REVIEW ARTICLE

Use of Myocardial Perfusion SPECT for Preoperative Risk Stratification of Non-Cardiac Surgery

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Abstract

It is difficult to assess the likelihood of perioperative cardiac events mainly because of complicated interrelationships between clinical risk and type of surgery. To overcome this problem, The American College of Cardiology/American Heart Association (ACC/AHA) Task Force published guidelines for perioperative cardiovascular evaluation for non-cardiac surgery. The guidelines offer the strategy of preoperative cardiac therapy, operative performance and perioperative management depending on the urgency of surgery, the patient's risk factors, findings of cardiac testing and specific surgical considerations. Non-invasive cardiac testing including myocardial perfusion single-photon emission computed tomography (SPECT) is recommended to be used mainly in patients with poor functional capacity, when the results will affect patient treatment and outcomes. In the current review, we summarized the use of stress myocardial perfusion SPECT referring to previous reports and our data, and provided the tips for indication of SPECT in preoperative risk stratification in non-cardiac surgery.

Keywords: Myocardial perfusion SPECT, Perioperative cardiac event, Preioperative risk stratification

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Cardiac events are important causes of perioperative mortality and morbidity in non-cardiac surgery. Thus, cardiac risk should be stratified in individual patients who are to undergo surgery, but it is difficult to assess the likelihood of perioperative cardiac events mainly because of complicated interrelationships between clinical risk and type of surgery. To overcome this problem, The American College of Cardiology/American Heart Association (ACC/AHA) Task Force published guidelines for perioperative cardiovascular evaluation for non-cardiac surgery (1-4). These guidelines divide clinical risk factors into major, intermediate and minor categories, and surgical procedures into high, intermediate and low-risk types. These are then used to determine further preoperative examinations, preoperative therapy, operative performance and perioperative management. The guidelines recommend non-invasive cardiac testing including myocardial perfusion imaging to be used mainly in patients with poor functional capacity (<4 METs).

In the current review, we summarized the use of stress myocardial perfusion single-photon emission computed tomography (SPECT) referring to previous reports and our data, and provided the tips for indication of SPECT in preoperative risk stratification in non-cardiac surgery.

Preoperative risk stratification in view of cardiac testing

As mentioned above, preoperative risk stratification is

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generally difficult mainly due to complicated interrelationships between clinical risk factors and type of surgery. Preoperative stress myocardial perfusion imaging provides excellent negative predictive values in forecasting perioperative cardiac events (5). We reported that normal perfusion and wall motion ensure a very low likelihood of perioperative cardiac events in intermediate and low-risk surgery (6). Accurate identification of low risk patients facilitates reductions in cost and preoperative waiting time because low risk individuals can be exempted from further cardiac testing, including catheterization, and proceed directly to surgery.

On the other hand, not only SPECT but also other modalities yield insufficient positive predictive values mainly because of the relatively low frequency of perioperative cardiac events (7). In addition, perioperative mortality and morbidity are related to management of patients. Surgeons and anesthesiologists are not blinded to the results of preoperative cardiac testing. This availability of results has an influence on decisions regarding perioperative management of patients, which could lower the cardiac event rate and underestimate the predictive accuracy of preoperative examinations including SPECT.

Since it is generally difficult to perform a prospective clinical trial for assessing the predictive value on patients undergoing surgery especially when the test results are blinded, most studies of this kind is retrospective. In such studies, authors analyzed the data obtained from patients who underwent preoperative SPECT. Most of them were referred for SPECT because of concern about perioperative cardiac risk. Thus, these patients do not epitomize the general population of non-cardiac surgery candidates in terms of the likelihood of cardiac events. This increases the rate of perioperative cardiac events.

Furthermore, the effect of preoperative revascularization remains unclear. There are some papers showing that preoperative revascularization is ineffective to reduce the cardiac event rate (8,9). However, the effect of preoperative revascularization depends on the selection of patients undergoing revascularization. Further studies are required to clarify the usefulness of SPECT in identifying patients who receive prognostic benefit from preoperative revascularization.

It is generally difficult to elucidate the cost-effectiveness of perioperative SPECT, because of relatively low frequency of perioperative cardiac events, high cost of examination and uncertainty of the effect of preoperative revascularization as mentioned above.

SPECT in preoperative risk stratification

Position of SPECT in risk stratification

Fig. 1 shows the stepwise cardiac evaluation and care program for non-cardiac surgery appeared in the ACC/AHA Guidelines (3). Except for the emergent surgery, patients with active cardiac conditions including unstable coronary disease, decompensated heart failure, significant arrhythmia or severe valvular heart disease, are recommended to undergo further cardiac evaluation and/or treatment. When low-risk surgery is performed on a patient without active cardiac conditions, incremental cardiac risk in undergoing surgery is thought to be negligible. The patient who have a functional capacity 4 METs or more can also proceed to the planned surgery. Preoperative cardiac evaluation of patients other than the above is performed by considering the number of clinical risk factors, type of surgery and results of cardiac testing. Preoperative SPECT is also considered to be used in this step.

Exercise or adenosine for stress testing

Exercise or pharmacological (adenosine) stress is used for myocardial perfusion SPECT to assess stress-induced ischemia. Exercise has advantages that stress is physiological and that exercise capacity can be an index associated with cardiac morbidity and mortality. In addition, exercise myocardial SPECT allows information whether ischemia occurs within the patient's work capacity or not. On the other hand, pharmacological stress has an advantage that ischemia can be induced even if the patient's functional capacity is low. Since perioperative cardiac stress is not dependent on the patient's activities of daily living, pharmacological stress is favorable especially in patients with insufficient functional capacity.

SPECT indices for risk stratification

Electrocardiogram (ECG)-gated stress myocardial perfusion SPECT yields information on myocardial perfusion, cardiac function and left ventricular volumes. It offers various indices including the summed stress score (SSS), summed rest score (SRS), summed difference score (SDS), ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), and so on. SRS and SDS reflect the size of myocardial scar and the amount of stress-induced ischemia, respectively. It has been reported that SRS, SDS and SSS are associated with perioperative cardiac events (6,10-13). The SSS is thought to have a considerable prognostic value because it reflects both scar and ischemia (6, 13).

Differences between rest and stress functional variables

Table 1 Clinical Risk Factors and Surgical Risk

	Grade	Contents
Clinical risk	Major	Unstable coronary syndromes; Decompensated heart failure; Significant arrythmias; Severe valvular disease
	Intermediate	Mild angina pectoris; Prior myocardial infarction; Compensated or prior heart failure; Diabetes Mellitus; Renal insufficiency
	Minor	Advanced age; Abnormal ECG; Rhythm other than sinus; Low functional capacity; History of stroke; Hypertension
Surgical risk	High	Emergent major operations; Aortic and other major vascular surgery; Peripheral vascular surgery; Anticipated prolonged surgical procedures associated with large fluid shift and/or blood loss
	Intermediate	Carotid endarterectomy; Head and neck; Intraperitoneal and intrathoracic; Orthopedic; Prostate
	Low	Endoscopic procedures; Superficial procedures; Cataract; Breast

（cited from reference No. 2）

are markers of stress-induced ischemia (14-16). However, it is reported that a post-stress depression of EF was not associated with perioperative cardiac events (6). This is attributable to the use of pharmacological stress instead of exercise, and to the cohort undergoing preoperative SPECT. Exercise increases myocardial oxygen consumption and facilitates the likelihood of post-ischemic stunning. On the other hand, pharmacological stress causes ischemia through coronary steal that develops mainly in patients with severe coronary stenosis. Since preoperative SPECT is usually performed as a screening procedure, only a limited part of the patients have severe coronary artery disease (CAD). Therefore, the EF depression after adenosine infusion is thought to have limited prognostic value for this cohort.

Clinical risk factors

Many investigators have identified preoperative clinical markers related to postoperative cardiac events, the most frequent being advanced age, hypertension, diabetes, angina pectoris, arrhythmias, history of myocardial infarction, heart failure, prior coronary artery bypass grafting (CABG) and abnormality in electrocardiography (10,11,17-20). As shown in Table 1, the ACC/AHA guidelines divide clinical risk factors into major, intermediate and minor categories (3).

The major category includes unstable coronary disease, decompensated heart failure, significant arrhythmia and severe valvular heart disease listed as active cardiac conditions in Fig. 1. The presence of 1 or more of these conditions mandates intensive management and may result in delay or cancellation of surgery unless the surgery is emergent.

The guidelines selected diabetes mellitus (DM), renal insufficiency, and the history of ischemic heart disease, heart failure, or cerebrovascular disease, as the intermediate risk factors. It is pointed out that 4 to 6 weeks are reasonable to wait to perform elective surgery after myocardial infarction, if a recent stress test does not indicate residual myocardium at risk.

The minor category comprises advanced age (greater than 70 years), abnormal ECG (LV hypertrophy, left bundle-branch block, ST-T abnormalities), rhythm other than sinus, and uncontrolled systemic hypertension. Although these are not proven to increase perioperative risk independently, the presence of multiple minor predictors might lead to a higher suspicion of coronary artery disease. These are not incorporated into the recommendations for treatment in the guidelines.

Risk of surgical procedures

As indicated in Table 1, the ACC/AHA guidelines divide surgical procedures into high, intermediate and low-risk types (3). The high-risk group mainly consists of vascular surgery, and the low-risk type comprises superficial or minimally invasive procedures including endoscopic surgery. The remaining general surgery is classified into the intermediate-risk group. Perioperative cardiac event rates expected are >5%, 1 to 5%, and <1%, corresponding to the high, intermediate and low-risk surgery.

Although there have been enough data concerning the use of SPECT for preoperative risk stratification in high and intermediate-risk surgery (3-24), little are available about low-risk surgery (6,12,13), despite recent widespread acceptance of minimally invasive surgical techniques including endoscopy. Accumulating prognostic data about operations associated with different levels of risk is useful especially when changing a surgical approach to minimally invasive one for

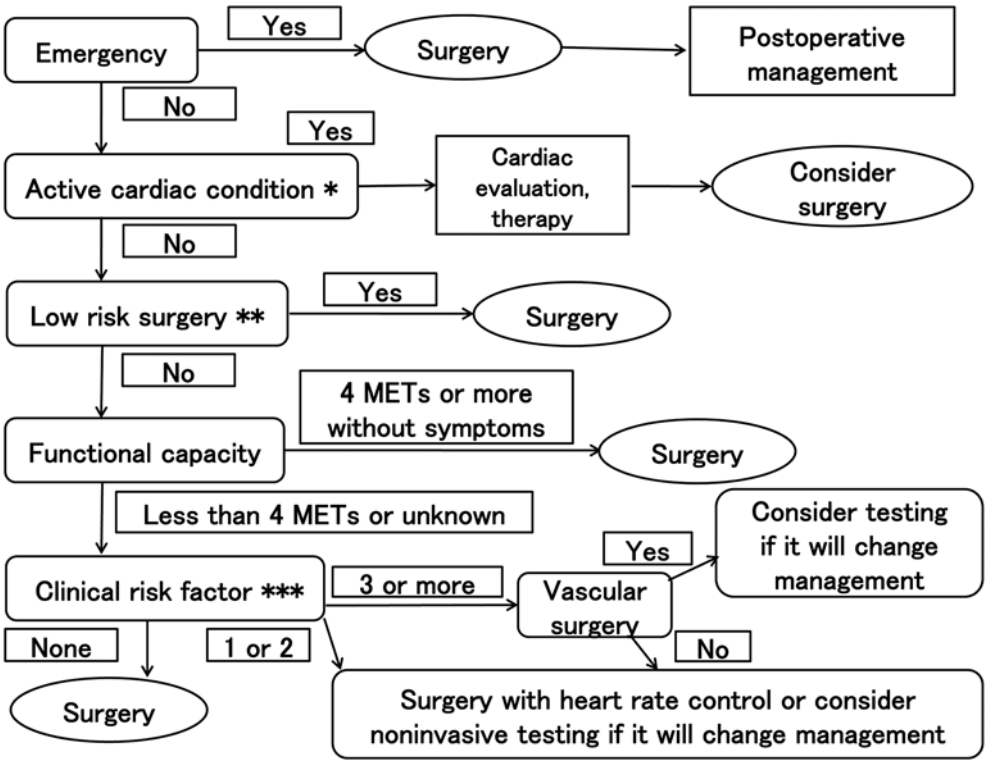

Fig. 1 Stepwise approach to preoperative cardiac assessment
*: unstable coronary disease, decompensated heart failure, significant arrhythmia and severe valvular heart disease, **: indicated in Table 1, ***: diabetes mellitus, renal insufficiency, and the history of ischemic heart disease, heart failure, or cerebrovascular disease.（cited from reference No. 3）

patients with a high estimated cardiac risk, because such data show that cardiac risk is reduced by such choices. We showed that gated myocardial perfusion SPECT has an incremental prognostic value in intermediate, but not in low-risk, non-cardiac surgery as indicated in Fig. 2（6）.

Integrating information in preoperative risk stratification

Before surgery, we can obtain various kinds of information, including clinical and surgical risk, and indices obtained from various preoperative examinations as mentioned above. Consequently, it is important to seek methods to integrate the above information in risk stratification.

Some investigators used mathematical models to provide the likelihood of perioperative cardiac events on the basis of clinical risk and SPECT findings（19,21）. They employed a Bayesian model or an artificial neural network as a tool to calculate the expected cardiac event rates. Advantages of the Bayesian model are that it permits consideration of the procedure-specific institutional complication rate in the estimation of risk and that it is not necessary to assume independence between variables included in the model（19）. The artificial neural network generally allows lower computational burden and is reported to be more accurate in predicting cardiac events for high-risk patients compared with a logistic regression model（21）.

We generated linear and support vector machine（SVM）classifiers, and evaluated their accuracies in predicting perioperative cardiac events in all types of non-cardiac surgery including high, intermediate and low-risk procedures（13）. In addition, we estimated an incremental prognostic value of SPECT indices in each model. The SVM is a kind of supervised learning methodology that yields an appropriate discrimination program by using data whose inputs and accurate outputs are already known（training dataset）. It first generates an N-dimensional hyperplane that best separates the training data into two different half spaces, and then classify unknown *de novo* data by determining the half space they belong to. We introduced a SVM in preoperative risk stratification. In this context, the above two half spaces equal to the two situations: the presence and absence of cardiac events, and the training dataset consists of data of each patient whose predictive variables and the prognostic outcome are already known. The hyperplane is determined by a cluster of data located near the border of the two spaces,

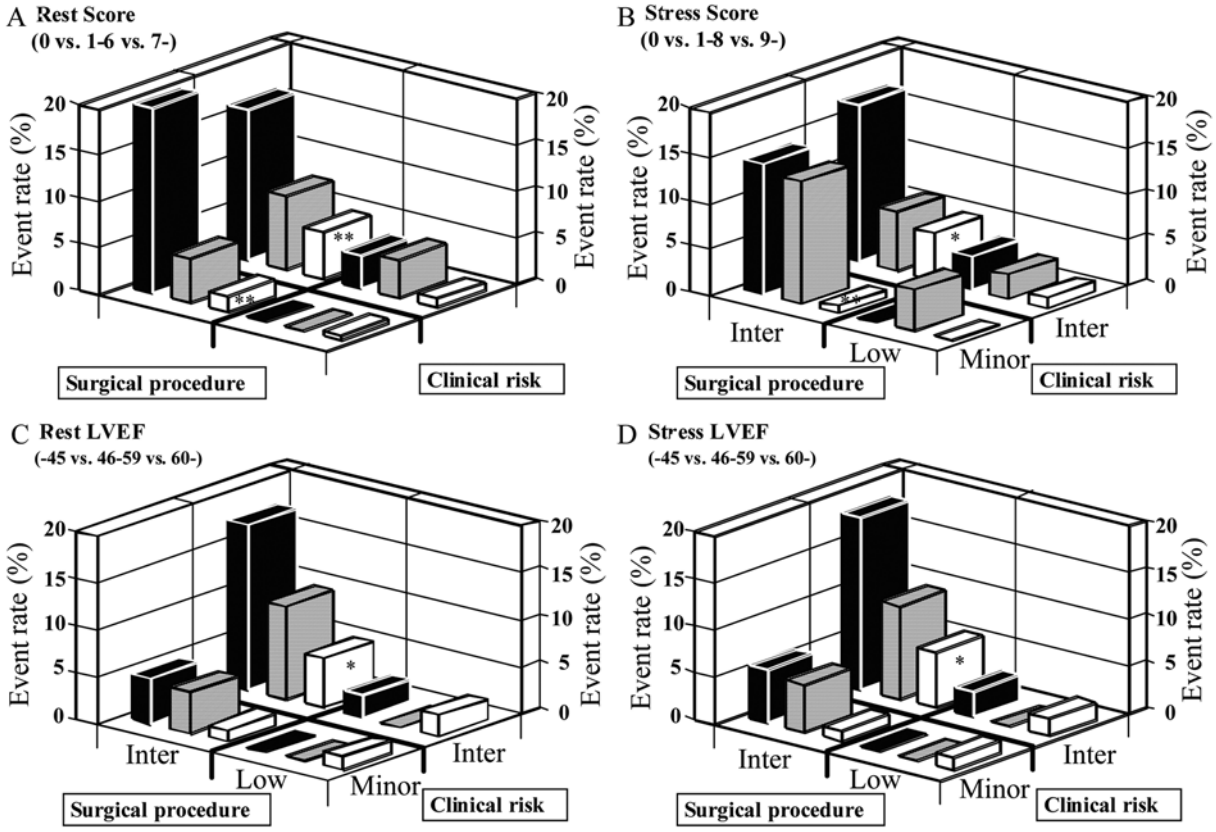

Fig. 2 Incremental value of information about myocardial perfusion or cardiac function in predicting all cardiac events
Stratification with summed rest score（A）, summed stress score（B）, LVEF at rest（C）, and LVEF after stress（D）.
In each panel, patients were divided into 4 subgroups with clinical risk factors and operation risk. In each subgroup, patients were sorted again into three groups（closed, hatched and unfilled bars）according to the following threshold values of SPECT indices.
closed bar,（A）summed rest score＞7,（B）summed stress score＞9,（C）and（D）LVEF＜45%; hatched bar,（A）1＜summed rest score＜6,（B）1＜summed stress score＜8,（C）and（D）46%＜LVEF＜59%; unfilled bar,（A）summed rest score＝0,（B）summed stress score＝0,（C）and（D）LVEF＞60%; *. p＜0.05; **, p＜0.01（comparison between the unfilled bar and others）.
The total numbers of patients are 1220 in（A）and（B）, and 868 in（C）and（D）. The threshold values（summed stress score＝9. summed rest score＝7, and LVEF＝45%）were determined on the basis of the mean and standard deviation: approximately mean＋s.d. in perfusion scores, and mean－s.d. in LVEF.（cited from reference No. 6）

which are called support vectors. The SVM analysis selects the appropriate hyperplane to maximize the margin between the hyperplane and support vectors. Among supervised learning methodologies, SVM is thought to be one of the most accurate techniques.

This study included 1351 consecutive patients who were referred for preoperative dipyridamole stress myocardial perfusion scintigraphy and underwent non-cardiac surgery. Predictors（the input candidates for the classifiers）comprise one operation risk, 13 clinical risk, 3 SPECT perfusion indices, and 3 SPECT functional indices. The results are indicated in Tables 2 and 3. In predicting all cardiac events, the SVM models yielded favorable predictive performance compared with the linear models regardless of the use of SPECT results（Table 2）. The incremental prognostic value of SPECT was considerable in the linear model. In predicting hard events（Table 3）, the percentage of the support vector was reduced by introducing SPECT indices（without SPECT: 34.9%, with SPECT: 22.1%）, which means that the analysis became stable.

Perioperative risk in specific group of patients

Clinical markers related to cardiac events

As mentioned above, various factors have been identified as preoperative clinical markers related to postoperative cardiac events, including advanced age, hypertension, diabetes, angina pectoris, arrhythmias, history of myocardial infarction, congestive heart failure, prior CABG and abnormal baseline electrocardiography（10,11,17-20）. In this review, we focused on aging, diabetes and ECG abnormality as clinical risk factors related to perioperative cardiac events.

Aging

Recently, the number of the aged undergoing surgical

Table 2 Predicting All Cardiac Events

Classifier	Input variables	Sensitivity（%）	Specificity（%）	AUC
SVM	Clinical＋SPECT	97.4	72.2	0.884
	Clinical only	85.5	76.5	0.861
Linear	Clinical＋SPECT	67.1	75.4	0.748
	Clinical only	72.4	62.4	0.677

AUC: area under the ROC curve, SVM: support vector machine-based classifier, Linear: linear classifier（cited from reference No. 13）

Table 3 Predicting Hard Events

Classifier	Input variables	Sensitivity（%）	Specificity（%）	AUC
SVM	Clinical＋SPECT	92.9	86.2	0.892
	Clinical only	85.7	76.7	0.867
Linear	Clinical＋SPECT	85.7	81.5	0.864
	Clinical only	71.4	79.4	0.768

AUC: area under the ROC curve, SVM: support vector machine-based classifier, Linear: linear classifier（cited from reference No. 13）

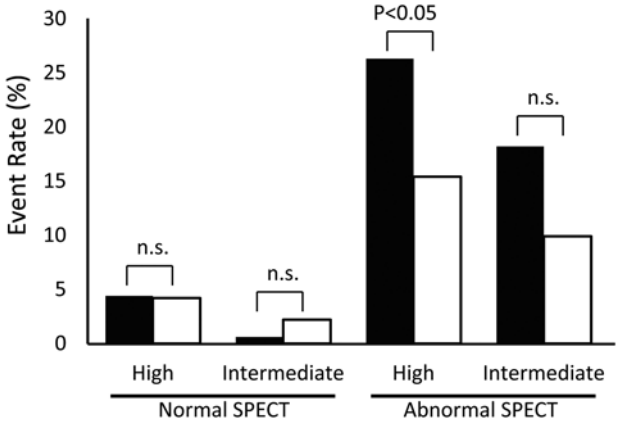

Fig. 3 Influence of aging on perioperative cardiac risk
Closed bar: aged 75 or more, unfilled bar: others, High: high-risk surgery, Intermediate: intermediate-risk surgery.
In patients with abnormal SPECT, aging had an influence on perioperative cardiac risk.（cited from reference No. 11）

treatment increases corresponding with the extension of the lifespan. The frequency of epicardial coronary artery stenosis increases with advancing age. Cardiac risk factors, which are more often present in the elderly than the younger population, are thought to facilitate the progression of epicardial coronary artery stenosis and to affect the coronary microcirculatory function (22). Besides these vascular conditions, age-related cardiac changes include decrease in contractility, increase in stiffness and ventricular filling pressures, decrease in beta-adrenoceptor and beta-adrenoceptor-mediated modulation of inotropy and chronotropy, increase in left atrial pressure/size and action potential time, and decrease in coronary flow reserve (23). All of the above changes are possible candidates for explaining increased perioperative cardiac risk in the elderly.

Preoperative diagnosis of ischemic heart disease is difficult in the elderly because of reduced physical activity resulting in the reduction of demand angina and suboptimal performance in exercise cardiac testing. In such patients, a pharmacological stress test incorporating myocardial perfusion SPECT or echocardiogram is often of greater diagnostic or prognostic accuracy (24-26). A number of investigators have pointed out that aging increases the likelihood of perioperative cardiac events in non-cardiac surgery, and that age is an independent predictor of perioperative events (10,17,27,28). On the other hand, advanced age is listed as a minor clinical predictor in the ACC/AHA Guidelines (1-3). In these guidelines, minor predictors are defined as markers for cardiovascular disease that have not been proven to independently increase perioperative risk. In addition, some authors reported that advanced age is not an independent predictor of perioperative outcome (29,30).

Furthermore, it remains unclear whether the cause of increased perioperative cardiac risk is attributable to aging itself or to the associated cardiac risk factors and coronary disease. In our previous report (11), we divided patients into different groups according to the age and SPECT findings to separate the influence of aging from that of associated coronary artery disease. As indicated in Fig. 3, aging itself had no appreciable influence on perioperative cardiac risk in patients with normal myocardial perfusion. In contrast, in patients with perfusion abnormality, cardiac event rate increases following aging, independently of other clinical variables.
DM

The prevalence of CAD is reported to be high in

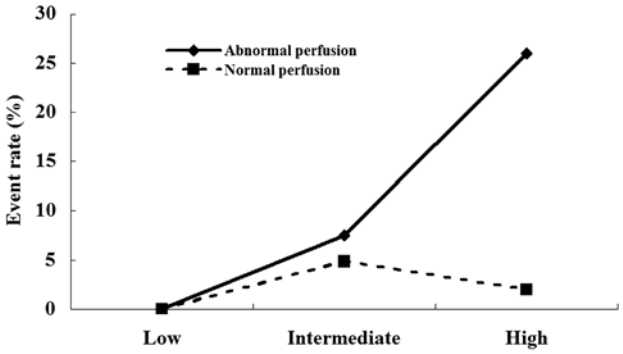

Fig. 4 Surgical risk and event rate in diabetic patients
High, Intermediate and Low denote high, intermediate and low-risk surgery, respectively.
The event rate increased depending on surgical risk when patients manifested abnormal perfusion findings, while such tendency was not observed in patients with normal perfusion.（cited from reference No. 12）

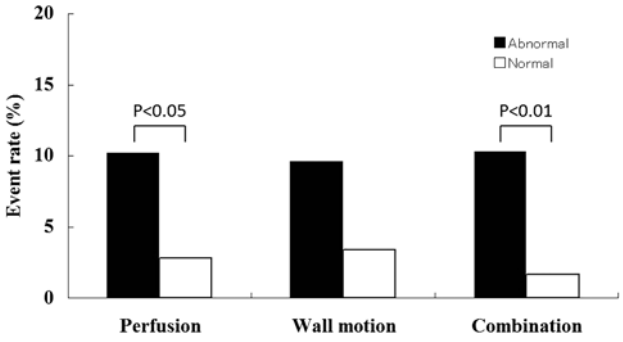

Fig. 5 Risk stratification by combining information about myocardial perfusion and cardiac function in diabetic patients
Abnormal means the presence of abnormality in perfusion and/or wall motion.
Combining information about myocardial perfusion and wall motion improved predictive value of cardiac events（cited from reference No. 12）

diabetic patients（31-33）. The AHA pointed out that patients with DM belong to the same high-risk category as patients with known CAD（34）. Furthermore, it is reported that cardiac death is the prominent cause for the mortality in type II DM patients（35,36）.

Diabetic patients also have higher postoperative cardiac mortality and morbidity rates than those without DM（37）. The leading causes of death in DM patients undergoing non-cardiac surgery are related to cardiac complications（38）. However, up to 65% of myocardial ischemia or infarction is clinically silent（39-41）. It is important and difficult to stratify perioperative cardiac risk of DM patients because of the high prevalence of asymptomatic myocardial ischemia or infarction that is not so easy to diagnose. Moreover, it is reported that that clinical risk factors are not of prognostic value in asymptomatic DM patients in predicting perioperative cardiac events（42）.

Myocardial SPECT is reported to have a prognostic value in DM patients with cardiac disease undergoing non-cardiac surgery（43）. However, it remains unclear whether SPECT is of prognostic value in DM patients without overt cardiac symptoms. We investigated the usefulness of clinical risk factors, DM indexes and ECG-gated SPECT findings in stratifying perioperative cardiac risk（12）. The duration was the only DM index of prognostic value. Normal myocardial SPECT findings ensure the low likelihood of perioperative cardiac events in DM patients without chest pain（Fig. 4）. Simultaneous assessment of myocardial perfusion and cardiac function by using ECG-gated SPECT was proved to yield more accurate risk stratification（Fig. 5）.

In clinical practice, it is also worthy investigating what kinds of surgery will augment cardiac risk in asymptomatic DM patients. As indicated in Fig. 4, the cardiac event did not occur when patients underwent low-risk surgery regardless of perfusion findings, indicating the limited value of SPECT before low-risk surgery. However, the DM patients undergoing high-risk operation should be of particular concern if they have abnormal SPECT findings.

ECG abnormality

Stress ECG is often used for selecting patients with a high probability of perioperative cardiac events because of its availability and low cost. The onset of a myocardial ischemic response at low exercise workload is associated with increased risk of perioperative cardiac events（2,3）. However, the usefulness of ECG for preoperative risk assessment is still controversial. A prospective study showed that ST segment depression in exercise ECG is an independent predictor of perioperative cardiac complications（44）. On the other hand, some papers clarified the superiority of myocardial perfusion imaging and limitation of exercise ECG in preoperative risk stratification（45,46）. Duke treadmill score（DTS）is widely used for risk stratification in patients undergoing treadmill test. It is reported that one third of patients with high-risk DTS manifested normal SPECT findings and that such patients are associated with low risk of cardiac events（47）. However, it is not easy to routinely conduct stress myocardial SPECT within limited time before surgery and the problem of the examination cost also exists. Although the ACC/AHA Guidelines recommend myocardial perfusion study in patients with high cardiac risk estimated by stress ECG

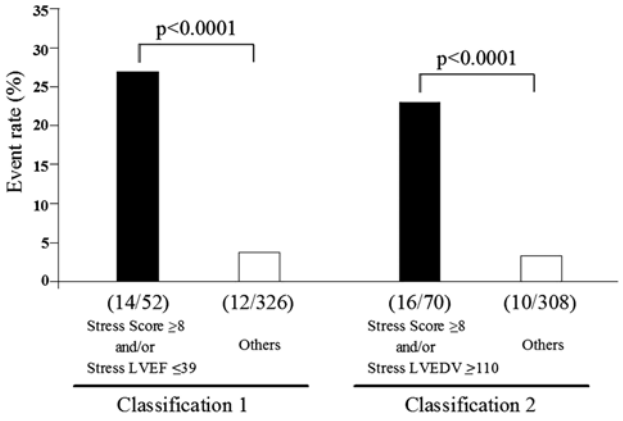

Fig. 6 Risk stratification by combining information about myocardial perfusion and cardiac function in patients with positive findings in stress ECG

Classification 1: combination of summed stress score and stress LVEF; Classification 2: combination of summed stress score and stress LVEDV.

The numbers in parentheses are the number of patients with cardiac events/total number in the category.

if it will change management, there seems to be limited number of reports about preoperative risk stratification with myocardial SPECT after sorting the patients with stress ECG（48）.

We collected data of patients with positive findings in preoperative stress ECG from our SPECT database to clarify whether myocardial perfusion SPECT stratifies risk of perioperative cardiac events. We also assessed prognostic value of combining perfusion and functional data obtained with ECG gated SPECT. Combination of information about myocardial perfusion and cardiac function was successful in separating patients of high risk causing 55% of all cardiac events from others of low risk including more than 80% of all the patients（Fig. 6）.

Conclusions

In non-cardiac surgery, preoperative therapy, operative performance and perioperative management are determined by considering the urgency of surgery, patient's risk factors, specific surgical risk and findings of cardiac testing including SPECT. Although myocardial perfusion SPECT has been used for risk stratification mainly in high-risk surgery, some investigators pointed out its prognostic value in intermediate-risk surgery. It is important to seek methods to evaluate perioperative risk by integrating information of clinical and surgical risk, and SPECT findings.

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Conflicts of Interest

None

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