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Review

Novel developments in non-invasive imaging of peripheral arterial disease with CT: experience with state-of-the-art, ultra-high-resolution CT and subtraction imaging

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Despite advances, challenges remain for less invasive imaging of peripheral arterial occlusive disease (PAOD) using computed tomography (CT) angiography. The application of dual-energy imaging to PAOD has been reported to improve the diagnostic accuracy of this application; however, severe arteriosclerosis with heavy arterial wall calcification still hampers definitive lesion characterisation, especially in distal and smaller arteries. Recently an ultra-high resolution scanner has been introduced. In combination with advances in post-processing, such as subtraction techniques, these developments may overcome some of the current challenges and allow far more detailed characterisation of PAOD non-invasively. The aim of this review is to describe our current experience with ultra-high resolution CT in combination with subtraction and discuss the potential advantages of their application for peripheral angiography.

Background

Peripheral arterial occlusive disease (PAOD) is a common condition associated with arterial wall degeneration mainly caused by arteriosclerosis.[1] Diffuse progressive accumulation of arterial wall plaque results in luminal narrowing of the peripheral arteries and ultimately leads to organ ischaemia. The atherosclerotic plaque itself has been shown to consist of various components such as fibrotic cells, smooth muscle cells, lipid (cholesterol crystals), calcium, and blood cells including leukocytes and macrophages.[2–4]

The first and typical symptom of PAOD is intermittent claudication; however, progression of the disease can result in more severe disturbances of the peripheral arterial circulation, leading to tissue damage or even tissue loss. In such conditions, restoration of the peripheral arterial circulation through limb revascularisation is required.[5]

Traditionally, surgical bypass has been the therapeutic choice for revascularisation.[6] More recently, endovascular therapy has become widely accepted as a routine treatment.

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Moreover, recent developments in interventional devices have further contributed to a continued shift towards less-invasive endovascular procedures. Along with the development of interventional techniques, detailed phenotyping of lesion characteristics, including the assessment of lesion localisation and severity as well as the upstream/downstream status, has become a requisite for accurate therapeutic decision-making.[7]

CT is a useful non-invasive technique not only for the detection of luminal stenosis but also for plaque characterisation; however, particularly in patients with PAOD, extensive arterial calcification accumulates in the distal arteries.[8] In such patients, accurate visualisation of the lumen with conventional CT is hampered by the artefacts caused by calcifications, as well as the lower resolution of CT than that of digital subtraction angiography (DSA)[9]; however, CT technology is rapidly progressing both in terms of hardware and software. Recently, an ultra-high-resolution CT (UHRCT) system has been introduced, and it allows a more than twofold increase in spatial resolution. The high spatial resolution may be particularly beneficial in the visualisation of small vasculature. In combination with advances in post-processing, such as subtraction techniques, these developments may overcome some of the current challenges and allow for more detailed and non-invasive characterisation of PAOD.

The aim of this review is to describe our current experience with UHRCT in combination with subtraction and to discuss the potential advantages of its application in non-invasive peripheral angiography.

Non-invasive imaging of peripheral arterial disease with CT

UHRCT in combination with subtraction CT

UHRCT (Canon Medical Systems, Otawara, Japan) is a 160-row multi-detector CT with superfine detector grids providing an effective detector element size as small as 0.25×0.25 mm and 1,792 detector channels (Fig 1). UHRCT also has a fine X-ray focus size as small as 0.4×0.5 mm. Gantry rotation speed is up to 0.35 seconds and iterative reconstruction is available. The matrix size of the reconstructed images can be selected, varying from 2,048×2,048 or 1,024×1,024 to the conventional 512×512, with a minimal section thickness of 0.25 mm.

To minimise motion and improve position matching, the patient table has a dedicated design that allows highly accurate and stable movement. Controlled-orbit helical scanning,[10–12] which synchronises the helical orbit of data acquisition and patient table feed is also available for the subtraction technique. As peripheral vascular imaging requires a long table feed with helical scanning, the spatial registration of datasets for subtraction is prone to error if these features are not applied. The other imaging parameters are comparable to those of conventional 80-row multi-detector CT.

Subtraction CT is a technique for extracting the contrast-enhanced area (vascular lumen) similar to DSA. Subtraction images can be obtained through additional post-processing

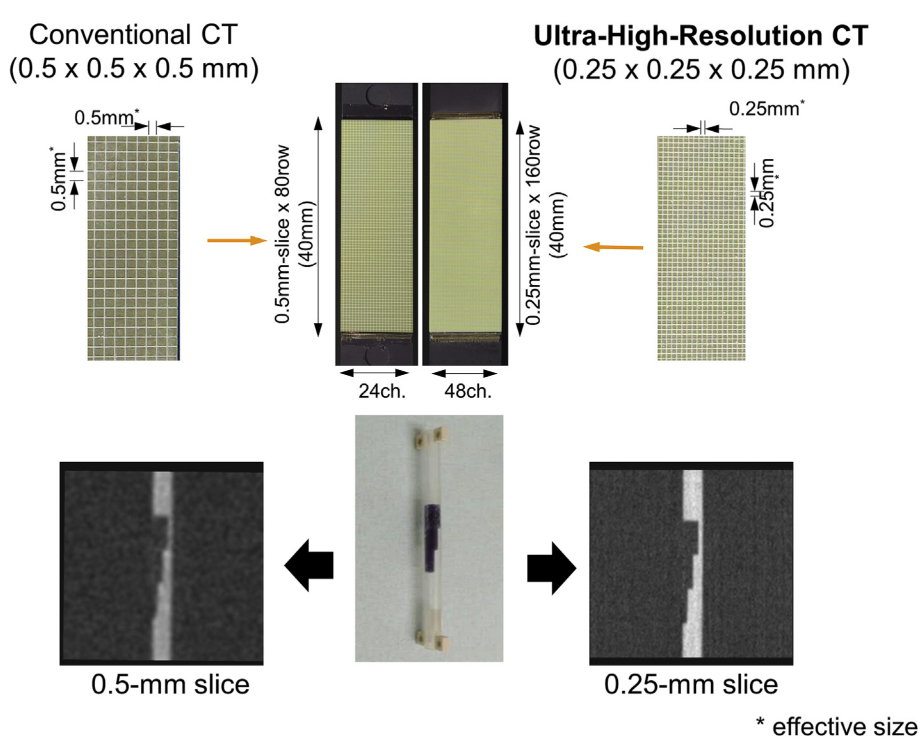

Figure 1 Superfine detector grids of UHRCT compared to those of conventional CT. The effective element size of the UHRCT detector is 0.25×0.25 mm, which is smaller than the 0.5×0.5×0.5-mm size used in the current technology. The effect on spatial resolution is clearly visible in the phantom example, which shows the potential for enhanced lesion delineation and quantification.

of conventional CT angiographic images and can provide complementary information. The subtraction dataset is obtained by subtracting non-contrast images from contrast images. As a result, high-density structures, such as calcifications and metals (for example, stents, surgical clips, and orthopaedic implants), are effectively removed while the contrast-enhanced area (such as the vascular lumen) remains. As high-density structures are removed, some artefacts (e.g., blooming and streak artefacts) caused by such structures are also effectively removed.[12]

Basic subtraction is effective when the object (patient) stands still; however, inconsistency between datasets can occur because of movements such as breathing, bowel motion, pulsation of vessels, and involuntary movement. Because subtraction CT is based on three-dimensional data, unlike DSA (which considers two-dimensional data), it is conceivable that such inconsistencies between two datasets may have substantially greater impact. Therefore, advanced post-processing is required for obtaining accurate subtracted images in CT.

The first step is "zero clipping" to eliminate the miscalculation of subtraction. Bowel motion can cause the displacement of bowel gas, which has a negative CT value. Simple subtraction of negative CT values would have the same effect as adding high CT values (Fig 2). The formula of subtraction at a certain voxel is as follows:

$$HU_{sub} = HU_{post\text{-}contrast} - HU_{pre\text{-}contrast}$$

HU_{sub} is the CT value after subtraction.
$HU_{post\text{-}contrast}$ is the CT value on contrast-enhanced CT.
$HU_{pre\text{-}contrast}$ is the CT value on pre-contrast CT.

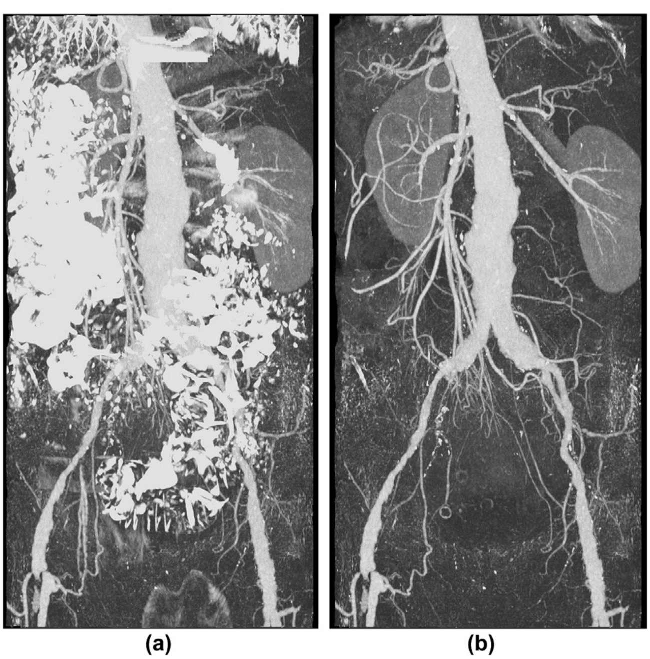

Figure 2 Zero-clipping to overcome the bowel motion artefact. (a) Subtraction CTA reconstructed without "zero-clipping" shows high-density misregistration artefacts due to bowel movement. (b) When "zero-clipping" is applied, misregistration artefacts are significantly reduced.

For example, when a certain voxel locates at bowel gas on pre-contrast CT ($HU_{pre\text{-}contrast}$: −1,000 HU) but at mesenteric fat ($HU_{post\text{-}contrast}$: −50 HU) on contrast-enhanced CT, the calculation of the CT value based on simple subtraction is as follows:

$$HU_{sub} = -50 - (-1000) = -50 + 1000 = 950\ HU$$

Thus, the displacement of bowel gas introduces a high-density artefact. When "zero clipping" is applied, negative CT values are set to 0, thus avoiding the subtraction of voxels that have negative CT values. Therefore, the calculation using "zero clipping" is as follows:

$$HU_{sub} = -50 - 0 = -50\ HU$$

Accordingly, this method can effectively avoid the misregistration artefact due to bowel movement.

The next step is the application of the position-matching technique to eliminate or suppress other motion artefacts (Fig 3). The position of the pre-contrast volume is matched to that of the post-contrast volume and then subtracted. As a result, high-density structures such as calcifications are effectively removed from the dataset. Maximum-intensity projections using the resulting dataset provide fine angiographic images like DSA images. Basically, rigid position matching is sufficiently effective for the subtraction of peripheral arteries; however, motion in the bilateral extremities is not always synchronised. Therefore, separate subtractions on the right and left extremities are necessary for optimal image quality. When the dataset has pulsation artefacts or involuntary movement, the use of a non-rigid position-matching technique in addition to rigid position matching is required. A patient-immobilisation system (Fig 4) is useful to suppress such involuntary movements and improve the accuracy of subtraction.

With dedicated patient preparation and precise volume position matching, subtraction CT angiography (CTA) can be highly successful in removing calcifications and providing

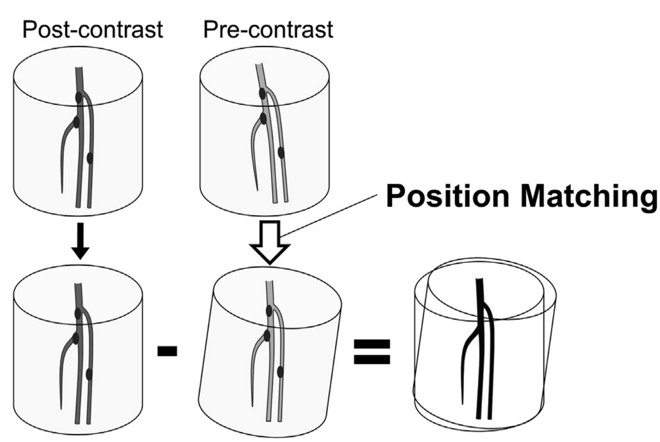

Figure 3 Basic concept of the rigid position-matching technique. The position of the pre-contrast volume is matched to that of the post-contrast volume and then subtracted. As a result, high-density structures such as calcifications are effectively removed from the dataset.

Figure 4 Patient-immobilisation system with polystyrene bead bags. Polystyrene bead bags have a one-way valve as an air vacuum port. When the valve is open, the bead bag is soft and can be used for wrapping patients' lower extremities. An additional small bag system supports the ankles and feet. Once the air in the bag is vacuumed, the bags become rigid and fix the position of the patients' lower extremities.

fine visibility of the lower extremity vasculature (Fig 5) even in below-the-knee regions (Fig 6).

Overall, image acquisition with UHRCT is similar to that with 80-row MDCT. The typical scan parameters of UHRCT are shown in Table 1. Bolus tracking is used for optimally timing the start of the scan. Evaluations using invasive angiography[21,22] have shown that long bolus contrast medium injections are key to reduce the poor opacification, especially seen in patients with asymmetric blood flow in both lower legs because of significant proximal stenotic and occlusive lesions. These invasive angiographic studies have also clarified the relatively slow arterial transit time from the abdominal aorta to the arteries at the level of the ankle. Therefore, a basic concept in subtraction CTA using controlled-orbit helical scanning is to scan slowly from the upper abdomen to the ankle and to maintain luminal radiopacity during the scan.[12] In patients with significantly slow blood flow, this slow scanning approach remains faster than the analysis of their blood flow. Additional (optional)

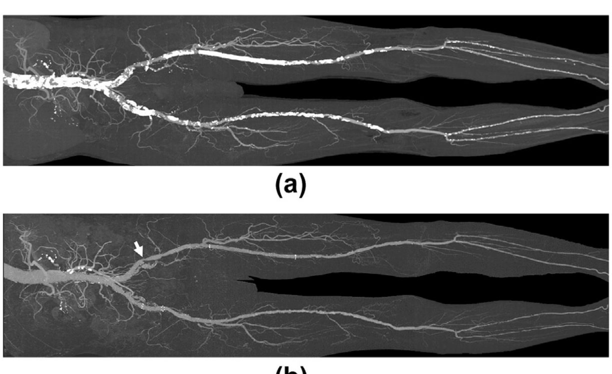

Figure 5 Subtraction CTA in a patient with severe arterial wall calcification and metallic stents. Conventional CTA shows severe arterial wall calcification of the abdominal aorta and both lower extremities. Metallic stents are present in the right external iliac artery and left superficial femoral artery. Because of these structures, the patency of the arterial lumen cannot be confirmed using the conventional CTA image (a). Subtraction CTA demonstrates severe stenosis at the proximal portion of the left external iliac artery (arrow) and patency of the abdominal aorta, femoral arteries, and metallic stents (b). Further, multiple severe stenoses are well demonstrated in the right anterior tibial artery.

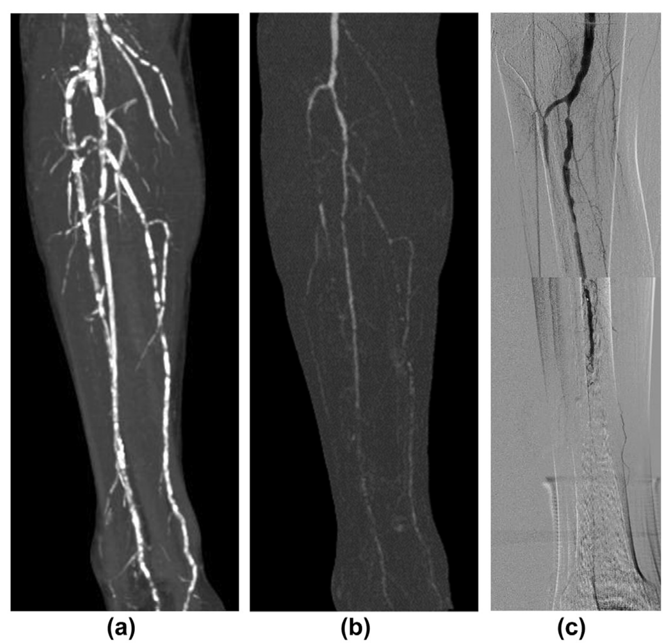

Figure 6 The evaluation of below-the-knee arteries in a patient with severe arterial calcification. Conventional CTA demonstrates diffuse severe arterial calcification in the below-the-knee arteries, rendering the evaluation of the arterial lumen very difficult (a). Subtraction CTA clearly demonstrates multiple stenoses and occlusion of the below-the-knee arteries (b). DSA confirms the presence of multiple severe stenoses and occlusion similar to those seen on subtraction CTA. Note that the distal portion of the below-the-knee arteries is not well visualised on DSA because of the slow blood flow due to proximal severe lesions.

Table 1
The typical scan parameters of UHRCT.

Parameters	Value
No. of rows	160
Slice thickness	0.25 mm
Gantry rotation	0.75 s
Pitch factor	0.569
Tube voltage	120 kVp
Tube current	100–320 mAs
Focus size	S1
Reconstruction kernel	FC13
Iterative reconstruction	AIDR 3D
Scan range	Supra renal abdominal aorta–toe
Controlled orbit helical scanning	Yes
Contrast medium	350 mg iodine/ml or 370 mg iodine/ml
Total volume	75 ml
Injection rate	2 ml/s
Saline chaser	30 ml
Reconstruction slice thickness	1 mm
Reconstruction FOV	
Abdomen–pelvis	250 mm
Femur	200 mm
Thigh	150 mm (left and right)
Foot	230–250 mm

scanning of the calves and feet may be needed for these patients. For the evaluation of pedal arteries, an optimal reconstruction field of view (FOV) is used to take full advantage of the increased spatial resolution. Thus, small vasculature such as the digital arteries of the toes can be observed (Figs 7 and 8).

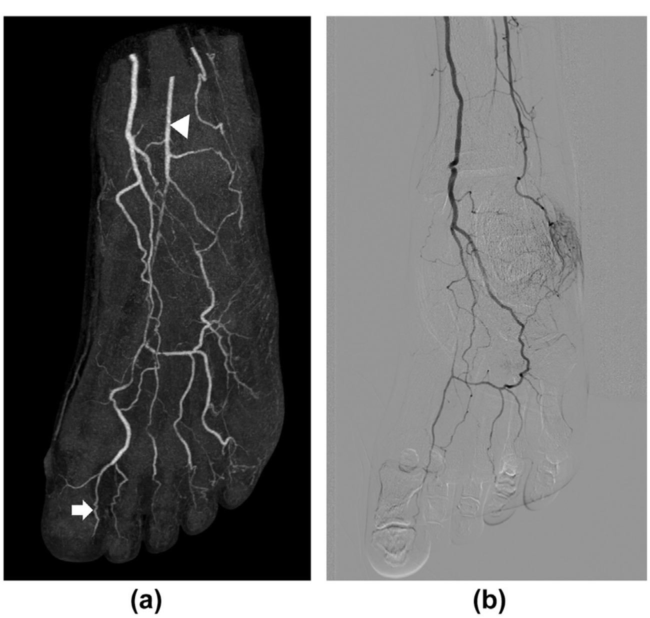

Figure 7 Visualisation of the arteries of the foot. Subtraction CTA using UHRCT enables fine visualisation of the pedal artery and digital arteries (arrow). (a) Partial early venous opacification is also observed (arrowhead). Selective DSA demonstrates arterial patency similar to that seen on subtraction CTA, even though the opacification of the digital arteries is not as good in this image. (b) The next phase of this DSA image did not qualify for evaluation because of involuntary movement of the patient.

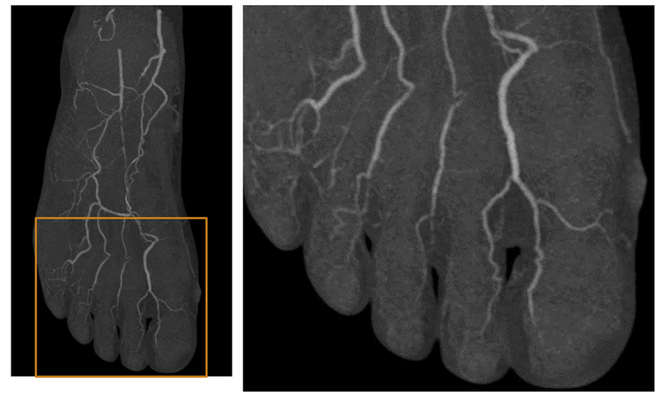

Figure 8 Visualisation of the digital artery of the foot. Subtraction CTA using UHRCT clearly demonstrates the digital arteries of the foot in greater detail.

In some patients with ulcers or gangrene of the lower leg, typically short arteriovenous transit times might hamper the evaluation of arterial disease at the level of the pedal arteries.[23] In these patients, early venous opacification of the calves and pedal regions is observed. For such regional assessment, another contrast medium injection or scan protocols such as dynamic CT might be necessary. Further adaptation of the scan protocol and evaluations are then required.

Alternative methods

Alternative approaches to overcome some of the limitations of CT in the visualisation of calcifications and the small arteries of the lower vasculature include dual-energy CT and dynamic CT. Currently, both techniques are unavailable in combination with UHRCT and will therefore only be discussed briefly.

Spectral/dual-energy CT

Several systems are available on the market that can provide dual-energy analysis. The majority of experience has been obtained using dual-source CT (DSCT, Siemens Healthcare GmbH, Erlangen, Germany), and several scientific evaluations of peripheral arterial angiography have been reported.[13–15] DSCT can provide different spectral data using two X-ray sources at different voltages. The spectral data acquired using these two different voltages enable the separation of contrast and calcification. The luminal image is obtained by subtraction between these two datasets. The projection size of the material changes according to the X-ray spectrum (i.e., the lower the energy peak of the X-ray, the larger the projection size of calcium). Accordingly, the processing of subtraction using these different spectral data might introduce some artefacts (typically a moth-eaten appearance). Moreover, high contrast medium concentration in the lumen is required to obtain good image quality. Thus, CTA using dual-energy reconstruction remains limited in the evaluation of poorly opacified lumen or small vessels.[13,16] For accurate and detailed preoperative mapping of the infrapopliteal arteries, selective intra-arterial dual-energy CTA has also been reported.[17]

Two X-ray sources are located at a right angle in DSCT, such that the acquired helical data by each source have different helical orbits. Subtraction between images from these different helical orbit data can result in misregistration artefacts. Therefore, other techniques such as single-source tube voltage switching dual-energy reconstruction (GE Healthcare, Chicago, USA) and double-layer detector dual-energy reconstruction (Koninklijke Philips, Eindhoven, the Netherlands) have been developed. In particular, single-energy or virtual mono-energic reconstructions could depict large- and medium-sized arteries.[18,19] Further studies might be necessary for determining their diagnostic accuracies in smaller and peripheral arteries where luminal radiopacity is more difficult to achieve.

Dynamic CT

For the evaluation of below-the-knee arteries, dynamic CT could be an alternative approach. Sommer *et al.* reported a technique of dynamic CTA in patients with critical limb ischaemia. This technique was introduced to overcome the drawbacks of DECT in evaluating smaller arteries (i.e., below-the-knee arteries). The concept is based on adding multiphasic dynamic CTA of the calves to a standard CTA without dual-energy reconstruction.[20] Improved diagnostic accuracies could be achieved because of the added dynamic information. As acknowledged by the authors, the increased radiation dose and amount of iodinated contrast medium could be limitations of this technique. Nonetheless, there seems to be room for minimizing these limitations by optimising scan intervals and contrast medium injection protocols.

How can state-of-the-art CT improve anatomical phenotyping?

Until the introduction of UHRCT, the smallest available effective detector element size was 0.5 mm. For the overall evaluation of aortic and lower limb occlusive diseases, this spatial resolution seems sufficient; however, even with the most recent CT technology, the evaluation of smaller arteries, particularly those with diameters <3 mm and arterial wall calcifications or metallic stents, has remained challenging and time-consuming. Such high-density structures result in blooming or streak artefacts, which can obscure the interpretation of the lumen. Accordingly, additional imaging with invasive angiography might still be required.

The 0.25-mm effective size of the detector element on UHRCT enables the visualisation of smaller structures more precisely, as previously shown in Figs 7 and 8. Indeed, compared to currently available CT systems, this system allows for extensive and more detailed visualisation of the distal vasculature. As can be appreciated from these examples, the images are approaching the reference standard of DSA, yet with better opacification in certain cases. The higher spatial resolution may also reduce blooming artefacts; however, improved spatial resolution cannot remove the streak artefact. Dual-energy reconstruction or iterative reconstruction has the potential to suppress this artefact, even though it may not be able to remove the artefact entirely. In particular, when visualising the lumen adjacent to a high-density structure, evaluating luminal stenosis remains very difficult. The addition of the subtraction technique to UHRCT may provide a powerful solution to this problem. A clear example is provided in Fig 9 using a conventional CT system, showing that subtraction CTA with controlled-orbit helical scanning in a patient who underwent knee joint replacement allowed the visualisation of the popliteal artery, which could not be visualised on conventional CTA.

Another use of UHRCT is the non-invasive visualisation of the collateral arteries, pedal arch, and digital arteries. Evaluation of distal smaller arteries is very important in patients with severe limb ischaemia (Fig 10). The status of distal run-off is thought to be an important predictor of remote patency of the bypass graft or re-canalised proximal artery. In addition, poor collaterals and severe stenosis at the level of the pedal arteries might lead to considerable tissue damage even if the proximal lesions are successfully treated. With super-selective angiography, these distal arterial segments can be visualised; however, in patients with severe proximal lesions, selective angiography can be difficult. Moreover, super-selective angiography sometimes fails to visualise collaterals, because the target infusion of contrast media cannot visualise other regional arteries. Therefore, non-invasive visualisation of such smaller distal arteries, especially prior to invasive procedures, is needed to determine an adequate treatment strategy.

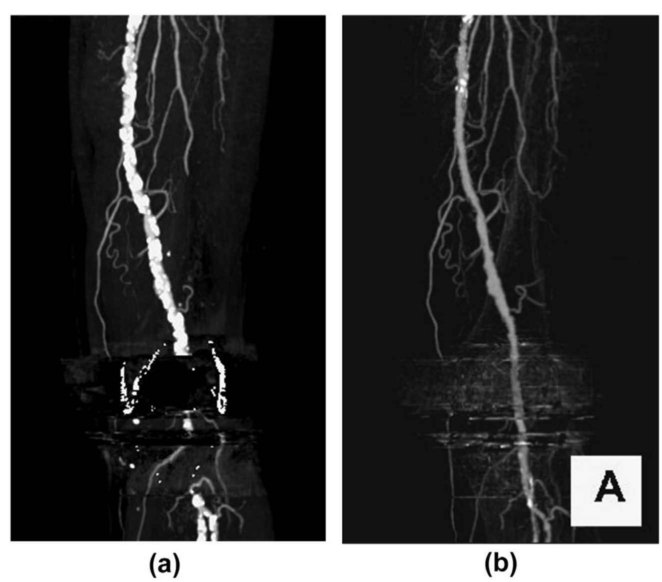

Figure 9 Visualisation of the popliteal artery behind an artificial knee joint. Conventional CTA at the level of an artificial knee joint demonstrates severe arterial wall calcifications and poor visualisation of the popliteal artery due to metal artefacts (a). Subtraction CTA demonstrates a patent popliteal artery (b).

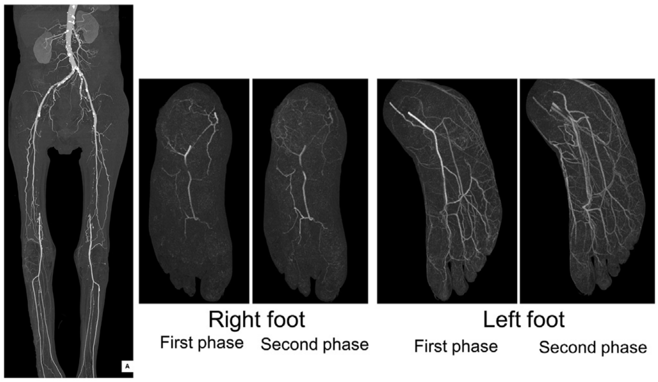

Figure 10 Visualisation of the peripheral arteries in a patient with critical limb ischaemia. A 75-year-old man with bilateral superficial femoral artery occlusion underwent amputation of the right second toe because of skin ulceration. Subtraction CTA using UHRCT showed the occlusion of the plantar arteries and severe stenosis of the dorsal pedis on the right foot. Note the poor opacification of digital arteries in comparison with the left side on the first phase. On the second phase, veins of the left foot are opacified but those of the right foot are not, despite the same severity of proximal femoro-popliteal lesions on both sides.

As UHRCT has only recently become available, no systematic studies have been conducted. Accordingly, while our initial experience is promising, its ability for visualising the entire lower extremity arterial circulation has not yet been established. Further evaluations are necessary to establish its full utility for diagnosis and decision-making in patients with PAOD.

Limitations of UHRCT

There are some limitations that should be addressed. First, acquiring thinner sections without changing the signal-to-noise ratio can result in higher radiation doses despite the use of a hybrid iterative reconstruction. A full iterative reconstruction method could be highly beneficial in this scenario and has recently been introduced for UHRCT. Second, the increase in image data volume is another concern that should be discussed. At present, the slice thickness was limited to 1 mm, because of the heavy load in creating subtraction or three-dimensional post-processing images. Moreover, the management of image size is another hurdle. Different sizes ranging from the conventional 512×512 matrix to the 1,024×1,024 matrix and 2,048×2,048 matrix can be selected. Higher matrix sizes or target reconstructions with smaller FOVs should be used for maximising the spatial resolution of UHRCT, but require higher processing power, larger storage, and faster network traffic. This can pose a substantial problem. We suggest use of the 512×512 matrix for conventional diagnostic imaging, and target reconstruction with smaller FOVs for the evaluation of detailed vascular structures. Such selective processes allowed the acceptable use of UHRCT on a conventional picture archiving and communication system.

Future outlook

UHRCT using subtraction technique has the potential for visualising small vascular structures and may improve our understanding of the distal run-off status especially in severe limb ischaemia. Such small vascular structures are located most peripherally, and their visualisation can be very difficult even when using invasive angiography. Pre-procedural imaging is crucial to determine the native artery status and is also important to use as a landmark for the interventional procedure, especially in below-the-knee occlusive diseases or pedal lesions. UHRCT is a novel cutting-edge technique for detailed non-invasive imaging of small vascular structures and could become a reference standard for the assessment of these regions.

Nowadays, improvements in interventional devices enable accurate and precise procedures even in smaller arteries such as below-the-knee arteries and pedal arteries. Trans-metatarsal retrograde puncture is becoming more common for the interventional treatment in cases with critical limb ischaemia. The angiosome concept is also becoming important. As a result of such developments, evaluation of the patency of peripheral small arteries could become increasingly important for deciding between the various invasive therapeutic options and in predicting their outcomes.

The evaluation of tissue perfusion and distinction between hyperaemia and congestion in damaged areas could also become important markers for avoiding major tissue loss.[24] Such information could also influence the decision to use invasive revascularisation or tissue reconstruction. The evaluation of tissue perfusion and its combination with microvascular imaging using UHRCT could provide useful information, especially for reconstruction surgery in critical limb ischaemia; however, such applications remain speculative at present, as currently there is only limited experience.

In the more near term, however, it is conceivable that UHRCT can enhance the evaluation of post-procedural complications by providing improved visualisation of in-stent hyperplasia or restenosis.

In addition to improved diagnosis and selection of therapy, UHRCT and subtraction may also be applied for monitoring the effects of therapy. Cell therapy to improve angiogenesis is an emerging alternative therapeutic option for critical limb ischaemia[25]; however, studies have shown a lack of correlation between the extent of collateral circulation and clinical response, suggesting that direct vascular imaging alone, even when using DSA, is not suitable.[26] As the spatial resolution of UHRCT is still larger than that of DSA, UHRCT may also not be appropriate for evaluating the neovascularisation and the extent of collateral circulation. Possibly, a combination of yet-undefined anatomical and physiological markers is needed. Moreover, to what extent the more detailed characterisation of PAOD with UHRCT in combination with subtraction and tissue perfusion analysis can contribute in this particular area remains to be established.

At this moment, UHRCT remains an investigational technique that will not yet replace the conventional methods of CTA and MRA that are currently used. Indeed, whether the application of UHRCT and subtraction can translate into the improved selection of therapy and improved outcomes for patients with PAOD remains an important and exciting topic of investigation. Other technical advances, development of clinical applications, and more research are needed to further validate the potential value of UHRCT in this field.

Conclusions

UHRCT for peripheral angiography has significant advantages in evaluating small arterial vasculature. In combination with subtraction CT, CTA can provide fine luminal imaging even in patients with severe arterial calcification. Further evaluation and other technical developments in full iterative reconstruction, clinical applications, and picture archiving and communication system environment are required to take full advantage of this novel technique.

Conflict of interest

None.

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