THE INTRADIALYTIC BIOFEEDBACKS AND THE CARDIOVASCULAR STABILITY IN HYPOTENSION-PRONE PATIENTS

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Disclosure of Interest
ANTONIO SANTORO

No interest conflicts to declare

The details of each Disclosure of Interest are available at the Invited Speakers’ desk (located in the Registration Area).
Mr Chairman, ladies and gentlemen, let me thank the organisers for their kind invitation to this meeting. My job today is to give a talk about the intradialytic biofeedback in the cardiovascular stability in hypertension-prone patients.

Slide 3

The hemodialysis is a undoubtedly a non physiological procedure

You know that haemodialysis procedure is not a physiological procedure.

Slide 4
The phenomenon of bioincompatibility in the circuit, the ultrafiltration induces hypovolemia and the diffusion may induce sudden changes, a sudden decrease in solute, pH, bicarbonate and electrolytes. So we can have some negative effects on the cardiovascular system.

Slide 5

Hemodialysis-induced myocardial stunning

HEMODIALYSIS

↓ Myocardial blood flow

↓ Myocardial ischemia

Regional wall motion abnormalities

↓ Cardiac failure

McIntyre CW, Blood Purif 2010

The first negative effect is myocardial stunning. Myocardial stunning is the result of the reduction in myocardial blood flow, myocardial ischemia, then regional wall motion abnormalities.
Episodic hypotension episodes (IDH) which typically occur during the course of dialysis, are related to hypovolemia or to an inadequate cardiovascular response. They are associated with vomiting, muscle cramps, and other vagal symptoms (such as yawning).

But episodic hypotension episodes, which typically occur during the course of dialysis, are related in general to hypovolemia or to an inadequate cardiovascular response. Frequently they are associated with vomiting, muscle cramps and other vagal symptoms such as yawning.

You know that the frequency of intradialytic hypotension has increased over the last few years and this is probably due to the growth of the mean age of the dialysis patient population and increase of the comorbid conditions in this population.
What about the aetiology of intradialytic hypotension? We have two causes, the autonomic causes that are related to the autonomic nervous system dysfunction but more common are the non-autonomic causes. When we have an impairment in vasoregulatory response, in myocardial insufficiency or volume depletion.

Slide 9

The Fluid Distribution

Volume depletion is the consequence of the discrepancy between the ultrafiltration rate and the refilling rate of the patient.

Slide 10
But intradialytic hypotension may interfere with the delivery of adequate dialysis, this is in particular in patients with cardiovascular disease, may induce or aggravate hypoperfusion in different vascular beds: cerebral, mesenteric, cardiac. It may induce vascular access thrombosis and influence the patient’s outcome.

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In this study Shih demonstrated that in hypotension-prone patients when these patients have hypotension during their dialysis session, there’s an increase in troponin and CK-MB enzymes. This means that probably we can have microinfarctions in these patients.

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So we have a reduction in myocardial blood flow but we can have also a reduction during the hypotension episode of the cerebral blood flow and we can have cerebral infarction and inflammation of vascular lacunae.

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Mesenteric ischaemia in hemodialysis

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>Cases (n=15) (%)</th>
<th>Controls (n=20) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pre-HD SBP (mmHg)</td>
<td>116.4 ± 18</td>
<td>139.1 ± 24</td>
</tr>
<tr>
<td>Mean end-HD SBP (mmHg)</td>
<td>87.8 ± 32</td>
<td>136.8 ± 28</td>
</tr>
<tr>
<td>△ SBP (mmHg)</td>
<td>-26.5 ± 24</td>
<td>-2 ± 21</td>
</tr>
<tr>
<td>△ SBP &gt; 40 mmHg</td>
<td>n=7</td>
<td>n=0</td>
</tr>
<tr>
<td>Mean pre-HD DBP (mmHg)</td>
<td>59.1 ± 18</td>
<td>69.9 ± 16</td>
</tr>
<tr>
<td>Mean end-HD DBP (mmHg)</td>
<td>49.2 ± 28</td>
<td>73.1 ± 21</td>
</tr>
<tr>
<td>△ DBP (mmHg)</td>
<td>-10.3 ± 12</td>
<td>3.0 ± 15</td>
</tr>
</tbody>
</table>

No difference in cardiovascular factors, comorbidity, drugs, HD characteristics

Log-Rank test p=0.013

Of course, we can have also ischemia in mesenteric beds and in hypotension-prone patients it is possible that we have several mesenteric ischemia episodes throughout the dialysis session.

Slide 14
Mesenteric ischaemia in hemodialysis

<table>
<thead>
<tr>
<th>Blood Pressure</th>
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</tr>
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<tbody>
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<td>Mean pre-HD SBP (mmHg) (*)</td>
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</tr>
<tr>
<td>Mean end-HD SBP (mmHg) (*)</td>
<td>87.8 ± 32</td>
<td>136.8 ± 28</td>
</tr>
<tr>
<td>Δ SBP (mmHg)</td>
<td>-26.5 ± 24 (n=7)</td>
<td>-2 ± 21 (n=0)</td>
</tr>
<tr>
<td>Δ SBP &gt; 40 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pre-HD DBP (mmHg) (*)</td>
<td>59.1 ± 18</td>
<td>69.9 ± 16</td>
</tr>
<tr>
<td>Mean end-HD DBP (mmHg) (*)</td>
<td>49.2 ± 28</td>
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</tr>
<tr>
<td>Δ DBP (mmHg)</td>
<td>-10.3 ± 12</td>
<td>3.9 ± 15</td>
</tr>
</tbody>
</table>

(*) p<0.05

Median survival rate after ischemic event: 600 days

Modified from:
Bassilios N et al. Nephrol Dial Transplant 2003

and the appearance of these negative episodes may influence the survival of the patients in the long-term.

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The effect of frequent or occasional dialysis-associated hypotension on survival of patients on maintenance hemodialysis

So the outcome of the patients is different according to whether you compare hypotension resistant patients or whether you compare patients with frequent hypotension throughout their dialysis session.

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Preventing measures that may mitigate the frequency of IDH:

- Limit interdialytic weight gain, dietary sodium restriction
- Avoid short acting BP medication prior HD session
- Avoid food intake during HD
- Reconsider dry-weight
- Hypertonic dialysis
- Sequential HD (UF-HD)
- Na and/or UF profiling
- High dialysate calcium
- Cool dialysate
- Potassium profiling in pts with intra-dialytic arrhythmias
- Haemodiafiltration/Haemofiltration
- Longer and more frequent HD

Biofeedback technology

So the measure to prevent or mitigate the frequency of intradialytic hypotension are several: limited interdialytic weight gain, dietary sodium restriction, avoid short acting blood pressure medication prior to haemodialysis session, avoid food intake during haemodialysis, reconsider the dry weight or the actual dry weight of the patient, hypertonic dialysis, sequential haemodialysis, profiling, sodium and ultrafiltration, high dialysis calcium, cool dialysate and changes in the frequency of the duration of dialysis or hemodiafiltration.

The other way is the biofeedback technology.

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CLOSED LOOP CONTROL ARCHITECTURE

You know that in engineering, in bioengineering when the engineer speaks about biofeedback or feedback, they speak about closed loop control in which you don’t have
the open loop control of the process but you have the closed loop control, a retroactive control in which it’s important that you have a sensor that is able to measure the controlled variable.

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The first biofeedback system in humans is the artificial pancreas. In this system you have a sensor for glucose, then you have an injection pump and on the basis of the trend of glucose the amount of insulin changes and you have a control of the glucose of the patients.

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**PHYSIOLOGIC CLOSED-LOOP CONTROLLER IN HD**

**Variables:**
- w: reference variable
- e: Error variable
- x: Controller output variable
- f: Sensor for Feedback variable
- y: Physiologic variable
- V_p: patient disturbance variable
- c: Command variable

**Manipulated variables**
1. Ultrafiltration rate
2. Dialysate sodium concentration
3. Dialysate temperature
4. Patient disturbance Variable (V_p)

**Physiological variables**
1. Blood volume
2. Plasma sodium
3. Blood temperature
4. Blood pressure
In dialysis we can control many physiological variables: blood volume, plasma sodium, plasma ---, blood temperature and the blood pressure also of the patient. The manipulated variable of the dialysis machine are the ultra-filtration rate, the conductivity and the temperature of the dialysate.

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**Blood volume controlled hemodialysis**

This is the blood volume control system that we designed in 1998. In this kind of system you have a sensor to measure the blood volume of the patients and the dialysis machine is stable on the basis of the controller. The controller is the brain of the system and the controller changes continuously the ultrafiltration rates, the dialysis conductivity in order to obtain the desired blood volume trend.

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**Blood Volume Tracking (BVT) hemodialysis**

Santoro A et al, Am J. Kidney Dis, 1998, 5, 739-748
The system is a little bit complicated because it's a multi input-multi output system where there is not only the blood control volume but there is also the control of the total weight loss of the water loss and the actual conductivity of the patients, the balance of the conductivity throughout the dialysis session.

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**Blood Volume Tracking**

The controller adjusts the UFR and DC in order to minimize the error between the BV-desired (blue line) and the observed (red line) trend.

*Optimisation of the BV trend is reached in the individual patient and at each HD session, by means of the combination of experimental data drawn from continuous BV % measures and processed data obtained from dynamic on-line models.*

As you can see in this slide the controller adjusts the ultrafiltration rate, the dialysis conductivity continuously in order to minimize the error between the blood volume desired that is the blue curve and the observed one that is the red one.

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This is the typical level of blood volume control on blood volume behaviour. This is the spontaneous trend of the blood volume in this patient and as you can see in this patient, we have the ups and downs of the blood volume. But when you perform automatic control of the blood volume, you can have this kind of curve. So you don't have the drops of the blood volume throughout the dialysis session.

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**Systolic arterial pressure in standard and biofeedback**

![Graph showing systolic arterial pressure changes](image)


This may influence the blood pressure behaviour because these are 15 hypotension-prone patients, they performed a standard dialysis session without control of the blood volume and in the next dialysis the biofeedback dialysis. As you can see, the behaviour of the blood pressure but also the behaviour of the blood volume is different. The blood pressure is more stable during biofeedback haemodialysis.

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**A multicenter randomized study**

A = conventional HD  
B = Blood Volume Controlled HD

![Randomization diagram](image)

Santoro A. et al., Kidney Int 2002
This is a randomised controlled study. This is a controlled study in which there are many hypotension-prone patients. It’s a crossover study.

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and in this study, as you can see, hypotension-prone patients with very high frequency of hypotension episodes throughout the dialysis session with the automatic system may have a reduction in hypotension treatment.

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Percentage of calls free sessions, in biofeedback and conventional hemodialysis

Déziel in Canada demonstrated that by means of biofeedback dialysis it’s possible to reduce the work of the nurse because the number of call free sessions is reduced when they use the biofeedback system.
But this is a very important result because Chris McIntyre and Selby demonstrated that in conventional dialysis, as I said earlier, there is some abnormality of wall motion when you have a reduction in myocardial flow. But in contrast if you keep blood volume constant or you minimise the reduction in blood volume, you can reduce the abnormality in the ventricular wall motion by means of the biofeedback dialysis.

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**Intradialytic hypotension**

The number of dialysis complicated by hypotensions over the total number of assessed dialysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HBS (Yes)</th>
<th>HBS (No)</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994 Santoro (1)</td>
<td>1</td>
<td>30</td>
<td>3.87 (0.91, 3.88)</td>
<td></td>
</tr>
<tr>
<td>1998 Santoro (2)</td>
<td>25</td>
<td>96</td>
<td>12.84 (6.37, 11.12)</td>
<td></td>
</tr>
<tr>
<td>2000 Ronco</td>
<td>24</td>
<td>72</td>
<td>10.94 (0.11, 0.12)</td>
<td></td>
</tr>
<tr>
<td>2001 Basile (3)</td>
<td>26</td>
<td>171</td>
<td>12.85 (0.29, 0.85)</td>
<td></td>
</tr>
<tr>
<td>2002 Santoro</td>
<td>180</td>
<td>766</td>
<td>14.84 (0.49, 0.77)</td>
<td></td>
</tr>
<tr>
<td>2002 Wolkotte</td>
<td>10</td>
<td>158</td>
<td>11.03 (0.15, 0.67)</td>
<td></td>
</tr>
<tr>
<td>2003 McIntyre</td>
<td>2</td>
<td>133</td>
<td>6.06 (0.03, 0.68)</td>
<td></td>
</tr>
<tr>
<td>2006 More (4)</td>
<td>110</td>
<td>110</td>
<td>10.35 (0.19, 1.06)</td>
<td></td>
</tr>
<tr>
<td>2007 Decol (5)</td>
<td>56</td>
<td>204</td>
<td>13.73 (0.65, 1.51)</td>
<td></td>
</tr>
<tr>
<td>2008 Winkler (6)</td>
<td>1</td>
<td>648</td>
<td>3.97 (0.00, 0.14)</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 2388 1967 100.00 0.35 (0.21, 0.56)

Total events: 334 572
Heterogeneity: Tau² = 0.33, Chi² = 47.17, df = 9 (P < 0.00001); I² = 81%
Test for overall effect: Z = 4.38 (P < 0.0001)

(1) Data pooled over A1, A2 study phases
(2) Data pooled over A1, A2 study phases
(3) Data referred to the short-term study phase
(4) Data referred to the conventional vs HBS phases
(5) Data referred to 4 weeks recording (2 weeks at the beginning and 2 weeks at the end)
(6) Data referred to the short-term study phase

Santoro A. Contrib Nephrol 2010

In a pooled analysis some years ago, we demonstrated that with automatic dialysis with blood volume control, we can obtain the reduction of the hypotension episode in dialysis patients.
Very recently, Nesrallah in NDT published this accurate meta-analysis and he demonstrated the same results that in many studies also in crossover trials, it’s possible to demonstrate that with this system we can reduce the frequency of the dialysis-induced hypotension.

**EBPG guideline on hemodynamic instability**

*Guideline 3.1.2a Individualized, automatic BV control should be considered as a second-line option in patients with refractory IDH (Evidence level II).*

**Rationale**

With blood volume controlled treatments, ultrafiltration rate and/or dialysate conductivity are adjusted according changes in relative blood volume.

[...] Nevertheless, several randomized cross-over studies have shown a reduction in IDH and intra-dialysis symptomatology with the use of automatic blood volume feedback [1,2,4-6]. Moreover, one study showed an increase in dialysis efficacy with the use of this approach, due to a reduction in intra-dialytic interventions [1].

[...] No adverse effects on sodium balance have yet been reported [2,7].

[...] Summarizing, various studies have shown a beneficial effect of automatic blood volume controlled feedback in the prevention of IDH episodes.

The European Best Practice Guidelines said that automatic blood volume control should be used as a second line option in patients with refractory intradialytic hypotension.
But, as I said earlier, there are other biofeedback systems in dialysis. In this system the variable that we measure and we control is the systolic arterial pressure of the patients. We need to measure the systolic arterial pressure of the patients at least 10 minutes throughout the dialysis session.

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Then in this system the brain of the system is a fuzzy controller. The fuzzy controller is a system working on the fuzzy logic and the controller has many adaptive rules based on the UF rate.

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There are continuous changes to the ultrafiltration rate throughout the dialysis session based on blood pressure profile.

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So as you can see when the blood pressure goes down, then the ultrafiltration, this bar, is reduced because the UF stops when the machine sees that there is a reduction in blood pressure. So it stops UF and allows a better refilling, then the blood pressure goes up and the machine starts with the UF but regulating UF on the basis of the trend of the blood pressure.

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With this system it’s also possible to reduce the severity of the number of hypotensive episodes in some patients and in some hypotension patients.

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**Electrolytic control system**

*(plasma conductivity, plasma sodium)*

The other possibility of biofeedback is to evaluate the sodium of the patients, the plasma sodium or the plasma conductivity of the patients continuously. Then we can have a retroactive mechanism in order to change the dialysis conductivity and the sodium content in the dialysate.

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With this system, it is possible at the beginning of dialysis to project the dialysate conductivity by the end of the session.

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**On-line conductivity control**

N. = 16 patients
Cross-over trial with two treatments:
A = Constant Dialysate Cond BD
B = Adapted Dialysate Cond BD
4 months per period

Peticlerc T et al, ND & T, 1995, 596-599

This system controls the plasma sodium, controls the blood volume, may reduce the hypovolemia throughout the dialysis session and may reduce the hypotension episodes and also the nausea and vomiting of the patient.

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The other possibility of this system is to use a special dialysis technique like this. This is a technique HFR in which we have a filter, a super flux-filter and then we have a low flux filter. In this filter we have the removal of the ultrafiltrate and the plasma water. In this kind of circuit we have the natrium sensor in order to measure the plasma conductivity and to measure the sodium of the patient. By means of a special algorithm, it is possible to profile, to obtain a good profile of the sodium balance of the patient.

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<table>
<thead>
<tr>
<th>Results about overall and cardiovascular tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (N = 143)</td>
</tr>
<tr>
<td>HFR (%)</td>
</tr>
<tr>
<td>HFR-Aequilibrium (%)</td>
</tr>
<tr>
<td>Wilcoxon, P</td>
</tr>
<tr>
<td>Primary end point</td>
</tr>
<tr>
<td>Dialysis</td>
</tr>
<tr>
<td>complicated by hypotension</td>
</tr>
<tr>
<td>31 ± 4</td>
</tr>
<tr>
<td>23 ± 3</td>
</tr>
<tr>
<td>0.03</td>
</tr>
<tr>
<td>Secondary end points</td>
</tr>
<tr>
<td>Symptomatic hypotensions</td>
</tr>
<tr>
<td>5 ± 1</td>
</tr>
<tr>
<td>3 ± 1</td>
</tr>
<tr>
<td>0.04</td>
</tr>
<tr>
<td>Intradialytic symptoms</td>
</tr>
<tr>
<td>9 ± 1</td>
</tr>
<tr>
<td>6 ± 2</td>
</tr>
<tr>
<td>0.01</td>
</tr>
</tbody>
</table>


Francesco Locatelli very recently demonstrated that by means of this system HFR-Aequilibrium it is possible to reduce the hypotension episode in the patients and the intradialytic symptoms with the correction of the trend of sodium throughout the dialysis session.
Apart from the hypovolemia, as I said before,

while some episodes are related to an impairment of compensatory mechanisms, of the cardio circulatory response of the patients.
you know that in hypotension-prone patients, we can have a reduction in cardiac output

but also we don’t have an increase in peripheral vascular resistance and renal stones of the patients.
So, in hypotension-prone patients you don’t have the reduction in unstressed blood volume; this is typical of the hypotension-resistant patients, the reduction in unstressed blood volume.

What is the possibility to increase the myocardial contractility or peripheral vascular resistance during dialysis? Well cool dialysate. Because when you cool dialysate, you can increase the catecholamine secretion, you can increase the systemic vascular resistances since the venous reactivity, the venous contractility reduce the heart rate and also you can reduce the streptokinase throughout the dialysis session in this.
Selby and McIntyre demonstrated that with cool dialysate is possible to reduce the hypotension throughout the dialysis session when you cool the dialysate.

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**Temperature control system**

The same is that if you use and this is better a temperature-controlled system. When you use a temperature-controlled system, you need the measurements of the temperature balance of the patients.

Slide 50
and you need a machine in which you have a dialysate temperature control, a venous temperature control and an arterial temperature control. The machine measures continuously the arterial temperature and changes the dialysate temperature in order to obtain a thermoneutral dialysis with no exchange of temperature or of energy in this.

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*Frequency of hemodialysis treatments with symptomatic hypotension for each 4-week phase with energy control (treatment A) or body temperature control (treatment B).*

Maggiore Q. Pizarelli F. Santoro A. et al. AJKD, 2002

Quirino Maggiore some years ago demonstrated that with this kind of system in a multicentre study it is possible to reduce the hypotension of hypotensive patients.

Slide 52
But also with this system it is possible to reduce the phenomenon of myocardial stunning. This is the study of Chris McIntyre and Selby and this is the temperature-control dialysis, reduction of abnormality in wall motion that we cannot serve in conventional haemodialysis.

Slide 53

But also with this system it is possible to reduce the phenomenon of myocardial stunning. This is the study of Chris McIntyre and Selby and this is the temperature-control dialysis, reduction of abnormality in wall motion that we cannot serve in conventional haemodialysis.

The biofeedback systems in hemodialysis:
1. Blood volume tracking systems
2. Blood pressure control systems
3. Temperature control systems
4. Conductivity based systems
5. Plasma sodium biofeedback systems

A question that we can might ask ourselves is, but because so many systems to solve a single problem the IDH?

It’s not possible to offer a unique, standard solution to fulfill all patient’s needs in term of cardio-vascular stability?

So there are many biofeedback systems in haemodialysis: blood volume tracking, blood pressure control system, temperature control system, conductivity based systems, plasma sodium biofeedback systems. So the question is but why do we have many systems like this in order to solve or to correct single problems and simple problems of intradialytic hypotension? Well the question is the same as Professor Jacob’s question, there are a lot of haemodialysis patients, they are old, different from each other and
it’s not possible to offer a unique standard solution to fulfil all patients’ needs in terms of cardiovascular stability.

So to conclude, the automatic feedback system of dialysis may improve patients’ tolerability to dialysis and reduce the frequency of intradialytic hypotension. Depending on the system used the better cardiovascular stability may be due to improvement of the phenomenon of myocardial stunning, preservation of the blood volume, better compensatory mechanisms to increase cardiac output and peripheral resistances (temperature driven systems). However larger and well-designed RCT are needed to assess the effects on survival, hospitalizations and QoL of these systems.

So to conclude, the automatic feedback system of dialysis may improve patients’ tolerability to dialysis and reduce the frequency of intradialytic hypotension. Depending on the system used the better cardiovascular stability may be due to improvement of the phenomenon of myocardial stunning, preservation of the blood volume, better compensatory mechanisms to increase the cardiac output and peripheral resistance in temperature driven systems. However, also in this case we need larger and well-designed randomised controlled trials to assess the effects on survival and probably the hospitalisation and quality of life of this system in the dialysis patient population. Thank you for your attention.