

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and Safety of Super-Selective Bronchial Artery Coil Embolization for Hemoptysis: A Single Center Retrospective Observational Study
AUTHORS	Ishikawa, Hideo; Hara, Masahiko; Ryuge, Misaki; Takafuji, Jun; Youmoto, Mihoko; Akira, Masanori; Nagasaka, Yukio; Kabata, Daijiro; Yamamoto, Kouji; Shintani, Ayumi

VERSION 1 - REVIEW

REVIEWER	Kei Nakashima Department of Pulmonary Medicine, Kameda Medical Center, Japan.
REVIEW RETURNED	06-Nov-2016

GENERAL COMMENTS	<p>Thank you for the opportunity to review this manuscript. This study provides additional evidence for bronchial artery embolization for hemoptysis because clinical studies assessing the efficacy of coil embolization are quite limited. In clinical practice, it is difficult to choose the method of embolization because every material has pro and con. This manuscript reported the high immediate successful rate, long-term efficacy, and safety of ssBA coil embolization and authors concluded this method might be one of good the strategies for the management of hemoptysis. However, additional information should be described to clarify the characteristic and weakness of coil embolization.</p> <p>Major revisions</p> <p>1 In introduction section, please add the information concerning rational of BAE with metallic coils. Why is this important?</p> <p>2 Studies assessing the BAE with metallic coil are limited. For reader's understanding of the method, could you describe the procedure more concretely and add the image of metallic coil in method section? In addition, please add the reference of procedure protocol if it exists.</p> <p>3 The most problematic issue to use metallic coil for embolization is high cost. Please discuss cost effectiveness of platinum metallic coil more deeply in discussion section.</p> <p>4 Do you have the scenario that operator removed the detachable metallic coil in some situations? The usefulness of detachable coil is discussed in page 18 line 45. Please describe the retrying situation clearly and show the advantage of the detachable devise.</p> <p>Minor revisions</p> <p>1 Page 9 line 22: The reason of exclusion of emergency ssBAE is</p>
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	<p>unclear. Emergent ssBAE is not so rare in clinical practice. Please provide additional information.</p> <p>3 Page 14 line 45, Page 26 Table 1: Could you provide the information concerning severity of hemoptysis?</p> <p>3 Page 15, Page 27 table 2: Could you add the median time (minutes) of procedures if you have data?</p> <p>4 Page 15 line 19: What is the mechanism of causing aortic dissection and cerebellar infarctions? Please describe concretely because the possibility of major complication cause concern for clinicians and make them hesitate to perform embolization in clinical practice though the rate is relatively low.</p> <p>5 Page 15: In some cases, additional material such as NBCA and gelatin sponge was used for embolization. Please describe in what kind of conditions did you need these additional materials?</p>
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REVIEWER	Ignasi Garcia-Olivé Hospital Universitari Germans Trias i Pujol. Badalona, Barcelona, Spain
REVIEW RETURNED	15-Nov-2016

GENERAL COMMENTS	<p>This is an observational, retrospective single-center study which analyses the safety and long-term efficacy of super-selective bronchial artery embolization (ssBAE) using platinum coils in patients with hemoptysis. It has several strengths (mainly it is a large sample). Nevertheless, it has several limitations. Some of them have been acknowledged by the authors, while some others have not.</p> <p>Firstly, I find the definition of hemoptysis poor. The amount of bleeding that defines the severity of hemoptysis is 20 ml, which is a small quantity of blood. In line with this, the definition of recurrence is not clear to me, as it is defined as the need of the patient to get another procedure performed.</p> <p>Secondly, several angiographic findings have been described in previous publications. Nevertheless, the authors describe only two signs to define hemoptysis related arteries.</p> <p>Thirdly, the authors explain that the procedures were performed by highly experienced physicians. Please define what that exactly means.</p> <p>Maybe not all institutions define what major or minor complications are in the same way. An interesting reference to define whether a complication is major or not would be this one: Angle JF, Siddiqi NH, Wallace MJ, et al. Quality improvement guidelines for percutaneous transcatheter embolization. Society of Interventional Radiology standards of practice committee. <i>JVasc Interv Radiol</i> 2010; 21:1479–1486.</p> <p>And last, but not least, the article should be reviewed preferably by a native English speaker.</p>
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VERSION 1 – AUTHOR RESPONSE

Comments from Reviewer #1:

Thank you for the opportunity to review this manuscript. This study provides additional evidence for

bronchial artery embolization for hemoptysis because clinical studies assessing the efficacy of coil embolization are quite limited. In clinical practice, it is difficult to choose the method of embolization because every material has pro and con. This manuscript reported the high immediate successful rate, long-term efficacy, and safety of ssBA coil embolization and authors concluded this method might be one of good the strategies for the management of hemoptysis. However, additional information should be described to clarify the characteristic and weakness of coil embolization.

Major revisions

[Major Q1]

1 In introduction section, please add the information concerning rational of BAE with metallic coils. Why is this important?

→ Thank you very much for your suggestion. Following your advice, we have provided the rationale of performing BAE with metallic coils in the Introduction section.

Page 7, Line 16–Page 8, Line 5

However, since extreme caution should be exercised when using blood stream dependent embolization materials, such as PVA or NBCA, controllable embolization materials, such as metallic coils, can also be a candidate material for safe and effective BAE procedures in theory [10-15]. Because little evidence is available on BAE with metallic coils, the aim of this study was to evaluate the safety and long-term (3-year) efficacy of...

[Major Q2]

2 Studies assessing the BAE with metallic coil are limited. For reader's understanding of the method, could you describe the procedure more concretely and add the image of metallic coil in method section? In addition, please add the reference of procedure protocol if it exists.

→ Thank you very much for your comment. In accordance with your suggestion, we have added Figure 3 and acknowledged this in the Methods section to describe our procedure more concretely. As this protocol is original, no appropriate reference is yet available. The figures were renumbered accordingly, and we uploaded a video version of Figure 3 as Supplementary Video 1.

Page 13, Line 16–Page 14, Line 1

The standard coil deployment maneuver is shown in Figure 3.

Figure 3. Schematic Diagram of the Standard Coil Deployment Maneuver in Bronchial Artery Embolization

Our standard bronchial artery coil embolization maneuver included 2 steps. First is anchoring coil deployment (A–C) followed by filling or finishing coil deployment (D–F). After placing the microcatheter in the arterial area of embolization (A), an IDC-18 soft interlocking detachable coil (Boston Scientific, Tokyo, Japan) was inserted as an anchoring coil (B). The detachable coil can be advanced and retracted before the final placement. The controlled coil deployment was achieved by isolating the interlocking arm (C). Then, we carefully removed the delivery wire, and a similar procedure was performed again with the VortX Fibered pushable coil (Boston Scientific, Tokyo, Japan) as a filling or finishing coil. The purpose of the anchoring coil deployment was to gain a foothold for the following dense coiling, named filling or finishing coil deployment. We prefer the use of a highly thrombogenic coil as a filling or finishing coil. You can also refer to Supplementary Video 1. More-detailed information is also available on each product Web site.

[Major Q3]

3 The most problematic issue to use metallic coil for embolization is high cost. Please discuss cost effectiveness of platinum metallic coil more deeply in discussion section.

→Thank you very much for the comment. First, we think issues of the cost-effectiveness of ssBAE are difficult to discuss in detail because the cost and standard procedures may differ among institutions. For example, we think NBCA embolization requires 1 microcatheter for each embolization maneuver (3 microcatheters for 3 HRA embolizations) because of microcatheter gums due to the high embolizing characteristics of NBCA, but other authors insist that only 1 microcatheter is needed in each ssBAE session. Thus, the balance between cost-effectiveness, and risk and benefit should be determined by each physician, depending on his/her level of experience. As the comparison of cost-effectiveness was not the purpose of our study and this is a slightly provocative issue, we have revised the Discussion section without direct comparison between coil and NBCA or other materials. In addition, we also need to remind readers that, as compared with the detachable coil, the pushable coil can reduce the material cost to about one fourth at this time point, and the cost may be comparable with that of NBCA. We have acknowledged these in the Discussion section as follows.:

Page 20, Line 11–Page 21, Line 2

Even though it is difficult to discuss issues on the cost effectiveness of ssBAE in detail because the cost and standard procedures may be different among institutions, the primary disadvantage of metallic coils for ssBAE is their cost, especially with detachable coils. However, this problem could be resolved with the increased use of pushable platinum coils for ssBAE by experienced interventionists since the cost is one fourth of that of detachable coils. Cost effectiveness, as well as the risks and benefits, should be determined by each physician depending on their experiences.

[Major Q4]

4 Do you have the scenario that operator removed the detachable metallic coil in some situations? The usefulness of detachable coil is discussed in page 18 line 45. Please describe the retrying situation clearly and show the advantage of the detachable devise.

→Thank you very much for your suggestion. We have revised the manuscript by presenting a specific scenario of a successful application a detachable coil. Please find the below changes:

Page 20, Lines 8–11

Further, authors especially find the utility of detachable coils in cases where the backup force of guiding catheters is insufficient. In this case, it is difficult to deploy the coil in the target site because the position of the microcatheter cannot be fixed easily, and retractions may be needed for several times.

Minor revisions

[minor Q1]

1 Page 9 line 22: The reason of exclusion of emergency ssBAE is unclear. Emergent ssBAE is not so rare in clinical practice. Please provide additional information.

→ Thank you very much for the comment. The reason for the exclusion of emergent ssBAE is that the purpose of ssBAE is different from that of emergent and elective ssBAE at our institution. The main purpose of emergent ssBAE is rapid hemostasis to achieve hemodynamic and respiratory stability, leaving aside long-term efficacy. By contrast, the main purpose of elective ssBAE is to achieve long-term hemostasis to improve the quality of life of patients. Thus, emergent ssBAE cases should be excluded to appropriately evaluate the long-term efficacy of elective ssBAE. We have acknowledged

this in the Methods section in the revised manuscript.

Page 9, Line 14–Page 10, Line 4

The reason for this is that the purpose of ssBAE is totally different between emergency and elective ssBAE at our institution. The main purpose of emergency ssBAE is rapid hemostasis to achieve hemodynamic and respiratory stability leaving aside a long-term efficacy. In contrast, the main purpose of elective ssBAE is to achieve long-term hemostasis to improve the quality of life of patients. Thus, exclusion of emergency ssBAE cases is needed to appropriately evaluate the long-term efficacy of elective ssBAE.

[minor Q2 and Q3]

2 Page 14 line 45, Page 26 Table 1: Could you provide the information concerning severity of hemoptysis?

3 Page 15, Page 27 table 2: Could you add the median time (minutes) of procedures if you have data?

→ Thank you very much for the important comments. Unfortunately, the data were not available because of the retrospective nature of the present study. Information of hemoptysis severity was not collected in a uniform quantitative way, and procedure time was not recorded because of the system change in our catheterization laboratory in December 2014. We have acknowledged these in the Study Limitations section and would like to ask for consideration of our situation. For reference, the 2-year (2015 and 2016) median procedural time was 113 minutes.

Page 23, Lines 1-3

First, it was difficult to objectively evaluate the amount of hemoptysis retrospectively because data on the severity of hemoptysis were not collected in a uniform quantitative manner [3].

Page 23, Lines 14–16

Fourth, some procedure-related information, such as procedural time was not available during the study period, although the median procedural time was 113 min recently.

[minor Q4]

4 Page 15 line 19: What is the mechanism of causing aortic dissection and cerebellar infarctions? Please describe concretely because the possibility of major complication cause concern for clinicians and make them hesitate to perform embolization in clinical practice though the rate is relatively low.

→ Thank you very much for the important comment. We have described in more detail the information in the Results section as follows:

Page 16, Line 6–Page 16, Line 15

Aortic dissection occurred in a patient with abdominal aortic aneurysm during the guiding catheter manipulation for intercostal arteriography. We speculated that the main cause of this complication was an aortic wall fragility. One case of cerebellar infarction occurred during the supreme intercostal arteriography via the femoral approach possibly because of atheromatous debris embolization in the vertebral artery derived from the tip of the catheter. This could be avoided with the trans-radial approach. The other case of cerebellar infarction occurred after the procedure; its possible mechanism included thrombus embolization derived from the proximal part of the embolized supreme intercostal and internal mammary arteries. Thus, coil embolization cases near the vertebral artery

need careful attention.

[minor Q5]

5 Page 15: In some cases, additional material such as NBCA and gelatin sponge was used for embolization. Please describe in what kind of conditions did you need these additional materials?

→ Thank you very much for your question. The combined-material procedure was performed on a trial basis in some cases. Our speculation for these subsidiary treatments is that pre-occlusion with a gelatin sponge may reduce the number of coils needed for embolization or that post-coiling NBCA may improve the long-term hemostatic effect after ssBAE. We have acknowledged these in the Methods section.

Page 14, Lines 2–6

NBCA and gelatin sponges were used in several cases as a subsidiary treatment on a trial basis. Our speculation for these subsidiary treatments was that pre-occlusion with gelatin sponges may reduce the number of coils needed for embolization or that post-coiling NBCAs may improve the long-term hemostatic effect after ssBAE.

Comments from Reviewer #2:

This is an observational, retrospective single-center study which analyses the safety and long-term efficacy of super-selective bronchial artery embolization (ssBAE) using platinum coils in patients with hemoptysis. It has several strengths (mainly it is a large sample). Nevertheless, it has several limitations. Some of them have been acknowledged by the authors, while some others have not.

[Q1]

Firstly, I find the definition of hemoptysis poor. The amount of bleeding that defines the severity of hemoptysis is 20 ml, which is a small quantity of blood. In line with this, the definition of recurrence is not clear to me, as it is defined as the need of the patient to get another procedure performed.

→ Thank you very much for raising this important issue. Our apologies for the vague explanation. We totally understand that 20 mL is too small for hemoptysis. However, we used this definition because we believe that even patients with this amount of hemoptysis will receive sufficient benefits from ssBAE in some situations. In fact, a 20-mL hemoptysis is the minimum required condition for candidates of ssBAE, but ssBAE was indicated comprehensively considering how severely hemoptysis can impair patients' quality of life. Most patients from all over Japan were referred by pulmonologists to our institution to undergo ssBAE as a last defense against hemoptysis in small amounts but important patient's problems associated with this neglected disease. Unfortunately, many patients have been recommended to receive regular follow-up without any treatment because the amount of hemoptysis is too small. For these reasons, we used 20 mL as the cutoff amount of hemoptysis.

In line with this, a similar definition (at least 20 mL of hemoptysis and patient's need) was applied to the definition of recurrence, and we described this as the need of the patient to undergo another procedure. Please understand that the clear quantitative definition and indication are difficult to describe in this retrospective study. To overcome this problem, however, we are planning to establish a multicenter prospective registry with clear quantitative definitions of hemoptysis and quality of life by using the SF-8 or SF-36 Health Survey questionnaire of quality of life. We have acknowledged these important limitations in both the Methods and Study Limitations sections.

Page 9, Lines 1-3

Approximately 20-mL of hemoptysis was the minimum required condition for candidates of ssBAE;

however, the indication of ssBAE was made in a comprehensive manner, considering how severely hemoptysis impairs the patients' quality of life.

Page 9, Lines 8–11

Recurrence of hemoptysis was defined as hemoptysis of at least 20 mL as defined above, making patients opt to undergo another BAE due to severe impairment of their quality of life, because our goal was to completely eradicate the hemoptysis and because most patients underwent ssBAE for eventless daily life.

[Q2]

Secondly, several angiographic findings have been described in previous publications. Nevertheless, the authors describe only two signs to define hemoptysis related arteries.

→ Thank you very much for the comment. We consider 2 signs (dilatation and tortuosity) as the most important classic findings of HRA. However, we also used other previously reported angiographic findings, including direct shunting of vessels, aneurysmal formation, pleural adhesion with intercostal artery invasion into the lung, and ground-glass opacity suggesting inhaled blood, to define HRA. We have acknowledged this in the Methods section.

Page 12, Lines 4–9

We identified several previously reported findings as signs of possible HRA as shown in Figure 2. These consisted of dilatation of the vessels as compared to the normal size for that site, tortuosity of the vessels, direct shunting of the vessels, aneurysmal formation, pleural adhesion with intercostal artery invasion into the lungs, and ground glass opacity, suggesting inhaled blood, although some of these signs were only identified in select cases [1,5,6,8,9].

[Q3]

Thirdly, the authors explain that the procedures were performed by highly experienced physicians. Please define what that exactly means.

→ Thank you very much for the comment. We have revised the corresponding sentences in the Methods section as follows:

Page 12, Line 16–Page 13, Line 2

All of the ssBAE procedures were performed by highly experienced interventional pulmonologists, who are respiratory physicians undertaking at least 50 interventional radiology procedures annually.

[Q4]

Maybe not all institutions define what major or minor complications are in the same way. An interesting reference to define whether a complication is major or not would be this one: Angle JF, Siddiqi NH, Wallace MJ, et al. Quality improvement guidelines for percutaneous transcatheter embolization. Society of Interventional Radiology standards of practice committee. *J Vasc Interv Radiol.* 2010; 21:1479–1486.

→ Thank you very much for the educational suggestion. We appreciate your kind advice. We have recounted mediastinal hematoma as a major complication in accordance with the definition of the referenced manuscript you indicated. By citing the recommended reference, we have acknowledged in the Study Limitations section that the definition of major complication varies among studies.

Page 5, Lines 4–6
 Page 16, Lines 4–6

There were 8 (1.6%) major complications: 1 aortic dissection, 2 symptomatic cerebellar infarctions, and 5 mediastinal hematoma cases.

Page 19, Lines 12–14

In fact, our total procedural success rate was 93.4% with only a 1.6% major complication rate, suggesting a consistent, secure, and controlled coil implantation.

Page 16, Line 15 – Page 17, Line 16

In addition, mediastinal hematoma was addressed by hemostasis with platinum coil embolization of the proximal arteries.

Page 23, Line 16–Page 24, Line 3

Fifth, the definition of major complications varies among studies; however, we employed the definition from the guideline of the Society of Interventional Radiology Standards of Practice Committee [22].

Page 28

22. Angle JF, Siddiqi NH, Wallace MJ, Kundu S, Stokes L, Wojak JC, Cardella JF; Society of Interventional Radiology Standards of Practice Committee. Quality improvement guidelines for percutaneous transcatheter embolization: Society of Interventional Radiology Standards of Practice Committee. *J Vasc Interv Radiol.* 2010;21:1479-1486.

[Q5]

And last, but not least, the article should be reviewed preferably by a native English speaker.
 → Our apologies for the poor English writing of our manuscript. In this revision process, we have taken assistances from a professional English editing service and attached the proof of editing as Supplementary File. Changes are highlighted blue in the revised manuscript.

Finally, we would like to thank Dr. Edward Sucksmith (BMJ Open Managing Editor), Dr. Kei Nakashima (Reviewer 1), and Dr. Ignasi Garcia-Olivé (Reviewer 2) for their dedicated thoughtful review and consideration of our work for publication in BMJ Open.

VERSION 2 – REVIEW

REVIEWER	Kei Nakashima Department of Pulmonary Medicine, Kameda Medical Center, Japan
REVIEW RETURNED	23-Dec-2016

GENERAL COMMENTS	The manuscript was revised properly according to my suggestions. Most of my instructions and questions were solved sufficiently. The figure 3 for methodology of ssBAE is easily understandable and major complications are described concretely. In addition, I think that limitations of this retrospective study are discussed appropriately.
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REVIEWER	Ignasi Garcia Olivé Hospital Universitari Germans Trias i Pujol Badalona, Barcelona, Spain
REVIEW RETURNED	22-Dec-2016

GENERAL COMMENTS	All suggested modifications have been addressed satisfactorily.
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