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ORIGINAL ARTICLE

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Humidity during high-frequency oscillatory ventilation compared to intermittent positive pressure ventilation in extremely preterm neonates: An in vitro and in vivo observational study

Claude Danan MD[1,2] | Manon Tauzin MD[1] | Camille Jung MD, PhD[3,4] | Xavier Durrmeyer MD, PhD[1,2,3,5,6] | Laurence Caeymaex MD, PhD[1,5] | Charles Treussart MD[1] | Fabrice Decobert MD[1,2] | Bruno Louis MD[2]

[1]Neonatal Intensive Care Unit, Centre Hospitalier Intercommunal de Creteil, Creteil, France

[2]EMR 7000, IMRB , CNRS, Universite Paris Est Creteil, Creteil, France

[3]Clinical Research Center, Centre Hospitalier Intercommunal de Creteil, Creteil, France

[4]Pediatrics, Centre Hospitalier Intercommunal de Creteil, Creteil, France

[5]Faculte de Sante, Universite Paris Est Creteil, Creteil, France

[6]GRC CARMAS, IMRB, Universite Paris Est Creteil, Creteil, France

Correspondence

Claude Danan, MD, Pédiatrie Néonatale, CHI Creteil, 40 Ave de Verdun, 94010 Creteil, France.

Email: claude.danan@chicreteil.fr

Abstract

Background: Inappropriate humidification of inspired gas during mechanical ventilation can impair lung development in extremely low birthweight (ELBW) infants. Humidification depends on multiple factors, such as the heater-humidifier device used, type of ventilation, and environmental factors. Few studies have examined inspired gas humidification in these infants, especially during high-frequency oscillatory ventilation (HFOV). Our objective was to compare humidity during HFOV and intermittent positive pressure ventilation (IPPV), in vitro and in vivo.

Methods: In vitro and in vivo studies used the same ventilator during both HFOV and IPPV. The bench study used a neonatal test lung and two heater-humidifiers with their specific circuits; the in vivo study prospectively included preterm infants born before 28 weeks of gestation.

Results: On bench testing, mean absolute (AH) and relative (RH) humidity values were significantly lower during HFOV than IPPV (RH = 79.4 ± 8.1% vs. 89.0 ± 6.2%, $p < 0.001$). Regardless of the ventilatory mode, mean RH significantly differed between the two heater-humidifiers (89.6 ± 6.7% vs 78.7 ± 6.8%, $p = 0.003$). The in vivo study included 10 neonates (mean ± SD gestational age: 25.7 ± 0.9 weeks and birthweight: 624.4 ± 96.1 g). Mean RH during HFOV was significantly lower than during IPPV (74.6 ± 5.7% vs. 83.0 ± 6.7%, $p = 0.004$).

Conclusion: RH was significantly lower during HFOV than IPPV, both in vitro and in vivo. The type of heater-humidifier also influenced humidification. More systematic measurements of humidity of inspired gas, especially during HFOV, should be considered to optimize humidification and consequently lung protection in ELBW infants.

KEYWORDS

ELBW, HFOV, humidification

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1 | INTRODUCTION

In extremely low birthweight (ELBW) infants, pulmonary fluid clearance and transcapillary water transport are crucial for pulmonary development.[1] The balance between inflammation, water transport, and upper and deep airway humidification is critical and plays a role in surfactant production and continued lung development during the critical period when the preterm infant is dependent on mechanical ventilation.[2] A relatively small change (increase or decrease) in the temperature or humidity of the inspired gas may be sufficient to impair the preterm infant's pulmonary function.[3] Recommendations in this field come from adult studies, are uncertain,[4] and stipulate that humidification must be maintained between 33 and 44 mg/L of absolute humidity (AH) and 75%–100% of relative humidity (RH).[5] Medical devices to heat and humidify the airways have been optimized for conventional intermittent positive pressure ventilation (IPPV) and can meet these humidification recommendations. High-frequency oscillatory ventilation (HFOV) uses very different settings than IPPV, often with high flow rates and always with small tidal volumes (V_T).[6]

Even though Tarnow-Mordi et al.[7] first raised the problem of the fragility of preterm patients with inadequate humidification in 1989, very few studies have since addressed humidification in ELBW infants. Chikata et al.[8] and Nagaya et al.[9] reported that humidification during HFOV bench testing may be more problematic than during conventional ventilation. More recently, Ralphe and Dail[4] dedicated a review to humidification during tracheal and noninvasive ventilation for ELBW and insisted on the relation between bronchopulmonary dysplasia and unsuitable humidification. We think, however, that conclusions based only on bench-test studies must also be examined in light of clinical and laboratory data. One animal study has highlighted an interesting link between the variation of humidification and lung inflammatory responses.[10] Ralphe and collegues[4,7–10] expressed regret about the lack of studies on humidification during ventilation.

Humidification of the preterm patient's airways depends on multiple factors, such as the ventilator, circuits, heater-humidifier, ventilatory mode and settings, and environmental factors.[4] We chose to study two of these: the heater-humidifier and the ventilatory mode. Hence, our aims were, first, to bench test recent heater-humidifiers during IPPV and HFOV, and, second, to compare in vitro and in vivo humidification achieved in each mode. Our hypothesis was that the specific parameters of HFOV could result in less adequate humidification in this mode than during IPPV.

2 | MATERIALS AND METHODS

Our study comprised two phases: a bench-test study and a prospective observational clinical study.

2.1 | Phase 1 (*n* = 12): Bench-test study

The ventilator was the VN500 (Drager) in volume guarantee (VG) mode during both IPPV (IPPV-VG) and HFOV (HFOV-VG). The ventilatory settings were the parameters usually used in clinical settings for each mode and repeated at each set of experiments. During IPPV, we targeted a V_T of 4 ml with positive end-expiratory pressure set at 4 mbar, frequency at 50/min, and an inspiratory time of 0.3 s. During HFOV-VG, we targeted a V_T of 2 ml, with frequency set at 12 Hz (720/min), mean airway pressure at 12 mbar, and the inspiratory/expiratory time ratio at 1:1 (i.e., an inspiratory time of 0.042 s).

The test lung was located in a Giraffe® closed incubator (GE Healthcare) with heat set to 37°C (Figure 1). The compliance of the test lung was calibrated around 0.3 ml/mb ± 5%, to be close to the usual lung compliance of ELBW patients.[11]

To test the influence of heating devices on humidification, we conducted the experiments with two heater-humidifiers: the MR850® with a RT265® as the ventilator circuit, referred to hereafter as MR-A and the MR950® with the 950-N81® circuit (F&P), referred to as MR-B. The heater-humidifiers were in automatic mode without any settings to adjust. For the RT265 circuit, we used a 30-cm extension circuit without wireless heating inside the incubator to leave the temperature sensor outside the incubator. The RT 950-N81 circuit did not necessitate an extension and was directly connected to the Y-piece.

We used the procedure described below to conduct 12 experiments (6 with MR-A and 6 with MR-B). First, the ventilatory circuit was dried until RH < 2% was reached. Then, we started ventilation and humidification in the randomly selected ventilatory mode — HFOV-VG or IPPV-VG — for at least 1 h without recording. Humidity and temperature recording started after 1 h and lasted for 4 h: 2 h in the first ventilatory mode (IPPV-VG or HFOV-VG) and 2 h in the other mode. The first ventilatory mode was selected randomly, via sealed envelopes.

2.2 | Phase 2: In vivo study

This prospective observational study took place between January 2021 and January 2022 in the neonatal intensive care unit (NICU) of the Centre Hospitalier Intercommunal de Creteil. We included ELBW born ≤28 weeks of gestational age with a body weight of less than 1500 g at the time of the study and requiring mechanical ventilation. Patients were included in the analysis when a recording of humidity was possible in both IPPV and HFOV during their ventilatory support course. The choice of ventilatory mode and ventilatory settings were left to the clinician's expertise and were not modified due to the study. Parents were informed of the study and stated that they did not object. The institutional ethics committee approved the study on December 1, 2020. The number of subjects to include could not be

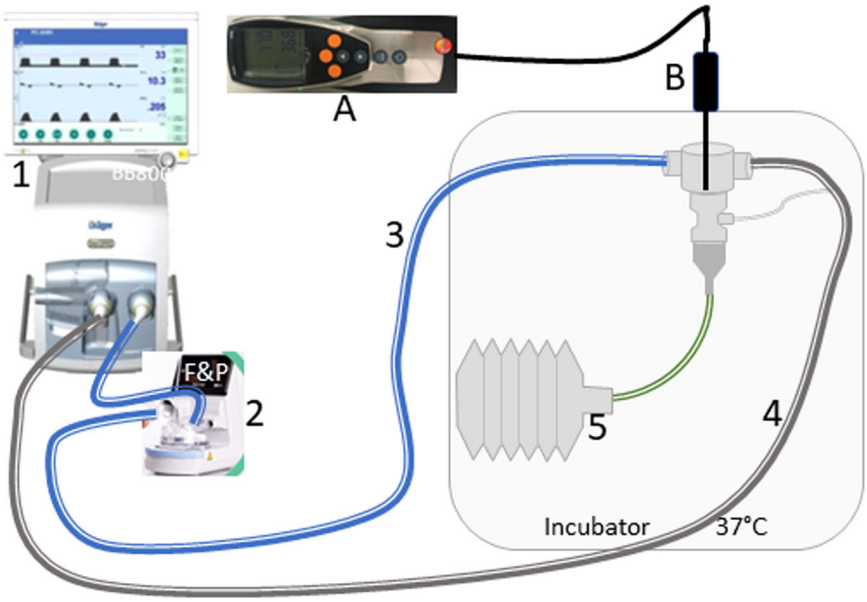

FIGURE 1 Description of testing setups for bench-test and in vivo study. Ventilation system: 1. VN500 Drager ventilator, 2. heater humidifier MR850 or MR950, 3. inspiratory line, 4. expiratory line, and 5. lung test for in vitro study and ventilated patient for in vivo study. Incubator temperature set at 37°C during in vitro study and automatically regulated on patient's temperature during in vivo study. Humidity measurements: A. hygrometer and B: temperature and humidity sensor. [Color figure can be viewed at wileyonlinelibrary.com]

predicted because the difference of inspired airway humidity between the two ventilatory modes has never been described. Thus, the study duration was set at one year.

The standard Y-piece was replaced by a sterilized Y-piece equipped with a hygrometer during nursing care to record the humidity and temperature (Figure 1). This recording lasted for 2 h for each patient and each ventilatory mode. The Y-piece with the hygrometer was removed the next time a nurse attended the baby. Ventilator settings, heater-humidifier device information (chamber inlet and outlet temperature and flow rate), ambient temperature, and barometric pressure were all collected during the 2-h recording. After a stabilization period, any intervention (such as opening the incubator or changing ventilatory settings) during the 2-h recording period was recorded. Only MR-B was used as a heater humidifier to adhere to the airway humidification protocol in the NICU.

2.3 | RH and temperature measures

For both in vitro and in vivo experiments, RH and temperature were recorded in the Y-piece just before the endotracheal tube (ETT) with a capacitive thermohygrometer and a sensor 4 mm in diameter (Testo Hygrometer 635-2® with sensor 2135®). The thermohygrometer was calibrated and measurement uncertainty was 1.51% for RH and 0.52% for temperature. The hygrometer was able to record data for a predetermined period of time (4 h for in -vitro- study and 2 h for in vivo study) at a predetermined frequency (every 1 min). The recordings were converted into two curves: RH (in %) and temperature (in °C) with PC-software (Testo Comfort Software x35 professional®). For analysis, we considered only the second hour of recording in each ventilatory mode. The first hour was considered a stabilization period. AH (in mg/L) was calculated with the following mathematical formula: $(287.7 \times RH \times Psat)/(T + 273)$[12] with the saturated vapor pressure of water (*P*sat) expressed as mmHg and temperature (T) as °C.

Beforehand, the introduction of the hygrometer into the Y-piece was tested to make sure that there was no pressure change.

2.4 | Statistical analysis

Data were described as means and their standard deviations. We compared relative and AH during IPPV versus HFOV during both the in vitro and in vivo experiments. We compared humidity during IPPV versus HFOV with two different heater-humidifiers (MR-A and MR-B) only during in vitro experiments. Paired Wilcoxon tests were used in the bench tests to compare HFOV versus IPPV as the comparisons were made at the same time with the same environmental conditions. Comparisons between MR-A and MR-B used Mann-Whitney tests. In the in vivo study, because the two modes were tested at two potentially separated periods, we used Mann–Whitney tests rather than paired tests. A $p \leq 0.05$ was considered significant.

3 | RESULTS

3.1 | Bench testing

RH (Figure 2) and AH were significantly lower during HFOV than during IPPV while temperature in the Y-piece was significantly higher during HFOV than IPPV (Table 1). Mean ± SD RH was significantly higher with MR-A than MR-B, regardless of the ventilatory mode (89.6 ± 6.7% vs. 78.7 ± 6.8%, respectively; $p = 0.003$) and in each ventilatory mode (Table 1, Figure 2).

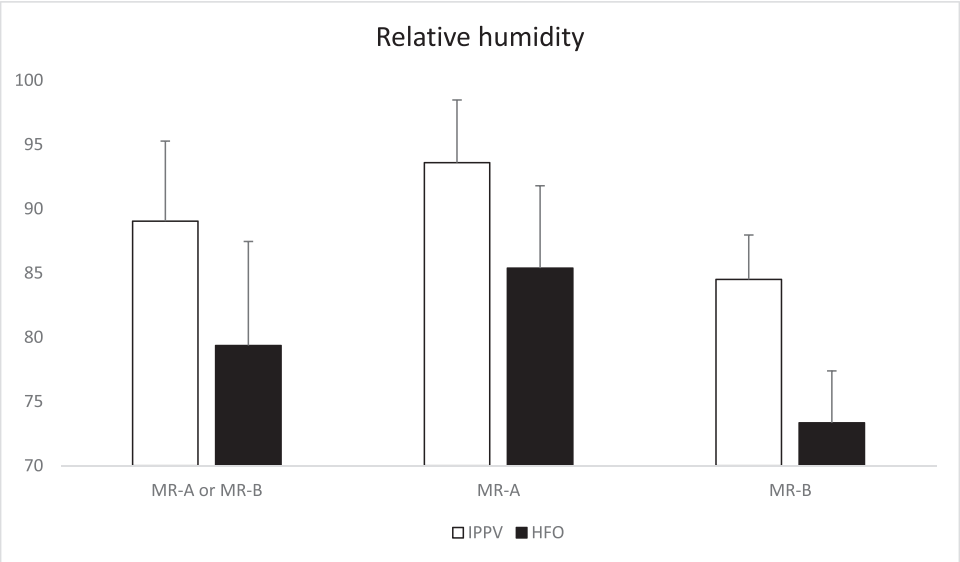

FIGURE 2 Relative humidity (in percentage in the *Y*-axis) was recorded during in vitro experiments comparing successively IPPV (white bars) and HFOV (black bars) with two different heater-humidifiers (MR-A and MR-B) and their specific circuits. HFOV, high-frequency oscillatory ventilation; IPPV, intermittent positive pressure ventilation.

3.2 | In vivo study

During the 1-year study, 10 patients received both IPPV and HFOV and were recorded in both ventilatory modes. Because six patients were recorded in only one ventilatory mode, they were excluded from the analysis. Patients included had a mean ± SD gestational age at birth of 25.7 ± 0.9 weeks and a mean ± SD birthweight of 624.4 ± 96.1 g. Twenty recordings were made (10 in each ventilatory mode) at a mean ± SD postnatal age of 8.8 ± 7.4 days for HFOV and 10.9 ± 8.7 days for IPPV. Patients' characteristics and ventilatory parameters at the time of recording are summarized in Table 2.

RH during HFOV was significantly lower than during IPPV (Table 2). Postnatal age, weight at the procedure, and environmental parameters were comparable during HFOV and IPPV, but the heater-humidifier inlet and outlet temperatures, flow rates, tidal volumes, and pressures differed significantly (Table 2).

4 | DISCUSSION

The two main objectives were to test the influence of the two ventilatory modes and simultaneously two different modern heater-humidifiers on humidification measured at the Y-piece. The two main results of this study were that humidity was lower during HFOV than during conventional ventilation and differed according to the heater-humidifier model. Results for the two ventilatory modes were consistent for the in vitro study, with strictly controlled ventilatory settings and ambient conditions, and the in vivo study, with its various ventilatory settings and ambient conditions. Several hypotheses may explain these results. The first and most intuitive explanation for this difference is that HFOV flow rates are much higher than IPPV flow rates.[13] At the same time, both the inlet and outlet chamber temperatures were found to be higher in HFOV than IPPV. This finding suggests that the heater-humidifier increases the heat of the plate to increase the energy delivered by the heater-humidifier, which should be proportional to the air volume delivered by the ventilator. However, the heater-humidifier regulation tends to stop the heater plate when the inlet chamber temperature is high.[13] In this situation, the water may be partially heated and the gas insufficiently humidified and heated. Nonetheless, the HFOV and IPPV chamber temperatures did not differ all that much clinically, although they were statistically different. This difference does not seem adequate to explain the temperature reduction of the heating plate.[13] A second explanation might be the frequency difference. For the same duct diameter, the thermal losses of the oscillatory flow increase with its frequency.[14] Thus, we can expect that this increasing loss will decrease temperature and AH. However, Nagaya et al.[15] showed that the temperature change in the ETT did not depend on the oscillatory frequency when the oscillatory volume was fixed; but, the temperature did depend on the oscillatory volume when the oscillatory frequency was fixed. It is also interesting to note the previous observation during IPPV that AH decreases linearly with the value of V_T,[16] although the reasons for this phenomenon remain unclear. All ventilatory parameters used were different between HFOV and IPPV (Paw, P) but the possible impact of using different parameters on humidification is not clear and further studies focusing on specific parameters could be useful.

Recommendations to target a RH of inspired gas between 75% and 100% come from recommendations for adults, but ventilation in ELBW patients is very different from that in adults, due to the use of low tidal volumes and high instrumental dead space. Because of these particularities, humidity at the tip of the ETT is different from that at

TABLE 1 Comparison of relative humidity (RH), temperature, and absolute humidity (AH) during HFOV compared with conventional IPPV, regardless of the heating system and for each heater humidifier

Ventilation mode	HFOV	IPPV	*p* Value*	HFOV		*p* Value**	IPPV		*p* Value**	HFOV or IPPV		*P* Value**
Heater-humidifier	MR-A or MR-B			MR-A	MR-B		MR-A	MR-B		MR-A	MR-B	
RH% (Y-piece)	79.4 (8.1)	89.0 (6.2)	<0.001	85.4 (6.4)	73.3 (4.0)	0.004	93.6 (4.9)	84.5 (3.5)	0.004	89.6 (6.7)	78.7 (6.8)	0.003
T °C (Y-piece)	40.2 (0.4)	38.7 (0.4)	<0.001	39.8 (0.3)	40.5 (0.2)	0.002	38.4 (0.2)	39.1 (0.2)	0.002	39.1 (0.8)	39.8 (0.8)	<0.001
AH mg/L (Y-piece)	40.8 (3.4)	42.6 (2.3)	0.012	43.2 (2.9)	38.4 (1.9)	0.01	44.0 (2.0)	41.1 (1.6)	0.04	43.6 (2.4)	39.6 (2.2)	<0.001

Note: Results are described as mean (SD).

AH, mg/L, calculated and RH, %, measured in the Y-piece.

Abbreviations: HFOV, high-frequency oscillatory ventilation; IPPV, intermittent positive pressure ventilation.

*Wilcoxon test.

**Mann–Whitney test.

the Y-piece.[15] Thus, it might not be possible to extrapolate adult recommendations on humidification to preterm neonates, who might even need higher levels of humidity.

It is important to note that the mean RH during HFOV in our study was below the recommended 75%. Poor humidification may have a deleterious effect on inflammation[10,17] and on water movements[18] at the respiratory tract level as well as at the cellular level. It may, thus, impair lung development as it can induce such adverse events as atelectasis or plugged ETT and unplanned extubations. The incidence of inadequate humidity as an associated risk factor of pulmonary inflammation and consequently part of ventilator-induced lung injury is poorly documented. The principal reason for the lack of literature on this subject may well be the lack of routine monitoring of humidity and temperature of inspired gases. This study presents a method for exploring humidity and temperature at the Y-piece during tracheal ventilation that could be routinely used for in vitro and in vivo studies. Monitoring humidity at the Y-piece is the first approach and is not yet sufficient to extrapolate the real humidity level in the trachea.

The superiority of HFOV over IPPV for lung protection has not yet been proven,[19] although we might expect superiority due to the use of lower tidal volumes[6] in this ventilatory mode in preterm patients.[20] IPPV with VG mode induces lower expression of early inflammation markers than HFOV,[21] which is contradictory to the expected protective effect of HFOV. Our study suggests that inadequate humidification could be a factor explaining potential excess inflammation during HFOV. Another important result of this study is that humidification is not easily predictable and depends not only on ventilation mode but also on the type of circuit and the specific heater-humidifier used.

Our study has several limitations. First, it is an observational study. An interventional study, however, appears difficult to conduct, given the variety of factors involved in determining the humidity level: the medical devices used, the ventilatory settings, and ambient conditions. In this in vitro and in vivo study, the only ventilator used was the Drager VN500. One advantage of using a single ventilator is the homogeneity of the study conditions, but its negative aspect is that we cannot extrapolate these results to other ventilators. The specific flow management of the VN500 during HFOV may influence the hygrometric results as the flow is quadrupled during HFOV compared to conventional IPPV. Nevertheless, because other ventilators do not systematically provide flow rates, it seems difficult not to remain vague for the moment. While waiting for humidity monitoring which is technically more difficult, we think that flow rate monitoring should be systematically reported for ventilators. Further studies could evaluate the effect of frequency or V_T variations on airway humidity, but preliminary studies showed a limited impact of these parameters on humidity during HFOV. Another limitation was the choice to study only invasive ventilation and, further studies on humidification could target nasal ventilation.

In conclusion, we found that during mechanical ventilation, humidity measured in vitro and in vivo in ELBW preterm infants was lower with HFOV than with IPPV and did not reach recommended

TABLE 2 In vivo study results and data for host and environmental factors that may influence humidity measurements

	HFOV	IPPV	*p*
Birthweight	624.4 ± 96.1 g		
Gestational age	25.7 ± 0.9 weeks		
Weight at the procedure	737.0 ± 144.8 g	737.0 ± 167.3 g	>0.99
Age at the procedure	8.8 ± 7.4 days	10.9 ± 8.7 days	0.5
Incubator temperature	32.5 ± 1.1°C	31.7 ± 1.1°C	0.2
Ambient temperature	26.1 ± 1.7°C	26.1 ± 1.0°C	0.9
Barometric pressure	1021.3 ± 9.4 hPa	1020.6 ± 11.9 hPa	0.8
HH inlet temperature	32.0 ± 1.6°C	30.0 ± 0.8°C	0.002
HH outlet temperature	40.3 ± 0.6°C	39.6 ± 0.4°C	0.008
HH flow rate	26.5 ± 3.6 L/min	6.7 ± 0.6 L/min	<0.001
Tidal volume	1.5 ± 0.6 ml	4.5 ± 0.9 ml	0.001
Mean airway pressure	13.6 ± 1.7 mbar	8.1 ± 1.2 mbar	<0.001
ΔP gradient airway pressure	23.4 ± 6.1 mbar	11.1 ± 2.1 mbar	<0.001
Y-piece relative humidity	74.6 ± 6.3%	83.0 ± 7.0%	0.004
Y-piece temperature	39.8 ± 0.2°C	38.2 ± 0.8°C	<0.001
Y-piece absolute humidity	37.6 ± 3.1 mg/L	38.8 ± 3.6 mg/L	0.68

Abbreviations: HFOV, high-frequency oscillatory ventilation; HH, heater-humidifier; hPa, hectopascal; IPPV, intermittent positive pressure ventilation; ΔP, maximal pressure–minimal pressure.

values during HFOV. Moreover, humidification values differed significantly according to the humidifier device used. These results suggest that humidification depends on the ventilatory mode and heating devices and that HFOV requires specific humidification management. It is suggested that the systematic control of humidity, temperature, and flow rate during mechanical ventilation may optimize lung protection strategies.

AUTHOR CONTRIBUTIONS

Claude Danan: Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; data curation; and supervision. **Manon Tauzin**: Writing – review and editing; and investigation. **Camille Jung**: Writing – review and editing; methodology; formal analysis; and supervision. **Xavier Durrmeyer**: Writing – review and editing. **Laurence Caeymaex**: Writing – review and editing; and supervision. **Charles Treussart**: Writing – review and editing. **Fabrice Decobert**: Methodology; writing – review and editing; and conceptualization. **Bruno Louis**: Conceptualization; writing – review and editing; validation; formal analysis; and supervision.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Claude Danan http://orcid.org/0000-0001-9204-5713
Manon Tauzin http://orcid.org/0000-0003-0547-4566

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