Applications of Computed Tomography in Peripheral Artery Disease

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Peripheral artery disease (PAD) is a common and debilitating condition characterized by the narrowing of the limb arteries, primarily due to atherosclerosis. Non-invasive multi-modality imaging approaches using computed tomography (CT), magnetic resonance imaging (MRI), and nuclear imaging have emerged as valuable tools for assessing PAD atheromatous plaques and vessel walls.

peripheral artery disease computed tomography

1. Introduction

Peripheral artery disease (PAD) is a common and debilitating condition characterized by the narrowing and obstruction of the antegrade flow of major systemic arteries other than those of the cerebral and coronary circulations, primarily due to the buildup of atherosclerotic plaques. PAD affects over 230 million people worldwide and is associated with significant morbidity, mortality, and reduced quality of life [1].

Several factors have been identified as major contributors to the development and progression of PAD. These include non-modifiable risk factors such as advanced age and genetic predisposition and modifiable ones such as smoking, diabetes, hypercholesterolemia, and hypertension. Lifestyle elements such as poor diet, physical inactivity, and obesity also play considerable roles [2][3].

Central to PAD's pathogenesis is atherosclerosis, which is initiated when low-density lipoprotein (LDL) cholesterol accumulates within the artery walls, triggering an inflammatory response. This response leads to the recruitment of immune cells, primarily monocytes, that transform into macrophages, ingest the accumulated lipids, and become foam cells. Over time, the accumulation of these foam cells forms a lipid core within the arterial wall, which constitutes the atherosclerotic plaque [4].

Endothelial dysfunction is another key factor that promotes atherosclerosis in PAD. A healthy endothelium maintains vascular homeostasis by regulating vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and inflammation. However, in conditions such as hypertension, hypercholesterolemia, and diabetes, the endothelium becomes dysfunctional, promoting the adhesion and infiltration of inflammatory cells and the formation of atherosclerotic plaques [4].

As plaques grow and arterial stenosis worsens, blood flow to the affected limb is significantly reduced, leading to the clinical manifestation of PAD. Symptoms can range from asymptomatic disease to intermittent claudication—characterized by muscle pain or cramping during physical activity—to critical limb ischemia, where the blood flow is so poor that it leads to gangrene, necessitating limb amputation. Moreover, these plaques can become unstable and rupture, leading to acute limb ischemia, a severe and painful condition that requires immediate attention [3][5].

Early detection and accurate characterization of PAD are crucial for effective risk stratification, appropriate therapeutic intervention, and monitoring treatment response. In the landscape of diagnostic tools for peripheral arterial disease (PAD), traditional methods such as the ankle–brachial index (ABI) and pulse wave velocity (PWV) measurements have long served as reliable indicators. ABI, a straightforward, non-invasive tool, offers a quantifiable measure of the presence and severity of PAD. It accomplishes this by comparing the blood pressure in the ankle to the blood pressure in the arm, thus reflecting the adequacy of the blood flow [5][6]. However, while ABI can indicate the presence of PAD, it provides limited information about the precise location or extent of the disease.

On the other hand, PWV is a measurement of arterial stiffness, which has been recognized as a potential predictor of PAD. PWV measurements are obtained by capturing the velocity of the pressure waveform between two points along the arterial tree [7][8]. While effective in measuring arterial stiffness, this method does not offer direct insights into the anatomical characteristics or biological activities of atherosclerotic plaques. Although these traditional techniques are valuable for initial screening and diagnosis, they mainly provide functional information and lack the ability to visualize in-depth anatomical details, plaque composition, or molecular activities in PAD.

With the advent of advanced imaging technologies, the ability to non-invasively visualize and quantify PAD has significantly improved. Non-invasive medical imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), and nuclear imaging, such as single-photon emission computerized tomography (SPECT) and positron emission tomography (PET), have emerged as valuable tools for imaging PAD atheromatous plaques and vessel walls. These modalities provide detailed information on plaque burden, morphology, and composition and insights into vascular function and blood flow. Despite their higher cost and less widespread availability, these newer modalities hold the potential to revolutionize PAD diagnostics and prognostics. Furthermore, integrating molecular markers with imaging markers from these modalities can enhance our understanding of PAD pathophysiology and improve patient outcomes.

2. Computed Tomography (CT)

In this section, it discusses the applications of CT in assessing PAD. With technological advances and accessibility, CT angiography (CTA) has become a popular choice for PAD evaluation. CTA utilizes the emission and detection of X-rays as the patient passes through a gantry that rotates the X-rays in a 360° arc to generate three-dimensional data [9]. An intravenous bolus injection of iodinated contrast material enhances the visualization of blood vessels and distinguishes them from surrounding tissues. The scanning is timed to coincide with the arrival of the bolus of contrast material in the desired artery or vein [9].

2.1. CT for PAD Assessment

CTA is extensively employed to evaluate PAD, as it facilitates detailed visualization of the arterial lumen [10], detection of stenosis [11], and assessment of the extent and severity of the disease [12]. Early-generation helical CT scanners had a single detector that rotated around the gantry, resulting in long scan times and low-quality images, which were inadequate for accurately locating and assessing the severity of stenoses in the lower extremity vasculature. Subsequent generations of multidetector CT (MDCT) utilize multiple rows of smaller detectors to detect a wider coverage of X-rays as the patient moves through the gantry simultaneously, thus allowing for the rapid acquisition of images with higher spatial resolution than those obtained using earlier-generation scanners [13]. Currently, MDCTA is highly accurate for detecting hemodynamically significant lower limb stenoses and lesions [6][14]. For instance, modern 256-slice scanners can assess the degree of stenosis in the aortoiliac and lower limb occlusive disease with high sensitivity (93%) and specificity (92.7%) [12]. CTA could also detect peripheral arterial in-stent restenosis in excellent agreement ($\kappa > 0.80$) with color Doppler ultrasound, the current standard for detecting in-stent restenosis [15]. However, compared to digital subtraction angiography (DSA), the current gold standard for PAD diagnosis and evaluation, CTA has lower accuracy for assessing below-knee stenoses and lesions in the infrapopliteal segment [11][12].

Despite its limited diagnostic ability in the below-knee region, CTA has several advantages over DSA. Firstly, unlike catheter-based DSA, CTA is non-invasive and reduces catheter-associated patient risks and operator dependency. Additionally, although both DSA and CTA involve ionizing radiation, the radiation dose exposure of CTA is significantly lower than that of DSA [16]. Furthermore, CTA allows for improved evaluation of vessel walls and extravascular pathologies [12].

2.2. CT for Plaque Calcification Assessment

In addition to evaluating luminal narrowing, stenosis, and the extent of lesions, CT also provides information about vascular and plaque calcification, which is crucial for risk stratification in PAD. Patel et al., 2015, found that the burden of calcified plaque, but not soft or fibrocalcific plaque, was related to restenosis, reintervention, and amputation-free survival of PAD patients, highlighting the importance of CT plaque analysis in risk stratification for patients undergoing femoropopliteal endovascular procedures [17]. Kaladji et al., 2018, using patients from the STELLA and STELLA PTX registries, discovered that patients with severe vascular calcification (vascular calcification rate > 20%) were associated with early in-stent thrombosis (<1 month), while patients with no vascular calcification (vascular calcification rate < 1%) were associated with late stent thrombosis (6–24 months) [18]. He et al., 2019, found that among patients who received pre-operative CTA, those with a high calcified plaque burden had a higher risk for unfavorable outcomes, including in-stent restenosis, amputation, and mortality [19]. In the same year, Chang et al. determined that the lower limb calcification score was positively associated with acute thrombosis events in symptomatic PAD patients [20]. In 2021, Megale et al. found that in critical limb ischemia patients undergoing lower limb revascularization, pre-operative calcium scores of the aorta and operated limb arterial calcium scores were higher in patients who died within one and six months [21].

CT studies have also revealed that diabetes, a common underlying condition of PAD, is associated with increased lower limb vascular calcification [22][23]. In 2014, He et al. found that diabetes was associated with increased plaque incidence, particularly mixed plaque (plaques containing a calcified component, defined by an average attenuation of 60–100 HU). They also discovered that, in diabetic patients, lesions were more localized to the distal lower leg segments than in non-diabetic patients [23]. However, Mary et al. observed that, in type 2 diabetes mellitus patients, the use of metformin, but not other antidiabetic medications, was associated with a lower below-the-knee arterial calcification score, indicating a vascular protective effect of metformin [24].

Although CTA-derived vascular and plaque calcification aids in PAD risk stratification, the presence of vessel wall calcification often hinders accurate interpretation of peripheral artery CTA examinations. Streak and blooming artifacts caused by vessel wall calcification can lead to overestimating the vessel stenosis [25]. It has been found that the presence of arterial calcification decreases the clinical utility of CTA and compromises the accuracy of assessing hemodynamically significant stenosis [11][16]. One potential solution to this issue is dual-energy CT (DECT). By utilizing two different tube voltages, DECT can generate two datasets and, in theory, enable the extraction of iodine-contrast-only images without artifacts from bone, stent, and vascular calcification [26]. However, a DECT plaque subtraction simulation study using vessel phantoms still demonstrated an underestimation of lumen area in regions with calcified plaques, and this underestimation was more profound in smaller vessels [10].

2.3. Recent Advances and Future Perspectives

Recent advances in CT imaging, such as microCT, photon counting CT (PCCT), and artificial-intelligence-based image analysis, show promise in improving plaque characterization and assisting PAD diagnosis. An *ex vivo* study demonstrated that microCT might have better diagnostic performance among three lower limb plaque types (lipid-rich, fibrous, and calcified plaque) than conventional CTA [27]. Due to the micron-level high spatial resolution of microCT, more detailed information regarding vessel wall calcification can be obtained. Using microCT, Cahalane et al. observed a high prevalence of microcalcification (defined as calcium loci ≤ 65.4×10^3 μm^3) in both carotid and lower limb arteries. However, they found that weight-based extra-coronary calcium scores (ECCS) of both carotid and lower limb arteries had only weak positive correlations with the distribution of calcified particles (CPF, $r_s = 0.422$, $p = 0.007$) and microcalcifications ($r_s = 0.361$, $p = 0.022$) [28]. Although no studies associated the presence of microcalcification and calcified particles with adverse outcomes in PAD, these calcification morphologies were considered high-risk in the carotid and coronary artery disease [29][30][31]. Thus, to guide tailored treatment of high-risk plaques, it might be necessary to perform calcium scoring that distinguishes between critical calcification morphologies instead of simply providing a density-weighted score [28].

PCCT is a recently introduced technique in the field of cardiovascular CT. Traditional CT scanners employ energy-integrating detectors (EIDs), which measure the total energy deposited by X-ray in a detector pixel during a specific time frame. These EIDs do not differentiate between the number of photons and their individual energies. In contrast, PCCT utilizes a distinct type of detector called a photon-counting detector. These detectors can count individual X-ray photons and measure each photon's energy, enabling enhanced image quality, superior contrast resolution, and the potential for reduced radiation dose to the patient [32][33]. In 2022, Si-Mohamed et al. published

the first-in-human results comparing PCCT coronary CTA with conventional CTA. They discovered that PCCT coronary CTA exhibited improved image quality and diagnostic confidence compared to the energy-integrating dual-layer CT [34].

In addition to advances in CT technologies, developments in deep learning models can help with PAD diagnosis. In 2021, Dai et al. used a supervised convolutional neural network–parallel efficient network (p-EffNet) to classify CTA-derived lower limb artery segments according to the degree of stenosis, with DSA results used as a reference standard. The p-EffNet performed well in classifying both above-knee (91.5% accuracy, 90.2% sensitivity, and 97.7% specificity) and below-knee (90.9% accuracy, 91.3% sensitivity, and 95.2% specificity) arteries. Compared to radiologist readers, the p-EffNet had comparable accuracy and specificity but a lower sensitivity [35].

In summary, CT, specifically CTA, is a valuable tool for PAD imaging, providing crucial information on the extent and severity of arterial stenosis, plaque calcification, and morphology. Despite its limitations, ongoing technological advancements in CT imaging promise to improve its capabilities in characterizing plaques and assessing PAD.

References

1. Aday, A.W.; Matsushita, K. Epidemiology of Peripheral Artery Disease and Polyvascular Disease. Circ. Res. 2021, 128, 1818–1832.
2. Simon, F.; Oberhuber, A.; Floros, N.; Düppers, P.; Schelzig, H.; Duran, M. Pathophysiology of chronic limb ischemia. Gefasschirurgie 2018, 23, 13–18.
3. Morley, R.L.; Sharma, A.; Horsch, A.D.; Hinchliffe, R.J. Peripheral artery disease. BMJ 2018, 360, j5842.
4. Signorelli, S.S.; Vanella, L.; Abraham, N.G.; Scuto, S.; Marino, E.; Rocic, P. Pathophysiology of chronic peripheral ischemia: New perspectives. Ther. Adv. Chronic. Dis. 2020, 11, 2040622319894466.
5. Criqui, M.H.; Matsushita, K.; Aboyans, V.; Hess, C.N.; Hicks, C.W.; Kwan, T.W.; McDermott, M.M.; Misra, S.; Ujueta, F. Lower Extremity Peripheral Artery Disease: Contemporary Epidemiology, Management Gaps, and Future Directions: A Scientific Statement From the American Heart Association. Circulation 2021, 144, e171–e191.
6. Conte, M.S.; Bradbury, A.W.; Kolh, P.; White, J.V.; Dick, F.; Fitridge, R.; Mills, J.L.; Ricco, J.B.; Suresh, K.R.; Murad, M.H. Global vascular guidelines on the management of chronic limb-threatening ischemia. J. Vasc. Surg. 2019, 69, 3S–125S.e140.
7. Behrooz, L.; Abumoawad, A.; Rizvi, S.H.M.; Hamburg, N.M. A modern day perspective on smoking in peripheral artery disease. Front. Cardiovasc. Med. 2023, 10, 1154708.

8. Ismaeel, A.; Brumberg, R.S.; Kirk, J.S.; Papoutsi, E.; Farmer, P.J.; Bohannon, W.T.; Smith, R.S.; Eidson, J.L.; Sawicki, I.; Koutakis, P. Oxidative Stress and Arterial Dysfunction in Peripheral Artery Disease. Antioxidants 2018, 7, 145.
9. Rubin, G.D.; Schmidt, A.J.; Logan, L.J.; Sofilos, M.C. Multi-detector row CT angiography of lower extremity arterial inflow and runoff: Initial experience. Radiology 2001, 221, 146–158.
10. Jin, K.N.; Chung, J.W.; Park, E.A.; Lee, W. Dual-energy computed tomography angiography: Virtual calcified plaque subtraction in a vascular phantom. Acta Radiol. Open 2017, 6, 2058460117717765.
11. Lim, J.C.; Ranatunga, D.; Owen, A.; Spelman, T.; Galea, M.; Chuen, J.; Lim, R.P. Multidetector (64+) Computed Tomography Angiography of the Lower Limb in Symptomatic Peripheral Arterial Disease: Assessment of Image Quality and Accuracy in a Tertiary Care Setting. J. Comput. Assist. Tomogr. 2017, 41, 327–333.
12. Mishra, A.; Jain, N.; Bhagwat, A. CT Angiography of Peripheral Arterial Disease by 256-Slice Scanner: Accuracy, Advantages and Disadvantages Compared to Digital Subtraction Angiography. Vasc. Endovasc. Surg. 2017, 51, 247–254.
13. Pomposelli, F. Arterial imaging in patients with lower extremity ischemia and diabetes mellitus. J. Vasc. Surg. 2010, 52, 81s–91s.
14. Met, R.; Bipat, S.; Legemate, D.A.; Reekers, J.A.; Koelemay, M.J. Diagnostic performance of computed tomography angiography in peripheral arterial disease: A systematic review and meta-analysis. JAMA 2009, 301, 415–424.
15. Langenberger, H.; Schillinger, M.; Plank, C.; Sabeti, S.; Dick, P.; Cejna, M.; Lammer, J.; Minar, E.; Loewe, C. Agreement of duplex ultrasonography vs. computed tomography angiography for evaluation of native and in-stent SFA re-stenosis—Findings from a randomized controlled trial. Eur. J. Radiol. 2012, 81, 2265–2269.
16. Meyersohn, N.M.; Walker, T.G.; Oliveira, G.R. Advances in axial imaging of peripheral vascular disease. Curr. Cardiol. Rep. 2015, 17, 87.
17. Patel, S.D.; Zymvragoudakis, V.; Sheehan, L.; Lea, T.; Modarai, B.; Katsanos, K.; Zayed, H. Atherosclerotic Plaque Analysis: A Pilot Study to Assess a Novel Tool to Predict Outcome Following Lower Limb Endovascular Intervention. Eur. J. Vasc. Endovasc. Surg. 2015, 50, 487–493.
18. Kaladji, A.; Vent, P.A.; Danvin, A.; Chaillou, P.; Costargent, A.; Guyomarch, B.; Quillard, T.; Gouëffic, Y. Impact of Vascular Calcifications on Long Femoropopliteal Stenting Outcomes. Ann. Vasc. Surg. 2018, 47, 170–178.
19. He, H.P.; Weng, J.C.; Zhao, Y.; Cai, S.H.; Zhang, X.L.; Yin, H.H. Impact of Plaque Calcification and Stent Oversizing on Clinical Outcomes of Atherosclerotic Femoropopliteal Arterial Occlusive

Disease Following Stent Angioplasty. Eur. J. Vasc. Endovasc. Surg. 2019, 58, 215–222.

20. Chang, Z.; Yan, H.; Zhen, Y.; Zheng, J.; Liu, Z. Lower Limb Arterial Calcification and Acute Thrombosis Risk in Patients with Peripheral Artery Disease. Ann. Vasc. Surg. 2020, 63, 227–233.
21. Megale, A.; Wolosker, N.; Kalil, V.; Nigro, J.; Wakisaka, C.; Dias, B.; Teivelis, M.; Rocha, M.; Mendes, C. Calcium Score Predicts Mortality After Revascularization in Critical Limb Ischemia. J. Endovasc. Ther. 2022, 29, 438–443.
22. Torii, S.; Mustapha, J.A.; Narula, J.; Mori, H.; Saab, F.; Jinnouchi, H.; Yahagi, K.; Sakamoto, A.; Romero, M.E.; Narula, N.; et al. Histopathologic Characterization of Peripheral Arteries in Subjects with Abundant Risk Factors: Correlating Imaging with Pathology. JACC Cardiovasc. Imaging 2019, 12, 1501–1513.
23. He, C.; Yang, J.G.; Li, Y.M.; Rong, J.; Du, F.Z.; Yang, Z.G.; Gu, M. Comparison of lower extremity atherosclerosis in diabetic and non-diabetic patients using multidetector computed tomography. BMC Cardiovasc. Disord. 2014, 14, 125.
24. Mary, A.; Hartemann, A.; Liabeuf, S.; Aubert, C.E.; Kemel, S.; Salem, J.E.; Cluzel, P.; Lenglet, A.; Massy, Z.A.; Lalau, J.D.; et al. Association between metformin use and below-the-knee arterial calcification score in type 2 diabetic patients. Cardiovasc. Diabetol. 2017, 16, 24.
25. Kock, M.C.; Dijkshoorn, M.L.; Pattynama, P.M.; Myriam Hunink, M.G. Multi-detector row computed tomography angiography of peripheral arterial disease. Eur. Radiol. 2007, 17, 3208–3222.
26. Huang, S.Y.; Nelson, R.C.; Miller, M.J.; Kim, C.Y.; Lawson, J.H.; Husarik, D.B.; Boll, D.T. Assessment of vascular contrast and depiction of stenoses in abdominopelvic and lower extremity vasculature: Comparison of dual-energy MDCT with digital subtraction angiography. Acad. Radiol. 2012, 19, 1149–1157.
27. Kuntz, S.H.; Jinnouchi, H.; Kutyna, M.; Torii, S.; Cornelissen, A.; Sakamoto, A.; Sato, Y.; Fuller, D.T.; Schwein, A.; Ohana, M.; et al. Co-Registration of Peripheral Atherosclerotic Plaques Assessed by Conventional CT Angiography, MicroCT and Histology in Patients with Chronic Limb Threatening Ischaemia. Eur. J.Vasc. Endovasc. Surg. 2021, 61, 146–154.
28. Cahalane, R.M.; Broderick, S.P.; Kavanagh, E.G.; Moloney, M.A.; Mongrain, R.; Purtill, H.; Walsh, M.T.; O'Brien, J.M. Comparative analysis of calcification parameters with Agatston Score approximations for ex vivo atherosclerotic lesions. J. Cardiovasc. Comput. Tomogr. 2020, 14, 20–26.
29. Yoon, W.J.; Crisostomo, P.; Halandras, P.; Bechara, C.F.; Aulivola, B. The Use of the Agatston Calcium Score in Predicting Carotid Plaque Vulnerability. Ann. Vasc. Surg. 2019, 54, 22–26.
30. Vancheri, F.; Longo, G.; Vancheri, S.; Danial, J.S.H.; Henein, M.Y. Coronary Artery Microcalcification: Imaging and Clinical Implications. Diagnostics 2019, 9, 125.

31. Nakahara, T.; Dweck, M.R.; Narula, N.; Pisapia, D.; Narula, J.; Strauss, H.W. Coronary Artery Calcification: From Mechanism to Molecular Imaging. JACC Cardiovasc. Imaging 2017, 10, 582–593.
32. Esquivel, A.; Ferrero, A.; Mileto, A.; Baffour, F.; Horst, K.; Rajiah, P.S.; Inoue, A.; Leng, S.; McCollough, C.; Fletcher, J.G. Photon-Counting Detector CT: Key Points Radiologists Should Know. Korean J. Radiol. 2022, 23, 854–865.
33. Willemink, M.J.; Persson, M.; Pourmorteza, A.; Pelc, N.J.; Fleischmann, D. Photon-counting CT: Technical Principles and Clinical Prospects. Radiology 2018, 289, 293–312.
34. Si-Mohamed, S.A.; Boccalini, S.; Lacombe, H.; Diaw, A.; Varasteh, M.; Rodesch, P.A.; Dessouky, R.; Villien, M.; Tatard-Leitman, V.; Bochaton, T.; et al. Coronary CT Angiography with Photon-counting CT: First-In-Human Results. Radiology 2022, 303, 303–313.
35. Dai, L.; Zhou, Q.; Zhou, H.; Zhang, H.; Cheng, P.; Ding, M.; Xu, X.; Zhang, X. Deep learning-based classification of lower extremity arterial stenosis in computed tomography angiography. Eur. J. Radiol. 2021, 136, 109528.