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Hemodynamics during General Anesthesia in Patients Receiving Propranolol

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To determine whether orally administered propranolol contributes to untoward hemodynamic function during general anesthesia, the authors divided patients undergoing myocardial revascularization into two groups: One group (n = 9) did not receive propranolol orally in the preoperative period. The other group (n = 10) received oral doses until five to six hours before induction of anesthesia, and the majority had demonstrable serum propranolol levels. Control (preanesthetic) hemodynamic values were determined following morphine–scopolamine premedication and percutaneous vascular cannulation. Post-intubation measurements were done following the sequence of thiopental, 2–3 mg/kg, succinylcholine, 1 mg/kg, and orotracheal intubation. Measurements were repeated at the following intervals after starting halothane–nitrous oxide and pancuronium, 0.1 mg/kg: 5, 15, 30, and 60 min. Comparison of hemodynamic values in the propranolol and non-propranolol groups revealed significantly lower heart rates at all measurement periods in the propranolol group. The groups showed no differences in cardiac output, mean arterial pressure, stroke volume, systemic peripheral vascular resistance, blood-gas, *p*H, or acid–base values. Patients in both groups responded to the "stress" of endotracheal intubation with increased heart rates and mean arterial pressures. In the absence of overt resting myocardial pain and frank left ventricular power failure, continuing oral administration of propranolol in moderate doses (average 140 mg/day) until a few hours before general anesthesia with thiopental–succinylcholine–nitrous oxide–halothane and pancuronium does not appear to lead to unusual hemodynamic function in patients who have coronary-artery disease. (Key words: Heart, propranolol; Heart, coronary artery disease; Heart, myocardial revascularization; Sympathetic nervous system, beta-adrenergic blockade.)

OPTIMAL ANESTHETIC MANAGEMENT of patients receiving propranolol prior to open-heart surgery remains controversial. Viljoen *et al.*[1] have recommended that propranolol be discontinued two weeks prior to open-heart surgery. Others[2–4] maintain that the drug can safely be continued until a few hours before myocardial revascularization. However, we are not aware of any prospective study of hemodynamics during general anesthesia in patients with coronary-artery disease maintained on propranolol until the time of operation. Thus, a study was designed to elicit such measurements during the first hour of anesthesia and to compare the results with corresponding values recorded in patients who had not received the drug.

Methods

Nineteen adult male patients scheduled for elective aorto-coronary saphenous bypass procedures were chosen for the study. All had severe coronary-artery disease confirmed angiographically. To minimize differences between the two study groups, patients with the following were excluded: 1) acute myocardial infarction within two weeks of operation; 2) persistent, intractable cardiac pain in the preoperative period; 3) left ventricular power failure manifested by cardiogenic shock or frank congestive failure; 4) augmented circulation (intra-aortic balloon); 5) adverse response to propranolol manifested by hypotension or low-cardiac-output state. Group A (n = 10) patients were receiving propranolol in the preoperative period in doses ranging from 40 to 240 mg/24 hours, with a mean of 140 mg. They continued to receive the drug in their regular oral doses. The interval between the last regular oral dose of propranolol and the induction of general anesthesia was five to six hours, our usual fasting period for elective surgical procedures. Group B (n = 9) included only patients who were not receiving propranolol. The mean body weight in the propranolol group was 83 ± 4 kg (SEM), which was not significantly different from 75 ± 3 kg in the non-propranolol group. Three patients in the propranolol group and four patients in the non-propranolol group had demonstrated abnormalities in left ventricular wall motion. Three propranolol and one non-propranolol patient(s) had occasional bouts of "atypical" nonexertional angina. Informed consent was obtained in writing. Premedication consisted of morphine, 8–12 mg, and scopolamine, 0.4 mg, intramuscularly, two hours before induction of general anesthesia. Upon arrival in the operating room most patients were sedated but easily arousable. Percutaneous radial-artery, right subclavian vein, and peripheral vein catheterizations were accomplished using lidocaine, 0.5 per cent. Pulmonary arterial catheterization was not included, since it was not part of the usual clinical monitoring

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at the institution where the studies were done. After a 5-minute rest period, a radial arterial blood sample was obtained for propranolol analysis from those patients receiving the drug. Frozen serum was subsequently analyzed using Shand and associates' adaptation of the fluorometric method of Black.[5] In both groups, preanesthetic blood-gas and hemodynamic values were determined as follows: iced heparinized arterial blood samples were analyzed for Pa_{O_2}, Pa_{CO_2}, and *p*H using an Instrumentation Laboratories model 313 blood-gas analyzer. Acid–base balance was determined using an IL blood-gas calculator. Statham P23Ia transducers were calibrated using an aneroid manometer–volume-bottle system. The Waters monochromatic cardiac output densitometer was calibrated using indocyanine green in 10 ml of the patient's blood. All estimations of cardiac output were done in duplicate and recorded on an Electronics for Medicine photographic polygraph, which also recorded standard and mean arterial pressures, mean central venous pressure and continuous (standard limb-lead) electrocardiogram. The lead selected was variable, dependent upon which gave the best-defined P and QRS waves. Cardiac output values for each dye-dilution curve were calculated manually using the fore-and-aft triangle method. Derived measurements included stroke volume and total systemic peripheral vascular resistance.

Control (preanesthetic) measurements were made 5 minutes after vascular cannulation. Anesthesia was then induced with thiopental, 2–3 mg/kg, and orotracheal intubation facilitated with succinylcholine, 1 mg/kg. Ventilation was controlled with an Ohio DO-300 ventilator using a ventilator output of approximately 10–12 ml/kg and rate of 8–10/min with an inspired oxygen concentration of approximately 100 per cent. Post-intubation arterial blood-gas and hemodynamic measurements were performed immediately after controlled endotracheal ventilation was begun. Following pancuronium, 0.1 mg/kg, intravenously, halothane, 0.5–2 per cent was administered with nitrous oxide–oxygen, 60:40 per cent. In the majority of patients, halothane, 1.5–2 per cent, was given to decrease post-intubation systemic arterial pressure, which had usually increased strikingly over preanesthetic values (fig. 1). Since arterial pressure decreased promptly, halothane was usually decreased to 0.5–0.75 per cent. When systolic pressure decreased below 90 mm Hg, halothane was discontinued for a short period. When arterial pressure increased above 90 mm Hg, halothane was reintroduced at 0.25–0.5 per cent. If arterial pressure again decreased below 90 mm Hg, halothane was continued and intravascular volume was expanded using 250–500 ml of albumin, 5

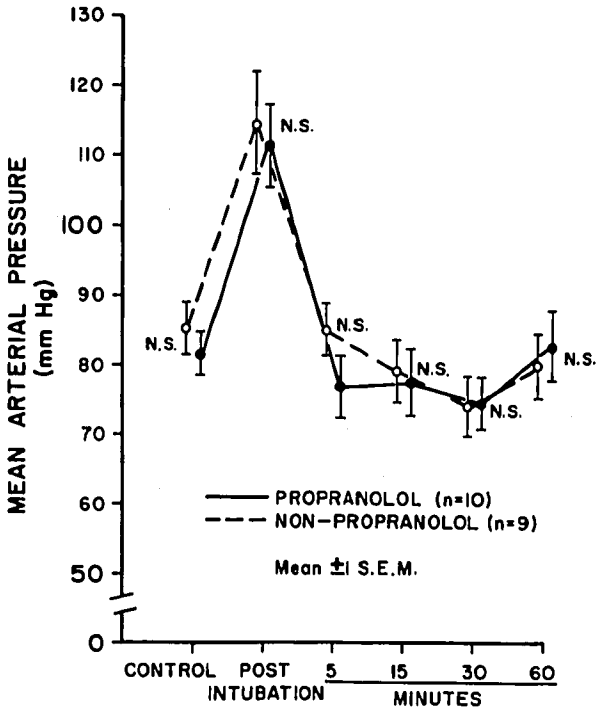

FIG. 1. Mean arterial pressure during halothane–N_2O–O_2–pancuronium anesthesia. During anesthesia, serial mean arterial pressures in patients receiving propranolol did not differ from corresponding values in patients who had not received the drug.

per cent, in saline solution (Albumisol® or Buminate®). Plasma protein fractions were avoided to minimize vasodilatory hypotension.[6] If arterial pressure remained below 90 mm Hg despite colloid intravascular expansion, either atropine or an infusion of isoproterenol or epinephrine, 2 mg/250 ml was given for a short interval. After an appropriate increase in systemic arterial pressure, halothane–nitrous oxide–oxygen was restarted. Operation was allowed during the one-hour measurement period, but was confined to harvesting saphenous veins and initial opening of the chest. Decreased arterial pressure following use of the chest retractor[7] was not observed in this study. Cardiac manipulation did not occur immediately before or during the measurement periods. Serial arterial blood-gas and hemodynamic measurements were done at the following intervals after starting halothane: 5, 15, 30, and 60 min.

Data analysis. Group means for each determination were compared using Student's t test for unpaired data. Additionally, within each group, the post-intubation values for heart rate, mean arterial pressure, cardiac output and systemic peripheral vascular resistance were compared with the control (preanesthetic) values using Student's t test for paired data. *P* values of less than 0.05 were taken as significant for all analyses.

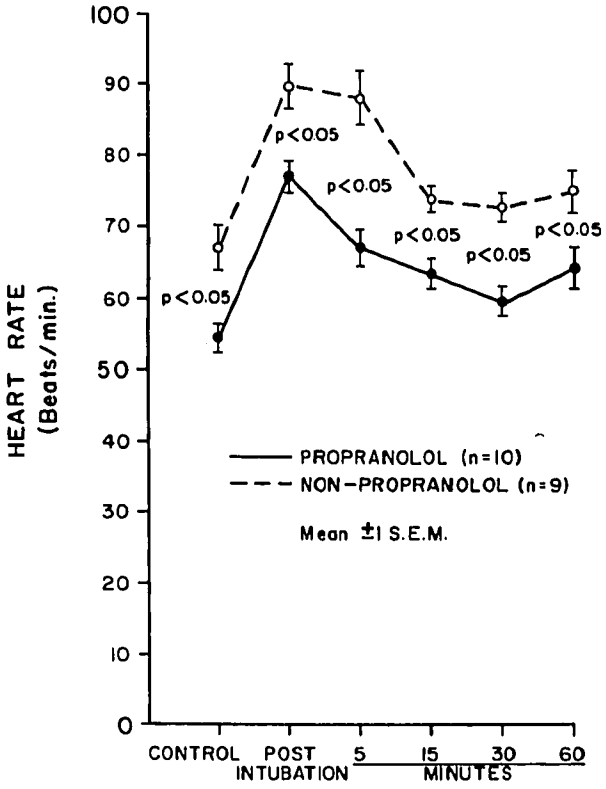

FIG. 2. Heart rate during halothane–N_2O–O_2–pancuronium anesthesia. Uniformly slower intra-anesthetic heart rates were apparent in patients who received propranolol, compared with those who did not.

Results

Propranolol was detected in the sera of eight of the patients taking the drug, the mean value being 31.6 ng/ml ± 6.5 SEM (range 12–71 ng/ml). In the non-propranolol group, eight patients needed fluid therapy, two patients were given atropine, and one patient was given a transient infusion of isoproterenol during the measurement period. In the propranolol group, nine patients needed fluid therapy, two were given atropine, and one was given an infusion of isoproterenol. Heart rates were significantly lower in the propranolol group than in the non-propranolol patients at all measurement periods (fig. 2). There was no significant difference in cardiac output (fig. 3), mean arterial pressure (fig. 1), left ventricular stroke volume (fig. 4), systemic peripheral vascular resistance (fig. 5), blood-gas, *p*H or acid–base values during the control (pre-anesthetic) or subsequent periods. Post-intubation recordings revealed significant increases from control in mean arterial pressure (fig. 1), heart rate (fig. 2) and systemic peripheral vascular resistance (fig. 5). After hemodynamic measurements had been completed but before cardiopulmonary bypass, severe hypotension and ST segment elevation developed in one patient receiving propranolol. The hypotension responded well to a slow infusion of phenylephrine. Because of a continuous need for phenylephrine while halothane was being administered, halothane was discontinued and anesthesia continued with an infusion of ketamine. The patient's further intraoperative course was not remarkable. Although this patient made an uneventful recovery, it is possible that he may have had an intraoperative myocardial infarction.

Although determinations of cardiac output and derived measurements were not documented following cardiopulmonary bypass, we did not find intractable or unusual problems in the patients receiving propranolol, and there was no intra- or perioperative death in this group.

Discussion

The critical balance between myocardial oxygen supply and myocardial oxygen demand may be easily upset in the patient who has severe coronary-artery disease. Common measures that decrease myocardial oxygen demand may not control severe episodes of cardiac pain. In such patients, propranolol may be useful in controlling symptoms[8,9] and possibly in minimizing ischemic myocardial damage.[10–13] In many centers, the practice of tapering propranolol dosages before anesthesia and operation has been followed in the hope of minimizing possible adverse synergism with anesthetic agents.[1,14] Recently, however, several reports have suggested that rapid withdrawal of propranolol may be attended by its own inherent risks.

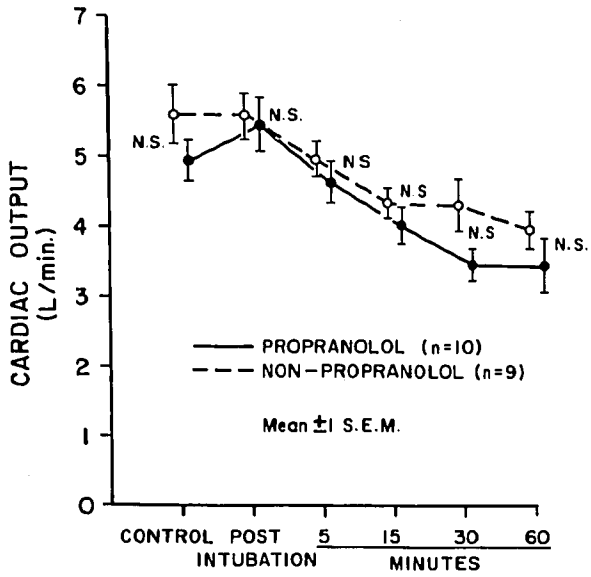

FIG. 3. Cardiac output during halothane–N_2O–O_2–pancuronium anesthesia. The presence or absence of oral propranolol therapy did not significantly affect cardiac output during inhalation anesthesia.

Following abrupt cessation of propranolol, Slome,[15] Nellen,[16] and Diaz *et al.*[17] observed temporally related myocardial infarctions. More recently, in a double-blind crossover efficacy trial, Miller *et al.*[18] observed serious ischemic events (intermediate coronary syndrome, ventricular tachycardia, fatal myocardial infarction and sudden death) in six of a group of 20 patients who were suddenly withdrawn from large doses of propranolol.

Various investigators, including Caralps,[2] Moran,[3] and Romagnoli[14] and their co-workers have suggested that weaning from propranolol before coronary revascularization procedures may not be necessary. Kaplan *et al.*[4] concluded that propranolol could be given safely to within 24–48 hours of anesthesia and operation, and perhaps to within 12 hours of operation if ischemic pain followed withdrawal attempts. In these studies, some attempt to withdraw propranolol had been made in most patients, the anesthetic agents were not described[2,3] or not constant in all patients,[4] and retrospective conclusions were based upon observation of routine clinical measurements.

In the present study, we compared basic hemodynamic values during the first hour of thiopental–succinylcholine–halothane–nitrous oxide–pancuronium anesthesia in two groups of patients undergoing myocardial revascularization procedures. One group had received propranolol orally until five to six hours before anesthesia, and the drug was present in the sera of the majority of patients at the time of induction of anesthesia. Patients in the other group had not received the drug. Comparison of the groups revealed many similarities. The majority of patients in either group required intra-anesthetic fluid therapy to maintain empiric blood pressure levels. Thus, in retrospect, pre-halothane intravascular volume loading might have been desirable. However, it is probable that this would necessitate simultaneous serial measurements of pulmonary-artery-occluded pressure to avoid increases in mean left ventricular wall tension and attendant increased myocardial oxygen consumption, which could accompany rapid fluid infusion. It is also possible that the high incidences of systolic pressures of less than 90 mm Hg in both groups resulted from our aggressive measures to lower post-intubation pulse rate and systolic pressure with halothane as rapidly as possible. Perhaps the use of lower concentrations of halothane might have decreased the need for fluid therapy in both groups. However, despite the

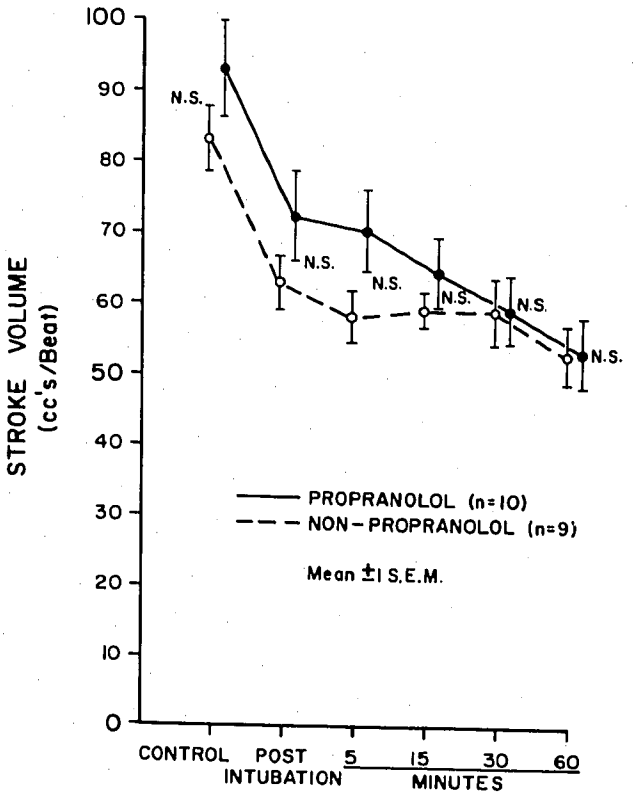

FIG. 4. Stroke volume during halothane–N_2O–O_2–pancuronium anesthesia. No significant difference in stroke volume was observed in patients receiving oral propranolol compared with those who were not.

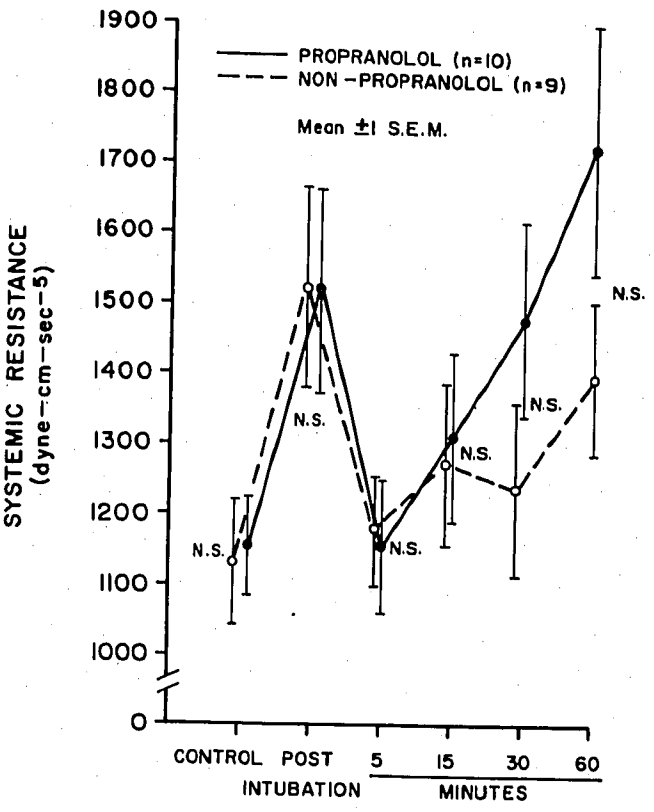

FIG. 5. Systemic peripheral vascular resistance during halothane–N_2O–O_2–pancuronium anesthesia. No significant difference in systemic peripheral vascular resistance was seen in patients receiving propranolol compared with those who were not.

relatively high halothane concentrations, only a minority of patients in either group needed atropine or sympathomimetic drugs. Cardiac output, mean arterial pressure, stroke volume, systemic peripheral vascular resistance, blood-gas, *p*H and acid–base values were not significantly different in the two groups. The lack of major hemodynamic differences in our patients is similar to the finding of Roberts *et al.* that propranolol pretreatment contributed only slight cardiac depression in a healthy, halothane-anesthetized, eucarbic dog model.[19]

Frederickson and Shimosato have expressed concern that propranolol might impair endogenously-mediated sympathetic responses during anesthesia.[20] However, the marked increases in mean arterial blood pressure and heart rate following intubation in our propranolol-treated patients suggest that propranolol did not block these sympathetic responses. Romagnoli and Keats[14] have suggested that isoproterenol would reverse beta blockade persisting in patients from whom propranolol had been withdrawn for 24 hours. Our finding that sympathomimetic drugs produced satisfactory increases in heart rate in propranolol-treated patients suggests that no withdrawal is necessary when patients receive propranolol in doses comparable to those reported in this study. Although we did not record sympathetic responses to blood loss, the recent work of Prys-Roberts *et al.*[21] in a canine model suggests that beta-receptor blockade does not cause unusual responses during graduated blood loss.

Since propranolol is known to depress the spontaneous rate of sinus node depolarization, it is not surprising that patients in the propranolol group had uniformly lower heart rates than the patients who had not received propranolol. It is important to note that despite the lower heart rates, the patients taking propranolol did not have significantly different cardiac output values, did not develop metabolic acidemia, and did not experience "ventricular-escape" rhythms. It appears that the slower heart rates in the propranolol group were not associated with overt adverse effects. Conversely, since myocardial oxygen demand may correlate with heart rate, it is possible that the slower rates in the propranolol group were beneficial to myocardial oxygenation. Both Linhart[22] and Dalton[23] have pointed out the dangers of rate-dependent myocardial ischemia in patients who have coronary-artery disease.

Since patients receiving propranolol had slower heart rates at all intra-anesthesia measurement periods, it is tempting to speculate that they may have had a lower incidence of myocardial ischemia or silent infarction. Critical comparison of the incidences of myocardial ischemia would require continuous "mapping" of precordial and standard limb electrocardiographic leads. To evaluate the incidences of perianesthetic "silent" myocardial infarction, serial determinations of the myocardial band fraction of creatine phosphokinase plus careful analysis of pre- and postoperative electrocardiograms would be necessary. Since these data were not accumulated in this study, we cannot comment on the relative incidences of ischemia or silent infarction. It is possible that administration of halothane–nitrous oxide–oxygen before intubation might have decreased the incidence and severity of hypertension and tachycardia associated with tracheal intubation and the attendant risk of intra-anesthesia myocardial ischemia.

The question of continuing or discontinuing propranolol before anesthesia and operation has been the subject of much discussion. In the past, many opinions have been expressed in the absence of relevant comparative studies of cardiac output and other hemodynamic values in patients with severe coronary-artery disease. Our work has compared perianesthetic hemodynamic values in patients with coronary-artery disease receiving moderate doses of propranolol with corresponding values in patients not receiving the drug. Although major hemodynamic differences between the groups were not apparent in this study, it is possible that the observations made may not apply to all patients with ischemic heart disease receiving propranolol. We excluded from both groups patients with persistent pharmacologically intractable cardiac pain and those receiving intra-aortic balloon counterpulsation. It is possible that the results might be different in such patients and in patients with persistently high pulmonary-artery-occluded pressures. We must also emphasize that the doses of propranolol were moderate. The hemodynamic responses to this anesthetic sequence might be different in patients receiving higher doses of propranolol. However, we believe the hemodynamic data reported herein strongly suggest that tapering from moderate doses of propranolol may not be routinely necessary. In patients with coronary-artery disease without recent myocardial infarction who do not have symptoms of persistent resting myocardial ischemia or frank left ventricular power failure, administering the last moderate dose of propranolol five to six hours before anesthesia does not lead to unusual hemodynamic function or irreversible clinical problems during thiopental–succinylcholine–halothane–nitrous oxide–pancuronium anesthesia.

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