30th Annual International IEEE EMBS Conference
Vancouver, British Columbia, Canada, August 20-24, 2008

Isothermic vs Thermoneutral Hemodiafiltration Evaluation by indirect Calorimetry

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Abstract—**HD and HDF as hemodialytic therapies normally alter patient's haemodynamic stability, due to the inflammatory response to extracorporeal blood circuit, producing increment of the core temperature (+1.0 ºC). However, such increase in temperature could be controlled by lowering dialysate's temperature using two main modalities techniques (isothermic and thermoneural) with different patient's thermal balance consequences, not yet well studied. In this work, energy expenditure (EE) was measured by indirect calorimetry in a group of 12 patients waiting kidney transplant. In each patient, EE was assessed (as a power generation) during isothermic and thermoneutral modalities as a manner of cross and prospective study (a) at before therapy, (b) during therapy and (c) at the end of the HDF therapy. Wheraeas, power extraction was measured by a BTM (Blood Temperature Monitor from Fresenius Inc) in order to determine power balance in a thermodynamic model of the extracorporeal circuit. The results showed significant differences in the power balance when EE at during therapy was subtracted from the EE at before therapy. Then, EE increments were 32 Kcal/4-hours during isothermic and 3.6 Kcal/4-hours during thermoneutral HDF sessions ($p < 0.05$). While, BTM totals power extraction was 91 and 16.1 Kcal/4-hours ($p<0.05$), respectively. Additionally, it was estimated a 12 % of EE/day increment during HDF-isothermic at during therapy stage compared with none significative EE increment during thermoneutral modality. The statistical evidence confirmed the expected hypothesis that both modalities affect in different manner the patient's EE. Also, we conclude there is no satisfactory data interpretation when the thermodynamic model was applied expecting null balance between EE increment and BTM power extraction. Therefore, these findings force to think there is need of different BTM design and measurement setting with ability to follow dynamic patient's EE changes with the purpose to achieve a better power balance.**

I. Introduction

THERMAL effects have a very important impact on patient's hemodynamic stability during hemodialysis and hemodiafiltration therapies. Dialysate temperature control has been shown to play a relevant role for patient's intradialytic blood pressure stability [1]. Thus, cold dialysate plus convective dialytic therapy has been used to increase the external heat loss compensation, when patient shows core temperature increments (+1.0 ºC) due to the inflammatory response as a consequence of the hemodialytic therapy itself. Then, the basic idea is to avoid patient's vasodilatation but controlling blood cooling negative effects such as myocardial contractility and venous tone diminishing together with hypothermia discomfort symptoms increasing [2]. Therefore, hemodynamic instability due to patient's heat accumulation remains as one of the most difficult medical and technological challenges to solve in hemodialysis (HD) and hemodiafiltration (HDF) therapies.

The clinic state of the art uses intradialytic adaptive empirical algorithmic approach to control the solutes and energy transfer over the cartridge-dyalysate circuit. The primary objective, if not the single, has been to govern by hypothesis the genesis of the heat accumulation to avoid the dialysis-related hypotension [3]. Specifically, the set of factors which avoid hypotension are related to the specific HD and HDF prescription such as the mode of patient's temperature control (isothermic or thermonatural modality), ultrafiltration rate prescription, osmolality control, electrolyte composition control, etc [4]. Others factors which promote the loss of hemodynamic homeostasis have been medically treated such as autonomic nervous dysfunction and cardiac diseases.

On the other hand, few and controversial studies have been reported about energy expenditure (EE) during HD and HDF therapies [5]. Increase in EE, as a consequence of the increased heat production, during HDF therapy has been suggested but so far there is no clear evidence of the amount of this and the particular differences of EE during isothermic or thermoneural HDF modalities [6].

Unfortunately, many and historical treatments where HD and HDF therapies prescription have preserved dialysate temperature constant, have not contributed for information about the real energy transfer statistics due to the lack of the appropriate technology. However, since 2003 using a BTM device (Blood Temperature Monitor, Fresenius, Bad Homburg, Germany) the extracorporeal energy transfer can be monitored and controlled so that algorithmically the heat removal can be on-line estimated and it is not longer empirically adjusted [7].

Therefore, one important premise for this work was that simultaneous measurement of extracorporeal heat loss

Manuscript received on April 16, 2008. This work was supported by Universidad Autónoma Metropolitana and Instituto Nacional de Cardiología Ignacio Chávez at Mexico City.

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together with the measurement of patient's EE could provide a modeling evaluation information about the patient's hemodynamic stability, the thermodynamic physiological process and the BTM's modalities effects over the patient's EE. To test this hypothesis, we designed an experiment where a patient population was submitted in different days to a cross-over prospective study using the isothermic or thermoneutral modalities with only the HDF therapy, while intradialytic patient's EE was measured.

II. Methodology

A. Model Formulation

This work assumed a simple thermodynamic lumped-concentrated parameters model (Fig.1) for easy understanding of heat balance in the extracorporeal blood-dialysate circuit. This model stands for the heat transfer flow taking the cartridge as the thermodynamic reference symmetrical point under steady state conditions and during HDF therapy at fixed time of approximately 4 hours. Then, power transfer was lineally modeled as in equations (1-2). Additionally, it was assumed an ideal power balance as in equation (3). This means that the power removed by the BTM is equal to the power generated by the patient's EE, avoiding heat accumulation and preserving homeostasis.

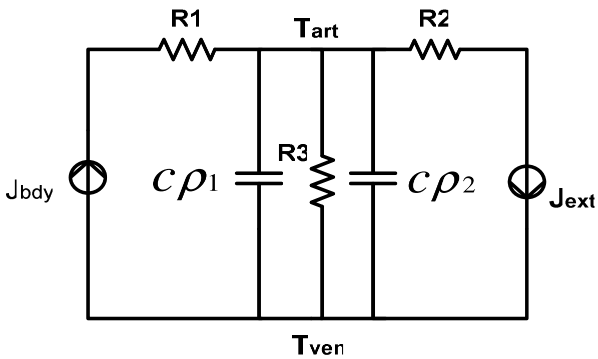

Fig 1. Steady state thermodynamic power model (lumped parameters) for the HDF therapy is shown. Energy expenditure is represented by Jbdy (Kcal/4 hours), while Jext (Kcal/ 4 hours) represents the power removed by the BTM. Observe that both power sources are modeled by electric current sources.

$$J_{bdy} = c\rho_1(Qb - UFR)(T_{art} - T_{ven})\left(\frac{R_2}{R_2 + R_3}\right) \quad (1)$$

$$J_{ext} = -[c\rho_2](Qd + UFR)(T_{art} - T_{ven})\left(\frac{R_1}{R_1 + R_3}\right) \quad (2)$$

$$J_{bdy} = EE = J_{ext} \quad (3)$$

Where:

J_{bdy} and J_{ext} are powers sources in Kcal/4-hours, where the former points out the power delivered to the extracorporeal circuit by the EE, while the second power source points out the power sink removed through out the dialysate using the BTM.

$c\rho_1$ and $c\rho_2$ are the blood and dialyzate heat capacity, respectively, with specific values due to their specific densities of $c\rho_1$ =3.81 and $c\rho_2$ =4.18 [Jouls/ºC/cm³].

T*art* and T*ven* refer to arterial and venous line temperatures in ºC at the fistula. Qb and Qd refers to the extracorporeal blood flow and the dialysate flow in ml/sec, respectively. UFR refers to the ultrafiltration rate in ml/sec. R_1 and R_2 refers to the circuit thermal conductivities per length [Kcal/4-hours/(meter-ºC)], which are generated by the blood flow and the dialysate flow, respectively. Finally, R_3 represent the high flux cartridge conductivity during HDF therapy, sustaining the mayor interface power transfer [(Kcal/4-hours/(meter^2/meter-ºC)],).

B. BTM modalities

The BTM works in active or passive mode (dT=0, dE=0) corresponding to the isothermic or thermoneural modalities, respectively. The BTM set-up connects in the extracorporeal circuit two sensors that continuously measure the arterial-vein blood temperature difference. Therefore, these sensors are placed in the arterial and venous extracorporeal lines such as in passive mode the patient's core temperature (T_A) is only registered, while in active mode (regimen T) the dialysate temperature is continuously adjusted every 1.5 minutes using a feedback transfer function {k(t).(Tart-Tven)} with the purpose that k(t) governs the rate the dyalizate is heating to reach a preset T_A cool temperature (typically 36.5± 0.1 ºC) respect to the body standard temperature (37 ºC) [8].

In this work, the therapy and BTM's modalities were selected to implement the isothermic-HDF and thermoneutral-HDF therapies with the premises that the former would prove equation (3) and the second implies theoretically none thermal power transfer into the dialyser system. Hence, the thermoneutral modality presets the dialysate to a fixed temperature value (typically equal to the initial patient's core temperature) with the option to be preset empirically at lower temperature. In any case thermoneutral-HDF modality has a high probability to develop body heat accumulation.

C. Therapies Evaluation

The premises encouraged us to assume the following methodological outcomes and interpretations for the therapies evaluation: (a) If there were EE increment, when any of the two thermal modalities were applied, then both modality-therapy would be responsible for increasing power production and its accumulation, (b) if an increment in EE occurred, when just one of the two modalities were applied, then this particular modality would be related to the respective power balance and not to the HDF therapy by itself. Also, this EE increment would be responsible for the increment in the patient's body temperature, (c) if the EE remained stable within the same values along the whole intradialitic therapy, in both thermal modalities, then power balance would be dependent on the extracorporeal heat flow extraction strategy.

C. Experiment Design

Twelve stable patients (7 women and 5 men) were studied from the kidney transplant program at the National Institute of Cardiology in Mexico City. The patient population had a mean age of 38.7±12.9 years. The average effective time on renal replacement therapy was 207±34 minutes. Pre and post weight therapy was 66.4±12.9 and 63.2±13.1 Kg, respectively.

The EE was measured by indirect calorimetry using a research hybrid calorimeter (MGM-3H) with mixing chamber and breath by breath measurements every 20 seconds as it shown in Fig. 2, [9-10]. Patients were undergoing to intradialytic exercise using pedal ergometers (approximately 10 watts of load). Thus, EE was estimated at three different stages (before, during and end of the therapy), using half mask with two valves to capture only the expired gases. It was used 22 mm of diameter of flexible tubing to connect the mask to the mixing chamber and to the breath by breath measurement system. Normally, EE measurements started with the first stage at most 1 h after the patients morning breakfast. Then, patients start with their exercise routine but suspending it when *during therapy* measurement was taken. This after one hour *before therapy* stage was taken. Finally, patients were studied at the *end therapy* once they were disconnected from the hemodyalitic unit.

The statistical modalities evaluation was carried out using a prospective cross-over study. Thus, isothermic-HDF and termoneutra-HDF therapies were applied to each patient in different days to generate six groups stage-dependent for paired analysis. For statistical analysis, non-parametric tests were employed. The variables (EE=J_{bdy}, VO2, VCO2, J_{ext}, systolic and diastolic presures) were characterized as medians and quartiles ranks. Prospective statistical differences analysis, among each set of groups (during each thermodynamic modality), were carried out using the Friedman test as it shown in Fig. 3. Particulary, for average statistical differences between the isothermic-HDF group versus thermoneutral-HDF group *during therapy stage*, the Wilcoxon test for paired analysis was used. In both techniques p<0.05 was considered statistically significant.

Fig 2. The MGM-3H hybrid research calorimeter is shown. This calorimeter estimates the EE using mixing chamber and breath by breath techniques for specific use in hemodialytic units.

III. RESULTS

The Fig. 3 shows the EE averages estimation (in Kcal/day) when the isothermic-HDF (black bars) and the themoneutral-HDF (gray bars) modalities were applied. The Friedman's test (with its "Ps") is shown to emphasize that only the isothermic-HDF modality was significant for the three groups along the therapy. Whereas, the themoneutral-HDF modality is showed with non statistical significance when the *before therapy* group and the *during therapy* group were compared.

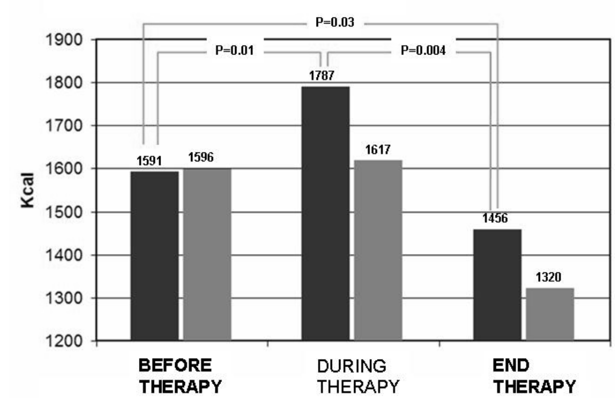

Fig 3. The EE measurement is shown. It was used three HDF therapy stages (before, during and at the end of the therapy). Significant changes were tested using the EE *before therapy* as a point of reference. Friedman test was used to prove the statistical significance among groups prospectively. Friedman's test was significant only during isothermal modality.

TABLE I
EE INCREMENT AVERAGES TEST FOR ISOTHERMIC-HDF VS THERMONEUTRAL-HDF MODALITIES AT *DURING THERAPHY*
N=12 PATIENTS

HDF Modality	J_{bdy} kcal/4Hours	J_{ext} kcal/4Hours	Syst B.P	Dyast B.P	Tem Dial
HDF-Isotherm (Quartile range)	**32** (15-64)	**91** (52-128)	**131** (113-141)	**69** (56-78)	**35.2** (35.1-35..3)
HDF-Thermo (Quartile range)	**3.6** (-22-16)	**16.7** (-1.7 - 48)	**118** (107-148	**66** (54-77)	**36.9** (36.6-37.1)
Wilcoxon test	p=0.02	p=0.004	p=ns	p=ns	p=.002

Table I shows the EE increments (EE at *before therapy* – EE at *during therapy*, in Kcal/day) at one hour, once the therapy had been started. This values are the differences when the EE of 1591 (1238-1924) was substrated from 1787 (1284-2200). Then 196 were divided by 6 in order to obtain the 32 Kcal but in 4 hours, which is similar to the BTM time power extraction, all this specifically for the isothermic-HDF therapy. Analogously, the EE of 1596 (1393-1962) was substrated from 1617 (1228-2004) in order to obtain only 3.6 Kcal/4 hours during the thermoneural-HDF modality. The rank sum of Wilcoxon test produced statistical significance for the EE changes and for the BTM power extraction when both modalities groups where compared.

Additonal, an important result is in Table I, where systolic blood pressure (Syst B.P.) was measured for both modalities without statistical significative differences (131 vs 118). Likewise, diastolic blood pressure (dyast B.P) was measured for both modalities without finding significative differences (69 vs 66 mmHg).

IV. DISCUSSION

The statistical evidence shows approximately 10 times of increment in the EE only during the HDF-isothermic modality when it was compared with the HDF-termoneutral power balance at *during therapy* stage. Another issue to note is the absolute increment of 12% in this isothermic-HDF modality at the same therapy stage that agrees well with other similar finding in the literature [3]. Also, it is worth to mention that in both thermal modalities there is a power over extraction by the BTM. Particularly, 91 Kcal/4-hours of thermal power were extracted by the BTU system when patients were producing an EE average of 32 Kcal/4-hour or the BTU was extracting 16.7 when patient's EE was around 3.6 Kcal/4-hours. Hence, this 35% of power unbalance is too high to be considered as a correct power balance, so that a primary analysis should consider the BTM as part of a thermodynamic system subject to be redesign with the purpose to support equation (3). However, it is necessary to consider other reasons for high values of the BTM's power extraction. For instance, the HDF therapy is a convective system that generates power by itself due to probably kinetic energy transformation inside the hemodyalitic cartridge. This keeps consistency with the evidence that isothermic modality is responsible for the power balance and not the HDF therapy by itself. Another possible explanation requires finding others power sources which effects are directly over the temperature sensors in the sense they govern the power extraction lowering the dyalisate temperature. One final explanation is that power balance can be achieved by extracorporeal heat flow with the possibility to cause hemodynamic stability but generating heat accumulation not detected by the patient's EE. Nevertheless, these hypothesis must be tested in future research work.

V. CONCLUSION

In summary, this work supports the following ideas: (1) the EE measurement provides an easy way to evaluate power balance no only to decide the benefit of the HDF therapy but also to evaluate the isothermic modality performance, once the cartridge power generation could be estimated, (2) clearly the HDF therapy by itself is not a direct factor for the patient's temperature increment, since only when the isothermic modality was applied an increment in the EE was produced, (3) the isotermic-HDF therapy showed better performance to maintain hemodynamic stability since the EE increment means a mayor body enthalpy, which can be considered with a mayor probability to generate free energy improving cell homeostasis. Additionally, isothermal-HDF therapy showed marginally higher systolic and diastolic blood pressures so that it was considered with better performance for hemodynamic stability.

ACKNOWLEDGMENT

This work was supported by grants from the Universidad Autonoma Metropolitana through out DCBI-Iztapalapa and under Acuerdo 14. Prof. Cadena gratefully thanks Instituto Nacional de Cardiología Ignacio Chávez for all the facilities provided for this research project in Mexico City.

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