TARGETED AIRWAY HYPERRESPONSIVENESS ASSESSMENT IN MICE

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ABSTRACT

INTRODUCTION: We previously reported that nebulizer settings affect airway hyperresponsiveness (AHR) assessment in mice (1). In this study, we evaluated the impact of modified ventilator settings during methacholine (Mch) nebulisation on respiratory mechanics in mice.

METHODS: Anaesthetized and tracheotomized A/J mice were connected to a SCIREQ *flexiVent*™ system for mechanical ventilation and respiratory mechanics measurements using low frequency broadband forced oscillation (LFOT: 1 - 20.5 Hz Quick Prime-3). Constant Phase Model (CPM) parameters (RN: airway resistance; G: tissue damping; H: tissue elastance) were recorded at baseline and after increasing concentrations of aerosolized Mch, generated via an in-line computer-controlled Aeroneb™ nebulizer (4-6 µm) synchronized with inspiration. Bronchoconstriction to inhaled Mch was studied under either a standard (150 breaths/min, 10 mL/min) or slow, deep ventilation pattern (SDV: 50 breaths/min, 30 mL/min) imposed during the nebulization period. The effect of modified ventilator settings was assessed under standard or reduced nebulization time (10 or 2.5s, respectively) and/or nebulization rate (50 or 25%, respectively).

RESULTS: Greater maximal responses to Mch were recorded when ventilation was switched from a standard to SDV pattern during nebulisation. Standard nebulizer settings (10s, 50% nebulization rate) resulted in statistically significant differences in SDV vs normal ventilation for all CPM parameters at either the highest (12.5 mg/mL; RN: 1.39 ± 0.11 vs 2.27 ± 0.37 cmH2O.s/mL, G: 13.19 ± 1.36 vs 24.20 ± 2.60 cmH2O/mL; H: 39.89 ± 4.60 vs 80.28 ± 14.74 cmH2O/mL), or second highest (6.25 mg/mL; G: 11.34 ± 0.97 vs 18.24 ± 3.10 cmH2O/mL; H: 30.59 ± 1.52 vs 63.17 ± 15.70 cmH2O/mL) Mch concentration studied. Under reduced nebulization time (2.5s, 50% nebulization rate), the SDV-induced increase in maximal response was restricted to the tissue component. Finally when both nebulization time and rate were reduced (i.e. 2.5s, 25%, respectively), the addition of a SDV mode produced an enhanced Mch response limited to airways resistance (RN: 1.30 ± 0.11 vs 2.02 ± 0.37 cmH2O.s/mL).

CONCLUSIONS: Results suggest that region specific aerosol deposition and targeted AHR assessment can be obtained in mice with appropriately designed nebulizer and ventilator protocols.

(1) Robichaud, A, LG Gold, P Lefebvre, TF Schuessler. Nebulization pattern affects airway hyperresponsiveness in mice. Am J Respir Crit Care Med 2009; 179: A2438.

BACKGROUND

- Airway hyperresponsiveness (AHR) assessment in mice using aerosolized methacholine is a procedure routinely performed in a large number of laboratories.
- Subtle protocol variations can be found in the literature.
- Modifications are often reported without systematic assessment of their impact.
- Varied nebulizer settings were previously reported to affect AHR in mice (1).

OBJECTIVE

- Evaluate the effect of varying ventilator settings during aerosol delivery on methacholine responsiveness in mice.

METHODS

EQUIPMENT

- SCIREQ *flexiVent*, first generation
- In-line computer-controlled Aeroneb nebulizer (standard particle size; 4-6 µm)

PROTOCOL

- Naive male A/J mice
- Anaesthetized, tracheostomized, mechanically ventilated
- Increasing methacholine aerosol challenges
- Ventilation during challenge:
  - Regular: 150 breaths/min, 10 mL/kg, 3 cmH_2O PEEP
  - Slow deep: 50 breaths/min, 30 mL/kg, 3 cmH_2O PEEP

MEASUREMENTS

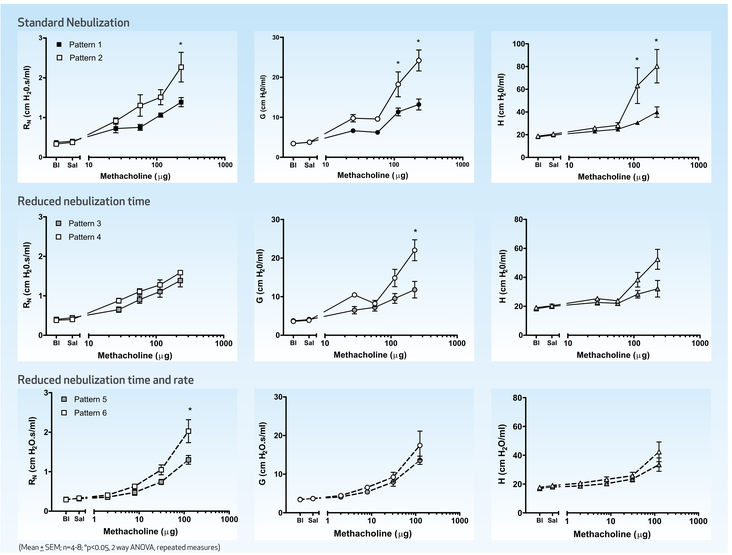
- Broadband low frequency forced oscillation (1 - 20.5 Hz; Quick Prime-3).
- Constant Phase Model Parameters: R_N (airway resistance), G (tissue damping), H (tissue elastance).

NEBULIZATION PATTERNS

Pattern	Nebulization Time (s)	Nebulization Rate (%)	Ventilation during Nebulization
1	10	50	Regular
2	10	50	Slow, deep
3	2.5	50	Regular
4	2.5	50	Slow, deep
5	2.5	25	Regular
6	2.5	25	Slow, deep

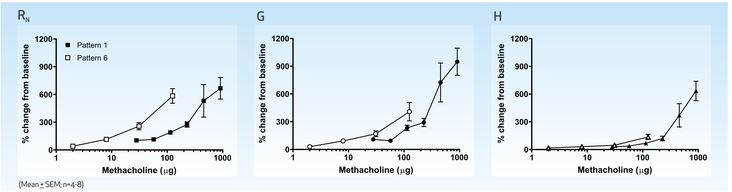
RESULTS

MODIFIED VENTILATOR SETTINGS



(Mean ± SEM; n=4-8; *p<0.05, 2 way ANOVA, repeated measures)

COMPARATIVE MEASUREMENTS



(Mean ± SEM; n=4-8)

SUMMARY

- Adding a slow deep ventilation profile during nebulization resulted in greater maximal responses to methacholine.
- Under reduced nebulization time, the SDV-induced increase was restricted to the tissue component.
- When both nebulization time and rate were reduced, the addition of a SDV mode produced an enhanced Mch response limited to airway resistance.
- In comparison to a standard nebulization pattern, Pattern 6 produced similar changes in R_N yet at much lower doses of Mch.

CONCLUSIONS

- Improved sensitivity and targeted delivery of small amounts of aerosolized substances can be obtained by adequately controlling nebulizer and ventilator settings.
- Results indicate that region-specific assessment of methacholine responsiveness in mice is possible.
- Targeted AHR assessment could prove to be the key in studying respiratory disease conditions or their underlying mechanisms.

References

(1) Robichaud, A, LG Gold, P Lefebvre, TF Schuessler. Nebulization pattern affects airway hyperresponsiveness in mice. Am J Respir Crit Care Med 2009; 179: A2438.

Disclosure

AR, LGG & TFS are employed by SCIREQ Scientific Respiratory Equipment Inc., A commercial entity involved in a subject area related to the content of this presentation. TFS also owns stock.

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