Farmacologische beïnvloeding van beademing

J.G. van der Hoeven
Intensive Care Radboudumc, Nijmegen
Wat gaan we bespreken?

- Inhalatie therapie - algemene aspecten
- Inhalatie van vaatverwijders bij pulmonale hypertensie en ARDS
- Onderdrukken van een excessieve ademdrive
- Stimuleren van een afgenomen ademdrive
Inhalatie therapie bij bronchusobstructie

Lokale concentratie

Hogere lokale concentratie met minder systemische toxiciteit

Verdeling over de long
Concentratie op plaats van bestemming

Effect

Dosis

Variability in lung deposition

The intersubject variability of lung deposition ranged from 9 to 62% CV in the scintigraphic studies whatever the device used (nebulizers or metered-dose inhalers) [18–20, 22, 23, 29, 35, 37]. Dugernier et al. [18] reported a wide variability in the right to left lung-deposition ratio (3.33 (0.7–5.38) in VCV and 1.39 (0.91–2.05) in PSV). The penetration index also varied among subjects with a CV of approximately 50% [18, 37]. Pharmacokinetics studies observed from 14 to 85% CV of antibiotic concentrations in tracheobronchial secretions [31, 32, 34, 36] and from 60 to 91% CV in ELF [14, 15, 27, 28].

Deposition in the ventilator circuit, artificial airways and nebulizer retention

Fifteen studies measured drug retention within nebulizers and the circuit [18, 22, 23, 29, 35, 37, 39, 41–46, 48, 49]. No data on aerosol loss with MDIs have been described. Drug doses retained in the nebulizer reservoir and the T-piece were approximately 50% ND with jet nebulizers, 15% to 30% ND with ultrasonic nebulizers and 3% to 10% ND with vibrating-mesh nebulizers. While drugs deposited in the artificial airways and/or the trachea and the main bronchi varied from 1 to 27% ND, drugs trapped in the ventilator circuit varied from 10% to 44% ND. Drug loss during expiration was 7 to 22% ND (Fig. 3).
Bij beademende patiënten gaat heel veel verloren.

<table>
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<tr>
<th>Study</th>
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% toegediende dosering

Neb retentie  Beademing circ  ET tube  Expiratie verlies
Efficiëntie bij beademing i.h.a omhoog...

- **Beademing parameter**
  - Lage flow (40 l/min)
  - Lange inspiratietijd
  - PEEP
- **Beademingscircuit**
  - Grotere luchtweg Ø
  - Zonder HME/bevochtiger

- **Patiënt**
  - Schone luchtwegen

- **Medicament**
  - Partikel Ø 2 - 5 μm
  - Off-label gebruik: let op bijwerkingen

- **Aerosol apparaat**
  - Vibrating mesh voor waterige oplossingen
  - MDI met spacer
  - Positie 15 cm voor Y-stuk
Vrouw - 32 jaar - HIV - shock
Vaatverwijders bij PHT en ARDS

Prostacycline en Stikstofoxide (NO) verwijden bloedvaten rondom open alveoli
Nitric oxide in the pulmonary circulation. For example, S-nitrosothiols may also "store" nitric oxide within the pulmonary vasculature associated with ventilated lung units (dilatation of these vessels would improve ventilation–perfusion matching (V/Q) across the alveolar-capillary membrane. Selective pulmonary vasoconstriction. In contrast, the adenosine-induced oxygenation owing to antagonism of hypoxic pulmonary vasoconstriction was within reach of an inhaled gas diffusing across the alveolar-capillary membrane. Such specific effects are the vantage of inhaled nitric oxide. Decreased responsiveness is of rapid hemoglobin-mediated inactivation of nitric oxide for the pulmonary circulation is the result of endogenous nitric oxide, influence the effect of endotoxin both in patients with ARDS and in animal models. Conversely, the positive effect of inhaled nitric oxide may sufficiently improve oxygenation only in the subgroups with the greatest degree of hypoxemia (those susceptible or not susceptible to high-altitude pulmonary edema, inhaled nitric oxide decreased the pulmonary arterial pressure of susceptible subgroups that react reversibly with nitric oxide to form S-nitrosothiols; these compounds are vasoactive and help in oxygen species (derived from activated leukocytes or ischemia–reperfusion injury) to form reactive nitrogen species such as peroxynitrite. In the vascular space, dissolved nitric oxide is scavenged by oxyhemoglobin (forming methemoglobin and nitrate) and to a lesser extent, plasma proteins (e.g., forming nitrosothiols, which are stable intravascular sources of nitric oxide activity).

Depending on the milieu of the lung parenchyma, nitric oxide may react with reactive oxygen species (derived from activated leukocytes or ischemia–reperfusion injury) to form reactive nitrogen species such as peroxynitrite. In the vascular space, dissolved nitric oxide is scavenged by oxyhemoglobin (forming methemoglobin and nitrate) and to a lesser extent, plasma proteins (e.g., forming nitrosothiols, which are stable intravascular sources of nitric oxide activity).
Mogelijke nadelen NO

Geen effect op mortaliteit

Meer acuut nierfalen
Vaatverwijdders bij PHT en ARDS

In vergelijking met NO verlaagt prostacycline sterker de MPAP en PVR en vergroot het hartminuutvolume

**Hoepel MM. J Am Coll Cardiol 2000;35:176-182**
Instillation, atomization, pressurized inhaler, a simple jet nebulizer, or a vibrating mesh nebulizer. These delivery systems are chosen for a number of reasons: medication or equipment availability, deposition site, speed of delivery, and onset of action for a particular medication. The confidence in achieving the desired effect is based on a wide range of evidence, and these administration techniques produce varying response curves based on how the medication is absorbed through the pulmonary circulation. The best location for the deposition of inhaled or intrapulmonary agents is not yet understood, although desired effect and available route for delivery play a large role.

Medication uptake into pulmonary circulation is attributed to molecular composition, including hydrophobicity, ionic charge, and tissue retention. Furthermore, the delivery systems themselves produce varying degrees of deposition within the lung tree, from lavaging lung tissue with intratracheal instillation to the small respirable mist of a pressurized inhaler delivering aerosolized particles to lung parenchyma.

The authors build upon their previous work, which compared vibrating mesh and simple jet nebulization of milrinone. During that study, vibration mesh nebulization delivered a greater volume to the distal airways as opposed to the simple jet nebulizer, which deposited more in the larger airways and validated what was known already about these 2 types of nebulizers. This could imply that simple jet nebulization targets a more appropriate location on the pulmonary arterial tree for iMil, which perhaps readily targets precapillary arterioles. The results in this present study suggest that the deposition of iMil in this model may not be best at the alveolar level given the improved response with simple jet nebulization. Furthermore, appropriate inhaled drug administration may be more device specific than originally thought.

Most aerosolized particles follow the anatomic straight line to the right- left lower lobes as recently illustrated in a study of pulmonary aerosol transport and deposition within a digital fluid dynamic model of 17-generation human pulmonary airways. Moreover, the predominant location for deposition occurs within the upper airways, but particles that "escape" this initial deposit location continue to follow the airway flow downstream beyond the 17th generation of airways, with a percentage of particles ultimately reaching the alveoli. This study by Gavra et al. indicates that the simple jet nebulizer is optimal for iMil delivery under such controlled circumstances in the swine model. Although the simple jet may have produced a greater effect than the intratracheal instillation, atomization, or the vibrating mesh methods, it is not without limitations. Simple jet nebulization adds flow to the ventilator circuit that may affect ventilator synchrony during spontaneous assisted ventilation, raise peak airway pressures during volume-cycled ventilation, and affect the actual delivered fraction of inspired oxygen. Therefore, translating the use of simple jet nebulization into clinical practice may be difficult, especially in the setting of an acutely ill cardiac surgical patient. The vibrating mesh method, however, is an attractive alternative because it provides the

![Image](https://example.com/fig1.png)

**Fig 1.** Continuous aerosolized medication therapy using a vibrating mesh (VM) nebulizer during clinical use. (A) Syringe pump delivery of medication is provided to the nebulization chamber (red box) for aerosolization. (B) Aerosolized mist is delivered to the VM "T"-connector in preparation for intrapulmonary delivery through the airway circuit (end expiration). (C) The aerosolized mist has been delivered through the circuit for intrapulmonary administration (end inspiration). VM, vibrating mesh.
Milrinone of levosimendan inhalatie is ook een optie

- Milrinone
  - Enkele dosis: 50 μg/kg
  - Effect voor 30 min: -16%

- Levosimendan
  - Enkele dosis: 24 μg/kg
  - Effect voor 180 min: -21%

Pulmonale hypertensie

Kundra TS. J Cardiothor Vasc Anesth 2018;32:2123-2129
Onderdrukken excessieve ademdrive
Therapeutische maatregelen

• Behandel acidose en hypoxemie + koorts/pijn
• Voldoende sedatie en pijnstilling
• Extracorporele CO₂ verwijdering
• Gebruik van (partiële) neuromusculaire blokkade

Verlaag de ademdrive
Partiële neuromusculaire blokkade met esmeron

A

1. pre-titration

2. titration

\[ V_1 \text{ [ml/kg]} \]

\[ p = 0.0007 \quad p < 0.0001 \]

B

\[ \text{delta } P_1 \text{ [cmH}_2\text{O]} \]

\[ p = 0.003 \quad p < 0.0001 \]

Doorduin J. Am J Respir Crit Care Med 2017;195:1033-1042
Stimuleren van een afgenomen ademdrive

Patiënt na langdurige beademing
Oorzaken van afgenomen ademdrive

- Disfunctioneren ademcentrum of van zenuwoverdracht
- Benzodiazepinen en opiaten
- Metabole alkalose
- Idiopatisch
CO₂ response test

Baseline = na 5 min PSV 7: RR, P₀₁, AMV en bloedgas
CO₂ response test = Idem na toevoegen dode ruimte op moment dat ETCO₂ is toegenomen met 10 mmHg: RR, P₀₁, AMV en bloedgas

Hypercapnic drive response = Δ P₀₁ / Δ PaCO₂
Hypercapnic ventilatory response = Δ VE / Δ PaCO₂
CO₂ response test en ontwenning

- **Langdurig ontwennen**
- **Snel ontwennen**

N = 102

P < 0.001

Raurich JM. Respir Care 2011;56:1130-1136
Persistente hypercapnie

Kracht

Dode ruimte

Ademprikkel
Mogelijke behandeling

Voor deze specifieke indicatie nog geen data beschikbaar
Conclusies

• Doseer inhalatie medicamenten op aantoonbaar effect (b.v. afname luchtwegweerstand)

• Epoprostenol, milrinone and levosimendan lijken geschikte middelen om PHT en/of hypoxemie bij ARDS te verbeteren

• Partiële neuromusculaire blokkade is een interessante optie voor een excessieve ademdrive als andere behandelingen falen

• Een belangrijke oorzaak voor hypercapnie na een langdurige IC opname is afgenomen gevoeligheid van het ademcentrum