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A pilot study of cardiopulmonary exercise testing and cardiac stress positron emission tomography before major non-cardiac surgery*

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Summary

Cardiac events are a common cause of peri-operative morbidity. Cardiopulmonary exercise testing can objectively assess risk, but it does not quantify myocardial ischaemia. With appropriate dietary preparation to suppress basal myocardial glucose uptake, positron emission tomography with ^{18}F-fluorodeoxyglucose can identify post-ischaemic myocardium, providing an attractive complement to exercise testing. We aimed to investigate the feasibility of this diagnostic algorithm.

Patients referred for cardiopulmonary exercise testing before major cancer surgery were prospectively recruited. Exercise testing and positron emission tomography imaging were performed after a high fat—low carbohydrate meal. Protocol feasibility (primary endpoint) included compliance with pre-test diet instructions and the completion of tests. Stress myocardial perfusion imaging was performed if either exercise testing or positron emission tomography was equivocal or positive for ischaemia. We recorded cardiac complications for 30 postoperative days.

We enrolled 26 participants, 20 of whom completed the protocol. Twenty-one participants proceeded to surgery: myocardial injury or infarction was diagnosed in three participants, two of whom had positive or equivocal positron emission tomography but negative myocardial perfusion imaging.

We have shown that pre-operative cardiac positron emission tomography after cardiopulmonary exercise testing is feasible; protocol deviations were minor and did not affect image quality. Our findings warrant further investigation to compare the diagnostic utility of cardiac positron emission tomography imaging with standard pre-operative stress tests.

Introduction

Each year over 10 million patients have postoperative cardiac complications [1]. Accurate cardiac risk prediction may reduce complications through targeted peri-operative management. Cardiac stress tests inadequately predict complications after non-cardiac non-vascular surgery [2].

Cardiopulmonary exercise testing is the standard method to objectively quantify functional capacity. It is used to assess patients' ability to meet the metabolic demands of major surgery and to predict postoperative morbidity and mortality, including from cardiac disease [3-6]. Pre-operative tests that can identify the site and severity of stress-induced myocardial ischaemia might complement cardiopulmonary exercise tests and increase the precision of predictions.

Cardiac positron emission tomography identifies ischaemic myocardium through its preferential metabolism of the radiolabeled glucose analogue ^{18}F-fluorodeoxyglucose [7]. A significant proportion of peri-

operative cardiac events are associated with myocardial metabolic demand exceeding supply [8, 9]. Positron emission tomography may detect stress-induced ischaemia more sensitively than myocardial perfusion imaging [10-12]. Technical advantages include superior spatial resolution acquired more rapidly with less radiation [12, 13].

The normal heart metabolises free-fatty acids unless stimulated by insulin [14]. Accurate identification of myocardial ischaemia with positron emission tomography depends upon suppressing basal myocardial glucose uptake, which can be achieved by eating a fatty meal containing little carbohydrate [15]. We conducted a prospective study to assess the feasibility of incorporating cardiac positron emission tomography with pre-operative cardiopulmonary exercise testing.

Methods

The Peter MacCallum Cancer Centre Human Research Ethics Committee approved this study (Fig. 1). We recruited adults from July 2014 to February 2016 for whom cardiopulmonary exercise testing was indicated before the intrathoracic, intraperitoneal or head and neck cancer resection or free-flap formation. The first ten participants scored no more than one on the Revised Cardiac Risk Index and the subsequent 20 participants scored at least two. We did not study patients unable to consent or those with insulin-dependent diabetes and women who were pregnant or breastfeeding. Participants provided written informed consent.

To promote myocardial fluorodeoxyglucose uptake after exercise participants ate a fatty dinner and breakfast with little carbohydrate and drank a fatty drink 4-6 h before testing ('Calogen', Nutricia Australia, North Ryde, NSW), whilst beta-blockers were withheld for the preceding 48 h [15, 16]. Before exercise we sampled blood for measurements of serum B-type natriuretic peptide (i-STAT BNP assay, Abbott Diagnostics Australasia, North Ryde, Australia) and troponin I and HS-troponin I (Architect STAT, Abbott Diagnostics Australasia, North Ryde, Australia). We used forearm reactive hyperaemia to indicate endothelial function and vasomotor tone (EndoPAT^{TM}, Itamar Medical, Caesarea, Israel).

One of two experienced anaesthetic consultants supervised standard cardiopulmonary exercise testing [17]. Breath-by-breath gas exchange analysis determined peak volitional oxygen consumption during ramped cycle ergometry, with continuous 12-lead ECG monitoring, after which we injected intravenously 3.6 MBq.kg^{-1} of ^{18}F-fluorodeoxyglucose within 15 min. We used the ECG to synchronise acquisition of the hybrid cardiac positron emission tomographic images (Discovery PET/CT 690, GE Healthcare). We defined myocardial ischaemia on exercise as flat or down-sloping ST-segment depression ≥ 1 mm in two consecutive leads, and we defined equivocal ischaemia as up-sloping ST-segment depression. One of two experienced nuclear medicine consultants interpreted the myocardial scans, which were categorised 'negative' if radiotracer uptake was diffuse or absent or if it was restricted to the papillary muscle [18, 19]. Focal low-grade radiotracer uptake in the territory of a coronary artery was reported equivocal and intense uptake was reported positive. Radiotracer uptake was quantified with an automated contour that encompassed areas

with standardised uptake values ≥ 2.5 (MIM Encore, MIM software, Cleveland, USA). Participants with ischaemia (or an equivocal result) on exercise or positron emission tomography had conventional stress testing one or two weeks later using ^{99m}Tc-sestamibi myocardial perfusion imaging, which could also be clinically indicated.

We decided to study 30 participants to assess the feasibility of cardiac positron emission tomography after cardiopulmonary exercise testing, including: compliance with diet and medication instructions; fluorodeoxyglucose injection within 15 min of peak exercise and positron emission tomography within the next 60-120 min; and the suppression of fluorodeoxyglucose uptake within normal myocardium. Secondary endpoints included: the rates of exercise-induced ischaemia detected by cardiopulmonary exercise testing, fluorodeoxyglucose PET imaging and myocardial perfusion imaging; and postoperative cardiovascular complications. We measured serum troponin concentrations and recorded 12-lead ECG daily for three postoperative days. Pre-defined cardiac events included: myocardial infarction [20]; myocardial injury (troponin I > laboratory upper reference limit, without a non-ischaemic cause); non-fatal and fatal cardiac arrest. We categorised postoperative complications with the morbidity survey (POMS) [21]. We used SPSS (version 25, IBM Corp., Armonk, NY) and R (version 3.4.2, R Core Team, R Foundation for Statistical Computing, Vienna, Austria) for statistical analyses.

Results

We discontinued recruitment after 26 participants due to insufficient funds and time (Fig. 2). The full protocol was completed by 20/26 participants: 23 ate the fatty dinner and breakfast, but four ate additional carbohydrate; 25 drank the fatty drink; 26 fasted for at least four hours before the exercise test; 24 completed a cardiopulmonary exercise test and had positron emission tomography (Table 1).

Seven beta-blocked participants discontinued the drug for at least 48 h. There were no adverse events with fluorodeoxyglucose injection, given within 15 min of exercise in all 24 participants, in 23 of whom positron emission tomography was completed within 120 min of injection. Myocardial ischaemia on cardiopulmonary exercise tests and positron emission tomography (Fig. 3) are detailed in Table 2, as well as myocardial perfusion imaging in nine participants, and postoperative complications in 21 patients who proceeded to surgery. Background myocardial fluorodeoxyglucose uptake was completely suppressed in 20/24 participants: three participants had low-grade papillary muscle uptake and one had low-grade diffuse left ventricular uptake. All participants had normal troponin levels before and after exercise. Five participants had raised BNP (> 92 ng.l^{-1}) on both measurements and one patient had a rise to 98 ng.l^{-1} (from 84 ng.l^{-1}) after exercise. No participant had a reactive hyperaemia index consistent with subsequent peri-operative myocardial injury (≤ 1.22) [22].

Discussion

We have shown that cardiac positron emission tomography can be incorporated into a pre-operative cardiopulmonary exercise service, with three-quarters of participants completing the protocol.

Positron emission tomography detects metabolic ischaemia, rather than the traditional assessments of perfusion or contractility and it might augment risk calculated from cardiopulmonary exercise testing [23, 24, 29]. It may also detect supply-demand imbalance in conditions such as hypertrophic cardiomyopathy [27] and coronary microvascular dysfunction [28].

The incomplete suppression of background myocardial fluorodeoxyglucose uptake in four participants was consistent with other studies [25, 33-35]. Diffuse uptake may indicate inadequate dietary preparation, although the participant complied with the protocol and had normal fasting blood glucose [36]. Focal papillary muscle fluorodeoxyglucose uptake in three participants might be a normal physiologic variant [18, 19].

Our study has several limitations. We relied on patient-reported dietary intake to assess dietary compliance. However, all fasting blood glucose levels were within acceptable limits and the average resting respiratory exchange ratio of 0.79 is compatible with the prescribed diet and the reliable interpretation of cardiopulmonary exercise [37, 38]. We did not perform myocardial perfusion imaging in all participants as we were concerned about unwarranted radiation. We did not conceal patient characteristics from investigators who reported positron emission tomograms and those who reported postoperative outcomes.

Further research may determine whether cardiac positron emission tomography can improve the prediction of postoperative outcomes and the thresholds for prognostically-significant uptake.

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Table 1 Characteristics of 26 participants who underwent cardiopulmonary exercise testing and positron emission tomography, 21 of whom proceeded to surgery. Values are mean (SD) or number.

Characteristic	
Age; years	69.9 (9.3)
Sex; male	20
BMI; $kg.m^{-2}$	27.8 (5.6)
Primary malignancy	
Colorectal	15
Oesophago-gastric	7
Other	4
Hypertension*	17
Prior myocardial infarction	7
Angina or prior revascularisation for stable coronary artery disease	5
Heart failure	2
Prior transient ischaemic attack	2
Prior stroke	3
eGFR (adjusted for age, CKD-EPI)	85 (25)

Type 2 diabetes	3
Obstructive pulmonary disease	7
ECOG performance status	
Fully active	8
Restricted in strenuous activity	16
Self-care but unable to work	2
Duke Activity Status Index	32.1 (12.3)
Neoadjuvant chemoradiotherapy	12
Cardiopulmonary exercise test	
Serum glucose before exercise; mmol	5.5 (1.4)
Peak power; W	106 (29)
Peak VO_2; $ml.min^{-1}$	1364 (360)
Peak normalised VO_2; $ml.kg^{-1}.min^{-1}$	17.5 (3.3)
Anaerobic threshold; ml $O_2.kg^{-1}.min^{-1}$	13.0 (3.2)
V_E/VCO_2	33.0 (6.9)
Reactive hyperaemia index	2.31 (0.62)
Portsmouth POSSUM	
Operative score	16.4 (5.5)
Physiologic score	17.3 (4.5)
Revised cardiac risk index: 1/2/3	11/11/4

BMI, body mass index; CKD-EPI, Chronic Kidney disease epidemiology collaboration; ECOG, Eastern Cooperative Oncology Group; POSSUM, Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity

*defined as a documented diagnosis of hypertension by a medical practitioner or antihypertensive therapy for hypertension.

Table 2 Characteristics compatible with myocardial ischaemia on pre-operative cardiopulmonary exercise testing (CPET), positron emission tomography (PET) and myocardial perfusion imaging (MPI) in 24

Ischaemia on testing	Revised cardiac risk index		Myocardial ischaemia on pre-operative testing						Complication	
			CPET		PET scan		MPI			
	≤ 1 (n = 10)	≥ 2 (n = 14)	Yes or equivocal	No	Yes or equivocal	No	Yes	No	Cardiac (n = 7)	Other (n = 18)
CPET (n = 24)										
No	10	10	-	20	2	18	0	5	6	14
Equivocal	0	2	4	-	2	0	1	1	1	2
Yes	0	2		-	2	0	1	1	0	2
PET (n = 24)										
No	9	9	0	18	-	18	0	3	5	12
Equivocal	1	1	1	1	6	-	1	1	1	2

participants. Values are number.

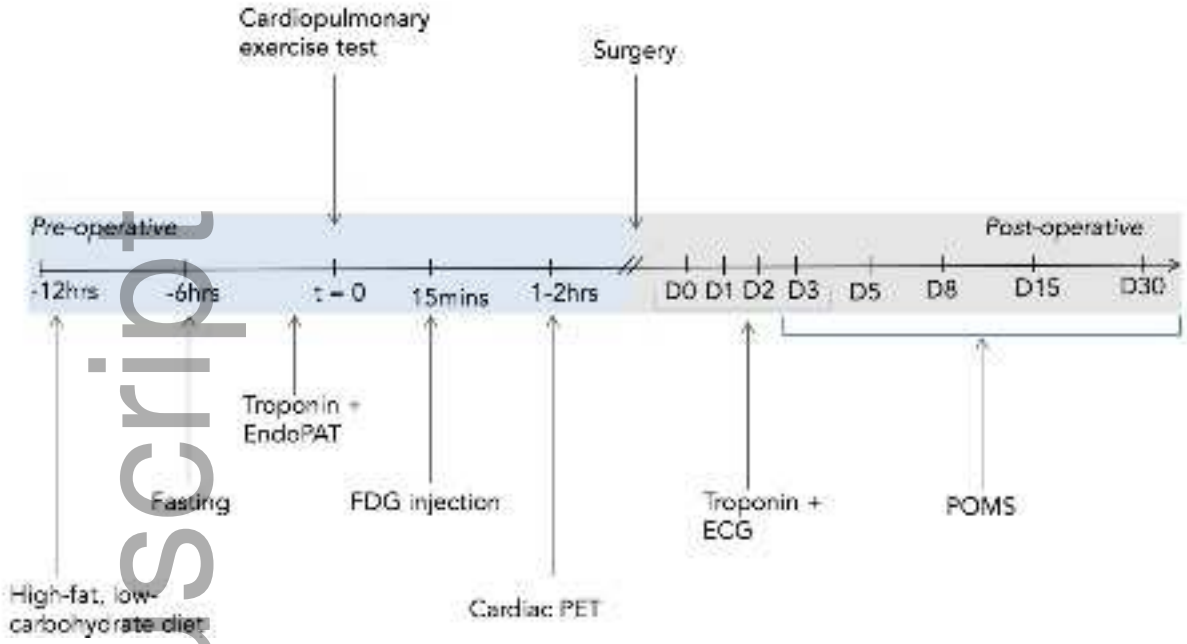
Yes	0	4	3	1		-	1	3	1	4
MPI (n = 9)										
No	1	6	2	5	4	3	-	7	2	4
Yes	0	2	2	0	2	0	2	-	0	2

Figure 1 Study timeline showing the study protocol and postoperative surveillance.
D0-D30, postoperative day zero to day 30; EndoPAT, forearm reactive hyperaemia; FDG, ^{18}F-fluorodeoxyglucose; POMS, postoperative morbidity survey.

Figure 2 Patient recruitment and protocol completion: 'low-risk' and 'high-risk' are revised cardiac indices of < 2 and ≥ 2, respectively.

CPET, cardiopulmonary exercise testing; MPI, myocardial perfusion imaging; PET, positron emission tomography

Figure 3 Patterns of myocardial fluorodeoxyglucose uptake: A, complete suppression; B, diffuse left ventricular myocardial uptake; C, equivocal low-grade focal left ventricular uptake; D, intense focal uptake by the left ventricle, interpreted as 'positive' for ischaemia.



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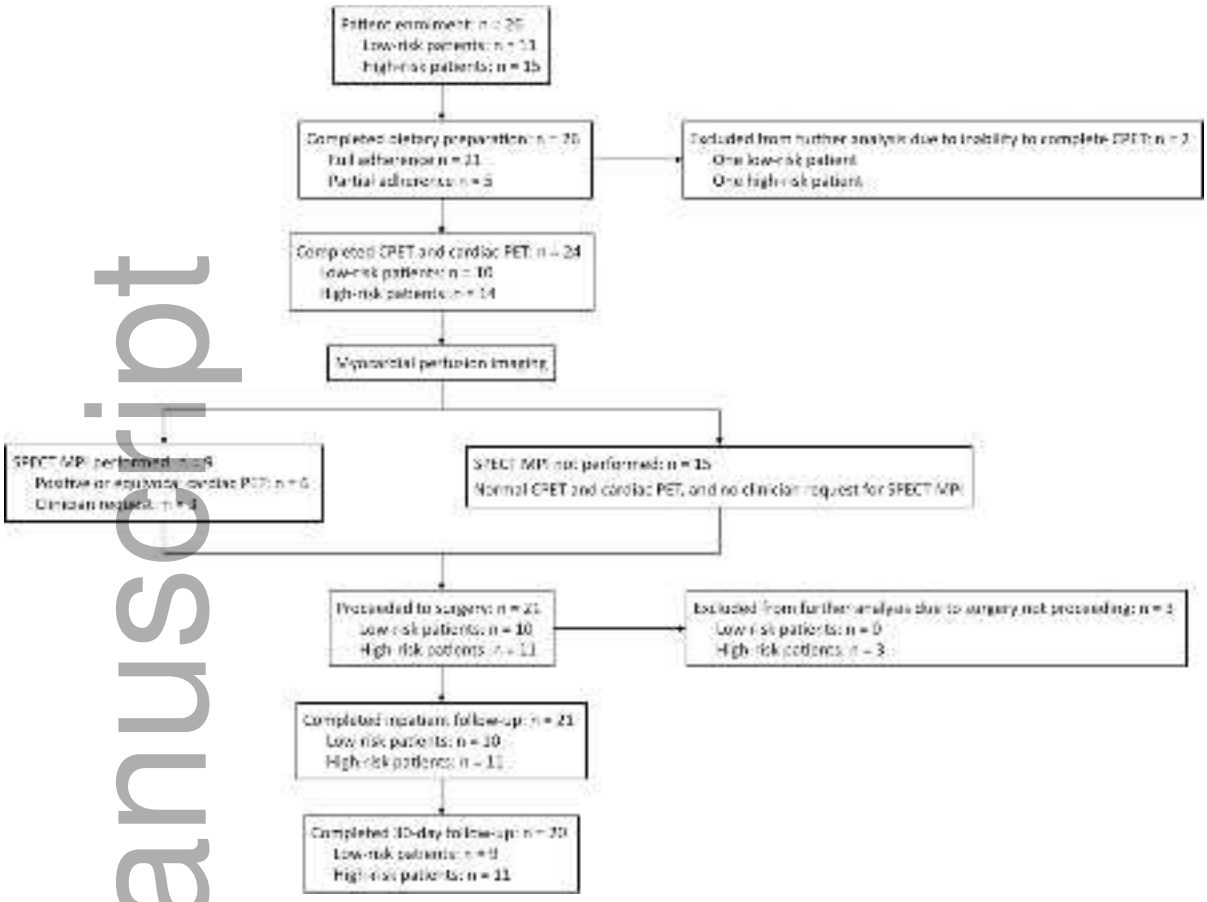

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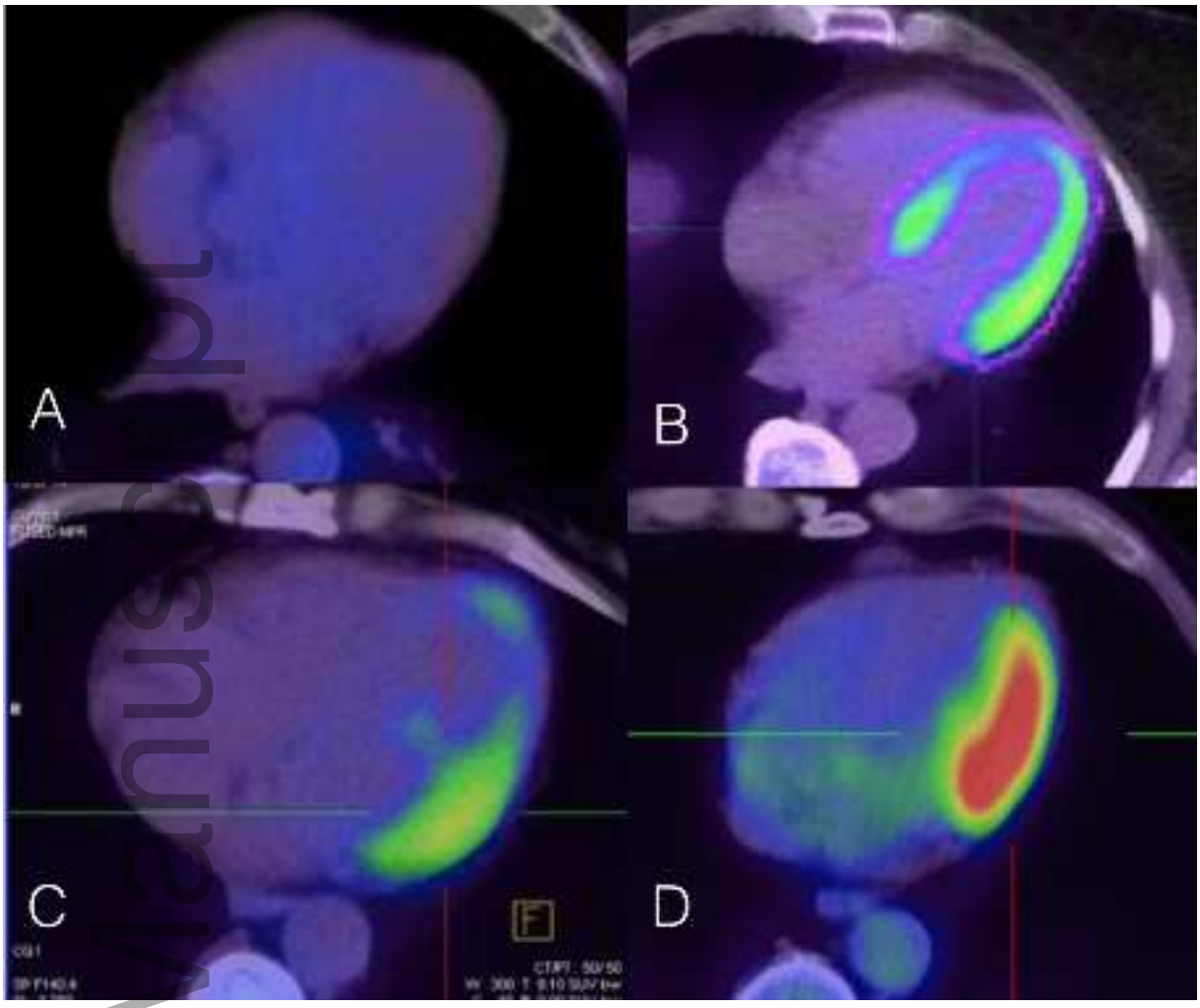

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