Biofeedback Control Of Ultrafiltration For Prevention Of Hemodialysis-Induced Hypotension

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Abstract- Hemodialysis-induced hypotension is still a severe complication in spite of all the progress in hemodialysis treatment. Because of its multifactor causes, hemodialysis-induced hypotension cannot be reliably prevented by conventional ultrafiltration and sodium profiling in open-loop systems, as they are unable to adapt themselves to actual decreases in blood pressure. Therefore, it is the ultimate goal to provide automatic control in hemodialysis. Furthermore, the treatment should improve patient comfort and be carried out without use of additional body sensors and without additional medication. Automatic control of hemodialysis has the potential to provide a better treatment to the ever increasing number of ESDR patients who present with more complicated co-morbid conditions.

Key words: Bio-feedback, Hemodialysis, Dialysis adequacy, System dynamics, hypotension, blood pressure, Ultrafiltration

I. INTRODUCTION

Hemodialysis (HD) is available through technology, which makes it possible in the first place. Over the last few years, technological innovations in dialysis equipment and new modalities have improved the quality and safety of HD treatment. The traditional HD treatment is managed in a typical forward manner, for example in the prescription and delivery of the dose of dialysis measured as Kt/V [1,2]. The medical staff acts as a part of the controller and determines time on dialysis (t) and clearance (K) for the estimated patient volume (V) to reach the prescribed Kt/V (set point). Disturbances such as errors in actual blood flow because of erroneous pump calibration, changes in dialyzer clearance because of fiber clotting, and reduction in effective clearance because of recirculation and compartment effects lead to a difference between the delivered (controlled variable) and the prescribed dose (set point) of dialysis [2,3]. In the forward control system there is no means to compensate for this difference because there is no information on the actual output.

The control of the system output is improved when the controller receives information from the actual output in the so-called feedback control system [4]. For example; to control dose of dialysis effective clearance must be measured and compared to prescribed clearance [5].

The machine receives information from the medical staff regarding the UF volume (UFV) together with a specific UF profile and the treatment time (t) derived from the dose of dialysis (Kt/V) which depends on patient volume (V) and dialyzer clearance (K_D) determined by the dialyzer mass transfer coefficient (K_0A), the dialysate flow (Q_D) and the effective blood flow (Q_B). Blood electrolytes, most importantly the concentration K^+, Na^+ and determine the composition of the dialysate bath. From the difference between delivered and prescribed clearance (negative feedback) the controller adjusts different actuators such as blood flow, dialysate flow, and treatment time to compensate for the error between output and set-point. In this case the controller does not require a complete and detailed knowledge of the plant.

Symptomatic hypotension occurs in up to 30% of hemodialysis treatments and represents one of the most severe complications during hemodialysis treatment [6]. Since a number of causal factors are involved [7,8], partly related to the dialysis technique itself (ultrafiltration, dialysate sodium and temperature, membrane) and partly related to the patient (hydration, anemia, cardiovascular pathologies, etc.), real prevention is almost unattainable. In an attempt to introduce something really new, as compared with traditional preventative measures (bicarbonate dialysis, fasting dialysis, adequate dialysis sodium, etc. largely resulted in being ineffective), over the past decade different systems have been devised and integrated into the dialysis machine, in order to artificially modify some parameters involved in the genesis of hypotension. Most of these systems exploit the idea of preventing severe hypovolaemia and improving vascular refilling by maximizing the ultrafiltration rate (UFR) in the first part of dialysis, thereby reducing the negative effect of fluid withdrawal over the cardio-circulatory adaptation mechanisms in the last part of the treatment. The concomitant capability of some systems to move the dialysate sodium concentration as well may further contribute to enhancing vascular refilling dynamics [9–13]. Alternatively, the control of the patient's thermal status, by preventing the heat gain responsible for vasodilation and possibly hypotension, has been considered [14]. Different clinical trials have actually proven the efficacy of all these systems in reducing the hemodynamic instability of hypotension-prone patients during dialysis [15–19]. However, what appears to be paradoxical is that blood pressure (BP), which is the real target of any form of control, cannot enter any of the control systems devised up to now as an input parameter, so the effect on BP remains indirect. Instead, just by considering the extreme complexity of the factors and mechanisms responsible for hypotension during dialysis, BP itself should be taken as the main input parameter for an automatic system capable of moving the UFR and/or the dialysate conductivity (DC) in a feedback manner.

II. SUBJECTS AND METHODS

A. The Biofeedback Approach

The concept of on-line monitoring is based on the real time and repeated measurement of chemical/physical signals coming from the patient. The meaning of these biosensors was to identify as early as possible inadequate performances of the treatment or physiological abnormalities induced by the treatment with consequent patient discomfort and dialysis-related side effects. Once the measurement of a given signal is taken, data are analyzed and evaluated. If the parameter is within the desired values, the treatment continues unchanged. If the parameter is not satisfactory, an action to bring it back to the desired value is needed. This action can be operated manually (by the operator), semi-automatically (authorized feedback by a nurse or a doctor) or automatically by a bio-feedback loop built in the machine [20]. This is the concept of automatic bio-feedback [21-23]. While any action performed by an operator necessarily implies a certain time lag, the power of the automatic feedback is that no lag is present between the analysis of the signal coming from the patient and the retroactive action to bring the parameter back to the desired value. The final result of automatic bio-feedback systems is that the control variable varies gradually and smoothly along a pre-defined trajectory towards a pre-defined target [23].

Biofeedback loops could be also used to modify blood flow rates in response to inadequate predicted Kt/V by a urea sensor. Today, the different parameters for which on-line monitoring is possible are: blood volume (BV) changes, dialysate conductivity, urea kinetics and thermal energy balance.

B. Patients

An experimental study with a comparison group was used. The study subjects consisted of 140 hemodialysis patients on 3-times-per-week dialysis regimens. No subjects dropped out of the study. The patients were divided into two groups: group A and group B. Patients in group A (n=80) were treated based on the decisions from system dynamics software (Hemodiadynamics) depending on the actual blood pressure variations and ultrafiltration profiling simultaneously. Patients in group B (n=70) were treated with conventional hemodialysis and without using the system dynamics control of ultrafiltration and blood pressure. Therefore, the following abbreviations were used to identify the sessions: A=SDBPS (system dynamics blood pressure stabilization system) sessions, with variable UFR; B=conventional dialysis, with constant UFR. This strategy was chosen in the study design as it represented the most immediate approach in sounding out the system's effectiveness.

The optimal weight of all patients is defined every 3 months by assessing chest X-ray, tissue bioimpedance measurement, blood pressure course and clinical signs. The interdialytic weight gain differed from 1.6 to 6.1 kg (average 3.4±1.2 kg). Comparisons of interdialytic weight gains after treatments were focused individually on the same patient during the normal rhythm of 2–2–3 days weekly. For reliable results only 2-day intervals were considered. Patients with vascular instability took their antihypertensive medication after hemodialysis. All patients were allowed to eat and to drink during hemodialysis.

C. Hemodialysis Procedure

Hemodialysis was routinely performed with a high-flux dialyzer. Patients had dialysis three times a week, in 3-4 hour sessions, with a pump arterial blood flow of 300-350 mL/min, and flow of the dialysis bath of 500 mL/min. Dialysate temperature in all treatments was 36-37°C. The dialysate consisted of the following constituents: sodium 141 mmol/l, potassium 2.0 mmol/l, calcium 1.3 mmol/l, magnesium 0.2 mmol/l, chloride 108.0 mmol/l, acetate 3.0 mmol/l and bicarbonate 35.0 mmol/l. All patients used hollow fiber dialyzers with high-permeability biocompatible membrane: 1.8 m^2 polysulphone with an ultrafiltration coefficient of 18 ml/h/mmHg. The dialysis technique was conventional hemodialysis, no patient being treated with hemodiafiltration. The hemodialysis session conditions were kept stable throughout the study. A Fresenius model 4008B dialysis machine equipped with a volumetric ultrafiltration control system was used in each dialysis. Fluid removal was calculated as the difference between the patients' weight before dialysis and their target dry weight. Pre-dialysis body weight, blood pressure and pulse rate were measured before ingestion of food and drink. Blood pressure was determined with a digital electronic sphygmomanometer with the patient on sitting position. In patients carrying an arteriovenous fistula, the contralateral arm was used for both BP measurements. BP, pulse rate, arterial line pressure, venous line pressure, blood flow rate, trans-membrane pressure and fluid loss were all measured hourly during dialysis. Weight, BP, pulse rate and temperature were recorded post-dialysis. Blood flow during dialysis was slowed to 100 ml/min before collecting post-dialysis blood samples for urea. Mean arterial pressure was calculated as the diastolic pressure plus one-third of the pulse pressure

D. Biofeedback System Dynamics Design

The feedback control provides for the measurement of arterial pressure and its trend during the treatment and an accurate regulation of ultrafiltration finalized to the maintenance of an adequate blood pressure. This system dynamics model allows the modulation of ultrafiltration proportionally to the variation trend in the arterial pressure and so small variations in blood pressure are matched by small variations in ultrafiltration or the maintenance of constant ultrafiltration, while large pressure variations are matched by large variations in the ultrafiltration. The advantages of biofeedback-controlled hemodialysis were demonstrated by both decreasing the frequency of hypotonic episodes and by increasing or maintaining constant levels of systolic blood pressure during the final phase of dialysis treatment. The actual blood pressure represents comprehensively the actual cardiovascular situation of the patient. Therefore, the actual systolic blood pressure and its trend are the guiding parameters for a biofeedback-driven monitor for blood pressure stabilization during hemodialysis. Figure 1 shows the schematic representation of the automatic closed loop regulation of blood pressure during dialysis therapy by using our system dynamics model. This feedback system consists in the setting of 2 clinical objectives: Total Weight Loss (TWL) for the restoration of the dry weight; Variation of the blood pressure (BP) for the preservation of cardiovascular stability.

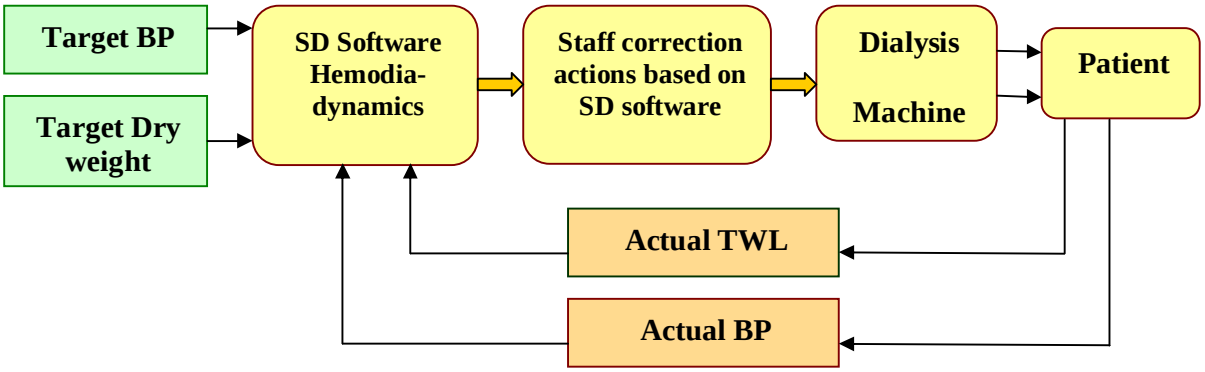

Figure 1 Closed-Loop System For The Simultaneous System Dynamic Control Of Ultrafiltration And Blood Pressure.

E. Model Description

The research analysis started by using the mental model (Dialysis performance causal loop diagram explaining and understanding the complex cause and effect relationships existing between dialysis variables. The model discussed in [24] was developed using Vensim DSS v 4.0a simulation software that evaluates the effect of dialysis policies on session performance, quantifying, optimizing dialysis efficiency and monitoring dialysis performance online. The model focused on analyzing and highlights factors which may alter the delivered dose and may lead to session degradation. The overall causal loop diagram of the system is shown in Appendix A. The goal of this study is to use and test a biofeedback system to monitor and regulate ultrafiltration volume during dialysis that will be helpful in:

- Achieving the desired dialysis dose Kt/V.
- Reducing the intradialytic complications.

Therefore, the loops that highlight the effect of ultrafiltration on dialysis adequacy and intradialytic complication will be described.

B4 – Effect Of Ultrafiltration On Complication Loop

Ultrafiltration Rate → probability of complications → Ultrafiltration Rate. Hemodialysis-induced hypotension is still a severe complication in spite of all the progress in hemodialysis treatment. Increases the intradialytic complications force us to decrease the Ultrafiltration rate to decrease it. This loop is considered the ultrafiltration controller to reduce the hypotension episodes for dialysis patients. Hence, the simultaneous control of ultrafiltration has proven the most effective means for automatic blood pressure stabilization during hemodialysis treatment. This loop behaves as a balancing loop as shown in figure 2.

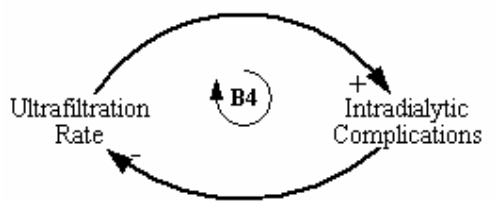

Fig. 2 Effect Of Ultrafiltration On Complication Loop

B1 –The Effect of Ultrafiltration on urea clearance loop

Dialysis Adequacy (Kt/V) → Ultrafiltration rate → modeled dialyzer clearance → blood urea nitrogen (BUN) → Dialysis Adequacy (Kt/V). Decrease in dialysis adequacy can force us to increase it by increasing the ultrafiltration rate to a value not affects the patient's blood pressure. This increase in the ultrafiltration rate will increase the in vivo dialyzer clearance and hence the blood urea nitrogen decreases which ultimately increases the dialysis adequacy. This loop behaves as a balancing loop as shown in figure 3.

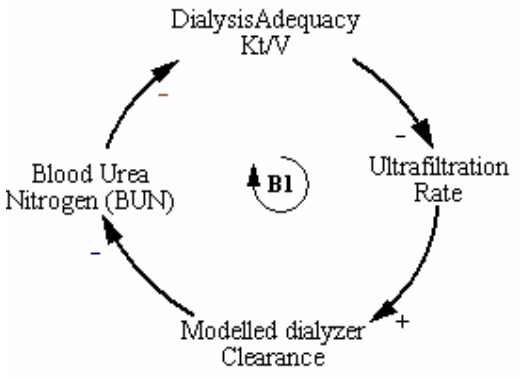

Fig. 3 The Effect of Ultrafiltration on urea clearance loop

B2 – The Effect Of Ultrafiltration On Urea Distribution Volume Loop

Dialysis Adequacy (Kt/V) → Ultrafiltration rate → modeled dialyzer clearance → Urea distribution volume (V_t) → Dialysis Adequacy (Kt/V). Ultrafiltration (UF) is assumed to enhance urea removal during hemodialysis because of convective transport and because of contraction of urea distribution volume, therapy increasing dialysis efficiency (Kt/V). Decrease in dialysis adequacy leads to an increase in the Ultrafiltration rate to a value not affects the patient's blood pressure. An increase in Ultrafiltration rate causes an increase in the in vivo dialyzer clearance and hence the urea distribution volume decreases which in turn increases the dialysis adequacy. This loop behaves as a balancing loop as shown in figure 4.

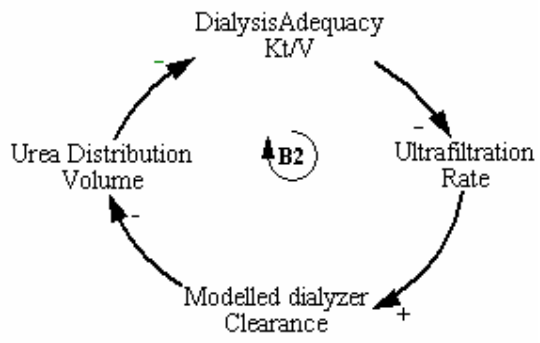

Fig. 4 The Effect Of Ultrafiltration On Urea Distribution Volume Loop

R5 – Effect Of Complication On Urea Removal Loop

Dialysis session performance → Intradialytic complications → Ultrafiltration Rate → modeled dialyzer clearance → blood urea nitrogen → Calculated Dialysis Adequacy (Kt/V) → Dialysis session performance. An increase in the intradialytic complications can force us to decrease the Ultrafiltration rate. The model decreases the ultrafiltration rate to a level not affects the urea reduction or the dialysis adequacy rate. Thus the dialysis dose increases and hence the dialysis session performance will increase. This loop behaves as a reinforcing loop as shown in figure 5.

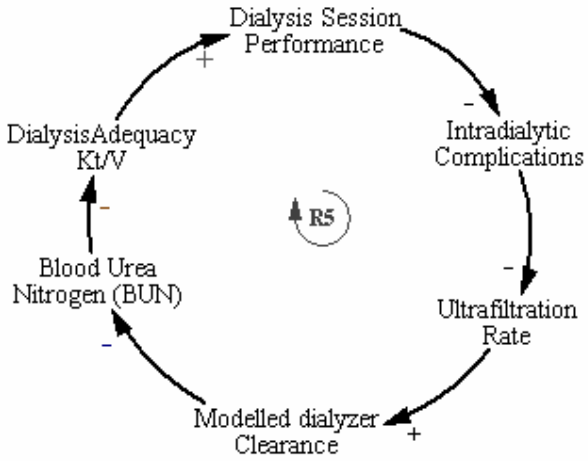

Fig. 5 Effect Of Complication On Urea Removal Loop

F. The Quantitative Description: Formulating a Simulation Model

This next step in modeling involves setting up a formal model complete with equations, parameters and initial conditions that represent the system. The overall stock and flow diagram was shown in [24] and is shown also in Appendix B. For each subsystem the assumed parameters, initial values, variable were ranged to be entered to the system for the sake of building the stock & flow diagram. After that the equations and graphs that describe the relationships between the various variables were entered to the system using the Vensim DSS software and were elicited from the experts in the field of nephrology. They were asked for their inputs on the units for measurement of different variables, the functional form of the various equations between variables, parameters of these equations (elicited through graphical portrayal of key relationships), and the initial values of all stock variables. To show the effect of the ultrafiltration control on the overall hemodialysis session performance and intradialytic complications, two structures will be described from the overall stock & flow diagram. These two structures are the ultrafiltration volume subsystem and the intradialytic complication structure.

- **The Ultrafiltration Volume Subsystem**

The ultrafiltration volume Subsystem is shown in figure 6. The ultrafiltration volume stock (dL) is fed into by ultrafiltration increasing rate (dL/Minute) and is depleted by ultrafiltration decreasing rate (dL/Minute). The ultrafiltration volume stock is an integral of the ultrafiltration increasing rate less the ultrafiltration decreasing rate.

Ultrafiltration volume (t) = ultrafiltration volume (0) + $\int$ [ultrafiltration increasing rate – ultrafiltration decreasing rate] dt (1)

Ultrafiltration volume (0) = 0

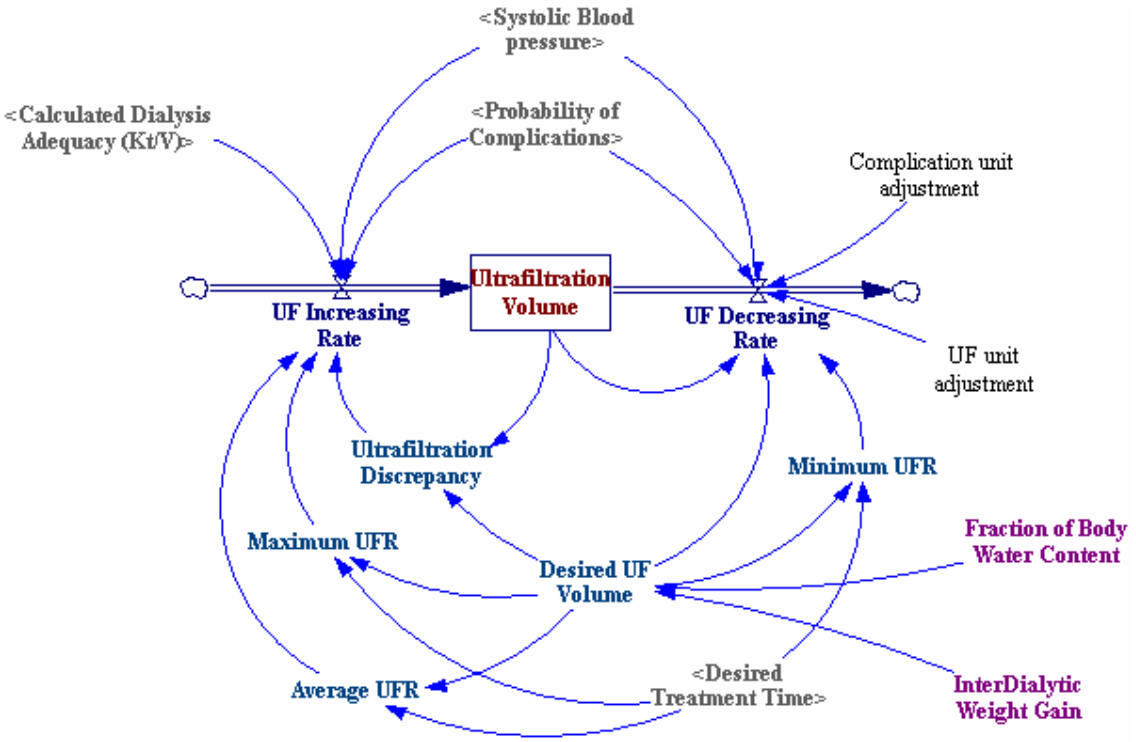

Fig. 6 The Ultrafiltration Volume Subsystem

Figure 7 shows the concept of the feedback control of ultrafiltration rate (UFR, vertical bars) and blood pressure (BP) during a dialysis session with the automatic blood pressure stabilization system. When the model (controller) highlights a negative trend in the blood pressure it makes a decision to staff for reducing the ultrafiltration to the extent of reducing it to zero when there is no pressure recovery. Obviously, a system limitation may be having to respond categorically to given constraints such as the duration of the session and the total ultrafiltration (total patient fluid loss). If rigid limits are set upon these parameters, then in some patients the control by the system becomes more difficult.

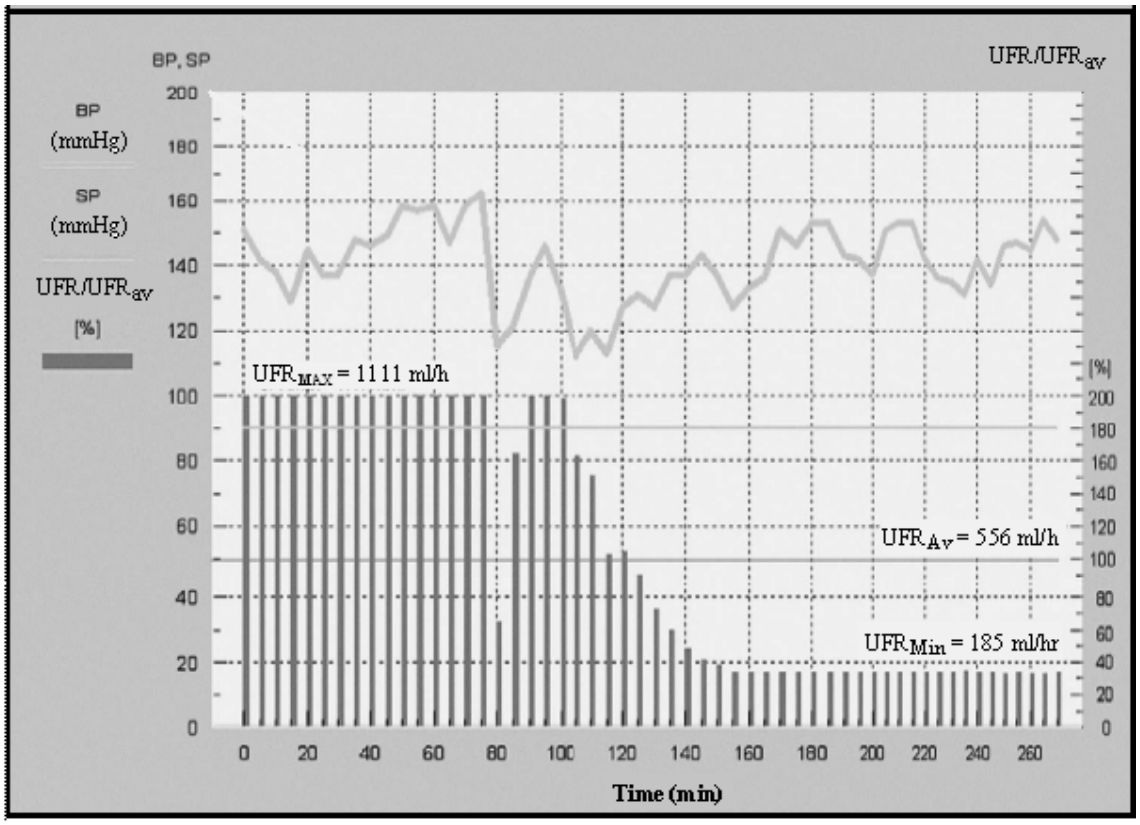

Figure 7 Feedback Control Of Ultrafiltration.

The ultrafiltration volume subsystem behaves as an ultrafiltration controller to control the rate of fluid removal throughout the dialysis session. When an ultrafiltration control device is not used, the fluid removal rate can fluctuate considerably as the pressure across the dialyzer membrane varies. Transiently rapid rates of fluid removal can then occur, causing acute contraction of the blood volume and hypotension. The best prevention is to use a dialysis machine with an ultrafiltration control device. If such a machine is not available, then one should use a dialyzer membrane that is not very permeable to water, so that the unavoidable fluctuations in the transmembrane pressure during dialysis will translate to small changes in the fluid removal rate. The ultrafiltration increasing rate is driven by the probability of hypotension and the patient's blood pressure. Ultrafiltration volume can not take value greater than the desired value to avoid excessive ultrafiltration.

If the ultrafiltration discrepancy between the desired UF Volume and the Actual UF Volume is equal zero, the ultrafiltration rate value is limited to 0, which indicated that the desired UF volume is achieved. It was noted that the first half of the hemodialysis treatment is much less hypotensive episodes in comparison with the second half of the treatment.

In conclusion, it was obviously more beneficial to ultrafilter in the first part of hemodialysis as much as the actual systolic blood pressure allows with the consequence of low ultrafiltration rates at the end of hemodialysis. This goal can be achieved by applying MAX rates up to 110-120% of the average ultrafiltration rate during the initial and medium phases of treatment as long as it is tolerated by the systolic blood pressure.

In order to adapt the control characteristics properly to the individual requirements of each patient, the critical borderline of systolic pressure (set point) is selected by the physician before starting the treatment Normally, set points of 90-100 mmHg are used for patients having initial systolic pressures of 90 mmHg or higher Thus, as the probability of hypotension is less than 50 % and the systolic blood pressure is more than or equal to 120 mmHg the max rate of ultrafiltration can be applied. The UFR is maintained constant at the maximum range until the probability of hypotension episodes exceeds or equal 50 % and a BP reduction is recorded then it is automatically by the software reduced to the average value. If a BP less than or equal 100 mmHg is recorded then the minimum UFR of less than 10-20% of the average ultrafiltration rate is applied.

UF Increasing Rate = IF THEN ELSE (Ultrafiltration Discrepancy = 0, 0, IF THEN ELSE ("Calculated Dialysis Adequacy (Kt/V)" <> 1: AND: Probability of Complications < 0.5: AND: Systolic Blood pressure >=120, Maximum UFR, Average UFR)) (2)

UF Decreasing Rate = IF THEN ELSE (Ultrafiltration Volume = Desired UF Volume, Desired UF Volume * UF unit adjustment, IF THEN ELSE (Probability of Complications * Complication unit adjustment > 0.5: OR: Systolic Blood pressure <= 100, Minimum UFR, 0)) (3)

Intradialytic Complication Structure

Intradialytic hypotension (IDH) is the most common complication of hemodialysis, occurring in 20 to 30% of treatments. It is an important clinical problem because associated symptoms, such as nausea and cramps, have a negative impact on health-related quality of life. Figure 8 shows the structure of intradialytic complication. Several factors influencing and modifying BP changes throughout dialysis treatment have been identified. Ultrafiltration changes and dialysate modifications are, however, the major and the most important dialysis variables in the control of hypotensive episodes. Ultrafiltration profiling can also have a beneficial impact on blood pressure behavior during hemodialysis. This new feedback control system can be used to estimate the probability of hypotension during dialysis. This probability is assumed to be a deterministic probability varies from 0 to 1. If the additive impact of ultrafiltration and dialysate modification is more than 1, its value is limited to 1 which indicated that the patient is completely hypotensive. The following equation can be used to estimate the intradialytic probability of hypotension:

Probability of Complications = IF THEN ELSE (Session Performance = 1, 0, IF THEN ELSE (Effect of Dialysate temperature on complications(Dialysate Temperature * Dialysate temp lookup conversion unit) + Effect of Dialysate type on complications (Type of Dialysate) + Effect of increasing ultrafiltration on complication generation (Ultrafiltration Volume * UF lookup Conversion unit) + Probability of morbidity + Effect of Blood pressure on complication generation (Systolic Blood pressure * Blood pressure lookup Conversion unit) > 1, 1, (Effect of Dialysate temperature on complications (Dialysate Temperature * Dialysate temp lookup conversion unit) + Effect of Dialysate type on complications (Type of Dialysate) + Effect of increasing ultrafiltration on complication generation (Ultrafiltration Volume * UF lookup Conversion unit) + Probability of morbidity + Effect of Blood pressure on complication generation (Systolic Blood pressure* Blood pressure lookup Conversion unit)))) (4)

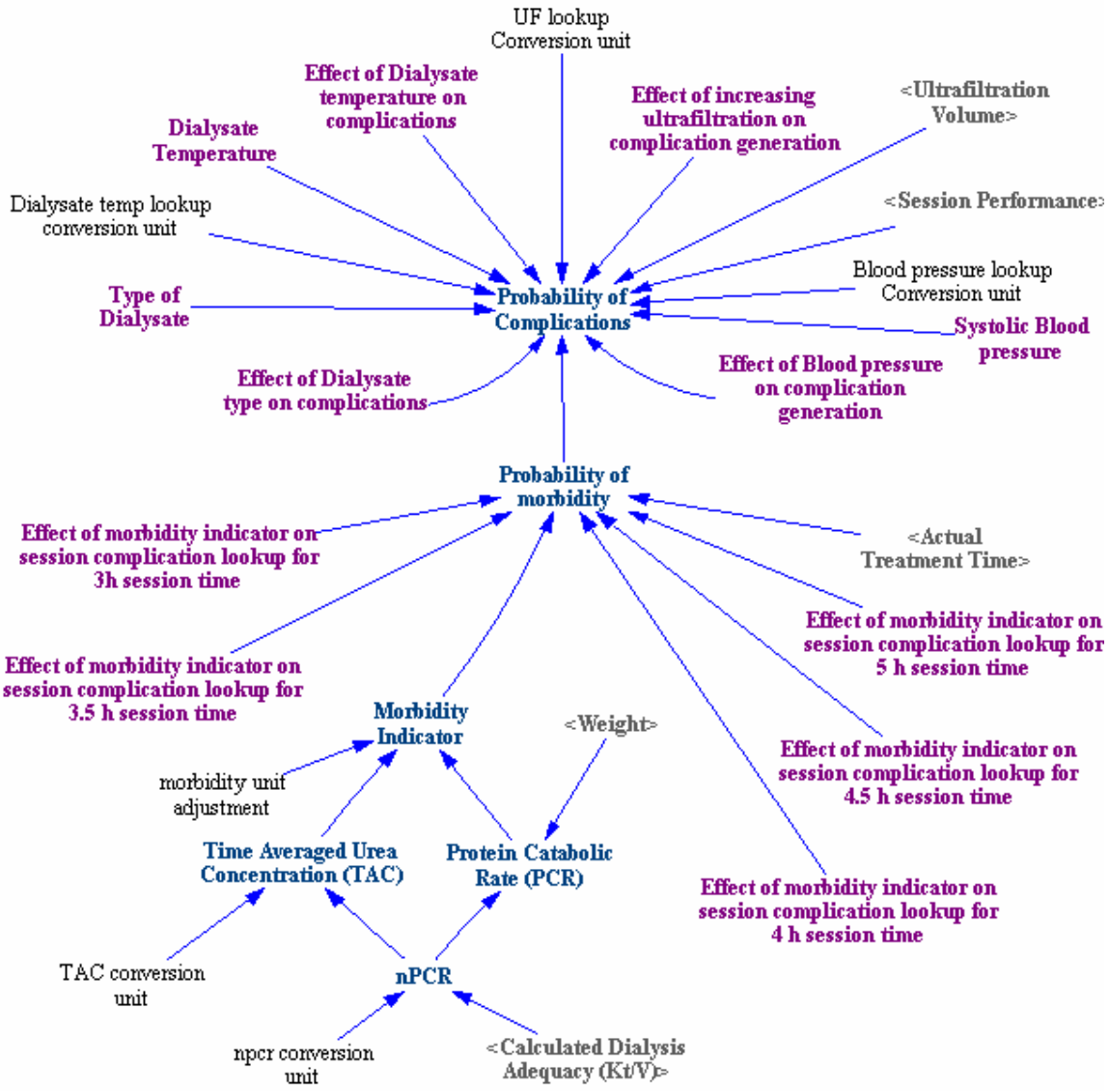

Figure 7 Intradialytic Complication Structure

It is assumed that there are no complications are generated if the session performance reaching 100 % because the increase in the probability of complications decreases the session performance. Both the ultrafiltration volume and the rate of ultrafiltration greatly affect blood pressure during dialysis. There is a non-linear relationship between ultrafiltration changes and the probability of hypotension. The lookup table (figure 8) shows the non-linear relationship in graphical format.

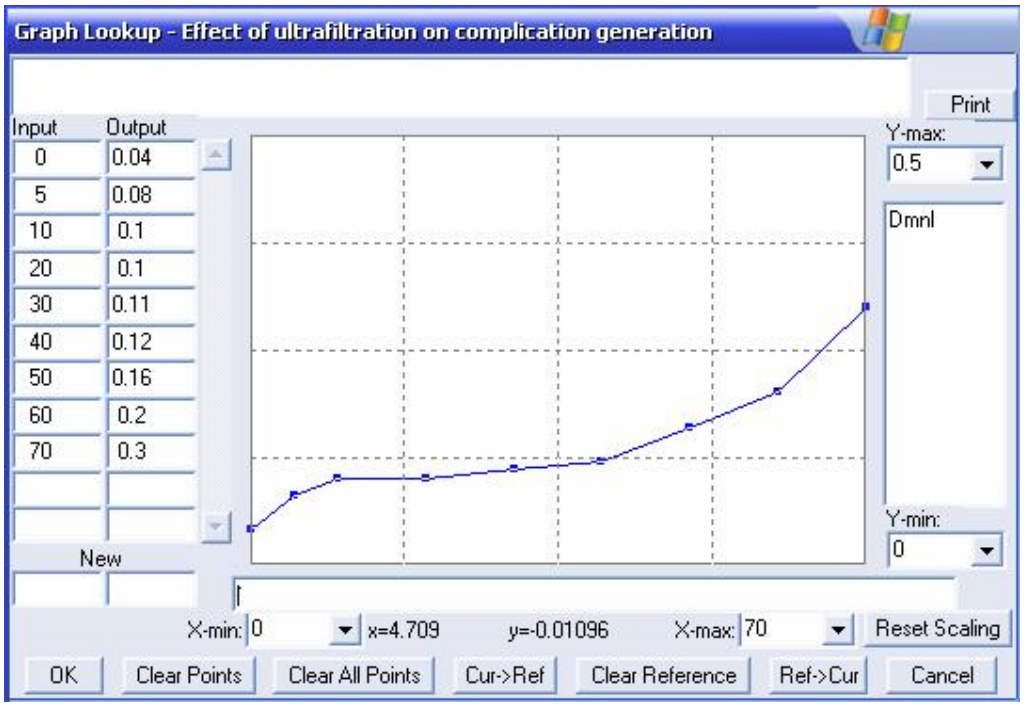

Figure 8 Effect of Ultrafiltration on Complication Generation

Reducing the dialysate temperature from 37°C to 34-35°C increases peripheral vasoconstriction and cardiac output, thereby reducing the occurrence of hypotension and accompanying symptoms. Cooling dialysate below 36.5°C has been recognized as an important factor contributing to haemodynamic stability of patients during hemodialysis. Blood cooling is used to stabilize blood pressure (BP) during very high efficiency hemodialysis with a high ultrafiltration rate, and helps to maintain BP without compromising the efficacy of hemodialysis. Decreasing the dialysate temperature to 35°C decreased the incidence of symptomatic hypotension from 44% to 34%. The benefit was greatest for patients with frequent episodes of hypotension and those with baseline mild hypothermia. This intervention is beneficial even in patients who have excessive weight gains. Cold dialysis does not compromise urea clearance or increase urea rebound, but does induce mild to intolerable symptomatic hypothermia in some patients. There is a non-linear relationship between dialysate temperature changes and the probability of hypotension. The lookup table (figure 9) shows the non-linear relationship in graphical format.

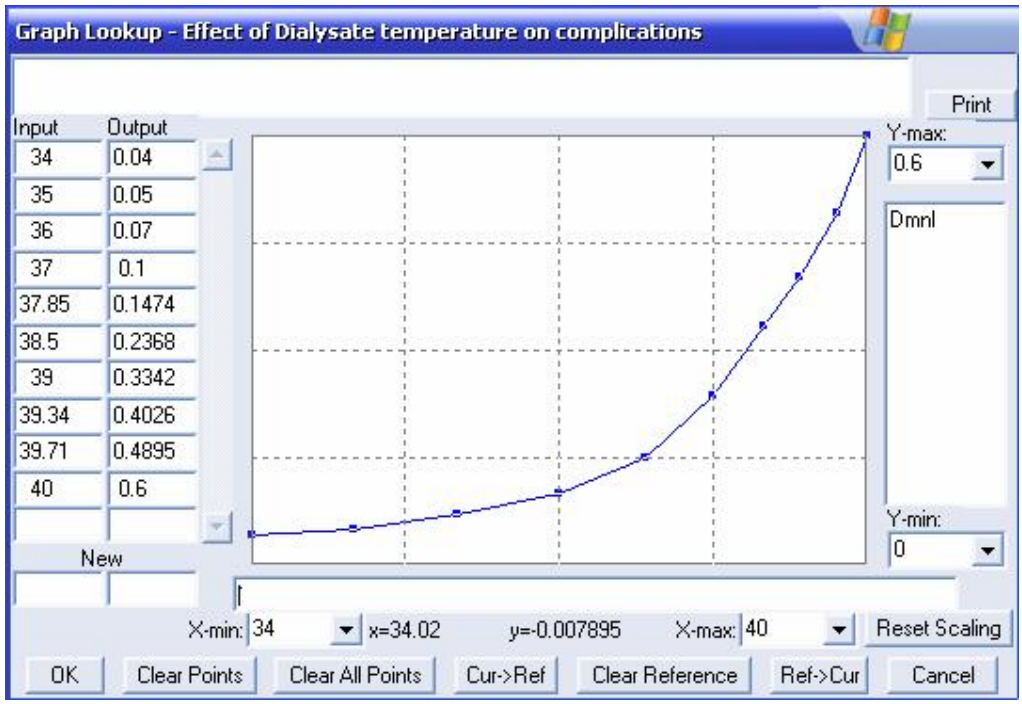

Figure 9 Effect of Dialysate Temperature on Complication Generation

Conversion from an acetate-containing dialysate to a bicarbonate-containing dialysate will also minimize hypotension and cramps. In addition to a beneficial effect on blood pressure, the use of bicarbonate results in fewer headaches and less nausea and vomiting. Acetate contributes to the occurrence of hypotension by inappropriately decreasing total vascular resistance and increasing venous pooling and myocardial oxygen consumption. It is assumed that the type of acetate is a binary variable. It takes the value of 1 if it is bicarbonate dialysate and 0 if it acetate. Table I is based on the observations of 134 dialysis patients during our study period and shows the effect of dialysate type on the probability of hypotension. It was noted that the conversion from acetate dialysate to bicarbonate dialysate reduces the hypotension episodes by about 11-12 %.

Table I Effect of Dialysate Type on Complication Generation

Dialysate Type	Probability of hypotension
0 (Acetate)	0.22
1 (Bicarbonate)	0.10

At the start of hemodialysis, the UFR is at its highest level (so-called UFR max), that is subsequently retroactively reduced and adapted, depending on the BP instant variation and on how much and how fast the BP gets close to the BP set point. The effect of blood pressure on complication generation is shown in figure 10.

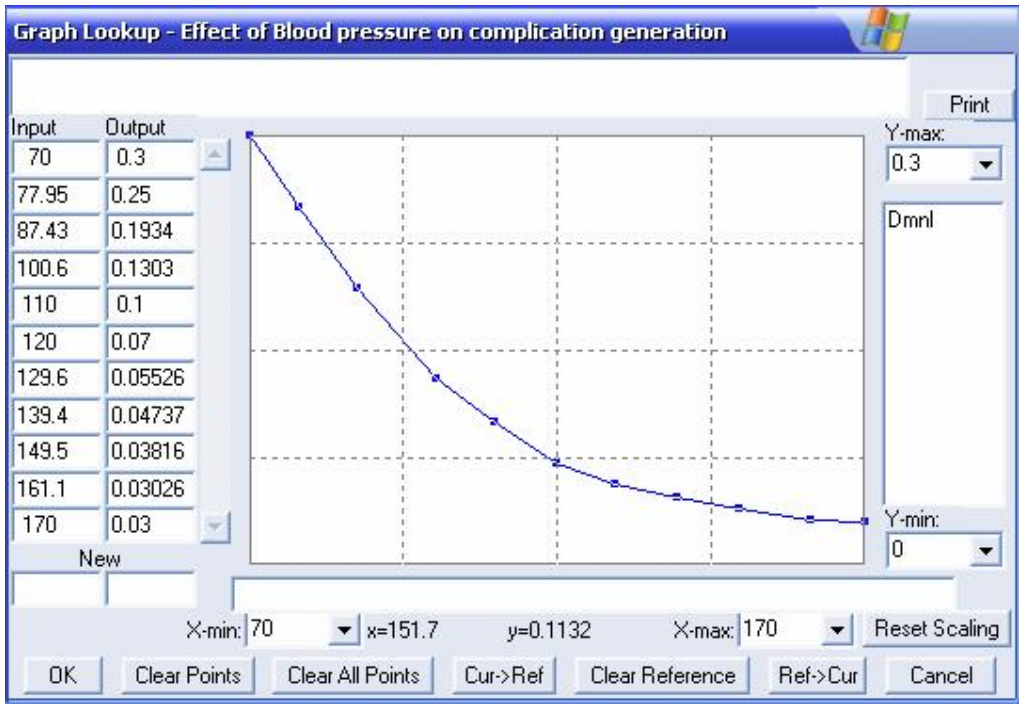

Figure 10 Effect of Blood Pressure on Complication Generation

It is obviously from figure 10 that the likelihood of intradialytic hypotension increases with the decrease in the systolic blood pressure of the patient.

The probability of intradialytic complications is also influenced by the morbidity rate of the patient. The nutritional status of the patient is a major factor in the outcome of hemodialysis and is associated with the treatment failure. The ratio of the protein catabolic rate to the time averaged urea concentration (PCR/TAC) is considered as a powerful predictor of treatment failure. For a given dose of dialysis and dietary protein intake (PCR/TAC), the outcome clearly worsened as dialysis was shortened.

The ratio of PCR/TAC gives us the number that can be used as a morbidity indicator. Increasing this ratio in the range of 1.2–1.5 might further reduce adult mortality and morbidity. As the dialysis duration increases the morbidity rate decreases which in turn decreases the probability of session complications. The effect of this ratio on session complication is shown graphically in figure 11 at four hour dialysis session. The probability of morbidity can be calculated at different dialysis times according to equation 5.

Probability of morbidity = IF THEN ELSE (Actual Treatment Time = 180, Effect of morbidity on session complication lookup for 3h session time (Morbidity Indicator) , IF THEN ELSE (Actual Treatment Time = 210, "Effect of morbidity on session complication lookup for 3.5 h session time" (Morbidity Indicator), IF THEN ELSE (Actual Treatment Time = 240, Effect of morbidity on session complication lookup for 4 h session time (Morbidity Indicator), IF THEN ELSE (Actual Treatment Time = 270, "Effect of morbidity on session complication lookup for 4.5 h session time" (Morbidity Indicator) , IF THEN ELSE (Actual Treatment Time = 300 , Effect of morbidity on session complication lookup for 5 h session time (Morbidity Indicator) , 0))))) (5)

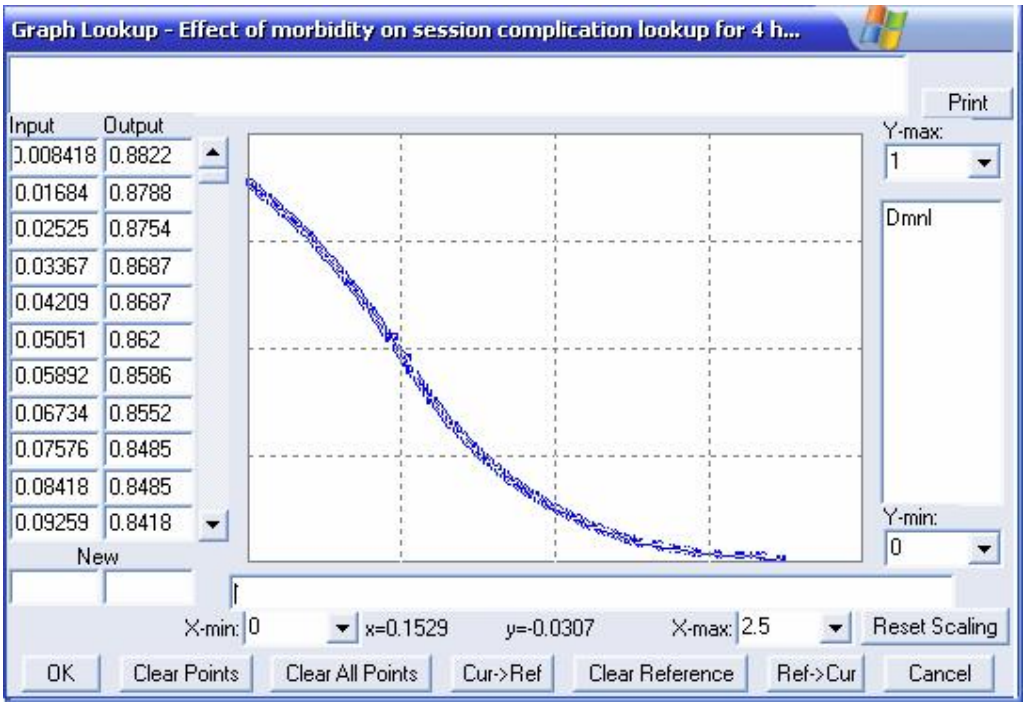

Figure 11 Effect of morbidity on session complication lookup for 4 hour session time

III. RESULTS AND BEHAVIORS

The treatment characteristics with SDBPS (treatment A) and without (treatment B) are shown in table II.

Table II. Comparison of treatment characteristics between the baseline group and the intervention group

Patient Characteristics	Group A (n = 80) With SDBPS	Group B (n = 70) without SDBPS	P-Value
Mean treatment duration (h)	3.87 ± 0.28	3.61 ± 0.38	NS
Difference (min) between actual and prescribed treatment times	16.8 ± 15.2	16.2 ± 12.0	NS
HD session (%) with actual treatment time < prescribed	6.67 ± 1.4	9.31 ± 2.01	0.0000
Interdialytic Weight Gain (kg) Range Mean IDWG	 0-5 2.52 ± 1.18	 0-5 2.048 ±1.24	 0.0183
Ultrafiltration Rate (L)	3.28 ± 1.32	3.20 ± 0.85	NS
HD sessions (%) with actually achieved UF < UF prescribed	28.9 ± 3.1	34.4 ± 3.39	0.0000
Difference (ml) between total UF prescribed and UF achieved	150 ± 190	180 ± 170	NS

Statistical analysis was performed using SPSS 10.0 and NCSS 2004 software packages. Mean errors relative to reference values were compared by one way ANOVA, with significant group differences ($p < 0.05$) localized by post-hoc application of the pairwise Least Significant Difference test. Confidence intervals on the discrepancy between different estimates of the same parameter are calculated as Bland-Altman 95% limits of agreement. Comparison of means between the two groups was made using paired-sample T-test.

No significant differences were found between the treatments A and B in the dialysis duration and total UF, as well as in the difference between the dialysis duration prescribed and the one actually realized (Table II). The statistical analysis demonstrated that there was a significant improvement in the HD session (%) with actual treatment time < prescribed ($P< 0.05$) in group A as compared with group B. This is because the interruption in dialysis time in group B is higher than group A due to hypotension episodes. It was noted also that the group A showed a statistically significant increase of 19.03 % in achieving the desired UF due to control of intradialytic complications as compared with group B (28.9 ± 3.1% vs. 34.4 ± 3.39, $P < 0.05$). The statistical analysis demonstrated the control of intradialytic complications increases the interdialytic weight gain in group A as compared with group B due to the increase in dialysis adequacy Kt/V and overall session performance (2.52 ± 1.18 vs. 2.048 ±1.24, P= 0.0183). These results match well with the relationships between variables as shown in the overall causal loop diagram in Appendix A (loop R6 and loop B6).

Pre-dialysis BP values showed no significant differences between the two treatments, either in the standing or in the lying position, while the post-dialysis values presented a significant difference in the standing position, even though too small to have a clinical impact (pre-dialysis, lying position: treatment A: systolic pressure 134±7 mmHg, diastolic pressure 70±12 mmHg; treatment B: 134±21 and 69±13 (P=NS); standing position: treatment A: 136±24 and 73±16; treatment B: 134±28 and 68±15 (P=NS). Post-dialysis, lying position: treatment A: systolic pressure 125±21 mmHg, diastolic pressure 66±11mmHg (P=NS); standing position: treatment A: 125±25 and 67±14; treatment B: 122±25 and 66±13 (P=0.007 for systolic and P=0.03 for diastolic pressure, respectively).

Dialysis was complicated by the appearance of at least one episode of hypotension (mild and severe) in 21% of the sessions (n=80) with SDBPS (treatment A), and in 28.1% of the sessions (n=70) without SDBPS (treatment B). An overall reduction in the DH frequency equal to 25.3% was obtained (P=0.02). In order to attain some more accurate results as to the effects on hemodynamic stability, dialysis hypotension (DH) episodes, defined as in the patient screening phase, were further subdivided into mild and severe on the grounds of the following criteria:

Mild hypotension: successfully treated with an UF withdrawal ≤ 5 min, with or without the infusion of 250 ml saline ±20 mEq NaCl.

Severe hypotension: needing > 5 min UF stop, plus plasma expander. The most important effect of the SDBPS system was to reduce the severe hypotension episodes, which showed a significant decrease as compared with what was observed in conventional treatments B (–39.1%, P=0.01), whilst the change in the mild hypotension episodes (–12.3%) was not significant (Figure 12). The scatter plot comparing the frequency of severe hypotension episodes in treatments without and treatment with SDBPS (Figure 13) shows that for most of the patients the switch from the conventional treatment to the use of SDBPS resulted in a real improvement in hemodynamic treatment tolerance. In effect, most of the patients are allocated below the identity line in the scatter plot, indicating that, on the whole, for a certain frequency of severe hypotension in the conventional treatments, the corresponding frequency in the SDBPS treatments was, in most cases, more or less reduced.

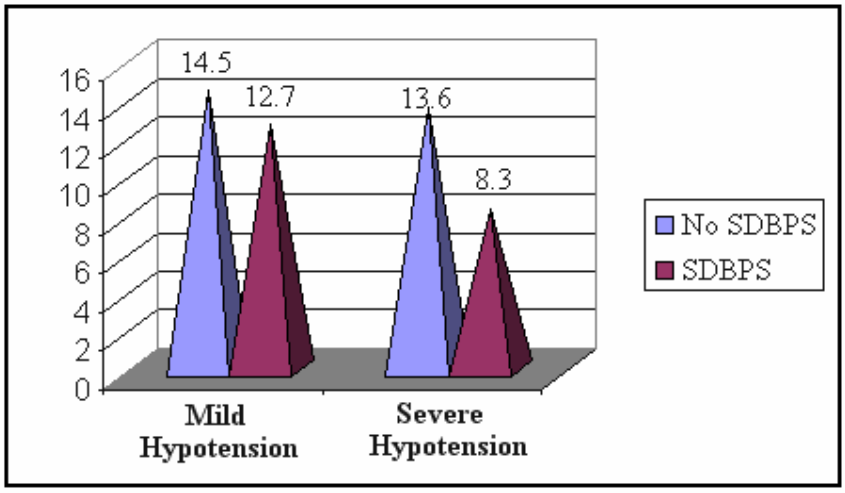

Figure 12 Subdivision of the results concerning DH episodes on the basis of their severity. While the difference observed in the incidence of mild hypotension was not significant, a highly significant reduction of most severe hypotensive episodes was found with the use of SDBPS (–39.1%, P=0.01).

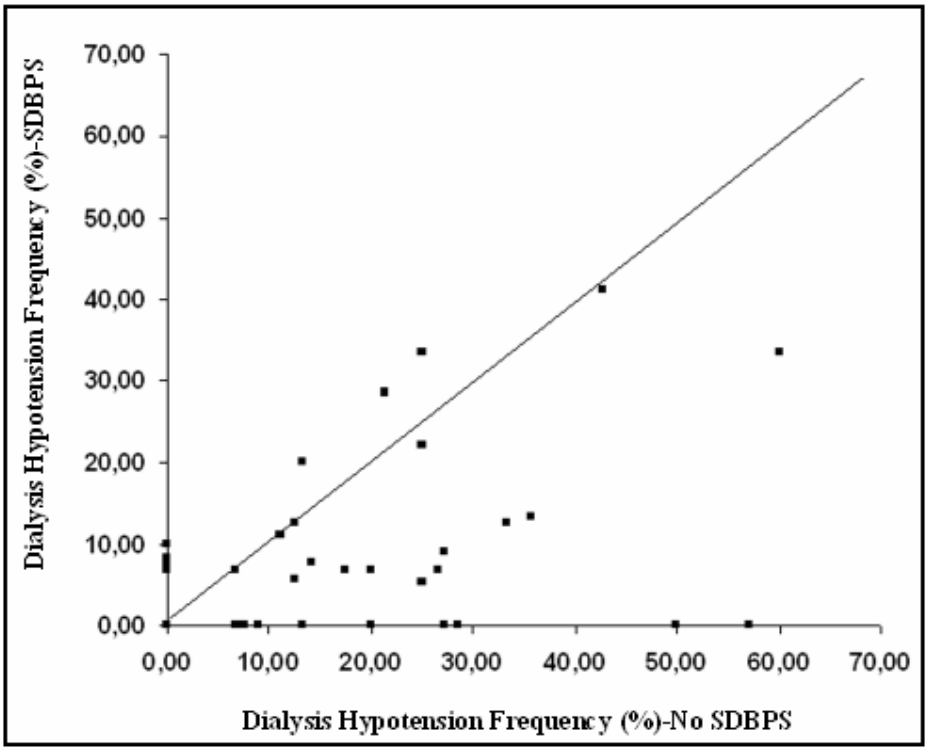

Figure 13 Scatter plot comparing the frequency of severe DH episodes in the treatments without and with SDBPS and the identity line. Any dot represents a single patient. Most of the patients, apart from six, lie below the identity line, indicating an overwhelming beneficial effect of the SDBPS in reducing the appearance of DH in the single patient. The sign test, used to test the efficacy of the system, proved highly significant (P=0.02).

To verify the system's efficacy in reducing the frequency of DH, the sign test for non-parametric data was used. By means of this test we compared the negative differences (number of patients in whom DH frequency was higher with the use of SDBPS than without it) the positive differences (number of patients in whom DH frequency was lower with use of SDBPS than without it) and the condition of equality (number of patients in whom the frequency of hypotension was comparable between the two treatments). This test resulted highly significant (P=0.02), indicating that the null hypothesis is highly unlikely. Fluids for the therapeutic interventions proved lower in the SDBPS sessions, significantly for hypertonic sodium (386±9.3 ml in A vs. 442±10.6 in B; –13%, P<0.05) and plasma expanders (1982±66 ml in A vs. 2783±84 ml in B; –29%, P<0.03), which are usually employed for treating the most severe hypotension events. Instead the amount of normosaline did not turn out to significantly different between the two dialysis strategies.

- **Sensitivity Analysis**

Sensitivity analysis is used to determine how "sensitive" a model is to changes in the value of the parameters of the model and to changes in the structure of the model. Parameter sensitivity is usually performed as a series of tests in which the modeler sets different parameter values to see how a change in the parameter causes a change in the dynamic behavior of the stocks. By showing how the model behavior responds to changes in parameter values, sensitivity analysis is a useful tool in model building as well as in model evaluation. Sensitivity analysis helps to build confidence in the model by studying the uncertainties that are often associated with parameters in models. Many parameters in system dynamics models represent quantities that are very difficult, or even impossible to measure to a great deal of accuracy in the real world. Also, some parameter values change in the real world. Sensitivity analysis indicates what level of accuracy is necessary for a parameter to make the model sufficiently useful and valid.

Five tests were performed as follows where the model yielded an expected behavior in all tests. (1) Effect of ultrafiltration on dialysis dose Kt/V, (2) Effect of ultrafiltration on urea removal rate (3) Effect of ultrafiltration on urea distribution volume, (4) Effect of ultrafiltration on overall session performance and (5) Effect of ultrafiltration on the intradialytic complications.

These tests were simulated at four levels of ultrafiltration rate (UFR). The first simulation was run at high level of UFR (25 ml/min). The second simulation was run at medium level of UFR (17 ml/min). The third simulation was run at low level of UFR (8 ml/min). The fourth simulation was run at zero level of UFR (0 ml/min).

The results of tests from 1-4 are shown in Figures 14, 15, 16 and 17 respectively. The simulated results were in agreement with expected outcomes. It was observed that as the UFR increases the dialysis adequacy and overall dialysis session performance increase. The dialysis adequacy increases by about 0.14 and the dialysis performance increases by about 5% for each 8 ml/min increasing of UFR. The results also indicated that the ultrafiltration during dialysis increases the amount of urea removed because by convention Kt/V is based on a post-dialysis value of V. The urea reduction ratio increases by about 2.5 % when the UFR increases by about 8 ml/min. Therefore, the higher the ultrafiltration rate, the greater the contribution of convection to solute removal, and the more the movement of large solutes is supported.

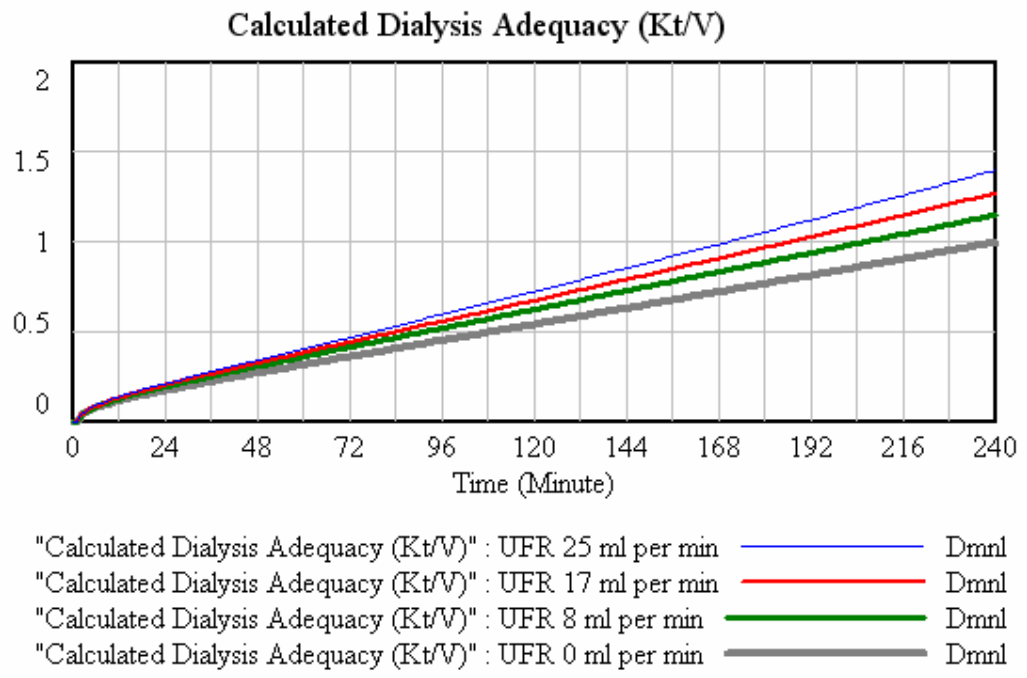

Figure 14 Dialysis Adequacy (Kt/V) At Various Levels Of UFR

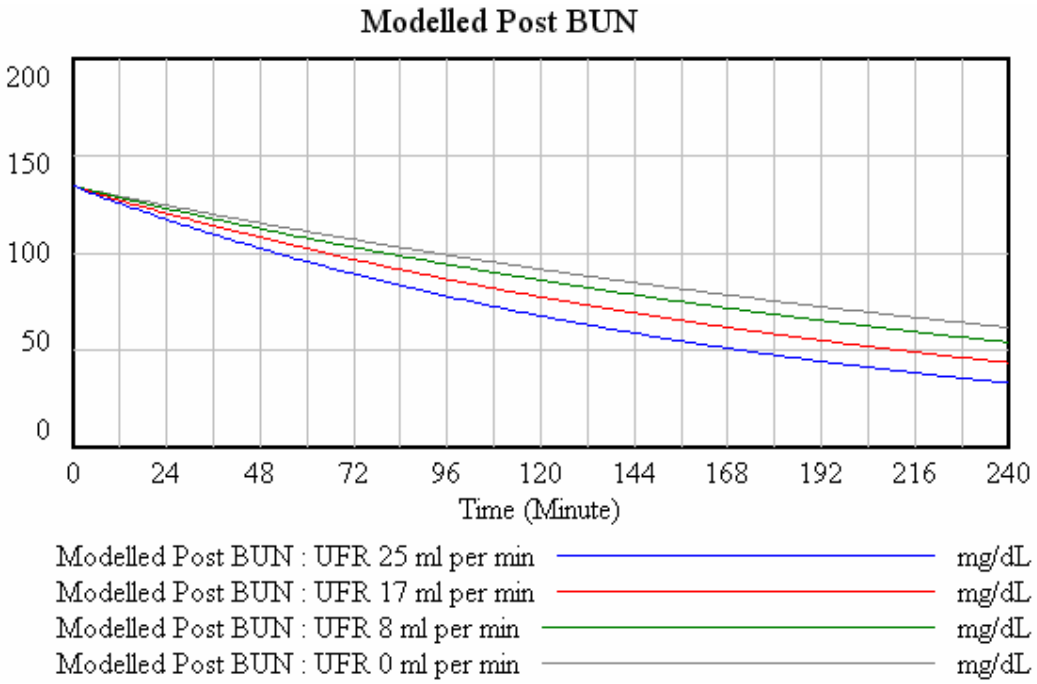

Figure 15 Modeled-Post BUN At Various Levels Of UFR

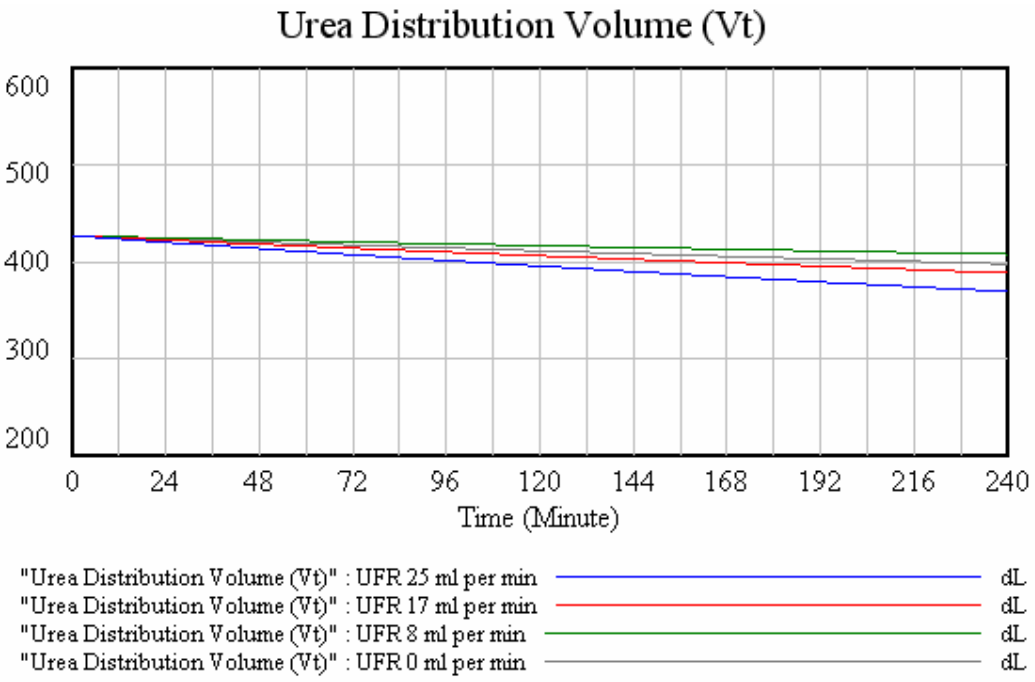

Figure 16 Urea Distribution Volume At Various Levels Of UFR

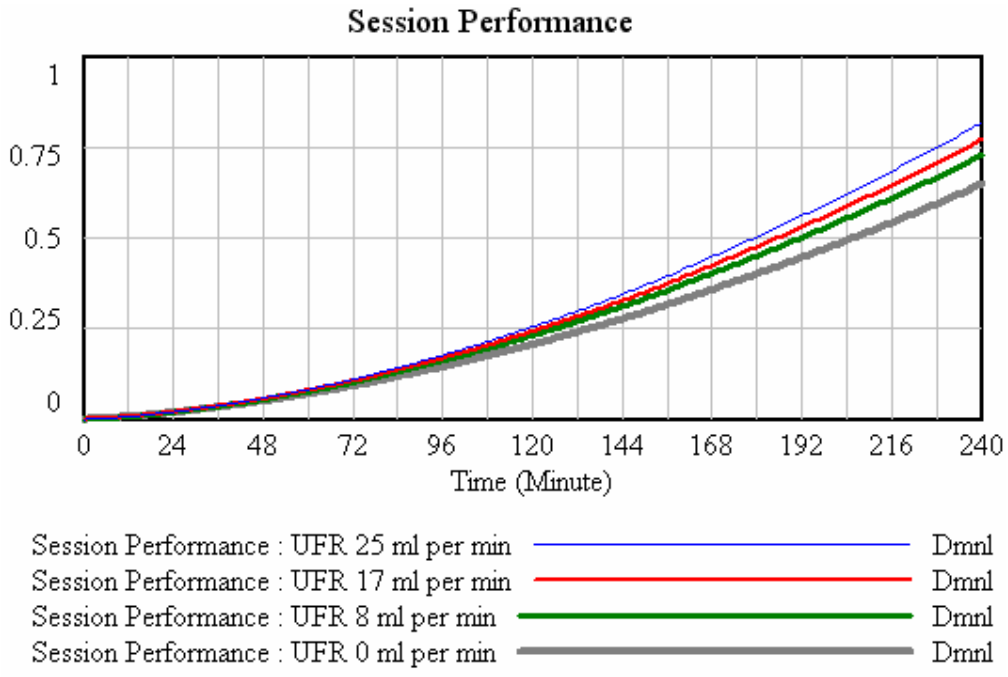

Figure 17 Dialysis Session Performance At Various Levels Of UFR

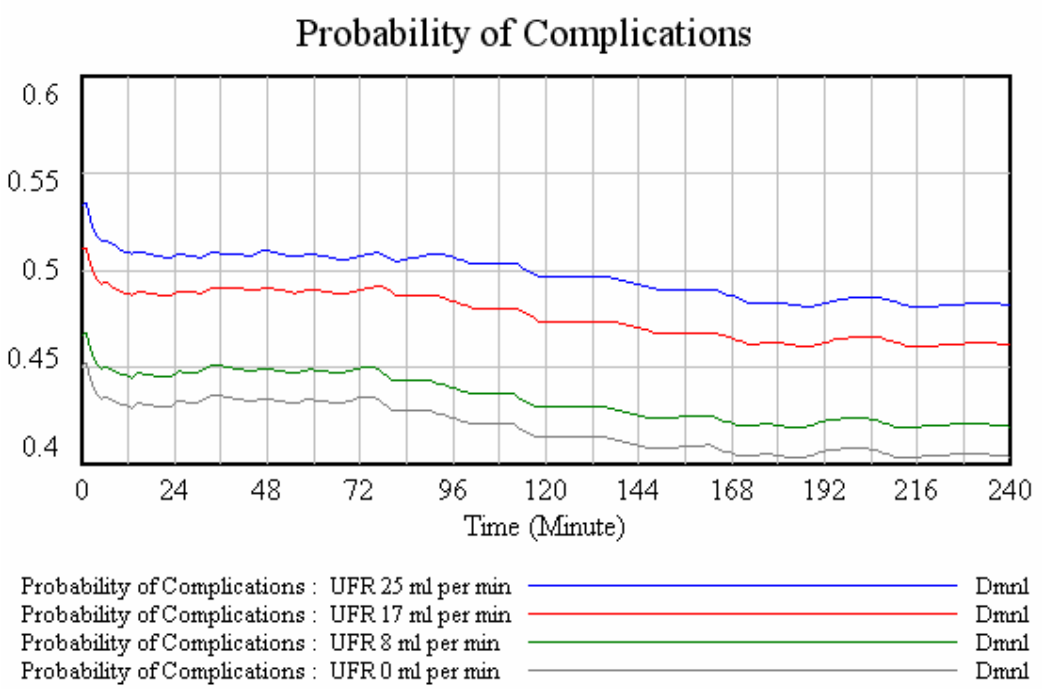

Figure 18 Intradialytic Complications At Various Levels Of UFR

It was noted from figure 18 that intradialytic hypotension (IDH) is rare in the absence of an ultrafiltration (UF)- induced reduction in blood volume. While there are hypotensive effects of hemodialysis independent of volume removal, they are usually inconsequential without accompanying volume depletion. The frequency of IDH increases with an increasing UF rate. It was found that hypotension occurred at a rate of 6.7/100 treatments when UF was 0.3 ml/min/kg increasing to 15.8 at an ultrafiltration rate (UFR) of 0.4 ml/min/kg, 25.6 at a rate of 0.5 ml/min/kg, and 67.4 at a rate of 0.6 ml/min/kg. The importance of the UFR (in addition to the total UF volume) is apparent from the observation that IDH fell by 28% after the UFR was limited to 0.35 ml/min/kg and treatment times extended to allow removal of interdialytic fluid gains.

- **Dialysis Session Simulator: Hemodiadynamics**

A simple simulator was designed to help the decision makers and dialysis staff to observe the impact of their decisions on the session's performance. The simulator has two parts; a dashboard and controls. The dashboard displays performance parameters such as dialysis adequacy, predicted post-BUN, Urea distribution volume, Ultrafiltration volume, Probability of intradialytic complications and overall session performance. The control section allows used to dialysis session parameters such as blood flow rate, dialysate flow rate, dialyzer clearance, etc. The user can choose the time of dialysis for which the model should be run with the current set of control parameters. Thus the simulator provides a user friendly interface which can be used by decision makers and medical staff for testing their policies. Screenshots of the simulator are shown in Appendix C.

IV. DISCUSSION

The prevention of dialysis-induced hypotension is still one of the hardest objectives to achieve. Moreover, the almost complete willingness to deliver dialysis treatment to every patient, independently of their age or degree of co-morbidity, largely aggravates the problem, in spite of the well-known progress made in dialysis technology (UF control, biocompatible membranes, convective treatments, acetate-free techniques) which have, instead, reduced the natural unphysiology of dialysis and have enhanced the patient's treatment tolerance. The intrinsic multifactorial nature of DH [7,8] makes an actual prevention of the onset of hypotension virtually impossible. The most traditional and simplest measures generally adopted (fasting dialysis, the avoidance of hypotensive drugs before treatment, the avoidance of short treatments, bicarbonate buffered dialysis, etc.) actually prove quite insufficient in the most compromised patients, like diabetic or heart-compromised subjects. In the past decade, many attempts have been made to devise new systems aimed at improving the hemodynamic tolerance to dialysis by working on the variables mainly involved in the problem, such as blood volume. With a view to adapting fluid removal to the patient's fluid status, profiling systems, both for UF and sodium, have been set up [9–13]. Generally speaking, these systems seek to enhance the cardiocirculatory tolerance to fluid withdrawal by removing more fluid at the beginning of the session, when the patient is more water-repleted, thus gaining an advantage to be used in the second part of the treatment when the UFR can instead be progressively decreased. Fluid shifts from the extra- to the intravascular space are facilitated [9], and the blood volume trend should result in being similar to what is observed in most stable patients [25], that is a more or less steep decline in the first part of dialysis and an almost linear trend in the last part of the treatment. However, dialysis profiling systems are, even from a strictly conceptual standpoint, self-limiting, in some way 'rigid': i.e. a pre-set profile of UF (or sodium) is applied throughout treatment, not adaptable to the different conditions of body fluid distribution and, above all, to the continuously changing fluid equilibrium at the arteriolar–capillary–venous level [26]. Since there is no retroactive control, but only a unidirectional one (i.e. from the machine to the patient), they are purely open-loop control systems. Biofeedback systems to control BP during dialysis [13,14], were the real leap ahead, in that they have revolutionized the technological approach to DH by means of a closed-loop control retroactively managing some machine parameters (UF, sodium, dialysate temperature) akin to what is already available in some other fields of medicine, such as, for example, in the infusion pumps for insulin. Closed-loop systems indeed enable a continuous adaptation of the output parameters depending on the patient response. The controlled variable re-enters the system, which 'sees' the result of the previous parameter change. Two systems of this type are today widely known: one of them, BVT (blood volume tracking), automatically controls blood volume [13], while the other, BTM (blood temperature monitoring) controls the patient's temperature [14]. A number of papers have described the excellent results in improving hemodynamic instability during hemodialysis in hypotension-prone patients [15–19] when these systems are used as compared with conventional treatments. However, the most striking drawback of the biofeedback systems known up to now is that, although BP is the real control target, it is not possible for BP itself to enter the system as an input parameter. Adding this parameter has always been thought to be troublesome as it would be necessary to know, first of all, which BP level is actually 'critical for the single patient'; secondly, it is necessary to fine-tune the system's response to the changes in BP in that particular patient, and lastly which type of response (magnitude, duration) the system should give.

SDBPS is a system dynamics biofeedback, a typical closed-loop control, solely based on the chance to use BP itself as the input parameter: the system counter-response is to modulate the only output parameter, i.e. the UFR, according to the BP trend. This possibility is offered by system dynamics, which processes the BP's instant value, a parameter with no absolute significance, but rather individually patient-related, thus involving the clinical experience and the physician's knowledge of the single patient.

A combination of these two aspects, the medical knowledge of the patient, expressed by the critical pre-set parameter BP level, and the interpretation of the patient's BP trend, enables an effective personalization of the treatment. In other words, the automatic system is indeed modeled upon the patient. Instead, our experience was carried out in hypotension-prone patients alternately treated with SDBPS-controlled BP or with conventional hemodialysis in a one-to-one ratio (one session SDBPS, one session without SDBPS, and so on) so that each patient was his/her own control. The results obtained on the DH incidence (a 25% reduction overall, with a 39% reduction in the most severe episodes) proves quite similar to what was obtained with the BVT system, aimed to retroactively control blood volume [13]. This is a well-confirmed result, considering that the SDBPS system, by moving the UFR, influences the blood volume behaviour, similarly (but not equally) to BVT. It could be argued that the 25–30% 'saving' in DH obtained with both the systems is what can be avoided when reducing the effect of uncontrolled blood volume behaviour on the cardiocirculatory response to fluid withdrawal. As with any automatic system modulating the UFR throughout the treatment, there actually is the risk that the target of the ideal dry body weight, by completing the schedule of the programmed total UF, is not accurately reached. This drawback may be reflected in the treatment time that, more or less often, must be prolonged in order to complete the fluid removal. On the other hand, the gain in BP stability reduces the risk of the temporary zero-setting of the UF, or its stable reduction, which is, instead, routine maneuvers in the event of tendency to hypotension. In effect, as illustrated in Table II, no significant differences appeared when comparing the actual dialysis time and total UF, as well as the actual treatment time was longer than that programmed. Even the difference in the UF volume or the minutes of treatment time (actual–prescribed) was comparable between the two treatment strategies. Nevertheless, the present study does have some limitations. The work was performed using a single blind procedure (blind to the patient), and inevitably the SDBPS sessions received special attention from the nursing staff, involved in understanding the workings of the SD software in response to the patient's BP behaviour. Data concerning dialysis-sodium concentration or temperature were not collected, meaning that some dialysis-related factors affecting the BP stability were not taken into account. At the same time, we did not consider the specific cardiac conditions of the population studied, thus we are unable to state whether the benefits were obtained in the presence of a certain cardiological pattern. Although the present study should therefore be considered as somewhat preliminary, we believe that this experience actually has its own intrinsic value, despite its manifest limitations. Actually, this was a pilot study with the specific aim of assessing, in a large number of patients, the applicability of this SD system during dialysis, in terms of user-friendliness, and the capacity to interpret a changeable, volatile variable such as BP, and finally to actually reduce the hypotension events in critical patients. From this point of view, the fact of not having over-emphasized the other parameters (dialysis time, conductivity, membranes, various habits, etc.) apart from the use of the system itself, enhances the result obtained. The aims we intended to pursue were all achieved. We believe that it is now worth applying this SD system further and studying it within other more complex protocols, also aimed at identifying those patients who might draw the greatest benefits from it.

V. CONCLUSION

System dynamics has proven capable of adequately interpreting and controlling the BP trends during hemodialysis. In our experience, the automatic SDBPS system (Hemodiadynamics) based on system dynamics has allowed for an overall reduction in the dialysis episodes in hypotension-prone subjects, equal to 25%, and nearly 40% as concerns the most severe episodes. The system is quite straightforward to use and only a few specific parameters are needed. Patients feel better monitored and staff appreciate biofeedback-controlled hemodialysis. Patients with a poor tolerance to fluid withdrawal, due to instability in plasma refilling or to an inadequate cardiovascular and/or autonomic nervous system response to dialysis, could accrue benefits from the use of SDBPS (Hemodiadynamics) during dialysis treatment.

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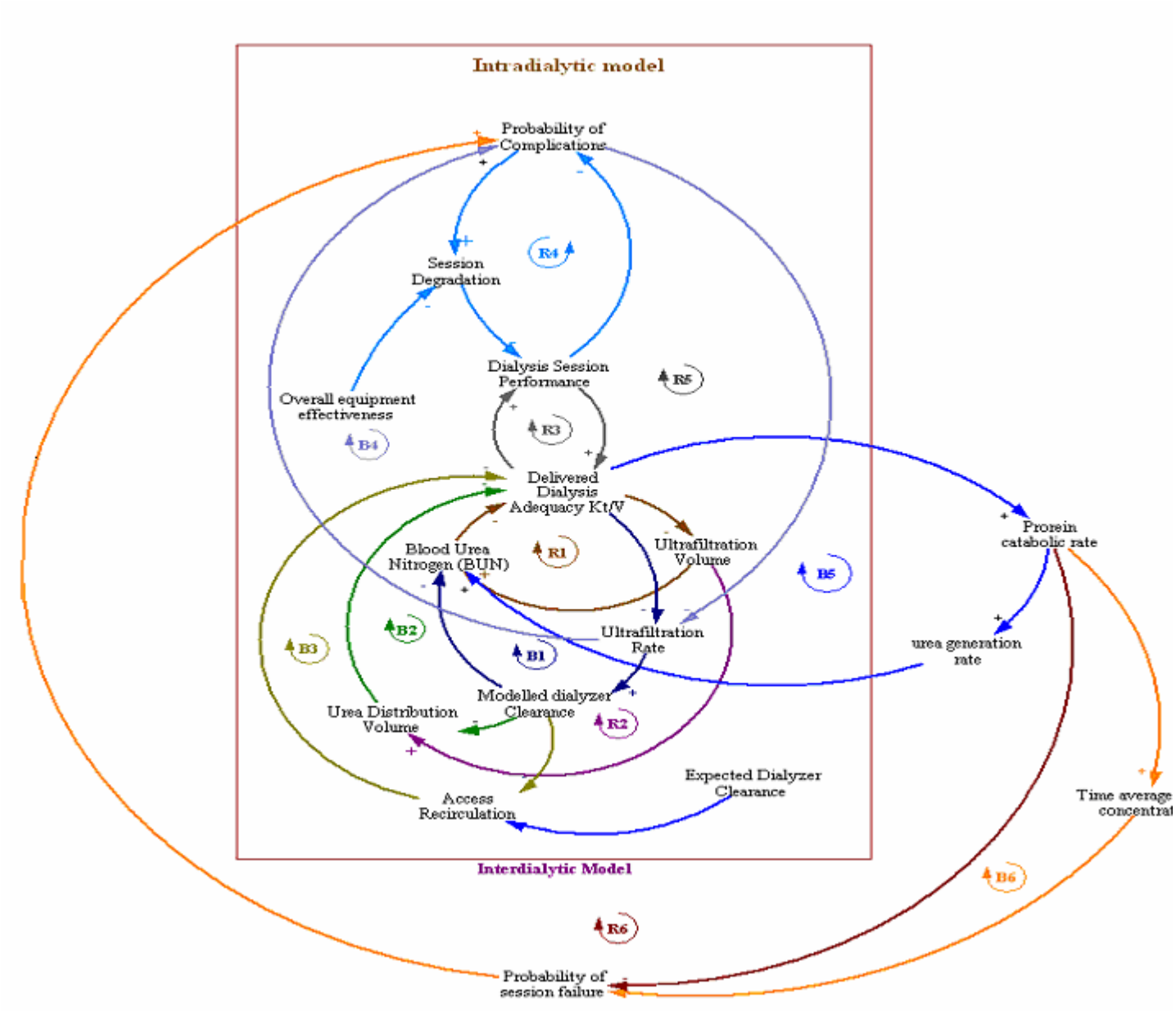
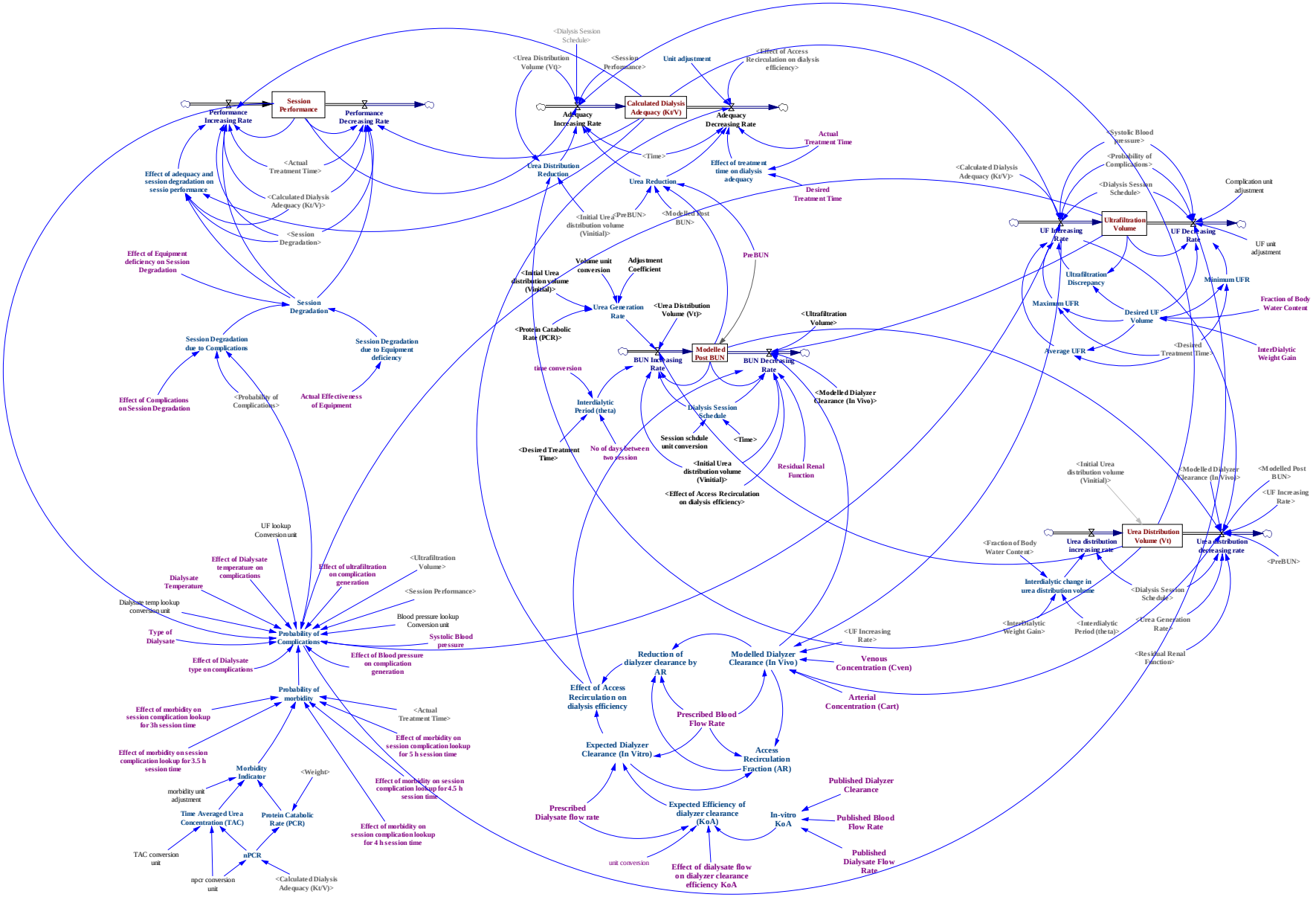
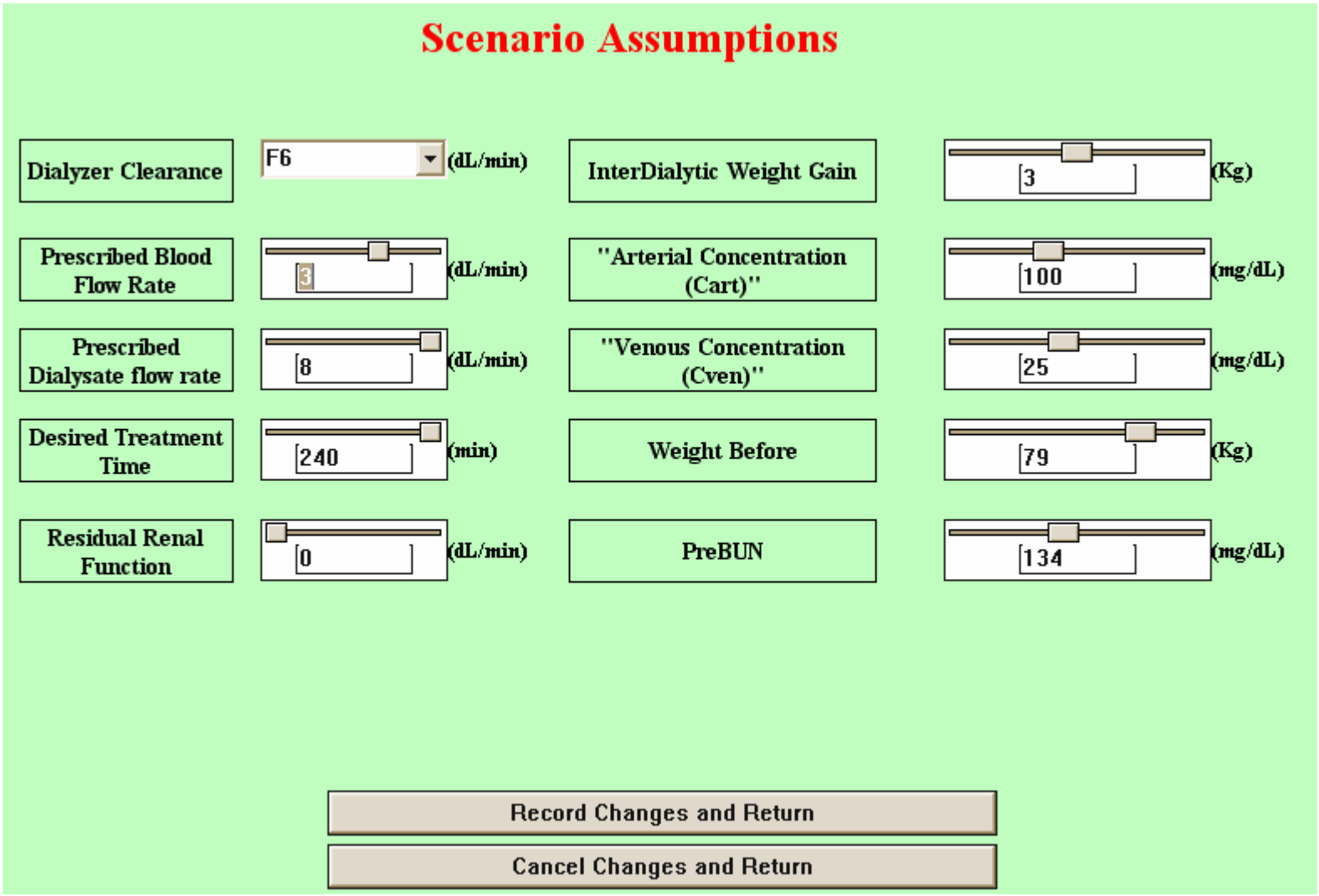
APPENDIX A: CAUSAL LOOP DIAGRAM OF HEMODIADYNAMICS



APPENDIX B: STOCK AND FLOW DIAGRAM OF HEMODIADYNAMICS



APPENDIX C: SCREENSHOT 1 OF HEMODIADYNAMICS



APPENDIX C CONTINUES:
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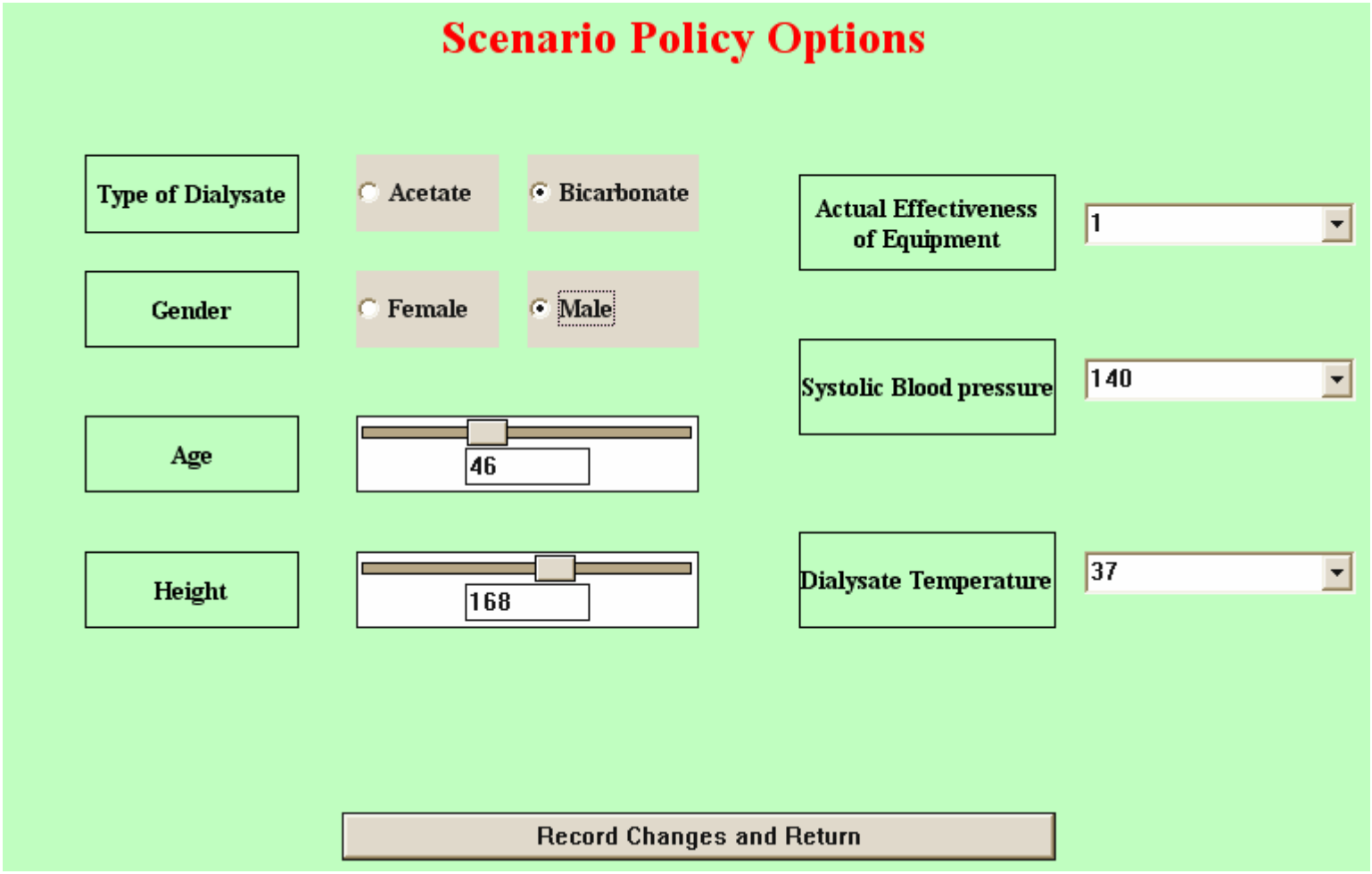

APPENDIX C CONTINUES:
SCREENSHOT 3 OF HEMODIAYNAMICS