Author’s response to reviews

Title: Evaluation of venous pathology of the lower extremities with triggered angiography noncontrast-enhanced magnetic resonance imaging (TRANCE-MRI)

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Evaluation the venous pathology of the lower extremities with triggered angiography non-contrast-enhanced sequence magnetic resonance imaging (TRANCE-MRI)

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BMC Medical Imaging

Dear Dr. Dominik Geisel, Dr. Boris Gorodetski and Dr. Saher Taman,

On behalf of all authors, I thank you and two reviewers very much for your thorough review of this manuscript. Your suggestions were instructive and thoughtful. The reviewers identified some serious concerns that we have never considered while making this study. We sincerely hope that our revisions to the document combined with our accompanying responses will render our manuscript more suitable for BMC Medical Imaging.
“BMC Medical Imaging” has world-wide readers and well reputations focused on advanced management of complex diseases. By providing our preliminary experience of TRANCE-MRI in venous pathology in the lower extremities, we think it can remind vascular specialists of this technique (TRANCE-MRI) and raise some discussions to this specific diagnostic tool.

All revised material was specifically responded to the reviewers’ questions and criticisms point-by-point as follows. All changes to the manuscript are indicated in the text by highlighting.

Thank you very much again for permitting our privilege to revise the paper. Please forward the revised manuscripts to the reviewers and give us a second chance of reconsidering for publication.

Sincerely,

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[Editor Comments]
Evaluate the clinical benefit in regard to ultrasound more thoroughly.

[Response]
At this version, we emphasize on the two points for the ultrasound comparisons; Comparative accuracy and more pelvis as well as arterial information.
(1) The sensitivity, specificity and accuracy of TRANCE-MRI were 85.7%, 88.9% and 88%, respectively. The inter-rater agreement for DVT of the thigh between the ultrasonography and TRANCE-MRI results was substantial agreement (Cohen's kappa κ, 0.72). Therefore, we believe that TRANCE-MRI can be used as an alternative and objective tool for assessing lower extremity diseases, especially suspected venous pathology. {Page 3 line 67-68}.

(2) Furthermore, in ultrasonography-negative cases, TRANCE-MRI could detect further cases of DVT, venous compression, vena cava anomaly, occult PAD and occluded bypass grafts. {Page 10 line 214-215}.

[Reviewer 1’s Comments]

[Comment 1]

The clinical benefit is not clear after reading the manuscript. Performing a 1h MRI-scan in order to exclude a deep venous thrombosis is surreal in the clinical setting, further, a fast, easy and cheap diagnostic modality already exists: ultrasound. The clinical impact or possible benefit should be elaborated in a more thoroughly way and more analysis of the current literature and comparison to the current literature and other studies should be made.

[Response]

We still consider that ultrasound should be used preferentially when assessing venous lesions in the lower extremities because it is non-invasive and cost-effective. {Page 10 line 217-219}. However, TRANCE-MRI can be used as an alternative and objective tool for assessing lower extremity diseases, especially suspected venous pathology. {Page9 line 205-207}.

Several advantages of TRANCE-MRI application in venous pathology in the lower extremities exist. First, TRANCE-MRI provides not only images of the arteries and veins in the lower extremities but also information on the pelvis and abdomen, which is valuable in patients with a venous scenario of DVT. DVT may be mistaken as external compression of the pelvic vessels. Moreover, it is notorious as a sign of occult malignancies. Among the 11 patients with a venous scenario of DVT, four of them (36.4%) had no DVT and the symptoms were attributed to malignancy, external compression by degenerated hip prosthesis, external compression by knee effusion, and congenital anomaly. Second, the thrombi and collateral veins can be clearly outlined, including deep femoral vein that might be difficult to detect by ultrasonography. This may be helpful in catheter-based thrombolytic therapy and rescue therapy in recurrent VV after truncal ablations of GSV. Finally, because TRANCE-MRI has no radiation and does not use contrast media, it is safe for patients with impaired renal function. {Page 11 line 241-252}. 
Ultrasonography serves as the standard first-line tool for evaluating lower limb swelling. However, ultrasonography is both difficult and insensitive in patients exhibiting obesity, oedema, or tenderness who have undergone recent hip or knee arthroplasty as well as those with casts, bandages, or immobilization devices. Ultrasonography also does not adequately assess the pelvic region or the deep veins [Karande et al. 2016]. {Page 4 line 81-85}.

Compared with TRANCE-MRI, ultrasonography played a relatively small role in assessing varicose veins of the lower extremities and deep veins of the pelvis and abdomen. We still consider that ultrasound should be used preferentially when assessing venous lesions in the lower extremities because it is non-invasive and cost-effective. But we also considered TRANCE-MRI can be used as an alternative tool for assessing lower extremity diseases. {Page 10 line 209-210}. Furthermore, if a patient has an abdominal pelvic venous problem or complicated varicose veins, TRANCE-MRI may be helpful for pre-intervention assessment and planning. {Page 10 line 212-221}.

[Comment 2]

Too many different diseases are mixed up in one study. It might be better to focus on one disease such as deep vein thrombosis or varicose. The manuscript is not really innovative and the clinical benefit is not clear. The authors should be overthinking the study design, major parts of the manuscript should be revised completely and be better focused on the main/relevant message of the manuscript.

[Response]

Thank you for your insightful comments that enable us to improve the quality of our research article.

Due to the lack of relevant TRANCE-MRI studies, we attempted to design a study to explore the clinical utility of TRANCE-MRI. To fully explore its clinical utility and potential diagnostic value, some of the designs in this study (such as the 1h MRI scan protocol) are indeed surreal in the clinical setting.

However, the study indeed provides some valuable results:

(1) The sensitivity, specificity and accuracy of TRANCE-MRI were 85.7%, 88/9% and 88%, respectively. The inter-rater agreement for DVT of the thigh between the ultrasonography and TRANCE-MRI results was substantial agreement (Cohen's kappa κ, 0.72). {Page 8 line 167-169}. Therefore, we believe that TRANCE-MRI can be used as an alternative and objective tool for assessing lower extremity diseases, especially suspected venous pathology. {Page 8 line 170-172}
(2) In the ultrasonography-negative patients, TRANCE-MRI detected four additional cases (16%, 4/25) of DVT; three cases (12%, 3/25) of venous compression caused by pelvic lymphadenopathy, hip prosthesis or knee joint effusion; one case (4%, 1/25) of vena cava anomaly; two cases (8%, 2/25) of occult peripheral artery disease (PAD); and one case (4%, 1/25) of an occluded bypass graft. {Page 8 line 173-177}

(3) In this study, the majority of patients (92%, 23/25) were attributed to venous disease only, and their MRA results were negative. Therefore, we recommend performed TRANCE-MRV protocol (acquisition time, 25 minutes) instead of the full protocol (MRV+MRA) in patients with venous scenario in the clinical setting. {Page 10 line 227-230}

[Comment 3]
Many spelling mistakes were made.

[Response]
To meet the reviewer's comment, we used the professional english edition service.

We acknowledge Wallace Academic Editing for editing the first version, and Nature Research Editing Service for this revised version of this manuscript. {Page 15 line 324-325}

[Reviewer 2’s Comments]

[Comment 1]
Regarding methods: As I have seen in your nice study, the aim of your work is to detect venous pathology, so why examination of the arterial system was done using post contrast CT scan (which has many side effects due to the high dose of contrast media) while you can use smaller dose of contrast media to do CT venography (which is your target to be examined)...also examination of the arterial system using your MRI technique (TRANCE) mad the time to be very long and could not be tolerated by some patients.
The reason for including this time-consuming arterial phase is that the TRANCE MR could evaluate the arteries without contrast-media and probably is less harmful to the patients. Moreover, the leg arterial status in the patients with venous static ulcers is crucial for further compressive therapy to enhance ulcer healing. {Page 7 line 151-154}.

TRANCE-MRI is a new MR technique that can images vascular structures based on signal differences between systolic and diastolic phases; it can provide background-removed blood vessel images, that can display MRA along, MRV along or background-removed all blood vessels. This is an initial study to prospectively collected large number of patients of vascular disease (arterial and venous/lymphatic) to explore the clinical utility of TRANCE-MRI. {Page 5 line 93-103}.

In the present study, we designed a complete MR protocol (total acquisition time, 60 minutes) for imaging acquisition of all (infra-diaphragmatic) lower extremity arteries (MRA; acquisition time, 35 minutes) and veins (MRV; acquisition time, 25 minutes) to fully explore its clinical utility and potential diagnostic value. Thus, this protocol is not suitable for critical and irritable patients and should be modified to reduce the imaging acquisition time in selective patients. {Page 10 line 222-227}

[Comment 2]

Regarding Figures: Figure 1. What about the reference of this figure.

[Response]

Figure 1 is an original and unpublished figure that was drawn for this research article.

[Comment 3]

Figure 2. Only correct the word arterieal to (arterial).

[Response]

The word in Manuscript and Figure 2 has been corrected.
[Comment 4]
Figure 3. Exchange superficial femoral vein (SFV) instead of femoral vein (FV). Exchange incomplete opacification instead of poor opacification.

[Response]:
The word in Manuscript and Figure 3 has been corrected.

[Comment 5]
Figure 4. Please mention the anatomical site, plane & pulse sequence of each image…like coronal MRI inguinal regions and proximal thighs on both sides showing…etc.

[Response]
The figure legend of Figure 4 has been revised according to your suggestion.

[Comment 6]
Regarding References: Need more update. Please specify what did you mean by FV…Is it Common femoral vein (CFV) or Superficial Femoral vein (SFV).

[Response]
1. All references have been checked and updated in accordance with the submission guidelines again.
2. The femoral vein (FV) in figure 3 means superficial femoral vein (SFV); the figure legend had been revised.