David S. Warner, M.D., Editor

Succinylcholine and Intracranial Pressure

James E. Cottrell, M.D.

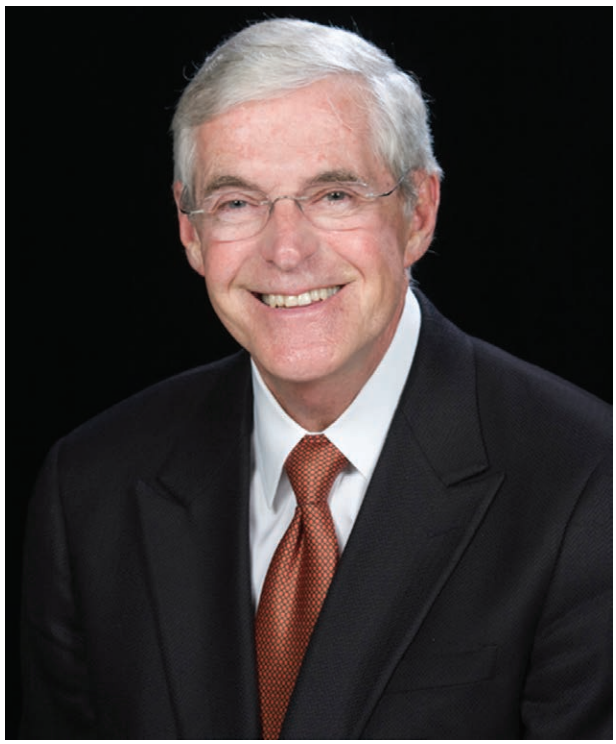
Intracranial and Hemodynamic Changes after Succinylcholine Administration in Cats. By Cottrell JE, Hartung J, Giffin JP, and Shwiry B. *Anesthesia & Analgesia* 1983; 62:1006–9. Reprinted with permission.

Abstract: Bolus injections of succinylcholine (1.5 mg/kg) significantly increased intracranial pressure (ICP) in cats under normal conditions from control levels of 8 +/- 1 mmHg to 16 +/- 3 mmHg (+/- SEM, P less than 0.01), and in the presence of artificially increased ICP from control levels of 27 +/- 1 mmHg to 47 +/- 4 mmHg (*P* less than 0.01). These approximately 100% increases in ICP were accompanied by a transitory decrease in mean arterial pressure (approximately 10 s), followed by a 15 to 20% increase (*P* less than 0.05). Pulmonary arterial pressure increased 20 to 30% (*P* less than 0.05). These results, when considered in conjunction with results previously obtained in humans, suggest that succinylcholine may be contraindicated in neurosurgical patients.

As residents, most of us are intimidated by the mountain of knowledge that we need to climb. As fellows, falsely confident that we have scaled at least halfway to the peak, an impish notion begins to insinuate itself—the possibility that we might be able to make the mountain a little higher. That was a stimulating aspiration for anyone lucky enough to work with the likes of Ephraim S. [Rick] Siker, M.D. (deceased, previously of University of Pittsburgh Medical Center Mercy Hospital, Pittsburgh, Pennsylvania), and Bernard [Bernie] Wolfson, M.D. (retired, previously of University of Pittsburgh Medical Center Mercy Hospital, Pittsburgh, Pennsylvania), in the early 1970s.

Our first article tested the hypothesis that preoperative intermittent positive pressure breathing therapy would improve postoperative pulmonary function in patients with chronic obstructive lung disease.[1] We were not able to reject the null hypothesis, but according to the custom of *Anesthesia & Analgesia* in 1973, as first author, I got my picture in the article (fig. 1)—and yes, I sent a reprint to my mother!

We had better luck with the null hypothesis in our 1976 paper on airway resistance during sedation of my fellow residents![2] So I got off to a lucky start with pulmonary studies before being drafted by the U.S. Navy, where my lucky streak continued. I was packed for Vietnam when a last-minute change of deployment landed me in the Naval Health Facility at Keflavik, Iceland, and I applied for a faculty appointment at Borgaspitalin in Reykjavik, Iceland, where I did some clinical work and taught medical students, residents, and anesthesia nurses.



James E. Cottrell, M.D.

Submitted for publication April 12, 2018. Accepted for publication August 8, 2018. From the Department of Anesthesiology, Downstate Medical Center, State University of New York, Brooklyn, New York.

 Anesthesiology 2018; 129:1159-62

<zdoi;10.1097/ALN.0000000000002429>

★ JAMES E. COTTRELL, M.D., is serving as Chief of Anesthesia, U. S. Naval Station, Keflavik, Iceland. A graduate of the University of West Virginia Medical School in Morgantown, Dr. Cottrell was a Resident in Anesthesiology at Mercy Hospital in Pittsburgh, Pennsylvania, where he subsequently held a Fellowship in Respiratory Research.

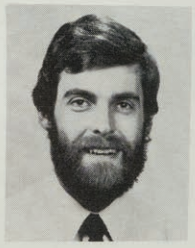


Fig. 1. From Cottrell JE, Siker ES: Preoperative intermittent positive pressure breathing therapy in patients with chronic obstructive lung disease: Effect on postoperative pulmonary complications. Anesth Analg 1973; 52:258–62. Reprinted with permission from Cottrell and Siker.[1]

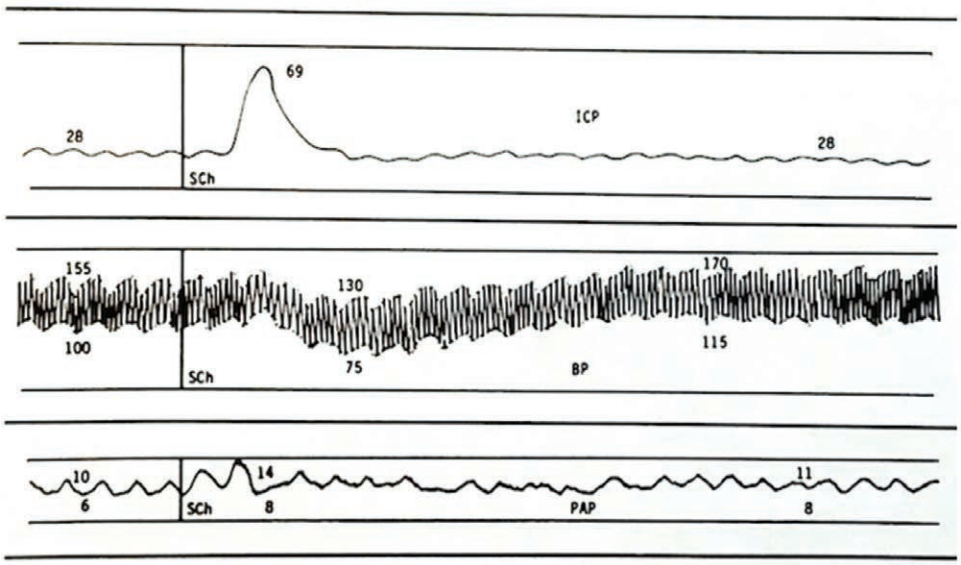


Fig. 2. Tracing of intracranial pressure (ICP), blood pressure (BP), and pulmonary arterial pressure (PAP) for approximately 100 s. *Vertical line*, injection of succinylcholine (Sch; 1.5 mg/kg; from cat No. 10, initial ICP increased). Reprinted with permission from Cottrell *et al.*[10]

After a year in Iceland, I was assigned to coordinate the neuroanesthesia section of the Philadelphia Naval Hospital, Philadelphia, Pennsylvania, which served as sufficient experience to land essentially the same job back in civilian life, as an assistant professor at New York University, New York, New York. As a level 1 trauma center, Bellevue Hospital, New York, New York, had an amazing team of neurosurgeons, neurologists, and vascular neuroradiologists, and a sophisticated brain and spinal cord monitoring facility. But I had mixed feelings. On one hand, with so many experts and so much high-end monitoring, I felt like a kid in a candy store; on the other hand, at times I felt like a first-year resident—if not a first-year medical student!

One of those amazing surgeons was always asking us about intracranial pressure (ICP) and commenting on brain swelling during open cranium procedures. After closure, he would leave a ventricular drain or place a Becker Bolt so we could directly monitor ICP in the neurointensive care unit. Meanwhile, our vascular surgeon loved to use vasoactive drugs to demonstrate how he could relax spastic vessels around an aneurysm with topical papaverine and an intravenous infusion of aminophylline. So, the time was right to formally investigate the effect of commonly used drugs on ICP and cerebral perfusion pressure.

Our first investigation measured changes in ICP, osmolality, and electrolytes after administration of mannitol and furosemide in craniotomy patients. The data warranted our recommendation "that furosemide be used instead of mannitol when diuresis is desired in patients with increased ICP, and in those who have pre-existing cardiac and electrolyte abnormalities."[3,4] Over the ensuing decades, we investigated these and other variables, *in vitro* and *in vivo*, after administration of nitroprusside,[5,6] nitrous oxide,[7] nitroglycerin,[8] naloxone,[9] succinylcholine,[10] nifedipine,[11] midazolam,[12] thiopental,[13] tetrodotoxin,[14] diltiazem,[15] atracurium,[16] trimethaphan,[17] lidocaine,[18] sevoflurane,[19] desflurane,[20] and protein kinase Mzeta,[21] among others.

From the above list, I chose the publication "Intracranial and Hemodynamic Changes after Succinylcholine Administration in Cats"[10] to serve as a Classic Paper Revisited—an article that addressed the concern that a commonly used muscle relaxant could cause ischemic damage from decreased cerebral perfusion pressure when given to a patient with low intracranial compliance, or even irreparable damage from

brainstem herniation through the foramen magnum consequent to a large, sudden increase in ICP.

The backstory on our succinylcholine investigation is that we were in the laboratory to determine whether we could measure ICP in cats *via* cisterna magna puncture with a double-lumen 18-gauge needle in preparation for testing the effect of nifidepine-induced hypotension on normal and elevated ICP. We were pleased to find that our double-lumen technique gave a breath-to-breath sensitive measure of ICP through one lumen with that sensitivity maintained while increasing ICP through the other lumen. We were about to inject a final test dose of nifedipine when pancuronium-induced paralysis appeared to be wearing off. We decided to give an injection of succinylcholine to buy the small amount of time needed give one last dose of nifedipine. To our surprise, the ICP tracing spiked immediately upon injection of succinylcholine (fig. 2). After establishing this effect of succinylcholine with repeated injections, we decided to delay the nifedipine study[11] and design a protocol for testing the effect of succinylcholine on ICP.[10]

Subsequent to our finding in cats, Lanier *et al.*[22,23] found convincing evidence that succinylcholine induces sufficient muscle afferent activity to generate immediate electroencephalographic arousal accompanied by rapidly elevated cerebral blood flow and increased ICP in dogs. To date, seven investigations have found that succinylcholine increases ICP in patients,[24–30] suggesting that our observations in cats warranted clinical concern. Two of those investigations also found that succinylcholine-induced increases in ICP can be ameliorated by previous administration of alternative muscle relaxants.[29,30]

Although reports relating succinylcholine administration to brain herniation have not been published, absence of evidence is not evidence of absence,[31] especially when dealing with rare and life-threatening events.[32] Brain herniation aside, empirical evidence supporting the physiologic basis for succinylcholine-induced cerebral ischemia has recently been published in a thoughtfully designed and analyzed retrospective study entitled "Succinylcholine Is Associated with Increased Mortality When Used for Rapid Sequence Intubation of Severely Brain Injured Patients in the Emergency Department."[33]

Competing Interests

The author declares no competing interests.

Correspondence

Address correspondence to Dr. Cottrell: State University of New York, Downstate Medical Center, Department of Anesthesiology – Box 6, 450 Clarkson Avenue, Brooklyn, New York 11203. James.Cottrell@downstate.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

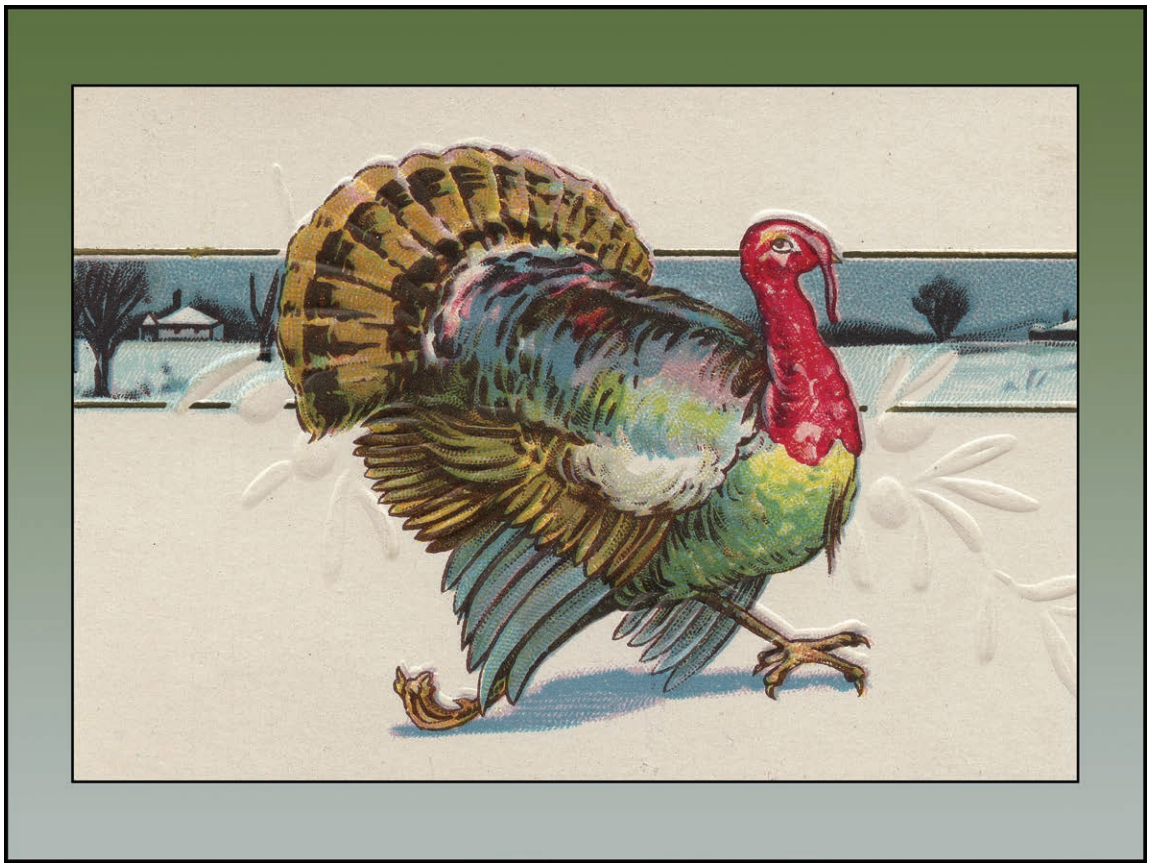
References

1. Cottrell JE, Siker ES: Preoperative intermittent positive pressure breathing therapy in patients with chronic obstructive lung disease: Effect on postoperative pulmonary complications. Anesth Analg 1973; 52:258–62
2. Cottrell JE, Wolfson B, Siker ES: Changes in airway resistance following droperidol, hydroxyzine, and diazepam in normal volunteers. Anesth Analg 1976; 55:18–21
3. Cottrell JE, Robustelli A, Post K, Turndorf H: Furosemide- and mannitol-induced changes in intracranial pressure and serum osmolality and electrolytes. ANESTHESIOLOGY 1977; 47:28–30
4. Cottrell JE, Marlin AE: Furosemide and human head injury. J Trauma 1981; 21:805–6
5. Cottrell JE, Patel K, Turndorf H, Ransohoff J: Intracranial pressure changes induced by sodium nitroprusside in patients with intracranial mass lesions. J Neurosurg 1978; 48:329–31
6. Cottrell JE, Casthely P, Brodie JD, Patel K, Klein A, Turndorf H: Prevention of nitroprusside-induced cyanide toxicity with hydroxocobalamin. N Engl J Med 1978; 298:809–11
7. Hartung J, Cottrell JE: Nitrous oxide reduces thiopental-induced prolongation of survival in hypoxic and anoxic mice. Anesth Analg 1987; 66:47–52
8. Cottrell JE, Gupta B, Rappaport H, Turndorf H, Ransohoff J, Flamm ES: Intracranial pressure during nitroglycerin-induced hypotension. J Neurosurg 1980; 53:309–11
9. Estilo AE, Cottrell JE: Hemodynamic and catecholamine changes after administration of naloxone. Anesth Analg 1982; 61:349–53
10. Cottrell JE, Hartung J, Giffin JP, Shwiry B: Intracranial and hemodynamic changes after succinylcholine administration in cats. Anesth Analg 1983; 62:1006–9
11. Griffin JP, Cottrell JE, Hartung J, Shwiry B: Intracranial pressure during nifedipine-induced hypotension. Anesth Analg 1983; 62:1078–80
12. Giffin JP, Cottrell JE, Shwiry B, Hartung J, Epstein J, Lim K: Intracranial pressure, mean arterial pressure, and heart rate following midazolam or thiopental in humans with brain tumors. ANESTHESIOLOGY 1984; 60:491–4
13. Bendo AA, Kass IS, Cottrell JE: Anesthetic protection against anoxic damage in the rat hippocampal slice. Brain Res 1987; 403:136–41
14. Cottrell JE, Hartung J, Giffin JP, Shwiry B: Intracranial pressure during tetrodotoxin-induced hypotension. Anesth Analg 1984; 63:1005–8
15. Mazzoni P, Giffin JP, Cottrell JE, Hartung J, Capuano C, Epstein JM: Intracranial pressure during diltiazem-induced hypotension in anesthetized dogs. Anesth Analg 1985; 64:1001–4
16. Giffin JP, Litwak B, Cottrell JE, Hartung J, Capuano C: Intracranial pressure mean arterial pressure and heart rate after rapid paralysis with atracurium in cats. Can Anaesth Soc J 1985; 32:618–21
17. Karlin A, Hartung J, Cottrell JE: Rate of induction of hypotension with trimetaphan modifies the intracranial pressure response in cats. Br J Anaesth 1988; 60:161–6
18. Lei B, Popp S, Capuano-Waters C, Cottrell JE, Kass IS: Lidocaine attenuates apoptosis in the ischemic penumbra and reduces infarct size after transient focal cerebral ischemia in rats. Neuroscience 2004; 125:691–701
19. Liu J, Yang L, Lin D, Cottrell JE, Kass IS: Sevoflurane blocks the induction of long-term potentiation when present during, but not when present only before, the high-frequency stimulation. ANESTHESIOLOGY 2018; 128:555–63
20. Dimaculangan D, Bendo AA, Sims R, Cottrell JE, Kass IS: Desflurane improves the recovery of the evoked postsynaptic population spike from CA1 pyramidal cells after hypoxia in rat hippocampal slices. J Neurosurg Anesthesiol 2006; 18:78–82
21. Hsieh C, Tsokas P, Serrano P, Hernández AI, Tian D, Cottrell JE, Shouval HZ, Fenton AA, Sacktor TC: Persistent increased PKMζ in long-term and remote spatial memory. Neurobiol Learn Mem 2017; 138:135–44
22. Lanier WL, Milde JH, Michenfelder JD: Cerebral stimulation following succinylcholine in dogs. ANESTHESIOLOGY 1986; 64:551–9

23. Lanier WL, Iaizzo PA, Milde JH: Cerebral function and muscle afferent activity following intravenous succinylcholine in dogs anesthetized with halothane: The effects of pretreatment with a defasciculating dose of pancuronium. Anesthesiology 1989; 71:87–95
24. Halldin M, Wahlin A: Effect of succinylcholine on the intraspinal fluid pressure. Acta Anaesthesiol Scand 1959; 3:155–61
25. Sondergard W: Intracranial pressure during general anaesthesia. Dan Med Bul 1961;8:18–25
26. Lewelt W, Moszynski K, Kozniewska H: Effects of depolarizing, nondepolarizing muscle relaxants and intubation on the ventricular fluid pressure. In: Beks JwF, Bosch DA, Brock M, eds. Intracranial Pressure III. Berlin, Springer-Verlag, 1976, pp 215–8
27. Moszyński K: Dynamic changes in cerebrospinal fluid pressure during neurosurgical operations. Acta Neurochir (Wien) 1976; 34:295–6
28. Marsh ML, Dunlop BJ, Shapiro HM, Gagnon RL, Rockoff MA: Succinylcholine-intracranial pressure effects in neurosurgical patients. Anes Analg 1980; 59:550–1
29. Minton MD, Grosslight K, Stirt JA, Bedford RF: Increases in intracranial pressure from succinylcholine: Prevention by prior nondepolarizing blockade. Anesthesiology 1986; 65:165–9
30. Stirt JA, Grosslight KR, Bedford RF, Vollmer D: "Defasciculation" with metocurine prevents succinylcholine-induced increases in intracranial pressure. Anesthesiology 1987; 67:50–3
31. Hartung J, Cottrell JE, Giffin JP: Absence of evidence is not evidence of absence. Anesthesiology 1983; 58:298–300
32. Hartung J, Cottrell JE: Negative inferences about rare events require large samples. Anesthesiology 1993; 79:1155–6
33. Patanwala AE, Erstad BL, Roe DJ, Sakles JC: Succinylcholine is associated with increased mortality when used for rapid sequence intubation of severely brain injured patients in the emergency department. Pharmacotherapy 2016; 36:57–63

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Chloroforming a Hoosier Holiday Turkey



On Christmas day in 1930, *The Indianapolis Star* featured the culinary adventures of a bride-to-be from Richmond, Indiana. In attempting to dispatch her plucky-but-unplucked holiday turkey in a humane manner, the young woman had chloroformed the feisty fowl before defeathering and then refrigerating it overnight. As the *Star* recorded, when "she opened the refrigerator the next morning, the turkey had recovered from the chloroform and although weak from the plucking and cold" …was still alive. The naked bird was chloroformed again until "thoroughly dead" and roasted in the oven. Not surprisingly, the fowl tasted foul. Indeed, the "turkey had been so thoroughly chloroformed that neither hostess nor guests could partake of it." (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.