Cardiothoracic Anesthesia, Respiration and Airway

Limitations of preoperative dobutamine stress echocardiography in identifying severe left main coronary artery stenosis: a report of two cases and a brief review

[Les limites de l'échocardiographie d'effort préopératoire avec dobutamine dans l'identification d'une sténose du tronc de l'artère coronaire gauche : observation de deux cas et brève revue]

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Purpose: Using case illustrations, to elucidate factors which increase the likelihood of false negative preoperative dobutamine stress echocardiography (DSE) studies in patients with severe left main coronary artery stenosis, and to provide criteria which must be met in order to ensure the accurate interpretation of these tests.

Clinical features and source: Two patients presented for elective abdominal aortic aneurysm repair within a one-month period of time. Both patients had DSE as part of their preoperative assessment, which were interpreted as normal. Nevertheless, both suffered major coronary events in the perioperative period, and both proved to have severe left main coronary artery stenosis on postoperative angiography. A narrative review is presented based on a selection of the current literature, and local experience with the technique. Some pitfalls in the interpretation of these tests are presented, along with modalities to increase their sensitivity and specificity.

Conclusion: DSE is an important and useful modality in the preoperative cardiac evaluation of patients who are unable to exercise. However the reliable interpretation of the test depends on an understanding of the limitations of the procedure.

Objectif: Éclaircir, à l'aide d'observation de cas, les facteurs qui augmentent la possibilité de résultats faux négatifs à l'échocardiographie d'effort préopératoire avec dobutamine (EED) chez des patients qui présentent une grave sténose du tronc de l'artère coronaire gauche, et fournir les critères à satisfaire pour produire une interprétation exacte de ces tests.

Éléments cliniques et source : Au cours d'un mois, deux patients ont été admis pour la réparation réglée d'un anévrisme de l'aorte abdominale. Les deux patients ont été évalués entre autres par un examen EED qui s'est révélé normal. Néanmoins, les deux avaient été victimes d'ennuis coronariens majeurs pendant la période périopératoire et présentaient une grave sténose du tronc de l'artère coronaire gauche à l'angiographie postopératoire. Nous avons préparé une revue descriptive provenant d'un choix documentaire actuel et d'une expérience locale avec la technique. Nous présentons certaines embûches rencontrées lors de l'interprétation des tests ainsi que les modalités pour accroître leur sensibilité et leur spécificité.

Conclusion : L'EED est une modalité d'évaluation cardiaque préopératoire, importante et utile chez les patients qui ne peuvent faire d'exercice. Toutefois, l'interprétation fiable du test dépend des connaissances de ses limites.

PREOPERATIVE cardiovascular assessment is essential to the identification of patients at risk for perioperative cardiac morbidity, in order to optimize their management and stratify perioperative risk. Literature supporting the use of noninvasive technology has prompted guidelines for the assessment of these patients.¹ Dobutamine stress echocardiography (DSE) is fre-

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quently used to provide preoperative functional assessment in patients at risk for coronary disease who are unable to perform exercise testing. Although the reported sensitivity of DSE is high,² there are inherent limitations to the accuracy and interpretation of this technology. The purpose of this brief review is to elucidate the factors which increase the likelihood of false negative DSE studies in this population, and to provide criteria which must be met in order to ensure the accurate interpretation of these tests. We begin by reporting two cases, occurring within a one-month period, of patients with preoperative DSE studies which were reportedly normal, who suffered perioperative myocardial infarction. Both patients were subsequently shown to have severe left main coronary artery (LMCA) stenosis.

Clinical features

Case history 1

A 67-yr-old male was scheduled for elective repair of an expanding 5.3-cm juxtarenal abdominal aortic aneurysm, which had diffuse calcified plaque involving visceral and renal arteries. A complicated surgical course with possible supraceliac cross clamping was anticipated.

Past history included hypertension, peripheral vascular disease, hypercholesterolemia, gastroesophageal reflux, and remote tobacco use. He had no history of angina, prior myocardial infarction or diabetes mellitus, but had poor functional capacity (< 4 METS) secondary to dyspnea without chest pain. His current medications included ramipril, ASA, lansoprazole, gemfibrozil, venlafaxine, and glucosamine. Exercise stress echocardiography done three years previously was negative for ischemia by electrocardiographic and wall motion criteria, reaching 9.5 METS at 7.5 min of the Bruce protocol. The test was discontinued due to hypotension, although the patient was asymptomatic.

A preoperative consultation with a cardiologist and DSE were obtained. DSE revealed normal resting wall motion with normal systolic augmentation to dobutamine and no induced wall motion abnormalities. The patient reached a heart rate (HR) of 132 beats·min⁻¹ (target HR 130 beats·min⁻¹) at a dose of dobutamine 40 µg·kg⁻¹·min⁻¹ and atropine 0.25 mg. The cardiologist, an experienced echocardiographer, reviewed the study and reaffirmed that there was no evidence of myocardial ischemia. He concluded that there was a low likelihood of significant coronary artery disease, and assessed the patient to be at low risk for a perioperative cardiovascular event. No further investigations were felt to be necessary.

The patient subsequently presented for surgery. Baseline blood pressure (BP) was 102/50 mmHg and

HR was 64 beats·min⁻¹. An epidural catheter was placed at the seventh thoracic interspace; 3 mL lidocaine 1.5% with epinephrine were instilled as a test dose, and general anesthesia was induced. The patient became hypotensive after induction to a systolic BP of 80 mmHg; this was treated with titrated bolus doses of ephedrine, phenylephrine and crystalloid volume replacement. Once the BP was normalized, 6 mL of bupivacaine 0.25% without epinephrine were instilled through the epidural catheter prior to skin incision. The patient then remained stable until 30 minutes after incision, when the electrocardiogram developed diffuse, marked ST segment depression, and systolic BP dropped to 60–70 mmHg. Treatment consisted of volume replacement and infusion of dopamine 3–10 µg·kg⁻¹·min⁻¹. The decision was made to abort the procedure prior to cross clamping of the aorta. The patient remained hypotensive during closure, and was treated with epinephrine 10 µg boluses to maintain SBP > 80 mmHg. He was transferred, ventilated, to the intensive care unit. A pulmonary artery catheter was inserted, and he was treated with norepinephrine 6 µg·min⁻¹, and dopamine 7 µg·kg⁻¹·min⁻¹. Hemodynamic values included mean BP 71 mmHg, HR 104 beats·min⁻¹, central venous pressure 12 mmHg, pulmonary artery wedge pressure 24 mmHg, cardiac index 3.6 L·min⁻¹·m⁻², and systemic vascular resistance 629 dynes·sec⁻¹·cm⁻⁵. A transthoracic echocardiogram indicated an ejection fraction of 50%, with mild hypokinesis anterolaterally. Troponin I enzyme was elevated (peak 28.1 ng·mL⁻¹; normal < 0.9 ng·mL⁻¹), as was creatine kinase (peak 3078 U·L⁻¹, MB fraction mass index 11.1%; normal $< 3\%$), confirming acute myocardial infarction. The patient remained unstable, and a coronary angiogram was carried out the following day. This showed a complex eccentric plaque with visible thrombus and 95% stenosis of the LMCA, 50% narrowing of the circumflex at its ostium, dominant right coronary artery with a long eccentric lesion proximally with 90% narrowing, and mild irregularity of the proximal left anterior descending artery. He was subsequently taken for urgent four-vessel coronary artery bypass grafting. Postoperatively, the patient recovered well, aside from intermittent atrial fibrillation. Unfortunately, two weeks after surgery, during discharge planning, the patient suffered a large left hemispheric cerebrovascular accident and died two days later, 20 days after his initial surgery.

Case history 2

A 71-yr-old male presented for elective repair of an expanding 6-cm infrarenal abdominal aortic aneurysm. He had a family history which was strongly positive for coronary artery disease, and was a 60 pack-year smoker. He had no history of myocardial

infarction, but had a positive exercise electrocardiogram ten years previously. This was followed by coronary angiography, which showed mild left ventricular dysfunction, 40% stenosis of the LMCA, occlusion of the right coronary artery, and 50% stenosis of the obtuse marginal branch of the left anterior descending artery. There was extensive collateralization from the left coronary system, and calcification of the distal vessels. As his anginal pattern was quite stable, it was felt that coronary surgery was unwarranted, and he was treated medically for his symptoms. Since that time, he described stable class II angina, although he was minimally active. His medications prior to surgery included ASA and atenolol 50 mg daily.

The patient was reassessed by his cardiologist in anticipation of the aortic procedure. Resting echocardiography showed hypokinesis of the basal and mid inferior septum and the basal and mid inferior wall, indicating infarction in the right coronary territory, as suggested by his angiogram ten years before. His ejection fraction was estimated at 50%. All 16 myocardial segments were visualized, and all stages of the dobutamine protocol with atropine were completed to the target HR. There were no new inducible wall motion abnormalities in any myocardial territory. Due to the reasonable ejection fraction and unremarkable DSE, repeat angiography was felt to be unnecessary, and he was considered to have an acceptable risk for surgery.

At the time of surgery, a thoracic epidural catheter was inserted at the T8–9 level and tested with 3 mL lidocaine 1.5% with epinephrine, and general anesthesia was induced. Bupivacaine 0.25% without epinephrine, 4 mL, were administered epidurally prior to skin incision.

An infrarenal aortic cross clamp was placed without significant hemodynamic alteration. Approximately 20 min after cross clamp, diffuse ST segment depression was noted, with hypotension to a systolic BP of 80 mmHg and HR 70 beats·min⁻¹. Blood loss was well-controlled surgically. Treatment included increasing FiO₂ to 1.0, phenylephrine boluses and volume replacement. Once BP was normalized, metoprolol 5 mg *iv* were given, with minimal improvement in ST segment depression. The cross clamp was removed after complete repair without any further change in hemodynamic status or electrocardiogram. Following closure of the incision, the patient became difficult to ventilate with a high airway pressure, and O₂ saturation dropped to 82%. The patient was transferred to the intensive care unit, and continued to require aggressive inotropic and ventilatory support. Chest radiography demonstrated changes consistent with severe pulmonary edema. Laboratory investigation revealed positive troponin T enzyme (peak 0.440

ng·mL⁻¹; normal < 0.1 ng·mL⁻¹), and elevated creatine kinase (peak 787 U·L⁻¹, MB fraction mass index 10.4%), confirming myocardial infarction. An urgent coronary angiogram was performed, showing 70% ostial LMCA stenosis, 50% distal LMCA narrowing, 50% narrowing of the left anterior descending artery, mild circumflex disease, and occluded right coronary artery. There was a right dominant circulation with collaterals present, but with diffuse irregularities.

The patient was taken for urgent triple-vessel coronary artery bypass grafting. He remained in intensive care for two weeks with problematic atrial fibrillation, and also required a laparotomy for a perforated duodenal ulcer. He recovered slowly, and was discharged from hospital 37 days after initial admission.

Discussion

Cardiac events are the major cause of perioperative and late mortality in major vascular surgery.³ The American College of Cardiology and American Heart Association have proposed joint guidelines for the pre-operative assessment of patients with cardiovascular disease based on expert opinion,¹ although the predictive value of using these guidelines to detect positive results has been challenged.⁴ Nevertheless, for major surgery in high risk patients, who are often elderly, have poor functional capacity and are unable to exercise, noninvasive pharmacologic testing is reasonable.¹

DSE is widely used to identify the functional consequences of physiologically important coronary disease.² Dobutamine is a selective beta₁ adrenoreceptor agonist, which increases myocardial oxygen demand through positive chronotropic and inotropic effects, and impairs myocardial oxygen supply by reducing the duration of diastole. Patients with inducible ischemia, detected by new reversible wall motion abnormalities developing during dobutamine infusion, have been shown to be at increased risk of cardiac death or myocardial infarction within 30 days after surgery.⁵ The reported sensitivity of DSE for the detection of myocardial ischemia is 57–89%, with a specificity of between 65 and 100%.⁴ On the other hand, the sensitivity of DSE for perioperative events has been reported to be somewhat higher (mean sensitivity 98%, mean specificity 75%),² with a negative predictive value for myocardial infarction or death ranging from 93 to 100%.¹

Patients with LMCA stenosis have poor long term prognosis.⁶ In many centres, significant stenosis of the LMCA is regarded as a life threatening lesion and an indication for urgent surgical intervention.⁷ Patients with high degree narrowing ($\geq 70\%$) of the LMCA managed surgically show improved survival *vs* those

managed medically, regardless of symptoms.⁸ The increased mortality seen with LMCA disease may be related in part to this lesion being a marker for widespread coronary disease: it is rarely found in isolation, and is almost always associated with stenoses in two or three coronary arteries.⁷ In addition, the large area of myocardium at risk of infarction from LMCA occlusion attests to the ominous nature of this disease.

The importance of preoperative identification of these high risk patients is apparent, but often proves difficult. Clinical indicators of LMCA stenosis are not distinctive as compared with more distal narrowing, although these patients have a higher prevalence of severe angina. On the other hand, up to 11% of these patients are asymptomatic.⁹ Resting electrocardiogram may be normal, and resting echocardiography has shown no relationship between severity of LMCA disease and left ventricular ejection fraction.⁷ Stress electrocardiography and stress perfusion scintigraphy have shown high sensitivity (> 80% and > 90% respectively), but have low specificity in distinguishing LMCA stenosis from other forms of severe coronary disease.^{10,11} Patients with complete occlusion of the LMCA and extensive right to left collaterals have been described as having an unusual characteristic scintigraphic pattern.¹² Dipyridamole echocardiography has been shown to have a 93% sensitivity for LMCA disease, although again there was low specificity in distinguishing LMCA from three-vessel disease.¹³

Precise localization of individual coronary lesions by DSE has been shown to be affected by the number of vessels involved and their distribution.¹⁴ DSE has the highest sensitivity for localizing single-vessel lesions, compared with the double- or triple-vessel group, and is more sensitive in more proximal segment lesions compared to distal lesions.¹⁴ For proximal lesions, the sensitivity of DSE is highest for left anterior descending (89%), then right coronary (81%), and least for circumflex (64%) lesions.¹⁵ DSE was unable to differentiate LMCA lesions from double-vessel lesions of left anterior descending and circumflex arteries.¹⁴ It has been suggested that deterioration of regional wall motion in the multiple vessel group can distort the geometric morphology of the left ventricle and make precise identification of segments difficult.¹⁴ Other possible reasons for altered sensitivities include traction by adjacent heart segments mimicking abnormal regional wall motion, and anatomical relationships being non-uniform in different patients.¹⁴ It is intuitive that distal lesions are likely to produce less significant wall motion abnormalities, because distal coronary artery supplies a smaller area of the myocardium.¹⁴ There is a paucity of data

regarding the use of DSE for the noninvasive identification of LMCA disease, although one might expect a similar sensitivity, as dipyridamole and dobutamine echocardiography show similar negative predictive values for perioperative events, and comparable positive predictive values.¹⁶

In spite of problems with the interpretation of stress echocardiography, studies have shown it to have sensitivity and specificity equivalent to other noninvasive imaging modalities, at lower cost.^{1,11} Other benefits include the portability of echocardiographic equipment, and its value in defining the presence of structural heart disease, which may produce symptoms that can be confused with coronary artery disease. Echocardiography also occasionally identifies structural lesions that may contraindicate stress testing, such as severe aortic stenosis.

How could the two patients presented above, with such severe LMCA lesions and poor outcome, have had seemingly normal findings during DSE? It is tempting to ascribe these results to the documented false negative rate of 1 to 2% attributed to DSE.² However, there is no specific pattern on DSE to distinguish LMCA stenosis from multivessel coronary disease, and the specific false negative rate for LMCA stenosis is unclear. Thus, in order to make informed clinical decisions, we must understand the limitations of DSE for preoperative assessment. These can be classified as physiologic (i.e., the inability to attain an adequate level of physiologic stress) or technical (i.e., ischemia and wall motion abnormalities occur but go unobserved) factors.

Physiologic factors

In interpreting the results of preoperative DSE, it is first essential to note the dose and duration of dobutamine infusion, and the HR and echocardiographic response. If myocardial ischemia was not elicited during infusion, then no wall motion abnormality will occur even in the presence of severe coronary disease. The most common reason for failure to meet maximum stress response is seen in patients receiving beta-receptor antagonist therapy. Dobutamine competitively antagonizes these drugs at the receptor level, and at peak doses can usually overcome their anti-ischemic effects. If maximal HR is not achieved with dobutamine alone then atropine is usually given in 0.25 mg increments to a total dose of 1 to 2 mg.² Failure of a patient to reach the target HR (85% of age-predicted maximum HR) may result in a falsely negative study. Vilacosta described a patient with 75% LMCA stenosis who had a negative test at a maximum dose of dobutamine of 40 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, where the patient's HR increased from 44 to 58 $\text{beats}\cdot\text{min}^{-1}$.¹⁷

With the addition of atropine 1 mg, the patient's HR suddenly increased to 133 beats·min⁻¹ and severe wall motion abnormalities were identified. These investigators recommended the discontinuation of negative chronotropic drugs, such as beta blockers, before testing, to produce a greater and more gradual increase in HR, in order to improve test sensitivity.

In approximately 10% of patients, dobutamine infusion causes hypotension, likely as a result of systemic vasodilatation mediated by peripheral beta₂ receptors, which is not fully compensated for by the increased cardiac output. As opposed to exercise echocardiography, during which hypotension usually heralds underlying coronary disease as in case 1, hypotension due to dobutamine leads to a relatively reduced myocardial workload, rate-pressure double product, and ischemic burden, but also potentially decreases the chance of wall motion abnormalities occurring.^{3,5} In addition, systemic vasodilatation may confuse quantitative estimates of global myocardial function.⁵ Although dobutamine related hypotension may be seen in the absence of coronary disease, there is some evidence that it may be useful in predicting perioperative cardiac events.¹⁸

In some patients, particularly those with single-vessel disease and collateral flow, ischemia induced wall motion abnormalities can be very transient and resolve over seconds; in this way areas of abnormal wall motion may be missed. This may be even more problematic with treadmill exercise, where only a peak stress snapshot is observed. Here, even during the time required to move the patient from the treadmill to the study table, there may resolution of short-lived wall motion abnormalities. In addition, tardokinesis, or delayed onset of wall motion abnormality, is a potential cause for missed ischemic wall motion changes during exercise or dobutamine infusion.

"Low dose" dobutamine protocols (< 20 µg·kg⁻¹·min⁻¹) may fail to produce a sufficient imbalance of myocardial oxygen supply and demand, and thereby confound testing.¹⁷ Duration of testing may also be important, as a biphasic response to prolonged dobutamine infusion has been observed, with increased contractile function initially followed by deterioration.¹⁹ Because of the potentially transient nature of these wall motion abnormalities, many echocardiographers collect peak stress images beginning with apical views. These views allow visualization of left ventricular regions supplied by distal arteries, which may recover earlier than proximal segments.

There is evidence that myocardial contractile reserve, as determined by DSE, is independent of the severity of coronary disease.²⁰ This may occur because, in the presence of severe coronary stenosis, there is a decline in

blood flow at rest. In this way dobutamine may fail to elicit a contractile response. Animal models of acute ischemia and reperfusion have provided data regarding left ventricular dysfunction during dobutamine infusion in the presence of severe stenosis.²⁰ There may be adaptive mechanisms in chronic coronary disease which may preserve the contractile response to low-dose dobutamine despite severe coronary stenosis. With chronic flow limiting lesions, there may exist a time dependent metabolic down-regulation associated with a stable but reduced level of contractile function, termed "hibernating myocardium".²¹ Under conditions of acute stress (such as during dobutamine infusion), these areas have been shown to sustain less myocardial injury compared to regions with abrupt decreases in flow.

Chronically, extensive collateralization may be a confounding variable which protects against ischemia, but limits DSE as a diagnostic tool for severe flow limiting lesions.²² Such collateral circulation is generally not well visualized on an angiogram due to inherent limitations of resolution of angiography.²³ The use of adenosine or dipyridamole is useful in this setting; these drugs work by inducing flow heterogeneity and coronary steal in regions in which coronary stenosis prevents a normal hyperemic response.

Technical factors

When evaluating DSE results, it is important to get an overall impression of the quality of the study, and know what steps were taken to improve the quality if necessary. For example, obesity and poor cooperation will both affect the quality, and thus the reliability of echocardiography. It is important to note whether all 16 segments of the left ventricle were visualized; if any two segments of the major left ventricular territories are not assessed, there is at least the potential for error.⁶

While it has been reported that it is impossible to obtain echocardiographic images in less than 4% of patients, poor or inadequate visualization of all 16 left ventricular segments occurs in a much larger percentage of the population, leading to missed wall motion abnormalities.² Fortunately, several technological advances have greatly reduced the incidence of this source of false negative scans. Harmonic ultrasound imaging increases visualization in patients who are difficult to image, facilitating endocardial border detection. This is especially important for the lateral wall, where echocardiography "dropout" can lead to poor visualization. If greater than two continuous segments are inadequately visualized even with second harmonic imaging, *iv* contrast agents may be used to opacify the ventricular chamber and thereby delineate the endocardial border, allowing the assessment of wall motion.

Other technical reasons for inadequate imaging result from pulmonary interference, as well as the distorting effects of cardiac rotation and translation, which can complicate the assessment of wall thickening and endocardial movement. Side by side analysis of individual wall segments should be compared at the same instant in the cardiac cycle, preferably during early systole, in order to minimize the effect of cardiac movement. Wall motion abnormalities may be obscured if they occur in late systole, where translational and rotational effects on the heart interfere with visualization. In addition, if the affected segment is pulled by adjacent hyperkinetic segments of normal myocardium, a false appearance of wall motion may occur.

Clinically, significant coronary lesions often go undetected, as there is frequently a poor correlation between the anatomic extent of coronary artery disease and the functional appearance of this disease.^{24,25} Coronary angiography is still considered the "gold standard" for defining coronary anatomy, although there remains significant interobserver variability in the estimation of the severity of stenotic lesions.²⁵ The LMCA has been described as a particularly troublesome site for angiographic imaging because it is often short and overlaps other structures, making it difficult to recognize a normal reference segment.²⁴ Plaque morphology and endothelial function, in addition to severity of stenosis, are also important determinants of coronary pathophysiology and clinical outcome.²³ In fact, results of dobutamine and dipyridamole stress echocardiography may be influenced more by plaque morphology than severity of stenosis.²³ These studies, however, looked at single-vessel disease and did not include any patients with LMCA stenosis.

Current advances which are improving the reliability of DSE include harmonic imaging, *iv* contrast and/or myocardial contrast perfusion imaging, acoustic quantification and automated endocardial border detection software. Accurate automated border detection algorithms permit quantitative approaches to wall motion analysis. Other quantitative methods to assess wall motion abnormalities involve ventricular wall segment velocity analysis using tissue Doppler. Regional wall stress analysis, stress myocardial contrast perfusion, and myocardial densitometry are other promising quantitative methods.

The importance of thorough preoperative assessment and optimization of comorbid conditions is well recognized. DSE is frequently employed in this setting, and a "normal" evaluation often leads to the confidence to proceed without anticipated complication. We have discussed two patients with normal preoperative DSE results who had severe LMCA disease, and significant

perioperative cardiac morbidity during major vascular surgery. We have reviewed the literature regarding LMCA disease and its preoperative detection, and have outlined possible reasons why this subgroup of patients may escape identification. DSE can provide useful information during preoperative assessment, although its limitations must be understood.

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