Review

Novel target-specific imaging techniques for better detection and quantification of vulnerable plaque and plaque progression

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Abstract

Atherosclerosis remains a leading cause of cardiovascular disease.[1] Current imaging techniques including invasive coronary angiography (ICA) and coronary computed tomography angiography (CCTA) are limited in evaluating the morphological changes of atheroma. They only provide visual assessment of luminal stenosis. Flow-limiting stenosis seen from ICA or CCTA often does not translate into causing myocardial infarction (MI). As a result, considering new imaging techniques that can provide information on plaque characterisation and assess the content and degree of stability of these rupture-prone plaques to prevent thrombotic events, is crucial. Thus, novel magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging techniques need to be explored. Imaging target agents bind to specific atherosclerotic biomarkers in vivo, providing non-invasive visualisation and quantification of plaque content with high signal amplification. This review provides an overview of the pathology of atherosclerosis, different plaque biomarkers and its target agents, as well as potential clinical applications.

Abbreviations

ACS - acute coronary syndrome
CAD - coronary artery disease
CCTA - coronary computed tomography angiography
ICA - invasive coronary angiography
LDL - low-density lipoproteins
MI - myocardial infarction
MRI - magnetic resonance imaging
PET - positron emission tomography
SMC - smooth muscle cells

Introduction

Atherosclerosis remains a leading cause of cardiovascular disease and results in 50% of all deaths in Western society.[1,2] Even with generally good health, people aged 40 and above have about a 50% increased likelihood of developing severe atherosclerosis, with this risk increasing with age.[3] Untreated atherosclerosis could lead to major complications such as ischaemic heart disease, coronary artery disease (CAD) and ischaemic stroke.[2] Plaque burden measures the percentage plaque area over the external elastic membrane of the arterial wall.[4,5] As a result, assessing plaque burden, its progression and evaluation of response to treatment are of growing importance.[4,5] The gold standard for diagnosing CAD is currently using invasive coronary angiography (ICA).[6] ICA involves intracoronary injection of radio-opaque dye to opacify the lumen and outline any occlusion with X-ray imaging. However, the invasive nature of this technique makes screening or further investigations a huge challenge in large patient populations.[3]

Recent developments in coronary computed tomography angiography (CCTA) have allowed for rapid, non-invasive and accurate imaging in patients with suspected coronary heart disease without severe disease such as patients presenting with atypical symptoms or moderate risk of disease. Results are detailed enough for doctors to make decisions that are 95-99% accurate in patients.[7] However, diagnostic accuracy is reduced in vessels with significantly high microcalcification due to poorer spatial resolution compared to ICA, thus limiting application of CCTA in this important patient group.[8] Moreover, prolonged exposure to ionising radiation can lead to malignancy.[9]

More importantly, visual assessment of luminal stenosis using ICA and CCTA correlates poorly with haemodynamic significance.[6] Significant CAD is defined by more than 70% stenosis in a major coronary vessel as diagnosed by ICA or CCTA.[10] The majority of plaques causing MI do not cause flow-limiting stenosis on ICA and up to 1/3 of ruptured plaques demonstrate less than 75% stenosis. Current imaging techniques, ICA and CCTA, focus on the lumen instead of the vessel wall providing only indirect detection of atherosclerosis. They fail to consider degree of plaque stability or other plaque characteristics associated with risk of rupture.[11] Hence, patients with

more vulnerable plaque and therefore at higher risk of stenosis, fail to be identified for treatment. Since these plaques are easily missed on angiography, insights into better imaging techniques that might enhance prediction of MI are surfacing. As a result, there is a need for more novel imaging modalities to target detection of atherosclerosis. This essay will explore current state-of-the-art molecular imaging approaches for the detection of atherosclerosis and discuss the need for these imaging techniques.

Pathology of atherosclerosis

Atherosclerosis can be characterised as a chronic inflammatory disease due to hardening or thickening of arteries due to plaque accumulation in the intima of an artery.[12] Hyperlipidaemia, hyperglycaemia, hypertension, tobacco smoke, obesity and sedentary lifestyle are important risk factors of the disease.[13] Excessive accumulation of low-density lipoproteins (LDL) due to these risk factors result in LDL oxidation. The oxidised LDLs are phagocytosed by macrophages known as foam cells.[14] Oxidative stress coupled with risk factors leads to endothelial dysfunction thereby resulting in endothelial permeability, cytokine expression, leukocyte adhesion and platelet aggregation.[15,16] Foam cells adhere and migrate into arterial intima through endothelial dysfunction and accumulate within the intima forming yellow fatty streaks.[13] Inflammation may promote the growth of plaques and trigger plaque rupture and thrombosis.[17]

Atheroma formation occurs when altered smooth muscle cells (SMC) and myofibroblasts, migrate from media to intima and synthesise collagen. The fibrous cap composes of collagen fibres, SMC, macrophages and T cells. As LDLs continue to accumulate under the fibrous cap within the arterial wall, a lipid-core is formed. These foam cells undergo apoptosis or necroptosis and increased oxidative stress, resulting in the formation of a necrotic core within the plaque.[18] As the plaque grows due to the proliferation of fibrous tissue, the bulge within the artery increases, reducing blood and oxygen supply to cardiac muscle.[13] Stenosis of coronary artery causes ischaemia of cardiac muscle and results in death of cardiac tissue, responsible for perfusion of the body, leading to MI.

There are two types of plaques (**Figure 1**): stable versus vulnerable. The major difference between these are that stable plaque is characterised by thick fibrous cap with poor-lipid core while vulnerable plaque has a rich-lipid core with thin fibrous cap prone to rupture causing thrombosis.[19] If rupture occurs in a coronary artery, downstream ischaemia and MI results. Other changes in vulnerable plaques include remodelling, microcalcification and angiogenesis.[10]

The composition of a vulnerable plaque (**Figure 1**) is characterised by low elastin and collagen, and high tropoelastin, albumin, intraplaque fibrin and microcalcification content.

Elastin is produced primarily by SMC. It is formed by polymerisation of tropoelastin monomers. However, there is increased expression of this extracellular matrix protein in the media during plaque development, making elastin a potential biomarker for atherosclerosis. Pathological stimuli are responsible for triggering elastogenesis and recruitment of proinflammatory cells in atherosclerosis, leading to a remarkable rise in elastin content during plaque progression. However, more recent studies show that ineffective elastogenesis and elastolysis favour the accumulation of tropoelastin rather than cross-linked elastin in atherosclerotic plaques. This reduces elasticity of the vessel, increasing risk of stenosis.[21]

During atherosclerosis, endothelial permeability is increased due to the damaged endothelial glycocalyx which albumin, the most abundant plasma protein in plaques, is bound within. During plaque development, there is increased albumin infiltration into the intima and deposition in the adventitia.[22]

Fibrin is a major constituent of thrombi formed following plaque rupture. Fibrin molecules bind to form long fibrin threads that trap platelets which hardens to form a blood clot.[23] Fibrin accumulation can also take place within the atherosclerotic lesions, contributing to their growth.[24] The necrotic core of advanced plaques can also accumulate fibrin.[25] Hence, fibrin is an important coagulant that is present throughout plaque development.

Microcalcification represents an active stage of intimal calcification associated with inflammation and contributes to mechanical instability of plaques.[26,27] Vascular SMCs have the potential to undergo osteoblastic differentiation and generate calcified deposits. Plaque rupture seems to correlate positively with the amount of microcalcifications and negatively with macrocalcifications.[26]

Imaging of atherosclerosis and its biomarkers

MRI

Molecular MRI is especially suited for imaging and detection of atherosclerosis as it can evaluate relatively thin arterial vessel walls. MRI takes advantage of the high prevalence of hydrogen in the body to produce images. After being excited by radiofrequency pulses from the MRI scanner, the time taken (T) for the hydrogen proton to recover back to equilibrium and subsequently the rate of relaxivity (R) is measured by the scanner. As different tissues differ in their amount of H atoms, tissues containing higher fat content recover faster. Gadolinium(Gd)-based contrast agent binds to tissue and decreases T1 relaxation, enhancing the signal and creating a brighter image.[4]

Molecular MRI is a non-invasive technique that allows for the visualisation of biological markers in vivo.[4] MRI provides excellent soft-tissue contrast and is able to achieve higher spatial resolution, compared to other modalities.[4] MRI also provides direct visualisation of thrombi, allowing for more rapid and reliable diagnosis and, ultimately, significantly improving the clinical outcome of thrombotic disease.[28] In the next part of this review, four of such biomarkers of atherosclerosis and their imaging techniques are expanded upon.

Elastin and tropoelastin

Makowski et al demonstrated the successful use of Gd-labelled elastin-specific MR contrast agent (Gd-ESMA) for the quantification of plaque burden using a mouse model (**Figure 2**). The high spatial resolution achieved through the amplified signal provided by Gd-ESMA allows for accurate evaluation of plaque burden, characterisation, progression and regression.[4] More currently, Phinikaridou et al used Gd-labelled tropoelastin-specific MR contrast agent (Gd-TESMA) for tropoelastin imaging of atherosclerosis in animals (**Figures 3 and 4**). The probe was able to distinguish between cross-linked elastin and tropoelastin. It provided favourable pharmacokinetics, increased R1 relaxation rate with disease progression. It also shows the effectiveness of treatment from disease regression as well as differentiate between stable and vulnerable plaques with a high level of specificity and sensitivity.[12]

Albumin

Phinikaridou et al also demonstrated gadofosveset as an albumin-binding MRI contrast agent. It is taken up through damaged endothelium and used as a surrogate marker to quantify vascular permeability and identify rupture-prone atherosclerotic plaque and its progression through a rabbit model (n=10). MRI is able to quantify both morphological and functional changes of the arterial wall which not only may be used to detect plaque progression but also unstable atherosclerotic plaques.[29]

Comparison between MR imaging of stable and rupture prone plaques at 3 and 12 weeks of high fat diet shows increased endothelial permeability in rupture prone plaque and increased vessel thickening caused by plaque formation from 3 to 12 weeks in both plaques. Corresponding R1 relaxation maps depicts higher R1 in rupture-prone compared to stable plaque at 12 week (R1; 2.30±0.5 versus 1.86±0.3 s^{-1}; $P<0.001$), suggesting higher endothelial permeability to gadofosveset.[29]

PET

PET scan uses an injected radioactive tracer for non-invasive, sensitive and relatively rapid imaging. However, due to its low spatial resolution and lack of anatomical information, it is compensated by hybrid imaging with MRI or CT.[30]

Microcalcification

PET/CT molecular imaging uses ^{18}Fluorine-Sodium Fluoride (^{18}F-NaF) radioactive contrast agent (**Figure 5**) to potentially detect clinically significant high-risk nascent microcalcification and active unstable atherosclerosis.[27,31] ^{18}F-NaF has a likely capacity to detect high-risk plaques indicating its possible role in identifying vulnerable plaques and in predicting MI. The basis for ^{18}F-NaF uptake in atherosclerosis is assumed to be analogous to its accumulation in areas of bone remodelling. Since macrocalcifications have a relatively small surface-to-volume ratio, the radioactivity signal detected is proportionally smaller than microcalcifications, with a larger surface-to-volume ratio, allowing for distinction and detection of mainly microcalcifications.[31]

Macrophages

^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) is another PET tracer detected by PET/CT (**Figure 6**) that is taken up by macrophages and has shown to be a robust surrogate of plaque activity and composition. In many preclinical and clinical studies, regions of high macrophage density are associated with increased FDG uptake in plaques.[32] During atherogenesis, the necrotic core formed within the atheroma due to hypoxia causes an increase in demand for glucose uptake. As ^{18}F-FDG is a glucose analogue, it will preferentially accumulate in macrophages. Thus, as ^{18}F-FDG uptake increases, its accumulation is readily detected and quantifiable. It can be used as a sensitive measure of metabolic activity, especially in vulnerable plaque with high concentration of proinflammatory macrophages which result in high metabolic activity. It is evidenced that higher FDG uptake in plaque is associated with higher risk of recurrent cerebrovascular event. Through FDG-PET imaging, the systemic nature of atherosclerosis has also been explored. FDG uptake is closely associated with the neighbouring tissues supplied by the artery, suggesting a systemic increase in expression of inflammation rather than a localised phenomenon.[11]

Discussion

Possible clinical application

Atherosclerosis remains a predominant trigger of many cardiovascular diseases such as CAD and acute coronary syndrome (ACS). Hence, MRI imaging of atherosclerosis is key to not only aid in detection and monitoring, but also quantify the change in plaque burden through morphology and anatomical structures over time. This is especially helpful in assessing disease progression and the usefulness of therapeutics. MRI imaging of specific biomarkers shows a significantly higher enhancement of signal intensity compared to other modalities. MRI imaging also provides better contrast-to-noise ratio (CNR) allowing for clearer and more accurate imaging. The prompt clearance of contrast agent from blood pool also prevents toxicity build-up. MRI imaging can also be used to identify inflammatory burden within plaque. Moreover, MRI imaging is non-invasive and does not require radiation exposure, which in the long term may cause cellular damage and malignancy.

Furthermore, several target specific contrast agents have been approved for clinical use (e.g. gadofosveset) and new agents (e.g. ESMA, TESMA) show promising results in several animal studies with hopes for future clinical usage.[25] In some cases, patients with CAD may present with symptoms of chest pain without diagnostic ECG changes. Therefore, early detection of fibrin-rich thrombus may prove to be useful in both diagnosis and early treatment. Monitoring of thrombolysis is another potential application.[33]

Limitations

An obstacle for clinical application of target specific MR contrast agents is the low sensitivity of MRI (microM) in comparison to PET (nM). Consequently, for decent signal detection, relatively high local concentration (~50microM) is required. Thus, for small molecular weight MR contrast agents, imaging is limited to high abundance biological target agents. A nanoparticle has been developed to reduce the injected dose to around 0.1 mmol/kg or lower due to its increased relaxivity upon binding. Moreover, more recent MR contrast agents prefer to use DOTA in lieu of DTPA chelates due to its markedly better stability to reduce safety concerns regarding toxicity.[25] The use of hybrid modalities such as PET/MR are being explored to overcome this. PET, though unable to provide anatomical information or high spatial resolution, has a higher sensitivity than MRI, hence lowering the injection dosage. However, low specificity of the PET tracer and high cost serve as major limitations and the use of cardiovascular PET/MRI is still in its budding stages of development.[34]

Moreover, many of these studies use animals and have small sample sizes. This may not truly reflect the human atherosclerosis pathology. Although there are some ex vivo human studies, this may not be representative of human atherosclerotic pathology. Therefore, more in vivo animal and human studies in larger sample sizes need to be undertaken to establish the translational potential of MRI imaging.[21]

Extensive preclinical evaluation is another potential hurdle in the shift of MRI of atherosclerosis from a preclinical to clinical level. Thorough assessment of drug safety through toxicity studies are required. Convincing production partners to manufacture, upscaling production and commercialising the contrast agents for clinical use also presents as an arduous process.

Vulnerable plaque versus vulnerable patient

Only a small proportion of these identified rupture-prone plaques result in clinically adverse events. As a result, all rupture-prone plaques with high risk of thrombotic complication and rapid progression should be considered as vulnerable plaques. Therefore, to support a more personalised medical approach, it may be more appropriate to use the term "vulnerable patient" in the assessment and identification of patients at high likelihood of developing adverse clinical events in the near future. One such assessment is CT calcium scoring. It can be used as a surrogate of the total coronary atherosclerotic plaque burden and enhance risk prediction in vulnerable patients. Despite recent technological enhancements, personalised risk prediction remains limited in identification and prevention of adverse clinical events.[10]

Conclusion

MRI imaging of specific biomarkers offers a potentially powerful strategy in personalised preventive and diagnostic medicine for atherosclerosis. Future developments in MR technique such as combining several biomarkers for better detection could be explored. Theranostic approaches, which provide diagnosis and treatment simultaneously, can also be looked into to provide more efficient and tailored therapy.

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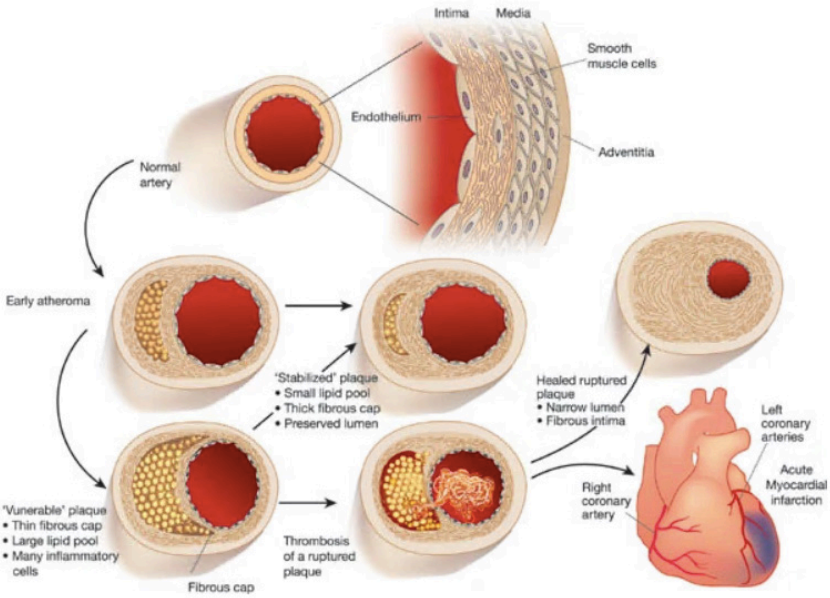


Figure 1. Illustration of plaque progression and rupture in a coronary artery: it also shows how the ruptured plaque could heal and result in subclinical events or proceed to lead to a myocardial infarction of the heart. Reprinted from Libby (2002),[20] by Nature.

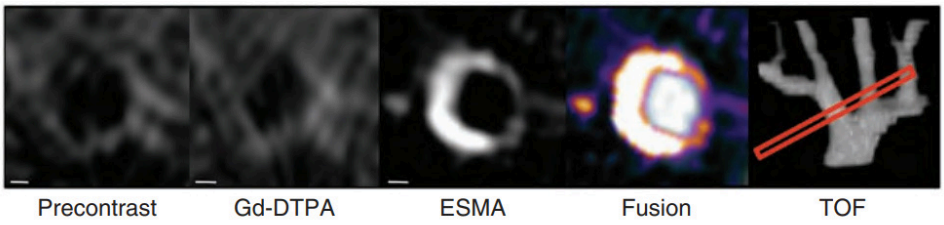


Figure 2. Cross sectional imaging of the brachiocephalic artery (BCA) in a male Apoe-/- mouse after consuming a high fat diet for 12 weeks: The time-of-flight (TOF) angiogram of the BCA visualises path and flow within the vessel. Fusion of high-resolution DE-MRI and TOF provides spatial information of luminal anatomy and contrast uptake. Reprinted from Makowski et al (2011)[4], by Nature Medicine.

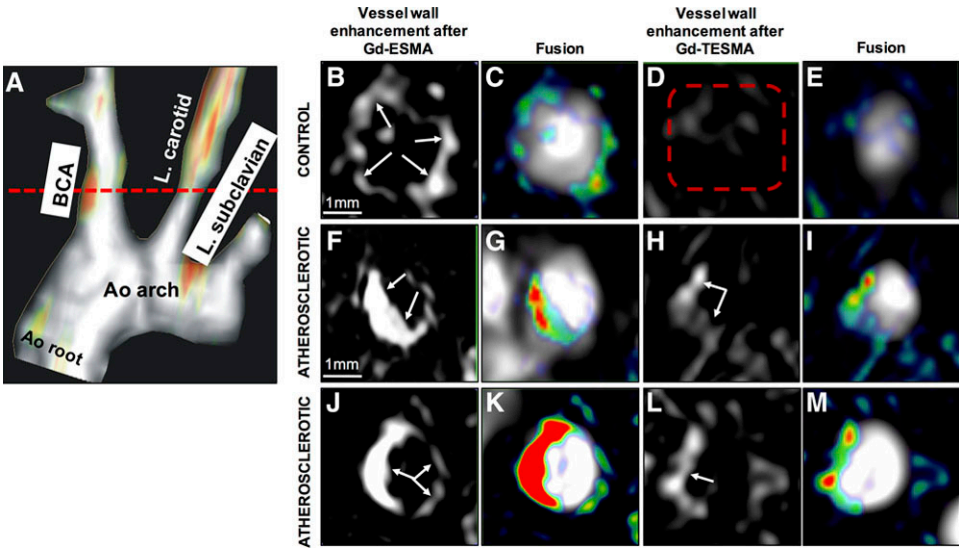
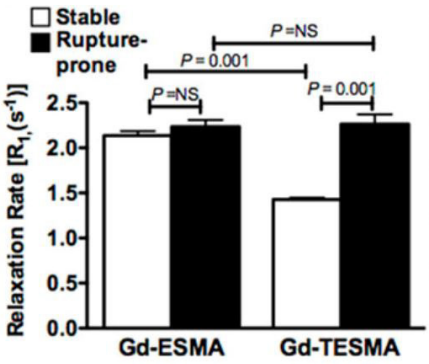


Figure 3. In vivo MR comparison of BCA vessel wall enhancement using Gd-ESMA and Gd-TESMA in ApoE-/- mice: there is a lack of uptake of Gd-TESMA in control **(D, E)** compared to Gd-ESMA **(B, C)** suggesting that there is an absence of tropoelastin accumulation in normal mice. **(F-M)** MRI images of 2 diseased mice show signal amplification with both Gd-TESMA and Gd-ESMA due to the presence of tropoelastin and cross-linked elastin respectively. Reprinted from Phinikaridou et al (2018)[21], by Circulation: Cardiovascular Imaging.



	$R_{1\ Gd\text{-}ESMA} \geq 2.2\ s^{-1}$ and % (CI)	$R_{1\ Gd\text{-}TESMA} \geq 1.65\ s^{-1}$ and % (CI)
Sensitivity	67.8 (48.6-83.3)	84.4 (67.2-97.7)
Specificity	66.7 (53.3-78.3)	92.3 (82.9-97.5)
PPV	51.2 (40.5-61.8)	84.4 (69.7-92.7)
NPV	80.0 (69.9-87.3)	92.3 (84.2-96.4)

Figure 4. Quantification of brachiocephalic vessel wall: Markedly higher R1 in vulnerable plaque compared to stable plaque on after administration of Gd-TESMA. Reprinted from Phinikaridou et al (2018)[21], by Circulation: Cardiovascular Imaging.

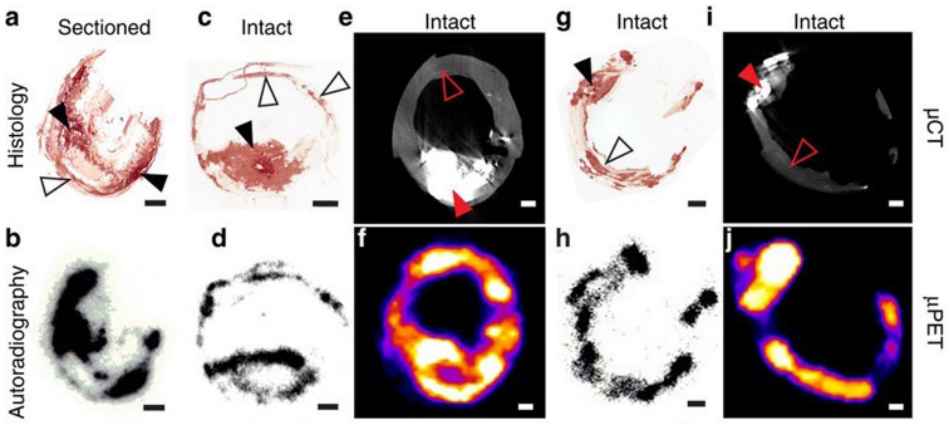


Figure 5. Pet/CT scans of micro- and macrocalcification compared to histology and autoradiology: (a,b) When the carotid artery is sectioned before incubating in ^{18}F-NaF, ^{18}F-NaF binds to both microcalcification (white arrowheads) and macrocalcification (black arrowheads) surfaces. **(c,d)** However, when the order is reversed such that the carotid is incubated fist and then sectioned, ^{18}F-NaF binds to all microcalcifications (white arrowheads) but only surface level of macrocalcifications (black arrowheads). **(e,f)** ^{18}F-NaF binds only to the surface level of macrocalcifications in a μPET/μCT. **(g,i)** A μCT scan on its own is unable to detect microcalcifications as seen in Alizarin Red histology due to low sensitivity. **(h,j)** However, ^{18}F-NaF μPET scan is able to match autoradiography signal and detect microcalcifications. Reprinted from Irkle et al (2015)[31], Nature Communications.

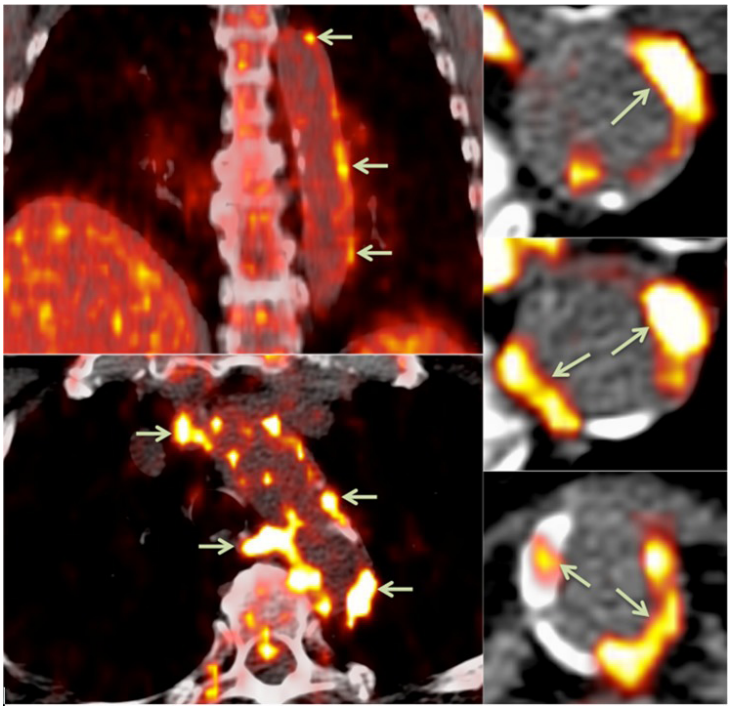


Figure 6. FDG-PET/CT indicating regions with focal radiotracer uptake in the descending aorta vessel wall (arrows). Reprinted from Evan, Tarkin, Chowdhury, Rudd (2016)[11], Current Atherosclerosis Reports.