Author’s response to reviews

Title: Catecholamine reversal: a case report on unexpected hypotension

Authors:

YOHEI OKADA (okadayohei1127@yahoo.co.jp)
Ryoji Iiduka (iizukar@kyoto2.jrc.or.jp)
Wataru Ishii (wataruaug0804@lily.ocn.ne.jp)
Hiromichi Narumiya (pyroli1117@gmail.com)

Version: 1 Date: 04 Jan 2017

Author’s response to reviews:

Cover letter for revise version

To the Editor in Chief,

Thank you very much for having considered our manuscript. I am very pleased to see the favorable comments of both Reviewers. I fundamentally agree with all these comments and incorporated them to the revised version. Red indicates the parts that I changed according to Reviewer’s comment.

I hope that you would evaluate this revised version positively.

Kind regards,

YOHEI OKADA
>For reviewer #1

Thank you for your consideration.

I am very glad to see your favorable comment.

Reviewer #1: good article.

only in tab 1 the PaO2 value is 483, it would be better to indicate p/f value or FiO2

I indicated FiO2 in the table, I am very glad if you confirm it.

>For reviewer #2

Thank you for your kind consideration, and I am very glad to see your favorable comment.

I agree with your comment, and I revised manuscript according to your advice.

I am very glad if you would consider positively my revised manuscript for publication.

Reviewer #2: The case report is unique since "catecholamine reversal" is rarely heard of. However, there are major issues in regards to the report, which are:

1. Vital signs such as heart rate, blood pressure, capillary refill time, urine output and patients' mental status are not complete (from day one through five).

For ex: line 42. Fluid resuscitation of 3000 mL crystalloid temporarily increased his BP. How much increase? ... But shock still persisted. Please describe his signs of shock.

Line 46: however his hypotension gradually worsened. What was his exact blood pressure and mean arterial pressure?

Overall, we missed partially the vital sign or patient’ condition. Thus, we added the information about the vital sign and the condition in detail.
2. In his shocked state, when did you decide to intubate? Please describe the chronological order of actions performed.

We immediately performed intubation because of shock and coma. I added this in the manuscript.

3. In line 49, you mentioned that systemic vascular resistance index (SVRI) was very low. How did you obtain this number? What device was utilized?

We used the Vigileo FloTracTM, and we added the information in manuscript.

4. Please state how much time has elapsed before you initiated norepinephrine and dobutamine infusion. And for how long did you continue to administer them before switching to vasopressin.

We added the time course about catecholamine infusion in the manuscript.

5. You mentioned that hemodiafiltration was performed due to the presence of metabolic acidosis. However, this data does not seem to match the data you presented on arterial blood gas on Table 1. His pH was 7.364 and base excess -3.9 mmol/L.

We added the results of arterial blood gas assessment on admission to ICU (Table2). It indicated metabolic acidosis.

6. Your patient was cared for five days, what happened to the data sets and vital signs on day three and four? How did you titrate down on vasopressin and was the noradrenaline infusion completely terminated?

After the vasopressin was induced, his hemodynamic state became stable. Thus the amount of catecholamine infusion was decreased, and finally terminated about 12 hours after admission.

Moreover, the vasopressin was terminated about 24 hours after admission. On day 2, he was extubated and his hemodynamic state was stable. On day 3, and 4, he was alert and stable.

We added these information in the manuscript.
7. Bibliography section only contains four references which have published dates as far back as 1964. Please find more references to support your case report and even to describe this rare condition you encountered; describing in detail its mechanism.

Thank you for your advice.

I added some literature to support my case and this rare condition in more detail.

8. Overall, you need to elaborate on the general well-being of this patient from admission up through his ICU discharge date. Describing a patient merely on one time monitoring of blood pressure and GCS score upon admission in addition to "worsened metabolic acidosis" is not enough to give reviewers the confidence to believe that your patient completely recovered on day 2 of his ICU care. This report needs to be revised extensively since core data sets are missing.

Thank you again for your good advice. I added the detail of patient’s condition and vital sign in the manuscript.

>For reviewers #3

Thank you for your important criticism.

I suggested my idea for your opinion, and I revised my manuscript according to your comment. I am very glad if you would reconsider my revised manuscript

Reviewer #3: Major concern:

- In this case norepinephrine was used for hypotension along with dopamine. Norepinephrine has predominantly alfa-1 and beta -1 adrenergic receptor action, thus cause vasoconstriction and modest increase in heart rate. There is little, if any, stimulation of the beta -2 adrenergic receptor to cause peripheral vasodilation, therefore, if a-1 adrenergic effect is blocked (by risperidone), would not cause hypotension due to high beta -1 adrenergic receptor action and almost null beta -2 adrenergic receptor activity.
- Similarly, Dopamine have almost no beta -2 adrenergic receptor adrenergic activity and some alfa-1 receptor activity on higher doses. Dopamine increases blood pressure by beta -1 adrenergic receptor and dopaminergic activity, therefore, blockage of a-1 receptor in
presence of dopamine should not cause hypotension due to it unaffected action on beta-1 adrenergic receptor and dopamine receptors.

- However, adrenaline has different mechanism of action, it has significant beta-2 adrenergic receptor activity, and alfa-1 activity, thus blockage of selective alfa-1 receptors may cause hypotension by uninhibited beta-2 receptor mediate vasodilatation.

Reply to your comment;

I understand that your comment is one of the reasonable ideas.

However, an animal experiment report (*1, ref 4 in the manuscript) obviously showed ‘noradrenaline reversal’ and we believed that noradrenaline works beta-2 effect as well as adrenaline.

Addition to that, another literature about dopamine (*2) proved that dopamine has beta-2 adrenergic effect in molecular level.

Moreover, the other literature clearly shows that dopamine and noradrenaline have moderate beta-2 adrenergic activity (*3).

Accordingly, We believe that the large amount of dopamine, and noradrenaline may cause hypotension as well as ‘adrenaline reversal’, if the alfa blockade effect is strongly highlighted.

We revised my manuscript to highlight these ideas in the manuscript.

I am pleased that you would reconsider my manuscript.

Ref)


*3 ‘Inotropes and Vasopressors Review of Physiology and Clinical Use in Cardiovascular Disease’ Circulation. 2008;118:1047-1056 Table
Minor Concern:

-Was Serum cortisol checked to rule out adrenal insufficiency?

Thank you for your kind consideration.

His blood sugar level and serum Na were not low, thus we ruled out adrenal insufficiency. (Unfortunately, our institution could not measure serum cortisol immediately.)

We checked thyroid function to rule out thyroid storm.