

The effect of non-contrast enhanced MRA on patients with renal insufficiency and foot pain

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Abstract

To investigate the feasibility of non-contrast magnetic resonance angiography of arteries and veins (NATIVE) sampling perfection with application optimized contrasts by using different flip angle evolution (SPACE) and quiescent interval single shot (QISS) in assessing foot arteries of patients with renal insufficiency and foot pain. Fifty-three patients (mean age = 44.2 ± 11.4 years, male: female = 27:26) underwent QISS and NATIVE-SPACE. The source images were reconstructed to maximum intensity projection and volume render. The image quality of QISS and NATIVE-SPACE was rated (0–3, poor to excellent), and was compared using Wilcoxon test. True or false positive was determined by comparing the findings of QISS and NATIVE-SPACE. The relative signal intensity of artery was obtained for each case, and was compared between QISS and NATIVE-SPACE using Mann Whitney test. The acquisition time of NATIVE-SPACE was significantly longer than that of QISS (178.4 ± 35.7 seconds vs 45.4 ± 8.9 seconds, $P < .001$). QISS had significantly lower image quality score versus NATIVE-SPACE (1.4 ± 0.5 vs 2.4 ± 0.6, $P = .02$). Fifteen percentage (8/53) NATIVE-SPACE cases had poor image quality due to the similarity of peak flow and minimum flow. The relative signal intensity was significantly lower in QISS versus NATIVE-SPACE (9.7 ± 1.3 vs 68.2 ± 12.4, $P < .001$). NATIVE-SPACE is valuable in evaluating foot arteries of patients with renal insufficiency. QISS can serve as an alternative test to NATIVE-SPACE.

Abbreviation: 2D = 2-dimension, CTA = computed tomography angiography, ECG = electrocardiogram, MRA = magnetic resonance angiography, NATIVE = non-contrast magnetic resonance angiography of arteries and veins, PC = phase contrast, QISS = quiescent interval single shot, rSI = relative signal intensity, SPACE = sampling perfection with application optimized contrasts by using different flip angle evolution, TOF = time of flight.

Keywords: fast spin echo, foot, MRA, non-contrast enhanced, stenosis

1. Introduction

Foot pain is a common clinical disease with many causes.^[1,2] Tissue ischemia caused by foot artery stenosis or occlusion is one of the reasons.^[3,4] Computed tomography angiography (CTA) and contrast enhanced magnetic resonance angiography (MRA) are both highly accurate in identifying stenosis of foot arteries.^[5,6] However, contrast agent is considered not suitable for patients with renal insufficiency.^[7,8] Ultrasound and non-contrast enhanced (NCE) MRA are alternative tests in such cases.^[9] Compared to operator-dependent ultrasound, NCE MRA is more objective.^[10]

In recent twenty years, 2-dimension (2D) time of flight (TOF) is the most frequently-used NCE MRA for lower extremities.^[11,12] Unfortunately, TOF needs relatively long acquisition time, and frequently suffers from artifacts or in-plane saturation.^[13] In recent years, electrocardiogram (ECG) trigger was used in order to eliminate in-plane saturation in TOF, which

further increases acquisition time.^[14] In addition, the 2D acquisition of TOF is not suitable for tortuous arteries in foot. Phase contrast (PC) MRA is another NCE option of foot,^[15] but does not perform better than TOF.^[16] Other NCE MRA sequences are urgently required for better depiction of foot arteries.

In recent years, quiescent interval single shot (QISS) and non-contrast magnetic resonance angiography of arteries and veins (NATIVE) sampling perfection with application optimized contrasts by using different flip angle evolution (SPACE) were used for evaluation of lower extremity arteries.^[17–20] There were many studies investigating the feasibility of QISS or NATIVE-SPACE in legs^[21–24] and reporting encouraging results. However, there are few publications reporting the feasibility of QISS or NATIVE-SPACE in evaluation of foot arteries. The purpose of the study is thus to investigate whether NATIVE-SPACE and QISS are feasible in assessing foot arteries of patients with renal insufficiency.

GW and YY contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Wu G, Yang Y, Liu L. The effect of non-contrast enhanced MRA on patients with renal insufficiency and foot pain. *Medicine* 2023;102:49(e36372).

Received: 12 September 2023 / Received in final form: 7 November 2023 / Accepted: 8 November 2023

<http://dx.doi.org/10.1097/MD.00000000000036372>

2. Methods

2.1. Participants

This study was approved by the Ethics Committee of Hubei No.3 People's Hospital of Jiangnan University. This is a prospective study approved by the Institute Review Board of the university. Each participant signed an informed consent before the study. Inclusion criteria: Meet the diagnostic criteria of renal insufficiency; Symptoms of foot pain; The age range is 18 to 70 years old. Exclusion criteria: receiving chemotherapy; Complications, brain, liver and other vital organ dysfunction, other tumors, coagulation dysfunction, blood system diseases, serious infectious diseases, congenital immune diseases, mental disorders or communication disorders, pregnancy or lactation. From August 2017 to September 2021, 55 patients were enrolled in the study. Two out of the 55 patients were excluded due to metal fixation. Fifty-three patients successfully underwent MRA examinations. Among them, the medical information of 53 patients was mainly collected, including whether they had other diseases (chronic nephritis, diabetes, hypertension, cardiovascular disease, etc.), Body mass index and whether the patients smoked.

3. MRA examinations

All MR examinations were performed on a 3.0T whole body scanner (Skyra, Siemens, Germany). Patients were put on the scanner in supine position, with feet in head-neck coil. Two-D ECG-triggered QISS was performed before 3D ECG-triggered NATIVE-SPACE. QISS was performed on the transverse plane with the following parameters: TR = cardiac circle; TE = 1.74 ms; FOV = 400 mm; matrix = 448; slice number = 60; slice thickness = 3 mm; parallel accelerator factor = 3 for cardiac circle shorter than 800 ms, or parallel accelerator factor = 2 for cardiac circle longer than 800 ms. The acquisition time of QISS was about 30 to 60 seconds. NATIVE-SPACE was performed after a PC sequence. PC method was used to determine the time points corresponding with minimum flow and peak flow. For this purpose, PC was repeated about twenty times during a cardiac circle. The main parameters of NATIVE-SPACE were as follows: TR = 680 ms; TE = 74 ms; FOV = 400 mm; matrix = 384; slice thickness = 1 mm; slice number = 56; parallel accelerate factor = 3; phase direction = right-left; TD-peak-flow = the time point with artery brightest on PC image. NATIVE-SPACE was performed for dorsalis pedis artery and plantar artery respectively. The imaging plane was set parallel to the arteries running direction. The acquisition time of 2 stops of NATIVE-SPACE was about 2 to 4 minutes. The images at the minimum flow time were subtracted by images at peak flow. The data of each enrolled patient was randomly assigned to a physician for review, and each physician did not know the disposition of each patient. The MRI operator is not responsible for the final data analysis process.

4. Data analysis

Reconstruction of source images of QISS and subtracted images of NATIVE-SPACE was performed immediately after scanning, by using maximum intensity projection and 3D volume render methods. The reconstructed images were then transferred to the PACS for review.

A subjective score of image quality was given to each case according to the following scale: 0 = poor depiction of dorsalis pedis arteries or plantar arteries, detection of artery disease impossible; 1 = moderate depiction of foot arteries, detection of occlusion of dorsalis pedis arteries or plantar arteries possible; 2 = good depiction of foot arteries, assessment of the stenosis degree available; 3 = excellent depiction of dorsalis pedis arteries, plantar arteries, and their branches, assessment of the

stenosis degree possible. Two radiologists with more than 10 years experience in diagnosing peripheral diseases separately rated the image quality of QISS and NATIVE-SPACE, using both source images and reconstructed images. If the 2 radiologists gave different score to a case, the scores were averaged.

A radiologist with more than 15 years experience in diagnosing peripheral diseases carefully compared the stenosis on QISS images and NATIVE-SPACE images for all cases. If a stenosis (or occlusion) was detected by 1 method, but was not detected by another, it was considered as a false stenosis (or occlusion). If a stenosis (or occlusion) could be detected by both methods, it was considered as a true stenosis (or occlusion). The radiologist was asked to measure the diameter of true stenosis.

Two radiologists with 6 and 7 years experience in diagnosing peripheral diseases separately measured the signal intensity of artery and adjacent soft tissue background by drawing ROI. A circular ROI was first put on the middle site of dorsalis pedis artery, and then was shifted to the adjacent soft tissue background. The signal intensity of artery was divided by that of soft tissue background, obtaining the relative signal intensity (rSI).

5. Statistical analysis

SPSS (version 24.0, IBM) was used for statistical analysis. Continuous data was presented as mean \pm SD. The non-paired t test was used to compare data obeying normal distribution. The rank sum test was used to compare data not obeying normal distribution. The chi square test was used to compare the classified counting data. Repeated measurement data were analyzed by repeated measurement analysis of variance. Main effect test results were used when there was no interaction and simple effect analysis was carried out when there was interaction. $P < .05$ indicated that the difference between groups is statistically significant.

6. Results

Fifty-three patients (mean age = 44.2 ± 11.4 years, male: female = 27:26) with renal insufficiency and foot pain underwent QISS and NATIVE-SPACE MRA. The estimated Glomerular Filtration Rate of these patients ranged from 22.4 mL/minutes to 51.3 mL/minutes, with an average of 38.7 mL/minutes. The main accompanied diseases of this cohort were as follows: chronic nephritis (n = 41), diabetes (n = 11), hypertension (n = 24), gout (n = 9); chronic respiratory disease (n = 7), chronic cardiovascular disease (n = 6), tumor (n = 4), tuberculosis (n = 2). Body mass index of these patients ranged from 16.7 to 26.1, with an average of 21.2. Twenty-two out of the 53 patients were smokers. Thirty-four out of 53 patients had pains in bilateral feet. Among the 34 patients with foot pain, 12 had foot fungus infection, including 8 with *Staphylococcus aureus*, 3 with coagulase-negative *Staphylococcus* and 1 with Gram-negative bacilli.

The acquisition time of QISS ranged from 30 seconds to 60 seconds, with an average of 45.4 ± 8.9 seconds. The acquisition time of NATIVE-SPACE ranged from 128 seconds to 237 seconds, with an average of 178.4 ± 35.7 seconds, significantly longer than that of QISS ($P < .001$, Table 1).

QISS had significantly lower image quality score versus NATIVE-SPACE (1.4 ± 0.5 vs 2.4 ± 0.6 , $P = .02$). In 45 out of 53 cases, NATIVE-SPACE obtained a higher score than QISS; in the other 8 cases, QISS received a higher score than NATIVE-SPACE. For the 8 poor NATIVE-SPACE cases, arteries were bright at the minimum flow time on the PC image, similar to that at peak flow time. For good or excellent NATIVE-SPACE cases, arteries were black at minimum flow time, significantly different from that at peak flow time. The rate of poor NATIVE-SPACE cases was 15% (8/53) in the study. There was no poor QISS case in the study.

The relative signal intensity of artery were obtained for 53 QISS cases, and inter-reader reproducibility was excellent (ICC = 0.87). QISS rSI ranged from 6.3 to 11.5 for Reader 1. For 45 good or excellent NATIVE-SPACE cases, rSI was obtained, and inter-reader reproducibility was excellent (ICC = 0.88). NATIVE-SPACE rSI ranged from 50.4 to 91.6 for Reader 1. For 8 poor NATIVE-SPACE cases, rSI was not obtained. The rSI was significantly lower in QISS versus NATIVE-SPACE (9.7 ± 1.3 vs 68.2 ± 12.4 , $P < .001$).

For the 8 cases with poor NATIVE-SPACE, stenosis or occlusion could not be confirmed. For the 45 other cases, stenosis (or occlusion) could be confirmed by comparing the findings of QISS and NATIVE-SPACE. False stenosis was observed in 22 QISS cases, and in 4 NATIVE-SPACE cases. False occlusion was observed in none of NATIVE-SPACE cases, but in 14 QISS cases. The incidence of false stenosis was significantly higher for QISS versus NATIVE-SPACE (22 vs 4, $P < .001$). True stenosis (or occlusion) was found in 11 out of 45 patients. In segment level, there were 29 true stenosis and 6 true occlusion. QISS and NATIVE-SPACE did not differ in the diameter of true stenosis (1.17 ± 0.21 vs 1.14 ± 0.19 , $P = .31$). The inter-modality agreement in the measurement of diameter of true stenosis was excellent (ICC = 0.91).

Figure 1 is an example of good NATIVE-SPACE case. Figure 2 is an example of poor NATIVE-SPACE case. Figures 3 and 4

were examples of false stenosis and occlusion on QISS. Figure 5 was an example of false stenosis on NATIVE-SPACE.

7. Discussions

QISS is a time-efficient NCE MRA sequence, providing excellent depiction of arteries of legs. The accuracy of QISS in detection of stenosis in lower extremity was reported high.^[25] Currently, QISS frequently served as an alternative to lower extremity CTA in some centers, especially for patients with renal insufficiency.^[26-28] However, due to the 2D acquisition, QISS is still limited in its application in the places where arteries are tortuous. Inversion recovery was used in QISS acquisition to decrease signal intensity of background tissues. The signal derives from the fresh blood flowing into the image plane.^[29,30] For the arteries with slow flow, inadequate fresh blood will generate relatively low intensity. It is well established arteries in foot are of tortuous shape and slow speed.^[31,32] 2D QISS is not expected to provide good depiction of foot arteries. The data of our study supported this point. About half of QISS cases were rated moderate image quality. False stenosis or occlusion occurred in about half of QISS cases. One possible reason is the slow speed in foot. Another possible explanation is that ECG-trigger fails to work due to the very far distance to heart.

NATIVE-SPACE is substantially different from QISS in the imaging acquisition. The former displays arteries by subtracting fast flow images from slow flow images. FSE T2 sequence is sensitive to flow speed. Bright blood corresponds with slow flow, while black blood is caused by fast flow. The subtraction method of NATIVE-SPACE is similar to that of contrast enhanced MRA.^[33-35] Before the acquisition of NATIVE-SPACE, a PC method should be used to determine the minimum flow time, as well as the maximum flow time. Although NATIVE-SPACE used long echo train and high parallel accelerator factor to reduce acquisition time, it still required more acquisition time than QISS. However, compared to 2D acquisition, 3D acquisition of NATIVE-SPACE allows better depiction of tortuous arteries. In the study, foot arteries were better depicted by NATIVE-SPACE versus QISS in most cases.

In the study, false stenosis was observed in small part of NATIVE-SPACE cases. One possible reason is the turbulence near the vessel wall. As a NCE MRA, NATIVE-SPACE sometimes still failed to avoid false positives. Contrast enhanced MRA or CTA could be used to confirm the stenosis observed in NATIVE-SPACE. For patients with renal insufficiency, at least 2 NCE MRA methods should be used for the purpose of comparison. By comparing the findings of QISS and NATIVE-SPACE, most false positives could be excluded.

It is well established the artery flow speed varies with time during the cardiac circle.^[36] By using PC method, the minimum flow and peak flow can be reliably determined. The speed difference between minimum flow and peak flow corresponds with the artery signal intensity on subtracted images of NATIVE-SPACE. In most cases, flow difference is adequate, and artery can be well depicted. In small part of cases, the minimum flow is similar to the peak flow, resulting in poor depiction of artery. In the study, NATIVE-SPACE failed to work in 15% cases. For these cases, the artery brightness on PC image was about the same at all time points, and no significant difference was observed between minimum flow and peak flow. One possible reason for the constant flow was early pathological changes of arterial wall. QISS could serve as an alternative to NATIVE-SPACE in such cases.

In 85% cases of the study, the image quality of NATIVE-SPACE was rated good or excellent. Three-D thin-slices and adequate artery-to-background contrast both contributed to the improvement in image quality. NATIVE-SPACE with better

Table 1
The comparison of QISS and NATIVE-SPACE.

	NATIVE-SPACE	QISS	P value
Scanning time (sec)	178.4 ± 35.7	45.4 ± 8.9	<.001
Image quality score	2.4 ± 0.6	1.4 ± 0.5	.02
Relative signal intensity	68.2 ± 12.4	9.7 ± 1.3	<.001
Incidence of false positives	4/45	22/45	<.001
Diameter of stenosis (mm)	1.17 ± 0.21	1.14 ± 0.19	.31

NATIVE = non-contrast enhanced MRA of arteries and veins, QISS = quiescent interval single shot, SPACE = sampling perfection with application optimized contrasts by using different flip angle evolution.

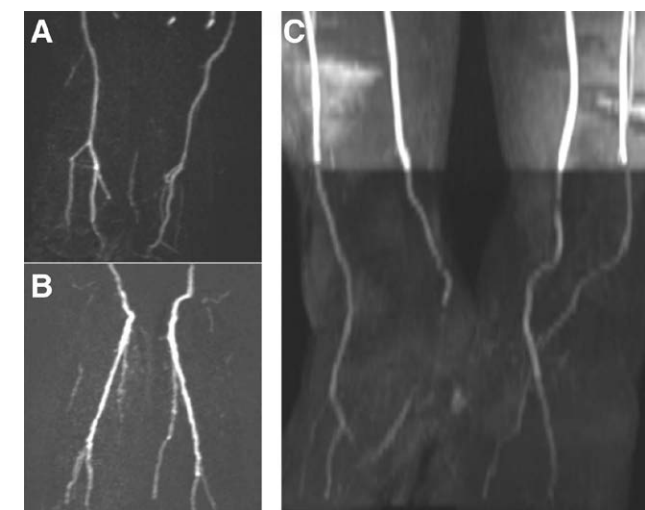


Figure 1. NATIVE-SPACE better than QISS, A 37 years female with renal insufficiency and foot pain. NATIVE-SPACE provided excellent depiction of dorsalis pedis artery (A) and plantar artery (B). The image quality of QISS (C) was significantly worse than that of NATIVE-SPACE. NATIVE = non-contrast magnetic resonance angiography of arteries and veins, QISS = quiescent interval single shot, SPACE = sampling perfection with application optimized contrasts by using different flip angle evolution.

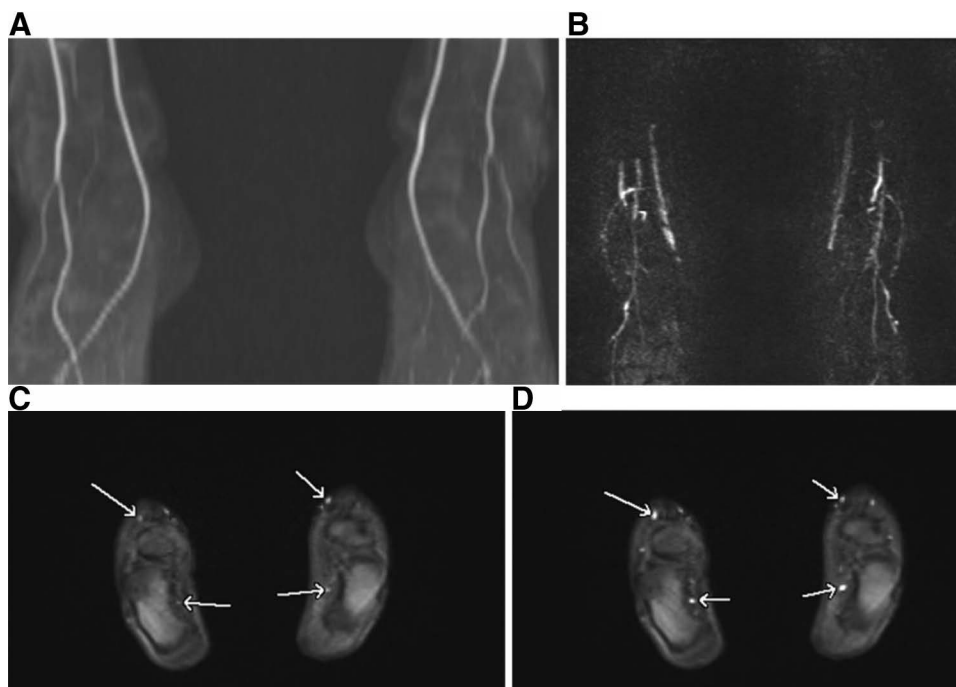


Figure 2. QISS better than NATIVE-SPACE, A 44 years female with foot pain and renal insufficiency. The image quality of QISS (A) was better than that of NATIVE-SPACE (B). NATIVE-SPACE provided poor depiction of dorsalis pedis artery. The dorsalis pedis arteries corresponding with minimum flow were bright on PC images (c, arrows), similar to those with peak flow (d, arrows). The little difference between c and d resulted in poor depiction of arteries on NATIVE-SPACE. NATIVE = non-contrast magnetic resonance angiography of arteries and veins, QISS = quiescent interval single shot, SPACE = sampling perfection with application optimized contrasts by using different flip angle evolution.

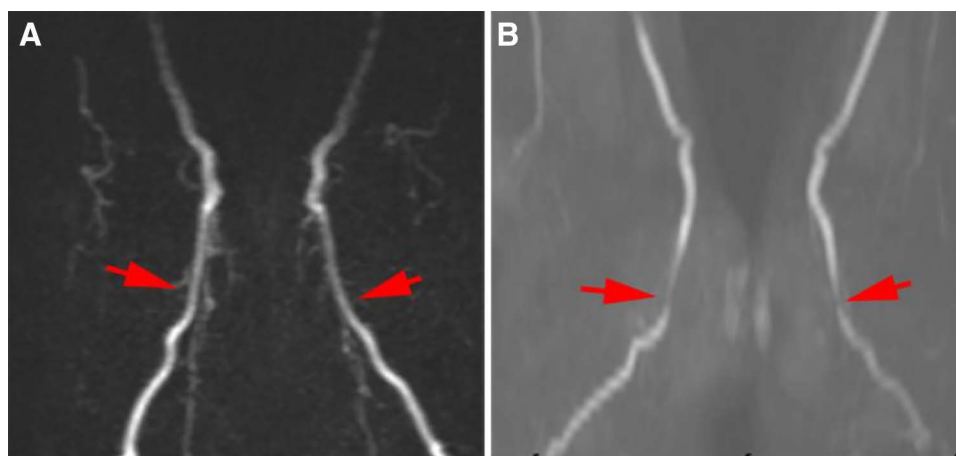


Figure 3. False stenosis on QISS, A 38 years male with renal insufficiency and foot pain. NATIVE-SPACE well displayed bilateral plantar artery (A). Stenosis could be seen on bilateral plantar artery of QISS image (b, arrows), but was not seen on NATIVE-SPACE (a, arrows). Thus the stenosis on QISS were false positives. NATIVE = non-contrast magnetic resonance angiography of arteries and veins, QISS = quiescent interval single shot, SPACE = sampling perfection with application optimized contrasts by using different flip angle evolution.

image quality and less false positives seemed more suitable than QISS for depiction of foot arteries. In the study, dorsalis pedis artery and plantar artery were separately imaged by NATIVE-SPACE, which reduced acquisition time of each stop. In consideration of the use of subtraction in NATIVE-SPACE, foot motion should be avoided. The acquisition of NATIVE-SPACE should be as fast as possible. We thus suggest 2 stops of NATIVE-SPACE in the foot.

Patients in the current study all had foot pain. It is well established artery stenosis or occlusion can cause foot pain.^[37] Thus we performed NCE MRA for these patients, and successfully detected stenosis or occlusion in about one 4th cases. The stenosis of artery seemed to be responsible for the pain. Thus, it may

be concluded that NCE MRA is a valuable test for patients with foot pain and renal insufficiency. QISS and NATIVE-SPACE in the study needed about 5 minutes. The scanning time could be acceptable by most patients.

The current study investigated the feasibility of QISS and NATIVE-SPACE in assessing foot arteries of patients with renal insufficiency and foot pain. The most important findings are as follows: NATIVE-SPACE had better image quality and less false positives compared to QISS; NATIVE-SPACE failed to work in 15% cases due to constant flow speed. This study still has some shortcomings. Firstly, the quality of this study is limited due to the small sample size we included in the study. Secondly, this research is a single-center study and our findings

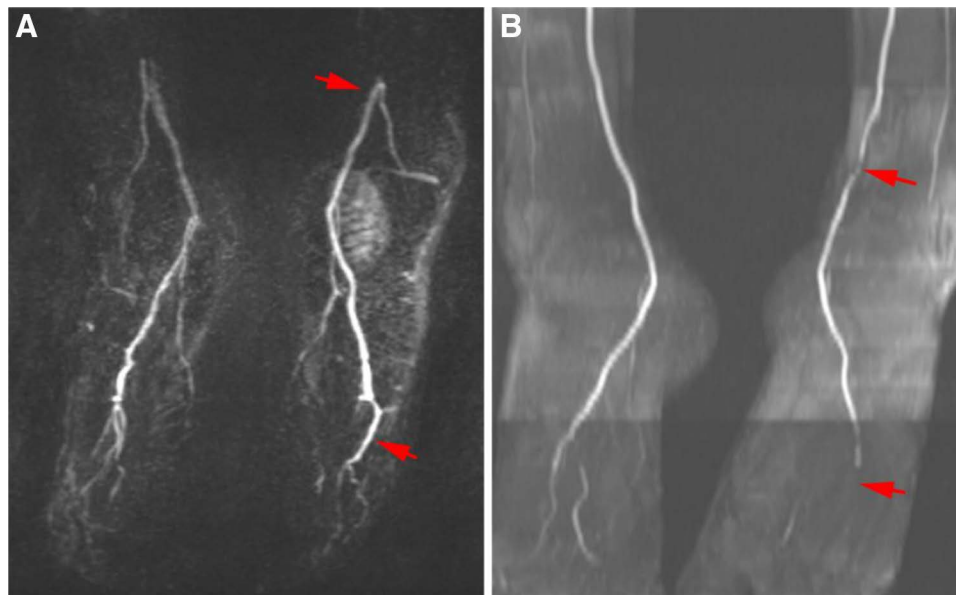


Figure 4. False occlusion on QISS, A 41 years female with renal insufficiency and foot pain. NATIVE-SPACE (A) provided excellent depiction of bilateral plantar artery. There were stenosis and occlusion on the left plantar artery of QISS (b, arrows), but they were not seen in the same places of NATIVE-SPACE (b, arrows). Thus there was a false occlusion on QISS. NATIVE = non-contrast magnetic resonance angiography of arteries and veins, QISS = quiescent interval single shot, SPACE = sampling perfection with application optimized contrasts by using different flip angle evolution.

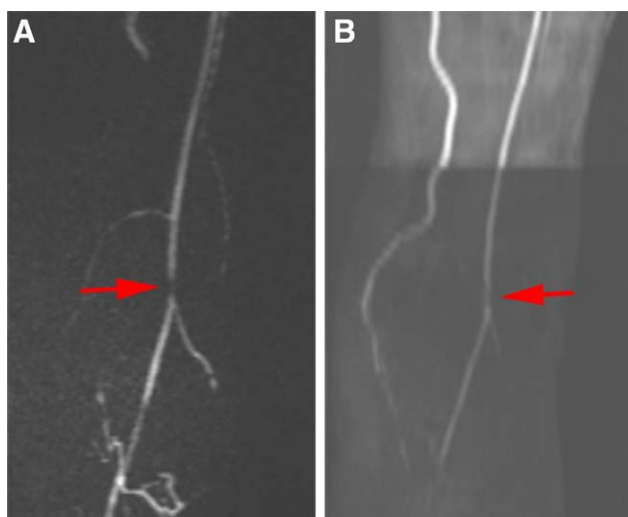


Figure 5. False stenosis on NATIVE-SPACE, A 44 years old male with renal insufficiency and foot pain. NATIVE-SPACE (A) and QISS (B) both displayed plantar artery. There was a stenosis on NATIVE-SPACE (a, arrow), but it was not seen on QISS (b, arrow). Thus this was a false stenosis on NATIVE-SPACE. NATIVE = non-contrast magnetic resonance angiography of arteries and veins, QISS = quiescent interval single shot, SPACE = sampling perfection with application optimized contrasts by using different flip angle evolution.

are subject to some degree of bias. Therefore, our results may differ from those of large-scale multicenter studies from other academic institutes. This research is still clinically significant and further in-depth investigations will be carried out in the future.

8. Conclusion

NATIVE-SPACE is valuable in evaluating foot arteries of patients with renal insufficiency. At least 2 NCE MRA methods are required to confirm a true stenosis. QISS can serve as an alternative test when NATIVE-SPACE did not work.

Author contributions

Conceptualization: Gang Wu, Yongli Yang, Liangjin Liu.

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