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## Prolonged Neuromuscular and Cardiovascular Effects of Succinylcholine in a Patient Homozygous for the Silent Gene

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**Abstract** We investigated the duration of cardiovascular as well as neuromuscular effects of succinylcholine in a patient homozygous for silent gene. The patient remained totally apneic for about 30 min, and the train-of-four ratio was 0.82 even at 150 min after succinylcholine 1 mg/kg iv. The plasma norepinephrine and epinephrine concentrations, and systolic blood pressure, which increased and reached the maximum at 4 min, were still 15-70% higher than the baseline values even at 20-30 min after succinylcholine iv. These results may suggest that cardiovascular and neuromuscular effects of succinylcholine are both prolonged in a patient homozygous for silent gene.

**Key Words:** Succinylcholine, Catecholamines, Abnormal Pseudocholinesterase

### Introduction

In patients homozygous for atypical<sup>1)</sup> or silent gene for plasma cholinesterase (ChE)<sup>2)</sup>, interaction of succinylcholine (SCh) with the nicotinic receptors on the endplate of the skeletal muscle is prolonged because of a decreased breakdown of the SCh molecule, leading to prolonged neuromuscular blockade. Meanwhile, it has recently been reported that, in patients with normal gene, SCh leads to a short-lasting release of endogenous catecholamines<sup>3,4)</sup>. Although the precise mechanisms of these cardiovascular effects of SCh are not clear, Nigrovic et al.<sup>5)</sup> postulated that SCh might interact with the nicotinic receptors on the postganglionic sympathetic terminals, leading to explosive release of catecholamines. If so, in patients

who are exposed to high blood levels of SCh for prolonged periods of time, SCh-induced catecholamine release might be prolonged like SCh-induced neuromuscular blockade does. Accordingly, in the present study, we investigated the duration of cardiovascular as well as neuromuscular effects of SCh in a patient homozygous for silent gene.

### Case Report

Informed consent was obtained from the patient. A 60-year old man, weighing 50 kg, was scheduled for elective resection of his left hemicolon under general anaesthesia. He had no surgical or anaesthetic history. Aside from past history of diabetes mellitus, there were no other medical problems. In the routine preoperative examination, EKG, chest roentgenogram,

lung function, and all laboratory values, except serum glucose level (178 mg/dl) and ChE activity, were within normal limits. Plasma ChE activity, measured by the propionylthiocholine-dithiobis (nitrobenzoic acid) procedure<sup>6)</sup>, was zero units (normal range 4.53-7.85 units/ml). Briefly, this method used propionylthiocholine as substrate and 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) for coloration of thiocholine, a hydrolysis product of the substrate. Coefficient of variation was 4%. On the day of operation, the patient was premedicated with scopolamine 0.4 mg im 30 min before induction of anaesthesia. Prior to induction, using a small amount of 0.5% lidocaine, 22-gauge catheters were placed percutaneously both in the superficial dorsal vein for infusion of drugs and lactated Ringer's solution and in the radial artery for pressure measurement and blood sampling. Anaesthesia was induced with thiopental 3 mg/kg iv, then ventilation was manually assisted by mask and reservoir bag in a semiclosed circuit with a fresh gas flow of 1.5% halothane and oxygen. After stabilization of the heart rate and blood pressure (about 15 min after thiopental iv) SCh 1 mg/kg was injected intravenously as a bolus. Ventilation was controlled thereafter, and intubation and surgery were delayed until after collection of the last blood sample.

Neuromuscular effects of SCh: Immediately before (baseline) and every 5 min after SCh iv, supramaximal train-of-four (TOF) stimulations were applied to the ulnar nerve at the wrist by means of steel needle electrodes<sup>2)</sup>. The resultant force of adduction of the thumb was measured using a force-displacement transducer and recorded. Figure 1 indicates the time course of spontaneous recovery of TOF ratio and first twitch height. The patient remained apneic for about 30 min, and the evoked responses could not be obtained until 35 min after SCh. The fade in the TOF stimulation following SCh indicated significant phase II block. The time course of the recovery of the neuromuscular block could be divided into four phases, i.e. complete neuromuscular block, rapid recovery, plateau, and slow recovery. The TOF ratios obtained 50 and 150 min after SCh were 0.43 and 0.82, respectively (Figure 1). 150 min after SCh, residual paralysis was reversed effectively with neostigmine 1.0 mg and atropine 0.5 mg iv.

Cardiovascular effects of SCh: Samples of arterial blood for measurement of plasma norepinephrine (NE) and epinephrine (E) concentrations were drawn immediately before (baseline)

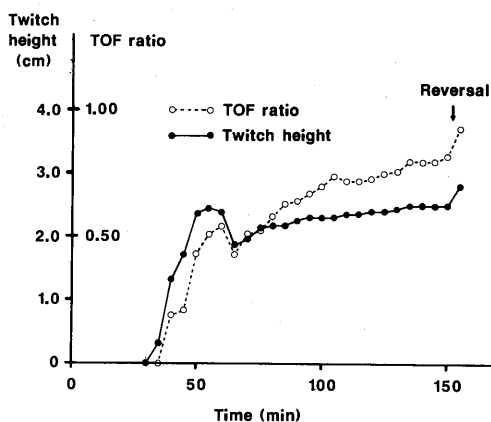


Figure 1 Time course of spontaneous recovery of the train-of-four ratio and the first twitch height in the train-of-four stimulation after succinylcholine 1 mg/kg iv, in patient genotyped as homozygous for silent gene.

and 1, 4, 10, 20 and 30 min after SCh iv. At the same time intervals, systolic blood pressure and heart rate were measured. Samples for the analyses of plasma catecholamine concentrations (5 ml) were immediately placed in capped containers with EDTA·2Na, then stored on ice and centrifuged within 15 min. The decanted plasma was stored at -40°C until analyzed for NE and E using high-performance liquid chromatography (Shimadzu LC-1, Japan) with electrochemical detection (Bioanalytical System LC3A, USA)<sup>4)</sup>. Briefly, this method used 200 pg dihydrobenzylamine as an internal standard and the catecholamines were eluted with 0.1 M perchloric acid. The lower limit of detection of the assay for the catecholamines was approximately 10 pg/ml, with an overall coefficient of variation of 5-10%. Arterial samples (3 ml) for the analyses of blood gas tensions and plasma halothane and potassium concentrations were collected in separate syringes immediately before (baseline), and 4, 10, 20 and 30 min after SCh. The results of the biochemical determinations and of the hemodynamic measurements are summarized in Tables 1 and 2. As shown in Table 1, the plasma NE and E concentrations, and systolic blood pressure increased and reached the maximum at 4 min after SCh iv. Thereafter, these variables progressively declined, but were still 15-22%, 40-70%, and 36-57% higher, respectively, than the

Table 1 Plasma Norepinephrine and Epinephrine Concentrations, Systolic Blood Pressure, and Heart Rate

	Plasma norepinephrine concentrations (pg/ml)	Plasma epinephrine concentrations (pg/ml)	Systolic blood pressure (mmHg)	Heart rate (beats/min)
Baseline	191	20	67	65
1 min	180	18	100	83
4 min	254	74	125	74
10 min	222	43	85	56
20 min	233	28	91	63
30 min	220	34	105	68

Table 2 Arterial Blood Gas Tensions and Plasma Halothane and Potassium Concentrations

	Pao <sub>2</sub> (mmHg)	Paco <sub>2</sub> (mmHg)	Plasma halothane concentrations (mg/dl)	Plasma potassium concentrations (mEq/l)
Baseline	601	36	9.1	3.8
4 min	595	40	10.4	4.0
10 min	614	37	11.6	4.1
20 min	621	37	12.0	4.4
30 min	604	40	12.3	4.4

baseline values even at 20-30 min after SCh iv. Heart rate also started to rise immediately after SCh iv, peaked at 1 min, but subsequently declined to the baseline level within 10 min. The results summarized in Table 2 show that the factors known to cause changes in plasma catecholamine concentrations remained stable throughout the study.

During the surgical procedure, vital signs were stable, and recovery from operation and anaesthesia were uneventful. The trachea was extubated after the confirmation that the TOF ratio was above 0.9, and the tidal volume, inspiratory force, and grip strength were totally adequate. There were no anaesthetic or surgical complications.

## Discussion

In the present case, plasma ChE activity was zero and the sensitivity to SCh was markedly increased. Among the genotypes whose sensitivity to SCh are markedly increased<sup>7)</sup>, plasma ChE activity is zero only in the genotype E1<sup>s</sup>E1<sup>s8)</sup>. Accordingly, the present case could be genotyped as hom-

ozygous for the silent gene (E1<sup>s</sup>E1<sup>s</sup>).

The type and duration of SCh-induced neuromuscular blockade observed in the present study were quite similar to those of our previous case<sup>2)</sup>, that was also diagnosed as E1<sup>s</sup>E1<sup>s</sup>, at the following four points. First, in both cases, the patient remained totally apneic for about 30 min. Second, when the response to nerve stimulation reappeared about 40 min after the injection of SCh, the block already was phase II. Third, the TOF ratio was depressed to the value of about 0.8 even at 150 min after SCh iv. Fourth, the time course of spontaneous recovery of the neuromuscular blockade could be divided into four phases and the time for each phase was quite similar in both cases.

In patients with normal gene for plasma ChE, SCh causes short-lasting increase of plasma catecholamine concentrations, blood pressure and heart rate, which disappear within 10 min after SCh iv<sup>3,4)</sup>. In the present case, however, plasma NE and E concentrations, and systolic blood pressure were 15-70% higher than the baseline values even at 20-30 min after SCh iv. These results

may suggest that the cardiovascular as well as the neuromuscular effects of SCh are prolonged in E1<sup>s</sup>E1<sup>s</sup> patients. Although the precise mechanisms of these cardiovascular effects of SCh are not clear at the present time, it has been postulated that SCh might interact with the nicotinic receptors on the postganglionic sympathetic terminals, leading to explosive release of catecholamines<sup>5)</sup>. This hypothesis is based on the facts that SCh is a cholinergic agent which interacts with the nicotinic receptors on the endplate of the skeletal muscle<sup>9)</sup>, leading to neuromuscular blockade, and that SCh-induced increases in plasma catecholamine concentrations, blood pressure and heart rate were significantly attenuated by prior administration of alcuronium<sup>4)</sup>, which is known to have sympathetic ganglion blocking action<sup>10)</sup>. In addition, the present results that cardiovascular and neuromuscular effects of SCh are both prolonged in E1<sup>s</sup>E1<sup>s</sup> patients may also support the possibility of this hypothesis.

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