

# Consequences of Succinylcholine Administration to Patients Using Statins

Alparslan Turan, M.D.,\* Maria L. Mendoza, M.D.,† Shipra Gupta, M.S.,‡  
Jing You, M.S.,§ Alexandru Gottlieb, M.D.,|| Weihan Chu, M.S.,‡ Leif Saager, M.D.,#  
Daniel I. Sessler, M.D.\*\*



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## ABSTRACT

**Background:** Statins cause structural changes in myocytes and provoke myotoxicity, myopathy, and myalgias. Thus, patients taking statins may be especially susceptible to succinylcholine-induced muscle injury. The authors tested the hypothesis that succinylcholine increases plasma concentrations of myoglobin, potassium, and creatine kinase more in patients who take statins than in those who do not and that succinylcholine-induced postoperative muscle pain is aggravated in statin users.

**Methods:** Patients who took statins for at least 3 months and those who had never used statins were enrolled. General anesthesia was induced and included 1.5 mg/kg succinylcholine for intubation. The incidence and degree of fasciculation after succinylcholine administration were recorded. Blood samples were obtained before induction and 5 and 20 min and 24 h after succinylcholine administration. Patients were interviewed 2 and 24 h after surgery to determine the degree of myalgia.

**Results:** The authors enrolled 38 patients who used statins and 32 who did not. At 20 min, myoglobin was higher in statin users *versus* nonusers (ratio of medians 1.34 [95% CI:

### What We Already Know about This Topic

- Statin therapy may adversely affect skeletal muscle
- Succinylcholine-induced muscle injury is more likely in patients with pathological muscle conditions
- Plasma myoglobin concentrations are a marker of muscle damage

### What This Article Tells Us That Is New

- Plasma myoglobin concentrations provoked by succinylcholine were higher in statin users than in nonusers, but were not clinically important in either group

1.1, 1.7],  $P = 0.018$ ). Fasciculations in statin users were more intense than in nonusers ( $P = 0.047$ ). However, plasma potassium and creatine kinase concentrations were similar in statin users and nonusers, as was muscle pain.

**Conclusions:** The plasma myoglobin concentration at 20 min was significantly greater in statin users than nonusers, although the difference seems unlikely to be clinically important. The study results suggest that the effect of succinylcholine given to patients taking statins is likely to be small and probably of limited clinical consequence.

\* Associate Professor of Anesthesiology, † Research Fellow, ‡ Medical Student, # Assistant Professor of Anesthesiology, Department of Outcomes Research, § Biostatistician, Departments of Quantitative Health Sciences and Outcomes Research, || Assistant Professor of Anesthesiology, Department of General Anesthesiology, Cleveland Clinic, Cleveland, Ohio. \*\* Professor and Chair, Department of Outcomes Research, Cleveland Clinic, and Visiting Scientist, Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada.

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Address correspondence to Dr. Turan: Department of Outcomes Research, Cleveland Clinic, 9500 Euclid Avenue, P-77, Cleveland, Ohio 44195. alparslanturan@yahoo.com. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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**S**TATINS are given to decrease plasma low-density lipoprotein concentrations and reduce the risk of ischemic heart disease and stroke.<sup>1,2</sup> In just 2 decades, use of the agents has grown to more than 100 million prescriptions per year. A consequence of the common use of these agents is that an increasing proportion of surgical patients take these drugs.

Long-term statin therapy generally is well tolerated, although these drugs potentially have serious adverse effects on skeletal muscle. Fatal rhabdomyolysis is rare, but lesser degrees of rhabdomyalgia, fatigue, weakness, and myositis are common, occurring in 10–93% of pa-

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tients.<sup>3–5</sup> The interruption of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase biosynthetic pathway and the consequent intracellular depletion of metabolites and end products are considered the cornerstone of the myotoxic effects of statins.<sup>6</sup> Statin-induced muscular injury includes breakdown of the T-tubular system and subsarcolemmal rupture.<sup>4,7</sup> Statins also impair sarcoplasmic reticulum calcium cycling in mitochondria, which contributes to apoptosis, oxidative stress, and muscle remodeling and degeneration, thereby causing the statin myotoxicity and functional symptoms frequently described by patients.<sup>7</sup>

Succinylcholine, a depolarizing muscle relaxant, has distinctive advantages, including low cost, fast onset, rapid recovery, and benign metabolites.<sup>8</sup> Administration of succinylcholine has well-known side effects, including increases in plasma myoglobin, creatine phosphokinase (CK), and potassium concentrations. Succinylcholine administration also often causes postoperative myalgia, a common and distressing symptom, which is associated with the muscular injury and an increase in muscle-related enzymes.<sup>9,10</sup> Patients with pathologic muscular conditions including myopathies are especially susceptible to the side effects with succinylcholine.<sup>11</sup>

Statins and succinylcholine both cause muscle injuries; thus, the combination may be especially deleterious. However, the effects of succinylcholine in patients taking statins remain unknown. We thus tested the hypothesis that succinylcholine administration increases plasma myoglobin concentration more in patients who take statins than in those who do not. Secondary outcome measures included muscle pain 2 and 24 h after surgery; serum potassium concentration; plasma CK concentration; and duration of succinylcholine-induced paralysis.

## Materials and Methods

The study was conducted with approval of the Cleveland Clinic Institutional Review Board and written informed consent from the participating patients. Patients with American Society of Anesthesiologists physical status I–III, age between 40 and 80 yr, who were scheduled to undergo elective surgery with planned tracheal intubation were eligible. We included patients scheduled for elective surgery (October 2009 between June 2010) in this comparative, prospective, nonrandomized study. Patients were screened for inclusion and exclusion criteria and statin use.

Patients taking simvastatin, lovastatin, atorvastatin, or pravastatin for at least 3 months and those who had never used statins were considered to be eligible for participation. Patients were excluded for the following reasons: orthopedic and spinal surgery, surgery involving extensive muscle manipulation, history of liver and kidney failure, neuromuscular disease, susceptibility to or family history of malignant hyperthermia, extensive denervation of skeletal muscle, chronic pain syndromes, taking medications that might in-

teract with the effect of succinylcholine or serum myoglobin, and anticipated difficult intubation.

## Protocol

An intravenous catheter was inserted into each arm of the patients: one was used for drug and fluid administration, and the other was used for blood sampling. Patients were premedicated with intravenous 0–2 mg midazolam. Monitoring, established on arrival in the operating room, included electrocardiography, noninvasive arterial pressure, pulse oximetry, and capnography. General anesthesia was induced with intravenous 1–3  $\mu\text{g}/\text{kg}$  fentanyl and 2–3 mg/kg propofol.

Over a period of 5 s, 1.5 mg/kg succinylcholine was injected intravenously. The trachea was intubated after fasciculations ended and muscles were completely relaxed. Subsequently, general anesthesia was maintained with sevoflurane in oxygen and air. No additional muscle relaxants were given until neuromuscular blockade dissipated, as defined by response to nerve stimulation.

Subsequently, rocuronium was given if clinically appropriate. Ventilation was controlled to maintain end-tidal carbon dioxide partial pressure between 35 and 45 mmHg. At the end of surgery, neuromuscular blockade was antagonized with neostigmine and glycopyrrolate if clinically indicated. Patients were then extubated, per routine, when the attending anesthesiologist determined that full recovery of neuromuscular function had occurred.

## Measurements

Morphometric and demographic parameters (height, weight, age, and race) were recorded before surgery. Patients were asked about muscle pain before surgery. Those with muscle pain were categorized by musculoskeletal region: neck or upper back, upper extremities (shoulder, arm, wrist or hand), lower back, and lower extremities (buttock, leg, or foot). We also recorded the amount of exercise, previous cardiac problems, history of coronary heart disease, history of hypertension, current smoking, high plasma cholesterol concentrations, diabetes, atherosclerosis, peripheral vascular disease, increased plasma transaminase concentrations, history of liver disease, current medications, myopathies, history of muscle disease, rhabdomyolysis, and history of allergic reactions to statins.

The arm contralateral to the intravenous catheter used for drug administration was immobilized. An accelerometer sensor was taped to the thumb, and the response to ulnar nerve stimulation of the adductor pollicis muscle at the wrist was recorded using the TOF-Watch SX acceleromyograph (Organon Teknica BV, Boxtel, The Netherlands). A 5-s, 50-Hz supramaximal tetanic stimulus was administered, and the TOF-Watch SX was calibrated. The system was calibrated with 0.1-Hz single twitch stimulation.

Standard anesthetic monitoring values were recorded before surgery and at 5-min intervals throughout surgery. After succinylcholine administration, masseter spasm and diffi-

culty with mouth opening, as determined by the anesthesiologist, were noted. The time required to reach maximum block by succinylcholine was recorded, as was block duration. Fasciculation intensity was scored and recorded by a blinded investigator: 0 = none; 1 = small movements around eyes and fingers; 2 = moderate movements in face, neck, fingers, and trunk; and, 3 = vigorous movements in trunk and extremities.<sup>12</sup>

Patients were interviewed by a blinded investigator 2 and 24 h after surgery to determine the incidence and intensity of myalgia. Patients were asked a standardized set of questions that evaluated pain and discomfort anywhere other than the incision site. Pain in nonsurgical areas was evaluated by a 0–100 verbal rating scale and also by using the following scale for degree of muscle pain: 0 = none; 1 = muscle stiffness or pain in the nape of the neck, shoulders, and chest; 2 = muscle stiffness and pain requiring analgesia; 3 = incapacitating generalized muscle stiffness or pain.<sup>13</sup>

Venous blood samples were collected from each patient before induction of anesthesia, defined as elapsed time 0 and then 5 and 20 min and 24 h after succinylcholine administration. Myoglobin concentrations were determined at each of the three sampling times; potassium concentrations were determined at 5 and 20 min; and CK concentrations were determined at 0 and 24 h. Plasma myoglobin concentrations were determined by the electrochemiluminescence immunoassay technique (Elecsys 2010 Modular Analytics E 170; Roche Diagnostics GmbH, Mannheim, Germany). The accurate measurement range extended from 21 to 3,000 ng/ml. The normal range (2.5–97.5 percentiles) for this test is 28–72 ng/ml in healthy men and 25–58 ng/ml in healthy women. Potassium and CK concentrations were determined per routine by the clinical laboratory.

### Statistical Analysis

The balance of baseline characteristics between statin users and nonusers were assessed using the standardized difference, which is the difference in means or proportions divided by the pooled SD. Any covariable with a standardized difference greater than 0.3 in absolute value was regarded as an imbalanced covariable or potential confounder, and was adjusted for in comparisons of statin users and nonusers on each of the outcomes by including them in the statistical models. Exceptions were medical conditions that are specific indications for taking statins or directly related to those. For example, hypercholesterolemia is the main reason for taking statins, and having increased cholesterol might be related to the presence of other diseases, such as diabetes, coronary artery disease, and hypertension. In addition, muscle pain is one of the side effects of taking statins. Thus, these factors were not considered as confounders and were not adjusted for in the analyses.

We compared statin users and nonusers on the primary outcome of myoglobin concentration at 20 min after succinylcholine administration (after logarithmic transformation) with use of analysis of covariance with adjustment for the baseline myo-

globin concentration and imbalanced baseline variables. Because the myoglobin values are not normally distributed, we needed to analyze the data on the log scale, and the succinylcholine effect was then reported as the ratio of medians (obtained by back-transforming the difference in means on the log scale) between groups, with 95% interim-adjusted CIs.

As a secondary analysis, we also compared the two groups on myoglobin concentration at 0 and 5 min and 24 h after succinylcholine administration using the analysis of covariance. We adjusted for the imbalanced baseline variables for each comparison and myoglobin at 0 min for comparisons at 5 min and 24 h.  $P < 0.017$  was considered statistically significant (*i.e.*, 0.05/3, Bonferroni correction).

In addition, we compared statin users and nonusers on median change in myoglobin concentration (after rank transformation) between all pairs of the four time points (0, 5, and 20 min and 24 h) using analysis of covariance, with the same covariable adjustment as for the primary outcome. A Bonferroni correction was used to adjust for multiple comparisons;  $P < 0.0083$  was considered statistically significant (*i.e.*, 0.05/6).

With a goal of  $N = 70$  patients, including an interim analysis at 35 patients, the study was planned to have 90% power at the 0.05 significance level to detect a ratio of means of 2.0 or more between statin users and nonusers on myoglobin concentrations at 20 min after succinylcholine administration. However, we excluded three patients who had missing myoglobin values at baseline (0 min) and/or at 20 min after succinylcholine administration. Therefore, with 67 patients, the group sequential efficacy and futility boundaries for comparing myoglobin at 20 min were  $P \leq 0.0414$  and  $P > 0.0555$ , using the  $\gamma$  spending function ( $\gamma = -3$  for efficacy and  $-1$  for futility). Each result was reported with an

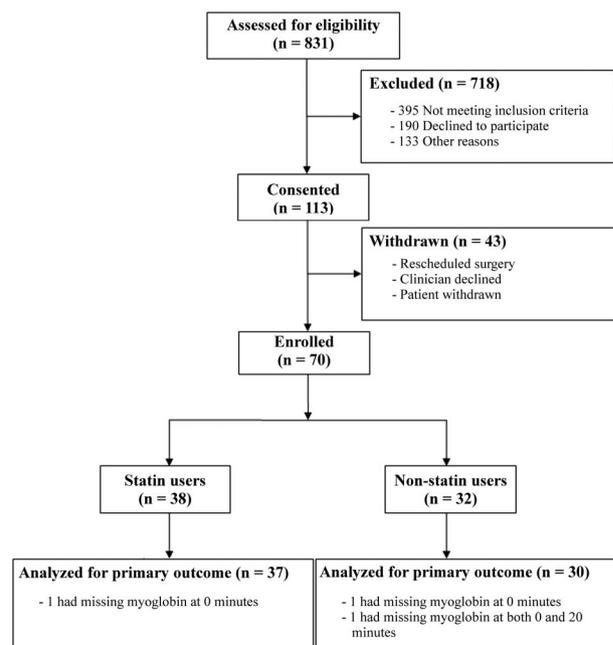


Fig. 1. Study flow chart.

interim-adjusted CI estimated using the Z-statistic criterion of 2.04 for rejecting the null hypothesis with 67 patients.

### Secondary Outcomes

All of the secondary analyses were adjusted for the baseline confounders and the corresponding baseline laboratory value, if applicable. CIs are interim-adjusted.

We assessed the between-group difference in duration of succinylcholine blockade with analysis of covariance and in median serum potassium concentration (at 5 and 20 min) with a repeated-measures linear model.

We compared the two groups on change in plasma CK concentration from baseline (at succinylcholine administration) to 24 h using analysis of variance by ranks (because a log transformation did not make the data normally distributed) and CI for the difference in medians.

We evaluated the difference between statin users and non-users in the intensity of muscle pain (including the verbal rating scale score and the pain score) at each assessed time point separately (2 and 24 h after surgery) using proportional odds logistic regression models to be able to adjust for covariables (otherwise a Wilcoxon rank sum test would be used). To facilitate analysis, the verbal rating scale was categorized as 0, 10–30, 40–70, 80–100. A similar model was also used to compare the two groups on the degree of fasciculation.

The significance level for each hypothesis was 0.05 for main effects and 0.10 for interactions. SAS software version 9.2.2 for Windows (SAS Institute, Cary, NC), R software version 2.8.1 for Windows (The R Foundation for Statistical Computing, Vienna, Austria), and East 5 software (Cytel

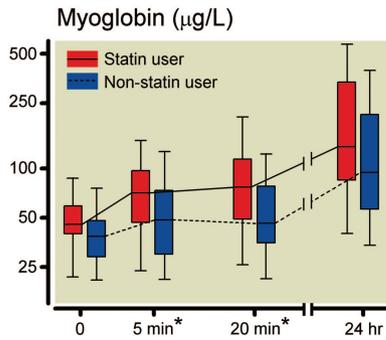
**Table 1.** Baseline Characteristics of the Patients\*

Variables	Statin (N = 38)	Nonstatin (N = 32)	Standardized Difference†
Age, yr	61 ± 9	57 ± 10	0.45
Sex (female), no. (%)	16 (42)	15 (47)	−0.10
Race (white), no. (%)	37 (97)	29 (91)	0.29
Weight, kg	91 ± 24	93 ± 24	−0.14
Height, cm	172 ± 10	172 ± 12	−0.04
Body mass index, kg/m <sup>2</sup>	31 ± 8	32 ± 8	−0.10
Smoker, no. (%)	5 (13)	4 (13)	0.02
Amount of exercise, no. (%)			−0.35
<2 h/week	28 (74)	28 (87)	
2–6 h/week	10 (26)	4 (13)	
Temperature, °C	36.6 ± 0.5	36.6 ± 0.3	0.00
Heart rate, beats/min	73 ± 12	74 ± 12	−0.11
Blood pressure, mmHg			
Systolic	136 ± 24	134 ± 25	0.09
Diastolic	76 ± 12	78 ± 13	−0.16
ASA status, no. (%)			0.42
II	16 (42)	20 (62)	
III	22 (58)	12 (38)	
Surgery type, no. (%)			0.36
General	18 (47)	15 (47)	
Urology	18 (47)	12 (38)	
Gynecology	2 (5)	5 (16)	
Medical history, no. (%)			
Muscle pain	24 (63)	15 (47)	0.33
Coronary artery disease	9 (24)	1 (3)	0.63
Myopathy	0 (0)	0 (0)	0.00
Diabetes type 2	11 (29)	3 (9)	0.51
Stroke/TIA	2 (5)	1 (3)	0.11
Peripheral vascular	1 (3)	0 (0)	0.23
Transaminase elevations	0 (0)	0 (0)	0.00
Hypertension	26 (68)	13 (41)	0.58
Hypercholesterolemia	37 (97)	4 (13)	3.27
Liver problems	0 (0)	1 (3)	−0.25
End-stage renal disease	0 (0)	0 (0)	0.00
Drug allergies (statin)	1 (3)	1 (3)	−0.03
Preoperative laboratory values			
CK, units/l	110 (63, 138)	91 (60, 121)	0.25
Creatinine, mg/dl	1.0 ± 0.2	0.9 ± 0.2	0.49

Because of rounding, not all percentages total 100.

\* Summary statistics are presented as number (%) of patients, mean ± SD, or median (Q1, Q3). † Standardized difference (statin-nonstatin) >0.3 in absolute value indicates imbalance.

ASA = American Society of Anesthesiologists; CK = creatine phosphokinase; TIA = transient ischemic attacks.



**Fig. 2.** Box plots of myoglobin concentration at 0, 5, and 20 min and 24 h after succinylcholine administration. The two groups were compared at each time, adjusting for the myoglobin at 0 min, as appropriate. \* Significant between-group difference at time point (adjusting for baseline).

Inc., Cambridge, MA) were used for all statistical analyses and graphics.

## Results

We enrolled 70 patients, 38 of whom were taking statins and 32 who were not taking statins (fig. 1). Statin users and nonusers were well balanced (absolute value of standardized difference less than 0.3) on most of the baseline characteristics (table 1), except for American Society of Anesthesiologists physical status, age, amount of exercise, type of surgery, and some medical history variables, including muscle pain, coronary artery disease, diabetes, hypertension, and hypercholesterolemia. However, having some of these medical conditions describes the statin user population of interest (see Methods); thus, only American Society of Anesthesiologists physical status, age, amount of exercise, and type of surgery were adjusted for in the analyses in comparisons of the statin users and nonusers on each of the outcomes.

**Primary Results.** The observed median (Q1, Q3) of myoglobin concentration at 20 min after succinylcholine administration was 77 (49, 112)  $\mu\text{g/L}$  in the statin group and 47 (35, 79)  $\mu\text{g/L}$  in the nonstatin group, respectively (univari-

able  $P = 0.007$ , Wilcoxon rank sum test; fig. 2). After adjusting for myoglobin concentration before succinylcholine administration (0 min) and the imbalanced covariables mentioned, myoglobin concentration at 20 min after succinylcholine administration was higher in the statin users than in nonusers (primary results:  $P = 0.018$ , crossing the efficacy boundary of  $P \leq 0.0414$ ); the corresponding estimated ratio of medians was 1.34 (95% interim-adjusted CI: 1.05, 1.72; table 2).

**Secondary Results.** No between-group difference was found in myoglobin concentration at 0 min ( $P = 0.33$ , table 2). In addition, median myoglobin concentration at 5 min was higher in statin users than nonusers ( $P = 0.001$ , table 2) after adjusting for myoglobin at 0 min and the imbalanced covariables; however, no between-group difference was found in myoglobin at 24 h ( $P = 0.34$ , table 2).

Table 3 shows the summary statistics of the changes in myoglobin between all pairs of measurement times. After adjusting for myoglobin at 0 min and the imbalanced covariables, increases in myoglobin concentration from 0 to 5 min and from 0 to 20 min were statistically higher in the statin group than the nonstatin group ( $P < 0.001$  and  $P = 0.002$ , respectively, table 3), although the differences seem unlikely to be clinically important. Changes in myoglobin concentration between other time points did not differ significantly between groups (table 3).

Statin users were more likely to experience a higher (worse) degree of fasciculation ( $P = 0.047$ , table 4) after adjustments were made for age, American Society of Anesthesiologists physical status, amount of exercise, and type of surgery. The corresponding estimated odds ratio (95% CI) was 1.8 (1.0, 3.3), meaning statin users were approximately 1.8 times more likely to have a worse fasciculation score.

No significant group differences were found on any other secondary outcomes (table 4), including the duration of recovery of 10% T 1 from succinylcholine injection, overall serum potassium concentration, change of CK concentration from baseline to 24 h, verbal rating scale score, pain

**Table 2.** Primary Results of ANCOVA\* Adjusting for Myoglobin at 0 Minutes (Except for Comparison at 0 Minutes); Comparisons between Statin Users and Nonusers on Myoglobin at Various Time Points after Succinylcholine Administration

Myoglobin, $\mu\text{g/l}$	Median (Q1, Q3)		Ratio of Medians (95% CI)†	P Value*
	Statin (N = 38)	Nonstatin (N = 32)		
0 min	46 (40, 59)‡	39 (29, 49)‡	1.14 (0.87, 1.49)	0.33
5 min	71 (47, 96)	49 (31, 75)	1.37 (1.13, 1.65)	0.001§
20 min, primary outcome	77 (49, 112)	47 (35, 79)	1.34 (1.05, 1.72)	0.018§
24 h	137 (86, 342)	95 (57, 210)	1.25 (0.78, 2.01)	0.34

\* Analysis of covariance on the logarithmic transformed myoglobin values, adjusting for the American Society of Anesthesiologists physical status, age, amount of exercise, type of surgery, and myoglobin at 0 min (for comparisons at 5 and 20 min and 24 h). The significance criterion was 0.05 for the primary outcome (myoglobin at 20 min) and was 0.017 (i.e., 0.05/3) for myoglobin at the other times. † Estimated using the group-sequential Z-statistic criterion of 2.04. ‡ One patient had missing myoglobin at 0 min. § Statistically significant. || One patient had a missing myoglobin value at 20 min, and one patient had missing values at 0 and 20 min.

**Table 3.** Secondary Results of Rank ANCOVA\* Adjusting for Myoglobin at 0 Minutes: Comparisons between Statin Users and Nonusers on Change in Myoglobin between All Pairs of the Four Time Points

Changes in Myoglobin, μg/l	Median (Q1, Q3)		Median Difference† in Changes (95% CI)‡ (Statin-Nonstatin)	P Value*
	Statin (N = 38)	Nonstatin (N = 32)		
0–5 min	11 (5, 32)§	3 (0, 9)§	8 (2, 17)	<0.001
0–20 min	24 (6, 43)§	5 (1, 18)#	13 (1, 24)	0.002
0 min–24 h	88 (33, 290)§	63 (23, 168)§	23 (–25, 84)	0.19
5–20 min	9 (2, 20)	3 (0, 11)#	3 (–2, 10)	0.05
5 min–24 h	69 (24, 200)	57 (10, 165)	18 (–34, 72)	0.61
20 min–24 h	73 (9, 193)	54 (–4, 18)#	14 (–48, 76)	0.74

\* Analysis of covariance on ranks of change in myoglobin, adjusting for myoglobin at 0 min, American Society of Anesthesiologists physical status age, amount of exercise, and surgery type. † Not covariable adjusted. ‡ The confidence interval was estimated using the group-sequential Z-statistic criterion of 2.04. § One patient had a missing myoglobin value at 0 min. || Statistically significant, using the significance criterion of 0.0083 (*i.e.*, 0.05/6, Bonferroni correction). # One patient had a missing myoglobin value at 20 min, and one patient had missing values at both 0 and 20 min.

score, or any side effect. Masseter muscle rigidity was not observed in any patient.

## Discussion

Our study did not demonstrate that patients using statins chronically have higher baseline myoglobin concentrations. Previous studies reported that patients taking statins often have increased myoglobin concentrations and report moderate-to-strong myalgias.<sup>14</sup> Succinylcholine also causes an increase in myoglobin concentrations. The increase we observed in plasma myoglobin concentration after succinylcholine administration in nonusers was similar to that reported previously by other investigators.<sup>15</sup> We also found that the increase in myoglobin concentrations after succinylcholine administration at 5 and 20 min was slightly higher in statin users than in nonusers. Myoglobin concentrations increased considerably over 24 h; however, the absolute values and increases were similar in the two groups.

Serum myoglobin is a biochemical marker for muscle damage, and its apparent function is to act as a reservoir of oxygen during brief periods of hypoxia.<sup>9,16,17</sup> We observed a higher myoglobin concentration with succinylcholine administration in statin users, which indicated muscle damage, but the degree of muscle injury is unclear. The myoglobin released into the plasma after muscle injury is rapidly excreted in the urine, and there is strong association between myoglobinuria and acute renal failure.<sup>18,19</sup> However, the observed myoglobin concentrations, even in statin users at 24 h, were less than the threshold for renal damage in patients with relatively normal kidneys, which is greater than 1,000 μg/ml.<sup>19,20</sup> That being said, caution may be warranted in patients at special risk for myoglobin increases, including those with limited renal function, obese patients, or those having major surgery involving muscles or the vascular system.<sup>20–22</sup> We also note that we sampled blood for myoglobin three times, with the last sampling done 24 h after surgery. The concentration increased substantially at each sample time, so it remains possible that potentially toxic concentrations would have been observed had sampling continued beyond 24 h. However, previous work suggests

that peak concentrations normally are observed roughly 24 h after succinylcholine administration.<sup>9,12</sup>

Muscle pain related to preoperative statin use was reported by 63% of patients, which was similar to the findings of previous studies, in which the percentage varies from 10% to 93%, depending on the type of statin used or concomitant use of other medications.<sup>3–5</sup> The etiology of statin-induced muscle pain remains unknown, but potential mechanisms include disruption of signaling pathways, depletion of constituents, alterations in membrane cholesterol content, and abnormality in the T-tubular system in skeletal myocytes.<sup>7,23</sup> Interestingly, structural changes have been observed even in patients who lacked muscle-related symptoms, which suggests that myocyte damage can be subtle.<sup>7</sup>

Muscle pain is also a well-recognized side effect of succinylcholine. Although the mechanism remains a matter of controversy, fasciculations are widely believed to be the primary cause of myalgias.<sup>9,24</sup> In support of this theory, pretreatment with small (nonparalytic) doses of nondepolarizing muscle relaxants reduces fasciculation intensity and muscle pain after succinylcholine administration.<sup>25</sup> The incidence of muscle pain in our patients who did not use statins was 22% after succinylcholine administration, which was similar to findings of previous studies.<sup>26</sup> Fasciculations in statin users were more intense than in nonusers, and statin users had greater baseline muscle pain, with both effects possibly being related to statin-induced structural changes in skeletal muscle. Nonetheless, postoperative muscle pain in statin users was nonsignificantly lower (11%) than in nonusers at 2 and 24 h after surgery. Why more intense fasciculations were not associated with increased pain is unclear, but others have noted a similar poor correlation.<sup>25</sup> It is also probable that postoperative analgesic medications, at least to some extent, masked muscle pain, which in most cases is considerably less intense than surgical pain.

Another common side effect of succinylcholine administration is acute hyperkalemia. Patients with congenital muscular dystrophies, spinal cord lesions with paraplegia, exten-

**Table 4.** Comparisons between Statin Users and Nonusers on Secondary Outcomes after Succinylcholine Administration

Secondary Outcomes*	Statin (N = 38)	Nonstatin (N = 32)	Ratio of Medians (95% CI)†	P Value‡
Recovery of 10% T 1 succinylcholine-induced blockade, min	4.2 (3.0, 6.0)	4.6 (3.3, 6.1)	0.94 (0.67, 1.31)	0.69§
Serum potassium,   mEq/l	4.1 (3.8, 4.4)	4.0 (3.8, 4.3)	1.01 (0.95, 1.07)	0.77#
CK change (0–24 h),** units/l	175 (11, 333)	78 (19, 354)	Median difference 8 (–78, 121)†† Odds ratio§§	0.39‡‡
Fasciculation, no. (%)			0.55 (0.30, 0.99)	0.047
0 (none)	9 (24)	13 (41)		
1 (small)	6 (16)	3 (9)		
2 (moderate)	10 (26)	8 (25)		
3 (vigorous)	13 (34)	8 (25)		
VRS score, no. (%)				
At 2 h:			0.66 (0.26, 1.67)	0.36
0 (no pain)	34 (89)	26 (81)		
10–30	2 (5)	0 (0)		
40–70	1 (3)	4 (13)		
80–100	1 (3)	2 (6)		
At 24 h:			1.04 (0.45, 2.38)	0.92
0 (no pain)	34 (89)	25 (78)		
10–30	2 (5)	4 (13)		
40–70	1 (3)	2 (6)		
80–100	1 (3)	1 (3)		
Pain score, no. (%)				
At 2 h:			0.67 (0.27, 1.69)	0.38
0 (no pain)	34 (89)	26 (81)		
1	4 (11)	3 (9)		
2	0 (0)	3 (9)		
At 24 h:			0.91 (0.39, 2.13)	0.82
0 (no pain)	34 (89)	25 (78)		
1	4 (11)	5 (16)		
2	0 (0)	2 (6)		

\* Summary statistics are presented as number (%) of patients or median (Q1, Q3). † Estimated using the Z-statistic criterion of 2.04. ‡ Adjusting for the American Society of Anesthesiologists physical status, age, amount of exercise, type of surgery, and the corresponding baseline laboratory value, if applicable, by proportional odds logistic regression, unless specified. § Analysis of covariance. || At 5 and 20 min after succinylcholine. One patient per group had missing values at 5 min. # Linear model with repeated measures. \*\* Two patients in the nonstatin group had missing baseline CK values. The observed median (Q1, Q3) CK concentration at baseline and at 24 h were 110 (63, 138) and 321 (136, 417) units/l for the statin group and 91 (59, 122) and 224 (108, 429) units/l for the nonuser group. †† Statin-nonstatin; not covariable adjusted. ‡‡ Analysis of variance on ranks of the change in myoglobin. §§ Odds ratio of rating a higher (worse) score.

CK = creatine phosphokinase; VRS = verbal rating scale.

sive burns, or major tissue trauma are more susceptible to the hyperkalemic effect of succinylcholine.<sup>27</sup> The main reason is that an isoform of the neuronal nicotinic acetyl choline receptor,  $\alpha 7$ AChR, is expressed and up-regulated in susceptible muscles.<sup>28,29</sup> A muscle with  $\alpha 7$ AChR isoforms is more sensitive to succinylcholine and its metabolite choline than are normal acetyl choline receptors. This accounts for the persistence of hyperkalemia and the risk of cardiac arrest seen more often in this patient population. Recent studies suggest that statins up-regulate  $\alpha 7$ AChRs channels and consequently can promote hyperkalemia in patients taking statins.<sup>30</sup> Nonetheless, serum potassium concentrations were similar in our statin users and nonusers.

Creatine kinase is an enzyme that exists within skeletal muscle, and increased CK concentrations indicate muscle

damage caused by chronic or acute muscle injury.<sup>31</sup> The change in median CK concentrations was considerably greater in statin users, but the difference between users and nonusers was not statistically significant because there was considerable variability among patients. However, CK concentrations peak a day or so after myoglobin concentrations do.<sup>31</sup> Thus, we may have missed the CK peak, which would be expected to occur on the second postoperative day.

There would be substantial practical difficulties in randomizing surgical patients to long-term statin use. Thus, our trial was not randomized. An unsurprising consequence is that there were differences between the treatment groups. In most cases, the observed differences were predictable from the indications for statin treatment, and the magnitudes of the differences were small and seem unlikely to have mark-

edly influenced results. But as always in nonrandomized trials, it remains possible that unrecognized and thus unrecorded factors may have confounded the results. Our study was limited by our use of a relatively high dose of succinylcholine (which is less likely to cause myalgia compared with a smaller dose); however, we believe that this is the most preferred dose used in rapid sequence intubation. Whether patients taking abnormally large doses of statins or those with increased myalgia have similar responses requires additional study.

In summary, plasma myoglobin concentrations were significantly increased in statin users than in nonusers at 5 and 20 min after succinylcholine administration; however, concentrations were similar 24 h after surgery. In addition, plasma potassium and creatine kinase concentrations were similar in statin users and nonusers, as was muscle pain at 2 and 24 h after surgery. Thus, our results suggest that succinylcholine-induced muscle injury is slightly worse in patients taking statins than in those not taking such drugs, but the difference seems unlikely to be clinically important.

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