sible occurrence of pneumothorax in patients with esophageal perforation contraindicates its use.

In summary, we have presented a case of esophageal perforation associated with anesthetic induction and endotracheal intubation, delineated the associated complications, and outlined appropriate management.

References

1. Dubost C, Kaswin D, Duranteau A, Jehanno C, Kaswin R: Esophageal perforation during attempted endotracheal intubation. J Thorac Cardiovasc Surg 78:44–51, 1979
2. Loop FD, Groves LK: Esophageal Perforations. Ann Thorac Surg 10:571–587, 1970
3. Phillips LG, Jr, Cunningham J: Esophageal perforation. Radial Clin North Am 22:607–613, 1984
4. Seybold WD, Johnson MA III, Leary WV: Perforation of the esophagus. An analysis of 50 cases and an account of experimental studies. Surg Clin North Am 30:1155–1183, 1950
5. Hankins JR, McLaughlin JS: Pericarditis with effusion complicating esophageal perforation. J Thorac Cardiovasc Surg 73:225–230, 1977
6. Macklin CC: Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum: clinical implications. Arch Int Med 64:913–926, 1939
7. Hirsch M, Abramowitz HB, Shapera S, Barki Y: Hypopharyngeal injury as a result of attempted endotracheal intubation. Radiology 128:37–39, 1978
8. O'Neil JE, Giffin JP, Cottrell JE: Pharyngeal and esophageal perforation following endotracheal intubation. ANESTHESIOLOGY 60:487–488, 1984

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Autonomic Neuropathy in a Diabetic Patient with Renal Failure

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Abnormalities of cardiovascular innervation in diabetes mellitus[1–4] and chronic renal failure[5] have been described. The prevalence of cardiac autonomic neuropathy in unselected diabetic patients is 20–40%, depending on the sensitivity of tests employed, indicating that the autonomic damage is more common than previously believed.[6,7] Once it develops, the prognosis is poor with the mortality rate approaching 56% over a 5-yr period.[3] A high proportion of these reported deaths were sudden and unexpected.[3,8,9] In diabetes mellitus, autonomic damage appears to occur at various sites in the reflex arc, but the precise location of damage remains controversial. In chronic renal failure, abnormalities are consistently located in the baroreceptor area.

This report concerns three episodes of rapidly progressing bradycardia and hypotension that occurred in a diabetic patient who had renal failure. These episodes occurred suddenly and unexpectedly, and were unresponsive to iv atropine or usual doses of ephedrine, ultimately requiring epinephrine and/or external cardiac massage for resuscitation.

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The cardiovascular reflexes of the patient were examined after discharge: beat-to-beat heart rate variation was minimal during both deep breathing and the Valsalva maneuver; the hand grip test was abnormal; and marked postural hypotension was present.

Report of a Case

A 33-year-old woman, 152 cm and 65 kg, was admitted for insertion of an Ash® catheter for peritoneal dialysis. She had become increasingly intolerant of hemodialysis for the past 3 weeks, with hypotension and severe nausea during the procedure. The patient was a known juvenile diabetic of approximately 20 yr duration. She had been receiving hemodialysis for the past 14 months for end-stage disease secondary to diabetes mellitus. In addition, she had a long-standing history of peripheral neuropathy, retinopathy, and peripheral vascular disease. More recently, the patient had developed various symptoms suggestive of autonomic nervous dysfunction (*i.e.*, frequent esophageal spasm for 2 years, dizziness on standing for 1 year, and intermittent diarrhea that developed without warning two to three times a week for 6 months). Approximately 2 weeks prior to her current admission, blood sugar decreased to 2.3 mM (43 mg%) and 1.2 mM (22 mg%) in two successive days without any subjective symptoms. The patient had not received general anesthetics in the past, and there was no family history of anesthetic problems. Current medications were NPH insulin, 26 units, and regular insulin, 8 units twice a day.

Pertinent findings in the physical examination included bilateral retinal scars due to laser surgery and advanced peripheral somatic neuropathy involving forearms, as well as lower thoracic and lumbosacral distribution. Pain sensation, tactile discrimination, vibratory sensation, and proprioception all were impaired. Deep tendon reflexes were weak at the knees and absent at the ankles. Arterial blood pressure was 130/80 mmHg and the heart rate was 98 beats/min. The hemoglobin was 7.7 g/dl and the serum potassium value was 5.1 mM on

the morning of the surgery. The ECG showed sinus tachycardia (110 beats/min) with nondiagnostic T-wave abnormality. Five ECGs on previous admissions, and two on subsequent admissions, showed similar ST–T or T wave abnormality, with heart rate ranging 101–109 beats/min. The chest roentgenogram was normal. The patient was premedicated with morphine sulfate, 4 mg, and atropine, 0.4 mg im. The morning dose of insulin was omitted.

In the holding area, the blood sugar was 14.4 mM. Anesthesia was induced with thiopental, 175 mg iv. Tracheal intubation was facilitated with succinylcholine, 40 mg iv. Anesthesia was maintained with fentanyl, 100 μg, and isoflurane 0.25% with 50% nitrous oxide. Skeletal muscle relaxation was provided by atracurium, 15 mg iv. Respiration was mechanically controlled. Arterial blood pressure and heart rate decreased from the preinduction value of 110/75 mmHg and 98 beats/min to 100/90 mmHg and 92 beats/min and remained at those levels.

Approximately 25 min after the induction and shortly after the incision, a sudden decrease in heart rate from 90 to 60 beats/min occurred. There was no dysrythmia. Arterial blood pressure was 90/60 mmHg. Nitrous oxide and isoflurane were discontinued immediately, and three boluses of atropine, 0.4 mg iv, were given rapidly without any effect. Two iv boluses of ephedrine, 20 mg, were given without effect. Both heart rate and blood pressure continued to decreased rapidly over a period of a few minutes to 38 beats/min and 50/30 mmHg, respectively, when external cardiac massage was instituted. The patient, however, responded immediately to epinephrine, 0.25 mg iv, increasing heart rate and blood pressure to 140 beats/min and 170/100 mmHg. A radial artery was cannulated; *p*H was 7.42; Pa_{O_2} was 380 mmHg; and Pa_{CO_2} was 44.8 mmHg. Serum potassium was 4.7 mM and glucose was 18.1 mM. Because of this patient's urgent need to acquire a route for dialysis, it was decided to proceed with placement of a catheter. The patient was then anesthetized with 50% nitrous oxide. The peritoneum was opened and the omentum was dissected for placement of a catheter. Arterial blood pressure and heart rate were sustained at 100/65 mmHg and 96 beats/min for several minutes, when suddenly the heart rate and blood pressure began to decrease again. Nitrous oxide was discontinued. There was no manipulation of the abdominal content at the time. There was no response to ephedrine, 40 mg iv. When the heart rate and blood pressure were 40 beats/min and 60/30 mmHg, a bolus of epinephrine, 0.1 mg iv, was given. The response was brisk, increasing the heart rate and blood pressure to 120 beats/min and 140/80 mmHg, respectively. An Ash catheter was inserted and the abdomen was closed quickly. While closing the skin, the third and identical episode occurred. Again, there was no response to ephedrine, but the response to epinephrine was brisk.

In the recovery room, a flow-directed, pulmonary artery catheter was inserted. Pulmonary artery pressure and pulmonary capillary wedge pressure were 28/16 and 14 mmHg, respectively. The patient was fully awake. The ECG showed a lateral injury pattern that returned to the preoperative pattern within 36 h. Cardiac enzymes were not elevated. The changes observed were consistent with myocardial ischemia. We considered these changes to be secondary to the hypotensive episodes and resuscitative efforts. The patient was discharged from the hospital in 6 days.

Approximately 2 months after the discharge, the patient's cardiovascular reflexes (*i.e.*, heart rate changes during deep breathing and the Valsalva maneuver) and the blood pressure response to sustained handgrip and standing were studied during one of her postoperative follow-up visits. An electrocardiographic tracing was recorded continuously during the tests. All tests were repeated three times and the mean values were used as the results. The beat-to-beat variation during deep breathing and the ratio of R–R intervals during the Valsalva maneuver were 1.8 beats/min and 1.04, indicating vagal damage. There was no change in diastolic pressure during the 1-min handgrip test and the arterial blood pressure decreased from 132/82 to 94/68 mmHg on standing, suggesting sympathetic nervous system damage.

During the following 14 months, the patient returned to the operating room five times: for removal of the Ash® catheter, revision of A-V fistula, debridement of an infected toe, and twice for debridement of an infected hand. Removal of the Ash® catheter was performed under local infiltration. The other four operations were performed under axillary block and ankle block. The axillary block was inadequate on one occasion and supplemented with fentanyl, 100 μg iv, and 50% nitrous oxide. The analgesia was adequate and the patient tolerated the operation and nitrous oxide well.

Discussion

Sinus dysrhythmia, tachycardia during the Valsalva maneuver, bradycardia after release, and the initial tachycardia of the biphasic heart rate response to standing are abolished with atropine, but not by β-adrenergic blockade.[10–12] This suggests that these heart rate responses are under vagal control. The response of heart rate to these maneuvers is reproducible in normal subjects, but often decreased in long-term diabetics. A beat-to-beat variation during deep breathing (*i.e.*, the difference between maximal and minimal heart rates) less than 10 beats/min, the Valsalva ratio (*i.e.*, the ratio of longest R–R after release to shortest R–R interval during strain) less than 1.10, and the ratio of R–R intervals at beats 15 and 30 after standing less than 1.03 have been considered abnormal.

The venous pooling of blood in the lower extremities and splanchnic vascular bed that occurs on standing results in a decrease in the central venous pressure, cardiac output, and arterial blood pressure. In normal subjects, reflex vasoconstriction and an increase in heart rate tend to restore blood pressure and cardiac output. There is also a sharp increase in the plasma norepinephrine concentration. A recent study in long-term diabetics of hemodynamic variables and plasma concentration of catecholamines has shown that the increases, after standing, in total peripheral vascular resistance, splanchnic vascular resistance, and subcutaneous vascular resistance were all significantly less in the diabetics with orthostatic hypotension.[13] The plasma norepinephrine response also was blunted. Blood volume and the decrease in cardiac output and plasma volume after standing were similar in diabetic with and without orthostatic hypotension. These findings suggested that the basic defect in diabetic orthostatic hypotension is a lack of vasoconstriction due to sympathetic nerve dysfunction. During sustained isometric muscular exercises (*e.g.*, handgrip) blood pressure increases due to increase in peripheral vascular resistance and cardiac output.[14] The blood pressure response is significantly decreased by phentolamine, indicating involvement of the sympathetic nerves. A decrease in the systolic blood pressure of more than 30 mmHg on standing, and an increase in the diastolic pressure of less than 15 mmHg during

sustained handgrip at 30% of the maximal voluntary contraction have been considered abnormal.

These tests obviously are not specific for autonomic nerve function. An abnormal result merely indicates that there is a defect in the reflex arc. The defect may be located in the afferent receptor, afferent nerve, reflex center, efferent nerve, or in the effector organ itself. However, the results of different tests for parasympathetic nerve function correlate closely with each other. There is also a close relationship between the results of autonomic and somatic nerve function tests. In addition, diabetics with clinical signs and symptoms of autonomic neuropathy invariably have abnormal results in one or more of the autonomic nerve function tests. Thus, abnormal results in diabetic patients have been considered indicative of autonomic neuropathy.[15] Survey of diabetics with these tests has so far shown that cardiac parasympathetic dysfunction appears to be more prevalent than sympathetic dysfunction when examined in unselected diabetics.[6,7] Some diabetics with signs of vagal dysfunction have normal sympathetic function, but diabetics with sympathetic dysfunction invariably have vagal dysfunction. However, plasma catecholamine responses to standing, exercise, and hypoglycemia in diabetics without signs of sympathetic dysfunction (*i.e.*, mild autonomic neuropathy) are blunted and correlate with cardiac vagal dysfunction.[13] Sympathetic and parasympathetic neuropathy, as well as somatic neuropathy, may develop in parallel in diabetic patients.

Plasma norepinephrine levels increase in response to phentolamine infusion in normal subjects.[16] Plasma epinephrine levels do not change. Since activation of presynaptic α-receptors of the postganglionic sympathetic axon terminals results in feedback inhibition of norepinephrine release, it has been suggested that the norepinephrine response to phentolamine is due to presynaptic α-receptor blockade.[16] Recently, Halter has shown, in six diabetic patients with autonomic neuropathy, that the norepinephrine response to phentolamine was decreased.[17] The norepinephrine release in response to tyramine was normal in four of these patients, suggesting that the lesion was proximal to the postganglionic axon terminal. In the remaining two patients, the norepinephrine response to tyramine was blunted, suggesting that the lesion was at the postganglionic axon terminal. In normal subjects, plasma levels of norepinephrine and epinephrine both increase in response to iv edrophonium due to its action at autonomic ganglia.[18,19] Leveston *et al.* demonstrated, in those diabetics with orthostatic hypotension and blunted norepinephrine response, that the response of plasma norepinephrine to edrophonium also was blunted.[20] The epinephrine response was intact. Therefore, they also postulated that the autonomic lesion in their patients was in the postganglionic neurons. Hilsted *et al.*, on the other hand, have demonstrated in their diabetic patients with clinical signs of autonomic neuropathy that epinephrine secretion from the adrenal medulla is impaired during exercise and hypoglycemia.[21] The adrenal medulla is innervated by preganglionic sympathetic fibers. Therefore, they suggested that the lesion in their patients was in the preganglionic neuron.[15] Thus, lesions appear to occur anywhere along the reflex arc. Pathological studies have demonstrated various lesions in the vagus nerve, the splanchnic nerve, autonomic ganglia, and cardiac plexus nerves in patients who died of "painless" myocardial infarction.[22–25] In contrast, in chronic renal failure, the abnormality is more consistently found in the baroreceptor system,[5] although a more recent report has suggested a defect at the adrenergic postsynaptic level.[26]

Many of the clinical features of autonomic neuropathy (*i.e.*, dizziness on standing, hypoglycemia unawareness, abnormal esophageal motility (spasm), nausea, intermittent diarrhea, and hypotension on hemodialysis) were prominent symptoms in our patient. There was advanced peripheral somatic neuropathy in both lower and upper extremities. Renal failure, retinopathy, and peripheral vascular disease (*i.e.*, the late complications of long-term diabetes) also were present. Resting heart rate was elevated persistently in the range of 101–110 beats/min, the values consistent with severe vagal damage or the intrinsic heart rate of the denervated or transplanted heart.[27] The results of postoperative study of cardiovascular reflexes were consistent with severe parasympathetic and sympathetic damages. There was essentially no change in heart rate during either deep breathing or the Valsalva maneuver. There was no change in blood pressure during static isometric exercise, and blood pressure decreased significantly on standing.

The intraoperative episodes of bradycardia and hypotension occurred unexpectedly without any apparent precipitating causes. The vital signs had been stable, and there was no major manipulation of abdominal contents or peritoneum at the time of the incidents. We did not think that hypoventilation or hypoxia was present in this patient because induction and maintenance of anesthesia were both smooth, and there was no difficulty with ventilation. The bradycardia did not respond to a large dose of iv atropine, suggesting damage to the cardiac vagal nerve or complete lack of vagal tone. The response of these episodes to iv ephedrine was poor, but that to epinephrine was brisk. These seem to suggest in our patient that the lesion, among other locations, was in the synaptic region of the postganglionic neuron. The response to resuscitation was rapid in all three episodes. The serum potassium, glucose, and bicarbonate values were within normal limits immediately after resuscitation. These features (*i.e.*, suddeness of onset, absence of apparent precipitating causes, absent or poor response to iv atropine and ephedrine, respectively, and rapid responses to resuscitatior

suggest that the underlying mechanism of these episodes may have been abnormalities of cardiac innervation. Myocardial infarction as a precipitating cause was ruled out postoperatively by serial enzymes and electrocardiographic study.

Isoflurane in clinical concentrations causes little or no depression of myocardial function,[28] but it produces a dose-dependent depression of isolated papillary muscle of cat heart.[29] Sustained myocardial function has been considered to be due to a mild sympathetic stimulating property of isoflurane.[30] Nitrous oxide has sympathomimetic and myocardial depressant effects. Nitrous oxide depresses denervated dog heart and cat papillary muscle.[31,32] The depressant effect may be antagonized partially or completely by the sympathetic activity and its cardiovascular effects, if any, are minimal in healthy subjects. Nitrous oxide, however, depresses myocardial function significantly in patients with coronary heart disease. A recent report suggested that nitrous oxide may have a direct detrimental effect on the areas of myocardium distal to a compromised coronary artery.[33] Fentanyl has little effect on myocardial function in doses used for clinical anesthesia.

Accelerated coronary artery disease is a prominent feature of diabetes mellitus and accounts for much of the mortality of the disease. Absence of cardiac symptoms in some of these patients has been considered due to the neuropathy of afferent cardiac nerves. Cardiomyopathy also is not uncommon in diabetics.[34] It seems probable that our patients who had already developed most of the complications of diabetes mellitus also had significant coronary artery disease and/or cardiomyopathy. The nondiagnostic ST-T changes present consistently in the electrocardiograms may have reflected such changes in the myocardium. It is not clear what caused the initial episode of bradycardia and hypotension. The combined MAC for the inspired concentrations of nitrous oxide and isoflurane was approximately 0.7, while the alveolar concentration of isoflurane must have been increasing steadily with a constant inspired concentration. Thus, the alveolar concentrations of anesthetics were relatively low when this episode occurred. The effect of nitrous oxide alone does not explain the episode because the patient tolerated the same concentration of nitrous oxide during an operation at a later date. Available reports also suggest that transplanted heart (*i.e.*, denervated heart) tolerates both nitrous oxide and narcotics well clinically.[35,36] The episode probably was initiated by both nitrous oxide and isoflurane which, despite low concentrations, caused significant depression and vasodilation of the denervated heart and peripheral vessels, respectively. The myocardium probably was already compromised and there was evidence in this patient of splanchnic neuropathy (*i.e.*, intermittent diarrhea and orthostatic hypotension). The rapid deterioration of bradycardia and hypotension most likely reflected the absence of reflex vagal withdrawal and increase in sympathetic activity. We think that the basic defect in this patient was an abnormality of the autonomic nervous system.

Unexpected sudden deaths have been reported in diabetic autonomic neuropathy, many without a demonstrable cause at autopsy.[3,8,9] The deaths generally were considered to be due to an abnormality of cardiovascular innervation. Page *et al.* have reported 12 cardiorespiratory arrests in eight young diabetics with severe autonomic neuropathy.[9] Two of these arrests occurred intraoperatively, and three in the recovery room. The circumstances under which these episodes developed frequently were associated with hypoxia (*i.e.*, pneumonia), immediate postoperative period, and spontaneous breathing during anesthesia. Therefore, Page *et al.* postulated that these cardiorespiratory arrests were due to abnormal hypoxic drive mechanisms. However, a more recent report suggests that the peripheral chemoreceptor pathways remain intact in diabetic autonomic neuropathy.[37] Thus, the abnormality may reside in other locations, possibly the brainstem area. Sympathetic neuropathy (*e.g.*, postural hypotension, sweating disturbances, and hypoglycemic unawareness) becomes symptomatic after the development of parasympathetic neuropathy. Postural hypotension, in particular, is invariably associated with other symptoms of autonomic neuropathy and abnormal cardiovascular reflexes. Thus, the patients with symptoms of autonomic neuropathy, particularly the sympathetic neuropathy, should be observed carefully for "unexpected" cardiorespiratory depression during the perioperative period.

References

1. Ewing DJ: Cardiovascular reflexes and autonomic neuropathy. Clin Sci 55:321–7, 1978
2. Clarke BF, Ewing DJ, Campbell IW: Diabetic autonomic neuropathy. Diabetologia 17:195–212, 1979
3. Ewing DJ, Campbell IW, Clarke BF: The natural history of diabetic autonomic neuropathy. Q J Med NS49:95–108, 1980
4. Clarke BF, Ewing DJ: Cardiovascular reflex tests in the natural history of diabetic autonomic neuropathy. NY State J Med 82: 903–8, 1982
5. Henrich WL: Autonomic neuropathy in dialysis patients. Trans Am Soc Artif Intern Organs 28:662–3, 1982
6. Hilsted J, Jensen SB: A simple test for autonomic neuropathy in juvenile diabetes. Acta Med Scand 205:385–7, 1979
7. Ewing DJ, Irving JB, Kerr F, Wildsmith JAW, Clarke BF: Cardiovascular responses to sustained handgrip in normal subjects and patients with diabetes mellitus: A test of autonomic function. Clin Sci Mol Med 46:295–306, 1974
8. Ewing DJ, Campbell IW, Clarke BF: Mortality in diabetic autonomic neuropathy. Lancet 1:601–3, 1976
9. Page MMcB, Watkins PJ: Cardiorespiratory arrest and diabetic autonomic neuropathy. Lancet 1:14–6, 1978
10. Wheeler T, Watkins PJ: Defective innervation of heart in diabetic autonomic neuropathy. Br Med J II:15–7, 1975
11. Spodick DH, Meyer MB, Quarry-Pigot VM: Effect of beta-adren-

ergic blockade on beat-to-beat response to the Valsalva manoeuvre. Br Heart J 36:1082–6, 1974
12. Ewing DJ, Hume L, Campbell IW, Murray A, Neilson JMM, Clarke BF: Autonomic mechanisms in the initial heart rate response to standing. J Appl Physiol 49:809–14, 1980
13. Hilsted J, Parving HH, Christensen NJ, Benn J, Galbo H: Hemodynamics in diabetic orthostatic hypotension. J Clin Invest 68:1427–34, 1981
14. Lind AR, Taylor SH, Humphreys PW, Kennelly BM, Donald KW: The circulatory effects of sustained voluntary muscle contraction. Clin Sci 27:229–44, 1964
15. Hilsted J: Pathophysiology in diabetic autonomic neuropathy: cardiovascular, hormonal, and metabolic studies. NY State J Med 82:892–903, 1983
16. Clarke WL, Santiago JV, Thomas L, Ben-Galim E, Haymond MW, Cryer PE: Adrenergic mechanisms in recovery from hypoglycemia in man: adrenergic blockade. Am J Physiol 236:E147–52, 1979
17. Halter JB: Diabetic autonomic neuropathy: A distal adrenergic lesion, Excerpta Medica, International Cong Series 481(211): 83, 1979
18. Tohmeh JF, Shah SD, Cryer PE: The pathogenesis of hyperadrenergic postural hypotension in diabetic patients. Am J Med 67:772–8, 1979
19. Rizza RA, Cryer PE, Gerich JE: Role of glucagon, catecholamines and growth hormone in human glucose counterregulation. J Clin Invest 64:62–71, 1979
20. Leveston SA, Shah SD, Cryer PE: Cholinergic stimulation of norepinephrine release in man. Evidence of a sympathetic postganglionic axonal lesion in diabetic adrenergic neuropathy. J Clin Invest 64:374–80, 1979
21. Hilsted J, Galbo H, Christensen NJ: Impaired responses of catecholamines, growth hormone and cortisol to graded exercise in diabetic autonomic neuropathy. Diabetes 29:257–62, 1980
22. Hensley GT, Soergel KH: Neuropathological findings in diabetic diarrhea. Arch Pathol 85:587–97, 1968
23. Low PA, Walsh JC, Huang CY, McLeod JG: The sympathetic nervous system in diabetic neuropathy, a clinical and pathological study. Brain 98:341–56, 1975
24. Faerman I, Faccio E, Milei J, Nunez R, Jadzinsky M, Fox D, Rappaport M: Autonomic neuropathy and painless myocardial infarction in diabetic patients. Diabetes 26:1147–58, 1977
25. Duchen LW, Anjorin A, Watkins PJ, MacKay JD: Pathology of autonomic neuropathy in diabetes mellitus. Ann Intern Med 92:301–3, 11980
26. Botey A, Gaya J, Montoliu J, Torras A, Rivera F, Lopez-Padret J, Revert L: Postsynaptic adrenergic unresponsiveness in hypotensive haemodialysis patients. Proc Eur Dial Transplant Assoc 18:586–91, 1981
27. Clark BF, Ewing DJ: Resting heart rate and diabetic autonomic neuropathy. NY State J Med 82:908–13, 1982
28. Stevens WC, Cromwell TH, Halsey MJ, Eger EI, Shakespeare TF, Bahlmann SH: The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. ANESTHESIOLOGY 35:8–16, 1971
29. Kemmotsu O, Hashimoto Y, Shimosato S: Inotropic effects of isoflurane on mechanics of contraction in isolated cat papillary muscles from normal and failing hearts. ANESTHESIOLOGY 39: 470–7, 1973
30. Skovsted P, Sapthavichaikul S: The effect of isoflurane on arterial pressure, pulse rate, autonomic nervous activity and barostatic reflexes. Can Anaesth Soc J 24:304–14, 1977
31. Craythorne NWB, Darby TD: The cardiovascular effects of nitrous oxide in the dog. Br J Anaesth 37:560–5, 1965
32. Price HL: Myocardial depression by nitrous oxide and its reversal by Ca.++ ANESTHESIOLOGY 44:211–5, 1976
33. Philbin DM, Foex P, Phil D, Drummond G, Lowenstein E, Ryder WA, Jones LA: Postsystolic shortening of canine left ventricule supplied by a stenotic coronary artery when nitrous oxide is added in the presence of narcotics. ANESTHESIOLOGY 62:166–74, 1985
34. Fein FS, Sonnenblick EH: Diabetic cardiomyopathy. Prog Cardiovasc Dis 27:255–70, 1985
35. Kanter SF, Samuels SI: Anesthesia for major operations on patients who have transplanted hearts, a review of 29 cases. ANESTHESIOLOGY 46:56–8, 1977
36. Eisenkraft JB, Dimich I, Sachdev VP: Anesthesia for major noncardiac surgery in a patient with a transplanted heart. Mount Sinai J Med 48:116–20, 1981
37. Ewing DJ, Campbell IW, Calverly PMA, Fraser DH, Clarke BF: Natural history of autonomic neuropathy in diabetes. Q J Med NS48:660–2, 1979