Opioids and Benzodiazepines Appear Paradoxically to Delay Inevitable Death After Ventilator Withdrawal

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INTRODUCTION

The following statement was published in 1941: "The use of narcotics in the terminal cancer is to be condemned if it can possibly be avoided… morphine usage is an unpleasant experience to the majority of subjects because of undesirable side effects." Although the focus of that article was addiction, it also listed respiratory depression (1). Stigmatization of morphine along with other opiates and opioids (collectively designated opioids) has a long history. In 1954, morphine and barbiturates further reduced ventilation in dyspneic, already hypoventilating patients during exacerbations of chronic obstructive pulmonary disease (COPD). Even though none of these patients then died, the authors presumed that opioids or sedatives would increase risk of premature death (2). This seemed logical, reinforcing a mind-set that continues to discourage many physicians from adequately palliating pain and/or dyspnea despite their ethical mandate to comfort (3).

However, is this presumption really true? In a recent retrospective review of 75 patients—most with a low Glasgow coma scale (GCS), the overall median being GCS-3—terminal ventilator-withdrawal with opioids (morphine and fentanyl) did not hasten death, whereas benzodiazepine sedatives (midazolam and lorazepam) even delayed death (4). By contrast, this report focuses on a fully conscious man with postpolio syndrome who underwent self-requested ventilator-withdrawal with inevitable death apparently delayed when morphine and/or midazolam relieved dyspnea. I later observed four other patients (three being fully conscious) with ventilatory failure (excluding patients with hypoxemic respiratory failure) who also had inevitable deaths apparently delayed. Together, there is a significant correlation between weaning parameters unsedated and survival time sedated.

Case Report 1

In 1991, as a retiring pulmonary/critical care physician turned medical ethicist, I encountered this 67-year-old man (identified as Patient 1). For 57 days, mechanical ventilation had averted death of ventilatory failure due to respiratory muscle weakness from clinically stable postpolio syndrome. Fully alert, mentally capable, and emotionally stable, he requested ventilator-withdrawal with adequate sedation to alleviate dyspnea, knowing he would then die.

Weaning parameter measurements (5–7) revealed severe lung function impairment, far worse than "threshold for weaning values" (6) (Patient 1, Table 1). During daily early morning attempts to measure weaning parameters, he had tolerated only one brief 30-second period off mechanical ventilation, developing severe respiratory distress at breathing frequency (f)=41/minute, forcing urgent rescue by mechanical ventilation. Without rescue, I later estimated that continued struggle to breathe at maximum ventilatory drive (designated *drive*) would produce respiratory neuromuscular fatigue (designated *fatigue*) and lead to apnea within a few minutes (5). Athletic exercise at levels >50%–60% of maximal capacity elicits anaerobic metabolism that is unsustainable, rapidly depleting nutrients and producing excess lactate (8,9). This probably applies to skeletal muscles involved in breathing, since maximum voluntary ventilation (MVV) in normal subjects is unsustainable beyond 1.5 minutes whereas less strenuous breathing at 50%–60% of MVV is sustainable (10).

Within two minutes before and during this inevitably fatal ventilator-withdrawal (disconnecting adapter from tracheostomy tube), we slowly and watchfully injected a total of 30 mg morphine sulfate and 15 mg midazolam intravenously, successfully titrating the dose to relieve apparent

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anxiety while preserving consciousness. I anticipated almost immediate death after disconnection, convinced that morphine and midazolam suppression of *drive* would hasten inevitable death from ventilatory failure (2). Instead, he breathed shallowly without struggle at *f*~28/minute, appearing comfortable and alert, and visually interactive with his adult daughter for 30 minutes before decreasing *f* coincided with the development of rapidly progressing coma. Bradypnea progressed to apnea at 45 minutes, with asystole and declared death following at 53 minutes. Recorded time to apnea with sedation at 45 minutes had greatly exceeded my estimation of time to apnea without sedation at within a few minutes (see preceding paragraph). Morphine and/or midazolam appeared to delay inevitable apnea and death.

In 1992, a colleague and I published our planning and the emotional distress we felt conducting this man's inevitably fatal ventilator-withdrawal, not yet acknowledging the significance of his surprising delay of death by morphine and/or midazolam (11). Over the more than 10 succeeding years as an ethicist, I learned of four other patients (Patients 2–5, Tables 1 and 2) with documented stable severe ventilatory failure who, undergoing terminal ventilator-withdrawal, also had inevitable deaths apparently delayed by opioids (morphine or fentanyl) and/or benzodiazepines (midazolam or lorazepam). I then finally concluded that the seeming delay of death of Patient 1 by morphine and/or midazolam (from more than 10 years earlier) had probably not been an aberration.

All Five Cases: Analysis of Variance

Of the five patients (including Patient 1), four were conscious and lucid when unsedated or lightly sedated. However, Patient 5 was unresponsive after suffering severe anoxic brain damage from cardiac arrest two months before. Although unresponsive to all other stimuli, he often exhibited grimacing with the appearance of respiratory distress and met criteria for ventilatory failure—rapid shallow breathing (Patient 5, Table 1). In these five patients, prior weaning parameter measurements (done unsedated) documented the lung function impairment of ventilatory failure, reaching *f* >38 breaths per minute in less than two minutes off mechanical ventilation (Table 1). All had tracheostomy tubes left in place after disconnection except for Patient 2, who underwent extubation (endotracheal tube size 7). Not only did diverse underlying diseases exist, but there was great variation in both level of diminished function (measured unsedated) and actual time of survival (sedated) after ventilator withdrawal. The multiplication product of two important weaning parameters, negative inspiratory force (NIF) and tidal volume/body weight (V_T/kg), correlated with later measured time of survival after ventilator withdrawal given opioids and benzodiazepines—correlation coefficient r=+0.927 ($p<0.005$) (Figure 1). Variation in lung function unsedated appeared to explain virtually all of the observed massive variance in survival time sedated. Patient 1, with the greatest impairment, had the shortest survival (53 minutes); whereas Patient 5, with the least impairment, had the longest survival (three days). Considering each patient separately, estimating outcomes without sedation, with weaning parameters serving as matched quasi-controls, opioids and/or benzodiazepines (dosing as listed in Table 2) appeared to remarkably delay all of these inevitable deaths (Figure 1).

Table 1 / WEANING PARAMETERS (UNSEDATED) VS. ACTUAL SEDATED TIMES TO DEATH AFTER VENTILATOR WITHDRAWAL

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Diagnosis	PPS	ALS	COPD, IDDM*	PPS	Atypical PVS
Sex	M	F	M	M	M
Age (years)	67	50	71	72	40
Weight (kg)	110	48	74	95	97
Weaning Parameters					
• unsedated:					
NIF	10	26	31	28	40
f	41	46	40	38	40
V_T	280	258	280	330	348
V_T/kg	2.48	5.27	3.68	3.37	4.35
f/V_T	146	178	143	115	112
To peak *f*	<$^1/_2$ min	<2 min	<2 min	<2 min	<2 min
• opioid-sedated: time to death	53 min	44 hr 35 min	27 hr 0 min	43 hr 40 min	72 hr 35 min

*insulin and intravenous fluids discontinued along with ventilator-withdrawal

Abbreviations: PPS=postpolio syndrome; ALS=amyotrophic lateral sclerosis; COPD=chronic obstructive pulmonary disease; IDDM=insulin-dependent diabetes mellitus; PVS=permanent vegetative state after cardiac arrest; M=male; F=female; NIF=negative inspiratory force in cm H_2O; *f*=frequency in breaths per minute (bpm); V_T=tidal volume in ml; V_T/kg=tidal volume in ml/kg body weight; f/V_T=frequency/tidal volume in bpm/L

Threshold for Weaning Values (6): NIF>20–30 cmH_2O; *f*<30–38/min; V_T>325–408 ml; V_T/kg>4–6 ml/kg; f/V_T<60–105 bpm/L

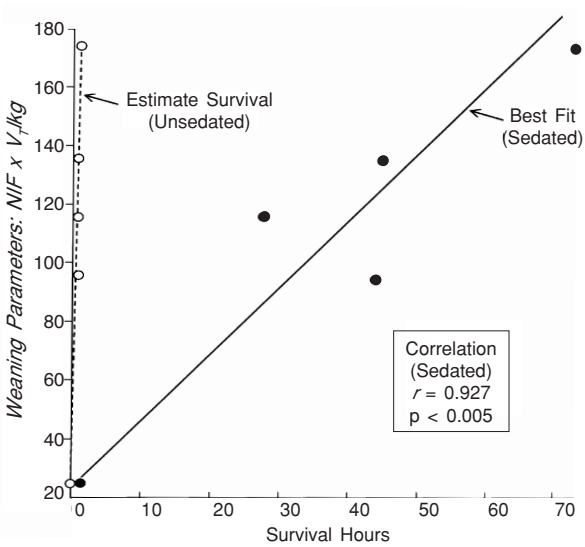
DISCUSSION

The already long-standing presumption of harm received support in 1954 when Wilson et al. reported five patients with exacerbations of COPD exhibiting dyspnea and peripheral edema, initially misdiagnosed as "heart failure" (2). Each patient had received ~11 mg of morphine sulfate (then considered appropriate for heart failure but contraindicated in ventilatory failure). Morphine drastically reduced mean ventilation from 7.5 L/min to 3.9 L/min, thereby increasing pre-existing hypercapnia and acidosis. However, by avoiding supplemental oxygen (then considered harmful) they unknowingly allowed (probably harmful) worsening of hypoxemia. After clearly demonstrating reduced ventilation, the authors presumed that morphine (like supplemental oxygen and barbiturates) would increase risk of premature death from uncompensated respiratory acidosis (2).

However, *control of breathing* is not the only issue in patients afflicted with ventilatory insufficiency. *Work of breathing* becomes problematic, with risk of ventilatory failure from *fatigue* (5,10). Ventilatory insufficiency/failure results from underlying disease sufficiently reducing respiratory neuromuscular capacity (designated *capacity*) and/or increasing load (designated *load*) by airflow obstruction and/or diminishing lung or chest wall compliance (5,6). In that setting, various intercurrent stresses (i.e., fever, anxiety, exercise, bronchoconstriction) may hasten *fatigue* by further increasing *drive*, effort, and *load*. Augmented *drive* by increasing ventilatory effort brings risk of *fatigue* manifest by rapid shallow breathing (5–7), fatal without rescue by mechanical ventilation.

Harm from *fatigue* is not a new concept. In 1954, when morphine and barbiturate suppression of *drive* was labeled harmful by Wilson et al. (2), others suggested that augmented (unsuppressed) *drive* by increasing *work of breathing* would bring *fatigue*, thereby endangering patients with severe COPD (12,13). Riley suggested that respiratory acidosis (from hypoventilation) would protect against *fatigue* (13). In 1963, Robin and O'Neill identified two groups of COPD patients, described as "fighters" and "nonfighters" (14). "Fighters", with fully augmented *drive*, had increased ventilatory effort (and dyspnea) struggling to avoid/minimize hypercapnia with respiratory acidosis, however, added *work of breathing* would

Figure 1 / SURVIVAL TIME UNTIL INEVITABLE DEATH AFTER VENTILATOR-WITHDRAWAL from patients having ventilatory failure (confirmed by failed weaning parameters) given opioids and benzodiazepines to relieve terminal dyspnea.



NIF=negative inspiratory force in cm H_2O; V_T/kg=tidal volume per kg body weight; closed circles=survival after ventilator-withdrawal given opioids and benzodiazepines to relieve dyspnea; open circles connected by dashed line=matched survival estimate if unsedated.

Table 2 / TIMES AND DOSES OF OPIOIDS AND BENZODIAZEPINES GIVEN BEFORE, DURING AND FOLLOWING VENTILATOR-WITHDRAWAL UNTIL DEATH

	Medication	1 hr pre-post	1–3 hr	3–6 hr	6–12 hr	12–24 hr	24–48 hr	48–72 hr
Patient 1	morphine (mg)	30						
	midazolam (mg)	15						
Patient 2	fentanyl (mcg)	150	400	450	750	1,800	850	
	lorazepam (mg)	8	8	9	18	9		
Patient 3	fentanyl (mcg)	150	300	450	800	hypotension, coma*		
	lorazepam (mg)	2				4		
Patient 4	morphine (mg)	4	18	15	30	64	120	
Patient 5	morphine (mg)	70	30	30	60	120	240	240
	lorazepam (mg)		2	2	6	3	1	6

All above medications given intravenously.

* This mentally lucid insulin-dependent diabetic requested simultaneous ventilator, insulin, and intravenous fluid withdrawals. These were followed at 12 hours by dehydration and hypotension (blood pressure=80/52 mmHg and pulse=130/minute) with deep coma attributed to impaired hepatic clearance of previously administered fentanyl (as with morphine)(20). He presumably would have survived longer if insulin and intravenous fluids not been withdrawn.

lead to *fatigue*. "Nonfighters" (somehow tolerant of hypercapnia) had less augmented *drive* and ventilatory effort, thereby protecting against *fatigue*. Support for this concept came when exogenous opioids improved exercise performance, decreasing dyspnea, and increasing distance walked in ambulatory but severely exercise-limited COPD patients (15), opioids apparently converting "fighters" into "nonfighters."

Severe dyspnea results from severe ventilatory insufficiency in whatever care setting. In the setting of palliative care, patients dying of cardiac, pulmonary, and/or neuromuscular disease suffer from dyspnea, as do many cancer patients (even without lung involvement), apparently due to respiratory muscle weakness (16). Without the prospect of cure or remission, mechanical ventilation is inappropriate and usually not desired, so patient comfort would ethically override concern about longevity through "double effect" (3). By contrast, in the intensive care unit (ICU), patients undergoing weaning with a better prospect for survival can realistically anticipate viable independence from mechanical ventilation. With fear of premature death (or failed weaning), opioids and benzodiazepines are not traditionally recommended during weaning (6,17).

However, the aforementioned contrast of medical goals and ethics between these clinical care settings exists despite a shared, perhaps erroneous, presumption of premature death (2). Care in both settings must confront the same physiology of ventilatory insufficiency in which *control of breathing* and *work of breathing* issues interact. Presumption that *drive* suppression causes premature death is unidimensional, not considering *work of breathing*. Also, hypercapnia is now known to be well tolerated, if gradual, allowing renal compensation of respiratory acidosis with hypoxemia avoided by supplemental oxygen (18,19). Principles of exercise physiology suggest that measures that would decrease *work of breathing* should protect against *fatigue* (5,8–10), otherwise further reducing *capacity* and thus causing a more likely dangerous fulminant hypercapnia (5). The principle of clinical equipoise, recognizing and balancing opposing forces (3), should ethically justify the conduct of careful clinical trials (as during weaning in the ICU) to seek scientific proof. Meanwhile, until scientific proof confirms or refutes this presumption, palliative care physicians might consider as credible an alternative logic, that palliating dyspnea by carefully providing opioids and/or benzodiazepines should reduce *work of breathing* thereby protecting against premature death from *fatigue*.

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