PART IX

GUEST LECTURE

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HAEMODIALYSIS HYPOTENSION: THE INTERLEUKIN HYPOTHESIS RESTATE

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Eureka
Archimedes [1]

Introduction

As the Middle molecule hypothesis has died slowly in the last decade, the metanephrologist (a term communicated to the author by the late Jan Brod in 1969 to describe physicians who were totally dedicated to the care of patients without renal function) has wandered from continuous ambulatory peritoneal
dialysis (CAPD) to biocompatibility in search of a new paradigm; whilst debating that well-known presocratic dialogue between Heraclitus and Democritus on patient well being [2] (Figure 1). This review on haemodialysis hypotension will be used to restate the Interleukin-1 hypothesis [3]. In addition, it will review the current thinking on the demography, mechanisms, and prevention of haemodialysis hypotension which is the most distressing cause of intra-therapy morbidity and possibly a major aetiological factor in long-term morbidity of end-stage renal disease patients.

Demography

The increasing age of the dialysis population world wide over the past 15 years reflects more available treatment, improvement in survival rates and the more frequent transplantation of young patients (Figures 2 and 3). It is not surprising, therefore, that the incidence of symptomatic hypotension of 25 per cent as a

Figure 2. The potential problem of age in end-stage renal disease therapy is well illustrated by this exponential curve of incidence of death from untreated renal failure as a function of age in England and Wales (Registrar General England and Wales, 1967)
Figure 3. Showing a curvilinear increase in mean age of end-stage renal disease population against time, with the reciprocal curve for total number of patients on treatment against time, suggesting that the patient pool is approaching a plateau as presumably older patients live less long and that therefore the forecasts based upon Figure 2 are perhaps overestimates rather than the contrary (derived from EDTA Registry data).

problem complicating all haemodialysis has not changed since 1977 [4,5]. Indeed, considering that the employment of short hour treatments and the acceptance of more patients with multi-systemic diseases (e.g. diabetes), it is a tribute to technical progress that the incidence has not increased.

Caveats

Before considering the mechanisms involved in the production of haemodialysis hypotension, it would be appropriate to consider the multiple known factors and their interaction which result in the reduction of blood pressure during treatment. In Table I an example of the way factors can interact has been given. Thus, if ultrafiltration produces hypovolaemia and decreases cardiac output; in the presence of autonomic dysfunction, the total peripheral resistance may not increase and hypotension could result. Under these circumstances, ultrafiltration is the external factor, hypovolaemia the mediating factor and autonomic dysfunction the intrinsic pathology. The failure to control these variables when they relate to intrinsic factors, is the underlying weakness in most reported experimental studies of vascular stability in haemodialysis. Poor attention has usually been given to variability in cardiac function from patient to patient. The usual criterion for homogeneity has been the presence or absence of symptoms during treatment associated with changes in the blood pressure. This has led to much controversy in interpretation of results.
TABLE I. The interaction of factors causing hypotension (see text)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Variable parameter</th>
</tr>
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<tbody>
<tr>
<td>Pathogenesis (external cause*)</td>
<td>Ultrafiltration/dialysis</td>
</tr>
<tr>
<td>Mediating (difficult to measure accurately)</td>
<td>Hypovolaemia/vasodilatation</td>
</tr>
<tr>
<td>Underlying pathology (intrinsic background*)</td>
<td>Failure to vasoconstrict/failure to increase cardiac output</td>
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* are often poorly controlled variables

Modified from Kjellstrand CM [6]

Another caveat worthy of mention is in the definition of the meaning of symptomatic hypotension. Unfortunately there is no consensus on the constellation of clinical observations which may extend from cramps (legs, back, abdomen), nausea, vomiting, malaise, and headache to loss of consciousness and grand mal epilepsy. Nor is there any agreed amount by which the blood pressure should go down for the drop to be called hypotension. Nevertheless, it is agreed that symptomatic hypotension is the most common reason for therapeutic intervention by the dialysis staff.

A third caveat must discuss the arbitrary and poorly defined value of 'dry weight'. According to Henderson [7] 'dry weight' is defined as "the weight obtained at the conclusion of a regular dialysis treatment below which the patient more often than not will become symptomatic and go into shock". Using this rather Draconian definition, the incidence of symptomatic hypotension in one form of treatment versus another may become as much a factor of the obsessionalism of the treatment staff as a function or otherwise of the treatment method.

A final caveat is the acceptance of space measurements as being meaningful on the assumption that the volume of distribution of the marker first measures the space, always an assumption, and secondly that this volume which has been verified in normal man or animal has the same boundaries in disease. This problem is particularly relevant in the discussion of the work of the 'Shifter' school which will follow.

Mechanisms

Until 1976 it was accepted dogma that hypovolaemia caused hypotension in haemodialysis. As a consequence the more weight that had to be removed the more the patient suffered; a sort of divine retribution for sinning attitude was not uncommon amongst dialysis staff in explaining to patients this distress. Indeed as the population became senile the failure of haemodialysis therapy to cope with this problem led to large scale desertions to competitive forms of therapy such as CAPD. An anecdotal comparison of the two forms of therapy was cited in the late seventies as "Haemodialysis takes it out of you: and CAPD does the same but puts it back again!". Thus this preoccupation with 'dry
weight' and suffering were to be even more accentuated when shorter hours of treatment became fashionable in the mid-seventies. However, in 1976 [8] it was demonstrated for the first time in a scientific manner that hypovolaemia per se was not necessarily responsible for hypotension in end-stage renal disease, as when fluid was removed by ultrafiltration without diffusion, the blood pressure remained constant. When haemodialysis was associated with the fluid removal the blood pressure went down. Later it was clearly demonstrated that with isovolaemic haemodialysis there was a reduction in blood pressure [9,10]. Haemodynamic measurements have subsequently confirmed that haemodialysis is associated with a failure of the peripheral resistance to rise appropriately in the presence of hypovolaemia and that this failure is procedure determined and not fundamentally dependent upon the type of membrane (biocompatibility vide infra) or the type of buffer (vide infra acetate/bicarbonate), or the linearity or not of weight loss, or the change in serum osmolality. It is associated with a failure of circulating catecholamines to rise (Figure 4) [11,12]. The phenomenon is patient independent as it is correctable when isolated ultrafiltration is employed. Even more convincing is the correction of the fault when haemofiltration is employed as the sole method of replacement therapy [13].

However, in 1976 the observation that isolated ultrafiltration and haemodialysis produced differing results in the same patient stimulated thought. The first explanation was hinted at in the original report [8], when it was observed that the serum osmolality dropped with haemodialysis and stayed constant with isolated ultrafiltration. However, it was obvious that even if a drop in serum osmolality could lead to water leaving the extracellular space for the intracellular one, the failure to increase total peripheral resistance during haemodialysis was not explained. Nevertheless, the 'Shifter' school gained credence from the original report on haemofiltration [14] claiming vascular stability and reporting a smaller drop in serum osmolality as one of the possible explanations [15]. It required over two more years before it was shown that in haemodialysis it was possible to have identical reductions in serum osmolality with significantly reduced hypotension if inefficient (low urea clearance) treatment were given in the same patient population, compared to efficient treatment (high urea clearance) [16]. In addition, it was shown that with high efficiency haemofiltration the reduction in serum osmolality was the same as with high efficiency haemodialysis but the response of the peripheral resistance to hypovolaemia was different [17,18]. Thus, although the 'Shifter' school could demonstrate differences in space measurements which correlated well with changes in serum osmolality, they could not explain the fundamental difference between haemodialysis and haemofiltration regarding the response of the peripheral resistance to hypovolaemia [19].

The treatment of symptomatic hypotension has always been most effective when osmols in the form of mannitol, glucose or sodium are given in hypertonic form. Thus, it was reasonable if not totally logical to argue that if replacing osmols cured hypotension then its prevention could be achieved by giving these osmols prophylactically and finally it might be argued that the cause of the hypotension was the reduction in serum osmolality occasioned by urea solute
Figure 4. Relationship between pre- to post-treatment change of total peripheral resistance (TPR) and of plasma noradrenaline (NA) concentration during isolated ultrafiltration (UF), post dilutional haemofiltration (HF), haemodialysis with acetate (HDA) and haemodialysis with bicarbonate (HDB). All treatments were matched for rate of weight loss, treatment time and in all but UF for whole blood urea clearances [11]. (Reproduced from [12] by kind permission of editor and publishers of Blood Purification)
removal especially at a rapid rate when short hour high efficiency haemodialysis became fashionable. It was appreciated in Europe since 1972 [20] that the dialysate sodium was a critical factor in the prevention of hypotension during dialysis. The universality of this truth came several years later with scientific confirmation from the USA of empirical European experience [21,22]. The mechanism by which sodium prevents hypotension has been well debated [12,23] and for the moment the simple explanation of osmotic control of vascular refilling rates will suffice. The problem is that this does not explain the failure of the peripheral resistance to rise with haemodialysis, unless sodium influences vascular tonicity rather than simply vascular refilling rates. Recently, it has been shown that hypotonic sodium dialysate is associated with a rise in arterial prostaglandin E₂ in haemodialysis. This might be the link between sodium balance and peripheral resistance [24], as there would be less peripheral vasodilatation with a higher dialysate sodium than a lower one because there would be less production of prostaglandin E₂ during haemodialysis. The difficulty with this argument is that for identical sodium balances in haemodialysis and haemofiltration a difference in response to peripheral resistance and vascular stability has been reported in both acute and chronic studies [25]. An alternative role of sodium in affecting peripheral resistance has been the speculation that the patient on haemodialysis has high circulating levels of vasopressin which fall during treatment and that this fall may be prevented by using high sodium dialysate. Finally, it has been suggested that haemofiltration is another form of high sodium dialysis due to selective retention of plasma sodium by the protein layer on the haemofilter membrane [23]. This hypothesis has been critically examined and found to be wanting both in logical reasoning and scientific merit [12]. Thus, although the role of sodium in the prevention of hypotension in haemodialysis is critical, the relationship of sodium balance to changes in peripheral resistance remains uncertain.

An increasing number of studies have suggested a role for acetate in the aetiology of vascular instability during haemodialysis [26–28] either because of its vasodilator effect on the peripheral resistance or its myocardial depressant action [29,30]. The clinical benefit attributed to bicarbonate dialysis is still controversial [31,32], but it is clear from a haemodynamic viewpoint that there is less reduction in peripheral resistance with bicarbonate than with acetate, and secondary symptoms such as nausea, headache and vomiting are less with bicarbonate than with acetate haemodialysis. These observations are dependent upon the comparison being made under high rates of acetate loading. It may be assumed that the acetate dialysance is about 70 per cent of urea clearance and plasma acetate will rise above 10 mmol/L when urea clearance exceeds 170 ml/min in a 60kg patient with a dialysate acetate of 40 mmol/L [33]. Under these conditions symptoms, including those associated with hypotension, are likely to occur. However, if inefficient dialysis (urea clearance less than 120 ml/min) is practiced it will be rare to see symptoms due to acetate dialysis [34]. The conflicting results of the benefit or otherwise of bicarbonate versus acetate dialysis could be explained by the assumption that acetate loading was not controlled from one series to the other, and that the cardiac reserve of the patients were
different. It is clear that a patient with a normal myocardium responds to acetate by increasing his cardiac output and thus maintaining blood pressure in spite of reduction in peripheral resistance, whereas a patient with a compromised myocardium responds to acetate dialysis by a drop in blood pressure as he cannot increase his cardiac output in response to a fall in peripheral resistance. This concept may be further extended with recent work on liver blood flow in haemodialysis [35]. This work suggests that in isolated ultrafiltration and haemofiltration liver blood flow is selectively preserved during hypovolaemia whereas it falls during haemodialysis. A consequence of this would be a reduced rate of hepatic clearance of acetate during haemodialysis. This would produce higher blood levels for the same net mass balance of acetate in haemodialysis as compared to haemofiltration [36]. Thus one can now explain why the peripheral resistance falls during acetate haemodialysis, but one cannot explain why it fails to rise during bicarbonate dialysis or why liver blood flow is reduced in haemodialysis.

It has been considered necessary in previous complete reviews of this subject [6,7,37] to discuss inadequate vasoconstriction during hypovolaemic haemodialysis as due to a defect in the afferent limb of the carotid and aortic body baroreceptor reflex. The evidence for this defect is tenuous and the incidence of uraemic neuropathy is decreasing. Nevertheless, many diabetic and elderly patients show evidence of autonomic insufficiency and tend to drop their blood pressure without developing tachycardia [38]. The importance of an intact autonomic nervous system during haemodialysis should not be underestimated, but it is unlikely to be responsible for the major difference in the vascular reactivity of an individual patient when different forms of therapy are compared.

It is now 17 years since the first observations on haemodialysis neutropenia were made [39] and eight years since Craddock's classical papers on complement activation, hypoxaemia and neutropenia induced by haemodialysis with cellulosic membranes were published [40,41]. The requisite clinical relevance of these fundamental observations is still sub judice. Undoubtedly, there is a reproducible acute difference when blood is circulated through a dialyser made of cuprophan compared to polyacrylonitrile (PAN). The complement fractions C₃₉ and C₅₉ are activated by the alternate pathway and appear rapidly in the venous blood leaving the cuprophan dialyser, whereas there is very little activity in blood leaving the PAN dialyser. C₅₉ has many actions and is commonly known as anaphylatoxin as it participates in all acute sensitivity reactions. It binds to granulocyte receptors and causes granulocyte clumping. This results in sequestration of granulocytes on the dialysis membrane and in the lungs and the transient neutropenia seen with cuprophan dialysis [42], but not with PAN. The relationship of hypoxaemia to this acute event is less evident as the hypoxaemia seen with acetate cuprophan dialysis is a late phenomenon in relationship to C₅₉ activity. Indeed, current thinking would believe that hypoxaemia is multifactorial in origin and the biocompatible membrane portion is relatively small compared to acetate metabolism and loss of CO₂ from the dialyser [43]. Nevertheless, sheep develop acute pulmonary hypertension with cuprophan dialysis. It is thought to be due to aggregation of granulocytes in pulmonary capillaries producing thromboxane [44]. However, in normal man exposed to
cuprophan during volunteer dialysis there is no change in pulmonary artery pressure or any drop in PO₂ as seen in the sheep, even though complement is activated [45]. Thus, one may assume that there is a large species variation in the sensitivity of the response. However, this does not eliminate the potential hazard of C₅₆ in the presence of other sensitivity reactions.

Recently claims have been made that the 'first use syndrome' was due to C₅₆ activation by cuprophan and that chronic complement activation favoured vascular instability and much else that is associated with intra-dialytic morbidity [46,47]. It would be inappropriate to allow these claims to go unchallenged. Concerning 'the first use syndrome', there is a significant difference in incidence between plate and capillary cuprophan dialysers, and in addition most investigated cases reveal high IgE levels with a positive RAST:ethylene oxide (ETO) test [48]. The importance of the difference between plates and capillaries may lie in the absence of polyurethane potting material in the plate. This plastic retains ETO after degassing and loses it more rapidly when immersed in water than by diffusion into air [49]. As new capillary dialysers are stored dry, it is only possible to lose the ethylene oxide during the rinsing phase before use. In the report of Hakim [46,47] the reused dialysers were stored in an aqueous media in formalin for 36 hours between uses, whereas the control new dialysers were filled with formalin but not stored for any time prior to use. In addition, none of the hyper-reactor patients, claimed to be exhibiting symptoms due to C₅₆ release, were ethylene oxide specific RAST tested. Thus it is possible to interpret these results by suggesting that these patients were all sensitive to ethylene oxide rather than to C₅₆ generated by blood contact with the cuprophan membrane. The claim to better vascular stability with PAN is largely anecdotal. Indeed, in most studies the rate of urea removal and acetate delivery were lower in PAN cases suggesting that the benefit may have been due to less efficient dialysis rather than biocompatibility [50]. The vascular stability seen with an isolated cuprophan dialyser is still the 'gold standard' in spite of high generation rates of C₅₆. In addition the peak C₅₆ levels are hours prior to classical dialysis vascular instability. Finally, it has been demonstrated that the reduction in peripheral resistance during haemodialysis with cuprophan and PAN are identical (Figure 5). The observation that the peripheral resistance drops with dialysis independently of the membrane used has been confirmed for PAN [51], cuprophan [52] and polysulphone [53]. In each of these studies the peripheral resistance rose when the dialyser was used as a haemofilter. These observations suggest that the presence of dialysis fluid separated by a thin membrane from the circulating blood may be the key factor in vascular instability.

The Interleukin-1 (IL-1) hypothesis: the incubator hypothesis

Two years ago [3], it was proposed that exposure of blood to a cuprophan dialyser in the dialysis mode would produce IL-1 in sufficient quantities to have both acute and chronic consequences for the dialysis patient. It is now proposed to modify the premise to any membrane dialyser used with the flow of dialysate on the dialyser side, with the consequence that the interface of
MEMBRANE EFFECT ON VASCULAR STABILITY DURING ACETATE (HDA) AND BICARBONATE (HDB) HAEMODIALYSIS

- polyacrylonitrile dialyzer
- Cuprophan R dialyzer

C₅a (µg/ml)

Treat. Time (min)

ΔTPR (%)

HDB

HDA

Figure 5. Reduction in total peripheral resistance (TPR) occurs with equal degree independently of membrane used. However, the effect of acetate is clearly greater than bicarbonate dialysis. The changes are not related to C₅a blood concentration. (Derived from [42])
**INCUBATOR MODEL**

Blood:

Membrane:

Dialysate:

**The Maximum Concentration of Both Activated Complement and of Dialysate Materials Occurs at The Membrane Surface.**

Figure 6. The potential effect of solute concentration at the membrane interface as small and large molecular weight solutes diffuse from dialysate to plasma water.

protein and cells layering the blood-side of the membrane will be exposed to the highest concentration of solutes as they diffuse from dialysate to blood. The solute concentration will decrease with respect to the membrane as diffusion from the boundary layer into the main stream occurs. No such effect will be found in isolated ultrafiltration or haemofiltration (Figure 6).

Interleukin-1 (IL-1), formerly endogenous pyrogen, designates the monocyte hormone. By the most acute and dramatic of its activities, it mediates fever and hypotension, through its stimulatory action on the cyclo-oxygenase cascade. The cascade produces hypothalamic and peripheral arterial PGE₂ and PGI₂ [54–56]. In addition, IL-1 activates several aspects of the acute phase response [54,55]. Relevant components of this acute phase are hepatic breakdown with hypercatabolism and increased urea generation rates. Chronic stimulation may lead to amyloidosis and progressive fibrosis in rheumatoid arthritis [56] (Figure 7).

Prostacyclin may be a mediator for the final action of IL-1 on vascular endothelium as has been recently suggested [57]. In addition, it is probable that prostacyclin formed in the dialyser because of ‘bio-compatibility’ is removed by the lungs. However, dialyser activated monocytes would traverse the lung capillaries and release prostacyclin locally or induce its production and release
INTERLEUKIN-1 AND UREMIC SYMPTOMATOLOGY

Figure 7. IL-1 and uraemic symptomatology. Note the separation of immunological functions from inflammatory and metabolic ones.

via IL-1 and thus cause peripheral vasodilatation. The most pertinent observations supporting this concept are:

1. PGE₂ may inhibit the release of catecholamines at the synapse of the nerve supply to arteriolar muscle [58]. This would explain the lower circulating catecholamines reported with haemodialysis as opposed to haemofiltration (Figure 4) [11].

2. PGE₂, together with IL-1, increases muscle protein catabolism [59]. In sham cuprophan dialysis without presence of dialysis fluid in normal man, muscle tyrosine release increases at three to five hours after the beginning of the experiment, and the effect may be blocked by indomethacin [60]. The magnitude of this effect might have been greater if dialysis fluid were present. Nevertheless, this confirms the mechanism of increased urea generation in dialysis as being due to endogenous protein catabolism induced by dialysis and this has been noted to be less with haemofiltration. The failure of indomethacin to prevent the fall in blood pressure during haemodialysis [6] may be explained by its direct action on the heart causing a reduction in cardiac output [61]. It will be necessary to measure the change in total peripheral resistance during haemodialysis whilst giving the patient indomethacin.

Thus the concept of Metchnikoff, that the macrophage represents the first line of defence against foreign substances and uses the inflammatory response to achieve this may be true [62]. IL-1 has been purified and cloned. It is a polypeptide (MW 15 000 daltons) whose biological activities may be blocked by a specific human IL-1 antibody. In addition there are non-specific inhibitors in plasma proteins which make bioassay difficult in blood or protein containing fluids. The inhibitors prevent IL-1 binding to receptor sites on the T-cell and
thus IL-2 is not produced and there is no T-cell replication. The assay exploits the immunological properties of IL-1, but when these are blocked the metabolic and primitive inflammatory functions dependent upon PGE₂, PGI₂ and fibroblast formation remain intact. Only very recently have these inhibitors been identified as polypeptides with molecular weights very close to IL-1. They are currently removed by separation from IL-1 by chromatography and elution of the column fractions. As recoveries are less than 70% per cent this diminishes the sensitivity of the assay, and may necessitate concentration of the sample. Nevertheless, it has been possible within the last year to measure IL-1 in circulating human blood under limited conditions [63]. It is known that the monocyte does not store IL-1 but releases it one to four hours after stimulation and that the concentration of inducers as well as the temperature are critical to its induction. Stimulated monocytes demonstrate messenger RNA specific for IL-1 synthesis prior to release of IL-1 from the monocyte. It has been suggested that depending upon concentration any biological material containing a dipeptido-glycan (MW 500 daltons) will stimulate the monocyte. In addition, dextrose, silicon, urates, and acetate have all been shown to have an effect. On the blood side, aggregated granulocytes are phagocytosed by the monocyte which then produces IL-1. In addition, C₅a will bind to the monocyte to produce IL-1 [64]. Recently, it was demonstrated that C₅a concentration in venous blood during cuprophan dialysis reached levels of 40ng/ml [65], this concentration has previously been shown to be adequate for IL-1 induction. In addition, it has just been shown that measurable quantities of IL-1 appear in the blood during haemodialysis [66] and that when endotoxin is recirculated in vitro on the dialysate side of a 15µ cuprophan capillary dialyser, significant induction of IL-1 occurs after four hours in the recirculated donor blood [67].

The observation that anaphylatoxin synthesis is reduced by cold dialysis [68], when extrapolated to IL-1 induction could explain the improved vascular stability that has been reported with the use of cold dialysate [69].

With this accumulation of data it seems reasonable to speculate that during cuprophan dialysis, monocytes adhere to the membrane and are exposed to C₅a and aggregated granulocytes on the blood side and to preferentially high concentrations of sub-units of endotoxin as well as acetate and possibly other inducers diffusing in from the dialysate side. A time of one to four hours elapses before the metabolic effects of IL-1 are seen, and a temperature of 37°C is essential for maximal induction. The acute effects are vasodilatation from locally produced arteriolar PGI₂ and PGE₂, a rise in the body temperature from hypothalamic PGE₂, increased urea generation rate from protein catabolism and a tendency to sleep. Hypotension develops during the course of haemodialysis if the cardiac output cannot rise to compensate for the reduction in peripheral resistance. The inability of indomethacin, a potent inhibitor of prostaglandin synthesis, to prevent hypotension is due to its direct depressive action on the cardiac output.

The chronic effects of repeated stimulation three times per week would be permanently raised levels of serum amyloid A protein, low serum zinc, amyloidosis and joint fibrosis. Many of these problems are now reported in the
long-term haemodialysis patient after 10 years of treatment. It remains to be proven whether haemofiltration by potentially producing a lesser stimulatory condition for IL-1 will have fewer long-term side effects as well.

Prevention of haemodialysis hypotension

If the Interleukin-1 hypothesis becomes generally accepted, the logical way to prevent haemodialysis hypotension will be to use bicarbonate haemofiltration with a biocompatible membrane haemofilter. Until that time, controlled ultrafiltration dialysis with bicarbonate dialysate and ideally a steam sterilized dialyser would seem better than a biocompatible membrane dialyser sterilized in ethylene oxide.

Conclusions

The demography of haemodialysis hypotension has been reviewed and current thoughts on mechanisms presented. In addition, the IL-1 hypothesis has been restated and if accepted would suggest that monocyte induced vasodilator prostaglandins are largely responsible for the failure of the peripheral resistance to rise during haemodialysis and thus result in hypotension when the cardiac output does not rise adequately in a compensatory manner. The most effective way of preventing this major problem in long-term haemodialysis would be to use bicarbonate haemofiltration as an alternative therapy in high risk patients.

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