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# Effect of severe cardiac valve regurgitation on the onset of the neuromuscular blocking action of pancuronium

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Monitoring the onset of neuromuscular block produced by nondepolarizing relaxants provides useful and important information on muscle relaxation and the timing of endotracheal intubation. Goat and her colleagues [1] initially reported that the onset and intensity of paralysis produced by gallamine were directly related to muscle blood flow. We also reported that the onset of neuromuscular blockade in the adductor pollicis muscles occurred more rapidly in patients given vecuronium via the pulmonary artery than in patients given the drug via a peripheral vein on the hand [2]. Furthermore, the onset time of a neuromuscular relaxant is governed by noncirculatory factors, such as the concentration gradient between plasma and receptor sites, the potency, and the administered dose [3,4]. It has also been reported that the onset of action of pancuronium is slower in children with congenital heart disease (CHD) than in children without CHD [5]. We examined the influence of severe cardiac valve disease on the time of onset of action of pancuronioum in adult patients.

With approval from our institution's human research committee and the informed consent of the patients, 47 patients scheduled for elective cardiac surgery (coronary artery bypass graft, $n = 22$; valve replacement, $n = 25$) aged 17–78 years (mean, 55) and weighing 40–75 kg (mean, 58) were included. The severity of mitral or aortic regurgitation in 25 patients with cardiac valve disease was qualitatively assessed by cardiac catheterization before surgery and was graded on a scale of I to IV in severity. Patients with moderately severe (grade III) and severe (grade IV) regurgitation were included in this study. All patients received midazolam 2.5 mg and either atropine 0.5 mg or scopolamine 0.4 mg i.m. 1 h before induction of anesthesia. Anesthesia was induced with midazolam 2.0–3.0 mg i.v. and maintained with fentanyl 10–25 $\mu g \cdot kg^{-1}$ and 50%–60% nitrous oxide in oxygen administered by face mask. Before insertion of an endotracheal tube, ventilation was controlled manually to keep $P_{ET}CO_2$ within the range of 35 to 40 mmHg.

At least 5 min after the induction of anesthesia, pancuronium 0.1 $mg \cdot kg^{-1}$ was randomly administered through an indwelling cannula on the dorsum of the hand and was flushed by a fast-running infusion. Neuromuscular block was evaluated every 12 s by the force-of-thumb adduction produced in response to supramaximal stimulation of the ulnar nerve with repetitive train-of-four using surface electrodes at the wrist (Myograph 2000, Biometer, Denmark).

Immediately after the administration of pancuronium, the cardiac output was measured with a pulmonary artery catheter inserted preoperatively, using 10 ml of iced 5% dextrose in all patients. The average of three measurements was taken as the cardiac index. Tracheal intubation was not performed until the relaxation, judged by twitch responses, was 95% or greater.

The degree of neuromuscular block was measured as the decrement in contractile response of the first response ($T_1$), relative to control. The times from the administration of neuromuscular relaxant to the first depression of $T_1$ (latent onset time) and to depression of $T_1$ to 5% of control were measured. The data were expressed as mean ± standard deviation and analyzed statistically by ANOVA, followed by Student's *t*-test. $P < 0.05$ was considered significant.

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**Table 1.** Cardiac indices and onset time following 0.1 mg·kg$^{-1}$ of pancuronium in patients with and without cardiac regurgitation[a]

| Patients' condition | Cardiac index (l·min$^{-1}$·m$^{-2}$) | Latent onset time (s) | Time to 95% $T_1$ depression (s) |
|---|---|---|---|
| CABG[b] ($n$ = 19) | 2.82 ± 0.7 | 65.3 ± 15.9 | 151.3 ± 30.2* |
| Aortic or mitral valve regurgitation ($n$ = 23) | 3.00 ± 1.1 | 71.8 ± 20.4 | 180.7 ± 48.8 |

* $P < 0.05$ *vs* value for patients with valve disease.
[a] All data represent mean ± SD.
[b] CABG, Coronary arterial bypass graft.

The results are summarized in Table 1. Data from three patients in the coronary artery bypass graft group and two patients in the cardiac valve disease group were excluded from the analysis because their cardiac indices were under 2.0 or over 6.0 l·min$^{-1}$·m$^{-2}$. There were no significant differences in sex, age, height, weight, or cardiac index between the two groups of patients. The times of onset of fade in train-of-four responses (latent onset time) after pancuronium administration were the same in patients with and without severe cardiac valve disease. On the other hand, the mean time from injection of pancuronium to development of 95% twitch depression for patients with severe cardiac valve disease was significantly prolonged ($P < 0.05$) as compared with that of patients without cardiac valve disease.

Several factors may be responsible for the delayed onset of action of pancuronium in patients with severe regurgitation. The effect of a neuromuscular agent occurs when a critical concentration is reached at the neuromuscular junction, and the length of time until this happens depends on many factors, including the injection dose, drug delivery via the cardiovascular system, the kinetics at the synaptic cleft, and the concentration-effect relationship. Since, in clinical practice, neuromuscular relaxant is administered intravenously, the onset of action is affected by the circulation time, which involves possible delay in the right heart, lungs, left heart, and peripheral vessels. We reported that the rapidity of the onset of paralysis in the adductor pollicis muscle after intravenous administration of vecuronium was clearly influenced by the cardiac output [6]. No significant difference between the groups in cardiac index was found before the administration of pancuronium in the present study. This circulatory factor, however, is not excluded from factors causing a slower onset of action of pancuronium in patients with severe cardiac regurgitation, because of the difficulty of accurately measuring cardiac output by the thermodilution technique in patients with cardiac regurgitation. In addition, the circulatory changes after injection of pancuronium might different between the two groups.

The onset of action of a neuromuscular blocking agent is also modified by the chemical structure and physicochemical properties of the agent. This non-circulatory effect has a time course of a few minutes and appears to be quantitatively important for the relatively late onset of action of neuromuscular relaxants such as pancuronium. Feldman and colleagues [7] showed that the onset of neuromuscular block after the administration of the same dose of nondepolarizing relaxant was much slower after infusion than after bolus injection, although the degree of maximum block was similar in both groups. Theoretically, it is possible that in patients with cardiac regurgitation the neuromuscular relaxant might recirculate in the heart and be carried to the peripheral circulation so that the concentration gradient between the receptor area and plasma would be less than that in subjects without cardiac valve disease. It has been reported that pancuronium had a slow access from plasma to the receptors by diffusion, which speed is mainly determined by a concentration gradient [8]. Although the cause of differences in response to pancuronium in patients with and without severe cardiac regurgitation remains unclear, it is thought that the decrease in the concentration gradient between the plasma and receptor sites from the recirculation of pancuronium in the heart would be related in part to the delayed onset of neuromuscular blockade in patients with severe cardiac valve disease.

In conclusion, we have demonstrated that the onset of the neuromuscular blocking action of pancuronium is delayed in patients with severe cardiac regurgitation in comparison with that in patients with ischemic heart disease.

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