Nitroglycerin-induced Severe Hypotension and Bradycardia in Patients with Acute Myocardial Infarction

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SUMMARY Seven episodes of simultaneous severe systemic arterial hypotension and absolute or relative bradycardia were observed in five patients receiving either sublingual nitroglycerin (two patients) or intravenous nitroglycerin (three patients) within the first 24 hours of onset of symptoms of acute myocardial infarction. Left ventricular filling pressure, measured as pulmonary artery diastolic pressure, decreased simultaneously in all four patients in whom pulmonary artery pressures were monitored. No initial increase in heart rate was observed in any of the five patients prior to the development of bradycardia. Possible mechanisms producing simultaneous bradycardia and hypotension during nitroglycerin administration are considered. The patient studies emphasize the importance of careful hemodynamic monitoring during administration of sublingual or intravenous nitroglycerin to patients with acute myocardial infarction.

SINCE THE FIRST REPORT of its efficacy in the treatment of angina pectoris in 1879, nitroglycerin has become the most commonly used drug in the therapy of chronic angina. Nitrates are currently being investigated for their potential role in the limitation of infarct size and for the treatment of congestive heart failure complicating acute myocardial infarction. Side effects of nitroglycerin administration, such as pulsatile headache, nausea, vomiting, flushing, lightheadedness and palpitations, often associated with minor decreases in systemic arterial pressure and compensatory tachycardia, are well recognized. Only a few reports are available, however, concerning severe complications such as syncope, documented severe hypotension, and serious arrhythmias occurring subsequent to nitroglycerin administration in patients with cardiac disease.

During the past three years, we have observed seven episodes of severe hypotension associated with sinus bradycardia, occurring in five patients receiving sublingual or intravenous nitroglycerin within the first 24 hours of onset of symptoms of acute myocardial infarction. This report presents our experience with this complication of nitroglycerin administration and emphasizes the need for careful observation of patients receiving nitroglycerin during acute myocardial infarction.

Methods

During a three year period from 1972 to 1975, 54 patients received either sublingual (14 patients) or intravenous (40 patients) nitroglycerin during clinical research studies investigating hemodynamic effects of nitroglycerin in patients with acute myocardial infarction. The diagnosis of acute myocardial infarction was based on electrocardiographic changes, coincident with enzyme elevations typical of acute infarction. The electrocardiographic changes were indicative of transmural myocardial infarction in 49 patients and subendocardial infarction in the remaining five patients.

A #7 Swan Ganz catheter was positioned in the pulmonary artery via antecubital vein cutdown. A short plastic catheter was inserted via cutdown or percutaneously into the radial artery. Pulmonary and systemic arterial pressures were measured with Statham P37b and P23Db transducers, respectively. Fourteen patients received 0.3 mg nitroglycerin sublingually according to a previously described protocol. Nitroglycerin, prepared as an aqueous solution, was administered intravenously to 40 patients as previously described. Consent was obtained from all patients prior to drug administration.

Severe systemic arterial hypotension, associated with sinus bradycardia, was observed in one of the 14 patients following sublingual nitroglycerin administration and in three of the 40 patients receiving nitroglycerin infusion. A fifth patient, admitted to the Coronary Care Unit for acute myocardial infarction, developed hypotension and bradycardia after receiving 0.4 mg nitroglycerin sublingually for pain recurring shortly after admission. Those five patients developing hypotension and bradycardia with nitroglycerin administration are described in the case reports which follow.

Cases

Case 1

HR, a 78-year-old normotensive male with a history of myocardial infarction, angina pectoris responsive to nitroglycerin, and stable symptoms of mild left ventricular congestive failure treated with digitalis and diuretics, was admitted following three weeks of increasing angina. Physical examination revealed a regular pulse of 120, a cuff blood pressure of 155/80 mm Hg, and signs of both right and left ventricular failure. The initial ECG revealed ST-segment depression in the anterolateral leads. The patient complained of recurrent chest pain and was given 0.4 mg nitroglycerin sublingually. Five minutes later a sinus bradycardia of 56 was observed on his bedside monitor. Over the next four minutes his sinus rate slowed to 38 per minute and emergence of a nodal bradycardia at a rate of 33 was subsequently observed (fig. 1). Systolic blood pressure was palpable at 90 mm Hg. Administration of 1 mg of intravenous atropine and leg elevation was associated with a rapid return of his heart rate to 120 (sinus) and gradual return of his blood pressure to 130/70 mm Hg.

The patient died following cardiac arrest on the fourth hospital day. Autopsy revealed recent infarction of the posterior left ventricle and anterior papillary muscle.

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Case 2*

JC, a 67-year-old male without a history of hypertension or ischemic symptoms was admitted with severe substernal chest pressure. Physical examination revealed signs of left ventricular failure. The ECG revealed ST-segment elevation in the inferior leads. Subsequent enzyme analysis confirmed the diagnosis of myocardial infarction. Initial hemodynamic measurements were stable over a 30 minute control period and included mean arterial pressure of 124 mm Hg, a pulmonary artery diastolic pressure of 20 mm Hg and heart rate of 87 beats/minute. Nitroglycerin (0.3 mg) was administered sublingually. Five minutes later, the pulmonary artery diastolic pressure had decreased to 15 mm Hg with no change in heart rate and a minor decrease in mean arterial pressure. Six minutes later the pulmonary artery pressure had decreased further to 3 mm Hg, the heart rate to 68 beats/minute and the mean arterial pressure to 59 mm Hg. No initial tachycardia was noted, and during the bradycardia the patient remained in normal sinus rhythm with a rare premature ventricular contraction. He developed chest pain during the period of hypotension and relative bradycardia. Elevation of the legs, followed by 1 mg of intravenous atropine, was associated with a rapid return of the heart rate to 92 beats/minute, mean arterial pressure to 104 mm Hg and disappearance of chest pain.

Case 3

JA, a 77-year-old hypertensive male with chronic mild congestive failure and angina pectoris treated with digitalis, alpha-methyl dopa, a thiazide and nitroglycerin, was admitted after one hour of severe left chest pressure. Cardiopulmonary examination was remarkable only for a few bibasilar rales. ST-segment elevation was noted in the anterior leads on the ECG. Cardiac enzyme analysis subsequently confirmed the diagnosis of acute infarction. Initial hemodynamic parameters were stable over a 30 minute control period and included a heart rate of 60 beats/minute, mean arterial pressure of 100 mm Hg and pulmonary artery diastolic pressure of 4 mm Hg. Intravenous nitroglycerin infusion was begun at 17.6 μg/min and discontinued four minutes later when the mean arterial pressure decreased abruptly to 56 and then to 53 mm Hg. Sinus rhythm continued but the rate decreased to 54 beats/minute. Pulmonary artery diastolic pressure decreased minimally to 3 mm Hg. After spontaneous increases in mean arterial pressure to 90 mm Hg and pulmonary artery diastolic pressure to 8 mm Hg and stabilization of the sinus bradycardia at a heart rate of 55, infusion of nitroglycerin was restarted at 5 μg/min and subsequently increased to 7 μg/min. Nine minutes later, a sudden decrease in mean arterial pressure to 64 mm Hg, associated with further slowing of the sinus rate to 50 and a decrease in pulmonary artery diastolic pressure to 3 mm Hg, prompted cessation of infusion. Mean arterial pressure, heart rate, and pulmonary artery diastolic pressure increased over the next ten minutes.

Case 4

RH, a 63-year-old normotensive male, with a history of inferior infarction and subsequent exertional angina pectoris responsive to sublingual nitroglycerin, was admitted with chest pain of 12 hours duration, unresponsive to nitroglycerin. Physical examination was remarkable for bilateral basilar rales and S₃ and S₄ gallops. The ECG revealed ST depression in leads V₅-V₆ and T wave inversion in leads II, III, F and V₅-V₆. Subsequent enzyme analysis confirmed a diagnosis of myocardial infarction. Initial hemodynamic measurements included a mean arterial pressure of 76 mm Hg and pulmonary artery diastolic pressure of 21 mm Hg. The initial heart rate was 99 beats/minute. Figure 2 shows his subsequent hemodynamic changes. Nitroglycerin infusion was begun at 5 μg/min and gradually increased over the next ten minutes to 26.6 μg/min. The heart rate subsequently decreased suddenly to a low of 47 beats/minute and the mean arterial pressure to a low of 33 mm Hg. Continuous electrocardiographic recordings, available for the

*The hemodynamic data from this patient have previously been reported.12
entire infusion period, revealed a rapid, progressive slowing of the heart rate, without initial tachycardia and with maintenance of normal sinus rhythm, coincident with the development of hypotension. Pulmonary artery diastolic pressure was not measured at the time of maximal bradycardia and hypotension but was 8 mm Hg three minutes after the peak fall in mean arterial pressure. The patient complained of nausea. With cessation of nitroglycerin infusion and leg elevation, mean arterial pressure, pulmonary artery diastolic pressure and heart rate rapidly returned toward control levels.

Case 5

MF, a 45-year-old hypertensive male with a history of inferior myocardial infarction and subsequent angina pectoris responsive to nitroglycerin, was admitted after prolonged substernal pain. Physical examination was remarkable for signs of left ventricular failure. The ECG revealed changes of acute transmural anteroseptal infarction. Subsequent enzyme analysis confirmed acute infarction. During the period of hemodynamic study the patient was maintained on continuous intravenous lidocaine and procainamide infusions, which were started on admission for treatment of ventricular ectopic activity. Baseline hemodynamic measurements, stable over a 30 minute control period, included a mean arterial pressure of 84 mm Hg and pulmonary artery diastolic pressure of 23 mm Hg. Initial heart rate was 120 beats/minute. Figures 3 and 4 illustrate the subsequent hemodynamic changes and the bradycardia, respectively. Intravenous nitroglycerin infusion was begun at 5 μg/min and gradually increased over the next 25 minutes to 56.5 μg/min. Sinus bradycardia with an occasional ventricular ectopic beat was then observed. The rate of infusion was decreased to 36.5 μg/min. However, a further decrease in heart rate to 45 beats/minute was noted and mean arterial pressure decreased to 38 mm Hg. Pulmonary artery diastolic pressure was 7 mm Hg at the time of maximal hypotension. Continuous electrocardiographic recordings revealed a rapid progressive slowing of the heart rate without initial tachycardia and with maintenance of normal sinus rhythm. After abrupt discontinuation of nitroglycerin infusion and administration of 0.5 mg atropine intravenously, mean arterial pressure, heart rate, and pulmonary artery diastolic pressure returned toward control levels. Reinfusion of nitroglycerin was begun 24 minutes after initial discontinuation and was increased from 10 to 36.5 μg/min over the next thirty minutes. Mean arterial pressure and pulmonary artery diastolic pressure again decreased to 62 and 8 mm Hg, respectively, and a relative slowing of the heart rate to 92 beats/minute was observed. Mean arterial pressure, pulmonary artery diastolic pressure and heart rate returned toward control levels with cessation of the infusion.

Discussion

Administration of sublingual and oral nitrates to normal volunteers and to patients with ischemic heart disease usually results in an increase in heart rate, which is thought to be mediated by reflex sympathetic discharge in response to decreases in systemic arterial pressure. The patients with acute myocardial infarction reported in this study developed severe systemic arterial hypotension in association with decreases in LVFP and the development of absolute or relative bradycardia following administration of
nitroglycerin. The sinus bradycardia observed in the present study was not preceded by transient tachycardia and appeared to be vagally mediated as evidenced by the response to intravenous atropine. Recurrence of hemodynamic changes with reinfusion of nitroglycerin in patients 3 and 5 suggests that the bradycardia and hypotension were due to nitroglycerin administration rather than to changes which might have occurred independent of drug therapy during the course of acute myocardial infarction.

There have been other documented instances of severe hypotension and bradycardia occurring after sublingual nitroglycerin administration to patients with hypertension or ischemic heart disease. Sprague and White in 1933, in a review of approximately 900 patients with angina pectoris, reported three cases of syncope following administration of sublingual nitroglycerin for chest pain. Two of their patients fainted while under observation and were noted to become diaphoretic, bradycardic and hypotensive prior to loss of consciousness. Prodger and Ayman observed four instances of bradycardia and hypotension occurring in a group of 110 patients with hypertension given sublingual nitroglycerin. All four patients developed hypotension and bradycardia, including one patient who developed transient complete heart block. One of their patients had a documented initial increase in heart rate prior to the onset of bradycardia. Oral and sublingual nitrate administration followed by tilting has also been associated with hypotension, bradycardia and syncope. An initial increase in heart rate is frequently observed, coincident with the onset of hypotension, in this situation. Bradycardia often occurs late, just prior to loss of consciousness. Prior treatment with intravenous atropine has been shown to eliminate the bradycardia, but has been reported to have no effect on the incidence of syncope or hypotension. Tilting alone can, however, produce hypotension and bradycardia independent of nitrate administration and the additional effect of nitroglycerin under these circumstances is therefore difficult to assess.

Intravenous nitroglycerin has been studied during acute myocardial infarction. Heart rate changes have, however, been variable. In the dog with experimental coronary artery ligation, significant decreases in mean arterial pressure resulting from intravenous nitroglycerin are accompanied by significant increases in heart rate. In contrast, in humans with acute myocardial infarction, intravenous nitroglycerin administration has not been associated with a significant mean change in heart rate, despite significant decreases in mean arterial pressure.

Carotid and aortic body baroreceptors normally cause a reflex increase in heart rate in response to a decrease in arterial pressure. The development of bradycardia associated with hypotension following nitroglycerin administration appears to represent a failure of normal compensation by the baroreceptor mechanisms and may involve both a partial failure of sympathetic activity as well as an enhancement of vagal tone. Similar mechanisms have been postulated for vasovagal syncope. Experimentally, simultaneous bradycardia and hypotension have been produced by chemical stimulation of the myocardium (the Bezold-Jarisch reflex) and by electrical stimulation of specific areas in the nervous system. Variations in heart rate can be effected by manipulation of venous return to the right and left heart. Bradycardia, which can be eliminated by vagotomy, has been produced experimentally by volume-induced elevation of right atrial or left ventricular pressures, suggesting that pressure or length receptors in the myocardial walls may elicit reflex changes in heart rate. In contrast, Sjostrand has recently suggested that bradycardia may be elicited by a decrease in central blood volume. In his experiments, the bradycardia produced by rapid arterial hemorrhage in the rat was less pronounced and appeared later when simultaneous venous infusions were given, despite similar decreases in mean arterial pressure. Those experiments suggest that decreases in venous return may be more important than decreases in systemic arterial pressure in eliciting reflex bradycardia. Although ventricular volume measurements were not performed in our patients, it is likely that ventricular volume diminished after nitroglycerin, in association with the potent vasodilatory effects of nitroglycerin on the venous circulation. The magnitude of changes in ventricular volume cannot be predicted, however, from changes in left ventricular filling pressures in the patients reported above because of changes in left ventricular compliance which may follow acute myocardial infarction. The possibility also exists that nitroglycerin may result in afferent sympathetic stimulation which elicits an efferent vagal response. Afferent sympathetic reflexes have been shown to be associated with vagally mediated bradycardia.

Patients with acute myocardial infarction, especially inferior infarction, not infrequently develop hypotension and
bradycardia, responsive to intravenous atropine, during the early phases of acute infarction. It is possible that nitroglycerin administration may enhance underlying mechanisms responsible for the development of bradycardia and hypotension in such patients. It should, however, be noted that four of the five patients in the present study had ECG evidence of acute anterior transmural or subendocardial, rather than inferior, myocardial infarctions.

In animals subjected to acute coronary occlusion, Costantin has demonstrated a transient, vagally-mediated sympathetic-pressor reflex resulting in blunting of the expected peripheral vasoconstrictor and cardiac sympathetic response to hypotension. Although it has not been demonstrated in man nor in animals subjected to prolonged periods of ischemia or infarction, such a reflex mechanism might possibly explain the failure of normal compensation by the aortic and carotid body baroreceptors to the hypotension observed with nitroglycerin infusion in our five patients.

Although the mechanism of bradycardia in association with nitrategenerated hypotension remains unclear, the cases presented above re-emphasize the potentially serious adverse effects of nitroglycerin. They underscore the need for careful observation during its use, particularly in the setting of acute myocardial infarction.

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