Use of Nanoparticles As Contrast Agents for the Functional and Molecular Imaging of Abdominal Aortic Aneurysm

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Abdominal aortic aneurysm (AAA) is a degenerative disease of the aorta common in adults older than 65 years of age. AAA is usually imaged using ultrasound or computed tomography. Molecular imaging technologies employing nanoparticles (NPs) have been proposed as novel ways to quantify pathological processes, such as inflammation, within AAAs as a means to identify the risk of rapid progression or rupture. This article reviews the current evidence supporting the role of NP-based imaging in the management of AAA. Currently, ultrasmall superparamagnetic NPs enhanced magnetic resonance imaging appears to hold the greatest potential for imaging macrophage-mediated inflammation in human AAA.

Keywords: abdominal aortic aneurysm, nanoparticles, diagnosis, human studies, animal studies

INTRODUCTION

Abdominal aortic aneurysm (AAA) is a degenerative disease of the aorta common in older adults (1–4). AAA is usually defined as a macroscopic permanent pathological dilatation of the infrarenal aortic diameter ≥30 mm (4–7). Most AAAs are asymptomatic until rupture, which is often fatal (1, 3, 4, 8). Patients with small AAAs usually undergo regular imaging to monitor AAA diameter until it exceeds 55 mm (4). At this point, patients are usually recommended to have open surgical or endovascular stent graft repair according to current guidelines (2, 8, 9). AAA management is primarily focused on averting rupture (8, 9). Rupture of small AAAs is uncommon (2, 10). It has been reported that approximately 1% of AAAs measuring <55 mm rupture each year while undergoing careful follow-up during which large, symptomatic, or progressively expanding AAAs are selected for surgical repair (11–13). For example, the UK small aneurysm trial reported that the rupture rate for asymptomatic AAAs measuring <55 mm was 1% per annum, and the risk of rupture was higher in women (12). The future management of AAA could be optimized through an enhanced ability to identify small AAAs at risk of rupture and identification of small AAAs that would benefit from early surgical intervention (3, 14). One potential way of doing this could be through functional or molecular imaging in which key pathological processes implicated in AAA rupture were quantified in individual patients.
Recent research has explored the efficacy of nanoparticle (NP)-enhanced molecular imaging technologies in identifying key pathological processes within AAAs (15, 16). NPs are constructs of sizes ranging from 1 to 100 nm in at least one dimension and are 100 to 10,000 times smaller than human cells (17–19). They are bioactive and can interact with biological molecules both intra and extracellularly (20). Generally, they are characterized by a long blood half-life and can evade elimination by the reticuloendothelial system (17, 21); hence, they are relatively stable in biological systems. NPs can be successfully delivered using optimized nanocarriers such as dendrimers, quantum dots, liposomes, albumin, gold, and iron oxide to target diseased or normal tissues as therapeutic or diagnostic agents (Figure 1) (19, 21, 22). Their unique properties include a high penetration power (23), ability to be modified with any molecule of choice (24–26), biocompatible size distribution (27), and image contrasting ability (28). The use of NPs in medicine (nanomedicine) is being investigated in a range of diseases, particularly cancers (17) and cardiovascular disease (29–31). Nanotube-antibody microarrays, for example, have been used to detect metastatic breast cancer cells in the circulation (32). NPs have been employed in imaging AAA (33, 34) and to enhance magnetic resonance imaging (MRI) detection of endoleaks following endovascular aneurysm repair (29). NP-based biofilms have been utilized to detect infection (35).

Magnetic NPs and quantum dots are being investigated as treatments to modify stem cell proliferation and differentiation in regenerative medicine (36, 37). For example, mice with spinal cord injury injected with nanofiber conjugated with laminin were reported to show improved neurological function (36). Polylactic-co-glycolic acid NPs conjugated to tissue plasminogen activator have been reported to gradually lyse fibrin-rich clots (38). This has been suggested as a potential strategy for removing intraluminal thrombus (ILT) to allow endovascular delivery of therapeutic agents to the wall of AAAs, although this has not been specifically investigated. Intra-arterial NP-based thrombolytic therapy combined with temporary endovascular bypass has also been reported to be more effective than temporary endovascular bypass alone in a rabbit model of carotid artery occlusion (39). This may potentially be important in the management of patients with arterial occlusion. For other potential applications of NPs in medicine, please refer to the articles by Wang and Wang (40) and Zhang et al. (41). A number of animal and human investigations have studied various NPs as nanocarriers or in combination with standard contrast agents in imaging AAA (33, 34, 42–45).

In this article, we discuss the findings of these studies and highlight the potential challenges in utilizing these novel molecules as contrast agents in the functional and molecular imaging of AAA.

**LITERATURE SEARCH**

A literature search was conducted to identify studies employing NPs for molecular imaging of AAA using the MEDLINE (1966),
Proposed stages in abdominal aortic aneurysm (AAA) pathogenesis and steps where nanoparticles (NPs) have been used to enhance imaging the disease process. This shows proposed stages in AAA pathogenesis from initiation to rupture. A combination of genetic and environmental factors and tissue injury may lead to recruitment of inflammatory cells, macrophages (M), and neutrophils (N) leading to vascular smooth muscle cell (VSMC) apoptosis and extracellular matrix (ECM) degradation. This leads to aortic wall weakening and subsequent aneurysm progression. The aorta tries to repair itself but is overwhelmed by continual inflammation and ECM degradation. Eventually, failure of this compensatory mechanism leads to aortic rupture and death. NPs target inflammatory cells and components of the ECM at steps 1, 2, and 3 to aid in the imaging of functional components implicated in AAA pathology.
is evidenced by previous research from our group and others demonstrating marked infiltration of macrophages, lymphocytes, and neutrophils in aneurysmal tissue (1, 46). Iron oxide NPs have been reported to have a high affinity for macrophages (48–50). Hence, these NPs, specifically the subset with diameters <50 nm known as ultrasmall superparamagnetic iron oxide nanoparticles (USPIOs), have been used as agents to aid imaging of AAAs in both animal models and patients (30–35). USPIOs such as ferumoxytrol are composed of an iron oxide core enclosed by a hydrophilic coating that readily accrues in neutrophils and macrophages (51). They have been employed as MRI contrasts agents for assessing tissues with active inflammation such as AAA. NPs have been employed as agents to target inflammation (macrophages, neutrophils), VSMC apoptosis, and ECM degradation (P-selectin) in AAA.

STUDIES ASSESSING NPs IN AAA IMAGING

Several molecular imaging approaches have been investigated for AAA, but their ability to clearly differentiate between AAAs at risk of rupture and predict AAAs that will benefit from a surgical intervention is still unclear (3, 14, 15, 59). Both animal and human studies have suggested that NPs, particularly those with an iron oxide component, can be taken up by AAAs and identified on imaging (30–35). We highlight some of these studies in the following sections.

Animal Studies

A number of studies have assessed the use of NPs to enhance imaging of AAA within animal models (Table 1) (58, 60, 61). ILT is common within AAAs, and a large volume of thrombus has been associated with more rapid AAA progression (62). Suzuki and colleagues reported that the detection of ILT within a rat model using MRI was enhanced by infusion of USPIOs coated with fucoidan (USPIO-FUCO) as a marker for the detection of macrophages in AAAs (58). Turner and colleagues evaluated the use of the USPIO (ferumoxtran) as a marker for the detection of macrophages in the angiotensin II (ang II)-infused apolipoprotein E deficient (Apoe−/−) AAA mouse model (45). They reported marked accumulation of USPIO-labeled macrophages within the aneurysmal aorta that could be identified by MRI and was confirmed by immunohistochemistry (45). Similarly, Yao et al. reported that superparamagnetic iron oxide (SPIO) enhanced MRI visualization of AAA in an angiotensin II-infused ApoE−/− model of AAA (42). They proposed that SPIO diffuses across the interendothelial junction of the vasa vasorum into the interstitium where they are engulfed by macrophages. These macrophages then migrate into the tunica media and tunica adventitia within the aneurysmal aorta. The authors suggested that SPIO-enhanced imaging may be useful for quantifying the risk of AAA rupture (42). This assertion by the authors is mitigated by the fact that the presence of endogenous iron within ILT may reduce the specificity of SPIO-enhanced imaging for localizing inflammation. ILT is reported to be rich in inflammatory cells (55, 63). In a mouse model in which AAAs were induced by ang II infusion and injection of transforming growth factor-β neutralizing antibody, Klink and colleagues reported that administration of paramagnetic/fluorescent micellar NPs functionalized with a collagen-binding protein (CNA-35) markedly increased high-resolution multisequence MRI visualization of aortic remodeling (31). AAA severity (Stages I–IV) was based on the classification by Alan Daugherty’s group (64). They imaged mice in which AAAs had been induced 5 and 15 days after CNA-35 NP injections and

| TABLE 1 | Examples of animal studies assessing the use of nanoparticles (NPs) in AAA imaging. |
|---|---|---|---|---|---|---|
| AAA model | AAA process | Target | NP | Imaging mode | Findings |
| Elastase-induced rat model | Inflammation | Platelets expressing P-selectin | USPIO-FUCO | MRI | USPIO-FUCO-enhanced MRI detection of ILT (61) |
| Ang II-infused Apo E−/− mice | Inflammation | Macrophages | USPIO | MRI | Reduced signal intensity in the post-USPIO transverse images of AAA (45) |
| Ang II-infused Apo E−/− mice | Inflammation | Macrophages | SPIO | MRI | Ang II infusion increased SPIO uptake. AAA wall contained significantly more iron-positive macrophages (42) |
| Ang II-infused and TGF-β neutralized C57BL/6 mice | ECM remodeling | Collagen | CNA-35 micelles | MRI | Increased MRI signal enhancement in AAA wall (31) |
| Ang II-infused Apo E−/− mice | Inflammation | Macrophages | RGD-HFn | NIR and MRI | RGD-HFn-enhanced NIR (65), and MRI (30) imaging of AAA |
| Ang II-infused Apo E−/− mice | Angiogenesis | Endothelial cells | 18F-CLIO | PET-CT | Improved PET-CT imaging of AAA (66) |

18F-CLIO, dextran-coated cross-linked iron oxide nanoparticles labeled with fluorine-18; AAA, abdominal aortic aneurysm; Ang II, angiotensin II; ApoE−/−, apolipoprotein E deficient; C57BL/6, C57 black 6; CNA-35, paramagnetic/fluorescent micellar nanoparticles functionalized with a collagen-binding protein; ECM, extracellular matrix; ILT, intraluminal thrombus; MRI, magnetic resonance imaging; NIR, near-infrared fluorescence imaging; PET-CT, positron emission tomography-computed tomography; RGD-HFn, Arg-Gly–Asp-conjugated human ferritin nanoparticle; SPIO, superparamagnetic iron oxide nanoparticles; TGFβ, transforming growth factor-β; USPIO, ultrasmall superparamagnetic iron oxide nanoparticles; USPIO-FUCO, USPIOs coated with fucoidan.
correlated the images to disease pathology (Figure 3). Marked CNA-35 NP uptake correlated with high collagen uptake (Stage II AAA) and hence less ECM degradation, while rupture Stage IV AAAs had negligible CNA-35 NP and low collagen uptake. These data suggested that CNA-35 micelles were able to identify some AAA pathological changes, but how this relates to rupture risk in patients is unknown (31).

Two further studies assessed Arg–Gly–Asp (RGD)-conjugated human ferritin nanoparticles (HFn) enhanced near-infrared fluorescence imaging (65) and MRI imaging (30) of AAAs in the ang II-infused Apo E−/− mouse model. In a proof-of-concept analysis, RGD-HFn was shown to co-localize with infiltrating macrophages and angiogenesis as assessed by immunohistochemistry (30, 65). Mural macrophage infiltration and angiogenesis were assessed by CD-11b and CD-31 immunohistochemistry (Figure 4). In addition, RGD− AAAs exhibited higher iron staining in the media and adventitia compared to the RGD+ ones, and this was correlated with the percentage signal intensity loss (30). Nahrendorf et al. employed dextran-coated cross-linked iron oxide nanoparticles (CLIO) labeled with fluorine-18 (18F) to image AAAs within the same mouse model (66). They reported that 18F-CLIO had a high affinity for inflammatory macrophages and enhanced AAA imaging by positron emission tomography-computed tomography (PET-CT). They reported that PET signal intensity was a good predictor of AAA growth. AAAs with marked uptake of F-CLIO had significant later expansion. They also reported a weak correlation between the AAA diameter measured by CT and the macrophage PET signal. Importantly, their study suggested that 18F-CLIO uptake by macrophages was a useful marker of subsequent AAA progression.

Together, these studies suggest that contrast agents employing NPs to target inflammation and thrombosis have potential to visualize pathological processes in AAAs. However, whether these imaging agents can advance current methods of identifying high risk AAAs remains to be established (67).

Human-Associated Studies

A number of clinical studies have assessed the potential of NPs for enhancing imaging of AAAs (Table 2). Truijers and colleagues conducted a clinical study investigating the uptake of macrophage-specific USPIO in 11 patients with an aneurysm (aortic, n = 6, and iliac, n = 5) and 11 age-matched non-aneurysmal controls (44). They reported that USPIO-enhanced MRI identified large number of USPIO-positive quadrants within the walls of two AAAs but limited or no USPIO uptake in the other aneurysmal patients and the controls. They hypothesized that the observed variation in USPIO uptake may be due to selective uptake of the NPs within AAAs with a propensity for growth or rupture (44). Sadat et al. reported the USPIO-enhanced MRI of the inflamed aortic wall of 13 patients with AAA. They also reported that quantitative $T_2^*$ (transverse relaxation time constant) and T2 values (decay of transverse magnetization) provided a reliable quantitative method for assessing USPIO uptake within AAAs (32). These findings provide some evidence that USPIO-enhanced MRI may visualize severe inflammation within AAAs, although no histological confirmation of uptake was available (43). SPIO-enhanced MRI has also been reported to enable successful visualization of AAA ILT morphology and localization of phagocytic leukocytes in a study of 15 patients (68). The authors reported a significant decrease in the MRI contrast-to-noise ratios in both the ILT and the deeper thrombus following SPIO administration, which was positively correlated with the levels of MMP-2, MMP-9, and CD68+ macrophages (68).

In a pilot study involving 27 male patients with AAAs (AAA diameter >4 cm) recruited from a surveillance program, it was reported that USPIO-enhanced MRI identified AAAs that subsequently rapidly expanded (33). The authors reported that patients with significant mural uptake of USPIO had a threefold higher AAA growth rate (measured over 6 months) compared to those with no or non-specific USPIO uptake (33). They also reported that USPIO co-localized with CD68+ inflammatory macrophages in the aneurysmal wall of patients who had open AAA repair, which was verified by immunohistochemistry (33). In a more recent study from the same group, the authors
FIGURE 4 | Histological analysis of abdominal aortic aneurysms and correlation with $T_2^*$ signal loss on MRI. (A) Immunohistochemical AAA staining showed mural macrophage infiltration and angiogenesis within the AAA wall. Perl’s iron staining showed greater accumulation of RGD-HFn-Fe$_3$O$_4$ in the media and adventitia of AAA wall (AAA RGD$^+$) compared to HFn-Fe$_3$O$_4$ (AAA RGD$^-$), co-localizing with both macrophages (asterisks) and areas of angiogenesis (dagger). The control aortic wall showed minimal Perl’s iron staining in both RGD$^+$ and RGD$^-$ groups. (B) There was a close correlation between the total number of Perl’s iron-stained cells and % signal intensity loss in the AAA ($n=10$, $r=0.83$, $P=0.003$). Reprinted from Kitagawa et al. (30), under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC). Abbreviations: AAA, abdominal aortic aneurysm; MRI, magnetic resonance imaging; RGD-HFn, Arg–Gly–Asp-conjugated human ferritin nanoparticle; $r$, Pearson’s correlation coefficient; $T_2^*$, transverse relaxation time constant.

compared $^{18}$F-Fludeoxyglucose ($^{18}$F-FDG) combined PET-CT ($^{18}$F-FDG PET-CT) and USPIO-enhanced MRI for assessing aortic tissue inflammation in 15 patients with asymptomatic AAA [mean AAA diameter 4.6 cm (Figure 5)] (34). Both areas of increased USPIO uptake with and without co-localization with $^{18}$F-FDG were identified in the same quadrant within the
TABLE 2 | Examples of human studies assessing the use of nanoparticles (NPs) in AAA imaging.

| AAA process | Target | Sample size | NP | Imaging mode | Findings |
|-------------|--------|-------------|----|--------------|---------|
| Inflammation | Macrophages | 22a | USPIO | MRI | USPIO-enhanced MRI detected inflammation in AAA (44) |
| Inflammation | Macrophages | 13 | USPIO | MRI | Significant difference in decay of transverse magnetization pre- and post-USPIO infusion in AAA (43) |
| Inflammation | Leukocytes | 15 | SPIO | MRI | SPIO-enhanced MRI detected inflammation in AAA (68) |
| Inflammation | Macrophages | 27 | USPIO | MRI | Patients with marked USPIO uptake had threefold higher AAA growth rate (33) |
| Inflammation | Macrophages | 15 | USPIO | PET-CT and MRI | F-FDG PET-CT appears to target glycolytic macrophages while USPIO-enhanced MRI appears to target phagocytic macrophages. Both methods improved AAA imaging (34) |

*a11 with aneurysm and 11 aged-matched non-aneurysmal controls.

AAA, abdominal aortic aneurysm; F-FDG, 18F-fludeoxyglucose; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; SPIO, superparamagnetic iron oxide nanoparticles; USPIO, ultrasmall superparamagnetic iron oxide nanoparticles.

Collectively, these studies suggest that NPs can be localized in some AAAs and may have a role in identifying higher risk AAAs. However, the studies currently published are pilot or feasibility studies with small sample sizes. It remains to be shown whether these findings can be validated in large scale clinical trials.

The Potential of Employing NPs to Identify High Risk AAA

Currently, available methods of imaging AAAs assess anatomical features, such as maximum AAA diameter and volume (67). Most AAAs identified by screening studies are small. There is a dearth of available imaging techniques that can identify pathological features of AAAs. The use of NPs as contrast agents could provide a means to identify such pathological features. Such functional imaging could provide a means to identify AAAs likely to rupture or grow more rapidly which should undergo early elective AAA repair. Larger studies are, however, needed to assess the value of this imaging in a more robust way. We have previously highlighted the difficulties in translating findings from pre-clinical animal models into practice (69), particularly as there is no current ideal AAA animal model. If further clinical studies are encouraging, there are also other challenges to overcome before the widespread clinical application of NP-enhanced imaging. These include cost, large scale production difficulties, and putative systemic toxicity of these agents (70, 71). The design of nanomaterials able to specifically target high risk AAAs (15) is complicated by the multifactorial nature of AAA. Problems with non-specific uptake of NPs by non-target tissues can complicate signal quantification. Hence, image acquisition, quantification, and analysis methods need standardization to ensure rigor, reproducibility, validity, and reliability. Another potential problem is that NP localization is unlikely to reflect the hemodynamic forces on the aortic wall, which are also relevant to AAA rupture risk (72).

Nanoparticle-associated toxicity has been suggested to depend on a number of factors including NP size, composition, or charge (17, 73). Gold NPs, for example, are implicated in the induction of reactive oxygen species and autoimmunity (74). Cationic liposomal NPs can interact with lipoproteins, serum proteins, and ECM, resulting in aggregation and oxidative stress with consequent non-target tissue damage (75, 76). None of these toxic effects were
reported in any of the human studies investigating AAA reviewed in this article. Assessment of toxicity is further compounded by the diversity of the constituents used in NPs constructs, since there are infinite numbers of combinations of nanomaterials possible (77). However, previous studies suggest that iron oxide NPs are degraded within a week by macrophage lysosomes and the iron incorporated into hemoglobin (78). They are also rapidly cleared from the circulation by the reticular endothelial system albeit in a dose-dependent manner (79, 80). These mechanisms may attenuate any toxicity associated with this form of NP. While NP-associated toxicity is of concern, evidence suggests that iron oxide NPs, such as USPIOs provide application possibilities with marginal potential for toxicity (33, 43, 78–80). In our opinion, additional studies using animal models of AAA and early phase clinical trials should focus on improving and fine tuning iron oxide NPs specifically USPIOs to better assess their efficacy in the functional and molecular imaging of AAA. These studies need to be better designed with adequate sample size. The potential of using these agent as dual imaging and therapeutic drug delivery agents cannot be overlooked. It may also be feasible to employ NPs as delayed imaging or therapeutic agents that are activated by the detection of key element such as inflammatory macrophages or neutrophils within the aneurysm prone aorta.

In summary, NPs enhanced imaging is currently being actively investigated as a way to identify high risk AAAs. Iron oxide NPs have shown some promise in identifying macrophage within AAAs. Further research is needed to optimize this imaging and more robustly examine its value in clinical management.

AUTHOR CONTRIBUTIONS

TE conceived, designed, critically appraised the literature, and wrote the article. FA, AS, FS, and TD critically appraised the literature. JG critically appraised and reviewed the article. All authors revised the article for intellectual content; read and approved the final manuscript for submission.

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REFERENCES

1. Emeto TI, Moxon JV, Biros E, Rush CM, Clancy P, Woodward L, et al. Urocortin 2 is associated with abdominal aortic aneurysm and mediates anti-proliferative effects on vascular smooth muscle cells via corticotrophin releasing factor receptor 2. Clin Sci (Lond) (2014) 126(7):515–7. doi:10.1042/CS20140529
2. Emeto TI, Moxon JV, Au M, Golledge J. Oxidative stress and abdominal aortic aneurysm: potential treatment targets. Clin Sci (Lond) (2016) 130(5):301–15. doi:10.1042/CS20150547
3. Emeto TI, Seto SW, Golledge J. Targets for medical therapy to limit abdominal aortic aneurysm progression. Curr Drug Targets (2014) 15(9):860–73. doi:10.2174/13894501156661480804155036
4. Moxon JV, Parr A, Emeto TI, Walker P, Norman PE, Golledge J. Diagnosis and monitoring of abdominal aortic aneurysm: current status and future prospects. Curr Probl Cardiol (2010) 35(10):512–48. doi:10.1016/j.cpcardiol.2010.08.004
5. Vardulaki KA, Prevost TC, Walker NM, Day NE, Wilmink AB, Quick CR, et al. Growth rates and risk of rupture of abdominal aortic aneurysms. Br J Surg (1998) 85(12):1674–80. doi:10.1046/j.1365-2168.1998.00946.x
6. Emeto TI. Urocortin 2: An Interesting Role in Human Abdominal Aortic Aneurysm. Townsville, QLD: James Cook University (2013).
7. Brady AR, Thompson SG, Fowkes FG, Greenhalgh RM, Powell JT; UK Small Aneurysm Trial Participants. Abdominal aortic aneurysm expansion: risk factors and time intervals for surveillance. Circulation (2004) 110(1):16–21. doi:10.1161/01.CIR.0000132729.07468.9F
8. Chakof EL, Brewster DC, Dalman RL, Raut M, Forestier F, et al. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. J Vasc Surg (2009) 50(4 Suppl):S2–49. doi:10.1016/j.jvs.2009.07.001
9. Golledge J, Norman PE. Pathophysiology of abdominal aortic aneurysm relevant to improvements in patients’ management. Curr Opin Cardiol (2009) 24(6):532–8. doi:10.1097/HCO.0b013e3283302c2d
10. Khosla S, Morris DR, Moxon JV, Walker PJ, Gasser TC, Golledge J. Meta-analysis of peak wall stress in ruptured, symptomatic and intact abdominal aortic aneurysms. Br J Surg (2014) 101(11):1350–7; discussion 7. doi:10.1002/bjs.9578
11. Thompson SG, Brown LC, Sweeving MJ, Bown MJ, Kim LG, Glover MJ, et al. Systematic review and meta-analysis of the growth and rupture rates of small abdominal aortic aneurysms: implications for surveillance intervals and their cost-effectiveness. Health Technol Assess (2013) 17(41):1–118. doi:10.3310/hta17410
12. Powell JT, Brady A, Brown LC, Forbes JE, Fowkes FGR, Greenhalgh RM, et al. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. Lancet (1998) 352(9141):1649–55. doi:10.1016/S0140-6736(98)10137-X
13. Collaborators R, Bown MJ, Sweeving MJ, Brown LC, Powell JT, Thompson SG. Surveillance intervals for small abdominal aortic aneurysms: a meta-analysis. JAMA (2013) 309(8):806–13. doi:10.1001/jama.2013.950
14. Goleshani R, Sadeghi MM. Emergence of molecular imaging of aortic aneurysm: implications for risk stratification and management. J Nucl Cardiol (2014) 21(2):251–67; quiz 68–70. doi:10.1007/s12350-013-9845-5
15. Sinha A, Shaporev A, Nosoudi N, Lei Y, Vertegel A, Lessner S, et al. Nanoparticle targeting to diseased vasculature for imaging and therapy. Nanomedicine (2014) 10(5):1003–12. doi:10.1016/j.nano.2014.02.002
16. Ploussi AG, Gazouli M, Stathis G, Kelekis NL, Efthathopoulos EP. Iron oxide nanoparticles as contrast agents in molecular magnetic resonance imaging: do they open new perspectives in cardiovascular imaging? Cardiol Rev (2015) 23(5):229–35. doi:10.1097/CRD.0000000000000055
17. Au M, Emeto TI, Power J, Vangaveti VN, Lai HC. Emerging therapeutic potential of nanoparticles in pancreatic cancer: a systematic review of clinical trials. Biomedicines (2016) 4(3):20. doi:10.3390/biomedicines4030020
18. Wilczewska AZ, Niemirowsicz K, Markiewicz KH, Car H. Nanoparticles as drug delivery systems. Pharmacol Rep (2012) 64(5):1020–37. doi:10.1016/j.pharmre.2012.01.002
19. Suris SS, Fennini H, Singh B. Nanotechnology-based drug delivery systems. J Occup Med Toxicol (2007) 2:16. doi:10.1186/1745-6673-2-16
20. Buzea C, Pacheco II, Robbie K. Nanomaterials and nanoparticles: sources and toxicity. Bioinforphases (2007) 2(4):Mr17. doi:10.1116/1.2815690
21. Zhao X, Zhao H, Chen Z, Lan M. Ultrasmall superparamagnetic iron oxide nanoparticles for magnetic resonance imaging as contrast agent. J Nanosci Nanotechnol (2014) 14(1):210–20. doi:10.1166/jnn.2014.9192
22. Jain KK. Advances in the field of nanooncology. BMC Med (2010) 8:83. doi:10.1186/1741-7015-8-83
23. Qi L, Wu L, Zheng S, Wang Y, Fu H, Cui D. Cell-penetrating magnetic nanoparticles for highly efficient delivery and intracellular imaging of siRNA. Biomacromolecules (2012) 13(9):2723–30. doi:10.1021/bm3006903
24. Deb S, Ghosh K, Shetty SD. Nanoimaging in cardiovascular diseases: current state of the art. Indian J Med Res (2015) 141(3):285–98. doi:10.4103/0971-5916.156557
62. Golledge J, Wolanski P, Parr A, Buttner P. Measurement and determinants of infrarenal aortic thrombus volume. *Eur Radiol* (2008) 18(9):1987–94. doi:10.1007/s00330-008-0956-3

63. Wang DH, Makaroun M, Webster MW, Vorp DA. Mechanical properties and microstructure of intraluminal thrombus from abdominal aortic aneurysm. *J Biomech Eng* (2001) 123(6):536–9. doi:10.1115/1.1411971

64. Manning MW, Cassi LA, Huang J, Szilvassy SJ, Daugherty A. Abdominal aortic aneurysms: fresh insights from a novel animal model of the disease. *Vasc Med* (2002) 7(1):45–54. doi:10.1191/1358863x02vm413ra

65. Kitagawa T, Kosuge H, Uchida M, Dua MM, Iida Y, Dalman RL, et al. RGD-conjugated human ferritin nanoparticles for imaging vascular inflammation and angiogenesis in experimental carotid and aortic disease. *Mol Imaging Biol* (2012) 14(3):315–24. doi:10.1007/s11307-011-0495-1

66. Nahrendorf M, Keliher E, Marinelli B, Leuschner F, Robbins CS, Gerszten RE, et al. Detection of macrophages in aortic aneurysms by nanoparticle positron emission tomography-computed tomography. *Arterioscler Thromb Vasc Biol* (2011) 31(4):750–7. doi:10.1161/ATVBAHA.110.221499

67. Wanhainen A, Mani K, Golledge J. Surrogate markers of abdominal aortic aneurysm progression. *Arterioscler Thromb Vasc Biol* (2016) 36(2):236–44. doi:10.1161/ATVBAHA.115.306538

68. Nchimi A, Defawe O, Brisbois D, Broussaud TK, Defraigne JO, Magotteaux P, et al. MR imaging of iron phagocytosis in intraluminal thrombi of abdominal aortic aneurysms in humans. *Radiology* (2010) 254(3):973–81. doi:10.1148/radiol.09090657

69. Trollope A, Moxon JV, Moran CS, Golledge J. Animal models of abdominal aortic aneurysm and their role in furthering management of human disease. *Cardiovasc Pathol* (2011) 20(2):114–23. doi:10.1016/j.carpath.2010.01.001

70. Mulder WJ, Jaffer FA, Fayad ZA, Nahrendorf M. Imaging and nanomedicine in inflammatory atherosclerosis. *Sci Transl Med* (2014) 6(239):239sr1. doi:10.1126/scitranslmed.3005101

71. Storey P, Lim RP, Chandarana H, Rosenkrantz AB, Kim D, Stoffel DR, et al. MRI assessment of hepatic iron clearance rates after USPIO administration in healthy adults. *Invest Radiol* (2012) 47(12):717–24. doi:10.1097/RLI.0b013e31826ed151

72. Boyd AJ, Kuhn DC, Lozowy RJ, Kulpisky GP. Low wall shear stress predominates at sites of abdominal aortic aneurysm rupture. *J Vasc Surg* (2016) 63(6):1613–9. doi:10.1016/j.jvs.2015.01.040