Reviewer Assessment

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Magnetic particle imaging in vascular medicine

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Reviewers’ Comments to Original Submission

Reviewer 1: anonymous
Jun 07, 2018

Reviewer Recommendation Term: Revise with Major Modifications
Overall Reviewer Manuscript Rating: N/A

Custom Review Questions
Is the subject area appropriate for you? 5 - High/Yes
Does the title clearly reflect the paper’s content? 5 - High/Yes
Does the abstract clearly reflect the paper’s content? 5 - High/Yes
Do the keywords clearly reflect the paper’s content? 5 - High/Yes
Does the introduction present the problem clearly? 5 - High/Yes
Are the results/conclusions justified? 4
How comprehensive and up-to-date is the subject matter presented? 5 - High/Yes
How adequate is the data presentation? N/A
Are units and terminology used correctly? 3
Are the number of cases adequate? N/A
Are the experimental methods/clinical studies adequate? N/A
Is the length appropriate in relation to the content? 4
Does the reader get new insights from the article? 5 - High/Yes
Please rate the practical significance. N/A
Please rate the accuracy of methods. N/A
Please rate the statistical evaluation and quality control. N/A
Please rate the appropriateness of the figures and tables. 5 - High/Yes
Please rate the appropriateness of the references. 5 - High/Yes
Please evaluate the writing style and use of language. 4
Please judge the overall scientific quality of the manuscript. 3
Are you willing to review the revision of this manuscript? Yes
Comments to Authors:
This work is a very comprehensive review article.

Recommendations:
General recommendations
1. As the term for the magnetic tracer material that has been adopted by the “MPI-Community” is superparamagnetic iron oxide nanoparticles (SPIONs or SPIOs) it might be appropriate to replace magnetic nanoparticle (MNP) with either SPION or SPIO.
2. The rather general term “interventional imaging” could be replaced with more specific terms (like cardiovascular imaging, real-time imaging etc.) where appropriate.
3. Somehow the impression is created that all magnetic nanoparticle are biocompatible. Although that is true for the established gold-standard for MPI (Resovist), new SPIONs will have to be designed and tested accordingly, to ensure biocompatibility (no oxidative stress, inflammatory response etc.). This safety consideration should be made clear.

Abstract
4. Typo: “... which makes MPI suitable as an intervention imaging technique.”
5. Typo: “In the first part of this article, the basic principle of MPI will be explained and a short overview of the principles of the generation and spatial encoding of the tracer-signal will be given.”
6. Typo: “... with an emphasis on vascular imaging. (such as ... could be erased).

1 Introduction
7. Digital subtraction angiography (DSA) is a fluoroscopy technique that uses a contrast agent and no tracer material. This should be considered when comparing DSA with Positron emission tomography (PET).
8. Although the development in MPI holds out the prospect of real-time imaging for MPI guided interventions, we should not create the impression that MPI is already a real-time imaging modality with instant image acquisition and reconstruction yet.
9. Typo: “Thus, it is often used when imaging dense material such as bone structures.” could be erased.
10. Typo: “... containing mostly fat and water.” could be erased.

2 Basic Imaging Principles
11. While it is true that in many actual implemented scanner systems the excitation field and the drive field are implemented using the same coils, it might be helpful for some readers, with no previous knowledge concerning MPI, to separate them. Using the term “excitation field” for the varying magnetic field that excites the SPIONs and the term “drive field” for the fields that enable the movement of the FFP or FFL respectively could help.
12. Some elaboration (more than in the caption of figure 1) on the nonlinearity of the magnetization curve of SPIONs and its importance for MPI could be useful.
13. Typo: “...called drive field HD(t), causes the magnetic moment to flip,...”. 
14. Typo: “In order to spatially encode the particle signal......”. 
15. Typo: “...Hs(i) is high enough to inhibit/negate the effect of the......”. 

5.1 MPI in Vascular Medicine
16. Typo: “...DSA, wich utilises ionizing radiation.” (“in the catheter laboratory. ” could be erased).

5.1.1 Visualization of Instruments for Cardiovascular Interventions
17. The paragraph about the heating of interventional instruments in MPI scanners is a bit ambiguous. It is not the SPION-coating that is responsible for the occurrence of heating. The tested devices had no such coating. The “signal” was generated by the devices and was not useable for MPI. It is the material and geometry that determined the heating (of up to 85°C not 80°C).

5.2.4 Thermo-Therapy with MPI
18. The reference MSS 14 does not support what is stated before.
19. Typo: “..... since imaging and heating of particles are very different propositions, it is necessary to tailor.....”. 
Reviewer 2: anonymous

Aug 20, 2018

**Reviewer Recommendation Term:** Accept with Minor Revision

**Overall Reviewer Manuscript Rating:** 70

**Custom Review Questions**

| Question                                                                 | Response |
|--------------------------------------------------------------------------|----------|
| Is the subject area appropriate for you?                                 | 4        |
| Does the title clearly reflect the paper’s content?                     | 4        |
| Does the abstract clearly reflect the paper’s content?                  | 3        |
| Do the keywords clearly reflect the paper’s content?                    | 4        |
| Does the introduction present the problem clearly?                      | 4        |
| Are the results/conclusions justified?                                  | 3        |
| Is the number of cases adequate?                                         | N/A      |
| Are the experimental methods/clinical studies adequate?                 | N/A      |
| Is the length appropriate in relation to the content?                   | 4        |
| Does the reader get new insights from the article?                      | 4        |
| Please rate the practical significance.                                 | 2        |
| Please rate the accuracy of methods.                                   | N/A      |
| Please rate the statistical evaluation and quality control.             | N/A      |
| Please rate the appropriateness of the figures and tables.              | 4        |
| Please rate the appropriateness of the references.                     | 4        |
| Please evaluate the writing style and use of language.                  | 3        |
| Please judge the overall scientific quality of the manuscript.          | 4        |
| Are you willing to review the revision of this manuscript?              | Yes      |

**Comments to Authors:**

**General comment:**

This review reports on the new and innovative imaging technique “Magnetic Particle Imaging” (MPI) and its possible role in diagnostic imaging of the vascular system and vascular disease/injury related disorders, its possible role in image guided vascular therapy, and its possible role in various other biomedical applications.

The review gives a rather optimistic perspective on the topic of MPI. MPI is in a very early phase of development. Therefore currently it is not sure if, this technique will ever be available for clinical use. Furthermore, the topic of appropriate tracers for MPI is dealed with in a simplifying way.

The topic of a possible role in supporting decision making in vascular therapy/surgery could be emphasized a little bit more.

The authors might think about reducing the description of theoretical and technical details of MPI technology.

Language editing seems to be necessary.

**Title:** Please put emphasis on “possible future clinical applications”

**Abstract:**

Second para: It is not possible to make a general statement on the possible clinical applicability of MPI tracers. Each individual product has to be developed as a parenteral drug.

**Key words:**

Should include “magnetic particle imaging”

**Introduction:**

statements on CT: Only partially true. CT is the workhorse in diagnostic in vivo imaging with the indications in musculoskeletal imaging, but also thoracic/lung imaging, abdominal imaging, and also vascular imaging including cardiac imaging, and head and neck imaging.

Statements on MRI: Wrong - signal intensities and contrasts mainly depend on proton T1- and T2-relaxation times and only in minor part on proton density. Additionally images can be generating, in which signal intensities and contrast depend on flow or diffusion.

Especially vascular surgeons are very well aware of the strength of CT and MRI in cardiovascular imaging (CTA, MRA). Therefore the authors should not give the impression, that CT and MRI are not suited for clinical diagnostic vascular imaging.

statement on DSA: More precisely - the lumen of the blood vessels is visualized.
Statements on MPI: “... especially for vascular interventions”: Please be a little bit more precise, e.g.: applications in diagnostic vascular in vivo imaging and in imaging guided vascular interventions.

Statements on MNPs: (“...biocompatible...”) This statement is not true in general. Furthermore, if the authors speculate on use in humans, the term “biocompatible” is meaningless in the context of regulators. Here, or lateron, the authors should clarify, that there is no approved tracer (based on magnetic iron oxide nanoparticles) available for diagnostic imaging. The authors should also discuss, that, even if a tracer would be approved for human MPI, institutions like the IQWiG (in Germany) will evaluate the added value of such a new diagnostic test (MPI in combination with the tracer) compared to established vascular imaging/intervention techniques, before reimbursement of the costs by the insurances will be possible.

2.3 end of section:

Challenge - will upscaling be possible?

2.4 line 3:

Again: There are currently no approved applications of magnetic nanoparticles for diagnostic imaging or for use as drug carriers. The only approved indication is use of magnetic nanoparticles as medical device for magnetic hyperthermia.

Page 6, line 1: “... used as a tracer ...”: experimentally or clinically? please be specific which each of such a statement.

Page 6, line 7: “... nephrotoxic ...” and so on: Please do not be overoptimistic regarding MNPs for clinical use. The coating material can cause allergic reactions, including those with fatal outcome (see ferumoxytol, clinically used for parenteral iron replacement therapy). Please comment on this topic.

Page 6, line 10: “gold standard” - please be specific: for experimental use only.

Page 6, line 11: Resovist: There is no approval any more.

Page 6, line 13: “off-label” - The term “off-label” does only make sense for clinical use. That is not the case for MPI.

3 page 7, 2nd para: Please make a comment on the size of the field of view, that can currently be achieved.

Page 8, 4th para: see previous comment.

5.1 first line: Please be more specific: “... Visualization of vascular and cardiac anatomy and of blood flow”, correct?

It would be more appropriate to differentiate between application in experimental biomedical research and possible future human applications.

References:

appropriate

Figures:

appropriate

Authors’ Response to Reviewer Comments

Aug 28, 2018

Reviewers’ comments:

Reviewer #1: This work is a very comprehensive review article.

Thank you very much for reviewing our manuscript. We appreciate your comments and recommendations, which have improved our article. We revised our work carefully and hope that we could clarify the issues you made with some additional explanations. Please find below our answers in detail.

Recommendations:

General recommendations

1. As the term for the magnetic tracer material that has been adopted by the “MPI-Community” is superparamagnetic iron oxide nanoparticles (SPIONs or SPIOs) it might be appropriate to replace magnetic nanoparticle (MNP) with either SPION or SPIO.

We appreciate the comment. Since we first introduce the MPI nanoparticle tracer as superparamagnetic iron oxide nanoparticles in 2.4, we
used the more general term “magnetic nanoparticles” before and, therefore, throughout the whole article. This also gives us the possibility to use the abbreviation in contexts where indeed MNPs that are not SPIONs can be used in an MPI applications such as magnetic manipulation. Thus, we emphasize that we are not strictly limited to particles that can be visualized with MPI.

2. The rather general term “interventional imaging” could be replaced with more specific terms (like cardiovascular imaging, real-time imaging etc.) where appropriate.

Thank you for the comment. The term “interventional imaging” refers to the imaging technique to be used during an operation. In our opinion, the term is therefore appropriate. MPI is an imaging modality suitable for cardiovascular imaging plus it is a real-time imaging modality plus it is radiation free and all these features together make MPI suitable as an image guidance for interventions.

3. Somehow the impression is created that all magnetic nanoparticles are biocompatible. Although that is true for the established gold-standard for MPI (Resovist), new SPIONs will have to be designed and tested accordingly, to ensure biocompatibility (no oxidative stress, inflammatory response etc.). This safety consideration should be made clear.

Thank you for this annotation. We hope it is now clearer that MNPs can be biocompatible, however, that needs to be approved. Hence, we added in section 2.3 “The biocompatibility of the tracer material can be achieved by a biocompatible coating of the MNPs (see section 2.4). However, for the use in clinical routine the tracer material needs to be officially approved” In section 2.4, we added “In future, optimized tracer materials need to be evaluated and approved for clinical applications.” Here, we also pointed out that Resovist was approved as a contrast agent for MRI, which is nowadays used for experimental and preclinical MPI applications.

Abstract

4. Typo: “… which makes MPI suitable as an interventional imaging technique.”

Thank you. The mistake is corrected.

5. Typo: “In the first part of this article, the basic principle of MPI will be explained and a short overview of the principles of the generation and spatial encoding of the tracer-signal will be given.”

Thank you. The mistake is corrected.

6. Typo: “… with an emphasis on vascular imaging. (such as … could be erased).

In our opinion, the second half of the sentence “such as the use of MPI during cardiovascular interventions by visualizing the instruments” gives some more details about what the reader can expect in this research field.

1 Introduction

7. Digital subtraction angiography (DSA) is a fluoroscopy technique that uses a contrast agent and no tracer material. This should be considered when comparing DSA with Positron emission tomography (PET).

It is unfortunate, that this is not clear. We have re-read the section and have adapted the following part: “The drawback of this technique is that ionizing radiation is needed and the iodine-based tracer material can be nephrotoxic…” to “The drawback of these techniques are that ionizing radiation is needed and the iodine-based contrast agent material can be nephrotoxic…”. However, this seems the only part where we have used the wrong term. If you have more concerns about this part, please let us know.

8. Although the development in MPI holds out the prospect of real-time imaging for MPI guided interventions, we should not create the impression that MPI is already a real-time imaging modality with instant image acquisition and reconstruction yet.

We appreciate your concern. However, for small volumes, MPI is able to image a 3D volume within 20 ms and the reconstruction is fast enough to show a reconstructed image with negligible time delay as we show with references in later sections. Especially, the applications performed with MPI shown in [WGR09] demonstrate that this statement holds. Thus, we think it is reasonable to state that MPI is a real-time imaging modality in the introduction to get the reader’s attention and describe the restrictions in the specific sections.

9. Typo: “Thus, it is often used when imaging dense material such as bone structures.” could be erased.

Thank you, we erased the second part of the sentence.

10. Typo: “… containing mostly fat and water.” could be erased.

Thank you, we erased the second part of the sentence.

2 Basic Imaging Principles

11. While it is true that in many actual implemented scanner systems the excitation field and the drive field are implemented using the same coils, it might be helpful for some readers, with no previous knowledge concerning MPI, to separate them. Using the term “excitation field” for the varying magnetic field that excites the SPIONs and the term “drive field” for the fields that enable the movement of the FFP or FFL respectively could help.

We thought it is easier to explain two fields instead of explaining first three fields and then why it is not necessary to use an excitation and drive field. We checked the section for consistency and added the following sentences, which clarifies that the FFP/FFL movement is generated by the drive field, which also flips the magnetic moment. “Due to the fact that the excitation of the particles is established by the drive field, this field is also referred to as excitation field.” And “A sufficiently large amplitude of the drive field leads to a significant
movement of the FFP or FFL along a line. A drive field applied in two or three dimensions enables a movement of the FFP or FFL in a plane or volume, respectively.”

12. Some elaboration (more than in the caption of figure 1) on the nonlinearity of the magnetization curve of SPIONs and its importance for MPI could be useful.

Thank you for the comment. We added the following in section 2.1: “A further increase of the applied magnetic field strength has therefore no impact on the magnetization. This behavior results in a characteristic nonlinear magnetization curve as a function of the magnetic field strength. Hence, the temporal evolution of the magnetization has a plateau at its minimum and maximum. That means that the magnetic moments of the MNPs flip with the same frequency as the drive field, but the temporal evolution of the magnetization is modulated.”

13. Typo: “…called drive field HD(t), causes the magnetic moment to flip,….”

Thank you. The mistake is corrected.

14. Typo: “In order to spatially encode the particle signal……”.

Thank you. The mistake is corrected.

15. Typo: “….Hs(i) is high enough to inhibit/negate the effect of the….”.

Thank you. The mistake is corrected.

5.1 MPI in Vascular Medicine

16. Typo: “…DSA, wich utilises ionizing radiation.” (“in the catheter laboratory.” could be erased).

Thank you, we erased it.

5.1.1 Visualization of Instruments for Cardiovascular Interventions

17. The paragraph about the heating of interventional instruments in MPI scanners is a bit ambiguous. It is not the SPION-coating that is responsible for the occurrence of heating. The tested devices had no such coating. The “signal” was generated by the devices and was not useable for MPI. It is the material and geometry that determined the heating (of up to 85°C not 80°C).

Thank you for pointing out this issue. We changed the corresponding paragraph from “For safety reasons, the heating of the instruments needs to be considered, which can occur due to the high frequency of the drive fields and the resulting eddy currents within the instruments. This may pose a limitation for the use of coated instruments for vascular interventions since guide wires temperatures of up to 80 °C have been observed [DWP14]. However, many devices did not show any heating behavior and are perfectly suitable for MPI.” to “For safety reasons, the heating of the instruments needs to be considered, which can occur due to the high frequency of the drive fields and the resulting eddy currents within the instruments’ material. This may pose a limitation for the use of instruments for vascular interventions since guide wire temperatures of up to 85 °C have been observed due to their material and shape [DWP14]. However, many devices did not show any heating behavior.”

5.2.4 Thermo-Therapy with MPI

18. The reference MSS 14 does not support what is stated before.

Thank you for this remark. Since in MSS14 the blood coagulation is measured due to the viscosity change of the matrix we moved this part to 5.1.4. Hence, we changed “This would allow for real-time monitoring of biological processes in terms of viscosity changes.” to “This would allow for real-time monitoring of biological processes in terms of viscosity changes, which can be e.g. used to monitor blood or tissue coagulation [MSS14].”

19. Typo: “….. since imaging and heating of particles are very different propositions, it is necessary to tailor…..”.

Thank you. The mistake is corrected.

Reviewer #2: General comment:

This review reports on the new and innovative imaging technique “Magnetic Particle Imaging” (MPI) and its possible role in diagnostic imaging of the vascular system and vascular disease/injury related disorders, its possible role in image guided vascular therapy, and its possible role in various other biomedical applications.

The review gives a rather optimistic perspective on the topic of MPI. MPI is in a very early phase of development. Therefore currently it is not sure if, this technique will ever be available for clinical use.

Furthermore, the topic of appropriate tracers for MPI is dealt with in a simplifying way.

The topic of a possible role in supporting decision making in vascular therapy/surgery could be emphasized a little bit more.

The authors might think about reducing the description of theoretical and technical details of MPI technology.

Language editing seems to be necessary.

Thank you very much for reviewing our manuscript. We appreciate your comments and edited the article carefully. We hope that we could clarify the technical aspects you mentioned, which were not clearly understandable and put effort in improving the language. Since your annotations are critical regarding MPI in clinical use and especially the approval of the tracer material we added a couple of statements to make clear that MPI is a promising method for vascular medicine, but is not yet in clinical use and several issues, such as upscaling and
safety, need to be faced. Further we emphasized that the approval of the tracer material is an open task, but please find our answers to your annotations in detail below.

Title: Please put emphasis on “possible future clinical applications”
We changed “In the last part, a variety of different clinical application scenarios will be presented with an emphasis on vascular imaging” to “In the last part, a variety of possible future clinical applications will be presented with an emphasis on vascular imaging” to point out that MPI is not in clinical use yet, but we will discuss future possibilities. However, we do not want to change the title of the article since the whole article is not only about future clinical applications, but deals with MPI in general with an emphasis on MPI for vascular imaging.

Abstract:
Second para: It is not possible to make a general statement on the possible clinical applicability of MPI tracers. Each individual product has to be developed as a parenteral drug.
We changed “… that the used tracer material is biocompatible” to “that the used tracer material can be made biocompatible”. In section 2.3 and 2.4 we also pointed out how MNPs can be made biocompatible, that Resovist was an approved tracer material for MRI liver imaging, but if MPI goes the step towards clinical investigation the used tracer material needs to be approved, which is not yet the case since all investigations are in vitro or preclinical so far.

Key words:
Should include “magnetic particle imaging”
Thank you for this advice. We added “Magnetic Particle Imaging” and “MPI” as well as “vascular imaging” to the list of key words. We were not sure if we have to add those keywords, since they are part of the title.

Introduction:
statements on CT: Only partially true. CT is the workhorse in diagnostic in vivo imaging with the indications in musculoskelettal imaging, but also thoracic/lung imaging, abdominal imaging, and also vascular imaging including cardiac imaging, and head and neck imaging.
We wanted to emphasize that the great advantage of MPI compared to CT is that no ionizing radiation is needed. That should not mean that CT is not suitable for vascular imaging, since as you said it is nowadays the “workhorse”, but we want to point out that MPI can be an alternative in future. Since we did not aim at keeping back that CT is suitable for vascular imaging we added: “CT is widely used for head and neck imaging and is especially suitable for vascular and cardiac imaging.” and “The continuous development of all these techniques has taken in vivo diagnostics a decisive step forward”

Statements on MRI: Wrong - signal intensities and contrasts mainly depend on proton T1- and T2-relaxation times and only in minor part on proton density. Additionally images can be generating, in which signal intensities and contrast depend on flow or diffusion.
Thank you for pointing out this issue. We changed “proton density” to “proton relaxation times” and added: “Further, MRI can provide information about flow and diffusion”
Especially vascular surgeons are very well aware of the strength of CT and MRI in cardiovascular imaging (CTA, MRA). Therefore the authors should not give the impression, that CT and MRI are not suited for clinical diagnostic vascular imaging.
As we said before, we want to present a future alternative method and we want to emphasize and explain why it might be worth thinking about using MPI for vascular imaging. Today, CT and MRI are the methods of choice for cardiovascular interventions. We hope that by adding the sentence “The continuous development of all these techniques has taken in vivo diagnostics a decisive step forward” we could address your concern.

statement on DSA: More precisely - the lumen of the blood vessels is visualized.
Thank you for your comment. We changed “To visualize blood vessels, Digital Subtraction Angiography (DSA) ….” to “To visualize the lumen of blood vessels, Digital Subtraction Angiography (DSA) ….”

Statements on MPI: “…. especially for vascular interventions”: Please be a little bit more precise, e.g.: applications in diagnostic vascular in vivo imaging and in imaging guided vascular interventions.
Thank you for your comment. We corrected this sentence by replacing “vascular interventions” with “for applications in diagnostic vascular in vivo imaging and imaging guided vascular interventions”.

statements on MNPs: (“ … biocompatible…” ) This statement is not true in general. Furthermore, if the authors speculate on use in humans, the term “biocompatible” is meaningless in the context of regulatorties. Here, or lateron, the authors should clarify, that there is no approved tracer (based on magnetic iron oxide nanoparticles) available for diagnostic imaging. The authors should also discuss, that, even if a tracer would be approved for human MPI, institutions like the IQWiG (in Germany) will evaluate the added value of such a new diagnostic test (MPI in combination with the tracer) compared to established vascular imaging/intervention techniques, before reimbursement of the costs by the insurances will possible.
We added “In future, optimized tracer materials need to be evaluated and approved for clinical applications.” in section 2.4.
2.3 end of section:
Challenge - will upscaling be possible?
For clarification we added: "Since human-sized MPI scanners would need large field amplitudes, this is a challenging task, but feasibility has already been demonstrated (see section 3)."

2.4 line 3: Again: There are currently no approved applications of magnetic nanoparticles for diagnostic imaging or for use as drug carriers.
The only approved indication is use of magnetic nanoparticles as medical device for magnetic hyperthermia.
We added: "...as well as they are being developed as contrast agents or drug carriers for future medical applications."
page 6, line 1: "...used as a tracer ...": experimentally or clinically? please be specific which each of such a statement.
We appreciate your concern. However, we make clear at different parts in the manuscript that the clinical use of MPI is a future perspective.
Thus, if we state "the used tracer material in MPI" it is always meant in an experimental/preclinical scenario. A specification for every statement in the manuscript would compromise the readability.
page 6, line 7: "...nephrotoxic ..." and so on: Please do not be overoptimistic regarding MNPs for clinical use. The coating material can cause allergic reactions, including those with fatal outcome (see ferumoxytol, clinically used for parenteral iron replacement therapy).
Please comment on this topic.
We added: "In future, optimized tracer materials need to be evaluated and approved for clinical applications."
Page 6, line 10: "gold standard" - please be specific: for experimental use only.
We added "experimental and preclinical" to be clear about the setup in which it is a gold standard.
Page 6, line 11: Resovist: There is no approval any more.
Thank you for pointing out. We changed the sentences to "...established as a gold-standard for experimental and preclinical MPI tracers, because it provides good performance for MPI." And "Resovist is made of MNPs covered with carboxydextrane in a water based isotonic suspension and was an approved contrast agent for MRI liver applications"
Page 6, line 13: "off-label" - The term "off-label" does only make sense for clinical use. That is not the case for MPI.
Thank you for this advice. We erased the term "off-label".
3 page 7, 2nd para: Please make a comment on the size of the field of view, that can currently be achieved.
We added the following about the single sided scanner: “Later, first 2D images were presented in [GGB16], in which the FFP trajectory covered an area of 30 x 30 mm² and images of a phantom in 10 mm depth were shown.”
Page 8, 4th para: see previous comment.
We added the following parameters about the preclinical Bruker MPI Scanner: “When applying maximal drive field strength (12 mT) and maximal gradient (2.5 T/m) a FOV of 19.2 x 19.2 x 9.6 mm² can be achieved, however the scanning volume can be further enlarged by use of focus fields as discussed in section 2.3”
5.1 first line: Please be more specific: "...Visualization of vascular and cardiac anatomy and of blood flow", correct?
We specified: "Therefore, applications of MPI as a molecular imaging tool, is an interesting research field. Further, due to the real-time capability of MPI, applications scenarios in vascular and cardiac imaging seem to be promising."
6 It would be more appropriate to differentiate between application in experimental biomedical research and possible future human applications.
Actually, it should be clear that MPI is not in clinical use yet and therefore all presented applications are experimental/preclinical. To point that out we added to the introduction of chapter 5 "In the following a selection on experimental and preclinical investigations are presented, which are intended to pave the way to clinical application”

References:
appropriate
Figures:
appropriate
Reviewers’ Comments to Revision

Reviewer 1: anonymous
Sep 02, 2018

Reviewer Recommendation Term: Accept
Overall Reviewer Manuscript Rating: 90

Custom Review Questions

| Question                                                                 | Response         |
|-------------------------------------------------------------------------|------------------|
| Is the subject area appropriate for you?                                | 5 - High/Yes     |
| Does the title clearly reflect the paper’s content?                    | 5 - High/Yes     |
| Does the abstract clearly reflect the paper’s content?                  | 5 - High/Yes     |
| Do the keywords clearly reflect the paper’s content?                    | 5 - High/Yes     |
| Does the introduction present the problem clearly?                      | 5 - High/Yes     |
| Are the results/conclusions justified?                                  | 5 - High/Yes     |
| How comprehensive and up-to-date is the subject matter presented?       | 5 - High/Yes     |
| How adequate is the data presentation?                                  | N/A              |
| Are units and terminology used correctly?                               | 5 - High/Yes     |
| Is the number of cases adequate?                                        | N/A              |
| Are the experimental methods/clinical studies adequate?                | N/A              |
| Is the length appropriate in relation to the content?                  | 5 - High/Yes     |
| Does the reader get new insights from the article?                     | 5 - High/Yes     |
| Please rate the practical significance.                                 | 5 - High/Yes     |
| Please rate the accuracy of methods.                                   | N/A              |
| Please rate the statistical evaluation and quality control.            | N/A              |
| Please rate the appropriateness of the figures and tables.             | N/A              |
| Please rate the appropriateness of the references.                     | 4                |
| Please evaluate the writing style and use of language.                 | 5 - High/Yes     |
| Please judge the overall scientific quality of the manuscript.         | 5 - High/Yes     |
| Are you willing to review the revision of this manuscript?             | Yes              |

Comments to Authors:
Thank you for your revision and the clarifications made. All the best and good success for the future.

Reviewer 2: anonymous
Sep 14, 2018

Reviewer Recommendation Term: Accept
Overall Reviewer Manuscript Rating: 75

Custom Review Questions

| Question                                                                 | Response         |
|-------------------------------------------------------------------------|------------------|
| Is the subject area appropriate for you?                                | 3                |
| Does the title clearly reflect the paper’s content?                    | 4                |
| Does the abstract clearly reflect the paper’s content?                  | 4                |
| Do the keywords clearly reflect the paper’s content?                    | 4                |
| Does the introduction present the problem clearly?                      | 4                |
| Are the results/conclusions justified?                                  | 4                |
| How comprehensive and up-to-date is the subject matter presented?       | 4                |
| How adequate is the data presentation?                                  | 4                |
| Are units and terminology used correctly?                               | 4                |
| Is the number of cases adequate?                                        | 5 - High/Yes     |
| Are the experimental methods/clinical studies adequate?                | 4                |
| Is the length appropriate in relation to the content?                  | 3                |
| Does the reader get new insights from the article?                     | 4                |
| Please rate the practical significance.                                 | 4                |

Please evaluate the writing style and use of language. 5 - High/Yes

Please judge the overall scientific quality of the manuscript. 5 - High/Yes

Are you willing to review the revision of this manuscript? Yes
Please rate the accuracy of methods. 4
Please rate the statistical evaluation and quality control. 4
Please rate the appropriateness of the figures and tables. 4
Please rate the appropriateness of the references. 5 - High/Yes
Please evaluate the writing style and use of language. 5 - High/Yes
Please judge the overall scientific quality of the manuscript. 4
Are you willing to review the revision of this manuscript? Yes

Comments to Authors:
In 1. Introduction, 2. paragraph, 1. Sentence: the applicability of CT should not be reduced to “head and neck imaging”.
“CT is widely used for imaging of all parts of the body, i.e. head and neck, chest, abdomen and musculoskeletal system.”