

The Effect of Succinylcholine on Canine Gastrocnemius-muscle Oxygen Consumption

Richard A. Theye, M.D.

In dogs anesthetized with halothane and maintained at 37 C, gastrocnemius-plantaris muscle \dot{V}_{O_2} increased with intravenously administered succinylcholine (SCh). With continuous paralyzing amounts of SCh, the increase in \dot{V}_{O_2} peaked at 50 to 60 per cent in the first 20 minutes and was sustained thereafter at approximately 20 per cent above control. Gallamine in paralyzing amounts prevented the initial peak increase but was without effect on the sustained increase. The peak increase is believed to result from the action of SCh at the motor end-plate, leading to generation of an action potential and contraction of the muscle fiber, and the sustained increase to result from an increase in the energy requirements that arises out of either an alteration in the normal activity of resting muscle or the presence in the muscle fiber of an agent causing sarcomeric oscillation. (Key words: Gallamine; Skeletal-muscle oxygen consumption; Succinylcholine.)

WE HAVE FOUND that succinylcholine (SCh) produces an increase in whole-body \dot{V}_{O_2} that is related in major part to increased skeletal-muscle \dot{V}_{O_2} .¹ Subsequently, it has been shown that the \dot{V}_{O_2} of the muscle preparation used for these purposes is unaffected by either gallamine (Flaxedil) or the mode of maintenance of core and muscle temperatures.² The present studies examine the effects of SCh on muscle \dot{V}_{O_2} in greater depth than has been attempted previously.

Material and Methods

Unpremedicated dogs weighing 15 to 23 kg were anesthetized with halothane* and intubated with the aid of 1 to 4 mg of SCh ad-

ministered intravenously. Pulmonary ventilation with halothane in 35 per cent O_2 and N_2 was provided by a Harvard pump, adjusted to result in a Pa_{CO_2} of 30 to 45 mm Hg. Average mean expired halothane was 1.5 ± 0.2 per cent, and there were no spontaneous movements. Catheters were placed in the carotid artery and in one or more peripheral veins for sampling, pressure measurements, and infusion of fluids and drugs.

The venous drainage of the left gastrocnemius-plantaris muscle group (gastrocnemius muscle) was isolated and, after heparinization, collected externally with the precautions previously described.² On occasion, electromyographic activity was sought by means of suitable electrodes and circuitry, with oscillographic display. Electrodes from a nerve stimulator (Grass, Model S-4, C) were attached to the distal end of the right sciatic nerve, divided proximal to the motor supply of the gastrocnemius muscle. The tendon of the latter was severed and connected to a force gauge with a recorder; tension on the tendon was adjusted to 100 g. The nerve stimulator was adjusted to deliver a single supramaximal stimulus to the nerve, as judged by the twitch response. Paralysis was considered total when no twitch response occurred with stimulation and partial when the response was approximately 50 per cent of that of the control. Right atrial and muscle temperatures were maintained at 37 C, as previously described.²

Gastrocnemius-muscle \dot{V}_{O_2} was calculated by the Fick formula, from direct measurement of blood flow and the difference between arterial and muscle venous O_2 contents, and expressed relative to the wet weight of the muscle as removed at necropsy. Blood O_2 content was calculated from P_{O_2} and oxyhemoglobin concentration with the use of conven-

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TABLE 1. Effect of Succinylcholine on Gastrocnemius-muscle $\dot{V}O_2$

Group	Experimental Circumstances	$\dot{V}O_2$ (A-V) $\dot{V}O_2$	Percentage Changes from Control for Intervals after Start of 8Ch Administration											
			Hour 0-0.5		Hour 0.5-1.0		Hour 1.0-2.0		Hour 2.0-3.0					
			Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
			$\dot{V}O_2$ (A-V) $\dot{V}O_2$		$\dot{V}O_2$ (A-V) $\dot{V}O_2$		$\dot{V}O_2$ (A-V) $\dot{V}O_2$		$\dot{V}O_2$ (A-V) $\dot{V}O_2$		$\dot{V}O_2$ (A-V) $\dot{V}O_2$		$\dot{V}O_2$ (A-V) $\dot{V}O_2$	
A	Continuous	Total	46.4*	7.1	16.7*	4.0	15.7*	5.5	20.3*	6.3	20.3*	6.3	20.3*	6.3
			31.2*	6.0	10.6	0.0	13.5	11.5	33.0	15.4	33.0	15.4	33.0	15.4
B	Continuous	Total	16.1*†	4.0	23.0*	5.8	17.4*	5.4	24.7*	2.8	24.7*	2.8	24.7*	2.8
			12.3	6.4	18.5	0.2	18.8	8.3	42.0*	13.7	42.0*	13.7	42.0*	13.7
C	20 min. only	Total	35.0*	7.1	25.7*	8.7	10.9	8.0	14.7	6.9	14.7	6.9	14.7	6.9
			22.0	10.4	15.1	14.7	11.4	17.0	20.0	24.7	20.0	24.7	20.0	24.7
D	Continuous	Partial	9.0*†	1.4	14.0*	5.7	21.2*	7.8	17.0*	5.5	17.0*	5.5	17.0*	5.5
			9.8*	1.1	13.0*	4.0	21.2*	5.0	30.0*	11.9	30.0*	11.9	30.0*	11.9

* Significantly different ($P < 0.05$) from control values; † test, paired data.† Significantly different ($P < 0.05$) from value observed during same interval in group A; ‡ test, unpaired data.

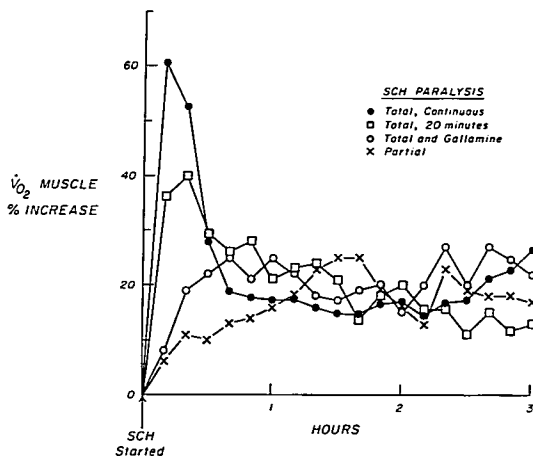
tional factors. Oxyhemoglobin concentrations were determined by means of an Instrumentation Laboratory Co-oximeter, Model 182, especially calibrated for dog blood by comparisons with values obtained by the Van Slyke-Neill procedure. PaO_2 , $Paco_2$, and pH and muscle venous Po_2 were determined by electrodes at 37°C. Arterial pressure was transduced by strain gauge. Halothane concentration in gas was determined by an infrared analyzer.

After control observations for an hour, the responses of four groups of five dogs each to intravenously administered 8Ch were studied during a three-hour period. 8Ch was given continuously in totally paralyzing amounts both in the absence (group A) and in the presence (group B) of gallamine in totally paralyzing amounts. 8Ch was also given continuously in totally paralyzing amounts for the first 20 minutes of the three-hour period only (group C) and in partially paralyzing amounts for the entire period (group D) and an additional hour during which gallamine in totally paralyzing amounts also was given. For total paralysis, 8Ch dosage was arbitrarily the same in all dogs, 0.3 mg/kg/min.¹ For partial paralysis, 8Ch dosage was varied as required, tending to become less after the first hour, and averaging 0.003 mg/kg/min. Total paralysis by gallamine was obtained with 4 mg/kg/hr after an initial 3 mg/kg in each dog.² The entire study required six to eight hours.

Results

Gastrocnemius-muscle $\dot{V}O_2$ increased with 8Ch without exception under each circumstance. The calculated increase in $\dot{V}O_2$ resulted primarily from an increase in (A-V) $\dot{V}O_2$ with only small and inconstant increases in blood flow (table 1). The mode of 8Ch administration influenced the magnitude and pattern of the initial $\dot{V}O_2$ response but was without significant effect after the first hour (table 1; fig. 1). The greatest average increase was 50 to 60 per cent, which occurred in the first 20 minutes with continuous, paralyzing amounts of 8Ch. A similar initial response occurred in the group receiving paralyzing amounts of 8Ch for the initial 20 minutes only. Significantly smaller initial increases were seen both when gallamine in paralyzing amounts

FIG. 1. Gastrocnemius-muscle \dot{V}_{O_2} responses to SCh (mean values). Note the influence of conditions of SCh paralysis on the initial but not on the sustained increase in \dot{V}_{O_2} .



preceded and accompanied paralyzing amounts of SCh and when partially paralyzing amounts of SCh were given continuously (table 1; figs. 2 and 3). After the first hour, \dot{V}_{O_2} remained at approximately 20 per cent above control in all groups. Significant differences between individual group responses were not present, nor were electromyographic activity or changes in tendon tension detected. Administration of gallamine during an additional hour while partially paralyzing amounts of SCh were continued resulted in a significant decrease in \dot{V}_{O_2} , averaging 12 per cent (table 2). This reduction was not seen when gallamine was given in the absence of SCh.² Furthermore, as noted previously, gallamine was without apparent effect on the response of muscle \dot{V}_{O_2} during the second and third hours of continuous administration of paralyzing amounts of SCh.

Control values in the four groups did not differ significantly and have been pooled (table 3). Of these, only \dot{V}_{O_2} and flow were significantly altered by SCh and gallamine. The small and insignificant changes in other measured entities have not been tabulated. The variability in control \dot{V}_{O_2} values could not be related to differences in any measured en-

tity, surgical technique, or variations in anatomy as revealed at necropsy.

Discussion

These results confirm and further define the findings of our previous study,¹ in which SCh in paralyzing amounts resulted in an increase in whole-body \dot{V}_{O_2} that peaked at approximately 10 per cent in the first 15 minutes, gradually lessened, but persisted throughout the three hours of observations. Neither the magnitude nor the time course of this response was significantly influenced by either the total amount of SCh or the duration of the infusion. The response of gastrocnemius-muscle \dot{V}_{O_2} to SCh was similar to that seen in the present study, differing only in a greater initial peak increase, approximately 50 to 60 per cent, and a more steady sustained increase after the first hour. These differences are believed to reflect primarily the greater definition available in a study of an isolated organ, wherein \dot{V}_{O_2} changes of the affected organ are free from the influence of \dot{V}_{O_2} changes in other tissues. The early peak increase with paralyzing amounts of SCh was prevented by paralyzing amounts of *d*-tubocurarine in the previous study and by gallamine in the present study. The later sustained increase, however, was unaffected by

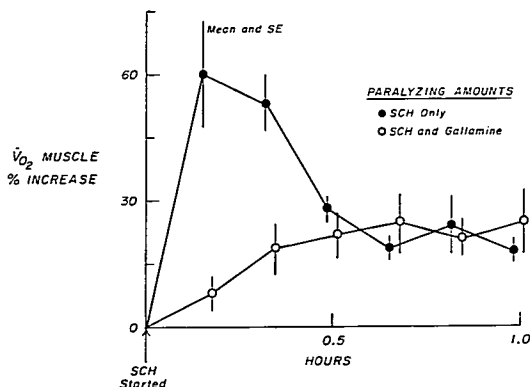


FIG. 2. Effect of gallamine on the initial response to paralyzing amounts of SCh.

gallamine. With partially paralyzing amounts of SCh, gastrocnemius-muscle \dot{V}_{O_2} increased gradually and plateaued in one hour at a level not significantly different from that with paralyzing amounts of SCh. In this situation, muscle \dot{V}_{O_2} was decreased by gallamine but did not return to control values.

Our earlier suggestion that at least two mechanisms are involved in the increased \dot{V}_{O_2} with paralyzing amounts of SCh is supported by these findings.¹ The early peak increase clearly appears to result from depolarization by SCh at the muscle end-plate, generation of

an action potential, and contraction of the muscle fiber. These events have been observed directly with SCh in isolated nerve-muscle preparations² and are manifested by the fasciculations commonly seen in clinical practice. As expected, the magnitude of this response is not altered by exceeding a totally paralyzing amount, but is attenuated or even totally blocked by the presence of totally paralyzing amounts of gallamine. This mechanism also appears to be involved to some extent in the response to partially paralyzing amounts of SCh.

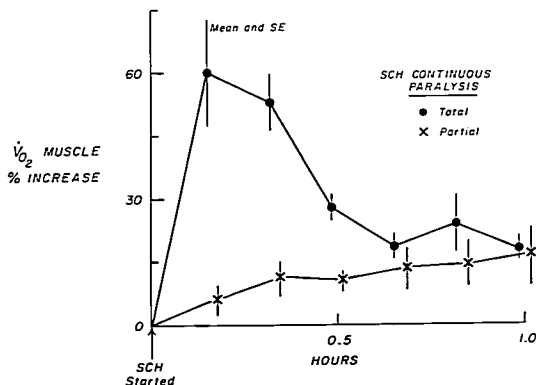


FIG. 3. Effect of less than totally paralyzing amounts of SCh on the initial response to SCh.

The sustained increase in muscle \dot{V}_{O_2} with paralyzing amounts of SCh, however, cannot be accounted for by events at the myoneural junction leading to muscle fiber contraction. The continued presence of "depolarizing agents" in paralyzing amounts at the muscle end-plate does not result in persistent depolarization, muscle contraction, and fasciculation; rather, it results in a repolarized, although inexcitable, end-plate.⁴ Accordingly, as expected, neither electromyographic activity nor changes in tendon tension were detected during the sustained increase. Furthermore, magnitude and time course of the increased \dot{V}_{O_2} were unaffected by paralyzing amounts of gallamine, and the increase persisted several hours after cessation of SCh administration.

In the search for other mechanisms to explain the sustained increase, two appear to merit serious consideration. In either instance, it seems likely that the eventual chemical mediator was choline rather than SCh, because the increase in \dot{V}_{O_2} appeared and disappeared slowly and SCh is rapidly hydrolyzed to choline in vivo. The first possibility is purely speculative and emerges from a consideration of the sizable metabolic activity of resting skeletal muscle required to maintain the integrity of the muscle membrane, preserve concentration gradients, transport various substances actively, and degrade and resynthesize certain cell constituents.⁵ Conceivably, choline, which has been shown to enter the skeletal muscle fibers in frogs⁶ readily, could result in an increase in energy requirements of one or more of these functions. The other possibility, choline-induced sarcomeric oscillation, is suggested by the response of frog muscle fibers to carbamylcholine, hexamethonium, and several other quaternary ammonium compounds, as observed by Marco and Nastuk.⁷ Introduction of these drugs into the solution bathing the muscle fiber resulted in brief, asynchronous, small-amplitude displacements of the sarcomeres of the muscle fibers. With time, these oscillations became synchronized and evolved into peristaltic-like movements involving adjacent sarcomeres. The response had a latency of two to six minutes and was spotty, in that not all the sarcomeres of

TABLE 2. Change in Gastrocnemius-muscle \dot{V}_{O_2} with Gallamine

Number of dogs	Control	Percentage Change after Gallamine	
		Mean	SE
5	SCh absent	-1.9	5.3
5	SCh present, partial paralysis	-11.9*	2.6

* Significantly different ($P < 0.05$); † test, paired data.

TABLE 3. Summary of Control Values (37°C, Halothane 1.5 ± 0.2 Per Cent Expired)

	Mean	SD
Gastrocnemius muscle		
\dot{V}_{O_2} (ml/min/100 g)	1.05	0.27
Flow (ml/min/100 g)	31.2	12.1
P_{O_2} (venous) (mm Hg)	55	7
Temperature (°C)	37.0	0.2
Weight (gm)	64	13
Arterial blood		
Pressure (mean) (mm Hg)	93	8
P_{O_2} (mm Hg)	165	21
P_{CO_2} (mm Hg)	37	3
Hb (gm/100 ml)	13	1

a given fiber were involved at any time nor were sarcomeres of adjacent fibers equally involved. The oscillations were believed to result from the local increases in concentration of Ca^{++} released from the sarcoplasmic reticulum by the oscillogenic agent. Presumably, the choline produced by hydrolysis of SCh in our studies would, after entering the muscle fiber, also result in sarcomeric oscillations and thereby increase the energy requirements of the muscle. A direct test of this hypothesis awaits studies that utilize canine gastrocnemius muscle under the conditions of the present study.

The results of the present study cannot be projected to all muscles of the dog or to skeletal muscle in general because skeletal muscle is known to be heterogeneous both between individual muscles of the same species and between the same muscle of different species. Although it has long been recognized that certain muscles of some species differed in gross appearance, some being more red and others

more white, recent studies have revealed, in addition, differences in fiber size, mitochondrial ATP-ase content, capillary density, metabolic pathways involved in ATP generation, and resting \dot{V}_{O_2} .⁸⁻¹¹ Currently, compared with white muscle, red muscle is considered to be composed of smaller fibers, with a greater mitochondrial ATP-ase content and capillary supply and with more reliance on aerobic metabolic pathways and a larger resting \dot{V}_{O_2} . Furthermore, red and white muscles of the cat respond differently in the rapid-eye-movement phase of sleep and to the defense reaction elicited by hypothalamic stimulation.¹¹ This may well carry over to the \dot{V}_{O_2} response to SCH, because red and white muscles differ markedly in fiber size and density of motor innervation.¹² Unfortunately for our purposes, similar studies have not yet been extended to the dog.

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Pediatrics

NEWBORN VENTILATION Six low-birth-weight infants in respiratory failure secondary to respiratory distress syndrome received mechanical ventilation beginning at an average of 33 hours. The infants' lungs were ventilated with a Harvard small-animal ventilator or a Bennett PR-2 respirator. Four studies of each infant were done at 24- to 36-hour intervals. In each of these studies an attempt was made to keep minute volume and P_{aCO_2} relatively constant. P_{aO_2} obtained from an indwelling catheter in the umbilical artery varied directly and significantly with the increase in peak airway pressure. This variation was maximal one to two days after institution of mechanical ventilation; a 20 cm H_2O increase in pressure resulted in an average increase in P_{aO_2} of 80 to 100 mm Hg. The absolute pressures in the airway varied from 25 to 50 cm H_2O , with large individual variations in absolute levels of P_{aO_2} . Four of the six infants survived. Increasing airway pressure and decreasing respiratory frequency will produce increases in P_{aO_2} at approximately the same levels of alveolar ventilation in infants with respiratory distress syndrome undergoing mechanical ventilation. (Smith, P. C., and others: *Mechanical Ventilation of Newborn Infants*. 1. Effect of Rate and Pressure on Arterial Oxygenation of Infants with Respiratory Distress Syndrome, *Pediat. Res.* 3: 244 (May) 1969.)