Airway Mucus in Invasively Ventilated Critically Ill Patients: Comparing Rheology to a Clinical Classification System

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Introduction

Patients who are critically ill and receiving invasive mechanical ventilation are at increased risk for accumulation of secretions in the lower airways.[1,2] Such accumulation of airway mucus can induce atelectasis and contribute to ventilator-associated pneumonia.[2] Preventive airway care interventions, including humidification, endotracheal suctioning, and pharmacologic interventions, are therefore frequently initiated during invasive ventilation.[3-5] However, evidence for the efficacy of these interventions is scarce, and the absence of guidelines enhances variation in indications for their use.[6-8]

Currently, the choice and timing of interventions are mainly driven by clinical assessment of mucus viscosity based on a mucus classification scale or preference by the treating physician.[9-11] Alternatively, airway mucus properties can be measured through rheology, a more objective parameter, which characterizes its biophysical properties (eg, viscoelasticity).[12] Previously, studies reported that rheology of airway secretions may help classify chronic muco-obstructive respiratory diseases and serve as a marker of disease progression.[12,13] In this study, we tested the hypothesis that airway mucus viscoelastic properties, as measured by rheology in patients who are critically ill and receiving invasive mechanical ventilation, correlates with its clinical mucus classification score.

Key words: Sputum; invasive ventilation; critical care; rheology; mucus; respiratory therapy

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Methods

Study Design

We performed a single-center observational pilot study in adults who were critically ill and invasively ventilated. The medical review board deemed this study exempt (W21_326 no. 21.361). Informed consent for the use of patient data were obtained post hoc via an opt-out system.

Subjects

All patients who were admitted to the adult ICU in the Amsterdam University Medical Centers, location Academic Medical Center the Netherlands from September to December 2021 were screened for inclusion. Patients with an expected duration of invasive ventilation for $>$ 2 days were eligible for participation. There were no exclusion criteria. In all the subjects, passive humidification of the ventilator circuit by using a heat-and-moisture exchanger was used.

Collected Data

We collected baseline and demographic variables, including sex, age, respiratory comorbidities, and APACHE

II. Mucus was collected in regular mucus containers via a closed or an open suctioning system during regular airway care by the ICU nurse at fixed time points. Time points were (1) directly after intubation, (2) after 2 d of invasive ventilation, and (3) at extubation. Mucus samples were stored at 4°C in the ICU shortly after collection and analyzed within 6 h after collection.

Clinical Assessment of Mucus Properties

Airway mucus samples were classified by the attending bedside nurses by using a previously described clinical classification system.[11] This classification system categorizes mucus into 3 categories: (1) watery, defined as sputum that can be suctioned like water (after suctioning, no secretions remain attached to the inner surface of the suction catheter); (2) moderate, sputum of moderate viscosity (after suctioning, some secretions remain attached to the inner surface of the suction catheter); and (3) tenacious, thick sputum (after suctioning, most secretions are still attached to the inner surface of the suction catheter and cannot be easily removed by suctioning water through the catheter).[11]

Rheology

The biophysical properties of mucus are involved in the mucociliary and cough clearance of secretions from the airways and can be measured by rheology. These rheologic properties consist of both the viscoelastic and flow-point properties of mucus. Under low shear stress, mucus is characterized by reversible deformation (energy storage), then the mucus elasticity (G') is greater than the viscosity (G"). With increasing shear stress, mucins will align along the stress direction[12] and both elasticity and viscosity will start to decline (energy dissipation). At the flow point (ie, critical strain and stress), viscosity overshoots elasticity and definite disruption of the mucus structure occurs. Further in-depth information about rheology and its nomenclature can also be found in the review by Lai et al.[14]

Rheologic properties were determined by using a dynamic rotational rheometer (Rheomuco; Rheonova, Saint Martin d'Hères, France). We performed a strain-sweep test in oscillatory mode, at 37°C, by using rough plates to avoid slippage of the samples. The linear viscoelastic regions for elasticity and viscosity were calculated at a 5% strain. Flow-point properties are displayed via critical strain and stress. Data quality was assessed by 2 independent investigators (RSNL and RAB) who were blinded for the mucus classification scores of the samples. As per discussion with Rheonova based on unpublished findings, samples with tan $\Delta > 0.70$, which thus displays Newtonian fluid–like behavior in the lower strain regions, were considered water contaminated and were excluded. When possible, rheologic measurements were carried out in duplicate.

Primary Outcome

The primary study outcome is the correlation between the mucus classification score and the viscoelastic properties of mucus (primarily the viscoelasticity). Secondary study outcomes include the viscoelastic properties at a 5% strain rate (elasticity and viscosity) and the flow-point properties (critical strain and stress) of mucus.

Statistical Analysis

For the calculation of the correlation between the continuous variable viscoelasticity and the ordinal classification score of mucus, a Kendall tau correlation coefficient was used.[15] The distribution of values classified via the clinical classification scale and the relationship between elasticity and viscosity is graphically visualized in a scatterplot. Only the mean values of the rheologic measurements performed in duplicate were used. Continuous distribution of the data was assessed by visual inspection of histograms.

Normally distributed variables are expressed by their mean and SD or, when not normally distributed, as medians with interquartile ranges. Categorical variables are expressed as frequencies and percentages. When appropriate, statistical uncertainty is expressed by the 95% confidence levels. *P* values of .05 were used for statistical significance. To assess the reliability of rheologic measurements performed, we used the Spearman rank test as well as 2-way mixed intraclass correlation coefficients for absolute agreement between 2 duplicate measures for the log-transformed values,[12] assuming normality. All analyses were performed with R v.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 194 eligible patients were admitted to our ICU. Of these patients, 41 subjects were included in the study, from whom 52 mucus samples were collected. Six samples were excluded because they were water contaminated or yielded too little volume. The mean ± SD age was 60.6 ± 11.2 y 61% were men, and comorbidity was present in the majority of the subjects (n = 30 [73%]), including 4 subjects with COPD and one with a history of asthma. Overall, the severity of illness was relatively low, with a median (interquartile range) APACHE II score of 13 (10–18).

Correlation Between Clinical Mucus Assessment and Mucus Rheology

Most of the samples (85%) were classified as moderately viscous by health-care professionals, whereas only 2 samples (4%) were classified as "watery," and 3 samples (6%) were

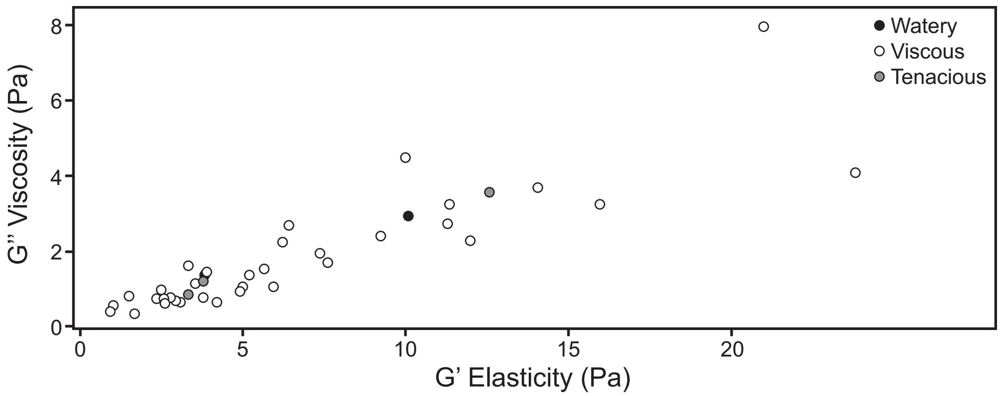

Fig. 1. The distribution of mucus classification values and elasticity (G') and viscosity (G'') properties.

classified as tenacious. There was no correlation between the clinical mucus classification and the viscoelastic sputum properties, with viscoelasticity, Kendall's tau-b (τ_b) = -0.00072, $P = .95$. Similarly, there was no correlation for the clinical mucus classification and elasticity ($\tau_b = -0.00067$, $P = .95$) or viscosity ($\tau_b = -0.00509$, $P = .90$). The distribution of mucus classification values and elasticity and viscosity properties are displayed in Figure 1.

Viscoelastic and Flow-Point Properties of Mucus in Subjects Who Were Invasively Ventilated

The mean ± SD outcomes for the viscoelastic and flow-point properties are presented in Table 1. The reliability of duplicate measures, assessed by the Spearman rank tests and intraclass correlation coefficients, showed a good correlation between duplicates ($n = 32$) (Table 1).

Discussion

In this pilot study, we found no correlation between the clinical mucus classification and the biophysical properties of mucus as measured via rheology in the subjects who were critically ill and receiving invasive ventilation. In this study, we reported on the viscoelasticity (or complex shear modulus) at low strain rates, which reflects the mean mechanical impedance being the vectoral sum of the elasticity of the mucus (or storage modulus, the potential of mucus to recover to its original shape after applied strain) and viscosity (or loss modulus, the tendency of mucus to flow) at that same strain rate.

The viscoelasticity of airway mucus reported in this study among the subjects who were critically ill and invasively ventilated was high, occasionally even exceeding those values previously reported for mucus from subjects with spontaneously breathing CF and subjects with COPD.[12] Importantly, duplicate measurements had good absolute agreement. The

Table 1. Rheologic Properties of Airway Mucus in Subjects Who Were Invasively Ventilated

	Raw Values, mean ± SD	Correlation Between Duplicates and ICC			
		Spearman Rank Tests (rho, P)		ICC (95% CI)	ICC Interpretation*
		r	P		
Viscoelasticity (G*)	7.21 ± 5.63 Pa	0.85	< .001	0.781 (0.575 < ICC < 0.893)	Fair-good
Elasticity (G')	6.93 ± 5.40 Pa	0.82	< .001	0.784 (0.578 < ICC < 0.895)	Fair-good
Viscosity (G'')	1.87 ± 1.63 Pa	0.83	< .001	0.784 (0.578 < ICC < 0.895)	Fair-good
Damping factor (tan Δ)	0.28 ± 0.09	0.77	< .001	0.78 (0.581 < ICC < 0.891)	Fair-good
Critical strain (γ_c)	20.08 ± 22.91	0.91	< .001	0.8 (0.616 < ICC < 0.902)	Fair-good
Critical stress (σ_c)	35.79 ± 41.76 Pa	0.88	< .001	0.791 (0.583 < ICC < 0.9)	Fair-good
Elastic force (viscoelasticity.σ_c)	338.64 ± 563.57 Pa^2	0.88	< .001	0.607 (0.313 < ICC < 0.796)	Poor-good

Spearman rank tests display the correlation (stability) between duplicate measures performed.
*ICC interpretation: < 0.50 poor, 0.50–0.75 fair, 0.75–0.90 good, 0.90–100 excellent.
ICC = intraclass correlation
viscoelasticity = the mean mechanical impedance being the vectoral sum of the elasticity and viscosity of the mucus
elasticity = the storage modulus, which reflects the potential of mucus to recover to its original shape after applied strain
viscosity = the loss modulus, which reflects the tendency of mucus to flow
Damping factor = the ratio of loss to storage modulus, which reflects the energy dissipation of mucus
Critical strain and critical stress = the amount of strain or stress applied after which the viscosity of the mucus overshoots elasticity due to critical breakdown of the mucus structure (crossover point)
Elastic force = multiplication of the viscoelasticity of mucus and corresponding amount stress applied at the crossover point

lack of correlation between the mucus classification scale and the viscoelastic properties of mucus may be explained as the distinction among the 3 categories is dominantly used for extreme values. This may lead the health-care professionals to classify mucus generally as moderately viscous. Importantly, the variance of viscoelasticity of the samples within this most common classification (moderately viscous) was very high, with values that ranged from 1 to 8 Pa for elasticity and 1 to 20 Pa for viscosity, which further underscores the lack of significant correlation.

To date, initiation of airway care interventions is based primarily on the clinical, macroscopic observations of viscous-like mucus.[9,10] By comparing such observations with more objective methods such as rheology measurements, our findings seriously question the use of such subjective classification scores in clinical decision-making. Currently, there are no readily available evidence-based alternatives for the classification of airway secretions to use in the clinic. In the past, the use of rheology has been hindered due to the need for specialized equipment, training, and a lack of knowledge hampering data interpretation.

Given the readily available samples of airway secretions in the ICU, as well as the development of more user-friendly rapid rheometers, rheology might be explored as a future alternative for the classification scores in the clinic. However, much more research is needed to address whether rheology outcomes are associated with the use of mucoactive medications, course of disease, or patient (sub) categories. Thereafter, and only if rheology proves to be helpful in predicting the success of interventions or outcomes in research settings, thorough clinical validation, implementation, and feasibility studies should be performed before larger prospective studies may be conducted to address the potential value of rheology as a bedside tool. This pilot study was performed to provide input for future measurements in randomized controlled trials that focus on airway care interventions in patients who are invasively ventilated.

This pilot study has several limitations. First, there may have been selection bias because patients were missed for sample collection and the included subjects had a relatively low APACHE II scores.[8] Second, the numbers of subjects and samples were small, although in line with previous studies on airway mucus rheology.[13] As such, care should be taken not to over-interpret the results. In this pilot study, the clinical assessment of airway mucus by a clinical classification scale did not correlate with its biophysical properties as measured via rheology.

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