

## Editors' pick



## Medical imaging in the 21st century: the promise and the challenges

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### Introduction

The latter part of the 20th century saw the practical application of computer technology and molecular biology, while the early 21st century is seeing the merging of these technologies and the application of bioinformatics to medical imaging. The development of computed tomography (CT) and magnetic resonance imaging (MRI) over the past two decades, and the more recent emergence of molecular imaging, has created diagnostic capabilities that will dramatically change the way medicine is practised. As well as providing new diagnostic modalities, advanced imaging will improve our understanding of disease processes and facilitate tailored patient treatment and follow-up. Although imaging technology requires major capital investment, costs may be offset by eliminating unnecessary procedures, improving outcomes, and optimising care.<sup>1</sup> This article discusses two emerging imaging technologies: molecular imaging (MI); and, computed tomography angiography (CTA).

### Molecular imaging

#### History

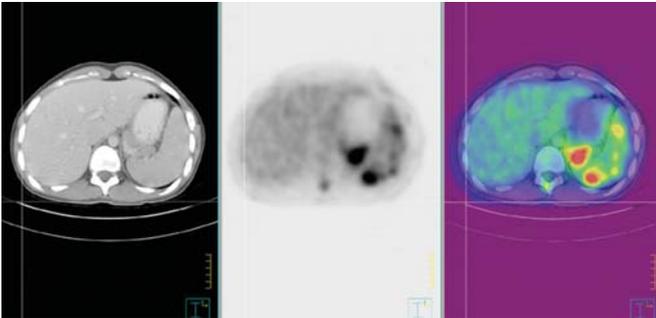
Molecular imaging dates back to the 1940s and gained momentum with the successful use of radioactive iodine to treat thyroid cancer.<sup>2</sup> This

was followed by the development of positron emission tomography (PET) technology in the 1950s and the synthesis of fluorine 18 fluoro-2-deoxy-D-glucose (FDG) in the 1970s.<sup>3</sup> Although the field has a seemingly long history, it was only in the last decade that researchers and physicians have been able to exploit the potential of molecular imaging. Growth in the understanding of basic cell and molecular biology has elucidated many of the key molecular pathways, signal transduction cascades, and receptor alteration abnormalities that lead to disease. This has led to the development of relevant molecular targets for existing imaging systems.

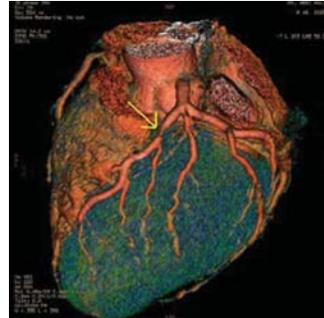
#### Principles

MI is defined as the *in vivo* characterisation and measurement of biologic processes at the cellular and molecular level. Traditional imaging modalities (x-ray, CT, MRI) are successful in obtaining anatomic and physiologic information but lack the ability to assess disease at a molecular level. The ability to measure metabolic processes with MI is beginning to change practice in oncology, cardiology, neurology, rheumatology, and infectious diseases. A number of imaging modalities (ultrasound, CT, MRI) now take advantage of newer biomarkers of disease.<sup>4</sup>

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Far left:  
FIGURE 1: PET-CT fusion images of splenic lesions in lymphoma.



Left:  
FIGURE 2: CTA three-dimensional reconstruction exhibiting a proximal stenosis of the left anterior descending coronary artery.

The basic concepts of molecular imaging are illustrated by the use of FDG as a positron emitting radioactive isotope used in PET. Neoplastic cells show an increased rate of glycolysis and glucose metabolism.<sup>5</sup> The initial step in glucose metabolism is the phosphorylation of glucose to glucose-6-phosphate by the enzyme hexokinase.<sup>6</sup> FDG, a glucose analogue, is initially converted to FDG-6-phosphate, but cannot be further metabolised. Furthermore, due to its negative charge, it is trapped within cells. Thus FDG is a biomarker for a rate-limiting step of glycolysis. The <sup>18</sup>F incorporated in FDG generates signal by positron emission radioactive beta decay, creating gamma photons whose energy is captured by a ring scanner and used to construct an image.<sup>7</sup> Neoplastic cells will emit more signal than normal cells, enabling comparison between the two on a metabolic level.<sup>8</sup> MI is not limited to FDG and the basic concept of labelling biomarkers to capture their location and activity holds vast potential.

### Clinical application: oncology

Thus far, oncology is the area of greatest success in molecular imaging. FDG use in PET for staging of cancers (breast, colorectal, oesophageal, melanoma, lymphoma) and monitoring response to treatment has been approved by the United States Food and Drug Administration (FDA) and is the standard practice in many centres.<sup>9</sup> Ralph Weissleder of Harvard Medical School, a leader in the field of molecular imaging, described in 2006 the goals of clinical molecular imaging as: "(i) the detection of molecular or physiological alterations that signal the presence of cancer when it is still at a curable stage; (ii) the ability to evaluate and adjust treatment protocols in real time; and, (iii) the ability to streamline the drug development process".<sup>10</sup> Currently, the most frequently used cancer imaging agent is FDG (Figure 1).

Smith *et al* demonstrated that after a single pulse of chemotherapy, FDG PET was able to predict breast tumour response with a sensitivity of 90% and a specificity of 74% based on a decline in FDG uptake compared to non-responsive tumours.<sup>11</sup> Another example utilises lymphotropic superparamagnetic nanoparticles and MRI to image lymph node metastasis in prostate cancer.

Harisinghani *et al* were able to detect millimetre-sized metastases and correctly identified patients with nodal metastases with a sensitivity of 90.5% compared to 35.4% with conventional MRI.<sup>12</sup> Drug development is another area of advancement. Imaging molecular processes will enable researchers to identify and validate

potential targets and efficiently monitor metabolic effects of drugs at therapeutic doses. For example, Wu *et al* describe the use of bioluminescence imaging of reporter genes to quantify efficacy of epothilones, a class of chemotherapeutic drugs that disrupt mitosis *in vivo*.<sup>13</sup> In addition, pharmacokinetic and pharmacodynamic data can be efficiently collected by radiolabelling cancer drugs.<sup>14</sup> These applications of MI allow more accurate diagnosis, staging and prediction of tumour response of many cancers, allowing individualisation of therapy, thus improving cost-effectiveness and clinical outcomes.<sup>15</sup>

### Clinical application: cardiovascular

Conventional cardiac imaging methods such as echocardiography, CT and MRI are effective at visualising anatomic and physiologic properties of the myocardium, but lack the ability to capture metabolic processes.<sup>16</sup> PET, by utilising <sup>82</sup>Rb, a potassium analogue and substrate for myocardial uptake via Na/K ATPase, can image myocardial perfusion and metabolic activity but lacks anatomic resolution. By combining techniques, PET-CT enables the construction of single images characterising anatomic, physiologic, and metabolic properties of the myocardium.<sup>17</sup>

Coronary artery disease (CAD) is an atherosclerotic process in which narrowing of the vessel lumen or complete obstruction of the lumen by a ruptured plaque results in tissue hypoxia and myocardial necrosis and apoptosis.<sup>18</sup> Invasive coronary angiography (ICA), directly injecting contrast into the coronary arteries to characterise vessel diameter, has been the principal diagnostic procedure to identify and predict the course of CAD. Unfortunately, acute coronary syndromes (ACS) often result from plaque rupture at sites not significantly stenosed.<sup>19</sup> Additionally, 50% of men and 64% of women who die suddenly because of CAD have no previous symptoms.<sup>20</sup> Other factors contributing to the risk of plaque rupture include plaque inflammation,<sup>21</sup> macrophage infiltration,<sup>22</sup> degree of apoptosis,<sup>23</sup> matrix degradation,<sup>24</sup> angiogenesis,<sup>25</sup> thrombosis, and smooth muscle proliferation.<sup>26</sup> Thus, molecular imaging provides the opportunity for a more detailed analysis of the structure and biology of the atherosclerotic process in coronary arteries. For example, the use of lymphotropic superparamagnetic iron oxide nanoparticles to label macrophages enables MR imaging to characterise plaque macrophage infiltration.<sup>22</sup> Radiolabelled Z2D3 antibody is currently used as a marker for smooth muscle cell proliferation.<sup>27</sup>

MI is currently used to predict acute coronary events, allowing for pre-emptive management and co-ordinated treatment plans.<sup>28</sup> Future developments will allow risk assessment for ventricular arrhythmias (neural imaging),<sup>29</sup> identify 'pre-disease' states enabling earlier treatment,<sup>30</sup> and target the biomechanisms associated with cardiac remodelling and the development of heart failure.<sup>31</sup>

## Computed tomography angiography

### History

The first CT scanner was developed in 1972 by Sir Godfrey Hounsfield<sup>32</sup> and independently by Allen Cormack.<sup>33</sup> At this stage, each tomographic slice required hours of scan time and days of computation to construct images. The early 1990s saw the introduction of continuous helical scanners, reducing scan times. Images were still not captured fast enough to view contrast, and clinical applications of CTA were limited by high slice thickness and low image resolution. The emergence of multirow detector scanners in the late 1990s allowed for many images to be acquired during a

**Table 1: Thrombosis In Myocardial Infarction (TIMI) risk score for unstable angina and non-ST segment elevation myocardial infarction (NSTEMI). Each factor is awarded one point. The low-risk group is defined by a score of 0 or 1 while the high-risk group is defined by a score of 6 or 7. Individuals at high risk are usually admitted and are candidates for PCI:**

- age  $\geq 65$  years;
- history of known coronary artery disease (documented prior coronary artery stenosis  $\geq 50\%$ );
- $\geq 3$  conventional cardiac risk factors (age, male sex, family history, hyperlipidaemia, diabetes mellitus, smoking, obesity);
- use of aspirin in the past seven days;
- ST-segment deviation (persistent depression or transient elevation);
- increased cardiac biomarkers (troponins); and,
- $\geq 2$  anginal events in the preceding 24 hours.

**Table 2: Patient selection criteria for TRO CTA:**

- clinical presentation: low to moderate risk of ACS;
- clinical presentation: non-ACS diagnosis considered;
- normal ECG or non-specific changes;
- no history to suggest extensive coronary calcium;
- not recommended for patients with bypass or stents;
- patient able to tolerate CT and hold breath;
- cardiac rhythm acceptable for ECG-gated scan; and,
- adequate renal function.

single helical revolution of the scanner. This further reduced scan times and slice thickness and enabled visualisation of contrast using CT.<sup>34</sup> Technology has improved over the past 10 years with the development of 16-, 32-, 64-, 128- and 256-row scanners, further reducing scan times significantly and increasing the resolution of CTA images.<sup>35</sup> Detailed analysis of coronary and peripheral vasculature is now possible and research efforts continue to increase the resolution of CTA studies.<sup>36</sup>

### Principles

CTA is a minimally invasive technique using peripheral infusion of intravenous contrast for visualisation of blood vessels, most commonly the coronary arteries (**Figure 2**). A typical scan usually requires a breath hold of 10 seconds and 60-80ml of contrast media. To avoid high radiation exposure, automated bolus timing can be used. CTA commonly images from the level of the carina superiorly to the apex inferiorly and has spatial resolution of 0.4mm<sup>3</sup> (64-slice).<sup>37</sup> Recent evidence shows that 64-slice CTA can accurately detect coronary lesions with a sensitivity of 99% and a specificity of 96% per coronary segment, with a negative predictive value of 99%.<sup>38,39</sup> ICA remains the 'gold standard' for detection of coronary artery stenosis<sup>40</sup> but requires cardiac catheterisation with its attendant complications, including stroke, local bleeding and vessel perforation.<sup>41</sup> The information provided by ICA is limited to luminal diameter, which is only one of many factors that contribute to cardiac risk. CTA provides a more rapid, less resource intensive, minimally invasive alternative with reduced complications and costs.<sup>42</sup>

### Clinical application: acute chest pain

A major clinical application of CTA is the evaluation of acute chest pain in the emergency department. This accounted for more than six million emergency department visits in the United States in 2006,<sup>43</sup> with between 30% and 72% of patients admitted to hospital.<sup>44</sup> Approximately 15-25% of admitted patients were eventually diagnosed with ACS, with 44% having significant pathology ruled out.<sup>45</sup> The cost of chest pain-related hospital admissions in the United States approaches US\$8 billion.<sup>46</sup> The missed diagnosis of ACS is a major reason for litigation against emergency department physicians (accounting for up to 20% of emergency department malpractice dollar losses) and consequently the threshold for hospital admission is low.<sup>47</sup> The need for a definitive, cost-effective test to distinguish between life-threatening (acute coronary syndrome, pulmonary embolism, aortic dissection) and non-immediate life-threatening (pneumonia, pulmonary neoplasm, pericarditis) conditions is essential.<sup>48</sup> Patients complaining of chest pain in the emergency room are risk stratified for ACS, with the Thrombosis In Myocardial Infarction (TIMI) risk score commonly used (**Table 1**). Management of low-risk patients includes serial biomarkers, observation in a telemetry setting and cardiac stress testing. However, this remains suboptimal, with an inappropriate discharge rate of 2-8% despite the expenditure of significant resources.<sup>37</sup> A triple-rule-out (TRO) CTA procedure is useful in such low-risk patients with a differential diagnosis of ACS in addition to non-cardiac causes (**Table 2**).

In stable patients where clinical evaluation primarily indicates chest pain of cardiac origin, dedicated cardiac CTA can be used to exclusively evaluate the coronary vessels. TRO CTA is an ECG-gated application of CTA intended to evaluate the aorta, coronary circulation, pulmonary arteries and the middle to lower portion of the chest with a single scan.<sup>49</sup> ECG-gating refers to the triggering of image acquisition by the ECG signal that coincides with the heart phase with least motion. This decreases motion artefacts, allowing for clearer images. Takakuwa *et al* demonstrated that TRO CTA is an effective tool for evaluating chest pain in low to moderate risk ACS patients, avoiding additional testing in 75% of patients. At 30-day follow-up, the negative predictive value of TRO CTA was 99.4%.<sup>50</sup>

Although CTA will not replace ICA for investigation of high-risk cardiac patients (as coronary intervention can often be done simultaneously during ICA), data suggests a significant role in the assessment of low-risk patients, and potentially for population screening.<sup>51</sup>

## Conclusions

Molecular imaging and CTA are two of many emerging imaging technologies that will greatly impact medical care. Advances in bioinformatics and improved acquisition and resolution of images will facilitate the continued expansion of MI. The high capital costs of commissioning imaging equipment and the need for multidisciplinary involvement will require large centres to allow MI to reach its full potential. Unfortunately, these technologies have progressed faster than the ability to validate their use and clinical evaluation of their effectiveness and the concurrent development of practice guidelines are essential. Ensuring cost effectiveness by avoiding use with little or no indication is an important factor in facilitating the success of these technologies, especially in the current economic climate. Although great progress has already been made, the potential for imaging to further improve patient care is significant. Medical imaging will continue to shape the practice of medicine in the 21st century.

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