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Extracorporeal treatment of acute renal failure in the intensive care unit: a critical view

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Abstract. Acute renal failure in critically ill patients is seldom an isolated problem but is more usually associated with multiple organ failure. When choosing an extracoporeal kidney replacement therapy, these other failing organs must be taken into account. Therefore the choice of an artificial kidney in patients requiring intensive care depends on both the efficacy of the technique and its possible adverse effects on cerebral, pulmonary and cardiovascular function. The most important pathogenic factors in the development of dysequilibrium syndromes, arterial hypoxemia and hypotension are treatment timing, diffusive solute transfer, bio-incompatible membranes and some specific dialysate components (buffer, electrolyte concentrations). It is important to understand the mechanisms by which these factors exert their adverse effects. Application of these pathophysiological mechanisms to the cardiopulmonary and neurologic status of the individual patient permits the prediction of their clinical outcome. This approach will lead to individualised treatment selection, thereby avoiding deleterious side-effects without loss of efficacy.

Key words: Acute renal failure – Artificial kidney – Dysequilibrium syndrome – Dialysis induced hypoxemia – Dialysis induced hypotension

The mortality rate of acute renal failure in critically ill patients remains strikingly high. This is mainly attributable to the severity of their underlying disease. In these patients, acute renal failure is seldom an isolated problem but is mostly a part of multiple organ failure and therefore frequently associated with respiratory failure, hemodynamic instability and neurological problems.

When choosing an extracorporeal treatment for acute renal failure, the physician must select an efficient "artificial kidney" but at the same time he has to ensure that the morbidity of the procedure does not add to the already high morbidity of the underlying disease, taking into account the other failing organ systems. The purpose of this article is:

- to give an overview of the various forms of extracorporeal treatment available today;
- to compare their efficiency as an "artificial kidney" and
- to analyse their neurological, pulmonary and hemodynamic side-effects.

This will lead to some guidelines for treatment selection adapted to the individual patient's condition.

Overview of the available forms of extracorporeal treatment

A variety of extracorporeal kidney replacement therapies are available today. They differ from each other with regard to seven aspects.

1. The physical principle used for solute transfer. Hemodialysis [40] uses diffusion through a semi-permeable membrane down a concentration gradient. Removal of fluid is achieved by ultrafiltration, where the driving force is a hydrostatic pressure gradient. This ultrafiltration can also be performed separately independent of solute transfer [65].

Hemofiltration [31] uses convection whereby solutes are carried along with the bulk flow of fluid through a highly permeable membrane down a pressure gradient (similar to glomerular filtration). Tubular function is partially replaced by infusion of a substitution fluid. Fluid balance is achieved by balancing

ultrafiltration and substitution. Both principles may be combined in hemodiafiltration.

Hemodialysis provides a better clearance of small solutes, whereas in hemofiltration clearance is independent of molecular weight up to the cut-off of the membrane. This results in a better clearance of middle molecules (MW 500–10000 dalton)

Hemodialysis requires the presence of a dialysate which is often a non-sterile and non-pyrogen-free solution. Hemofiltration requires the intravenous administration of large volumes of (expensive) sterile, pyrogen-free substitution fluid.

2. Treatment-timing: the artificial kidney can function continuously or intermittently for various periods of time.

3. Access to the circulation can be achieved by cannulation of a large vein (veno-venous), by cannulation of an artery and a vein (arterio-venous) or by an arterio-venous shunt.

The need for arterial cannulation in the spontaneous techniques increases the risk of complications of vascular access [29] and represents a limitation of these techniques in patients with severe vascular disease or after vascular surgery.

4. The bloodflow through the device can be *generated* by a blood pump as in the veno-venous techniques or by cardiac contraction as in the spontaneous arterio-venous techniques.

Most extracorporeal kidney replacement therapies represent different combinations of these four aspects (Table 1). A diagram of these techniques is shown in Fig. 1.

5. The buffer in the dialysate or substitution fluid can be acetate, lactate or bicarbonate. The use of bicarbonate in the dialysate raises important technical problems [73], whereas acetate dialysis has deleterious side-effects (see below).

6. Anticoagulation is necessary to prevent clotting in the extracorporeal circuit. It can be achieved with standard heparin, low molecular weight heparin, citrate, prostacyclin, ancrod or gabexate mesilate (for a more extensive review see [66]).

The need for continuous anticoagulation in the continuous techniques may represent a problem in the perioperative period or after major trauma. In these patients the risk of hemorrhage has to be weighed against the risk (cost !) of thrombosis in the filter. A high bleeding risk requires tight heparinisation with low dose heparin providing extracorporeal anticoagulation without affecting systemic coagulation [59]. Sometimes anticoagulation may even be omitted, particularly when the underlying disease is associated with a coagulopathy [27, 67].

7. Membranes used in artificial kidneys can be cellulose or non-cellulose (synthetic) membranes (Table 2). The choice of a membrane will be guided by:

A) The *solute transfer principle*: hemofiltration requires membranes with high hydraulic permeability so

Table 1. Extracorporeal kidney replacement therapies

IUF	= intermittent ultrafiltration (65)
SCUF	= slow continuous ultrafiltration (54)
HD	= intermittent hemodialysis (40)
CAVHD	= continuous arteriovenous hemodialysis (27)
HF	= intermittent hemofiltration (31)
CAVH	= continuous arteriovenous hemofiltration (41)
CVVH	= continuous venovenous hemofiltration
HDF	= hemodiafiltration
CAVHDF	= continuous arteriovenous hemodiafiltration (64)

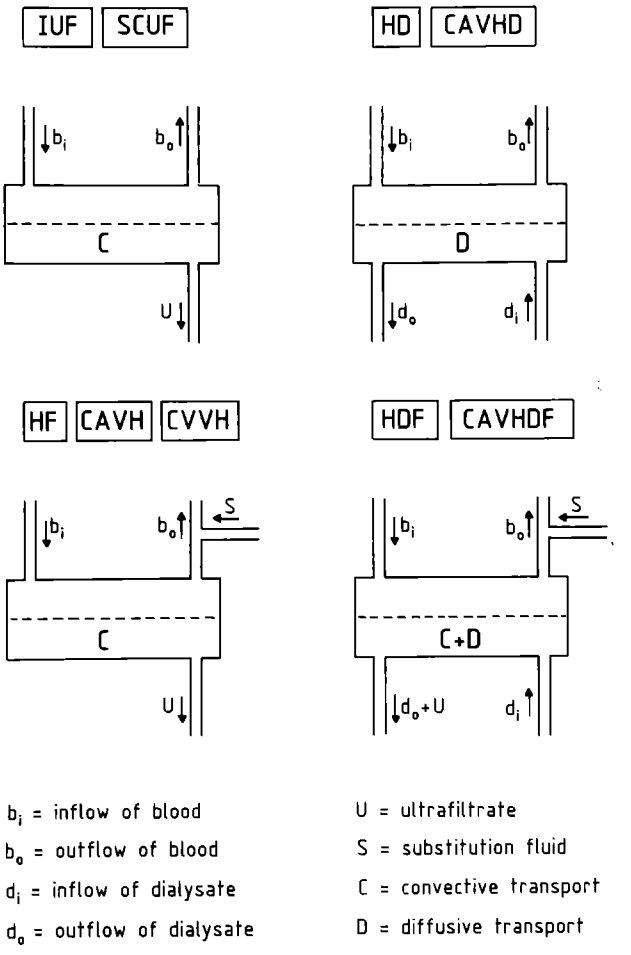

Fig. 1. Schematic representation of the different modes of extracorporeal treatment of ARF. For abbreviations see Table 1

Table 2. Membranes used in extracorporeal treatment

Cellulose membranes:
– cuprophan
– regenerated cellulose
– cellulose (di) (tri) acetate
Synthetic membranes:
– polyacrylonitrile (PAN, AN69)
– polysulfone (PS)
– polyamide (PA)
– polycarbonate
– polymethylmethacrylate (PMMA)

that non-cellulose membranes are preferred in this technique.

B) *Bioincompatibility* is the result of interactions between plasma proteins and blood cells on the one hand and the membrane surface on the other. Bioincompatibility has several pathways.

- *Thrombogenesis*: although comparative data are limited and inconclusive, there is some evidence that cuprophan is less compatible than synthetic membranes with respect to platelet aggregation [68].

- *Complement activation* [15, 71] is more extensive with cellulose membranes than with the synthetic membranes and results from binding of complement components to reactive sites on the membrane surface. The complement system is activated through the alternative pathway with generation of the anaphylatoxins C3 and C5a. C5a promotes chemotaxis of polymorphs, enhances their aggregation, stimulates formation of superoxide radicals and arachidonic acid metabolites, and induces secretion of lysosomal enzymes. The synthetic membranes used in hemofiltration not only generate less C5a but they also remove this mediator (MW 11300) because of their greater permeability for middle molecules [16]. Moreover, some of these membranes (e.g. the Hospal polyacrylonitrile AN 69) can adsorb C5a onto their surface, further reducing the systemic effect of complement activation [14]. With respect to complement activation, cuprophan and regenerated cellulose are therefore the least biocompatible, cellulose acetate is more compatible whereas synthetic membranes are probably the most biocompatible.

- *Interleukin-1 production by monocytes.* Attachment of blood monocytes to the membrane is usually the first step in monocyte activation. Adhesion of monocytes to synthetic membranes (polysulfone, polyacrylonitrile) leads to enhanced secretion of interleukin-1 compared to that observed with cellulose membranes [2, 46]. The physical contact between blood cells and membranes, however, is only a mild stimulus for interleukin-1 production. More important is the subsequent stimulation of these adherent monocytes by components of the dialysate [16, 23], such as endotoxin fragments and muramyl peptides produced by enzymatic degradation of the bacterial wall (MW 1000–20000). Acetate in the dialysate has also been suggested to be a stimulant for interleukin-1 production [7]. The absence of dialysate in hemofiltration techniques may therefore be an important factor in improving biocompatibility (interleukin-1 being a potent mediator of the acute phase response). Moreover hemodialysis mostly uses complement activating cellulose membranes and C5a is also a known interleukin-1 inducer [23].

- *Shear forces* are inevitable in the extracorporeal circulation and may be enhanced by the use of blood pumps. These shear forces have deleterious effects on red blood cells, polymorphs and platelets.

C) *Filter geometry:* hollow fiber and flat sheet devices have completely replaced the coil dialyzers. In the spontaneous techniques filter geometry is always a compromise between the membrane surface area on the one hand and filter resistance and priming volume on the other.

D) *Cost:* the newer synthetic membranes are more expensive.

Efficacy of artificial kidney systems

The efficacy of all available kidney replacement therapies is limited, as no more than four aspects of the natural kidney function can be replaced and these only to some extent.

1. Control of hydration. Critically ill patients are often fluid overloaded and require in addition a daily fluid intake of 2 to 3 liters for parenteral nutrition and other medication. The importance of adequate parenteral nutrition in critically ill patients with acute renal failure was confirmed by Bartlett [4] who found a survival of 38% in a high calorie group of patients compared with 9% in the low calorie group. To achieve a positive caloric balance it is necessary to administer large amounts of fluid. For obvious reasons the removal of this fluid is easily achieved and well tolerated with the continuous techniques. The high fluid handling in continuous arteriovenous hemofiltration (CAVH), however, may induce important balance errors [70]. This fluid balancing problem is greatly simplified in continuous arteriovenous hemodialysis (CAVHD) and continuous arteriovenous hemodialfiltration (CAVHDF) where less substitution fluid needs to be administered. In addition CAVHD and CAVHDF permit the administration of nutrients via the dialysate

[26]. With the intermittent techniques removal of fluid will be more difficult, although in this respect intermittent hemofiltration (HF) is better tolerated than intermittent hemodialysis (HD) (see below).

2. Electrolyte homeostasis is achieved by adjusting the composition of the dialysate or substitution fluid. Severe hyperkalemia in hypercatabolic patients cannot be controlled with low clearance systems (e.g. CAVH with a low blood pressure) [70].

3. Acid-base balance is achieved by adding buffers to the dialysate of substitution fluid: acetate, lactate or bicarbonate. Acetate and lactate must first be metabolised to bicarbonate. Metabolism of acetate occurs mainly in the skeletal muscles, whereas lactate is metabolised in the liver. The use of lactate in patients with liver failure or the use of acetate in hemodynamically compromised patients with diminished perfusion of the skeletal muscles may thus lead to a slower or incomplete correction of acidosis. On the other hand the use of bicarbonate requires separate supplementation of Ca2+ and Mg2+ thereby increasing the complexity of the system.

4. Elimination of uremic toxins. Small uremic toxins (urea, creatinine) are more efficiently eliminated with diffusive transport whereas elimination of larger toxins is better achieved by convective transport. However, the importance of removing "middle molecules" with regard to the improvement of the clinical uremic syndrome has not yet been clearly proven [16, 52].

Diffusive clearance of a solute depends on its molecular weight, the concentration gradient between blood and dialysate, the membrane surface area and the ratio of dialysate flow and blood flow. Convective clearance is identical to the filtration/substitution flow rate. In spontaneous hemofiltration the determinants of this filtration rate are: membrane hydraulic permeability and surface area, hematocrit, colloid oncotic pressure, blood pressure, resistance of extracorporeal circuit and access and the negative pressure in the filtrate compartment [47, 55]. Most of these parameters are not subject to control. Therefore control of azotemia with CAVH may become insufficient in hypercatabolic patients with low blood pressure. CAVH can be modified to increase solute clearance (predilution, suction-assisted CAVH [38]) but these measures increase the complexity of the system and render fluid balancing even more difficult.

A more efficient way to increase small solute clearance in hypercatabolic patients is the use of CAVHD or CAVHDF (where diffusive and convective clearance are additive) [60, 74].

Side-effects of the artifical kidney

1. Central nervous system effect of the artificial kidney: the dialysis dysequilibrium syndrome

The dialysis dysequilibrium syndrome [48] is characterised by headache, nausea, muscle cramps, hypertension, disorientation and eventually coma and seizures. The cerebral edema, which is the cause of this syndrome, can be explained by two mechanisms:

A) *The reverse urea hypothesis:* due to the blood brain barrier, urea is cleared more rapidly from the plasma than from the brain. This will lead to an osmotic gradient between brain tissue and plasma resulting in displacement of water to the brain.

B) Dialysis induces *a paradoxical acidosis of the cerebral spinal fluid.* This H^+ ion increase in the brain, the mechanism of which is unknown, is accompanied by an increase in osmole content.

The dialysis dysequilibrium syndrome can lead to dangerous increases in intracranial pressure in patients with pre-existing cerebral edema (traumatic, post-hypoxic). Prevention of this artifical kidney induced (aggravation of) cerebral edema consists of limiting osmolality changes. Therapy should be started early and osmols should be added to the dialysate [58]. Because of a lower clearance of small solutes, hemofiltration causes less osmolality changes and should be used rather than hemodialysis in cases of acute renal failure complicated by raised intracranial pressure [20]. The gradual osmolality changes associated with the continuous techniques obviously provide the best protection from developing the dialysis dysequilibrium syndrome. Continuous hemofiltration has even been advocated for the treatment of cerebral edema [21].

2. Pulmonary effects of the artificial kidney

The net effect of the artificial kidney on pulmonary function can be either an improvement or worsening of the arterial oxygen tension (PaO_2) depending on the patient's cardiopulmonary condition and the technique which is used. Several mechanisms are involved (Table 3).

It is evident that removal of fluid can decrease extravascular lung water and thus improve gas exchange [69]. Gotloib, moreover, suggests that the artificial kidney could function as a kind of artificial endocrine lung that eliminates mediators which play a role in the pathogenesis of ARDS [28]. This hypothesis, however, needs further investigation.

Artificial kidney therapy can also result in a decrease in PaO_2 based on one or more of the following mechanisms.

A) *Membrane dependent* mechanisms [18, 71]: cellulose membranes induce *complement activation* with generation of C3a and C5a which may result in pulmonary leuco-sequestration and the subsequent release of mediators (O_2 radicals, proteases, arachidonic acid metabolites, serotonin, histamine). This may cause plugging of pulmonary vessels, bronchoconstriction and a capillary leak resulting in ventilation-perfusion mismatch, diffusion impairment, shunting and pulmonary hypertension.

B) *Acetate-induced hypoventilation* [24]: Acetate dialysis causes extrapulmonary CO_2 removal by loss of dissolved CO_2 in the dialysate and by consumption of CO_2 in the metabolism of acetate, which is converted to bicarbonate in the following reaction:

$$CH_3COO^- + H_2CO_3 + CoA \rightarrow \text{Acetyl-CoA} + HCO_3^-$$
$$\uparrow$$
$$H_2O + CO_2$$

Extrapulmonary CO_2 removal with constant CO_2 production induces a special type of hypoventilation where the arterial PCO_2 does not increase but the alveolar oxygen tension (PA O_2) decreases as becomes evident from the alveolar gas equation:

$$PAO_2 = PiO_2 - \frac{PaCO_2}{R} + \frac{PaCO_2 \cdot FiO_2 \cdot (1\text{-}R)}{R}$$

$$R = \frac{\dot{V}CO_2}{\dot{V}O_2}$$

FiO_2 = inspired oxygen fraction
PAO_2 = alveolar oxygen tension
PiO_2 = oxygen tension in the inspired gas
$PaCO_2$ = arterial carbon dioxide tension
R = respiratory exchange ratio
$\dot{V}CO_2$ = pulmonary carbon dioxide elimination
$\dot{V}O_2$ = oxygen consumption

If the pulmonary CO_2 elimination ($\dot{V}CO_2$) decreases, the respiratory exchange ratio (R) will also decrease. A decrease of R with constant $PaCO_2$ will result in a decrease in alveolar PO_2.

C) Alveolar hypoventilation with increase in $PaCO_2$ can be the result of the *correction of acidosis*. The rate of correction of acidosis depends on the buffer concentration in the dialysate and the rate of its metabolism [24].

D) The vasodilating effect of acetate might *decrease pulmonary hypoxic vasoconstriction* resulting in increased shunting, but this remains a hypothesis [57, 12].

E) A decrease in PaO_2 during artificial kidney therapy can also be the result of *a decrease in venous oxygen tension* (PvO_2) [24], the latter being the result of a decrease in cardiac output or an increase in oxygen consumption. Most studies find some increase in O_2 consumption during acetate dialysis [8,49].

The question arises concerning the relative importance of these different mechanisms:

- Removal of fluid is certainly the most important factor leading to an increase in PaO_2 in patients with pulmonary edema.
- As far as dialysis induced hypoxemia is concerned, acetate induced hypoventilation is probably the most important mechanism in patients with normal pulmonary function. Igarashi [36] has compared acetate dialysis with bicarbonate dialysis using two different membranes in chronic renal failure patients without pulmonary problems. He was able to demonstrate that, in contrast to bicarbonate dialysis, acetate dialysis induces a decrease in both PaO_2 and PAO_2, but with no change in the alveolar-arterial oxygen gradient (P(A-a) O_2). This occurred in spite of a decrease in transfer factor to 88% using a synthetic membrane compared with 77% using cuprophan. These findings suggest that the induction of moderately impaired diffusion in previously normal lungs does not lead to hypoxemia because the contact time is long enough to achieve complete equilibrium between air and blood. This also explains why Bouffard [9] found little or no dialysis induced hypoxemia in ventilated patients with normal pulmonary function, even when a cuprophan membrane was used (controlled mechanical ventilation preventing acetate induced hypoventilation).
- In patients with impaired pulmonary function neither mechanical ventilation [10] nor the substitution of bicarbonate for acetate [56] can entirely prevent dialysis induced hypoxemia. These findings suggest that other mechanisms besides acetate induced hypoventilation must play a role in these patients, membrane dependent complement activation being the most plausible one.

The prevention of dialysis induced hypoxemia in patients with impaired oxygenation is achieved by the

Table 3. Pulmonary effects of the artificial kidney: mechanisms

$PaO_2\uparrow$	1. decrease of EVLW
	2. elimination of mediators?
$PaO_2\downarrow$	1. membrane dependent complement activation
	2. acetate induced hypoventilation
	3. hypoventilation resulting from correction of acidosis
	4. acetate induced decrease of pulmonary hypoxic vasoconstriction?
	5. decrease in PvO_2: decreased cardiac output, increased O_2 consumption.

avoidance of acetate dialysis (especially in spontaneously breathing patients) and the use of biocompatible membranes. Supplemental oxygen and/or adjustments of the ventilator may be necessary during artificial kidney therapy, especially in patients whose PaO_2 is on the steep portion of the haemoglobin dissociation curve, since the simultaneous correction of acidosis will shift this curve to the left, with further impairment of tissue oxygenation.

3. *Hemodynamic effects of the artificial kidney*

The hemodynamic effects of the artificial kidney are rather complex, the net result depending on the patient's hemodynamic status, the efficiency of his compensatory mechanisms and the type of artificial kidney. Several mechanisms play a role.

A) *Changes in circulating volume and preload* may be the result of ultrafiltration or volume shifts [32].
– The removal of plasma water (ultrafiltration) changes the Starling forces leading to refilling of the vascular compartment with interstitial fluid. Hypovolemia results only when this refilling rate cannot keep up with the ultrafiltration rate. This is usually the case with intermittent treatment during which large volumes are filtered within a limited period of time.
– Volume shifts between the intracellular and extracellular compartments are the result of concentration changes of solutes which pass very slowly or not at all through the cell membrane e.g. sodium, glucose. A decrease in their extracellular concentration induces an osmotic gradient causing cellular edema and impairing the refilling of the vascular compartment [48].
– Volume shifts can also occur within the vascular compartment. Chaignon [11] has demonstrated a venous pooling during hemodialysis. He suggests this venodilation could be provoked by correction of acidosis.

B) *Changes in electrolyte concentrations* will influence hemodynamics via rhythm disturbances (K^+) [51], an effect on myocardial contractility (Ca^{2+}) [33] or on vascular smooth muscle (Ca^{2+}, Mg^{2+}, Na^+).

C) The artificial kidney induces *concentration changes of various vasoactive substances* such as catecholamines (MW 160), atrial natriuretic factor (MW 3000), bradykinin (MW 1206), serotonin (MW 210), histamine (MW 127) myocardial depressant factor (MW 800–1000), leukotrienes (MW 600), prostaglandins (MW 600). Theoretically these concentration changes will be more pronounced with either diffusive or convective transport depending on the molecular weight of these substances. Few studies of the clearance of vasoactive substances with the different extracorporeal epuration techniques have been carried out. Baldamus [3] even found a 50% higher noradrenaline/urea clearance ratio during hemofiltration than during hemodialysis and concluded that the improved hemodynamic tolerance of hemofiltration cannot be attributed to a higher noradrenaline removal in dialysis compared to hemofiltration. Coraim [17] used CAVH in patients with severe cardio-circulatory failure after cardiac surgery and observed a significant improvement of cardio-circulatory and pulmonary function which could not be attributed to fluid removal. Since the plasma concentration of myocardial depressant factor decreased during CAVH, he suggests that CAVH might eliminate cardiopulmonary toxic agents.

An improvement in hemodynamics might also be the result of the removal of uremic toxins [63].

D) *Bioincompatibility* of artificial kidney membranes with resultant complement activation and production of interleukin-1 [15, 23, 71] can lead to pulmonary hypertension and systemic hypotension, either directly via release of vasoactive mediators (thromboxane, PGE2, prostacyclin, histamine) or indirectly via hypoxemia.

E) Artificial kidney induced hypotension has also been related to the use of *acetate*. The hemodynamic effects of acetate are rather complex and remain a matter of debate.

Whenever acetate is infused in large amounts it becomes a major metabolic substrate for overall energy metabolism, the muscle being the major site of acetate utilisation. The metabolic consequences of rapid acetate oxidation are a fall in tissue ATP, a trapping of CoA, a degradation of tissue adenylates, a local production of peroxide radicals, a trapping of cell Pi into PPi and a local production of adenosine [73].

The functional consequences of this acetate metabolisation are threefold:

- The increased level of adenosine mediates vasodilation. The vasodilating effect of acetate was demonstrated as early as 1928 by Bauer and Richard [5] and was later confirmed by several other investigators.
- The reduced cellular ATP leads to organ dysfunction and might explain the negative inotropic effect of acetate, which Kirkendol [39] demonstrated on the isolated rabbit papillary muscle. Acetate might even mimic the electrical and clinical signs observed during myocardial ischemia due to a fall in myocardial ATP and a stealing of blood away from arteriosclerotic coronary arteries [73].
- Of more importance probably is the positive inotropic effect which some authors [44, 53] have observed during infusion of acetate. This positive inotropic effect is ascribed to peripheral metabolic

changes induced by acetate metabolisation (decreased ATP/AMP ratio). Nitenberg [53] infused acetate in humans during cardiac catheterisation for stable coronary artery disease. He found an enhancement of both systolic pump function (ejection fraction, left ventricular stroke work) and left ventricle contractility (V_{max} and end systolic stress / end systolic volume ratio) and an enhancement of left ventricular relaxation indices (peak negative dP/dt and relaxation time constant T). Preload, afterload and heart rate were kept constant during the experiment. Intracoronary administration of acetate induced no hemodynamic changes, excluding a direct effect of acetate on the myocardium. Impairment of acetate metabolisation (e.g. in shock with diminshed perfusion of skeletal muscle) could prevent acetate from exerting its positive inotropic effect as was suggested by Huyghebaert [35].

For several reasons clinical studies during acetate dialysis [1, 72, 13, 50, 62, 42, 43, 35, 19] cannot elucidate the mechanisms underlying the hemodynamic effects of acetate. The patient populations studied are very inhomogenous particularly with respect to left ventricular function. These studies also combine the hemodynamic effects of acetate with the hemodynamic effects of dialysis per se, which in turn differs according to the sodium concentration of the dialysate, the ultrafiltrate volume etc. Finally we still lack a reliable clinically measurable index of myocardial contractility which is independent of heart rate and loading conditions.

Most clinical studies compare acetate and bicarbonate dialysis and show more hemodynamic instability with acetate. Besides vasodilation [1, 13, 43], a negative inotropic effect [1, 72, 42], or the absence of a positive inotropic effect [35] other mechanisms have been suggested to explain acetate dialysis induced hypotension: chelation of Ca^{2+} [62], a slower refilling of the vascular compartment [43, 34], hypoxemia [62] increased O_2 consumption [49] or a transient increase in acidosis (provoked by impaired acetate metabolisation) [62, 42, 35].

F) *Impaired sympathetic response to a reduction in intravascular volume.* Several investigators observed an improved hemodynamic tolerance to the removal of plasma water with pure ultrafiltration and hemofiltration compared to hemodialysis [3, 6, 30, 75]. Zucchelli [75] found a significant increase in concentration of plasma catecholamines during pure ultrafiltration but not when ultrafiltration was combined with hemodialysis. He suggested that diffusive removal of catecholamines was responsible for the increased incidence of hypotension during hemodialysis. Baldamus [13] compared pure ultrafiltration, hemofiltration, acetate dialysis and bicarbonate dialysis with the same volume removal, the same clearance of small solutes (and thus the same osmolality changes and the same clearance of catecholamines) and the same buffer (acetate hemofiltration). He found that the sympathetic response to fluid removal (secretion of noradrenaline resulting in an increased systemic vascular resistance) was qualitatively adequate in pure ultrafiltration and hemofiltration, but not in acetate or bicarbonate dialysis. The causative mechanism of this diffusion related impairment of the symphathetic response to hypovolemia remains unknown.

Table 4. Hemodynamic effects of the artificial kidney

Preload↓	
– ultrafiltration	
– impaired refilling	intermittent therapy osmolality changes acetate
Contractility↑	
– removal of toxins	
– acetate	
– Ca^{2+}	
Contractility↓	
– acetate ?	
– hypoxemia	bioincompatibility acetate
– acidosis	
Afterload↓	
– acetate	
– vasoactive mediators (bioincompatibility)	
– impaired sympathetic response (diffusive solute transfer)	

The hemodynamic effects of the artificial kidney can thus be summarized (Table 4) as a decrease in preload (ultrafiltration; impaired refilling by intermittent techniques, osmolality changes, acetate), an increase (removal of toxines; acetate; Ca^{2+}) or a decrease (acetate ?; hypoxemia; acidosis) in myocardial contractility and a decrease in afterload (acetate; bioincompatibility mediated vasoactive substances; diffusion related impaired sympathetic response to volume removal).

Understanding the above mentioned mechanisms permits the rational choice of an extracorporeal kidney replacement therapy adapted to the hemodynamic status of the patient. If the hemodynamic state of the patient is stable, hemodialysis can be used. Hypotension can be prevented by infusion of human albumin (enhanced refilling) [37], by increasing the sodium concentration of the dialysate (minimizing volume shifts) [45], by sequential ultrafiltration and dialysis (separating ultrafiltration and volume shifts) [61], by using bicarbonate and synthetic membranes. The use of cold dialysate can further reduce complement activation and interleukin-1 production [22, 25].

In the hemodynamically unstable patient preference should be given to hemofiltration. The physiolog-

ical response to hypovolemia is better preserved with hemofiltration and the absence of dialysate limits monocyte stimulation. Hemofiltration induces less change in osmolality and thus a smaller volume shift and is more efficient in terms of the removal of middle molecular weight vasoactive substances. In the very unstable patient (septic shock, cardiogenic shock) it may be useful to prolong the therapy using one of the continuous methods.

Conclusion

The appropriate choice of an artificial kidney is an important part of the optimal management of the critically ill patient with acute renal failure. In many instances a compromise has to be made between the efficiency of the technique as a kidney replacement therapy and the morbidity of the procedure itself. Associated cardiopulmonary problems preclude a method which further impairs O_2 delivery. These considerations may explain why, in critically ill patients, intermittent dialysis has now been largely replaced by (intermittent or continuous) hemofiltration or continuous hemodialysis.

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