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Sensitivity and Specificity of Heat and Moisture Exchange Filters Sampling for HSV1 Detection in Mechanically Ventilated Patients with SARS-CoV-2 Infection

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Abstract

Background: Sensitivity and specificity of HSV1 detection by real real-time reverse transcriptase PCR in Heat and Moisture Exchange Filters (HMEF) was assessed in mechanically ventilated COVID- 19 patients. As previously shown for SARS-CoV2 detection, our data suggest that testing HSV1 in HMEF might obviate the need for a tracheal sample.

Keywords: Community pharmacist; Control of high blood pressure; Primary health care system; Screenings; Hypertensive patients; Services.

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Introduction

Herpes Simplex Virus 1 (HSV1) reactivation is frequent in mechanically ventilated critically ill patients and may cause bronchopneumonitis and the Acute Respiratory Distress Syndrome (ARDS) [1]. Its microbiological diagnosis is established by PCR anaysis of Lower Respiratory Tract (LRT) secretions samples, usually obtained by tracheal suctioning or Bronchoalveolar Lavage (BAL) fluid using PCR. Interestingly, SARS-CoV-2 lung infection is a well described infection leading to frequent ventilator-associated pneumonia and viral reactivations, including HSV1 [2,3]. Those viral reactivations may be promoted by the "immune-paralysis" of the critically ill [1], local or systemic lymphopenia, and the use of systemic corticosteroid therapy or other immunosuppressant drugs as initially recommended in patients with COVID-19-related ARDS [4,5].

Even though tracheal suctioning and BAL are routinely performed in the Intensive Care Unit (ICU), these procedures carry inherent risks for the patient such as alveolar DE recruitment and hypoxemia, and pose additional hazards to healthcare workers in the context of a viral pandemic with a high potential for airborne transmission. Therefore, the development of alternative techniques is desirable to mitigate those risks. Thus,

as we did for SARS-CoV2 [6], we explored the opportunity to detect HSV1 in Heat and Moisture Exchange Filters (HMEF), which are routinely inserted within the ventilator circuit of mechanically ventilated patients.

Methods

The ethic committee of the French intensive care society approved the study protocol (CE SRLF 23-055) prior to its initiation. Prior to data usage, oral consent was obtained from all included patients or their family members.

The primary study samples consisted of LRT secretions samples obtained by tracheal suctioning or BAL and concomitant samples of HMEF collected through a standardized procedure of HMEF rubbing [6] in consecutive, mechanically ventilated COVID-19 patients who had a HMEF (Humid-Vent™ Filter Compact, Teleflex® Medical Europe Ltd, Westmeath, Ireland [dead space of 38 mL]) inserted within their ventilator circuit. These samples were stored at -80°C in our microbiology laboratory and handled in accordance with current recommendations, and then were re-used for HSV1 PCR analysis in the present study.

After Nucleic Acid (NA) extraction on LRT secretions and HMEF-rubbed samples, HSV1 was assessed by PCR, using "RealStar® alpha Herpesvirus PCR Kit 1.0" (Altona) and QuantStudio™5 thermocycler (Applied Biosystems). The PCR cutoff was set at a Cycle Threshold (Ct) of 40. A PCR Cellular Control (CC) (*RNAse P* gene) was performed to ascertain the presence of biological material in both the LRT and HMEF samples.

Sensitivity, specificity, Positive and Negative Predictive Values (PPV, NPV), and False Positive and Negative Rates (FPR, FNR) of HSV1 PCR performed on HMEF samples to predict the positivity of PCR analysis of the LRT samples were calculated. Data analysis was performed using GraphPad Prism 7.00 (GraphPad Software, USA) and continuous variables are expressed as mean ± SEM. A two-sided $p<0.05$ was chosen to indicate statistical significance.

Results

Out of the initial 130 pairs of LRT and HMEF samples employed in the primary investigation [6], 13 pairs were deemed unusable due to insufficient material for NA extraction. This resulted in 117 viable pairs of samples procured from 25 patients. Samples from the LRT exhibiting negative results for HSV1 and negative or missing results for CC (n=17) were considered invalid and were subsequently excluded.

This left (rest) 100 LRT/HMEF pairs from 24 patients for analysis. Fifteen (62.5%) patients exhibited at least one positive result for HSV1 in the LRT sample over the study period, and in total, 49 (49%) of the LRT samples were positive for HSV1.

Table 1 shows the confusion matrix and the performance of PCR analysis of HMEF samples to predict the positivity of LRT samples.

Among the 49 pairs of samples with detection of HSV1 in LRT, 34 (69.4%, sensitivity) were also positive in HMEF and 15 (30.6%, FNR) were negative in HMEF (Table 1). The mean Ct in LRT for these 15 false negative cases was 36.5±0.47. Among the 51 pairs with no detection of HSV1 in LRT, two (3.9%, FPR) tested positive for HSV1 in HMEF with Ct values of 37.6 and 34.3, and 49 tested negative. For all these 49 negative and concordant pairs regarding HSV1 detection, the HMEF tested positive for CC detection.

In the positive and concordant pairs (n=34) the Ct for CC detection was significantly lower in LRT (18.41±0.66) compared to HMEF (26.03±0.83) ($p<0.0001$). Notably, the Ct for CC detection in HMEF of the discordant pairs (LRT+/HMEF-) was 25.27±1.34, not different from that of the concordant pairs. In the discordant pairs, the viral load in LRT samples was relatively low with a Ct for HSV1 detection of 36.53±0.47 and a Ct ratio HSV1/CC of 1.89±0.07. In the concordant pairs, the Ct for HSV1 detection was significantly lower in LRT (26.63±0.78) compared to HMEF samples (30.88±0.71) ($p<0.0001$).

Table 1: Performance of the PCR test for HSV1 detection in Heat and Moisture Exchange Filters (HMEF).

		PCR test on HMEF		
		Negative	Positive	
PCR test on LRT secretions	**Negative**	49 [a]	2	51
	Positive	15 [b]	34	49
		64	36	100

Se	Sp	PPV	NPV	FPR	FNR
69.4%	96.1%	94.6%	76.6%	3.9%	30.6%

HMEF: Heat and Moisture Exchange Filter; LRT: Lower Respiratory Tract; FNR: False Negative Rate; FPR: False Positive Rate; NPV: Negative Predictive Value; PPV: Positive Predictive Value; Se: Sensitivity; Sp: Specificity.

[a]: All the 49 HMEF had positive cellular control detection, ascertaining that the negative test for HSV1 was not due to the absence of biological material.

[b]: Cellular control was missing for 4 HMEF and was negative for 1 HMEF

Discussion

In addition to confirming that HSV1 reactivation is a frequent encounter in mechanically ventilated ICU patients [1,3], our small cohort study yielded noteworthy results. Firstly, over 70% of patients experiencing respiratory HSV1 reactivation could be identified through simply sampling the HMEF, a less invasive procedure, which poses lower contamination risks for caregivers compared to sampling of the LRT. Secondly, the relatively high FNR of 30.6% was hard to ascribe to insufficient amounts of biological material in HMEF samples, as indicated by similar Ct for CC detection in HMEF from discordant (positive in LRT but negative in HMEF for HSV1) and concordant (positive for HSV1 in both LRT and HMEF) pairs. Notably, in the discordant pairs, the viral load in LRT samples was relatively low, with a mean Ct for HSV1 detection of 36.53. For these discordant pairs, this suggests that the discordance may be due to an insufficient sensitivity of the test to low viral loads rather than insufficient biological material in HMEF samples.

Our study was a small-sized single-center pilot study which needs to be replicated with a large cohort. However, it provides additional support for the potential identification of respiratory pathogens through the analysis of HMEF in mechanically ventilated patients. Specifically, technical improvements may be necessary in HMEF preparation and sampling methods. Regarding HSV1 detection, enhancing the sensitivity of the PCR test may be worth considering.

Declarations

Author contributions: TK, FL, CG, and TB conceived and designed the experiments. FL performed the PCR experiments. TK, GM, M-AN, AM, MS and TB managed the biological sampling.

TK, FL, LBr, LBa and TB carried out the statistical analysis and TK, FL and TB drafted and edited the manuscript. All authors read and approved the final manuscript.

Ethics statement: As the study did not change routine practice nor imposed new treatments, procedures, or additional biological samplings, it was considered not to involve the human person, in the meaning of the French law, but only health data. Hence, submission of the protocol to the national competent authorities and registration in a trial registry were not required. This second study protocol was approved by the ethic committee of the French intensive care society (#CE SRLF 23-055) before the beginning. Written and oral information was given to patients and their family. Oral consent for the utilization of the data collected was obtained from all included patients or their family at the first study.

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Availability of data and material: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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