Imaging of atherosclerosis

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Abstract Cardiovascular disease (CVD) is a major health concern worldwide and atherosclerosis is the main cause of CVD. Atherosclerosis is a systemic and chronic inflammatory disease, which is characterized by plaque formation and can affect different vascular beds. Imaging of atherosclerosis could guide therapeutic interventions. Ultrasound, computed tomography, magnetic resonance imaging (MRI), positron emission tomography (PET) and interventional angiography are the main imaging modalities available for the assessment of atherosclerotic burden and for potential prediction of future events. In addition, the introduction of new hybrid imaging techniques like PET/MRI allow for the simultaneous evaluation of anatomical and metabolic characteristics tissues. This article provides an overview of coronary and non-coronary atherosclerosis and summarizes the current understanding of different available imaging techniques. The integration of these techniques in clinical practice may allow for superior risk stratification and therapeutic planning as well as monitoring of interventional and medication based treatment strategies.

Keywords Atherosclerosis · Cardiovascular disease · Ultrasound · CTA · MRA · PET

Cardiovascular disease

Cardiovascular disease (CVD) is a major health concern worldwide. About one in three American adults have one or more types of CVD, with 15.5 million people having coronary heart disease [1]. CVD is globally the leading cause of death, accounting for one in three deaths in the US and claiming the lives of more people than cancer and chronic lower respiratory disease combined [1]. Moreover, life expectancy could be increased by almost 7 years if all forms of major CVD were eliminated [1].

Atherosclerosis

Atherosclerosis is a systemic and chronic inflammatory disease involving not only the vasculature, but also the metabolic and immune systems. It is characterized by plaque formation within the intima of arteries and is the main cause of CVD [2]. These plaques consist of inflammatory cells and fibrofatty deposits. Stable atherosclerotic plaques are slowly increasing and have a dense fibrous cap. The gradual increase in plaque size allows for the devolvement of collaterals. In contrast, unstable atherosclerotic plaques are characterized by macrophage infiltration, necrotic core, lipid pools, spotty calcification and intraplaque haemorrhage [3]. The fibrous cap is usually thin and prone to rupture, thus resulting in release of pro-thrombogenic cells and thrombus formation [3]. The initial manifestation of the atherosclerosis is usually in the form of a severe cardiovascular or cerebrovascular event (e.g. stroke, myocardial infarction, or cardiovascular death) [2, 4]. Therefore, early diagnosis prior to the initial event using non-invasive imaging approaches could be of significant benefit for the individual patient.
Coronary atherosclerosis

Atherosclerosis is the underlying pathology that results in acute coronary syndrome (ACS). Traditionally, the degree of stenosis was thought to be the underlying cause of ischemia, however dissociation has been observed between stenosis degree and the propensity to cause an ACS [5]. Plaque rupture and consequent thrombus formation are now considered the main cause of ACS [4]. Thrombin generation, platelet activation and aggregation are triggered by the production of tissue factor by the macrophages in the plaque [6]. A substrate of coronary thrombosis is superficial erosion of coronary plaques. These lesions occur without the rupture of the fibrous plaque and are more often found in younger patients and females. They tend to have less luminal stenosis and less calcification [7]. Nevertheless, they are responsible for 40% of sudden coronary death [7, 8]. Myocardial ischemia is dependent on the severity and the duration of hypoperfusion. When epicardial coronary flow is limited it triggers the ischemic cascade: perfusion abnormality, regional diastolic and systolic ventricular dysfunction, ischemic ECG changes and finally angina pectoris occurs [9]. This cascade clearly demonstrates that ECG changes and symptoms are occurring at a later time point whereas perfusion abnormalities stand out as the initial pathophysiological alteration. These can be appreciated with different imaging approaches, such as myocardial MR perfusion studies including the assessment of late gadolinium enhancement [10] or regadenoson stress cardiac MR perfusion scans [11] to name a few. In addition, microvascular dilation is essential to match myocardial oxygen demand. The dysregulation of microvascular resistance can contribute to myocardial ischaemia [12].

Non-coronary atherosclerosis

Atherosclerosis is a systemic disease and as such affects not only the coronaries but all vascular beds [13, 14]. Imaging of carotid atherosclerosis is relevant since it is responsible for about 15% of ischemic strokes [15, 16]. The carotids are subject to high blood flow velocities and are more often found in younger patients and females. They tend to have less luminal stenosis and less calcification [7]. Nevertheless, they are responsible for 40% of sudden coronary death [7, 8]. Myocardial ischemia is dependent on the severity and the duration of hypoperfusion. When epicardial coronary flow is limited it triggers the ischemic cascade: perfusion abnormality, regional diastolic and systolic ventricular dysfunction, ischemic ECG changes and finally angina pectoris occurs [9]. This cascade clearly demonstrates that ECG changes and symptoms are occurring at a later time point whereas perfusion abnormalities stand out as the initial pathophysiological alteration. These can be appreciated with different imaging approaches, such as myocardial MR perfusion studies including the assessment of late gadolinium enhancement [10] or regadenoson stress cardiac MR perfusion scans [11] to name a few. In addition, microvascular dilation is essential to match myocardial oxygen demand. The dysregulation of microvascular resistance can contribute to myocardial ischaemia [12].

Imaging of atherosclerosis

Ultrasound

Ultrasound imaging is used to assess the arteries without ionizing radiation exposure and is most commonly used to non-invasively visualize the carotid (Fig. 3), the renal
arteries, the abdominal aorta and the peripheral vessels. Ultrasound allows for the evaluation of atherosclerotic plaques as protrusions of the intima-media, total plaque area/volume and blood flow (by means of duplex ultrasound) [32]. Nevertheless, ultrasound is associated with a trade off between resolution and penetration. The resolution improves with increasing frequency, however the penetration depth decreases. The carotids can be easily evaluated by ultrasound, however carotid media thickness measurements only adds little incremental prognostic information over the traditional risk scores in the general population [33]. A recent development is the assessment of the intraplaque neovascularization and the adventitial vasa vasorum using contrast enhanced ultrasound (CEUS). It has been shown that the presence and degree of both parameters are associated with CVD and cardiovascular events [34]. Further neovascularization as assessed by CEUS is indicative for plaque severity and instability of carotid atherosclerotic lesions [35]. Ultrasound for the peripheral vasculature is especially useful in the assessment of patency of a single segment, however it is inadequate for the assessment of the entire lower extremity arterial tree [36]. For visualization of the coronary arteries invasive intravascular ultrasound (IVUS) is used with a 20–45 MHz frequency [37]. It allows for accurate visualization of the vessel wall and through “virtual histology” can detect four types of tissue (necrotic core, fibrous, fibrofatty, and dense calcium). However, due to a limited axial resolution IVUS can not necessarily accurately measure a thin fibrous cap [38]. Optical coherence tomography (OCT) is the optical equivalent of intravascular ultrasound and has a 10-fold higher spatial resolution, almost to the cellular level, though tissue penetration is less compared to IVUS [39]. OCT imaging of the coronary arteries is based upon polarization characteristics. OCT can also distinguish the different plaque components and is capable of assessing the fibrous cap (Fig. 4c) [39].

**Computed tomography angiography**

Computed tomography angiography (CTA) with an isotropic spatial resolution of less than 1 mm allows for rapid evaluation of the vasculature using iodine contrast media for opacification of the vessel lumen (Fig. 4a). CT is most widely applied for visualization of the coronaries and the aorta, but is also performed for the carotids, renal arteries and peripheral vessels. Coronary CTA has an excellent negative predictive value and coronary plaque burden is
associated with an increased risk of adverse cardiac events [40, 41]. Based on Hounsfield units CT can differentiate three different plaque components (non-calcified, calcified or mixed), which allows for the treatment evaluation [42, 43]. Coronary CTA is capable of identifying four distinct high risk plaque features, namely low CT attenuation, napkin-ring sign, positive remodeling and spotty calcification, all of which are vulnerable to rupture and could result in sudden luminal thrombosis [44]. CTA is superior to MRA for assessment of restenosis in metallic stents [45]. CTA exposes the patient to ionizing radiation, nevertheless the dose is typically less than that of conventional angiography, especially with the use of dose saving protocols and iterative reconstruction [46, 47].

**Magnetic resonance angiography**

Magnetic resonance angiography (MRA) allows for comprehensive assessment of the atherosclerotic burden in arteries from head to ankle without the use of ionizing radiation [48]. In addition, it can identify vulnerable plaques and its content [49]. T1-weighted Gadolinium-enhanced MRA is a robust technique that allows for accurate vessel assessment of arteries and veins with large coverage and high spatial resolution [48]. Time of flight (TOF) MRA and phase contrast (PC) MRA are non-contrast MRA techniques, which is of importance since gadolinium is a potential causative factor in nephrogenic systemic fibrosis [50], particularly in patients with chronic kidney disease. Though the non-contrast enhanced techniques have potential challenges concerning the long acquisition time and robustness of the technique (especially when flow is slow) [51]. Visualization of the vasculature is enhanced by removing the background signal using mask subtraction. Peripheral MRA is considered the technique of choice for visualizing the lower extremities vasculature [52]. MRA is also widely applied for evaluating the carotids, allowing for the depiction of intra plaque hemorrhage, which is associated with prior plaque rupture and future embolic events [53, 54]. MRA of the coronaries (Fig. 5) is still technically challenging and studies are ongoing investigating the use of faster image acquisition techniques like parallel imaging at higher field strengths and the use of novel multichannel cardiac coils [55].

**Positron emission tomography**

The combination of positron emission tomography (PET)/CT (and more recently MR) allows for the evaluation of the inflammatory component of atherosclerotic plaques within the vessel walls (Fig. 6) [56]. Increased FDG uptake has been associated with increased macrophage activity [57]. PET might prove useful in evaluating the effects of treatment for atherosclerosis [58]. Visualization of PET activity in the coronaries is still challenging, due to their small size, constant motion and the use of glucose by the heart [56]. Myocardial FDG uptake can be suppressed by administration of a high-fat, low-carbohydrate diet [59]. PET/MR
has potential for the evaluation of patients with acute ischemic heart disease by delineating the area at risk visualizing the area of decreased FDG uptake [60]. One of the challenges for vascular applications of PET/MRI remains MR attenuation correction [61, 62].

Invasive angiography

Invasive angiography is the reference standard for visualizing atherosclerosis and allows for simultaneous diagnosis and treatment (Fig. 4b). To see the vasculature more clearly digital subtraction angiography (DSA) is applied, which subtracts pre-contrast images (e.g. the mask) from the contrast enhanced images. For evaluating hemodynamically significant coronary artery stenosis fractional flow reserve (FFR) is considered the reference standard, still FRR does not account for dysregulation of the microvasculature or vasoreactivity [12]. FFR is measured during invasive angiography and is calculated as the ratio between the pressure distal to the coronary stenosis divided by the proximal pressure under maximum achievable myocardial blood flow [63]. The other non-invasive techniques have progressively replaced invasive angiography’s role in diagnostic imaging, mainly due to relative high levels of radiation, the invasive nature of the procedure and potential procedure-specific complications [64]. Therefore invasive angiography is mainly used for angioplasty and stenting of relevant stenotic sites in today’s clinic arena.

Personalized medicine

Clinical risk prediction models are insufficient for the assessment of events in individual patients [65]. Non-invasive imaging allows for direct measurement of atherosclerotic burden and as such can be a valuable...
imaging biomarker. Imaging techniques allow for the monitoring of treatment response on the level of the individual atherosclerotic plaque at risk for rupture [43, 58]. This will be of increasing importance with the introduction of targeted therapy into the clinical arena, for example with the arrival of monoclonal antibodies (PCSK9) that may reduce low-density lipoprotein (LDL) and may yield fewer cardiovascular events [66, 67].

**Conclusion**

The fight against CVD continues and with increasing emphasis on available imaging tools nowadays for non-invasive evaluation of atherosclerotic burden the future looks bright. Non-invasive imaging techniques are experiencing a tremendous development and will become more relevant in clinical decision-making, superior risk stratification and therapeutic monitoring.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

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Fig. 6 PET image of a 91-year-old female, demonstrating increased FDG uptake in the aortic (a, b). The PET/CT image also shows moderate calcifications in the aortic wall (b)
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