oxygen leaves the blood:
 - Affinity of oxygen for haemoglobin
 - Rate of dissociation of oxygen from haemoglobin
 - Oxygen solubility in plasma

Rate of transport of oxygen in tissue:

Krogh's oxygen diffusion coefficient
 Difference in oxygen partial pressure
 Diffusion distance

Rate of consumption of oxygen by tissue as influenced by:

Work

Drugs

Hormones:

Epinephrine

Corticosteroids

Thyroxine

Insulin

Temperature of the tissue

peripheral tissue perfusion (Kessler *et al.*, 1970; Rosenbaum *et al.*, 1972; Furuse *et al.*, 1973; Kessler *et al.*, 1973; Lang *et al.*, 1973; Brantigan *et al.*, 1974; Wakabayashi *et al.*, 1975; Kessler *et al.*, 1976; Niinikoski & Halkola, 1978).

Tissue oxygen pressure measurements indicate the net result of the simultaneous changes occurring in the factors mentioned above and listed in Table 1. However, they provide no information as to the cause of such changes (Greene, 1966).

Skeletal muscle PO₂ assessment

Since there is an oxygen partial pressure field within any tissue, no single value of tissue oxygen partial pressure is representative (Kreuzer *et al.*, 1980). The measured oxygen profile is the result of the interference of the diffusion field induced by the electrode with the oxygen field of the muscular tissue. A single measurement is not sufficient and *PO₂* values at different places in the tissue have to be obtained (Lubbers, 1969, 1980; Baumgartl, 1983). The *PO₂* data are best represented as an oxygen distribution curve (Lubbers, 1969). A carefully prepared sensor, a stable polarization voltage, no leaking currents, suitable electrical shielding, and stable and sensitive amplifiers are necessary (Baumgartl, 1983).

In Nijmegen a recessed polarographic needle electrode was developed. Skeletal muscle *PO₂* was assessed in the quadriceps femoris muscle using a polarographic needle electrode. The electrode was calibrated before the measurement and positioned in the vastus lateralis of the quadriceps femoris muscle approximately 3–4 cm deep, using a 20-gauge needle as a guiding cannula. The electrode was withdrawn stepwise and after each step of 200 μm a *PO₂* value was measured. In this way 100 *PO₂* values from 100 different places in the skeletal muscle were obtained. From these 100 *PO₂* values the median, representing the skeletal muscle *PO₂* assessment, was calculated. At the end of each skeletal muscle *PO₂* assessment the electrode was withdrawn. One complete skeletal muscle *PO₂* assessment took 5 min. The skeletal muscle *PO₂* assessments in 31 healthy humans showed a mean of 4.2 kPa and a standard deviation of 1.8 kPa.

EXPERIMENTAL STUDIES

Mass spectrometry and tonometry with an implanted silicone rubber tube have shown that during periods of experimentally induced low cardiac output, tissue *PO₂* decreased virtually proportionally to decreases in cardiac output (Niinikoski, 1977). In haemorrhagic shock, *PO₂* in the gracilis muscle, recorded continuously by means of a platinum multiwire surface electrode according to the technique of Kessler & Grunewald (1969), decreased very early during the period of decreasing blood pressure (Sinagowitz, 1973).

We have shown that in experimental haemorrhagic shock skeletal muscle *PO₂*, measured with a recessed needle electrode, decreased early during haemorrhage before arterial blood pressure dropped (van der Kley *et al.*, 1983) (Figure 1).

In experimental septic shock we found a 52% reduction in skeletal muscle *PO₂* within 30 min after the start of an *E. Coli* infusion, while arterial blood pressure was unchanged (van der Kley, 1983; Goris *et al.*, 1984) (Figure 2). The early decline of skeletal muscle *PO₂* found during the onset of *E. Coli* sepsis may have been caused by a decrease in blood flow to the skeletal muscle due to a decrease in cardiac output, or by redistribution of blood flow in favour of other organs. We studied the relationship between cardiac output and blood flow to skeletal muscle, liver, kidney and intestines during the onset of septic shock. After the onset of *E. Coli* infusion marked changes occurred in the blood flow to several organs. After the start of the *E. Coli* infusion the reduction of blood flow to skeletal muscle corresponded with the fall in systolic arterial blood pressure. The decline of blood flow to the skeletal muscle could only partially explain

the early reduction of skeletal muscle PO_2 . Thus during *E. Coli* septic shock redistribution of blood flow to the vital organs occurred at the cost of the blood flow to skeletal muscle.

During the first 5 min after the start of the *E. Coli* infusion the oxygen availability to the hindlimb decreased by 18%. At this time the oxygen consumption of the hindlimb was not altered, the oxygen extraction of the hindlimb increased by 32%, femoral venous PO_2 decreased by 31% and skeletal muscle PO_2 decreased by 52%. The magnitude of these changes and the time relationship provide no satisfactory explanation for the fall in skeletal muscle PO_2 . The early decline of skeletal muscle PO_2 during the start of the *E. Coli* infusion is not caused by an increased affinity of haemoglobin for oxygen, nor by an increase of oxygen consumption nor by a decreased arterial oxygen content. A reduction in diffusing capacity for oxygen in the skeletal muscle tissue and changes in other determinants of skeletal muscle tissue PO_2 , as described before and listed in Table 1, might be important factors in the decrease of skeletal muscle PO_2 .

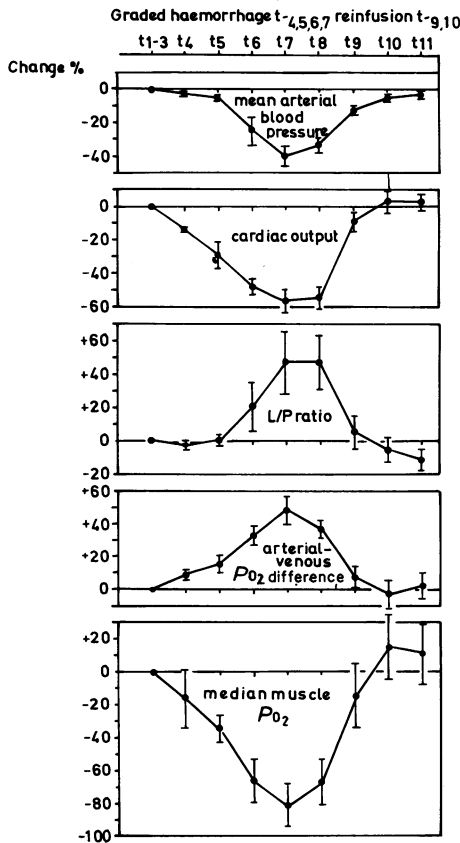


Fig. 1 Haemodynamics and skeletal muscle PO_2 during graded haemorrhage.

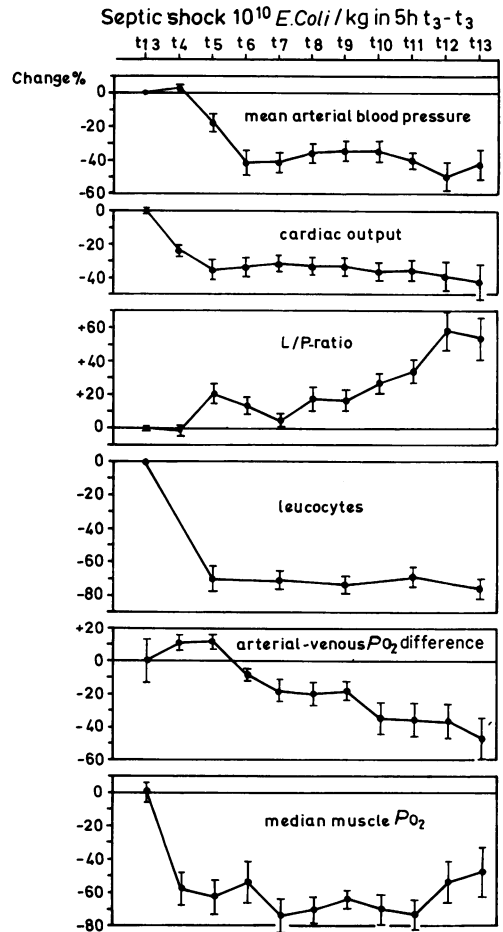


Fig. 2 Haemodynamics and skeletal muscle PO_2 during experimental *E. Coli* sepsis.

CLINICAL STUDIES

Burn shock

In the treatment of burn shock, hourly urinary output and arterial blood pressure have been considered the most important indices of the effectiveness of therapy (Moncrief 1966; Christopher, 1980). Maintenance of optimal tissue perfusion in these patients is essential for survival as well as to prevent morbidity (Christopher, 1980; Pruitt, 1981; Aikawa *et al.*, 1982).

Large amounts of infusion fluids are needed to resuscitate severely burned patients. The rate of infusion must be regularly adjusted in each patient. Hourly urinary output is commonly used as parameter for fluid therapy (Christopher, 1980; Cuono, 1980) although its accuracy has been disputed by several authors (Christopher, 1980; Cuono, 1980; Caldwell, 1981; Agarwal *et al.*, 1983). In fact urinary output is related not only to tissue perfusion but also to serum osmolality (Caldwell, 1979). The use of a Swan-Ganz catheter has been advocated to determine cardiac output as a more accurate estimate of the circulation than hourly urinary output (Agarwal *et al.*, 1983). But Swan-Ganz catheterization is not without risk and produces complications in 21% of cases (Aikawa *et al.*, 1978).

Skeletal muscle *Po₂* was studied as a parameter of tissue perfusion in 13 patients suffering from burns of more than 25% body surface area. After 6, 8, 10, 14, 18, 24, 30, 36 and 48 h routine clinical measurements were performed. Skeletal muscle *Po₂* was measured in the quadriceps femoris muscle using a polarographic needle electrode. The relationship between skeletal muscle *Po₂* and subsequent resuscitation problems was studied. These problems were defined as a urinary output <0.5 cc kg h and/or a systolic arterial blood pressure <90 mm Hg.

Urinary output below 0.5 ml kg⁻¹ h⁻¹ occurred in patients with low as well as high skeletal muscle *Po₂* values. Skeletal muscle *Po₂* preceding urinary output problems did not differ significantly from skeletal muscle *Po₂* prior to periods without urinary output problems. In patients with clinical shock, the skeletal muscle *Po₂* (the median of all the skeletal muscle *Po₂* assessments obtained in the patient) was significantly lower than the skeletal muscle *Po₂* level in patients without clinical shock. Skeletal muscle *Po₂* preceding clinical shock was significantly lower than skeletal muscle *Po₂* prior to periods without clinical shock ($P=0.01$). If skeletal muscle *Po₂* was above 2.5 kPa no hypotension occurred in the subsequent period of 2–6 h until the next skeletal muscle *Po₂* assessment.

Skeletal muscle *Po₂* decreased before hypotension occurred and enabled early detection of impairment of the circulation before arterial blood pressure dropped below 90 mm Hg. Skeletal muscle *Po₂* significantly increased during the period of investigation and was significantly higher 24–30 h postburn as compared with 6–24 h postburn. These results are in agreement with low cardiac output and elevated systemic vascular resistance as found by others during the first 24 h postburn (Shoemaker *et al.*, 1973; Aikawa *et al.*, 1978; Caldwell, 1979). As burn shock develops gradually, intermittent skeletal muscle *Po₂* assessment enables early detection of imminent shock and might also be used to evaluate the effectiveness of shock therapy.

Critically ill patients

Oxygen is the most flow limited of all substances necessary for metabolism (Gump *et al.*, 1970). The oxygen transport system is thus of vital importance for the integrity of cellular metabolism, but one or more of the several components of the oxygen transport system may function abnormally in critical illness. Critically ill patients were studied to establish whether skeletal muscle PO_2 assessment could detect developing shock at an early stage and whether skeletal muscle PO_2 assessment could predict the risk of shock during a period after the skeletal muscle PO_2 assessment. Measurements were performed according to a fixed protocol. Skeletal muscle PO_2 was assessed in the quadriceps femoris muscle using a polarographic needle electrode. All measurements were performed on entry into the study and repeated 2, 4, 6, 8 and 16 h later. The dose of inotropes administered was recorded. For each period, the presence of shock was registered. In some patients shock occurred when inotropic drugs were not administered, in other patients inotropic drug treatment was already instituted. In this study no shock occurred during the study period if skeletal muscle PO_2 was normal (> 4.2 kPa, mean value for healthy humans). During the study period significantly more patients had one or more periods of shock when at least one of the values was less than 2.0 kPa ($P=0.007$). Significantly fewer patients had one or more periods of shock if their skeletal muscle PO_2 was at least once above 4.0 kPa ($P=0.015$). If skeletal muscle PO_2 was below 3.0 kPa, shock was found significantly more often than if the skeletal muscle PO_2 was above 3.0 kPa ($P<0.01$). If the skeletal muscle PO_2 was below 3.0 kPa the risk of shock was 2.3 times higher than if skeletal muscle PO_2 was above 3.0 kPa. The predictive value of the median skeletal muscle PO_2 assessment in patients not using inotropic agents was even better ($P<0.001$). If, in those patients not receiving inotropes, skeletal muscle PO_2 was below 3.0 kPa, a positive shock score occurred in 73% of the assessments during the subsequent period of 2 h, and a positive shock score always occurred in the period of 4 h before and 6 h after the skeletal muscle PO_2 assessment. These results demonstrate that, in critically ill patients, skeletal muscle oxygenation is decreased before clinical shock occurs.

In patients using inotropes the skeletal muscle PO_2 assessment was not predictive when using the 3.0 kPa limit ($P>0.2$). These findings confirm that inotropes such as dopamine, dobutamine or epinephrine may maintain arterial blood pressure by increasing systemic vascular resistance at the cost of peripheral tissue perfusion. However, the use of inotropes impaired skeletal muscle oxygenation as the mean of the skeletal muscle PO_2 was below 3.0 kPa in 9 out of 10 patients receiving inotropes. In these patients treated with inotropes, shock defined as inadequate tissue oxygenation occurred, but clinical shock as defined by low arterial blood pressure did not occur in four patients.

The early decrease of tissue perfusion in critically ill patients has also been demonstrated by techniques more extensive and invasive than skeletal muscle PO_2 assessment. Skeletal muscle PO_2 was monitored with a multiwire surface electrode in 55 patients and low values were found to correlate with a low circulatory blood volume (Schonleben *et al.*, 1978). In another study oxygen partial pressure was measured by using an implanted Silastic catheter in the subcutaneous tissue of the arm in 33 post-operative patients on the day of the operation and the first five post-operative days. Tissue hypoxia was a common finding and was most pronounced immediately after

abdominal, vascular and cardiac operations. A supplemental bolus of infusion fluid increased low tissue PO_2 in all of 19 measurements, implicating hypovolaemia as a common cause of post-operative tissue hypoxia (Chang *et al.*, 1983). Tissue PO_2 measurements were also performed by continuous *in vivo* measurements with a mass spectrometer in the deltoid muscle of nine patients in shock after severe trauma (Rosenbaum *et al.*, 1972). Tissue PO_2 values were lower post-operatively (2.7 kPa) despite the maintenance of PaO_2 above 13 kPa. In shock low tissue PO_2 levels were found (2.0 kPa) (Rosenbaum *et al.*, 1972).

Further studies are necessary to assess whether keeping skeletal muscle PO_2 above 4.0 kPa during all periods of the illness may result in a lower morbidity and mortality of patients at risk.

In conclusion, in critically ill patients skeletal muscle PO_2 assessment estimates the severity of shock and is able to predict the risk of shock, provided no inotropes are given.

Skeletal muscle PO_2 haemodynamics and oxygen related parameters

We studied the relationship between skeletal muscle PO_2 haemodynamics and oxygen related parameters in critically ill patients. A significant within patient correlation was found between the skeletal muscle PO_2 and arterial SO_2 , mixed venous SO_2 and arterio-venous oxygen difference, parameters which most closely reflect the balance between oxygen supply and oxygen consumption. This supports the value of the skeletal muscle PO_2 assessment in determining the balance between oxygen supply and oxygen consumption in skeletal muscle tissue in critically ill patients. If skeletal muscle PO_2 is decreased in critically ill patients, the measurement of haemodynamics, especially the oxygen related parameters such as oxygen extraction, reveal the cause of a decreased skeletal muscle PO_2 .

Skeletal muscle PO_2 and multiple organ failure

Multiple organ failure (MOF) is presently one of the leading causes of death in critically ill patients. Mortality is high (59–74%) (Eiseman *et al.*, 1977; Fry *et al.*, 1980; Goris *et al.*, 1985) despite intensive care treatment. The causative factors remain poorly understood (Fry *et al.*, 1980; Goris *et al.*, 1985), but severe infection, severe metabolic injury, shock, microemboli, complement activation and massive blood replacement have been suggested as initiating factors (Eiseman *et al.*, 1977; Fry *et al.*, 1980; Cerra, 1985; Goris *et al.*, 1985; Nuytinck, 1985). In these patients regional hypoxia has been suggested to contribute to multiple organ failure (Danek *et al.*, 1980; Cerra, 1985; Goris *et al.*, 1985) and tissue perfusion probably is an important factor for survival (Shoemaker & Czer, 1979; Groeneveld, 1986). There is at present no study available on tissue PO_2 in MOF patients; we therefore studied the relationship between skeletal muscle PO_2 and the incidence and severity of multiple organ failure. From each patient a multiple organ failure score (MOF score) was calculated (Goris *et al.*, 1985). This score measures the severity of organ failure in three gradings and seven organ systems. If the mean skeletal muscle PO_2 was below 2.0 kPa, significantly more severe multiple organ failure occurred (MOF score > 5). The patients with a MOF score above five had a mean

skeletal muscle PO_2 of $2.4 \text{ kPa} \pm 1.8 \text{ SD}$, whereas the patients with a MOF score of five or less had a mean skeletal muscle PO_2 of $3.6 \text{ kPa} \pm 1.4 \text{ SD}$. These findings suggest that regional hypoxia is related to multiple organ failure.

CONCLUSIONS

Measuring skeletal muscle PO_2 , as described in this article, is a valuable method to assess skeletal muscle oxygenation. Skeletal muscle PO_2 assessment enables to monitor patients at risk, to detect imminent shock, to assess the severity of shock and to evaluate the effects of therapy in a wide variety of experimental and clinical conditions. The consistent finding in all experimental and clinical studies of septic shock performed by others and by us, that tissue PO_2 decreases before cardiorespiratory parameters deteriorate, strongly suggests that the initiating event of septic shock is not a decreased oxygen supply to the tissue, but rather a disturbance in the microcirculation, possible maldistribution of blood flow and/or impaired diffusion of oxygen to the mitochondria.

REFERENCES

- Agarwal N., Petro J. & Salisbury R. E. (1983) Physiologic profile monitoring in burned patients. *Journal of Trauma* **23**, 577–83.
- Aikawa N., Ishibiki K., Naito C. & Abe O. (1982) Individualized fluid resuscitation based on haemodynamic monitoring in the management of extensive burns. *Burns* **8**, 249–55.
- Aikawa N., Martyn J. A. J. & Burke J. F. (1978) Pulmonary artery catheterization and thermodilution cardiac output determination in the management of critically burned patients. *American Journal of Surgery* **135**, 811–7.
- Baumgartl H. & Lubbers D. W. (1983) Microaxial needle sensor for polarographic measurement of local O_2 pressure in the cellular range of living tissue. Its construction and properties. In: *Polarographic Oxygen Sensors*. Gnaiger E. & Forstner H. (Eds) pp 37–65, Springer Verlag, Berlin, Heidelberg.
- Brantigan J. W., Ziegler E. C., Hynes K. M., Miyarawa T. Y. & Smith A. M. (1974) Tissue gasses during hypovolaemic shock. *Journal of Applied Physiology* **37**, 117–22.
- Bryan-Brown C. W. (1977) Wrecking the machinery (Editorial). *Critical Care Medicine* **5**, 163–4.
- Caldwell F. T. (1979) Hypertonic versus hypotonic resuscitation. *Journal of Trauma* **19**, 374.
- Caldwell F. T. (1981) Hypertonic saline. *Journal of Trauma* **21**, 693–4.
- Cerra F. B. (1985) The systemic septic response: multiple systems organ failure. *Intensive Care Medicine* **1**, 591–607.
- Chang N., Goodson W. H., Gottrup F. & Hunt H. K. (1983) Direct measurement of wound and tissue oxygen tension in post-operative patients. *Annals of Surgery* **197**, 470–8.
- Christopher K. C. (1980) The use of a model for haemodynamic balance to describe burn shock. *Nursing Clinics of North America* **15**, 617–27.
- Cuono C. B. (1980) Early management of severe thermal injury. *Surgical Clinics of North America* **60**, 1021–33.
- Danek S. J., Lynch J. P., Weg J. G. & Dantzker D. R. (1980) The dependence of oxygen uptake on oxygen delivery in the adult respiratory distress syndrome. *American Review of Respiratory Disease* **122**, 387–95.
- Duling B. R. (1980) Local control of microvascular function: role in tissue oxygen supply. *Annual Review of Physiology* **42**, 373–82.
- Eiseman B., Beart R. & Norton L. (1977) Multiple organ failure. *Surgery, Gynecology and Obstetrics* **144**, 323–6.

- Fry D. E., Pearlstein L., Fulton R. L. & Polk H. C. (1980) Multiple system organ failure. *Archives of Surgery* **115**, 136–40.
- Furuse A., Brawley R. K., Struve E. & Gott V. L. (1973) Skeletal muscle gas tension: indicator of cardiac output and peripheral tissue perfusion. *Surgery* **74**, 214–22.
- Goris R. J. A., Boekhorst te Th. P. A., Nuytink J. K. S. & Gimbriere J. S. F. (1985) Multiple organ failure. Generalized autodestructive inflammation? *Archives of Surgery* **120**, 1109–15.
- Goris R. J. A., Kleij van der A. J., Beerthuisen G., Kreuzer F. J. A., Kimmich H. P. & Koning de J. (1984) Early detection of *E. Coli* sepsis by muscle PO_2 assessment. *Bulletin and Clinical Review of Burn Injuries* **1**, 17–19.
- Greene N. M. (1966) Tissue oxygen tension in the anaesthetized patient. *Archives of Surgery* **92**, 164–77.
- Groeneveld A. B. J., Bronsveld W. & Thijs L. G. (1986) Haemodynamic determinants of mortality in human septic shock. *Surgery* **99**, 140–53.
- Grunewald W. (1968) Theoretical analysis of the oxygen supply in tissue. In: *Oxygen Transport in Blood and Tissue*. Lubbers D. W., Luft U. C., Thews G. & Witzleb E. (Eds) pp. 100–14, Georg Thieme Verlag, Stuttgart.
- Gump F. E., Kinney J. M. & Price J. B. (1970) Energy metabolism in surgical patients: oxygen consumption and blood flow. *Journal of Surgical Research* **10**, 613–27.
- Gutierrez G. (1986) The rate of oxygen release and its effect on capillary O_2 tension: a mathematical analysis. *Respiration Physiology* **63**, 79–96.
- Hardaway R. M. (1981) Prediction of survival or death of patients in a state of severe shock. *Surgery, Gynecology & Obstetrics* **152**, 200–6.
- Hardaway R. M. (1969) Clinical management of shock. *Military Medicine* **134**, 643–54.
- Kessler M., Gornandt L., Thermann M., Lang H., Brand K. & Wessel W. (1973) Oxygen supply and microcirculation of liver in haemorrhagic shock. In: *Oxygen Supply, Theoretical and Practical Aspects of Oxygen Supply and Microcirculation of Tissue*. Kessler M., Bruley D. F., Clark L. C. Jr., Lubbers D. W., Silver I. A. & Strauss J. Urban & Schwarzenberg, pp. 252–5, Munchen–Berlin–Wien.
- Kessler M. & Grunewald W. (1969) Possibilities of measuring oxygen pressure fields in tissue by multiwire platinum electrodes. *Progress in Respiratory Research* **3**, 147–52.
- Kessler M., Hoper J. & Krumme B. A. (1976) Monitoring of tissue perfusion and cellular function. *Anesthesiology* **45**, 184–97.
- Kessler M., Thermann M., Lang H., Hartel W. & Schneider H. (1970) O_2 -versorgung lebenswichtiger Organe im Shock mit besonderer Berücksichtigung der Leber. In: *Shock, Stoffwechselveränderungen und Therapie*, Zimmermann W. E. & Staub I. (Eds) pp. 117–31, Schattauer, Stuttgart–New York.
- Kleij van der A. J., Koning de J., Beerthuisen G., Goris R. J. A., Kreuzer F. & Kimmich H. P. (1983) Early detection of haemorrhagic hypovolaemia by muscle oxygen pressure assessment: preliminary report. *Surgery* **93**, 518–24.
- Kleij van der A. J. (1983) Skeletal muscle PO_2 in shock (Thesis). Nijmegen.
- Kreuzer F., Cain S. M. (1985) Regulation of the peripheral vasculature and tissue oxygenation in health and disease. *Critical Care Medicine* **1**, 453–70.
- Kreuzer F., Kimmich H. P. & Brezina M. (1980) Polarographic determination of oxygen in biological materials. In: *Medical and Biological Applications of Electrochemical Devices*. Koryta J. (Ed.) pp. 173–261, John Wiley, New York.
- Lang H., Kessler M. & Starlinger H. (1973) Signs of hypoxia measured by means of PO_2 -multiwire electrodes by NADH and NADPH fluorescence and determination of lactate and pyruvate formation. In: *Oxygen Supply, Theoretical and Practical Aspects of Oxygen Supply and Microcirculation of Tissue*. Kessler M., Bruley D. F., Clark L. C. Jr., Lubbers D. W., Silver I. A. & Strauss J. (Eds). Urban & Schwarzenberg, pp. 193–198, Munchen–Berlin–Wien.
- Lubbers D. W. (1969) The meaning of the tissue oxygen distribution curve and its measurement by means of Pt electrodes. *Progression Respiration and Resuscitation* **3**, 112–23.
- Lubbers D. W. (1980) Determinants of tissue PO_2 and the PO_2 histogram. *Arzneimittel-Forschung/Drug Research* **30**, 2204.
- Miller M. J. (1982) Tissue oxygenation in clinical medicine: an historical review. *Anesthesia and Analgesia* **61**, 527–35.
- Moncrief J. A. (1966) Effect of various fluid regimens and pharmacologic agents on the circulatory haemodynamics of the immediate post-burn period. *Annals of Surgery* **164**, 723–50.

- Niinikoski J. (1977) Tissue oxygenation in hypovolaemic shock. *Annals of Clinical Research* **9** 151–6.
- Niinikoski J. & Halkola L. (1978) Skeletal muscle P_{O_2} : indicator of peripheral tissue perfusion in haemorrhagic shock. *Advances in Experimental Medicine and Biology* **94**, 585–92.
- Nuytincq J. K. S. (1985) The adult respiratory distress syndrome and multiple organ failure (Thesis). Nijmegen.
- Orlando R. (1986) Continuous mixed venous oximetry in critically ill surgical patients *Archives of Surgery* **121**, 470–1.
- Pruitt B. A. (1981) Fluid resuscitation for extensively burned patients. *Journal of Trauma* **21** (suppl.) 690–2.
- Rosenbaum R., Hayes M. F., Wolferth C. C., Frajola R., Jones N. & Matsumoto T. (1972) On line *in vivo* measurement of tissue and blood gases in patients with severe trauma. *Surgery, Gynecology and Obstetrics* **135**, 605–7.
- Schonleben K., Hauss J. P., Spiegel U., Bunte H. & Kessler M. (1978) Monitoring of tissue P_{O_2} in patients during intensive care. *Advances in Experimental Medical Biology* **94**, 593–8.
- Shoemaker W. C. (1971) Cardiorespiratory patterns in complicated and uncomplicated septic shock: physiological alterations and their therapeutic implications. *Annals of Surgery* **172**, 119–25.
- Shoemaker W. C. (1973) Pathophysiologic basis of therapy for shock and trauma syndromes. *Semin Drug Test* **3**, 211–29.
- Shoemaker W. C., Boyd D. R., Corley R. S., Reinhard J. M. & Dreiling D. A. (1971) Sequential haemodynamic events after trauma to the unanesthetized patient. *Surgery, Gynecology & Obstetrics* **132**, 651–6.
- Shoemaker W. C., Boyd D. R., Kim S. I., Brown R. S., Dreiling D. A. & Kark A. E. (1971) Sequential oxygen transport and acid-base changes after trauma to the unanaesthetized patient. *Surgery, Gynecology & Obstetrics* **132**, 1033–8.
- Shoemaker W. C. & Czer L. S. C. (1979) Evaluation of the biologic importance of various haemodynamic and oxygen transport variables: which variables should be monitored in post-operative shock? *Critical Care Medicine* **7**, 424–431.
- Shoemaker W. C., Montgomery E. C., Kaplan E. & Elwyn D. H. (1973) Physiologic patterns in surviving and non-surviving shock patients. *Archives of Surgery* **106**, 630–6.
- Shoemaker W. C. & Reinhard J. M. (1973) Tissue perfusion defects in shock and trauma states. *Surgery, Gynecology & Obstetrics* **137**, 980–6.
- Shoemaker W. C., Vladeck, B. C., Bassin R., Printer K., Brown R. S., Amato J. J., Reinhard J. M. & Kark A. E. (1983) Burn pathophysiology in man. 1. Sequential haemodynamic alterations. *Journal of Surgical Research* **14**, 64–73.
- Sinagowitz E., Rahmer H., Rink R., Gornandt L. & Kessler M. (1973) Local oxygen supply in intra-abdominal organs and in skeletal muscle during haemorrhagic shock. *Advances in Experimental Medical Biology* **37A**, 505–11.
- Snyder J. V., Carroll G. C. (1982) Tissue oxygenation: a physiologic approach to a clinical problem. *Current Problems in Surgery* **19**, 650–719.
- Wakabayashi A., Nakamura Y., Woolley T., Mullin P. J., Watanabe H., Takashi I. & Connolly D. E. (1975) Continuous percutaneous monitoring of muscle pH and oxygen pressure: a new technique for *in vivo* use. *Archives of Surgery* **110**, 802–4.
- Wilson R. F. (1980) The pathophysiology of shock. *Intensive Care Medicine* **6**, 89–100.