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Where is The Evidence? The Problem with Ventilation Research

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I dedicate this column to the late Dr. Andrew (Andy) Shennan, the founder of the perinatal program at Women's College Hospital (now at Sunnybrook Health Sciences Centre). To my teacher, my mentor and the man I owe my career as it is to, thank you. You have earned your place where there are no hospitals and no NICUs, where all the babies do is laugh and giggle and sleep.

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This is not surprising given the highly varied practices out in the clinical world. Even the most carefully designed study cannot control what happens at the bedside when investigators are "out of sight, out of mind." How are patients suctioned? Are manual breaths given, and with what pressures? How are babies manually ventilated, and with what devices and pressures? What monitoring is used, and how accurate is it? What ventilators are used? Even third-generation microprocessor-controlled ventilators have subtle (and sometimes not so subtle) differences in function and accuracy (1,2). Other clinical interventions, such as blood transfusions, may also impact outcomes.

Before enrolling in a study involving ventilation, what happens to a baby in the delivery and resuscitation rooms has far-reaching effects on outcomes, ranging from pulmonary to neurological. Similarly, how a patent ductus arteriosis is managed and treated (if at all), the presence of reflux (if indeed it can be detected), and antenatal factors all may sully the findings of an investigation.

A well-designed study can factor out confounding variables if known, but as the number of variables involved increases, so does the complexity of accounting for them. As a result, recruiting for large investigations is challenging and takes a lot of time. Additionally, studies involving ventilation cannot be quickly blinded, if at all.

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For example, studies on high-frequency oscillatory ventilation (HFO) are all over the map; some have shown benefits, some have not, and some have found a negative effect. Here, equipment differences come into play, as all HFO studies out of the U.S. have been done using the Sensormedics® oscillator. 3rd generation ventilators that offer HFO mode are currently unavailable to U.S. clinicians. This machine cannot be compared to newer ones; it is not apples to apples. It is apples to carports. Then, the infamous "HiFi" study from the 1980s almost stopped HFO in its tracks (3). Babies in the HFO group had significantly more severe intraventricular haemorrhages and periventricular leukomalacia than those in the conventional arm. The study did not use the "open lung" approach to ventilation, now universally recognised as being essential to the success of *any* form of ventilation, whether HFO, conventional, or even non-invasive. We at least learned that from this otherwise flawed work.

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The difficulty conducting and interpreting ventilation research notwithstanding, the question that crosses my mind when reading them is often, "What did they expect would happen?" Parameters used may differ from those typical in my practice, be they targeted volumes, $PaCO_2$ and SpO_2 targets, or pressures used and/or accepted. The marked differences in pulmonary development between gestational ages make a one-size-fits-all approach dubious when ventilating premature infants.

Following are a few examples of, in my opinion, poor study designs from personal experience.

A study examining higher CPAP pressures vs. NIPPV used these NIPPV parameters: rate of 30 with an inspiratory time of 0.5 seconds. Humans do not breathe with a 1:1 I: E ratio. Additionally, babies had to be supine (generally a position not preferred by most babies) and use non-invasive nasal prongs, again an interface many babies do not tolerate, as well as nasal masks.

A study of aerosolised surfactant limited CPAP pressures to a maximum of 7 cmH_2O, a pressure that will fail to recruit the lungs of many babies. Trying to deliver aerosolised surfactant to lungs that are not recruited will not meet with great success.

There is another factor involved in any research, that being equipoise. Many years ago, the unit I work in was invited to participate in a large trial involving high-frequency jet ventilation (HFJV). We were generally excited to participate, but upon examining the entry criteria, we concluded that we would have already started HFJV before those criteria were met; we did not have equipoise and thus had to decline participation.

While there are many studies involving HFJV, further study is stymied by the fact that, for the most part, clinicians who routinely use HFJV (and thus likely do so well) are unlikely to be involved because, to them, there is nothing to prove -- there is no equipoise.

This begs the question: Are studies *always* required to establish the efficacy of practice? The question of evidence to back up common practice within my workplace often comes up, particularly from trainees. Many of these trainees hail from countries with few allied health professions, particularly respiratory therapists. Outcome statistics for our unit are available going back decades, and they are consistently world-class, particularly regarding our low incidence of chronic lung disease. The chances of consistently excellent outcomes year over year are unlikely the result of chance. One might say we **are** the evidence.

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Finally, respiratory therapists are largely excluded from research on ventilation. There are notable exceptions, but there are also roadblocks in the way of our participation. In Canada, for instance, respiratory therapy is not a degree program. Those who do not have at least an undergraduate degree are rarely sought out for advice on study design and are even more rarely listed as contributing authors. Outside North America, respiratory therapists are generally unknown, degree-holding or otherwise. Other obstacles include shift work, bedside duties, scarcity of funding, and a lack of protected time for clinical research participation. We are often called upon to do "the dirty work," but this is after the fact.

It is unfortunate for all concerned, not the least of our patients, for the nature of our specialisation makes us a logical go-to for advice on ventilation and the intricacies of various equipment. I urge those contemplating researching mechanical ventilation to seek us out. You may be surprised at what we can teach you.

References:

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