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Incidence, Pathophysiology, and Treatment of Complications During Dobutamine-Atropine Stress Echocardiography

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Dobutamine stress echocardiography was clinically introduced in the mid-1980s.[1,2] Indications for this stress modality rapidly expanded from diagnosing coronary artery disease (CAD) to risk stratification of patients undergoing vascular surgery; risk stratification of patients with chronic CAD, unstable angina, acute or chronic myocardial infarction (MI), or valvular heart disease; and the assessment of myocardial viability in patients with severe left ventricular (LV) dysfunction. Thus, dobutamine stress has been applied to progressively more complex, older, and higher-risk patients. Additionally, stress protocols became more aggressive, with higher dobutamine doses and the addition of atropine.[3] Although generally regarded as a safe stress modality, serious complications do occur. In this review, we will describe the incidence, pathophysiology, and treatment of complications during dobutamine-atropine stress echocardiography (DASE). Data on incidence of complications were obtained from 26 studies including >400 patients that reported at least the major complications of mortality, acute MI, ventricular fibrillation, and sustained ventricular tachycardia,[4–29] for a total of 55 071 patients (Table 1). In addition, references are given to case reports and studies dealing specifically with a particular complication.

Potentially Life-Threatening Complications

Mortality

Incidence

Incidence is <0.01% (0.002%; range, 0.00% to 0.01%). Case reports are available.[30–33]

Pathophysiology

In DASE safety studies, mortality as a result of ventricular fibrillation was reported only once.[22] In 4 case reports, lethal cases of cardiac rupture were described (see next section).[30–33]

Treatment

See other specific sections for treatment of potentially fatal complications.

Cardiac Rupture

Incidence

Incidence is <0.01% (0.002%; range, 0.00% to 0.01%). Case reports are available.[30–35]

Pathophysiology

Cardiac rupture was reported in 7 patients undergoing DASE with akinetic or dyskinetic inferior myocardium resulting from a recent (4- to 12-day-old) inferior MI. In all cases, the patient suddenly developed (atypical) chest pain and lost consciousness with pulseless electromechanical dissociation. In 4 patients, cardiac rupture was fatal.[30–33] Strong inotropic stimulation of necrotic and thinned myocardium may increase wall stress to such an extent that rupture results in that part of the myocardial wall with the least resistance. Of note, low-dose dobutamine provides strong inotropic stimulation, as was shown in 2 case reports with ruptured myocardium at doses of only 10 μg/kg per minute.[30,34] Whether the inferior myocardial wall is more prone to rupture is controversial.[36,37] Diagnosis should be based on the detection of sudden development of pericardial effusion. Of note, in 1 patient mild pericardial effusion was seen on the rest echocardiogram.[31] It may be good practice to exclude cardiac pseudoaneurysm or rupture first in patients after an acute MI.

Treatment

Discontinue dobutamine infusion. Emergency pericardiocentesis and surgery should be performed.

Myocardial Infarction

Incidence

Incidence is 0.02% (range, 0.00% to 0.10%). Case reports are available.[38–43]

Pathophysiology

Dobutamine-atropine stress may cause an acute MI through different hypothetical mechanisms. In a coronary artery with an unstable atherosclerotic plaque, increment of heart rate and contractility may mechanically increase shear forces, resulting in plaque disruption and thrombosis. Additionally, dobutamine has been shown to induce platelet activation and

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Table 1. DASE Safety Reports in >400 Patients

	Mertes[4]	Picano[5]	Pellikka*[6]	Zahn[7]	Hiro[8]	Lamisse[9]	Pinton[10]	Hennessy[11]	Secknus[12]	Bremer*[13]
Year of publication	1993	1994	1995	1996	1997	1997	1997	1997	1997	1998
Stress protocol	40/1†	40/1	50/2†	50/1	40/1	40/1	50/0	50/1	40/2	40/2
No. of patients	1118	2949	1000	1000	732	600	735	474	3011	1035
History of MI, %	33.5	69.0	NA	21.5	NA	21.2	NA	40.9	15.8	25.8
Mean age, y	60	56	69	59	62	62	57	59	66	69
Complications, %										
Death	0	0	0	0	0	0	0	0	0	0
Cardiac rupture	0	0	0	0	0	0	0	0	0	0
MI	0	0.07	0.10	0	0	0	0	0	0.03	0
Cerebrovascular accident	0	0	0.10	0	0	0	0	0	0.03	0
Atropine intoxication	0	0.17	0	0	0	0	0	0	0	0
Asystole	0	0	0	0	0	0	0	0	0	0
Atrioventricular block	0.63	NA	NA	0.10	NA	NA	0.68	NA	NA	NA
Ventricular arrhythmias										
Ventricular fibrillation	0	0.07	0	0.10	0	0	0	0	0	0.10
Ventricular tachycardia										
Sustained	0	0.07	0.40	0	0	0.54	0	0.21	0.17	0.10
Nonsustained	3.6	NA	5.6	1.8	NA	1.1	0.5	1.7	2.3	7.3
Premature ventricular complex	15.4	NA	18.9	7.1	NA	8.0	11.8	NA	8.0	NA
Supraventricular arrhythmias										
Supraventricular tachycardia	3.4	NA	7.0	0.3	NA	0.4	0.0	3.0	1.7	NA
Atrial fibrillation or flutter	0.7	NA	2.2	1.0	NA	1.1	0.3	1.1	1.1	1.9
Premature atrial complex	7.7	NA	NA	NA	NA	5.6	3.8	NA	NA	NA
Other end points, %										
Hypotension	3.2	2.1	2.9	2.5	3.6	0.3	0.8	0.2	3.7	1.6
Hypertension	0.9	0.8	1.3	1.0	NA	2.6	3.5	0.2	0.8	0.9
Side effects	3.2	2.4	3.0	4.4	NA	1.0	3.1	0	1.5	5.1
Wall motion abnormalities	2.9	NA	10.6	10.0	NA	0	9.0	NA	0.9	6.3

	Pezzano[14]	Plonska[15]	Mathias[16]	Takeuchi[17]	Poldermans[18]	Chenzbraun[19]	Hirano[20]	Cortigiani[21]	Rodriguez Garcia[22]
Year of publication	1998	1999	1999	1999	1999	1999	2001	2001	2001
Stress protocol	40/1	40/1	40/1	40/1†	40/1	50/1	40/0	40/1†	40/0
No. of patients	3041	582	4033	1090	1659	400	897	636	6832
History of MI, %	63.0	0.0	22.7	50.4	42.5	NA	NA	NA	NA
Mean age, y	58	52	56	63	62	67	NA	60	NA
Complications, %									
Death	0	0	0	0	0	0	0	0	0.01
Cardiac rupture	0	0	0	0	0	0	0	0	0.01
MI	0	0	0.02	0.09	0.09	0	0	0	0.06
Cerebrovascular accident	0	0	0	0	0	0	0	0	0.01
Atropine intoxication	0	0	0.12	0	0	0	0	0	0
Asystole	0.03	0	0	0	0	0	0	0	0
Atrioventricular block	0.03	0.17	0.40	0.28	NA	0.25	NA	NA	0.03
Ventricular arrhythmias									
Ventricular fibrillation	0.07	0	0.02	0	0.18	0	0	0	0.04

(*Continued*)

Table 1. Continued

	Pezzano[14]	Plonska[15]	Mathias[16]	Takeuchi[17]	Poldermans[18]	Chenzbraun[19]	Hirano[20]	Cortigiani[21]	Rodriguez Garcia[22]
Ventricular tachycardia									
Sustained	0	0	0.20	0.09	0.78	0.25	0	0.31	0.13
Nonsustained	2.1	1.0	3.5	0.8	2.7	NA	NA	1.3	NA
Premature ventricular complex	33.7	4.6	31.2	43.6	NA	NA	34.1	NA	NA
Supraventricular arrhythmias									
Supraventricular tachycardia	1.6	0	0.9	0.2	NA	NA	NA	NA	NA
Atrial fibrillation or flutter	0.5	0.5	0.8	0.6	1.5	0.5	NA	0.3	NA
Premature atrial complex	8.6	1.2	9.5	27.8	NA	NA	NA	NA	NA
Other end points, %									
Hypotension	0.2	7.6	0.4	0.4	0.36	7.0	NA	0.8	NA
Hypertension	0.4	2.6	1.5	NA	0.2	3.5	NA	0.6	NA
Side effects	0.5	0.7	NA	NA	0.2	4.0	NA	NA	NA
Wall motion abnormalities	NA	19.8	NA	32.0	0.2‡	0	NA	NA	NA

	Tsutsui[23]	Abreu[24]	Tsutsui[25]	Timperley[26]	San Roman[27]	Aggeli[28]	Kane*[29]
Year of publication	2004	2005	2005	2005	2008	2008	2008
Stress protocol	40/2§	40/2	50/2‖	40/1‖	40/1§	40/1‖	40/2
No. of patients	1664	5467	2498	751	962	5250	6755
History of MI, %	20.0	NA	13.2	NA	27.3	36.2	16.0
Mean age, y	60	60	62	64	64	65	69
Complications, %							
Death	0	0	0	0	0	0	0
Cardiac rupture	0	0	0	0	0	0	0
MI	0	0	0	0	0	0	1
Cerebrovascular accident	0	0	0	0	0	0	0
Atropine intoxication	0	0	0	0	0	0	0
Asystole	0	0	0	0	0	0	0
Atrioventricular block	NA	NA	NA	NA	NA	NA	NA
Ventricular arrhythmias							
Ventricular fibrillation	0.06	0.04	0	0	0	0.02	0.03
Ventricular tachycardia							
Sustained	0.30	0	0.32	0.27	0.10	0.18	0.06
Nonsustained	1.5	0.2	1.1	0.3	0.7	0.34	NA
Premature ventricular complex	22.8	NA	24.3	3.3	2.2	4.0	NA
Supraventricular arrhythmias							
Supraventricular tachycardia	NA	NA	1.6	NA	1.2	0.1	NA
Atrial fibrillation or flutter	1.2	NA	1.7	NA	0.6	0.5	NA
Premature atrial complex	5.1	NA	4.8	0.8	0.7	NA	NA
Other end points, %							
Hypotension	1.9	NA	NA	NA	0.7	NA	NA
Hypertension	5.5	NA	1.7	0.3	1.5	2.1	NA
Side effects	NA	NA	NA	NA	1.8	NA	NA
Wall motion abnormalities	NA	NA	NA	NA	0.9	NA	4.0

NA indicates not available.

*Completely or partially supervised by trained registered nurses.

†Patients within an early, initial time frame underwent DASE without atropine. Stress protocol is displayed as follows: dobutamine dose in μg/kg per minute; atropine dose in mg.

‡Obtained by a prior smaller safety study from the same author.[60]

§Accelerated protocol.

‖Contrast-enhanced imaging in 59%[25] and 56%[26] of patients, respectively.

aggregation[44] and α_1-mediated coronary vasoconstriction, which may paradoxically be exacerbated by administration of a nonselective β-blocker (see section on coronary spasm). Dobutamine stress–induced expansion of a sinus of Valsalva aneurysm, with compression of a coronary artery, was once reported as a potential mechanism for MI.[42]

Treatment
Discontinue dobutamine infusion. Consider thrombolysis or immediate coronary angiography followed by angioplasty.[45]

Cerebrovascular Accident

Incidence
Incidence is <0.01% (0.005%; range, 0.00% to 0.10%). A complication-specific publication is available.[46]

Pathophysiology
Dobutamine-atropine stress may cause a cerebrovascular accident through different mechanisms. Increment of heart rate and blood pressure may mechanically increase shear forces across an aneurysmal arterial wall, leading to hemorrhagic stroke, although in a series of 40 patients with at least 1 intracranial aneurysm, no evidence of aneurysm instability was seen.[46] Ischemic stroke (including transient ischemic attack) may be caused by the same mechanisms as described in the previous section on MI. Additionally, ischemic stroke may occur in the setting of dobutamine stress–induced hypotension (see later) as a result of high-grade carotid artery stenosis[6] or LV thrombus. However, in 1 study no thromboembolic complications were seen in patients with LV thrombus.[47]

Treatment
Discontinue dobutamine infusion. Hospitalization in a stroke unit should occur. Consider immediate imaging with magnetic resonance imaging or computed tomography and thrombolysis.[48]

Cardiac Asystole

Incidence
Incidence is <0.01% (0.002%; range, 0.00% to 0.03%). Case reports are available.[49–51]

Pathophysiology
The syndrome of sinus bradycardia with or without hypotension is well known during DASE. Eventually, this may lead to asystole lasting for 6 to 8 seconds.[14,49] Although, in an early report, sinus node deceleration was linked to ischemia in the inferior myocardial wall,[52] a powerful cardioinhibitory vagal reflex seems a more likely mechanism.[53] This reflex, known as the Bezold-Jarisch reflex, is a neurally mediated mechanism in which vigorous myocardial contraction stimulates intramyocardial mechanoreceptors, resulting in sympathetic withdrawal and enhanced parasympathetic activity.[54] Alternatively, it was suggested that prohibition of oral intake before DASE may lead to volume depletion, and experimental data have demonstrated that in the presence of reduced cardiac volume, β_1-adrenergic stimulation can elicit paradoxical bradycardia.[55] In contradiction to the earlier described life-threatening complications, patients with asystole usually had good baseline LV function with a hyperdynamic response to dobutamine and usually an absence of myocardial ischemia.[49–51]

Treatment
Discontinue dobutamine infusion. Administer intravenous bolus of atropine (0.5 to 2 mg).

Ventricular Fibrillation

Incidence
Incidence is 0.04% (range, 0.00% to 0.18%). Case reports are available.[43,56–59]

Pathophysiology
All but 3 patients[16,43,59] with ventricular fibrillation and available data had impaired LV function, and all had evidence of (usually severe) myocardial ischemia on DASE.[5,7,16,28,56–60] Furthermore, except for 1 patient with ST-segment elevation, nonsignificant CAD, and suspected coronary spasm,[58] all patients who underwent coronary angiography showed left main, severe proximal left anterior descending, or 3-vessel CAD.[5,7,13,24,28,43,59] Therefore, ventricular fibrillation seems to occur mainly in patients with structural heart disease (presence of persistent factors such as scar tissue) in combination with inducible, dynamic factors such as severe and/or extensive myocardial ischemia and possibly electrolyte disturbances (see also the next section on other ventricular arrhythmias).

Treatment
Discontinue dobutamine infusion. Cardiopulmonary resuscitation was successful in all but 1 patient.[22]

Sustained Ventricular Tachycardia

Incidence
Incidence is 0.15% (range, 0.00% to 0.78%). Complication-specific publications are available.[61–63] Case reports are available.[64–66]

Pathophysiology
Dobutamine may provoke ventricular arrhythmias by several mechanisms. Dobutamine has differential effects on action potential duration,[67] QRS duration, and QTc interval[68] in normal and ischemic myocardium. The abnormal dispersion of conduction in adjacent areas of ischemic and nonischemic myocardium thus created may be important in β-receptor–mediated (reentry) arrhythmogenesis. Additionally, dobutamine may increase intracellular calcium concentration by second messenger cyclic AMP.[69] Increased intracellular calcium has been shown to increase automaticity in ventricular myocardium and provoke triggered activity in the form of delayed afterdepolarizations.[70] Finally, β-receptor stimulation reduces plasma potassium level, which may temporarily predispose patients to ventricular arrhythmias.[71] In many safety studies, clinical predictors for these arrhythmias were analyzed. Ventricular arrhythmias have quite consistently been related to impaired LV function[17,18,28,29,60–63,72,73] and a history of ventricular arrhythmias[60,62,72] but not to atropine addition[12,22,60,62,63] or myocardial ischemia.[12,14,18,19,22,60–63,73,74] However, in most of these studies a distinction between nonsus-

tained and sustained ventricular arrhythmias was not made (probably because of the small number of the latter), and the incidence of ventricular tachycardias may be overestimated because of difficulties in differentiation with supraventricular tachycardia with aberration.[61] Nonsustained ventricular tachycardias do not seem to be related to long-term adverse outcome.[61,73]

Treatment

Dobutamine infusion should be discontinued (ventricular arrhythmias are usually brief and self-terminating). Administer intravenous β-blocker as a natural dobutamine antagonist (metoprolol 5 to 10 mg over a 5-minute period). Administer intravenous procainamide (10 mg/kg body weight over a 5-minute period) or amiodarone (150- to 300-mg bolus) in β-blocker–resistant sustained ventricular tachycardia. Cardiovert if the patient is hemodynamically unstable or persistent.

Other Rhythm and Conduction Disturbances

Supraventricular Arrhythmias

Incidence

Incidence of premature atrial complex is 7.8% (range, 0.7% to 27.8%). Incidence of supraventricular tachycardia is 1.3% (range, 0.0% to 7.0%). Incidence of atrial fibrillation is 0.9% (range, 0.3% to 2.2%). A complication-specific publication is available.[63]

Pathophysiology

Little is known about the mechanism of dobutamine stress in the induction of supraventricular arrhythmias. In 1 study,[63] supraventricular arrhythmias occurred more frequently in patients with more extensive impairment of LV function. The associated increases in left atrial size and pressure in such patients are well-known predictors of these arrhythmias. In another study,[9] supraventricular arrhythmias occurred more frequently in elderly patients.

Treatment

In the case of sustained supraventricular arrhythmias, dobutamine infusion should be discontinued (supraventricular arrhythmias are usually brief and self-terminating). Administer an intravenous β-blocker (metoprolol 5 to 10 mg; dose may be increased in case of existing maintenance dose), verapamil (10 mg over 10 minutes; dose may be reduced in case of previous use of a β-blocking drug or hypotension), or digoxin (bolus of 0.5 mg). Digoxin effects may take several hours and are therefore less useful for rapid rate control[75] but may be preferred in patients with LV dysfunction. In regular supraventricular tachycardias, adenosine (intravenous bolus of 6 or 12 mg) may be helpful for diagnosis by induction of atrioventricular block and may actually end circus movement tachycardias. Adenosine has a half-life of only 2 seconds, and therefore adverse reactions (facial flushing, dyspnea) last only a short time.[76] Cardiovert if the patient is hemodynamically unstable.

Atrioventricular Block

Incidence

Incidence is 0.23% (range, 0.03% to 0.68%). A complication-specific publication is available.[77]

Pathophysiology

Transient second- or third-degree atrioventricular block may be induced by several mechanisms such as myocardial ischemia (the conduction system is supplied mainly by the right coronary artery and also more distally by the left anterior descending artery), the Bezold-Jarisch reflex, and latent abnormalities in the His-Purkinje system. In a detailed study in patients with dobutamine stress–induced second-degree atrioventricular block by Hung et al,[77] the incidence of atrioventricular block was 4.0% (12 of 302 patients), indicating a higher incidence than that reported in the safety studies. All 6 patients with second-degree atrioventricular block Mobitz type II (usually located in the His bundle or bundle branches) had CAD (usually left anterior descending artery or 2-vessel CAD). In all but 1 patient, atrioventricular block occurred concomitantly with the onset of new wall motion abnormalities. After successful coronary revascularization, AV block could not be induced by repeat DASE. In the 6 patients with second-degree atrioventricular block Mobitz type I (Wenckebach block, usually located in the atrioventricular node), the relation with CAD and myocardial ischemia was less clear. Vagal-mediated effects by the aforementioned Bezold-Jarisch reflex (see section on asystole) could be a contributing factor is these patients. This assumption was supported by positive head-up tilt testing in all 3 patients with second-degree atrioventricular block Mobitz type I without CAD. Atrioventricular block is less common during this vagal reflex than sinus bradycardia, sinoatrial block, or sinus arrest, probably because these sinus node problems protect the atrioventricular node. Finally, dobutamine enhances atrioventricular nodal conduction and may thus unravel latent abnormalities in the more distal His-Purkinje system.

Treatment

In Mobitz type II, discontinuation of dobutamine infusion is indicated (of note, atropine may actually worsen subnodal block[78]). In Mobitz type I (Wenckebach) block, administer an intravenous bolus of atropine (0.5 mg; may be repeated up to 2.0 mg) if necessary.

Coronary Spasm

Incidence

True incidence is unknown but is 0.14% in 1 safety study.[9] Case reports are available.[58,79–86] A complication-specific publication is available.[87]

Pathophysiology

Coronary spasm during dobutamine stress is believed to result from α_1-receptor–mediated coronary vasoconstriction,[88] particularly in patients with endothelial dysfunction due to smoking, hypertension, or diabetes mellitus.[89,90] Systolic "spasm" (or better compression) during dobutamine stress may be caused by myocardial bridging.[86] In 1 study,[87] including 51 patients with angina at rest accompanied with electrocardiographic ST-segment elevation, nonsignificant CAD, and proven spasm (induced with acetylcholine), dobutamine stress provoked ST-segment elevation in 7 patients (14%). In another study,[80] ST-segment elevation and wall motion abnormalities became evident only after dobutamine stress after the administration of propranolol, and it has been

suggested that nonselective β-blockers may paradoxically exacerbate spasm by blocking the β_2-receptor–mediated coronary vasodilatory effects of dobutamine. Alternatively, coronary spasm may be caused by hyperventilation in an anxious patient.[91] Coronary spasm should be suspected in patients with dobutamine stress–induced ST-segment elevation in noninfarct leads and severe new wall motion abnormalities, although these may be absent in distal spasm,[85] in combination with nonsignificant lesions on coronary angiography. ST-segment elevation in noninfarct leads has also been linked to transmural myocardial ischemia due to severe CAD.[92–97] The final diagnosis of coronary spasm can only be confirmed on coronary angiography with ergonovine, acetylcholine, or dobutamine provocation.[85,87]

Treatment

Sublingual nitroglycerin should be administered first rather than β-blocking agents[83,84] because of a small risk of exacerbation of spasm with a β-blocker.[80] Long-term treatment with calcium channel blockers should be considered, as well as risk factor modulation.

Disturbances in Blood Pressure

Hypotension

Incidence

As test end point, incidence is 1.7% (range, 0.2% to 7.6%). Dependent on definition, the overall incidence is much higher; a decrease of >20 mm Hg is noted in ≈20% of patients.[98,99] Complication-specific publications are available.[98–106]

Pathophysiology

Hypotension may result from an inadequate increase in cardiac output to compensate for an expected decrease in systemic vascular resistance and/or a disproportionate decrease in systemic vascular resistance. An inadequate increase in cardiac output may be due to inadequate contractile reserve, severe ischemic LV dysfunction, or fixed or dynamic left-sided obstructive heart disease. Dynamic LV cavity obliteration due to strong inotropic stimulation was proposed as an important cause for reduced cardiac output and hypotension,[103] but in later studies conflicting results have been reported for this mechanism as an important cause of hypotension.[101,104–106] The second mechanism, a disproportionate decrease in systemic vascular resistance, may be due to the aforementioned Bezold-Jarisch reflex or, rarely, an allergic reaction to dobutamine (see later section on dobutamine hypersensitivity). The consistent absence of histories of prior MI or congestive heart failure,[98,99] ischemia,[17,98–102] or CAD[17,98,99,102] in studies with heterogeneous patients is indirect evidence of a dobutamine-induced hypotension mechanism that is based primarily on an excessive decrease in systemic vascular resistance instead of a mechanism principally involving inadequate cardiac output in most patients. In patients with impaired LV function (and thus a lesser role for the Bezold-Jarisch reflex), there is some evidence that contractile reserve plays a more important role in the pathogenesis of hypotension[72,107,108] and that hypotension has adverse prognostic value.[107]

Treatment

Discontinue dobutamine infusion in symptomatic, severe (≥40 mm Hg) hypotension. Trendelenburg position should be considered. Rapid fluid infusion should be started if the patient is symptomatic. In combination with sinus bradycardia, exclude inferior wall ischemia and consider an intravenous bolus of atropine (0.5 to 2 mg).

Hypertension

Incidence

As test end point, incidence is 1.3% (range, 0.2% to 5.5%). A complication-specific publication is available.[109]

Pathophysiology

Stress-induced hypertension normally constitutes an end point for test termination because of safety concerns.[110] The clinical characteristics of patients with a marked hypertensive response were analyzed in only 3 studies.[12,27,109] Such patients more often had a history of systemic hypertension and higher resting blood pressure and were more often on treatment with β-blockers compared with patients without a hypertensive response. These findings underscore the importance of adequate blood pressure control before dobutamine-atropine stress to avoid nondiagnostic tests. Alternatively, the earlier use of atropine has been proposed[109] in patients with a marked hypertensive response because of only a mild additional effect on blood pressure and a marked chronotropic effect.

Treatment

Discontinue dobutamine infusion; in the case of persistent hypertension, administer an intravenous β-blocker.

Direct Side Effects of Dobutamine-Atropine

Atropine Intoxication

Incidence

Incidence is 0.03% (range, 0.00% to 0.17%). No case reports are available.

Pathophysiology

Atropine intoxication is a central anticholinergic syndrome in which atropine acts on central nervous system cholinergic receptors, causing altered mental status (confusion, delirium, hallucinations) or prolonged sedation for several hours. This syndrome seems more common in elderly patients and generally requires a dose of atropine of several milligrams.[111] Of note, the incidence rates reported in this review concern the total number of atropine intoxications divided by the total number of patients who underwent DASE published in reports that specifically provided information on atropine intoxication (Table 1). Because the number of patients who actually received atropine is much lower, the incidence in patients who received atropine may be ≈2 to 3 times higher.

Treatment

Physostigmine 1 to 2 mg intravenously can reverse central atropine effects. Its administration also acts as a diagnostic test; rapid improvement rules out other causes of confusion such as cerebral stroke. Alternatively, avoidance of atropine in the elderly and administration of glycopyrrolate, an anti-

cholinergic drug that does not cross the blood-brain barrier and therefore cannot cause a central anticholinergic syndrome, have been proposed.[112]

Dobutamine Extravasation

Incidence

Dobutamine extravasation was reported only once in 2 patients in a safety study[6] but is probably underreported. Case reports during continuous therapeutic infusion are available.[113,114]

Pathophysiology

Dobutamine accumulation in subcutaneous tissue can cause local vasoconstriction by stimulation of α_1-receptors, which may result in limb ischemia[115] and during longer infusion may result in necrosis.[113] Dobutamine accumulation in subcutaneous tissue may also cause a local hypersensitivity reaction (see next section).

Treatment

Discontinue dobutamine infusion. Elevate the involved extremity. Consider local injection of 5 to 10 mg phentolamine mesylate in 10 to 15 mL saline, which is a reversible, nonselective α-receptor antagonist.

Dobutamine Hypersensitivity

Incidence

Only 3 patients were described in safety studies.[7,16] Case reports of local dermal lesions[116–118] and asthma[119] during continuous therapeutic infusion are available.

Pathophysiology

Dobutamine solution contains sodium bisulfite, which may cause allergic-type reactions with systemic symptoms and/or signs such as bronchospasm, flushing, tingling, pruritus, urticaria, angioedema, and hypotension or local dermal lesions characterized by erythema, pruritus, cellulitis, and phlebitis with or without bullae formation at the side of the injection.[120]

Treatment

Discontinue dobutamine infusion. Administer antihistamine therapy.

Discussion

Today's aggressive DASE protocol and expanding indications with inclusion of sicker patients have raised concerns about the safety of this stress modality.[121] In the present review, potentially life-threatening complications (cardiac rupture, acute MI, cerebrovascular accident, asystole, ventricular fibrillation, and sustained ventricular tachycardia) occurred in 116 patients, of whom 1 died, accounting for 1 complication in 475 tests (Table 2). This number is in reasonable agreement with the complication rate found in the recently published International Stress Echo Complication Registry (Table 2).[122]

It is important to note that for exercise stress testing, dipyridamole stress echocardiography, and dipyridamole stress scintigraphy, lower complication rates were reported of 1 complication in approximately each 1100,[123] 1400,[124] and 1600[125] tests, respectively. Several reasons may account for this difference. Patients referred for DASE are usually unable to exercise adequately, and such patients are known to have a higher incidence and extent of CAD.[126,127] In addition, the high-dose dobutamine-atropine stress protocol has a strong potential to induce myocardial ischemia. Exercise-induced ischemia may limit workload in a patient, and this may prevent the development of severe ischemia during exercise stress. Pharmacological stress with the vasodilator dipyridamole primarily creates blood flow heterogeneity and true ischemia in only a limited number of patients with significant CAD.[128] Finally, as described earlier, dobutamine may provoke ventricular arrhythmias by several unique mechanisms. Indeed, the striking difference in complication rate is, to a great extent, caused by the high incidence rate of sustained ventricular tachycardia (and to a lesser extent also ventricular fibrillation) during dobutamine-atropine stress. When sustained ventricular tachycardia is excluded from our analysis, the complication rate is 1 complication in approximately each 1573 tests for dobutamine-atropine stress, each 1500 tests for exercise stress,[123] and each 1700 tests for dipyridamole stress.[124,125] Obviously, it is still essential to optimize the safety profile of DASE. This may be achieved by paying attention to patient selection, identification of patients at relatively high risk for complications, personnel issues, and DASE protocol.

Table 2. Incidence of Major Complications in This Meta-Analysis and the International Stress Echo Complication Registry[122]

	Present Meta-Analysis (n=55 071)		Complication Registry[122] (n=35 103)	
Complication	No. of Patients	Incidence Rate	No. of Patients	Incidence Rate
Mortality	1	1: 48 316	5	1: 7021
Cardiac rupture	1	1: 48 316	5	1: 7021
Asystole	1	1: 48 316	2	1: 17 552
Cerebrovascular accident	3	1: 16 105	3	1: 11 701
Myocardial infarction	11	1: 5006	11	1: 3191
Ventricular fibrillation	19	1: 2898	11	1: 3191
Sustained ventricular tachycardia	81	1: 680	27	1: 1300
Total major complications	116*	1: 475	59†	1: 595

Causes of mortality were *ventricular fibrillation and †cardiac rupture in 3 and ventricular fibrillation in 2 patients.

Patient Selection

Safety starts with verification of test indication. Stress testing for diagnostic purposes is most useful in patients with an intermediate pretest probability of CAD.[129] In patients with a high pretest probability of CAD, there may be a case for prognostication, but only then will DASE results really affect patient management decisions. Subsequently, contraindications to DASE should be identified (Table 3). Absolute contraindications include, for dobutamine, hypersensitivity, symptomatic severe aortic stenosis (except for diagnosis in low-flow, low-gradient aortic stenosis), acute aortic dissec-

Table 3. Contraindications to DACE

Absolute, dobutamine
Symptomatic severe aortic stenosis
Acute aortic dissection
Unstable coronary syndrome
Obstructive hypertrophic cardiomyopathy
Hypersensitivity
Absolute, atropine
Narrow-angle glaucoma
Pyloric stenosis
Myasthenia gravis
Relative
Electrolyte abnormalities (hypokalemia)
Intraventricular thrombus
Intracranial arterial aneurysm
Abdominal aortic aneurysm
Known severe ventricular arrhythmias
High-degree atrioventricular block
Uncontrolled hypertension
Uncontrolled atrial fibrillation
Obstructive uropathy (atropine)

tion, unstable coronary syndromes, obstructive hypertrophic cardiomyopathy, and, for atropine, narrow-angle glaucoma, myasthenia gravis, and pyloric stenosis. Relative contraindications include electrolyte abnormalities (hypokalemia), intraventricular thrombus, intracranial arterial aneurysm, abdominal aortic aneurysm, known severe ventricular arrhythmias, high-degree atrioventricular block, uncontrolled hypertension, atrial fibrillation, and, for atropine, obstructive uropathy. Although small DASE safety reports have been published in patients with a history of ventricular arrhythmias,[130] LV apical thrombus,[47] intracranial aneurysms,[46] and abdominal aneurysms,[131] vasodilator stress testing seems intuitively the stress test of choice in such patients. After verification of indication and exclusion of contraindications, the procedure as well as side effects and potential complications should be explained to the patient. In patients at relatively high risk for complications (see next section), it may be good practice to obtain written informed consent from the patient. In some countries, dobutamine and atropine have not been approved for pharmacological stress testing, making written informed consent by the patient necessary.

Identification of High-Risk Patients

Although severe complications can be sudden and unpredictable, clearly not each patient carries the same risk. All patients with cardiac rupture had a recent inferior MI, although whether this particular myocardial region is relatively susceptible for rupture is controversial.[36,37] Ventricular fibrillation occurred almost exclusively in patients with impaired LV function with induction of extensive myocardial ischemia. Identification of patients at relatively high risk for acute MI may be more difficult. Although all but 3 patients had a history of CAD (usually prior MI), approximately half of the MIs occurred in a myocardial territory without evidence for myocardial ischemia. This is consistent with the angiographic study by Ambrose et al,[132] in which the culprit vessel leading to acute MI had a mean initial stenosis of only 34%. Dobutamine-atropine stress will normally not induce myocardial ischemia in a myocardial territory supplied by a vessel with such a minor stenosis.[133] As with other stress tests, the relative risk of cardiac rupture, ventricular fibrillation, or acute MI was 4 times higher in patients with a history of MI and/or impaired LV function. Therefore, the risk-benefit ratio of DASE in these patients should always be evaluated carefully.

Personnel

The current era of cost containment makes it challenging to dedicate physician time solely to the supervision of a time-consuming test such as DASE. Paramedical supervision of exercise testing has been well established in the literature,[134] and in selected patients this is allowed according to the American College of Cardiology/American Heart Association Guidelines for Exercise Testing.[135] Some have proposed that trained registered nurses or sonographers could also fill the supervisory role during DASE.[6,13,29] However, patients referred for DASE are usually not able to exercise adequately and therefore a priori are at higher risk for induction of severe myocardial ischemia and complications. Furthermore, the published experience with trained registered nurses or sonographers to fill the supervisory role is (although extensive) limited to only 1 center.[6,13,29] Although some complications are largely independent of the operator's experience and there is no evidence that physician supervision reduces complications, there is a relation between the number of complications and the years of experience and volume of a center.[22] Therefore, it may be preferable that a physician with better knowledge of the incidence, pathophysiology, and treatment of complications attends the test in patients at high risk for complications, in particular those with recent MI. In case of complications, the trained registered nurse or physician should be able to prove that indications were appropriate, the protocol followed standard guidelines, the patient was aware of the inherent risks of the procedure, and standard treatment was provided in a timely fashion.

DASE Protocol

Controversy exists about the use (and definition) of stress-induced wall motion abnormalities as a test end point. This is clearly reflected in the 0% to 32% range in which this end point was used in the DASE safety studies. One may question whether continuation of DASE after the first clear signs of myocardial ischemia provides additional diagnostic or prognostic information and whether it is safe. There may be little loss of information when an examination is stopped because of signs of ischemia in 1 coronary territory because the timing of ischemia (ischemic threshold) already provides excellent diagnostic[136] and prognostic[137] information. It is not known whether continuing DASE and potentially inducing ischemia in a multivessel distribution carries additional and independent information over the ischemic threshold. In patients with prior (nonrevascularized) MI, ischemia outside the infarction territory may certainly be a test end point because this usually

confirms multivessel CAD. In regard to safety, it is important to note that provocation of severe myocardial ischemia played an important role in patients with ventricular fibrillation. The incidence of ventricular fibrillation was highest in studies with the most conservative use of this end point[18,60] and lowest in studies with the most liberal use of this end point.[15,17]

It is well known that some life-threatening complications such as ventricular fibrillation,[57] cerebrovascular accident,[22] and, in particular, acute MI[5,6,12,22,38–41,74] can occur after dobutamine discontinuation, usually within 20 minutes, but up to 60 minutes is also not uncommon, despite its short half-life time and antidote administration. Thus, particularly in patients at risk for these complications, close cardiological monitoring is required during the recovery phase, and any possible cardiovascular or neurological symptoms should be reported immediately.

Safety of Contrast Addition

Suboptimal images are an important problem in stress echocardiography. Numerous studies have shown that intravenous contrast for LV opacification and endocardial border definition improve the diagnostic accuracy of DASE, particularly in patients with suboptimal acoustic windows.[138] In 2007, the Food and Drug Administration mandated that a "black box" warning be placed on Definity (perfluoropropane; Bristol-Myers Squibb Medical Imaging, Billerica, Mass) and Optison (perfluoropropane; GE Healthcare, Princeton, NJ) after 11 deaths (4 within 30 minutes of contrast administration) were temporally related to but not clearly caused by contrast injection. In addition, in a Bracco company postmarketing analysis in 157 838 patients, 19 nonfatal severe and 3 fatal complications after the use of SonoVue (sulfur hexafluoride; Bracco, Milan, Italy) were reported.[139] Despite similar questions about the causal relationship, the European Medicines Agency also took precautionary measures to limit the use of SonoVue in patients with cardiac disease. Recently, the Food and Drug Administration modified their original warning; contrast agents are only contraindicated in patients with cardiac shunts or with hypersensitivity to the agent. The safety of Definity and Optison in the context of stress echocardiography was shown recently from large registries.[140] Nevertheless, we recommend keeping the patient under close medical supervision during and briefly after the administration of contrast agents. Intravenous antiallergic and anaphylactic drugs (H1 and H2 antihistamines, corticosteroids, and epinephrine) should be available in the echocardiography room in addition to standard resuscitation equipment.

Conclusions

Potentially life-threatening complications during DASE occur in 1 of 475 studies. Important complications occur not only during but also after discontinuation of dobutamine infusion. The relatively high complication rate is driven particularly by the occurrence of sustained ventricular tachycardia. After exclusion of sustained ventricular tachycardia, the event rate is 1 in each 1573 studies. Patients with a history of MI and/or impaired LV function are at highest risk for complications. The risk-benefit ratio of DASE should always be evaluated carefully.

Disclosures

None.

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