Author's response to reviews

Title: Vagal baroreflex activation resulting in acute coronary stent thrombus associated with myocardial infarction: a case report

Authors:

Jun Yang (whitneyeva1@gmail.com)

Version: 3 Date: 2 July 2014

Author's response to reviews: see over
Title: Vagal baroreflex activation resulting in acute coronary stent thrombus associated with myocardial infarction: a case report

Dear Editor,

We greatly appreciate your efforts on our manuscript. Following your comments and suggestions, we have carefully revised the manuscript. Please see the following response to reviews. All detailed revisions are highlighted with Red-Color in the manuscript.

We do wish these revisions are satisfied with your requirements.

Again thanks for your time and great suggestions.

Jun Yang
Reviewer's report (1)

Title: Vagal baroreflex activation resulting in acute coronary stent thrombus associated with myocardial infarction: a case report

Version: 1 Date: 15 May 2014

Reviewer: Ahmed Dr Mahmoud

Reviewer's report:
- Major Compulsory Revisions:
  1- Introduction:
  a) The 1st sentence “…have been reported extensively in patients who have undergone carotid angioplasty and stenting” this is not related to the topic of PCI, authors need to illustrate supportive evidence related to coronary intervention rather than carotid. It is more logic that carotid interventions would cause baro-reflex activation as the receptors are located at or near the site of intervention. This paragraph needs to be reformatted in a way to support the author’s theory of having increased vagal stimulation during and post PCI (either by case reports or studies illustrating the incidence of this clinical presentation in PCI).
  Answer: Thanks for reviewer’s indication. We have changed as the reviewer indicates, and added some sentences.
  b) “VBA-caused hemodynamic alterations are indeed common after percutaneous coronary intervention (PCI) in clinical practice” this sentence needs more explanation either in the introduction or discussion, with references (why do they think it is common? How frequent is it? what is the theory behind it?).
  Answer: the sentences are changed to” there are few data available about the hemodynamic alterations resulting from VBA in PCI patients [4].

  2- Case presentation:
  a) “coronary artery disease of more than 10 years’ duration with progressively increasing frequency of angina for the past 2 years” this presentation is vague, the authors need to clarify the exact presentation of the patient, was it acute coronary syndrome? or chronic stable angina? With more details, in the history, regarding the chest pain (onset, course, duration, frequency, at rest? Relieved by nitroglycerine or rest? Location and radiation, if possible).
  Answer: We have changed as the reviewer indicates
  b) “The patient reported a history of taking medication for hypertension and diabetes for almost 10 years.” What about other risk factors for CAD (Family history, smoking, dyslipidemia, CKD (chronic kidney disease), etc)?
  Answer: We have added as the reviewer indicates
  c) “An electrocardiogram (ECG) showed abnormal T-waves.” This is so vague, authors need to explain what did the ECG show exactly, for example: inverted T
waves in leads V1-V6 or biphasic non-specific T-waves. Also they need to comment on the time of ECG related to chest pain and presentation.

**Answer:** We have changed as the reviewer indicates

d) “The patient was prepared for coronary angiography and coronary stenting.” Authors need to explain many points before declaring that the decision was to do coronary angiography. Did they perform any lab tests (CBC, BMP (basal metabolic profile))? What about the cardiac markers? Any stress testing? Was it abnormal? Why did they decide to go for PCI not medical treatment? Was it emergency or elective PCI? If elective, did they test for CYP450 genetic polymorphism to detect clopidogrel resistance?

**Answer:** We have changed as the reviewer indicates

e) “Six hours before the patient underwent coronary angiography, he was given aspirin and clopidogrel.” It is important for the authors to explain in details the exact dose of both medicines, as IST commonly occurs with inadequate doses of both, especially clopidogrel.

**Answer:** We have added as the reviewer indicates

f) “The angiogram showed diffuse stenosis in the middle segments of the left anterior descending artery (Fig. 1A), the left circumflex artery (Fig. 1B) and with occlusion in the middle segment of the right coronary artery.” Authors need to be more detailed in this part of the clinical presentation; actually this is the most important part of the case report, where the authors should explain the coronary finding and how they dealt with it. The description of the lesions needs to be more detailed with further characterization of the length, exact position, and degree of stenosis of each lesion. Was the approach radial or femoral?

**Answer:** We have added as the reviewer indicates

g) “Two overlapping sirolimus-eluting stents without a gap were implanted in the left anterior…” This is also a major part of the case presentation. Authors need to explain the exact dimensions (length and diameter) of the stent, the pressures used, if they used any balloon and if so, it’s type and name. What was the type of wires used? Was there any residual lesions post deployment? Did they have to use a balloon post deployment of the stents? Also it is important to comment on the TIMI flow post stenting.

**Answer:** We have changed as the reviewer indicates

h) “Because of occlusion in the right coronary artery, attempts at stenting were abandoned.” Authors need to explain this statement in more details. Was the lesion chronic total occlusion? Did they attempt passing a wire through the lesion but it failed? Was a collateral circulation present already, with no evidence of ischemia, in the stress testing? Or was the RCA territory already infarcted and non-viable and this was why they did not intervene?

**Answer:** We have added as the reviewer indicates
i) “During the procedure, 100U/kg heparin was administered and the patient was doing well.” The authors need to explain the route of administration of heparin, was this one time dose? When was it administered in relation to the PCI? Was the dose repeated? Was the activated clotting time measured after giving heparin and if so what was the number? Did the patient receive any Glycoprotein IIb-IIIa inhibitors, given the complexity of the procedure and high risk of IST?

Answer: We have added as the reviewer indicates

j) “Approximately 20 minutes after the procedure, the patient developed a series of clinical alterations…” where was the patient at that time? Was the sheath removed? Any evidence of bleeding/hematoma? What do the authors mean by series of clinical alteration? What kind of resuscitative measures (CPR? intubation? IV pressors?) Was an ECG done at that time? Did the monitors show any ST/T wave changes? Which event started 1st was it the vagal symptoms or ECG changes? Was the patient conscious at that time and did he have any chest pain? If yes, then what was presenting first, the chest pain or vagal symptoms?

Answer: We have changed as the reviewer indicates

k) “An ECG showed ST elevation in leads V1, V2, V3 and V4; reciprocal ST depression in leads I, aVL and aVF; and sinus bradycardia with first-degree heart block.” It is extremely important to state the exact timing of this ECG in relation to the patient’s symptoms (was it done during the initial presentation, 20 min from the procedure or later on).

Answer: We have changed as the reviewer indicates

l) “An intra-aortic balloon pump (IABP) was immediately inserted through the femoral artery after thrombi in the implanted stents of both left anterior descending and circumflex arteries were visualized on a coronary angiogram…” Authors need to explain the findings in the 2nd angiography in far more details, especially TIMI flow in both LAD and LCX, amount of thrombus burden, the presence of any evidence of dissection. Also, the authors need to explain either in the case report or the discussion later on, why they used IABP only with no aspiration of the thrombus or placement of another DES, which are the usual approaches towards dealing with early IST.

Answer: We have changed as the reviewer indicates

m) “Thrombolysis, including tirofiban, aspirin…” The authors need to clarify what they meant with thrombolysis? Did they mean tPA (tissue plasminogen activator)? Or just the antiplatelets and anticoagulants? (Which is not thrombolysis and in such case, they need to remove that expression). Why did they shift the patient from heparin initially to fondaparinux? Was there any evidence of HIT (Heparin induced thrombocytopenia)?

Answer: We have changed as the reviewer indicates

n) “The patient was discharged with normal echocardiographic evaluation and was asymptomatic at the time of follow-up” again was the patient tested for
clopidogrel resistance post discharge? And if yes what was the result? If no, why not?

Answer: We have changed as the reviewer indicates

3- Discussion:

a) “Arterial baroreflex and cardiac autonomic control play important roles in hemodynamic instability during arterial stenting” The authors referred to an article about carotid stenting, this is a totally different entity than coronary stenting, the authors cannot generalize the theory behind carotid stenting and baro-reflex activation to include coronary stenting, as it is well known that there are multiple baroreceptors at the carotid sinus and surrounding the wall of the carotid arteries but this is not the same case in the coronaries. The authors need to support their theory of baro-reflex activation by studies done on the coronary arteries (either animal models or human trials). I hope that the authors are not confusing the carotids with the coronaries as the 3 reference articles that they used as a supporting evidence of their theory were done on carotid artery intervention rather than coronary intervention.

Answer: We have changed as the reviewer indicates

b) “PCI with stenting in patients with coronary athermanous stenosis carries an inherent risk of affecting the baroreflex-mediated regulation of hemodynamic alterations, especially with regard to HR and BP”. Although I agree with the authors’ statement from a clinical experience aspect (It is not uncommon to see patients, who develop bradycardia and hypotension during the PCI procedure), they need to support this statement with evidence and reference. The authors also need to support their theory of having vagal stimulation 20 minutes after the procedure, which is extremely uncommon, usually these changes are instantaneous and last for seconds during the PCI itself and they may either terminate spontaneously or lead to cardiac arrest during the procedure.

Answer: We have changed as the reviewer indicates

c) “Coronary stenting in patients with coronary athermanous stenosis offers an opportunity for elucidating the cardiovascular autonomic response to direct intravascular stimulation of the baroreceptors” this sentence needs reference.

Answer: We have changed as the reviewer indicates

d) In the 1st paragraph of the discussion the authors need to explain why they think that the vagal stimulation resulted in IST and not the opposite, which is rather more common to occur. They need to illustrate the time intervals accurately in relation to the clinical, ECG and angiography findings. The patient is already high risk of developing IST as he is diabetic and the coronary vessels appear to be small (from the figures). He had 2 overlapping long DES placed, with only heparin for anticoagulation, thus the more logic explanation would be having early IST that led to bradycardia (from the affection of SA node and AV node blood supply) and then progressed to cardiogenic shock.

Answer: We have changed as the reviewer indicates
e) “The alterations in HR, BP and breathing components were initially due to VBA. With continuing increases in vagal activity and baroreflex sensitivity, development of hemodynamic alterations, including hypotension and decreased blood flow in the coronary artery, subsequently were complicated by thrombosis in the implanted stents”. This paragraph needs to be supported by time intervals and ECG changes that proves that the vagal stimulation happened 1st not the IST as STEMI from IST can cause vagal stimulation on it’s own resulting in the stated clinical picture.
Answer: We have changed as the reviewer indicates

f) “The examination of BRS and HRV is a method of identifying patients at high risk for cardiovascular disease with autonomic dysfunction” I could not understand the relation of this sentence with the rest of the paragraph. What do the authors mean by high cardiovascular risk? This sentence needs further explanation.
Answer: We have changed as the reviewer indicates

g) “…and the patient’s cardiogenic shock was successfully managed by removing the thrombi in the stents.” The authors need to explain this sentence in more details. Did they do any intervention? If yes, what was it?
Answer: We have changed as the reviewer indicates

h) “The most common cause of an acute myocardial infarction is occlusion of coronary vessels” this sentence does not add any information to the paragraph and should be rephrased or removed.
Answer: We have changed as the reviewer indicates

i) “…as the smallest minimal luminal diameter was located within the zone of the stent overlap” this is one of the many reasons that made the patient high risk for IST, the other risk factors need to be addressed by the authors, as discussed before.
Answer: We have changed as the reviewer indicates

- Minor Essential Revisions

1- In the figures:
Figure A the upper arrow needs to be adjusted as it is not pointing on the lesion in LAD.
Answer: changed

2- Spelling mistakes: There are multiple mistakes regarding punctuation, preposition use, spelling and grammar. For example:
In the Introduction:
- 1st line: coronary atheromatous not athermanous
- 3rd line: To the best of our knowledge.
- 7th line: overlapping not overlap.
- 8th line: it is not necessary to use passive voice in the sentence “vagal baroreflex sensitivity was increased”.
The whole article needs to be reviewed and corrected to ensure a scientific and punctual writing. I appreciate that English is not the first language of the authors. However, major adjustments are required in the spelling and punctuation of the article before being published.
Answer: the manuscript has been revised by a professional English agent

- Discretionary Revisions
1- It would be helpful to add in the discussion a paragraph about in-stent thrombosis, as it is the main presentation of the case (Risk factors, demographics, etiology, common presentations and standard care management).
Answer: added

2- There were some case reports in the literature of severe vagal stimulation causing STEMI. The authors can refer to them in support of their theory of IST due to vagal stimulation.
Answer: new references were added

2- In the case presentation part, adding the patient’s vitals and the exact medications that he was taking during pre-admission and during the hospital stay, would be helpful to rule out medications as the cause of bradycardia and hypotension e.g. Beta blockers or calcium channel blockers.
Answer: added

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Not suitable for publication unless extensively edited
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer's report (2)

Title: Vagal baroreflex activation resulting in acute coronary stent thrombus associated with myocardial infarction: a case report

Version: 1
Date: 19 May 2014

Reviewer: Alexander Becker

Reviewer's report:
Major compulsory Revisions:
The authors report a case of stent thrombosis as a result of vagal baroreflex activation. Still it might just be vice versa and the observed hemodynamic changes could also be the result of a stent thrombosis. At least this differential diagnosis should be mentioned in the discussion and the authors should stress, why they believe that the vagal baroreflex activation is the initial activator of this cascade. Further it should be mentioned, that the use of IABP is at least controversial after the IABP Shock trial and can not be considered as the optimal therapy. The PCI of the thrombi should be in the first place.

Answer: It was added in the second paragraph in the Discussion.

Minor essential revisions:
The author should give the stent parameters. Further it would be interesting, if the patient was a clopidogrel non responder

Answer: added.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I have no competing interests