Title

Dialysate Temperature Adjustment as an Effective Treatment for Baroreflex Failure Syndrome in Hemodialysis Patient

1) Natsumi Tanabe, MD, E-mail: h19mstanabe@gmail.com
2) Koki Takane, MD, E-mail: koki555@hotmail.com
3) Keitaro Yokoyama, MD, PhD, Email: keitaro@mrj.biglobe.ne.jp
4) Yudo Tanno, MD, E-mail: yudo@msd.biglobe.ne.jp
5) Izumi Yamamoto, MD, PhD, Email: izumi26@jikei.ac.jp
6) Ichiro Ohkido, MD, PhD, E-mail: iohkido@jikei.ac.jp
7) Takashi Yokoo, MD, PhD, E-mail: tyokoo@jikei.ac.jp

1) Jikei University Hospital.
   3-25-8, Nishishimbashi, Minato-ku, Tokyo, Japan.

2)(3)(4)(5)(6)(7)
2) The Division of Nephrology and Hypertension, Jikei University School of Medicine.
3-25-8, Nishishimbashi, Minato-ku, Tokyo, Japan.
[ Abstract ]

Background: Baroreflex failure syndrome is a rare disorder which causes labile blood pressure, headache, flushing, diaphoresis and emotional lability. It is caused by history of trauma or radiotherapy in the cervical legion, bilateral carotid-body tumor or section of glossopharyngeal nerve. We experienced a case of hemodialysis patient who had difficulty in controlling blood pressure during dialysis because of his baroreflex failure syndrome and successfully controlled his blood pressure by adjusting dialysate temperature.

Case Presentation: We report a case of a 68-year-old CKD5 patient who had difficulties of hemodialysis treatment because of severe fluctuations in blood pressure with hypertensive attacks and hypotensive episodes which caused him a severe discomfort. His dialysis treatment was started in 2010 and since that time baroreflex failure syndrome has been suspected because of his clinical manifestations and history of radiotherapy in the cervical region for his lingual cancer in 1994. Baroreflex failure syndrome is diagnosed by symptoms and cold stressor test. We performed a cold stressor test to an experimental baroreflex failure syndrome mouse which caused a significant elevation of blood pressure. From this experimental finding of model mouse, we changed the patients dialysate temperature between 34-38° according to his change in blood pressure though 80-240 mmHg. From this attempt, his blood pressure was successfully controlled between 100-180 mmHg and he was able to continue hemodialysis without any discomfort.

Conclusion: In our case, environmental stimulation such as temperature change modified the patients fluctuating blood pressure. Change of dialysate temperature could be an option for controlling the unstable blood pressure due to baroreflex failure syndrome.

[Keywords]
Baroreflex Failure, Hemodialysis, Hypertension
[Background]

The arterial baroreflex which involves multiple components of the baroreflex arc, prevents excessive fluctuations of arterial blood pressure. The signals by distention of the vessel wall are sent from baroreceptors in each carotid sinus to the brain stem via the glossopharyngeal nerve (cranial nerve IX). The information from other baroreceptors in the aortic arch and the great vessels of the thorax are sent through the vagus nerve (cranial nerve X) to the brain stem. Thoracic blood volume change detected by low-pressure receptors is also sent by the vagus nerve to the brain stem.

According to these mentioned mechanism of baroreflex, any abnormalities in the vascular baroreceptors, the glossopharyngeal or vagus nerves, or the brain stem could cause baroreflex failure.  

In clinical setting, baroreflex failure is often caused by denervation of carotid body tumor resection, carotid artery surgery, neck irradiation and neck trauma. The frequent symptoms are labile hypertension and hypotension, often with headache, diaphoresis, face flashing and emotional instability.

We experienced a hemodialysis case with labile blood pressure which fluctuated through 80 mmHg to 240 mmHg during dialysis (Fig 1). Although it was hard to diagnose, we differentiated our case from autonomic failure, which is common in chronic hemodialysis patients, by the hyperactive result to cold pressure stimuli. This is because sympathetic efferents to the vasculature is intact in baroreflex failure and patients exhibit a normal or even an increased pressor response to cold-pressure test.  

In general, the use of low-temperature dialysate is recommended to decrease the frequency and intensity of symptomatic hypotension. From this evidence, we considered applying this method to stabilize the patients labile blood pressure. This is a case report of baroreflex failure hemodialysis patient in whom dialysate
temperature adjustment was an effective treatment for labile blood pressure
during hemodialysis caused by baroreflex failure syndrome.

[Case Presentation]

Case
A 68-year-old Danish male presented with multiple episodes of lightheadedness
and the feeling of ‘passing out’ while he was getting out of his bed or when food
was administered to his gastric fistula tube. And he also had sudden onset of
hypertensive attacks several times a day. His past medical history was significant
for chronic kidney disease and hypertension since he was 30-years-old. The
patient was diagnosed having lingual cancer for which he received external
radiation therapy (RT) at 45-year-old. Ten years after RT, the patient started
having dysphagia and had several episodes of aspiration pneumonia. Modified
barium swallow was done and he was suspected having silent aspiration, so
Percutaneous Endoscopic Gastrostomy (PEG) was created. Although the patient
didn’t have any oral intake, he still repeated pneumonia and eventually he
underwent tracheotomy. At the same time, his renal function declined and
hemodialysis was started three times a week. Since then he has been suffering
labile blood pressure. Especially while hemodialysis, blood pressure fluctuated
through 80 mmHg to 240 mmHg which were difficult to be controlled (Fig 1).
He had been treated by Ca-channel blocker and ARB but his labile blood pressure
could not be stabilized and he had frequent episodes of fainting and several
occlusion of his arteriovenous fistula (AVF) caused by extreme hypotension. His
current medication included Droxidopa and Midodrine Hydrochloride for
hypotensive episodes but his labile blood pressure during hemodialysis was
difficult to control with these medications.
The dialysate had the following ionic concentration: 140 mEq/L of sodium, 2.0
mEq/L of potassium, 3.0 mEq/L of calcium, 1.0 mEq/L of magnesium, 113 mEq/L
of chloride, and 10 mEq/L of acetate.
Although his blood pressure was extremely unstable, heart rate was stable and
didn’t change more than 10 bpm during hemodialysis.
Eventually, fifteen years after the neck irradiation, this patient suffered from
edema of his arm with his AVF. It was caused by the stenosis of his brachial vein
and cured by Percutaneous Transluminal Angioplasty (PTA).
From his current symptom of labile blood pressure with stable heart rate and medical history of RT and brachial vein stenosis, we diagnosed him having Baroreflex Failure.

**Examination**

His physical exam was negative except his hypertension. Extensive laboratory examinations did not show any abnormal findings. Cold pressor test showed 26mmHg, 15mmHg increase in sBP, dBP, respectively.\(^2\)

The patient’s labile blood pressure during hemodialysis was treated with dialysate temperature change. We decreased dialysate temperature to 34° when patient’s blood pressure was low and increased it to 37° when pressure was getting high. From this trial, his blood pressure was stabilized between 120-180 mmHg which was ranging through 80-240 mmHg before the temperature adjustment (Fig 2).

**Discussion**

At the beginning of every hemodialysis, the patient’s BP was always higher than normal range with his systolic blood pressure around 170 mmHg and it gradually dropped to around 80 mmHg in the first one hour of hemodialysis. After reaching the bottom it kept on rising to 240 mmHg toward the end of the dialysis. Several factors causing intra-dialysis hemodynamic instability have been reported in many articles in the past. It was reported that activation of RAA or sympathetic activity during hemodialysis is the main cause of intradialytic hypertension.\(^3\)

However, there wasn’t a significant change in electrolyte levels, activation of RAA system nor sympathetic nerve activity from the blood test pre and post dialysis. (Table 1)

In the process of making the diagnosis, we noticed that the patient’s heart rate did not change and was stable compared to his blood pressure instability. From his
past medical history of RT and unusual blood pressure elevation in cold pressor
test, we diagnosed him having baroreflex failure.

The key for diagnosing this case was his medical history of RT in the cervical
region. Among several causes of baroreflex failure, a history of irradiation
around the cervical region is one of the main reasons.4) Since the average
duration of time until symptomatic is 5-6 years, it is often seen as an chronic
complication in RT. In particular, after neck irradiation, long-term injury occurs
commonly in the carotid arteries. Atherosclerotic and thrombotic complications
occur and cause significant carotid stenosis and stroke in many patients. In fact,
this patient had medical history of TIA ten years after the irradiation. Besides
atherosclerosis, chronic inflammation and fibrosis of carotid arterial walls might
lead to “splinting” of carotid sinus baroreceptors. Since these receptor are
sensitive to stretch or distortion, stiffening of the carotid sinus would be expected
to lead to decreased gain of the arterial baroreflex.5) In this case, Right Internal
Carotid Artery (R-ICA) starting point and Left common carotid artery(L-CCA)
bifurcation points Max Intima-media Thickness (IMT) was 3.41 mm homogenous
iso-echoic plaque and 3.68 mm heterogenous iso-echoic plaque, respectively.
While hypo echoic plaque is usually compatible to hematoma or atheroma, and
hyper echoic plaque is usually reflect calcification, homogenous iso-echoic plaque
is often seen in case of the fibrosis of the artery.6)

In addition, three years after starting the temperature adjustment dialysis, this
patient suffered from edema of his arm which he had his AVF. It was caused by the
stenosis of his brachial vein and cured by Percutaneous Transluminal Angioplasty
(PTA). ( Fig 3 )

By the facts that Carotid Ultrasonography showed iso-echoic plaques and he had
a brachial vein stenosis which was cured by PTA, it was compatible to our thought
that the fibrosis of the artery is main reason to cause his baroreflex failure after
radiation therapy.

The recommended medication for baroreflex failure is antihypertensive and/or
vasopressor agents to prevent labile change in blood pressure.4) Our patient took
droxidopa, which was somewhat effective, before meal and lying in bed because
these two situations caused hypotensive episodes. However the labile blood
pressure during hemodialysis was not able to be stabilized by medications.
The 2005 K/DOQI guidelines\(^7\) recommends the use of cool dialysate temperature dialysis in patients with frequent episodes of uncontrolled hypotension during hemodialysis treatment.

And from our cold pressor experiment on vagotomy model mouse, we found that vagotomy mouse, which is a model of baroreflex failure, has more increase in blood pressure than normal mouse when the tail was exposed in 4\(^\circ\) water for 2 minutes (Fig 4). In addition, the patients use of droxidopa during summer was more frequent than during winter. This also tells us that blood pressure changes according to the temperature. From these findings, patients with baroreflex failure have more susceptibility to temperature change and the patient was treated successfully by changing the dialysate temperature according to his blood pressure change during hemodialysis.

[Conclusion]
Baroreflex failure occurs as a chronic complication for neck irradiation therapy. Patients who have baroreflex failure often suffer from their unstable blood pressure. Baroreflex failure dialysis patient who had an extreme change in blood pressure during dialysis was treated successfully by adjusting the dialysate temperature according to his labile blood pressure during hemodialysis.

[Consent]
Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

[List of Abbreviations]
CKD: Chronic Kidney Disease
RT: Radiation Therapy
AVF: Arteriovenous Fistula
PTA: Percutaneous Transluminal Angioplasty
sBP: systolic Blood Pressure
dBP: diastolic Blood Pressure
RAA: Renin Angiotensin Aldosteron
The authors declare that they have no competing interests

NT, KY, KT, IY, IO, and YT treated the patient. NT drafted the manuscript. KY and TY helped to draft the manuscript. KY performed the model mouse experiment. All the authors contributed to preparation of the manuscript, and approved the final version.

[Author’s information]
1 Jikei University Hospital. 3-25-8, Nishishimbashi, Minato-ku, Tokyo 105-0003, Japan.
2 The Division of Nephrology and Hypertension, Jikei University School of Medicine. 3-25-8, Nishishimbashi, Minato-ku, Tokyo 105-0003, Japan.

[Acknowledgements]
There are no conflicts of interest.

[References]


[Figure Explanations]

Fig 1: **Labile blood pressure change during hemodialysis before changing the dialysate temperature.** The patient's systolic blood pressure during hemodialysis changed through 80 mmHg to 240 mmHg before we started the dialysate temperature therapy. The patient suffered from headache and diaphoresis from this blood pressure change.

Fig 2: **Less fluctuating blood pressure during hemodialysis after starting the dialysate temperature therapy.** After starting the dialysate temperature therapy, the patient's blood pressure was less fluctuating and remained between 120 mmHg to 180 mmHg. This figure shows the association between the temperature change and the blood pressure change.

Fig 3: **An image of the patients brachial artery, pre and post PTA.** The patient's brachial artery was stenosed because of the fibrosis from the irradiation. We performed PTA and the fibrotic brachial artery was dilated.

Fig 4: **Cold pressure test on vagotomy model mouse.** This figure shows the systolic blood pressure change of the vagotomy model mouse during cold pressure test. This experiment shows that the blood pressure of baroreflex failure model mouse is more susceptible to cold stimulation.
Table 1. The various changes during hemodialysis

<table>
<thead>
<tr>
<th>Time from starting HD (min)</th>
<th>0</th>
<th>60</th>
<th>120</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>sBP (mmHg)</td>
<td>150</td>
<td>109</td>
<td>125</td>
<td>210</td>
</tr>
<tr>
<td>dBP (mmHg)</td>
<td>97</td>
<td>74</td>
<td>88</td>
<td>110</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>66</td>
<td>61</td>
<td>65</td>
<td>77</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>PAC (pg/ml)</td>
<td>91.6</td>
<td>45.6</td>
<td>52.9</td>
<td>48.4</td>
</tr>
<tr>
<td>Adrenaline (pg/ml)</td>
<td>20</td>
<td>32</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Noradrenaline (pg/ml)</td>
<td>158</td>
<td>147</td>
<td>208</td>
<td>227</td>
</tr>
<tr>
<td>Dopamine (pg/ml)</td>
<td>38</td>
<td>38</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>34.3</td>
<td></td>
<td>35.8</td>
<td></td>
</tr>
<tr>
<td>Na (mEq/L)</td>
<td>140</td>
<td></td>
<td>139</td>
<td></td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>4.1</td>
<td></td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Ca (mEq/L)</td>
<td>9.2</td>
<td></td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Plasma Osml (mOsm)</td>
<td>305</td>
<td></td>
<td>287</td>
<td></td>
</tr>
<tr>
<td>hANP</td>
<td>111</td>
<td></td>
<td>73.8</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1

Labile Blood Pressure during Hemodialysis

BP (mmHg)

Time (min)

sBP

dBP

HR

Figure 1
Stabilized BP by Dialysate Temperature Adjustment

- sBP
- dBP
- HR
- Temp

Time (min)

BP (mmHg)

Dialysate Temp. (°C)
Effect of Vagotomy on the Cold Pressure Test

**Figure 4**

- **Cold stimulation of the tail:**
  1. Placed cold water (4°C) for 2 min
  2. 30 min interval

- **General:**
  1. Adult rat (SD Male 400g)
  2. Urethane anesthesia (1.2 g/kg)
  3. Body temperature: 38°C
  4. MAP monitor; right femoral artery
Additional files provided with this submission:

Additional file 1: Table 1.pdf, 20K