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REVIEW

Opportunities and Challenges of Computed Tomography Coronary Angiography in the Investigation of Chest Pain in the Emergency Department—A Narrative Review

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Chest pain is one of the most common presentations to emergency departments. However, only 5.1% will be diagnosed with an acute coronary syndrome, representing considerable time and expense in the diagnosis and investigation of the patients eventually found not to be suffering from an acute coronary syndrome. PubMed and Medline databases were searched with variations of the terms "chest pain", "emergency department", "computed tomography coronary angiography". After review, 52 articles were included. Computed tomography coronary angiography (CTCA) is a class I endorsement for investigating chest pain in major international societal guidelines. CTCA offers excellent sensitivity and negative predictive value in identifying patients with coronary disease, with prognostic data impacting patient management. If CTCA is to be applied to all comers, it is pertinent to discuss the advantages and potential pitfalls if use in the Australian system is to be increased.

Keywords Computed tomography coronary angiography • Acute coronary syndrome

Introduction

Chest pain is one of the most common presentations to emergency departments in Australia [1]. Over 80% will not be diagnosed with an acute coronary syndrome (ACS), incurring significant cost in testing and hospital stays [2]. Adding to the diagnostic difficulty is that 4% of patients presenting with chest pain with normal electrocardiogram (ECG) and biomarkers can have underlying coronary artery disease [2]. Risk stratification of patients presenting with chest pain is aimed at diagnosing the probability of ACS and ACS-related morbidity and mortality. Risk factor scoring

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systems have emerged with the History, ECG Age, Risk factors, and Troponin (HEART) score being of most value [3,4] The importance of risk stratification is shown by data regarding harm and unnecessary expenditure that arises from hospitalisation of low-risk patients [5]. These scores decide which patients are safe for discharge [6].

Current Australian guidelines recommend functional testing over computed tomography coronary angiography (CTCA) for investigation of patients discharged from the emergency department [6]. These guidelines differ from those of the European Society of Cardiology, the UK National Institute for Health and Care Excellence, and the American College of Cardiology (ACC)/American Heart Association (AHA) chest pain guidelines, which endorse CTCAs alongside functional testing [7–9]. This discussion will initially cover the evidence base for functional testing currently used in Australia, showing how the sensitivity and negative predictive value lag compared to CTCA. The advantages and disadvantages of CTCA will be discussed in the context of applying it to all comers in the emergency department, including downstream resource utilisation and radiation exposure. A key difference is that, in Australia, the approach to investigating chest pain is predominantly outpatient based, compared to an inpatient approach in the USA.

Search Strategy

PubMed and Medline databases were searched to identify relevant journal articles. Search terms included "chest pain AND emergency department", "chest pain AND computed tomography coronary angiography". Reference lists of articles were reviewed further to identify articles. Inclusion criteria included original research, review articles, meta-analyses; and exclusion criteria were language other than English and case reports with the end result of 54 articles being included.

Non-Invasive Investigation of Patients With Chest Pain in Australia

Non-invasive approaches for the investigation of chest pain include exercise treadmill testing (ETT), stress echocardiography (SE), myocardial perfusion imaging using single photon emission computed tomography (SPECT), CTCA, positron emission tomography (PET) and cardiac magnetic resonance imaging (CMR). The dominant modalities in Australia are SE and SPECT [10].

A direct comparison of modalities has been difficult due to two main factors. First is inclusion of older technologies no longer used in clinical practice (for example, planar imaging in SPECT). The second is the "gold standard" diagnostic tool used for detecting significant CAD. The gold standard of correlation with invasive coronary angiography (ICA) using diameter stenosis (DS) has evolved, with more recent studies using invasive fractional flow reserve (FFR), due to FFR being a better indicator of functional significance [11].

With invasive FFR as the new gold standard, it is useful to look at studies comparing modalities which use invasive FFR as a correlation. There are three meta-analyses by Dai et al. [12], Danad et al. [13], and Takx et al. [14] which showed consistently that sensitivity of stress echo and SPECT was reduced compared to CTCA and a reduced specificity of CTCA compared to SE and SPECT. Limitations in comparing modalities were that the stress echo and SPECT studies tended to be retrospective, single centre, and smaller sample sizes.

A notable strength of the meta-analysis by Danad et al. [13] was the inclusion criterion of at least 75% of vessel assessment with FFR. The 23 studies meeting this inclusion criterion resulted in an analysis of 5,323 vessels from 3798 patients. In this study, the sensitivity of SPECT was lowest of the modalities at 70% per patient and 57% per vessel. The sensitivity per patient for SE was 77%, CMR 90%, CTCA 90% per patient, CT-FFR 90% and invasive coronary angiography 69%. SPECT and SE were inferior in their negative likelihood ratios (NLR) compared to CMR and CT.

Takx et al. compared perfusion modalities (SPECT, CT-Perfusion [CT-P], CMR, PET and echo) for the diagnostic accuracy of haemodynamically significant coronary artery disease in a meta-analysis which looked at 4,721 vessels from 2,048 patients and found that the sensitivity for SE was 69%, SPECT 74%, CMR 89% and PET 84%. A major limitation was that FFR could only be confirmed as the correlative tool in 43% of studies. Takx et al. showed the NLR was higher for CT-P compared to SPECT and echo (0.22 vs 0.47 vs 0.42) [14].

Dai et al. [12] compared SPECT, dobutamine stress echo (DSE), CMR, PET, CT-P and CT-FFR using invasive FFR for correlation. In this study, sensitivity and specificity for CT-P and CT-FFR was 89%, 89%, 86% and 83%, respectively, which is much improved compared to CTCA.

The PACIFIC[1] study was unique in that 208 patients underwent concurrent assessment with SPECT, PET, CMR, CTCA alongside invasive correlation with FFR [15]. The strength of this study was that all vessels were assessed with FFR regardless of the stenosis and used contemporary hardware which avoids a limitation of the meta-analyses. CTCA had a very high sensitivity of 90% and a negative predictive value of 89%, which outperformed SPECT (57% sensitivity and negative predictive value 73%). The intermediate specificity of CTCA compared to SPECT was confirmed with specificity of 60% and a positive predictive value (PPV) of 64% (SPECT 94% specificity and PPV 88%). The intermediate specificity associated with CTCA was improved when comparing CT-FFR to functional modalities in a substudy of the PACIFIC study [16]. Currently, CT-FFR is not licensed for use in Australia and CT-P is limited to a small number of centres.

[1] Prospective comparison of cardiac PET/CT, SPECT/CT perfusion imaging and CT coronary angiography with invasive coronary angiography study.

In summary, CTCA is more sensitive than the non-invasive modalities of SE, SPECT and similar to CMR to identify anatomically significant CAD using the reference standards of ICA >50% DS and/or invasive FFR <0.80.

Non-Invasive Investigation of Patients With Chest Pain Using CTCA

Considering the limited and variable accuracy of functional testing, it is worthwhile reviewing the advantages and disadvantages of CTCA. These include the high sensitivity and negative predictive value related to diagnosis and management advantages related to strong prognostic data, and the resultant opportunity to initiate primary prevention following identification of non-obstructive CAD. Other advantages currently not in clinical use relate to plaque quantification and composition, assessing functional significance of lesions, and detection of coronary inflammation. Challenges of applying CTCA to all comers in the emergency department include reduced specificity, as discussed above, and addressing radiation minimisation and downstream resource utilisation.

The accuracy of CTCA for visualisation of CAD has been studied in single-centre and multicentre trials [17–20]. Early single-centre studies were performed in patients referred for invasive coronary angiography raising concerns of biases. These were addressed by later multicentre studies undertaken during a period (2008–2020) in which advances in CT hardware led to previous absolute contraindications (elevated heart rate, arrhythmia and the presence of calcification) becoming relative contraindications, thus expanding the utility of CTCA [21].

When correlating to invasive coronary angiography DS, CTCA demonstrates a superior sensitivity for detecting CAD of 85% to 99% with a negative predictive value of 88% to 99% [22]. The high concordance between CTCA and invasive coronary angiography has also been confirmed in patients with moderate to severe ischaemia on functional testing as demonstrated in the post-hoc analysis performed on the invasive arm of the ISCHEMIA[2] study [23]. This study enrolled patients with moderate to severe ischaemia on functional testing randomised to either invasive coronary angiography or optimal medical management. A CTCA was performed prior to randomisation to exclude patients with left main disease >50% DS. Of the 1,728 patients identified by CTCA as having left main disease <50% and at least single-vessel coronary artery disease, invasive coronary angiography was concordant confirming 97% with left main DS <50% and 92% with at least one diseased coronary vessel plus left main DS <50%. Invasive coronary angiography did not confirm the presence of significant coronary artery disease in 4.9% (which had been demonstrated on CTCA).

CTCA and Prognostication

The prognostic benefit of CTCA has been confirmed in registries [24,25] and randomised controlled trials [26,27]. The prognostic implications span from a normal CTCA to CTCA demonstrating non-obstructive and obstructive CAD. Compared to SE and SPECT, CTCA provides additional information (the presence of non-obstructive CAD) that leads to implementation of downstream therapies, which have been shown to alter outcomes [26,28]. It is worthwhile reviewing registry data and the three major randomised controlled trials in the last 5 years with the Scottish Computed Tomography of the Heart Trial (SCOT-HEART) [29] and PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) [30] trials focussing on stable chest pain, and the "Early computed tomography coronary angiography in patients with suspected acute coronary syndrome: a randomised controlled trial looking at patients with acute chest pain" [31].

Prognosis of Patients With Normal Coronary Arteries on CTCA

Chow et al. [25], in a large provincial registry with 100% follow-up, demonstrated that patients with no CAD on CTCA have extremely low rates of major adverse events (MACE—defined as all-cause mortality, cardiac death and non-fatal MI) of 0.45% annually and a MACE rate of 0.19% annually. Longer follow-up (up to 10 years) of patients with a normal CTCA reveals an annual adverse event rate of 0.04% [32] which portends very favourably for not requiring reinvestigation of these patients for an ischaemic aetiology should they represent to the emergency department.

Prognosis of Patients With Normal Coronary Arteries on CTCA

The implication for the presence and severity of CAD identified on CTCA on prognosis has been confirmed by multiple studies linking the extent and severity of CAD to adverse events [33–35]. CTCA has been shown to have incremental prognostic benefits over traditional cardiac risk factors and calcium scoring [24].

The PROMISE [30] and the Scottish Computed Tomography of the Heart Trial (SCOT-HEART) [26] are significant randomised controlled trials that investigated clinical outcomes in patients with stable chest pain. The PROMISE study comprised stable symptomatic outpatients randomised to anatomical testing with CTCA or functional testing with ETT, SE or SPECT. The primary composite endpoint was death, myocardial infarction, hospitalisation for unstable angina and procedural complication. While there was no difference in the primary endpoint between the CTCA and functional groups, when the results were stratified into normal CTCA versus the mild (non-obstructive CAD), moderate (obstructive CAD >70% in 1 vessel branch) or

[2] International study of comparative health effectiveness with medical and invasive approaches.

severe (high-risk CAD with >2 vessel disease with >/=70% or >/= left main [LM] stenosis with >/= 50% or >/= 70% proximal left anterior descending [LAD]) disease, hazard ratios for the CTCA arm increased proportionally, indicating that risk stratification is feasible with CTCA, and was only seen in functional tests showing moderate or severe ischaemia [27]. The improved risk stratification was thought to be due to two main reasons. Firstly, patients with a normal CTCA suffered 10.2% of all events compared to 56.8% of all events occurring in the normal functional studies arm (ETT, SE, SPECT). Secondly, most events (54%) in the CTCA arm occurred in patients with non-obstructive disease (1–69%), an effect that was still present in patients with a stenosis of 1–49% [27]. This sub-analysis within the PROMISE study demonstrated the importance of non-obstructive CAD in prognosticating events and the advantage of the visualisation offered by CTCA.

The SCOT-HEART trial was a prospective open-label parallel randomised controlled trial studying patients referred for the evaluation of angina. The primary endpoint was the certainty of the diagnosis of angina being due to CAD at 6 weeks. Compared to standard care, CTCA increased the certainty and frequency of diagnosis of CAD at 6 weeks with a patient reclassification of 27% in the CTCA arm compared to 1% in the standard arm [29]. In total, the diagnosis of angina attributed to CAD involved 23% of the CTCA arm versus 1% of the standard arm. The downstream results of CTCA were significant, including the cancellation of 24 invasive angiograms and 121 functional tests, ordering of 94 ICA following a CTCA-based diagnosis of CAD, and an increase in commencement of preventive medications [29].

In the initial SCOT-HEART follow-up study (which lasted an average duration of 1.7 years), CTCA was associated with a 38% reduction in CAD death and non-fatal myocardial infarction, results which were very close to statistical significance [29]. The subsequent 5 year follow-up study showed a statistically significant reduction of 41% in this primary endpoint in the CTCA arm (hazard ratio, 0.59; 95% CI 0.41 to 0.84; P=0.004) [26] which confirmed the benefit of CTCA.

No significant difference was observed in the rates of ICA or revascularisation between both groups. Like the PROMISE study, most events in the CTCA arm occurred in patients with the non-obstructive disease [26]. Intriguingly, event rates were similar between the CTCA and standard of care groups for the first 7 weeks but diverged afterward [26]. The observed similarity is thought to be attributable to CAD as the cause of angina being confirmed and commencement of treatment [26]. Improved outcomes following diagnosis by CTCA were attributed to aspirin commencement and revascularisation. In contrast, the improved 5-year outcomes were attributed to secondary interventions such as statin medication and lifestyle modifications. The higher rates of invasive coronary angiography and revascularisation in the standard of care arm are thought to be due to untreated and unrecognised CAD, which were not identified with standard of care non-invasive functional testing.

The "Early computed tomography coronary angiography in patients with suspected acute coronary syndrome" was a randomised controlled study performed in 37 centres across the UK [31]. Inclusion criteria were symptoms of suspected ACS or those with a provisional diagnosis of ACS and one or more of prior coronary heart disease, elevated troponin, or abnormal electrocardiogram. Hardware was minimum 64-slice scanners, with all sites encouraged to pursue dose minimisation measures. The primary endpoint was time to first event of all-cause death or subsequent non-fatal Type 1 myocardial infarction or Type 4b myocardial infarction at 1 year. The endpoints were aligned with the SCOT-HEART trial to enable a direct comparison. Diagnostic quality was achieved in 91.3% of CTCA scans with a median effective dose of 5.8 mSv (using a conversion factor of 0.026 mSv/mGy cm). There was no significant difference in the primary outcome between the two arms, with rates of 5.8% in the early CT arm and 6.1% of the standard of care arm. A significant difference was observed with regards to the rates of invasive angiography which was lower in the early CTCA arm but which did not lead to a difference in the rates of revascularisation in the two arms. Downstream testing for ischaemia was lower in the early CTCA arm. Interestingly, compared to prior trials, there was no difference in the rates of preventive treatments in the two arms. Follow-up at 12 months also did not show any difference with regards to re-presentation, symptoms and quality of life between the two arms. The early CT arm showed increased patient satisfaction and greater clinician certainty. The value of CTCA was shown in that up to 50% of patients with normal or non-obstructive disease had an elevated troponin.

The differences in outcomes between these trials is interesting as SCOT-HEART and PROMISE showed a positive outcome with the use of CTCA. These trials were also performed in three different health care systems, but the negative trial in the intermediate risk population is deserving of further study to see if the loss of benefit seen in performing CTCA in this population compared to lower-risk populations is replicated. The lack of difference in rates of preventative medications in the Early CTCA trial is an important point to keep in mind also, as the benefit of CTCA in SCOT-HEART and PROMISE was not by virtue of having a CTCA scan but in the medications that were started after identification of coronary disease. Intermediate risk patients in the emergency department could be treated at a higher level with regards to being on evidence-based medications, but this is an area which needs to be studied further.

The Emergence of CT-Fractional Flow Reserve (CT-FFR) and CT-Perfusion (CT-P)

The reduced specificity of CTCA has seen the emergence of CT Fractional Flow Reserve (CT-FFR) and CT-Perfusion

(CT-P). As discussed above, CT-FFR and CT-P increases the specificity of CTCA to being comparable to the specificities of SE and CMR [14]. An approach that matches invasive FFR would be helpful as its use is not universal despite its status as a gold standard [36].

CT-FFR is emerging as a non-invasive alternative to invasive FFR and has been included in the ACC/AHA chest pain guidelines to assess the functional significance of 40–90% lesions [9]. CT-FFR assessment offers the advantage of requiring only the original images at acquisition and can be retrospectively applied to prior acquisitions. CT-FFR currently exists in the form of a proprietary model utilising computational fluid dynamics by HeartFlow (HeartFlow Inc, Redwood City, USA) and workstation-based models by Siemens Healthineers (Siemens Medical Solutions, Forchheim, Germany) and Canon (Canon Medical Systems, Japan). HeartFlow is currently the only model that is licensed by the Food and Drug Administration in the US and by the National Institute for Health and Care Excellence in the UK as it has the most extensive evidence base [22] and is not currently available in Australia.

The most recent meta-analysis of HeartFlow CT-FFR confirmed the association of a negative CT-FFR result with a lower rate of all-cause mortality or myocardial infarction at 12 months [37]. The utility of CT-FFR has also been shown to be maintained in patients with an Agatston Score of >399 [38], which is important if it is to be used in a wider population.

The requirement of HeartFlow to send images off-site for analysis with turnaround times of 4hrs to 24hrs [39] and a prohibitive cost of up to USD$1,500 per study have led to the emergence of onsite workstation-based models. However the workstation models are still not licensed for clinical use and are only for research use currently. Common to all of these CT-based methods of FFR assessment is the importance of image quality with administration of glyceryl trinitrate to achieve maximal vessel diameter and heart rate control to avoid motion artefact, which was the most common cause of image rejection for FFR-CT analysis in the ADVANCE registry [40].

Additionally, CT-P offers an alternative method with principles similar to other approaches of assessing perfusion. The incremental value of CT-P compared to CTCA alone to identify haemodynamically significant CAD has been shown in studies and meta-analyses [12,14,41], demonstrating a specificity of 89% on a per coronary territory basis and 87% per patient, with a positive likelihood ratio (per patient) of 6.97 [12] and an improvement of specificity from 43% to 77% [41]. CT-P's challenges relate largely to the high level of expertise required from both the radiographer and reporting doctor, including incorrect recognition of perfusion defects (due to beam hardening) and motion artefacts (caused by elevated heart rates secondary to the use of pharmacological stress agents) and increased radiation doses following multiple CT acquisitions. These factors have tended to complicate workflows, limiting widespread use.

Downstream Resource Use Following CTCA

The intermediate positive predictive value of CTCA necessitates further downstream functional testing to confirm functional significance. Literature for downstream resource use following CTCA is predominantly from the USA, limiting its applicability to Australia due to the differences in health systems. Studies from the USA show that CTCA leads to increased functional testing and invasive coronary angiography. Australian studies are limited, with only two single-centre studies. Hamilton-Craig et al. in a randomised controlled trial [42] evaluated CTCA versus ETT in patients presenting to the emergency department (ED) with low to intermediate risk after a single negative troponin. Primary endpoints were diagnostic performance with regards to ACS and hospital cost at 30 days. Secondary endpoints included time to discharge, rates of admission and downstream resource utilisation. CTCA had a sensitivity of 100% compared to 83% for ETT and had a reduced cost at 30 days. The reduction in cost was mainly driven by the reduced length of stay associated with CTCA and is impressive considering that CTCA had increased downstream utilisation. In a retrospective single-centre study, Leong et al. investigated the use of CTCA in patients presenting to the ED associated with an expanding CTCA service. CTCA led to increases in downstream functional testing, invasive coronary angiography and revascularisation [43]. A major limitation of this study is the retrospective aspect. Given the relatively small sample sizes and single-centre nature of these two studies, further large-scale studies are needed to confirm these findings.

Radiation

If CTCA is to be used widely, minimising radiation exposure needs to be addressed, given that 95–99% of the radiation that enters or is released within the body is absorbed or scattered within the body [44].While trying to reduce radiation exposure, it is also important to ensure diagnostic image quality to avoid additional testing, inappropriate testing or delay in initiation of appropriate treatment. The study of radiation in CTCA has been driven by the PROTECTION[3] series of studies. The original PROTECTION study in 2009 drew attention to the wide variability in practice with regards to acquisition and use of dose reduction measures with resulting high radiation doses [45]. This discrepancy in practice spurred subsequent research and led to studies PROTECTION II–V examining the impact of the dose reduction measures on image quality. Use of low tube voltage in PROTECTION II [46] prospective scanning in PROTECTION III [47], high-pitch scanning (restricted to dual source scanners) PROTECTION IV [48] and iterative reconstruction with PROTECTION V [49] showed that dose reduction did not impact diagnostic image quality. The

[3] PROspective multicentre registry on radiaTion dose Estimates of cardiac CT angIOgraphy iN daily practice.

PROTECTION II–V studies culminated in the 2018 PROTECTION VI study, which repeated PROTECTION I with modern hardware. PROTECTION VI showed a 78% reduction in the median dose length product compared to PROTECTION I. Reduction in use of retrospective gating from 94% in 2007 to 11% in 2017 led to a 74% reduction in dose [50]. Iterative reconstruction was credited with a 33% reduction in dose. Encouragingly, increased use of dose reduction measures did not lead to an increased rate of non-diagnostic imaging. Despite modern hardware and dose reduction measures, obesity, high heart rate and absence of sinus rhythm were associated with higher radiation doses in PROTECTION VI. These factors highlight the challenges inherent in applying CTCA as a universal test given the increasing prevalence of obesity and atrial fibrillation in the community [51]. The radiation dose in the Rule Out Myocardial Infarction by Computer Assisted Tomography (ROMICAT), showed a 50% reduction in dose when performed on 128-slice dual-source scanners compared to 64-slice scanners [52]. The mean radiation dose overall however was quite high at 11.3 mSv [52]. The "Early computed tomography coronary angiography in patients with suspected acute coronary syndrome" showed that the median effective dose was 5.8 mSv (3.5–10.3 mSv) [31]. The wide variation in effective dose in 2021 shows that, despite the evidence for dose reduction measures, awareness and usage need to be increased if CTCA is to be used on all comers. A structured education solution, such as that proposed and implemented by Hamilton-Craig et al. which resulted in dose reduction [53] could be a solution, given that there is no diagnostic reference level guidance by the Australian Radiation Protection and Nuclear Safety Agency [54]. Encouragingly, increased use of dose-reduction measures was not associated with an increase in the rate of non-diagnostic imaging in the study by Hamilton-Craig et al [53]. Given the recommendations for using CTCA as a first-line investigation for chest pain, radiation dose exposures have not been specifically studied in the population of patients who present to emergency departments, an essential factor that needs to be addressed.

Conclusion

Compared to functional testing, CTCA has high sensitivity and excellent negative predictive value, and offers the opportunity for early initiation of preventive treatments. The low adverse event rate of a normal CTCA offers an opportunity to streamline the investigation of patients with repeat presentations with chest pain to the ED. Further studies in an Australian context are needed to see if the difference between low- and intermediate-risk patients with regards to CTCA use is replicated. If CTCA is to be applied to all comers, there are factors to be considered, such as patient-related factors of obesity and atrial fibrillation, and facility-related factors such as hardware and awareness of dose-reduction measures which impact radiation exposure to patients. Downstream resource utilisation with CTCA is an important area deserving of further study given its intermediate specificity and limited data in Australian settings. Despite these challenges, the opportunities offered by CTCA merit its consideration by the relevant stakeholders such as the Cardiac Society of Australia and New Zealand, the Australian College of Emergency Medicine and the Royal Australia and New Zealand College of Radiologists with regards to increasing the use of CTCA in chest pain pathways.

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