In-Depth Review

From cold dialysis to isothermic dialysis: a twenty-five year voyage

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Introduction

Twenty-five years have passed since our group described for the first time the role played by temperature (T) in cardiovascular stability. ‘Cold’ treatments prevented the hypotension induced by ‘warm’ treatments, whether in haemodialysis (HD) or in isolated ultrafiltration [1] or in haemofiltration [2,3]. Though some notes of caution were sounded [4], all researchers studying the problem in the years that followed confirmed the role played by T in short-term [5–9] as well as in long-term studies [10,11]. As compared to standard HD or ‘warm’ HD, that is with dialysate T of 37–37.5°C, ‘cold’ HD, that is with dialysate T of 35–35.5°C, ensures better cardiovascular stability. In 1997, reduction of dialysate T was recommended by the DOQI Guidelines as a means to prevent intradialytic hypotension [12]. A systematic review recently published found that ‘intradialytic hypotension occurred 7.1 (95% CI, 5.3–8.9) times less frequently with cool-temperature dialysis’. A total of 22 studies comprising 408 patients were included, all studies were of crossover design and relatively short duration’ [13]. Lastly, the European Best Practice Guideliness on cardiovascular instability, announced at the 2006 ERA-EDTA Congress, scored only cold dialysis with evidence level I, among the different dialysis techniques usually adopted to prevent intradialytic hypotension.

The terms ‘warm’ and ‘cold’ HD, though immediately understandable, are in reality too simplistic to describe the complex interrelations between the thermal profile of the dialytic treatment and its impact on the patient’s body T and cardiocirculatory function. Since 1984 a good correlation (r = 0.75) between variations in dialysate T in the 34–38°C range and concomitant changes in patients’ body T has been found [14]. However, in standard HD with a dialysate T of 37°C no thermal exchanges, on average, took place in the extracorporeal circuit, in that the T of the blood in the venous line was equal to or slightly lower than that of the arterial line [14]. Despite this thermoneutral behaviour however, an average rise in patient’s body T of ~0.5–0.7°C takes place [14,15], and this is the reason for defining standard HD as a ‘warm’ treatment. However, further analysing the behaviour of individual patients, differentiated responses (with some subjects who tended to warm up and others to cool down), for the same T of the dialysate were described [15].

To better understand the physio-pathological mechanisms and the clinical implications underlying dialytic hyperthermia, it is useful to review the physiology of the relations between T and arterial pressure, to evaluate whether the haemodynamic profile during HD is in accordance with physiology and finally, to study what determines thermal balance in the course of HD.

Notions of physiology on the relations between body temperature and cardiocirculatory function

In human beings, body T is closely regulated by a fine balance between production of heat, proportional to the consumption of oxygen and the production of carbon dioxide, and its dispersion. That is why the cutaneous blood flow is regulated so as to ensure transfer of heat from the internal organs to the surface, with its successive dispersion into the environment. Studies in normal subjects have shown that an increase in the temperature of the external environment involves profound haemodynamic changes with an increase in cardiac output and a reduction in peripheral vascular resistances [16]. These effects are all the more evident in conditions of high humidity, which renders dispersion of heat from the organism more difficult. The increase in cardiac output is sustained essentially by an increase in cutaneous flow, for the purpose of heat dispersion. If the muscle-cutaneous nerve is blocked, cutaneous hyperaemia is prevented, which shows that this circulatory adaptation is mediated by

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the nervous system [16]. It is important to stress that such changes in cardiocirculatory function occur even for modest thermal variations, within the range of those that can be encountered in dialytic treatment.

Concomitant with heat stress, standard HD is associated, however, with hypovolaemic stress, secondarily to the removal of fluids. Hypovolaemic stress brings with it a haemodynamic response exactly opposite to the response evoked by heat: vasoconstriction instead of vasodilatation. How does the organism react to such opposing demands? Once again, physiology comes to our aid. When normal volunteers are subjected simultaneously to a heat stimulus (an arm immersed in hot water) and a hypovolaemic stimulus (negative pressure applied to the lower part of the body), the response to hypovolaemic stress is surpassed by the response to thermal stress, with the result that such subjects develop vasodilation and not vasoconstriction, as shown with digital plethysmography applied to the upper controlateral joint [17]. Such experiments demonstrate that, in the order of homeostatic priorities, euthermia is more important than euvolemia.

Haemodynamic profile and dialytic efficiency in cold dialysis

The better cardiovascular stability encountered during cold HD is sustained by a greater catecholamine release [11,18], an increase in peripheral vascular resistances [11,19–21] and in venous tone [21,22] which, however, do not occur during standard HD. On the contrary, in standard HD an increase in cutaneous T, apparently from vasodilation whose purpose is dispersion of accumulated heat, has been documented [14]. Nitric oxide synthesis was also augmented during standard HD but not during cold HD [23].

Clinical findings in HD are, therefore, perfectly in line with what we should expect from the physiology.

Cardiac performance, too, is better maintained [24], which is explained by the fact that the activation of the sympathetic nervous system induced by cold HD has a positive effect on the heart, either directly or indirectly, since it produces vasoconstriction of the capacitance vessels [21,22], thus favouring the venous return to the heart. Some studies [20,25], though not all [21,26], have also shown how such a better haemodynamic response occurs despite the fact that the drop in blood volume is greater in cold HD. The greater reduction in blood volume is probably related to the fact that the cutaneous vasoconstriction that comes about in cold HD reduces the blood volume from which the water is subtracted. That, however, does not translate into a reduced dialytic efficiency [13,26,27] either because the better cardiovascular tolerance allows a dialytic treatment that adheres more closely to duration and blood flow targets, or because the quantity of azotated catabolytes contained in the skin is trivial.

Aside from such haemodynamic effects, it was also demonstrated that cold HD attenuates the hypoxaemia [28,29], leucopenia and the generation of C5a [29] induced by HD with cuprophan membranes.

Determinants of thermal balance in dialysis

The works of the Austrian physiologist Schneditz are a key to the understanding of the issue [25,30] and they are recommended to the reader who is interested in a more thorough study of the subject.

Briefly put, the formula that regulates thermal energy flow in the extracorporeal circuit is: \( E = c \rho (T_{ven} - T_{art}) Q_{b} \). Subtracting \( T_{art} \) from \( T_{ven} \), and not the reverse, we obtain the correct direction of corporeal thermal flow: positive indicates heat gain, and vice versa.

The product of the constants \( c \) (specific caloric capacity of the blood) and \( \rho \) (haematic density) is equal to 3.81 J/ml and depends on the haematocrit. \( T \) of the blood re-entering the patient (\( T_{ven} \)) is directly and predominantly influenced by the \( T \) of the dialysate, but also by ambient \( T \) and the length and thermal conductivity of the haematic lines. \( T \) of the blood leaving the patient (\( T_{art} \)), corrected for vascular access and cardiopulmonary recirculation, provides a good estimate of core body \( T \).

One of the assumptions of standard HD is that the \( T \) of the dialysate at 37°C is physiological, in that it is similar to the patient’s body \( T \). That assumption is mistaken for two reasons. First, in normal subjects, blood \( T \) varies according to where it is measured: it is higher than 37°C in the central blood, that is, blood that flows through the central organs, and somewhat lower in the peripheral vessels. For example: between the radial artery and vein in the elbow, that is the vessels involved in the distal artero-venous fistula, there is a drop in \( T \) of at least 2°C, owing to heat exchanged between the vessel, skin and external environment [31]. Second, a considerable percentage, 20–25%, of HD patients present predialytic body temperatures below 36°C [32] with mean values of 35.5°C [33]. Lastly, we have documented in 23 chronic stable dialysis patients a considerable variability, not only inter-patient but intra-patient as well, in predialytic \( T \)-values measured consecutively over the span of 1 month (Figure 1).

Finally, we must not underestimate the different thermal effects induced by varying blood flow rates [25,34] as well as interdependence of the various elements in conditioning thermal balance. For example, a patient with a body \( T \) of 36°C and dialysate \( T \) of 37°C will warm up to a \( Q_{b} \) of 450 ml/min while he cools down to a \( Q_{b} \) of 200 ml/min [35].

In light of what has been said thus far, it therefore seems arbitrary to define a dialysate \( T \) of 37°C as ‘physiological.’ Rather, it is correct to state that the patient may gain or lose heat as a result of the interrelations between HD-related factors and the characteristics of the patient himself.
Why does body $T$ increase in standard dialysis?

If not solely the consequence of too warm a dialysate, what then is the origin of dialytic hyperthermia? Two fundamental hypotheses are proposed.

According to the interleukin hypothesis [36], dialytic fever and the resulting hypotension can be attributed to the production of cytokines in the presence of endotoxins and their fragments in the dialysate. It is possible that such a cascade of events would be triggered in the presence of contaminated dialysate, but it is certain that contamination is not a necessary condition. We have in fact shown that dialytic hyperthermia also occurs when dialysate is substituted with haemofiltration reinfusion fluid, a sterile and pyrogen-free fluid, or when infusing, in the course of treatment, aspirin in doses such as to inhibit possible cytokine production [15].

According to Gotch’s volume hypothesis [37], the reduction in blood volume induced by ultrafiltration causes both greater heat production mediated by catecholamine secretion, and cutaneous vasoconstriction with consequently less dispersion of accumulated thermal energy. At a certain point, the resulting hyperthermia induces vasodilation for heat dispersion. This occurs at the price of a triggering of hypotension in which, as we have seen, euthermia prevails over euvolaemia.

In accordance with this hypothesis, Schneditz has demonstrated a good correlation between reduction of blood volume and increase in thermal balance. To prevent the increase in body $T$ during HD, 1 W [38], or 6% of the caloric expenditure [39], should be removed from the patient for every per cent reduction in blood volume.

However, hypovolaemia is not the single cause of the increase in core $T$ during HD, as recently shown by van der Sande et al. [40]. We can thus imagine a complex scenario in which the principal actor in inducing dialytic hyperthermia is the rate of ultrafiltration, with which we can rank other ‘second leads’, such as contaminated dialysate and/or dialysate $T$ disproportionately elevated in relation to body $T$ or extracorporeal blood flow.

Who benefits from cold dialysis?

First of all, haemodynamically unstable subjects. In such patients, a good correlation between reduction in blood pressure and increase in body $T$ has actually been demonstrated; in stable subjects, this correlation was either absent or was weaker [14]. It has also been shown that cold HD is particularly indicated in patients with comorbidities [11,41]. In that respect, predialytic body $T$ also plays a pivotal role. van der Sande et al. [42] found that changes in body $T$ during HD are significantly related to the predialytic body $T$-value, both during cold HD and standard HD. Moreover, Fine and colleagues found, in a broad population studied, that the beneficial effects of cold HD were confined to the subgroup of hypothermic patients, that is, those who repeatedly presented predialytic values of body $T < 36°C$, while no benefit was found in euthermic patients with predialytic body $T > 36.5°C$ [33].

The BTM

The Blood Temperature Monitor (BTM, Fresenius®) is a device that provides continuous readings of the three elements of the thermal balance formula, namely $T_{art}$, $T_{ven}$ and $Qb$. By means of a closed loop whose input parameters are the blood Ts, dialysate $T$ is continuously regulated to modify the $T_{ven}$ so as to obtain the $\Delta A-V$ that, in relation to blood flow, allows the predetermined targets to be obtained. The device makes it possible to perform:

- Isothermic haemodialysis: the BTM is set to prevent increase of body $T$ in the patient (body $\Delta T = 0$).
- Thermoneutral haemodialysis: the BTM operates to prevent passage of heat between the artero-venous extracorporeal circuit ($\Delta T _{a-v} = 0$).

With the advent of the BTM, van der Sande et al. [42] quantified for the first time energy balance in the course of HD; in standard HD body $T$ increased, despite a small negative energy balance, while during cold HD, energy loss was much more pronounced, e.g. $-286\text{ kJ}$, on average. This study is relevant because it provides an objective numerical figure to our studies of the early 80s [14,15].

From cold dialysis to isothermic dialysis

The main point against cold HD is that a fair percentage of patients have poor tolerance for
dialysate $T$-values of 35–35.5°C for the whole duration of the dialytic treatment [10,32]. Compliance aside, cold HD does not represent the gold standard, even from a pathophysiological point of view. From everything said thus far, it seems evident that the objective of the treatment is not to subject the patient to an extended cold pressor test, as cold HD sometimes seems to be, but rather to remove only the surplus heat energy generated and by doing so, preventing the body accumulation of heat in a personalized manner. The surplus heat energy is specific for each individual treatment and for each individual patient, dependent on his body $T$ and the rate of ultrafiltration, both parameters variable between one treatment and the next. To keep body $T$ stable in isothermic HD, energy loss was estimated between 187 kJ [39] and 229 kJ [38], on average. Although that energy loss is not inconsiderable, since on average it amounts to 30% (and can go as high as 50%) of the daily resting energy expenditure [30,38], it is however definitely less than that found in cold HD, e.g. $-286$ kJ on average [42].

We challenged isothermic HD in a prospective, cross-over, European study which has enrolled more than 100 elderly patients with numerous co-morbid factors and with a marked propensity to intradialytic hypotension [43]. In accordance with others [38,39], the estimated extracorporeal $T$ removal was $-220$ kJ, on average. With isothermic HD we have observed a reduction of 50% in dialyses disturbed by hypotension; therapeutic interventions to re-establish adequate haemodynamic conditions were also drastically reduced. It must be emphasized that in isothermic HD, no patient complained of a sensation of cold with shivering, as frequently happens with cold HD.

In our study, intradialytic hypotension has been halved but not eliminated. What remains to be defined is the marginal advantage of a moderately hypothermic treatment, say with reduction in body $T$ of 0.1°C/h. However, it must be emphasized that many factors of instability are patient related, which technological advances can do little or nothing to change.

The crucial point in isothermic HD is the accurate evaluation of the predialytic physiological body $T$. A patient who is feverish or with hyperthermia from a long stay in an overheated environment before entering the HD room [44] will have his pathological body $T$ ‘blocked’ for the entire duration of the treatment, with negative fallout on his dialytic tolerance. Afternoon dialytic shifts can bring out such problems too. In fact, according to circadian rhythm, zenith body $T$ is reached in early afternoon with subsequent $T$-values decline. We would like to report here an anecdotal observation of a young patient who complained of ‘feeling unbearable heat’ in the course of isothermic HD. His predialytic body $T$ was probably increased by the abundant meals and drinks that he was accustomed to consuming before his afternoon dialytic shift. Modifying his eating habits lessened his intolerance to isothermic HD.

If the BTM is unavailable, it is still possible to surrogate isothermal HD by monitoring peripheral body $T$ at regular intervals and manually adapting dialysate $T$ so as to maintain body $T$ constant [33]; where this maneuver might appear too time-consuming, a good surrogate is to lower dialysate $T$ only in the second part of the dialytic treatment, when hypotensive crises are more frequent [44]. In our experience, however, patients adapt to low dialysate $T$ and the cold feeling disappears. This is more easily reached by progressively reducing dialysate $T$ over a span of some weeks.

**Comparison of methods/methodologies for preventing hypotension**

In a ‘head-to-head’ comparison, the only one valid for defining a supposed superiority, no maneuver has been shown superior to cold HD for preventing hypotension: not the 21-adrenergic agonist midodrine [45], nor the use of dialysate with high Na [46,47], nor Na modelling [47]. It is interesting to note how Cruz and colleagues [45] found no additive effect in the combined use of midodrine and cold HD, probably because both maneuvers act against the same effector, namely arterio-venous vasoconstriction. As far as we know, there are no studies combining Na/UF modelling with isothermic HD, and this is a field that deserves to be explored.

Nor do convective methodologies appear to better maintain arterial pressure and/or offer a better haemodynamic profile as compared with cold HD or isothermic HD, and this holds true for isolated ultrafiltration [1,21,22], haemofiltration [2,3,48] and standard [49] or online [50,51] haemodiafiltration. However, that statement needs validation, as many of these studies [21,22,48,49,51] were shortterm and have selected a population of stable patients, while it would seem logical to verify the difference in haemodynamic unstable subjects in the longterm. The modality of reinfusion may also play a role; Beerenhout et al. [34] found different thermal effects in on-line convective treatments according to whether reinjection was performed in pre-dilution or in post-dilution.

**Conclusions**

Standard HD induces an increase in body $T$ which, in association with the hypovolaemia due to ultrafiltration and possibly other patient-related factor(s), promotes a hypotensive crisis. ‘Cold’ HD prevents that sequence of events, but is not always well tolerated by patients, since it involves an excessive and undifferentiated subtraction of heat. Isothermic HD ensures equal cardiovascular stability to subtraction of fluids, associated with fewer collateral effects.

Isothermic HD and haemo(dial)filtration form the most effective toolbox available to the nephrologist today for the prevention of cardiovascular instability during dialytic treatment.
In our view there is a need for well-designed comparative studies to establish, in reference to specific patient characteristics, the relative efficacy of each of those methodologies and the potential additive clinical advantages connected with the combined use of a number of methodologies. Such studies do not exist at this point in time [52].

Enrolment is underway for an Italian study that will compare, in the long term and exclusively in a population of unstable patients, the propensity for hypotension during on-line haemodiafiltration and haemodialysis, both conducted under identical conditions, including isothermia. We hope that the results of that study will definitively resolve this debated question.

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