BRONCHOSPASM AND HYPOTENSION DURING CARDIOPULMONARY BYPASS AFTER PREOPERATIVE CIMETIDINE AND LABETALOL THERAPY

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A 64-yr-old asthmatic patient underwent a two-vessel aortocoronary vein grafting. Before surgery, the patient received cimetidine 400 mg and labetalol 650 mg. During the first 60 min of bypass, hypotension (40–45 mm Hg) was observed in spite of phenylephrine 14 mg. This initial hypotension was followed, during rewarming, by a slow increase in arterial pressure to 150 mm Hg. On cessation of bypass, bronchospasm was observed and was protracted. It is assumed that labetalol clearance and metabolism were reduced by cimetidine, that labetalol alpha-antagonism was responsible for the vasodilatation withstanding the phenylephrine, and that a combination of labetalol beta-antagonism and phenylephrine alpha-agonism initiated the bronchospasm. These observations indicate that, after labetalol therapy, higher doses of vasopressor agents such as phenylephrine may be necessary, but that such therapy may lead to bronchospasm in asthmatic patients.

CASE REPORT

The patient, a 64-yr-old, 74-kg male, had no known allergy, but had suffered from spastic bronchitis with occasional crises of asthma since 1977. In May 1982, angina was noted for the first time. Arterial hypertension (180/110 mm Hg at rest) was diagnosed at that time and treated with prenylamine, nitrates and diet. Spirometry showed a mild obstructive syndrome with FEV1 92% of the predicted value. In August 1982, a gastric ulcer was diagnosed and cimetidine 400 mg twice daily by mouth commenced. In September 1982, he was admitted to hospital for angina on minimal exertion with no symptoms of congestive heart failure. After 1 week of therapy with metoprolol 100 mg a day by mouth, shortness of breath with wheezing occurred and the metoprolol was replaced with prenylamine. Cardiac catheterization revealed normal left ventricular function. The coronary arteriogram identified a 70% obstruction of the left main stem artery and a subtotal obstruction of both the left anterior descending (LAD) and the right coronary (RCA) arteries. The patient was scheduled for a two-vessel aortocoronary vein grafting (LAD and RCA) in November. One week before the scheduled operation he was admitted as an emergency on account of unstable angina and hypertension (200/75 mm Hg). An intra-aortic balloon pump (IABP) was inserted. Nitrates i.v. and labetalol 50 mg as a bolus, followed by an infusion of labetalol 600 mg during the next 15 h, were administered. Other haemodynamic data, arterial blood-gas tensions (room air), chest x-ray and haematological investigations, including cardiac enzymes, were normal. The patient was scheduled for surgery the day after admission.

At 7 a.m., the patient was premedicated with morphine 10 mg, atropine 0.5 mg and cimetidine 400 mg i.v. The infusion of labetalol was stopped at 7.30 a.m. At 8 a.m., the patient arrived in the operating theatre under IABP and still receiving nitroglycerine i.v. Arterial pressure was 140/80 mm Hg and heart rate 70 beat min⁻¹. He was not wheezing. Anaesthesia was induced with fentanyl 0.25 mg and etomidate 12 mg. Intubation of the trachea was accomplished following suxamethonium 75 mg and the topical administration of lignocaine 160 mg. Pancuronium 0.1 mg kg⁻¹ i.v. was given and the lungs ventilated artificially with 50% nitrous oxide in oxygen. An ultrasonic nebulizer was not used. The peak inspiratory pressure was 18 cm H2O. Anaesthesia was maintained with incremental doses of fentanyl, and pancuronium was administered as required. Haemodynamic values remained satisfactory until extracorporeal circulation and hypothermia were initiated.

At 10.45 a.m., the aorta was cross-clamped and cardioplegia started. Cardioplegia solution con-
was made when close examination of the chest, not known precisely and the presumptive diagnosis reported (Vanetti et al., 1973; Shiroka, Rah and To our knowledge, only three cases of broncho-
spasm during cardiopulmonary bypass have been reported. A peak inspiratory pressure of 50 cm H2O was noted with no movement of the chest. Arterial pressure and heart rate decreased and the patient was placed back on partial bypass. The ventilator was carefully checked and was found to be working satisfactorily. Suction via the tracheal tube and a bolus of hydrocortisone 100 mg did not improve the situation. Fibreoptic bronchoscopy revealed a small amount of mucous plugging and widespread oedema, and a presumptive diagnosis of asthma was made. Aminophylline 6 mg kg⁻¹ i.v. and hydrocortisone 250 mg i.v. did not alleviate the bronchospasm. An infusion of adrenaline 2–5 µg min⁻¹ was started and the bronchospasm subsided in 30 min. During that time, an arterial pressure of 120/70 mm Hg and a heart rate of 95 beat min⁻¹ in sinus rhythm were recorded. A second attempt to terminate bypass was successful. The procedure was terminated at 3.15 p.m. with no other major respiratory or cardiovascular changes.

In the Acute Care Unit, the recovery of the patient was uneventful. The infusion of adrenaline was discontinued 1 h after admission. The tracheal tube was removed the following morning and the patient was gradually weaned off the IABP in the afternoon. He was discharged from the hospital 3 weeks later with no further episode of bronchospasm. Six months after the procedure, the patient was in a satisfactory condition.

DISCUSSION

To our knowledge, only three cases of bronchospasm during cardiopulmonary bypass have been reported (Vanetti et al., 1973; Shiroka, Rah and Keenan, 1982). On each occasion, the aetiology was not known precisely and the presumptive diagnosis was made when close examination of the chest, checking of equipment, suction of the tube and fibreoptic bronchoscopy had ruled out all other possible mechanical causes of the increase in inspiratory pressures. According to Aviado (1975) and Hirshman (1983), numerous factors modify airway reactivity during anaesthesia. Some may be implicated in the present case: light level of anaesthesia; decreased temperature in the bronchi; mechanical irritation of the respiratory tract (endotracheal tube and surgical manipulations); histamine release from blood products, anaesthetic agents, priming or cardiopulmonary bypass. The ventilator was carefully checked and was found to be working satisfactorily. Suction via the tracheal tube and a bolus of hydrocortisone 100 mg did not improve the situation. Fibreoptic bronchoscopy revealed a small amount of mucous plugging and widespread oedema, and a presumptive diagnosis of asthma was made. Aminophylline 6 mg kg⁻¹ i.v. and hydrocortisone 250 mg i.v. did not alleviate the bronchospasm. An infusion of adrenaline 2–5 µg min⁻¹ was started and the bronchospasm subsided in 30 min. During that time, an arterial pressure of 120/70 mm Hg and a heart rate of 95 beat min⁻¹ in sinus rhythm were recorded. A second attempt to terminate bypass was successful. The procedure was terminated at 3.15 p.m. with no other major respiratory or cardiovascular changes.

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possible vasodilating effect of beta_{2}-stimulation must be considered (Wunderlich et al, 1980). Such therapy would merit further study after labetalol administration.

Continued hypotension occurring in the presence of high doses of phenylephrine during bypass has not been reported previously. A rational explanation of the resistance to a selective alpha-receptor agonist, such as phenylephrine, is a pre-existing alpha-receptor blockade. Alpha-blocking activity with increasing doses of labetalol i.v., as judged by progressive parallel inhibition of the vasopressor responses to injection i.v. of phenylephrine, has been demonstrated in human volunteers (Boakes, Knight and Prichard, 1971) and anaesthetized dogs (Kennedy and Levy, 1975; Sybertz et al., 1981). Therefore, the alpha-blocking effect of labetalol was gradually overcome by the intense alpha-stimulating effect of phenylephrine, and may explain the low arterial pressure during the first 60 min of bypass, followed by a steady increase up to 150 mm Hg during the 30 min of rewarming. Furthermore, in anaesthetized dogs and cats, labetalol (in doses greater than 1 mg kg^{-1}) is a relatively ineffective antagonist of vasopressor responses to noradrenaline. This paradoxical effect may occur secondary to a blockade of adrenergic re-uptake (Farmer et al., 1972; Kennedy and Levy, 1975). Therefore, after labetalol therapy, pressor responses to noradrenaline may be less predictable than those to phenylephrine. Further investigations of these differences would be valuable.

In conclusion, should labetalol be discontinued before surgery? No generalization can be made from the present case. However, higher doses of vasopressor agents such as phenylephrine may be necessary during surgery, although such vasopressor therapy may lead to bronchospasm in asthmatic patients.

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REFERENCES

malgré l’administration de 14 mg de phényléphrine. Cette hypotension initiale a été suivie lors du réchauffement d’une lente augmentation de pression artérielle jusqu’à 150 mm Hg. À la sortie de CEC, survint un bronchospasme. Ces constatations indiquent que, aprè s traitement par le labetalol, des doses plus importantes d’agents vasoconstricteurs tels la phényléphrine peuvent être nécessaires, mais que de tels traitements peuvent induire un bronchospasme chez des sujets asthmatiques.

**BRONCHOSPASMUS UND HYPOTENSION WÄHREND KARDIOPULMONALEM BYPASS NACH PRÄOPERATIVER THERAPIE MIT CIMETIDINE UND LABETALOL**

**ZUSAMMENFASSUNG**

Ein 64 Jahre alter Asthmapatient unterzog sich einer Zweigefäß-aortokoronarer Venenplastik. Präoperative erhielt der Patient 400 mg Cimetidine und 650 mg Labetalol. Während der ersten 60 Minuten des Bypasses wurde trotz Gabe von 14 mg Phenylephrin Hypotension (40–45 mm Hg) beobachtet. Diese initiale Hypotension wurde während des Wiederaufwärmen von einem langsamen Anstieg des arteriellen Drucks auf 150 mm Hg gefolgt. Nach Ende des Bypasses trat ein protrahierter Bronchospasmus auf. Es wird vermutet, daß (1) die Labetalol-Clearance und der Metabolismus durch Cimetidine herabgesetzt waren, (2) der Alpha-Antagonismus des Labetalol für die auf Phényléphrin nicht reagierende Vasodilatation verantwortlich war und (3) eine Kombination des Beta-Antagonismus von Labetalol und des Alpha-Antagonismus von Phényléphrin den Bronchospasmus herbeiführten. Diese Beobachtungen weisen darauf hin, daß nach Labetalol-Therapie höhere Dosen vasopressorischer Substanzen wie Phényléphrin benötigt werden können, doch daß ein solches Vorgehen bei Asthmatikern zu Bronchospasmus führt.

**BRONCOESPASMO E HIPOTENSION DURANTE PUENTE EXTERNO CARDIOPULMONAR DESPUÉS DE TERAPIA PREOPERATORIA POR CIMETIDINA Y LABETALOL**

**SUMARIO**

Un paciente asmático de 64 años de edad fue sometido a un transplante de la vena aorto-coronaria. Antes de la cirugía, se administró al paciente 400 mg de cimeti dina y 650 mg de labetalol. Durante los primeros 60 minutos del puente externo, se observó una hipotensión (40–45 mm Hg) a pesar de los 14 mg de fenilefrina. Esta hipotensión inicial fue seguida, durante el recalentamiento, de un lento aumento de la presión arterial hasta 150 mm Hg. Al momento de terminar el puente externo, se observó un broncoespasmo que se extendió. Se supone que la eliminación y el metabolismo del labetalol se redujeron bajo la acción de la cimetidina, que el alfa-antagonismo del labetalol fue responsable por la vasodilatación no obstante la fenilefrina y que la combinación del beta-antagonismo del labetalol y del alfa-agonismo de la fenilefrina dieron lugar al broncoespasmo. Las observaciones hacen pensar que, después de la terapia por labetalol, puede ser necesario administrar mayores dosis de agentes vasopresores tales como la fenilefrina, pero que dicha terapia puede acarrear broncoespasmos en pacientes asmáticos.