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The Role of Myocardial Perfusion Scanning, Heart Rate Variability and D-dimers in Predicting the Risk of Perioperative Cardiac Complications after Peripheral Vascular Surgery

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Objectives: *to study the value of a number of proposed prognostic factors in prediction of the risk of perioperative cardiac events after vascular surgery.*
Design and Methods: *two hundred and ninety-seven patients undergoing peripheral vascular surgery were prospectively studied. Patients underwent preoperative 24 h ambulatory electrocardiography, measurement of haemostatic variables, myocardial assessment of perfusion by dipyridamole–thallium scintigraphy and radionuclide ventriculography. The primary endpoint was cardiac death or nonfatal myocardial infarction within 30 days of surgery. A combined endpoint included the primary endpoint plus occurrence of cardiac failure, unstable angina or serious arrhythmias.*
Results: *the primary endpoint occurred in 21 (7%), and the combined endpoint in 41 (14%) of patients. On multivariate analysis, increased age, previous myocardial infarction, aortic surgery, impaired heart rate variability and a positive thallium scan were independent predictors of primary end-points. Preoperative atrial fibrillation and increased fibrin D-dimer were additional predictors of the combined endpoint. Construction of receiver-operator characteristic curves to examine the incremental value of predictive models showed that sensitivity and specificity of clinical data alone for primary endpoints was 71% and 72% respectively, while for the full model (incorporating heart rate variability and thallium data) this rose to 84% and 80% ($p = 0.0001$).*
Conclusions: *preliminary screening using clinical data has limited value in risk assessment prior to vascular surgery but preoperative heart rate variability, D-dimers and thallium scanning provide modest incremental predictive value.*

Key Words: Postoperative complications; Thallium radioisotopes; Ambulatory electrocardiography; Fibrin fibrinogen degradation products.

Introduction

Perioperative myocardial infarction remains a common and serious complication of surgery, particularly in those undergoing peripheral vascular surgery.[1] Preoperative risk assessment is difficult[2] but important. Current risk assessment is based on clinical criteria plus the demonstration of reversible ischaemia by thallium scanning, while recent studies have used 24-h ambulatory electrocardiography to identify ST segment depression.[3,4] This study aims to determine the value of clinical risk factors, ambulatory electrocardiography and thallium scanning in determining the risk of perioperative cardiac complications. In addition, it considers two new risk factors, fibrin D-dimer and heart rate variability. D-dimer levels have been shown to correlate with the risk of coronary events in patients with peripheral arterial disease,[5] while impaired heart rate variability is a predictor of mortality in patients with known ischaemic heart disease.[6] The incremental predictive value of all of these parameters over routine clinical assessment is considered.

Materials and Methods

Between 1994 and 1996, a total of 608 patients underwent surgery within the Glasgow Royal Infirmary Vascular Unit. Among these, 311 were not included in the study (17 no consent, 188 urgent or emergency surgery precluding work-up, 106 logistics preventing work-up), whereas 336 patients were recruited into the study. Of these, 2 died before surgery, 18 were deemed unfit for surgery and 19 underwent a change

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in treatment plan, leaving 297 patients undergoing peripheral arterial surgery (92 aortic, 47 carotid, 37 infrainguinal, 13 major amputation and 108 miscellaneous [femoral or extra-anatomical] procedures). These patients were studied prospectively. All patients gave informed consent approved by the local ethical committee. Standard clinical data were collected preoperatively as listed in Table 1. Blood samples were taken for full blood count, electrolytes, serum lipids, fibrinogen (Clauss assay), fibrin D-dimer (ELISA; AGEN, New Jersey, U.S.A., upper limit 250 ng/ml), plasma viscosity (Coulter capillary viscometer) and von Willebrand factor (ELISA; DAKO, Copenhagen, Denmark) prior to surgery. Twenty-four-hour ambulatory electrocardiography was performed, using bipolar chest leads to give quasi V1 and V5 recordings. The tapes were analysed using an Oxford Excel 2 Analyser (Oxford Instruments, Abingdon, U.K.), with further review by a cardiologist unaware of the patients' clinical details. The following parameters were derived from the ambulatory ECG: transient ST depression (more than 0.1 mV ST segment depression 60 ms from the J point, occurring for more than 30 s), total ischaemic burden (the product of depth and duration of ST segment depression)[7] and number of ventricular ectopic beats over 24 h. Persistent ischaemia was defined as ST depression occurring throughout the recorded ambulatory ECG. Heart rate variability was calculated using an in-house software package, which analysed the R–R intervals from 24-h tapes. The programme determined the mean normal R–R interval (Mean NN), the standard deviation of this mean (SDNN), and the averaged mean and standard deviation of groups of normal beats over five minute intervals (Mean ANN, SDANN).[8] The triangular index[6] was derived by dividing the total number of normal RR intervals by the modal count (number of RR intervals with the most frequently observed duration of RR interval). The package also calculated the pNN50, defined as the percentage of all RR intervals differing by more than 50 ms from the previous RR interval.

Patients underwent planar stress-redistribution dipyridamole-thallium scanning and radionuclide ventriculography.[9,10] Patients were given an infusion of dipyridamole and asked to exercise on a bicycle ergometer. 60 MBq of thallium-201 were injected intravenously before the end of exercise. The heart was imaged in 3 projections, with simultaneous ECG recording enabling images to be gated to the cardiac cycle. Scans were repeated 4 h after dipyridamole, and images acquired as before. Thallium scans were assessed quantitatively by two independent, blinded observers and disagreement resolved by a third. Each projection was subdivided into 5 segments. A perfusion score of 1 to 4 was given for each segment, giving a possible total score of 60 each for the stress (after dipyridamole) and reperfusion (at rest) scans. A positive scan was defined as a scan with both a stress score over 20 and a reversibility score (stress score minus reperfusion score) greater than 10. After thallium scanning, 3 mg of pyrophosphate followed by 600 MBq of technetium^{99} were given and gated images acquired in 2 projections (40° left anterior oblique and 75° left anterior oblique) and reconstructed into a 24 frame representative cardiac cycle to obtain a ventriculogram.The clinical team was blinded to the results of the haemostatic studies, and of the ambulatory and signal-averaged electrocardiography. Radionuclide scans were only made available when specifically requested by a cardiologist carrying out a preoperative risk assessment. The results of thallium scanning were seen for 28 patients, of whom 3 had their operation cancelled due to a perceived high perioperative risk; 2 of the remainder had a perioperative cardiac event.

Patients were screened for myocardial infarction using daily electrocardiograms (ECG) and cardiac isoenzymes for the first three postoperative days. The enzyme criteria for the diagnosis of perioperative myocardial infarction were a total creatine kinase (CK) level $\geq 2\times$ upper limit of normal, plus CK-MB >10 ng/ml and CK-MB: CK ratio >5%. ECGs were reviewed independently by two experienced, blinded observers. Myocardial infarction was diagnosed if new Q waves or transient ST segment elevation appeared on the ECG, if the enzyme criteria were satisfied, or if there was post-mortem evidence of infarction.

The primary end-point of the study was the occurrence of myocardial infarction or cardiac death within 30 days of surgery. The combined endpoint comprised the primary endpoint or any of the following: left ventricular failure (clinical pulmonary oedema requiring intravenous diuretic therapy), unstable angina (angina associated with transient ST-T changes) or serious arrhythmias (sustained ventricular arrhythmias or atrial fibrillation requiring intervention).

Statistical analysis

Data were analysed with SPSS version 7.0. The data were split into 4 main screening areas: clinical, rheological, thallium and ambulatory ECG to best represent the clinical setting in which clinical data are routinely available, and the results of any special investigations are added to complete the risk assessment. Logistic

Table 1. Preoperative variables tested against perioperative cardiac events.

From clinical history	From examination and basic investigation	Rheological data	Ambulatory ECG, heart rate variability and signal-averaged ECG	Thallium and radionuclide ventriculography
Sex	Weight	Haematocrit	**Transient ischaemia**+	**Stress score***+
Age*+	Height	White cell count	Persistent ischaemia	Reperfusion score
No of previous MI	Body mass index	Platelets	Total ischaemic burden	**Reversibility score***+
Recent MI (<6 months)	Heart rate	Plasma viscosity	Ventricular ectopics/24 h	**Positive thallium scan***+
Grade of angina (Canadian Classification)	Systolic blood pressure	Fibrinogen	Mean NN	**LVEF***+
Unstable angina	Diastolic blood pressure	Von Willebrand factor	SDNN	RVEF
Atrial fibrillation	Aortic stenotic murmur	**Fibrin D-dimer***+	Mean ANN	
Recent heart failure (<1 week)	Left ventricular failure	Factor VII	SDANN	
Heart failure ever	Right ventricular failure		**Triangular Index***	
Grade of dyspnoea (NHYA)	Respiratory disease		pNN50	
Respiratory disease	**ECG rhythm**+		QRSd	
Current smoker	**Infarct on ECG***+		RMS40	
Hyperlipidaemia	Location of infarct		LAS40	
Hypertension	**Abnormal ECG**+			
NIDDM	Ankle–brachial pressure index			
IDDM*	Abnormal electrolytes			
Previous stroke	Carboxyhaemoglobin			
Frequent (>5/min) ventricular ectopic beats	Blood glucose			
Previous vascular surgery	Abnormal liver function tests			
Using aspirin+	Total cholesterol			
Using anti-coagulants	High density lipoprotein			
Using beta-blockers	Low density lipoprotein			
Using ACE inhibitors	Very low density lipoprotein			
Using digoxin	**Triglyceride**+			
	Abnormal chest radiograph			
	Poor general medical status			
	Detsky score			
	Type of surgery(aortic v rest)*+			
	Urgency of surgery			

*=$p<0.05$ for primary events on univariate analysis (in bold type).
+=$p<0.05$ for combined events on univariate analysis (in bold type).
Abbreviations: MI=Myocardial infarction, NYHA=New York Heart Association, NIDDM=non-insulin dependent diabetes, IDDM=insulin dependent diabetes, LVEF=left ventricular ejection fraction, RVEF=right ventricular ejection fraction.
Measures of heart rate variability are defined as follows: Mean NN is the mean normal R–R interval, SDNN is the standard deviation of this mean, and Mean ANN and SDANN the averaged mean and standard deviation for groups of normal beats over 5 min intervals. The triangular index is the total number of normal RR intervals divided by the modal count (number of RR intervals with the most frequently observed duration of RR interval). pNN50 is the percentage of all R–R intervals differing by more than 50 ms from the previous R–R interval.

regression analysis was employed at both the univariate and multivariate levels for the primary and combined endpoints. The models were built in a stepwise fashion by including variables for which $p<0.05$. Initially, the clinical data were modelled using the stepwise procedure and a basic clinical model was derived for each endpoint. This clinical model became the building block from which 3 intermediate models were obtained. The clinical factors were forced into the intermediate models and the remaining factors entered in a stepwise manner. Finally, the full model was obtained by forcing the clinical factors and entering simultaneously the significant factors of the 3 intermediate models in the stepwise manner. Receiver operator characteristic curves were produced for each model with their respective sensitivity and specificity values, and the areas under the curves.[11]

Results

The primary endpoint occurred in 21 patients; non fatal perioperative myocardial infarction in 7 and cardiac death in 14. Forty-one patients experienced the combined endpoint. The results of univariate analysis for all preoperative risk factors are given in Table 1, and the actual values for significant variables are shown in Table 2. Variables which remained significant on logistic regression analysis are shown in Table 3, along with the odds ratios and respective confidence intervals for an event. Increased age, ECG evidence of previous myocardial infarction, aortic surgery, impaired heart rate variability (triangular index) and a positive thallium scan were the only independent predictors of primary end-points. Preoperative atrial fibrillation/flutter, previous myocardial infarction, aortic surgery, increased fibrin D-dimer and a positive thallium scan were independent predictors of the combined end-point. Clinical risk factors, including the Detsky score, were poor predictors of perioperative cardiac risk. Ischaemia on the ambulatory ECG was a weak univariate predictor of combined end-points.

Eight of 30 (27%) patients with a positive thallium scan sustained a primary event, while 13 of 253 (5%) with a negative scan had an event. Similarly, reversibility score (i.e. the size of the reversible defect) was a univariate predictor of both primary and combined endpoints; for primary endpoints, median scores were 12 in those with an event, and 6 in those without ($p=0.0001$, Mann–Whitney *U*-test) and for combined endpoints, scores were 8 in those with an event, and 6 in those without ($p=0.0586$, Mann–Whitney *U*-test).

Table 4 shows the incremental value of the preoperative investigations described over standard clinical risk factors. Multivariate significance values for investigations or operative factors *in combination* with clinical factors are given. Intra-operative data such as the type and length of anaesthetic were not predictive of outcome, with the exception of the amount of fluid or blood transfused intra-operatively, which were significant univariate predictors of primary and combined end-points.

Figure 1 shows the incremental value of the preoperative investigations described over standard clinical risk factors, in the form of receiver-operator characteristic curves.The sensitivity and specificity of each model was calculated for the best point of each curve. For primary end-points these were 71% and 72% respectively for clinical factors alone, 74% and 71% for clinical factors plus ambulatory ECG data, 71% and 72% for clinical factors plus fibrin D-dimer, 71% and 69% for clinical plus thallium data and 84% and 80% for the full model.

Figure 2 shows the effect of using a selective, stepwise approach to investigation and risk stratification. This enabled 91 patients to be classified as low risk (1 primary, 2 combined events) using routine clinical criteria plus measurement of fibrin D-dimer. One hundred and twenty three patients were ultimately classified as high-risk after selective use of thallium scanning and ambulatory ECG. Of these 18 sustained a perioperative myocardial infarction or cardiac death (Sensitivity 86%, Specificity 62%, PPV 15%, NPV 98%) while 27 had a combined end-point (Sensitivity 66%, Specificity 63%, PPV 22%, NPV 92%). The remaining 83 intermediate risk patients sustained 2 primary and 12 combined events.

Discussion

This study is consistent with published data in indicating that the risk of perioperative myocardial infarction or cardiac death after peripheral vascular surgery is around 7%, with a 14% risk of any perioperative cardiac event.[1] Previous risk assessment studies have considered the value of individual investigations,[3,12–14] have used selected high risk groups[4,15] or have not blinded clinicians to test results.[16,17] It is difficult to translate results of such studies into clinical practice, where the majority of patients are in an intermediate risk category.[18] In our study, the results of all but standard clinical data were blinded, although in a small number of cases thallium results were revealed at the request of the cardiologist reviewing

Table 2. Predictors of primary and combined events on univariate analysis.

Variable	Primary events		*p*-value	Combined events		*p*-value
	With event	Without event		With event	Without event	
Mean age (s.e.)	71 (1.1)	65 (0.5)	0.0001	69 (1)	65 (0.6)	0.003
IDDM	2/21	5/276	0.01 (Fisher's exact)			
No use of aspirin				35/41	117/256	0.003
Atrial fibrillation on ECG				6/41	11/256	0.009
Infarct on ECG	7/21	37/276	0.01	12/41	32/256	0.005
Abnormal ECG				26/41	110/256	0.015
Mean Triglyceride (s.e.)				1.7 (0.1)	2.15 (0.08)	0.008
Aortic v other surgery	12/21	80/276	0.007	25/41	67/256	0.0001
Mean Log D-dimer (s.e.)	2.75 (0.08)	2.47 (0.02)	0.003	2.66 (0.05)	2.46 (0.02)	0.001
Transient ischaemia				14/38	48/237	0.023
Mean Triangular Index (s.e.)	21.5 (1.7)	26.6 (0.6)	0.009			
Mean Stress score (s.e.)	22.2 (1.8)	14.4 (0.5)	0.0004	18.3 (1.5)	14.4 (0.5)	0.015
Mean reversibility score (s.e)	12 (1.6)	6.4 (0.3)	0.002	8.8 (1.1)	6.5 (0.3)	0.048
Positive Thallium scan	8/21	30/270	0.0001	10/41	28/250	0.02
Mean LVEF (s.e.)	31.3 (2.3)	37.5 (0.7)	0.016	33 (1.7)	37.7 (0.7)	0.014

Continuous variables by *t*-Test, discrete variables by Chi-square unless otherwise stated.
s.e. = standard error, IDDM = insulin dependent diabetes mellitus, ECG = electrocardiogram, LVEF = left ventricular ejection fraction.

Table 3. Odds ratios for predictors of primary and combined endpoints on univariate and logistic regression analysis.

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% C.I.)	*p*-value	Odds ratio (95% C.I.)	*p*-value
Primary endpoints				
Age of patient at time of operation	1.1 (1.02, 1.15)*	0.006	1.09 (1.02, 1.17)*	0.011
Previous infarct ECG (yes vs no)	3.2 (1.21, 8.46)	0.019	4.84 (1.38, 17.04)	0.014
Type of operation performed (aortic vs other)	3.00 (1.18, 7.69)	0.035	6.12 (1.85, 20.28)	0.009
Triangular index ($\leq$25.8 vs >25.8)	2.98 (1.04, 8.52)	0.042	6.0 (1.56, 22.83)	0.009
Thallium scanning (positive vs negative)	5.5 (2.02, 14.99)	0.001	13.62 (3.66, 50.76)	<0.001
Combined endpoints				
Cardiac rhythm on ECG (atrial fibrillation, flutter, vs sinus)	2.94 (1.06, 8.15)	0.038	4.59 (1.40, 15.01)	0.012
Previous infarct ECG (yes vs no)	2.87 (1.33, 6.19)	0.007	3.94 (1.60, 9.68)	0.003
Type of operation performed (aortic vs other)	4.85 (2.30, 10.22)	0.001	6.51 (2.75, 15.46)	0.001
Fibrin D-dimer	3.17 (>311.1 vs $\leq$3.11.1 ng/ml#)	0.002	3.23 (1.41, 7.38)	0.006
Thallium scanning (positive vs negative)	3.15 (1.33, 7.47)	0.009	5.47 (1.95, 15.31)	0.001

* Odds ratio per year increment.
# Median value.

the patient prior to surgery. These cases may have resulted in an underestimation of the predictive value of preoperative thallium scanning, but it was felt unethical to withold these results.

We have found clinical risk factors, including the Detsky score,[19] to be poor predictors of perioperative cardiac risk. The patient's age, the presence of previous infarction or abnormal rhythm on the preoperative ECG and aortic versus other types of arterial surgery were the only independent clinical predictors of perioperative cardiac risk. Insulin dependent diabetes mellitus showed borderline significance, but too few patients (7 of whom 2 had a primary event) had this factor to be included in our multivariate analysis. The Detsky score is derived from multivariate analysis of clinical risk factors in a specific group of peripheral vascular patients, but showed no predictive value in our patients. These findings are unsurprising; almost two-thirds of patients undergoing peripheral vascular surgery will have angiographic evidence of severe coronary artery disease, and a third of patients with no clinical evidence of ischaemic heart disease will have severe disease on angiography.[20] The poor predictive value of clinical risk factors has been docu-

Table 4. Logistic regression analysis is showing incremental value of additional investigations over basic clinical data, for primary and combined endpoints.

Clinical + ECG data			Clinical + Rheological data			Clinical + Thallium data			Clinical + Operational data			Full model		
Variable	Primary endpoint *p*-value	Combined endpoint *p*-value	Variable	Primary endpoint *p*-value	Combined endpoint *p*-value	Variable	Primary endpoint *p*-value	Combined endpoint *p*-value	Variable	Primary endpoint *p*-value	Combined endpoint *p*-value	Variable	Primary endpoint *p*-value	Combined endpoint *p*-value
Triangular Index	0.0248		Log FDP	0.0518	0.0164	Positive thallium	0.0012	0.0066	Vol of blood replaced	0.0502		Positive thallium scan	0.0001	0.0012
Atrial fibrillation on ECG		0.0016	Atrial fibrillation on ECG		0.0068	Atrial fibrillation on ECG		0.0185	Atrial fibrillation on ECG		0.0032	Log FDP	0.0708	0.0055
Previous infarct on ECG	0.0269	0.0161	Previous infarct on ECG	0.0338	0.0087	Previous infarct on ECG	0.0467	0.003	Previous infarct on ECG	0.0393	0.0024	Triangular Index	0.0083	
Operation type	0.0222	0.0001	Operation type	0.0567	0.0003	Operation type	0.0151	0.0001	Operation type		0.0394	Atrial fibrillation		0.0117
Age	0.0531					Age	0.0083		Age	0.0039		Previous infarct on ECG	0.0198	0.0028
												Operation type	0.01	0.0001
												Age	0.0738*	

Abbreviations: VPBS = ventricular ectopic beats/24 h, LVEF = left ventricular ejection fraction, RVEF = right ventricular ejection fraction, VWF = von Willebrand Factor, FDP = D-dimers, univar = univariate, multvar = multivariate.
* NB. Although p value >0.05, variable is included in model as all univariately significant clinical variables were forced into subsequent models.

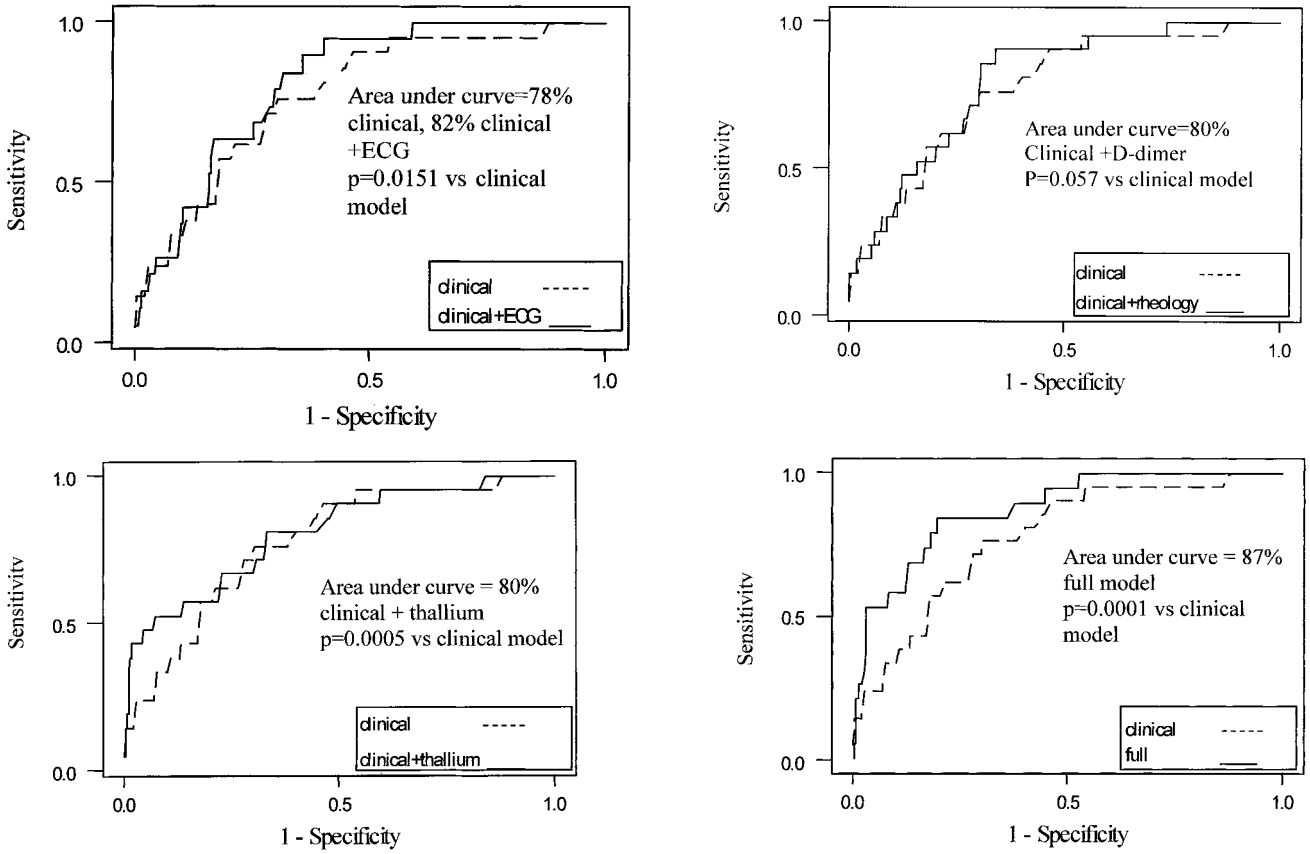

Fig. 1. Receiver–operator characteristic curves for primary endpoints.

mented by other authors.[21,22] An extensive review[23] found heart failure, rhythm other than sinus on the preoperative ECG and diabetes to be the only robust clinical predictors of perioperative risk. A study of 353 patients undergoing peripheral vascular surgery[24] found, in agreement with the present study, that age and previous infarction on the ECG were independent risk predictors, as was angina. We conclude that age, the preoperative ECG and the type of surgery planned are the only routinely acquired clinical indicators of risk, although diabetes may also be important.

This study has shown for the first time that hypercoaguability is important in perioperative myocardial infarction. Patients with raised preoperative fibrin D-dimer levels had a higher risk of perioperative cardiac events and this parameter added information to basic clinical data. Fibrinogen, von Willebrand factor and fibrin D-dimer levels are strong predictors of long-term coronary risk in patients with peripheral vascular disease,[5] and of poor outcome after peripheral vascular surgery,[25] but the former were less useful than D-dimer. A recent small study of 42 patients undergoing vascular surgery did not find a correlation between preoperative D-dimer levels and perioperative myocardial ischaemia, but found that transient ST depression occurred more frequently in those with lower postoperative D-dimer, indicating impaired fibrinolysis.[26] A raised level of fibrin D-dimer is an indicator of a hypercoaguable state[27] and we hypothesise that the further increase in coaguability provoked by surgical stress[28,29] may lead to an increased risk of cardiac complications in those with raised preoperative levels of fibrin D-dimer.

This study is the first to show that reduced heart rate variability is a predictor of perioperative cardiac events. Low heart rate variability is an indication of autonomic imbalance,[30] with a relative reduction of vagal and increase in sympathetic tone.[9] Low heart rate variability has been shown to be a strong independent predictor of mortality[6,31] in post-myocardial infarction patients. There is also a clear association with chronic coronary artery disease[32] and sudden death.[8] In our study, the triangular index retains its predictive value for primary end-points over clinical data, so that its value as a risk factor is clear. This may also suggest the possibility of intervention, since ACE inhibitors

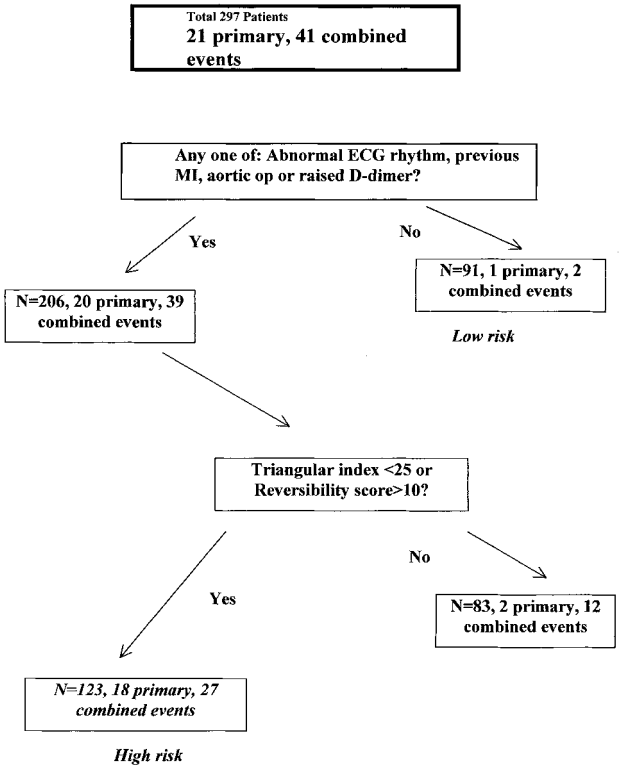

Fig. 2. Algorithm for risk stratification by clinical data, D-dimers, heart rate variability and thallium scanning. Previous MI = previous myocardial infarction.

and β-blockers improve heart rate variability.[31] Indeed, the only interventions clearly shown to reduce the risk of perioperative cardiac events are the administration of β-blockers or α_2-agonists. Poldermans *et al.* found that perioperative bisoprolol reduced perioperative myocardial infarction or cardiac death from 34% to 3.4% in a randomised trial of 112 high-risk patients undergoing peripheral vascular surgery,[33] while in the European Mivazerol trial a subgroup analysis of 904 peripheral vascular patients with known ischaemic heart disease found fewer cardiac deaths (RR 0.33, 95% C.I. 0.13–0.82) in those who were given perioperative mivazerol.[34] We postulate that these benefits may be due to improved heart rate variability, which has important implications for the identification of those most at risk. Interestingly however, in the patients in our study already taking β-blockers (31) or ACE inhibitors (36), perioperative cardiac risk was unchanged; this may have been due to the small numbers involved. The explanation of the relationship between low heart rate variability and perioperative events is unclear. Most of our patients did not die suddenly or from arrhythmias and it should be noted that low heart rate variability may also predict non-arrhythmic cardiac death.[31] The presence of transient ischaemia on the preoperative ambulatory ECG was not useful in risk assessment. Of seven studies which have considered the value of preoperative ischaemia in perioperative risk prediction,[3,4,12,15,35–37] only five have found it to be of value.[3,4,35–37] Three studies have used the presence of ischaemia as the only indicator of a positive test,[3,12,36] while three others also considered the number and duration of ischaemic episode,[4,35,37] with only one author[37] finding an association between this and perioperative events. One study recorded the presence of ischaemia and the maximum degree of ST depression and found this to be of uncertain value.[15] The only study which has examined ventricular arrhythmias in risk prediction also found a poor predictive value.[38] The total ischaemic burden and the number of ventricular ectopic beats on the ambulatory ECG were of no value in the present study.

The dipyridamole–thallium scan was confirmed as a predictor of perioperative cardiac risk. Indeed, a positive scan had higher odds ratios (13.6) than other tests in the prediction of perioperative infarction. Furthermore, on univariate analysis the risk of perioperative cardiac events was positively correlated with the size of the stress perfusion defect and degree of reversibility (the reversibility score). We found that ejection fraction was not an independent predictor of perioperative cardiac events, in keeping with the only other large study to examine radionuclide derived ejection fraction as a predictor of perioperative risk.[13] This may be due to the fact that the ejection fraction is a static measure of cardiac function and unless very low may give little information about how the heart performs under stress. Two meta-analyses have confirmed the predictive value of a reversible defect on thallium scanning.[39,40] Five studies have shown that quantitative analysis is of value,[14,16,41–43] but only two have adopted a Bayesian approach. Vanzetto *et al.*[43] showed that the addition of the results of thallium scanning to clinical data significantly increased the ability to predict a perioperative cardiac event, while L'Italien *et al.*,[44] in a large group of patients, found that the addition of dipyridamole–thallium data to clinical data enabled over 80% of "moderate risk" patients to be reclassified into either "high" or "low" risk groups.

The predictive value of a reversible defect remains significant after clinical risk factors are considered. Adopting the stepwise approach shown in Figure 2, it is possible identify a low risk group in which thallium scanning would be unnecessary. In contrast, those stratified as high risk have an overall 15% risk of a perioperative myocardial infarction or cardiac death, and a 22% risk of any perioperative cardiac event. We believe this to be useful in clinical decision making,

as it may lead to a reassessment of the risk/benefit balance in an individual, and could act as a basis for selection into clinical trials of new strategies to reduce perioperative myocardial infarction. Nevertheless, it should be noted that using the full model described here, only relatively small gains in the ability to predict perioperative risk were obtained; we have been unable to demonstrate a highly accurate method of risk prediction.

This study has a number of limitations. Although this is a large study, the number of patients who sustained a perioperative event is relatively low, making statistical analysis difficult. A large number of parameters have been examined in an attempt to control for confounding factors, but this raises the possibility of false positive findings. Finally, the model given for risk stratification has been derived arbitrarily from the data and not validated (in this study) in a separate group; nevertheless, this paper presents an initial attempt to show that a combination of clinical, rheological, electrocardigraphic and radionuclide parameters can be used incrementally to predict risk.

In summary, this study has shown that, in patients undergoing peripheral vascular surgery, basic clinical data alone are insufficient to predict perioperative risk, but the addition of D-dimer measurement, heart rate variability and thallium scanning provides incremental predictive value. However the gains obtained remain modest, and inclusion of all of these factors was required to increase the senstivity and specificity of risk prediction significantly in clinical terms. Furthermore, the finding that D-dimers and low heart rate variability are related to the risk of perioperative cardiac events may explain the pathophysiology of perioperative myocardial infarction, and explain the recently described protective effect of β-blockers.

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