On-Demand Nitric Oxide for Ventilator-Based Nitric Oxide Inhalation: A Risk-Reduction Perspective

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BACKGROUND

Inhaled nitric oxide (NO) for the treatment of Persistent Pulmonary Hypertension of the Newborn has been delivered by diluting the contents from high-pressure gas cylinders. The AIT Therapeutics system in development uses plasma arc technology to generate a controlled concentration of nitric oxide gas over a wide range of gas flows. The system is being designed to provide reservoir-free, real-time NO generation from a room air gas source and will operate in the same fashion as current cylinder-based nitric oxide (NO) delivery systems for use with mechanical ventilators.

Nitric oxide gas cylinders are typically supplied at a concentration of 400 ppm or 800 ppm (balance nitrogen) in high pressure aluminium cylinders with the following specifications: diameter 18.4 cm, height 83.6 cm (internal volume of 15.7 litres) and mass of 20 kg. When filled to 2000 psi, the volume of contained gas per cylinder is approximately 2239 litres at STP. The cylinders, usually two per delivery device, are located on the side or back of the delivery device cart, and the delivery device itself is situated in an intensive care unit patient room that is shared with other equipment and monitors, making access to the cylinders challenging. The size, mass, contents, and location of NO cylinders during patient use introduces many potential physical injury risks to the health care workers responsible for supplying the NO delivery devices with a nitric oxide gas source.

Nitric oxide gas is supplied as a hypoxic mixture with nitrogen and dilutes the ventilator gas flow by up to 10% (with 80 ppm NO set delivered concentration and 800 ppm NO source). When exposed to oxygen, NO quickly converts to nitrogen dioxide, which is toxic to tissues at low concentrations, with a short term exposure limit of 5 ppm[1]. To minimize NO_2 exposure to the patient, any stagnant NO source exposed to oxygen for more than a few minutes must be flushed from the system. NO_2 exposure poses risks to both patients and health care workers, and an undetected change in delivered FiO_2 associated with NO delivery exposes the patient to additional risks. By comparison, on-demand nitric oxide generation delivers nitric oxide in the set concentration with room air as the carrier gas, which prevents hypoxic gas delivery and decreases the effects on ventilator-set FiO_2. There are no cylinders used in the process. These characteristics are projected to have a significant impact on the risk profile for both patient and health care worker.

METHODS

A risk analysis was conducted, using commonly available metrics[2], by individuals familiar with NO delivery systems and their use in an intensive care environment. The analysis was limited to situations involving the most notable difference between on-demand NO generation and NO cylinders.

Table 1: Severity Ranking Table

Rank	Effect	Criteria
1	Negligible	Little or no potential of injury
2	Marginal	Some potential of injury
3	Serious	Injury requiring medical intervention
4	Critical	Critical injury
5	Catastrophic	Death

Note: Only whole numbers may be used. If the numerical value falls between two numbers, select the higher number.

Table 2: Probability Table

Rank	Occurrence	Criteria
1	Incredible	Implausible that the Hazard can occur
2	Improbable	Hazard is not likely to occur at all
3	Remote	Slight possibility that Hazard may occur
4	Occasional	Hazard may occur one or more times
5	Frequent	Hazard is likely to occur often

Note: Only whole numbers may be used. If the numerical value falls between two numbers, select the higher number.

Table 3: Hazard Classification Ranking Table Method

Risk Priority Number (RPN)	Rank	Risk Description	Acceptance Criteria
RPN < 10	MINOR	Broadly Acceptable (BA) Region	Acceptable without review
10 < RPN ≤ 25	MODERATE	As Low As Reasonably Practicable (ALARP) Region	Written and reviewed risk decision required.
RPN > 25	MAJOR	Intolerable (I) Region	Unacceptable

RESULTS

Comparing cylinder based NO delivery systems and the AIT on-demand NO generator based system, the risk analysis demonstrated 17 areas where the Risk Priority Number decrease from a moderate ranking to a minor (essentially non-existent) ranking. There were 3 areas where a moderate ranking remained in place, although in each case the probability and severity scores were decreased.

Table 4: Risk Analysis Comparing Cylinder Based Delivery to On-Demand NO Generation Based System

			Cylinder-Based System				On-Demand NO Generation Based System		
Potential Failure Modes	Potential Effect(s) of Failure	Potential Cause / Mechanism of Failure	Probability	Severity	Risk Priority Number	Effect on Risk of On-Demand NO generation replacing cylinder	Probability	Severity	Risk Priority Number
High NO_2 exposure, Patient	Airway damage	Inadequate purge during setup	3	3	9	Disappear	1	1	1
		Inadequate purge prior to initiation following delay	4	3	12	Disappear	1	1	1
		Inadequate purge with manual resuscitator use	4	3	12	Disappear	1	1	1
		Inadequate purge post manual resuscitator use	4	3	12	Disappear	1	1	1
		Inadequate purge with cylinder change	3	3	9	Disappear	1	1	1
Decrease FiO_2 delivered to patient	Desaturation	Unrecognized need to increase fio_2 when NO started	3	3	9	Decrease	2	2	4
		Unrecognized need to increase Fio_2 when NO increased	3	3	9	Decrease	2	2	4
Increase FiO_2 delivered to patient	Increased blood flow to lungs	Unrecognized need to decrease fio_2 when NO decreased	3	4	12	Decrease	2	3	6
Exposure to NO_2, Health Care Worker	Airway damage	Cylinder leak when cylinder opened	4	2	8	Disappear	1	1	1
		Damage to regulator-del device line	3	2	6	Disappear	1	1	1
		Damage to regulator	3	2	6	Disappear	1	1	1
		Damage to cylinder stem -- vent cylinder contents into room	2	3	6	Disappear	1	1	1
Physical Injury to Health Care Worker	Back Injury	Cylinder manipulation during in-use change injures back	4	3	12	Disappear	1	1	1
		Cylinder manipulation during backup stock change injures back	4	3	12	Disappear	1	1	1
	Foot Injury	Drop cylinder on foot -- in-use change	4	3	12	Disappear	1	1	1
		Drop cylinder on foot --backup stock change	4	3	12	Disappear	1	1	1
	Arm strain	Cylinder manipulation causes arm strain -- in-use	4	3	12	Disappear	1	1	1
		Cylinder manipulation causes arm strain -- backup stock change	4	3	12	Disappear	1	1	1
	Eye injury	Damage to regulator causing rapid release of gas	2	3	6	Disappear	1	1	1
	Frostbite injury	Damage to regulator causing rapid release of gas	2	3	6	Disappear	1	1	1

RESULTS

Figure 1: Patient Risk Priority Number (RPN) Differences Between On-Demand NO Generation Based System and Cylinder Based System. First row in each diagram: Failure mode, Second row: Effect of failure, Third row: RPN for On-Demand NO Generation based system (Green Clouds) and Cylinder based system (Yellow Hexagons).

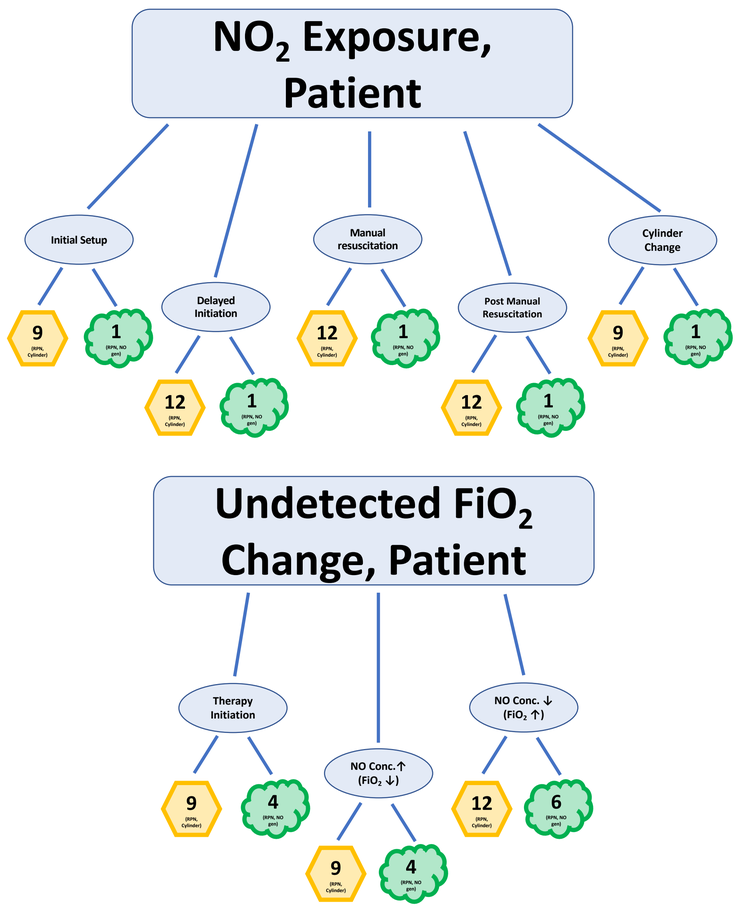
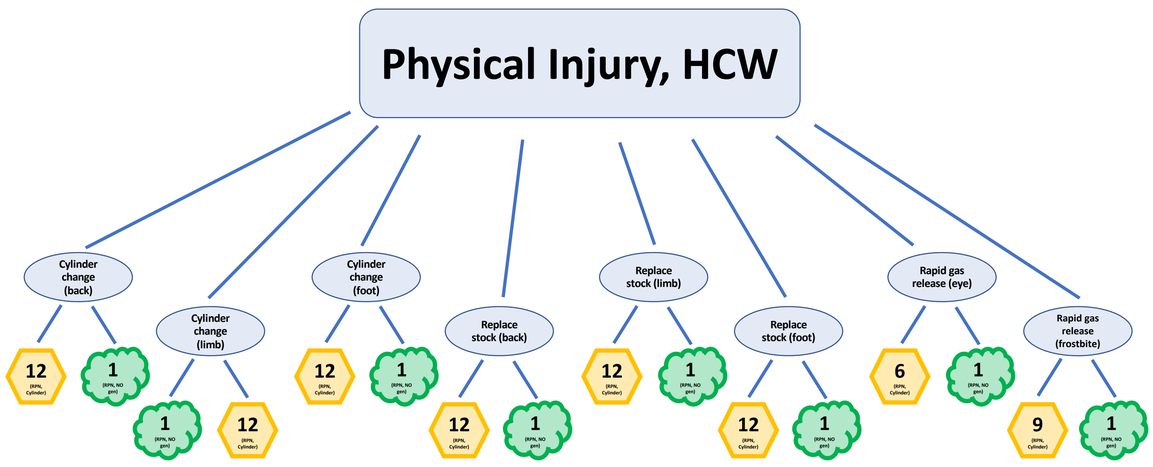


Figure 2: Health Care Worker (HCW) Risk Priority Number (RPN) Differences Between On-Demand NO Generation Based System and Cylinder Based System. First row in each diagram: Failure mode, Second row: Effect of failure, Third row: RPN for On-Demand NO Generation based system (Green Clouds) and Cylinder based system (Yellow Hexagons).



CONCLUSIONS

- **On-demand generation of nitric oxide for the treatment of ventilated patients may substantially improve the risk profile for both patient and health care worker by:**
  - **Decreasing the risk of NO_2 exposure to the patient from moderate to acceptable**
  - **Decreasing the risk of undetected FiO_2 changes to the patient**
  - **Decreasing the risk of NO_2 exposure to the health care worker from moderate to acceptable**
  - **Decreasing the risk of physical injury to the health care worker from moderate to acceptable**

REFERENCES

1: *National Institute for Occupational Safety and Health,* https://www.cdc.gov/niosh/pel88/10102-44.html

2: Three level risk assessment based on ISO 14971: 2007 Annex D