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Take-home message: A 30-minutes musical intervention applied to acute respiratory failure patients requiring non-invasive ventilation does not reduce respiratory discomfort but significantly decreases peri-traumatic symptoms at ICU discharge.

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Short take-home message

A 30-minutes musical intervention applied to acute respiratory failure patients requiring non-invasive ventilation does not reduce respiratory discomfort but significantly decreases peritraumatic symptoms at ICU discharge.

Abstract

Non-invasive ventilation (NIV) associated discomfort may participate in its failure. We aimed to determine the effect of a musical intervention on respiratory discomfort during NIV in patients with acute respiratory failure (ARF).

Three centers, open-label controlled trial; randomization of patients requiring NIV for ARF to a musical intervention (MI - receiving a MI and visual deprivation during the first 30-minutes of each NIV session); a sensory deprivation (SD - wearing an insulating headphone and visual deprivation during the first 30-minutes of each NIV session), and a control group (CG) receiving NIV as routinely performed. The primary outcome was the change in respiratory discomfort before and after 30-minutes of the first NIV session.

113 patients were randomized (39 in the CG, 36 in the MI, 38 in the SD). Median change in respiratory discomfort was 0 [-1;1] between MI and CG (*P*=0.7). In-between groups comparison did not evidence any significant variation of respiratory parameters across time or health-related quality of life at day-90. The Peritraumatic Distress Inventory at ICU discharge was reduced in MI-group patients.

A 30-minutes musical intervention did not reduce respiratory discomfort during NIV for ARF in comparison to conventional care or sensory deprivation.

Trial Registration ClinicalTrials.gov NCT02265458

Introduction

Non-invasive ventilation (NIV) use in acute respiratory failure (ARF) is known to reduce intubation rates, nosocomial infections [1] and mortality [2] in some critical care situations [3, 4]. Nevertheless, NIV drawbacks includes poor tolerance [5], known to increase the risk of intubation [6–8]. In addition, setting and conducting NIV is time-consuming and generates a high level of stress to the patients, their relatives and caregivers [9]. Among pharmacological strategies to enhance patients' tolerance to NIV, sedation has been shown to reduce NIV-induced discomfort [10–13]. Nevertheless, these anesthetic treatments might be dangerous if not used cautiously, and require additional precautions by trained staffs.

Among non-pharmacological interventions, music therapy is increasingly investigated [14]. In patients undergoing invasive mechanical ventilation, music therapy facilitates a reduction in anxiety, and sedation exposure in comparison with conventional strategies or sensory deprivation [15]. Furthermore, significant changes in physiologic variables have been evidenced [16, 17]. These positive findings led us to conduct a trial to ameliorate the tolerance of a stressful ICU technique [9]. We therefore aimed to assess the potential benefit of music therapy as a non-pharmacological adjunct to NIV to enhance acceptance and tolerance of the technique. As "music therapy" implies the intervention of a qualified music therapist, we chose to use the term "musical intervention", which refers to a receptive music session administered to a patient by trained caregivers. In order to distinguish the effect of music and of noise, and because no side sensory deprivation had been described [18], we choose to test the sensory deprivation strategy.

Methods

Study design and participants

Mus-IRA is a prospective, multicenter, open-label, three-arm randomized trial [19]. Patients were enrolled from May 2015 to June 2016, in three adults French ICUs. All three participating ICUs already provided patient-centered care [19]. Written informed consent was obtained from all the patients. Patients older than 18 years with ARF and a sufficient level of consciousness (Glasgow coma scale ≥ 12) were enrolled if they required non-invasive ventilation (NIV). Non-inclusion criteria were a severe hearing impairment, a classical contra-indication to NIV, a decision to withdraw life-sustaining therapies with an estimated life expectancy of less than 48 hours or participation to another trial dealing with ARF.

The protocol was approved by the Comité de Protection des Personnes Paris-Ile-de-France IV (N°2014-A00643-44), and the Ethics Committee of French Society for Intensive Care Medicine (Société de Réanimation de Langue Française approval CE SRLF 14-21).

Randomization and masking

All procedures are summarized in the electronic supplemental material (ESM)

Briefly, eligible participants were randomly allocated to one of the three study arms, in a 1:1:1 ratio, via a computer-generated, interactive web-response system (Cleanweb®, Telemedecine technologies S.A.S, Boulogne-Billancourt, France). The primary outcome was blindly assessed by a nurse or a nurse-assistant from another unit, after having removed and stored all the material.

Procedures

After inclusion, all participants underwent NIV in a similar manner, according to standards of care and in-line with each participating ICU practices, as described in the ESM. Once NIV mask was fitted and ventilator settings optimized, participants allocated to the "Musical Intervention" (MI) group had dedicated headphones (BOSE AE2®) positioned. They were shown how to handle the tablet interface (Samsung Galaxy®) by the trained nurse or nurse-assistant. Their musical tastes were determined by a caregivers-administered questionnaire. The patients chose their musical program according to their preferences, set the volume level and began a 30-minutes "L-type" MI session (MUSIC CARE© Paris, France; see ESM). A sleeping mask concealing their eyes was then applied.

In the “Sensory Deprivation” (SD) group, once NIV session was initiated, the same insulating headphone was placed on the patients’ ears (BOSE AE2®), but without any music, and eyes were concealed by applying the sleeping mask. In both intervention groups, headphones and masks were left in place for 30 minutes.

In the “control group” (CG), NIV was conducted as usually done in the participating units.

All subsequent NIV session were conducted according to the randomization group, until NIV discontinuation, day-28 or ICU discharge. In all three randomization arms, the other treatments were left to the discretion of the treating physicians.

The patient rated his respiratory discomfort with the use of a visual scale. The patients were asked to rate the intensity of their respiratory discomfort on a 10-cm long ruler, shaped like an arrow. It was bounded by the “0: no respiratory discomfort” (the smallest base of the arrow) and to the right “10: maximal respiratory discomfort” (the head of the arrow). Patients marked directly on the ruler the level of their perception of discomfort. This measure was assessed prior to each NIV session, immediately after NIV was correctly set (5 minutes), at 30 minutes, and at 1, 2, 3, 4, 6, 8, 12, 16, 20, 24 hours according to NIV session length. Quality of life was determined by Hospital Anxiety and Depression Scale (HADS) questionnaire [20] and Short Form-36 (SF-36) [21] at baseline and day-90. At ICU discharge and day-90, the research team submitted to the participants the Peritraumatic Distress Inventory [22, 23] applied to NIV, and a survey of numeric scaling of NIV satisfaction, discomfort, and NIV-associated trauma.

Objectives and outcomes

We aimed to assess the hypothesis that a musical intervention administered to ARF ICU patients would reduce respiratory discomfort and thereby improve NIV tolerance and ventilation parameters after 30 minutes of NIV, in comparison to conventional care or to an isolation from ICUs’ noise and light nuisance; and assess the effect of musical intervention on physiological parameters, NIV failure and tolerance, and patient-centered outcomes such as anxiety and depression, peri-trauma stress, and NIV appreciation.

The primary endpoint was the change in respiratory discomfort before the initiation and after 30 minutes of the first NIV session after randomization.

Secondary endpoints were: 1) evolution of respiratory discomfort during the first NIV session and at the end of the session, and similarly for each subsequent NIV session, 2) changes in

respiratory parameters during NIV sessions (respiratory rate, transcutaneous oxygen saturation, exhaled tidal volume), 3) changes in cardiovascular parameters during NIV sessions (heart rate, arterial pressure) – all endpoints assessed at the same time-points (see above and ESM for details) 4) percentage of patients requiring endotracheal intubation (NIV failure) at the end of a NIV session, 5) agreement in NIV session duration between the prescribed and the actual delivered session, 6) number of sessions interrupted before the end of the prescribed time, 7) percentage of patients requiring physical restraint, sedative or anxiolytic treatments during NIV sessions and ICU stay, 8) anxiety / depression and health-related quality of life by HADS and SF36 scores at baseline and after 3 months, 9) peri-trauma stress, measured with the Peritraumatic Distress Inventory immediately at ICU discharge, and after 3 months of inclusion, and 10) patients' overall assessment of NIV (in terms of discomfort, satisfaction, and trauma) at ICU discharge and day-90.

In order to explore musical intervention effect, some other outcomes were assessed in a *post-hoc* analysis. The assessment of NIV tolerance was completed by the number of NIV sessions with an attempt to pull off the NIV interface and the relative risk of premature interruption of NIV sessions; the agitation assessment comprised its evolution, by the Richmond-Agitation and Sedation Scale (RASS); and efficacy was assessed by the number of days of NIV treatment, of NIV sessions per patient and survival at ICU discharge.

Statistics

The sample size was a priori calculated, and detailed in the ESM. It was expected to randomize a total of 99 participants (33 per arm). A blinded quality assessment of study data (which did not involve any comparison of study outcomes between groups), in May 2016 after the inclusion of 80 subjects showed that the primary endpoint had not been collected for 15 participants, as they were asleep under NIV after the first 30 minutes of therapy. The number of randomization was therefore increased to 113 subjects.

Continuous data are presented as median and 25-75 interquartile range (med [IQR 25-75]) unless otherwise indicated. Dichotomous data are presented as number and percentage – n (%). All analyses were performed on the intention-to-treat population. Unless otherwise specified, categorical variables were compared by a Chi2 test or Fisher test as appropriate, and continuous variables were compared by a Student's t test or Wilcoxon test as appropriate (when two groups are compared), and by an ANOVA or Kruskal-Wallis test as

appropriate (when more than two groups are compared). The analyses were performed with SAS version 9.4, and further details are given in the ESM.

Results

Patients

Between May 2015 and June 2016, 311 consecutive patients were screened in the 3 participating ICUs. One hundred and thirteen were included and randomized: 39 were allocated to the CG, 36 to the MI group, and 38 to the SD group (Figure 1). Baseline characteristics of the 3 groups are shown in Table 1. The main reason for NIV initiation was acute-on-chronic respiratory failure (n=61; 54%).

Tolerance of musical intervention and sensory deprivation

During the first NIV session, 15/38 (39.5%) patients of SD group complied with the protocol, and accepted both visual and sound deprivation, 9 patients (23.6%) rejected both visual and sound deprivation; 9 (23.6%) only rejected the visual deprivation; and 2 (5.2%) only rejected the sound deprivation. All MI patients accepted the musical intervention, and 14/36 (38.9%) of those accepted the visual deprivation

Primary and secondary outcomes (Table 2 and 3)

The change in respiratory discomfort before the initiation and after 30 minutes of the first NIV session after randomization was not different in-between groups with a median difference of -1 [-2-0] for the CG, 0 [-2-0] for the SD group; and -1 [-3-1.1] for the MI group (*P*=0.7 Wilcoxon rank sum test) (Figure 2). Sensitivity analyses of the primary outcome (adjustment on stratification factors and potential confounders, imputation of missing values, and per-protocol analysis) were performed and no significant difference in change in respiratory discomfort before the initiation and after 30 minutes of the first NIV session was evidenced. Respiratory discomfort variation remained non-significantly different between subsequent time-points and for the subsequent sessions.

In a similar manner, respiratory parameters did not significantly vary across time in-between groups. A significant reduction in systolic and mean arterial pressure was evidenced in MI group for the first NIV session. No significant variation of those parameters was observed for the subsequent sessions. NIV failure rates did not differ significantly (7.7 vs 2.6 vs 0%, *P*=0.32).

Health-related quality of life at day-90 did not differ in-between groups, with regard to

anxiety and depression sub-scores of HADS, or physical and mental dimensions of Short-form 36 questionnaire.

However, the Peritraumatic Distress Inventory at ICU discharge was significantly reduced in MI-group patients (16 [12-25] vs. 16 [5-23] vs. 8 [5-13] respectively for CG, SD and MI; *P* =0.03). This difference was no longer significant at day-90.

Other outcomes are detailed in the ESM.

Discussion

This prospective randomized controlled assessment of a musical intervention during NIV for acute respiratory failure in ICU patients failed to evidence a significant reduction in respiratory discomfort in comparison to conventional care. It did show however a significant decrease in systolic and mean arterial blood pressure at the end of the first NIV-session associated with the musical intervention along with a significant reduction in the Peritraumatic Distress Inventory at ICU discharge.

Musical intervention is gaining interest among non-pharmacological interventions [15, 24]. However, to the best of our knowledge, its benefits to improve NIV tolerance had never been assessed. Its easy implementation is a major argument for its generalizability.

Our study failed to show a significant reduction in respiratory discomfort during NIV acute respiratory failure ICU patients. Nevertheless, numerical values of slopes of changes actually differed, with MI groups' discomfort decreasing faster than the other groups (as shown in ESM Figure 1). Four major putative explanations for these results deserve discussion: 1) the levels of respiratory discomfort might have been only moderate at baseline (4 [1-6]; 5 [2-6]; and 5 [1.5-7] in the CG, SD and MI groups), and could have led to a "floor effect" (i.e. made it difficult to show an effect of the intervention); 2) because all the patients received NIV, NIV in itself led to an important respiratory improvement, thereby potentially masking the additional benefit of MI; 3) the effect of MI was negated by the additional sensory deprivation; 4) MI was simply not effective.

Although the latter conclusion is "technically" valid given the negative results of the present trial, we believe that the more negative slope of changes of respiratory discomfort for the MI group observed in the present study and positive results from studies performed in other stressful situations suggest that other explanations may prevail [15–17, 25, 26]. Indeed, the three first conclusions may appear more plausible and are not mutually exclusive. Retrospectively, one may question the choice of respiratory discomfort as outcome measure because it relates also to the patient's respiratory status and breathlessness. Hence, as mentioned above, the respective contribution of the intervention and of the treatment itself is difficult to decipher. Given the universally recognized major positive effect of NIV on breathlessness during acute respiratory failure, one may hypothesize that NIV markedly improved patient comfort, especially after the first NIV session, that outgrew the effect of the music intervention. Thus, it is possible that the added value of MI may have been more

preeminent – in terms of NIV tolerance – for the subsequent sessions. Conversely, we felt that patients would have benefited "too much" from NIV (and, to some extent, from etiological treatments, such as diuretics or β2-agonists) had we focused on the subsequent NIV sessions. The first NIV session tended to be longer in MI group. This finding is in line with an increased tolerance of NIV in patients treated with MI. A deeper insight is therefore needed, with the assessment of other outcomes, more likely to be influenced by music, such as anxiety, for example.

Visual deprivation was – to a certain extent – unexpectedly poorly tolerated. Consistently, the patients in the SD group reported a significantly lower satisfaction related to NIV at day-90, reflecting a poor experience of NIV in these conditions. As previously done [15], we considered it important to precisely assess the respective input of sensory deprivation and musical intervention in a potential alleviation of respiratory discomfort. Although the use of earplugs and eye masks has been shown effective in improving sleep quality in critically ill patients [27], compliance to sensory deprivation is reported to be low in ICU patients [18], with over 51% of patients rating eye masks' use as very uncomfortable or uncomfortable [28]. These arguments taken altogether, we strongly believe visual deprivation should not be used during NIV in the acute setting of respiratory distress.

We found that systolic and mean arterial pressure were significantly lower one hour after NIV in patients receiving the MI in comparison with the other groups. Because the MI lasted only 30 minutes, we believe a noticeable remnant relaxing and anxiolytic effect of the MI was present. A previous study [17] described such an hemodynamic effect during MI in invasively ventilated subjects but with no information on its lasting effect. We show here that the lowering of blood pressure is sustainable, after the end of the MI. A lower secretion of stress hormones in music-exposed patients might explain the mechanism involved in the lowering of the blood pressure [29]. A neuro-vegetative response, induced by the alleviation of stress and anxiety might be the key of the lowering of cardiovascular parameters.. These findings shed light on potential mechanisms of action of music in humans.

In spite of a solid design, some limitations can be acknowledged. As discussed earlier, visual deprivation was poorly tolerated. One may object that the absence of assessment of the delirium before enrolment might have biased the patients' self-reporting of respiratory discomfort. It has to be underlined that discussing with the patient to get the written

consent, as required by French legislation was considered an acceptable screening for delirium assessment. Moreover, no French version of the Confusion Assessment Method for the Intensive Care Unit existed at this time [30]. Next, this study could not be blinded, either on the patient's, or of the caregivers' side. However, the primary endpoint was assessed blindly from the treatment group, according to the Prospective Randomized Open-Blinded Endpoint method (PROBE), by an independent member of the staff, who did not participated in the conduct of the NIV session. The choice of respiratory discomfort as primary endpoint by itself might be questioned, as it is directly linked to patients' disease, rather than to the therapies used. Moreover as previously described for dyspnea and pain [31], tolerance or comfort is a multidimensional experience and at least some of the dimensional variation results from different afferent mechanisms. It may be possible that music therapy may have a greater impact on other dimensions than the one explored in this study.

On the one hand, the design of our trial might have hindered positive results: 30 minutes might have been too short (i.e. an "under-dosed" music intervention) to induce an effect on respiratory discomfort; the patient-directed music settings (type, volume…) could have influenced these negative results. On the other hand, we wanted to perform a pragmatic trial, and we acknowledge it could have negatively biased this study. Lastly, some might criticize the lack of direct involvement of a music therapist in the patients' care. It is true that no music therapist intervened as a consultant at bedside. Nevertheless, these consultations are time- and person-consuming. The advantage of the application used in our trial was that a skilled music therapist designed each musical piece, and that his presence was not mandatory at bedside, allowing generalizability beyond the presence of a music therapist.

In conclusion, a musical intervention did not significantly reduce respiratory discomfort of patients requiring NIV for acute respiratory failure. It did, however, exert positive hemodynamic effects and reduce traumatic experience at ICU discharge. Visual deprivation was poorly tolerated. This exploratory trial gives several clues to launch further studies, in order to determine the optimal settings for MI in this indication.

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Tables

Table 1: Baseline data

	Control Group (n=39)	**Sensory Deprivation (n=38)**	**Musical Intervention (n=36)**
Age, years, median [IQR]	68 [61-76]	64 [57-72]	66 [58.5-71]
Male gender, No (%)	18 (46.2%)	21 (55.3%)	23 (63.9%)
BMI, kg/m^2, median [IQR]	24.9 [22.3-31.9]	25.1 [21.3-31.5]	26.6 [23.3-32.2]
SAPS II, median [IQR]	35.5 [27-47]	32 [24-40]	35 [27-41]
Comorbid conditions, No (%) - Chronic cardiopathy - Chronic respiratory disease - Obstructive sleep apnea - Psychiatric disorder - Alcohol consumption - Smoker or ex-smoker	 5 (12.8%) 30 (76.9%) 6 (15.4%) 2 (5.1%) 4 (10.3%) 28 (71.8%)	 8 (21.1%) 25 (65.8%) 10 (26.3%) 5 (13.2%) 9 (23.7%) 24 (63.2%)	 2 (5.6%) 22 (61.1%) 6 (16.7%) 5 (13.9%) 10 (27.8%) 27 (75%)
Health-related quality of life Hospital anxiety and depression score, median [IQR] - Anxiety sub-score - Depression sub-score Short-Form 36, median [IQR] - Physical sub-score - Mental sub-score	 16 [12-23] 8.5 [6-12] 8 [5-10] 27.7 [12.5-46.3] 41.4 [28.1-56.9]	 17 [15-19.5] 8.5 [5.5-10.5] 8 [7-11] 27.8 [15.9-47.1] 41.9 [19.2-54.2]	 15 [13-19] 8 [6-10] 7 [5-9] 32.5 [18.3-50.8] 45.3 [24.9-59.7]
Reason for non-invasive ventilation[a], No (%) - Acute-on-chronic respiratory failure - Pulmonary edema - *De novo* respiratory failure - Post-extubation respiratory failure - Post-operative respiratory failure - Chest trauma - post-extubation respiratory failure prophylaxis	 24 (61.4%) 10 (25.6%) 6 (15.4%) 2 (5.1%) 3 (7.7%) 0 0	 19 (50%) 11 (28.9%) 8 (21.1%) 3 (7.9%) 3 (7.9%) 2 (5.3%) 2 (5.3%)	 18 (50%) 10 (27.8%) 7 (19.4%) 3 (8.3%) 5 (13.9%) 0 1 (2.8%)

ICU therapies prior to enrolment - Invasive mechanical ventilation, No. (%) - Non-invasive mechanical ventilation, No. (%)	 3 (7.7%) 18 (46.2%)	 5 (13.2%) 22 (57.9%)	 6 (16.7%) 14 (38.9%)
Glasgow score at enrolment, median [IQR]	15 [15-15]	15 [15-15]	15 [15-15]
Respiratory rate, /min, median [IQR]	25 [20-29]	24 [21.5-28]	24 [20-27]
Heart rate, /min, median [IQR]	99 [89-110]	95 [83-110]	96 [84-115]
PaO_2/FiO_2 ratio at enrolment, median [IQR] PaO_2/FiO_2<200 mmHg, No. (%)	227 [181-287] 13 (35.2%)	224 [157.5-259.5] 15 (41.7%)	189 [144-281] 17 (51.5%)
$PaCO_2$ at enrolment, mmHg, median [IQR]	63 [45.7-72]	53 [44-70.8]	50.7 [41.5-71.5]

Abbreviations: BMI, body mass index; SAPS II, Simplified Acute Physiologic Score; ICU, Intensive Care Unit; Demographic characteristics and comorbid conditions were recorded at study inclusion.
[a] Multiple reasons might have led to the initiation of NIV.
SAPS II scores can range from 0 (lowest level of critical illness) to 163 (most severe level of critical illness with 100% predicted mortality). A score of 50 predicts a 46.1% risk of death. SAPS II was calculated 24 h after ICU admission.

Table 2: Clinical outcomes

	Control Group (n=39)	**Sensory Deprivation (n=38)**	**Musical Intervention (n=36)**	***P*-value**
Respiratory discomfort at T0 of the first NIV session, median [IQR]	4 [1-6]	5 [2-6]	5 [1.5-7]	-
Respiratory discomfort at T30 of the first NIV session, median [IQR]	3 [0-5]	4 [2-5]	4 [2-5.5]	-
Primary outcome				
T0 to T30 change in respiratory discomfort during the first NIV session, median [IQR]	-1 [-2-0]	0 [-2-0]	-1 [-3-1.1]	0.86[a] and 0.79[b]
Secondary outcomes				
Adequacy of the prescribed duration of NIV session and their actual duration, median [IQR]	1.07 [1.00-1.33]	1.00 [0.87-1.26]	1.08 [0.93-1.26]	0.29
Number of patients requiring physical restraint during NIV, No. (%)	2 (5.1%)	0	0	0.33
Number of patients requiring sedative or anxiolytic treatments during NIV, No. (%)	2 (5.1%)	4 (10.5%)	1 (2.8%)	0.32
Patients requiring endotracheal intubations, No. (%)	3 (7.7%)	1 (2.6%)	0	0.32
Peritraumatic distress inventory at ICU discharge, median [IQR]	16 [12-25]	16 [5-23]	8 [5-13]	0.03
Overall assessment of NIV at ICU discharge, median [IQR] - Discomfort - Satisfaction - Trauma	 5 [2-6] 7.5 [5-9] 3.5 [0-7]	 5 [2-8.5] 6.3 [5-9.5] 4 [0-7.5]	 4 [1-5] 8 [5.2-9] 2 [0-5]	 0.21 0.78 0.72
Hospital anxiety and depression scale at D90, median [IQR] - Anxiety sub-score - Depression sub-score	12 [8.5-20.5] 6 [3-9] 7 [4-10]	16.5 [11-21] 6 [5-11] 9 [4-13]	10 [8-16] 5 [3-9] 5 [4-10]	0.14 0.17 0.33

Short form-36 at D90, median [IQR] - Physical sub-score - Mental sub-score	 46 [27.1-61] 53.8 [31.1-70.5]	 42.7 [22.9-64.4] 55.4 [22.8-72.3]	 45.2 [32.1-63.3] 65.5 [30.1-87]	 0.75 0.22
Peritraumatic distress inventory at D-90, median [IQR]	12 [4-20]	14 [8-20]	9 [5-12]	0.18
Overall assessment of NIV at D-90, median [IQR] - Discomfort - Satisfaction - Trauma	 4 [1-6] 10 [8-10] 1 [0-8]	 6 [3-9] 5 [3-8] 2 [0-8]	 4 [2-7] 8 [7-10] 0 [0-5]	 0.29 0.02 0.78
Other outcomes				
Length of the first NIV session, minutes, median [IQR]	70 [60-140]	60 [50-75]	82.5 [60-145]	0.21
Number of NIV sessions per patient, median [IQR]	7 [3-17]	6.5 [4-10]	5.5 [2-8.5]	0.06
Length of NIV support, days, median [IQR]	3 [2-5]	3 [2-4]	3 [2-4]	0.16
Length of ICU stay, days, median [IQR]	7 [4-9]	6 [3-10]	6 [3-10.5]	0.63
ICU survival, No. (%)	36 (92.3%)	38 (100%)	33 (91.7%)	0.21
Patients with a do-not-intubate decision, No. (%)	10 (25.6%)	4 (10.5%)	7 (19.4%)	0.23
D-90 survival, No. (%)[c]	21 (53.9%)	22 (57.9%)	20 (55.6%)	0.84

P-value is provided [a] for the comparison of musical-intervention group *versus* the control-group; [b] for the comparison of sensory deprivation *versus* the control-group; all other p-values are given for the comparison between the 3 groups.

[c] Vital status has been assessed for 63 subjects at day-90.

T0 is the time of assessment of respiratory discomfort prior to each non-invasive ventilation session. T30 is the time of the assessment of respiratory discomfort after 30 minutes of each non-invasive ventilation session.

Abbreviations: NIV, non-invasive ventilation; ICU, intensive care unit.

The assessment of respiratory discomfort used a visual scale, which combined numeric and analogic evaluation. The patients were asked to rate the intensity of their dyspnea on a 10-cm long ruler, shaped like an arrow. It was bounded by the "0: no respiratory discomfort (the smallest base of the arrow) and to the right "10: maximal respiratory discomfort" (the head of the arrow).

The adequacy of the prescribed duration of NIV session and their actual duration was calculated as the sum of the actual durations of all NIV session per patient divided by the sum of their prescribed time.

Health-related quality of life was measured using the physical and mental subscales of the Short Form-36 and the Hospital Anxiety and Depression Scale (HADS). The HADS is a 14 items questionnaire, each of them scored from 0 to 3, a higher score indicating a higher level of anxiety or depression. A cut-off point of 8/21 for anxiety or depression identifies either anxiety or depression. The Short Form-36 is a 36-item questionnaire ranging form 0 to 100. The lower the score the more disability. The higher the score the less disability: a score of 0 is equivalent to maximum disability and a score of 100 is equivalent to no disability.

Posttraumatic stress disorder-related symptoms were assessed in patients using the Peritraumatic Distress Inventory (PDI). The PDI is a 13-item questionnaire, each ranging from 0 to 4, the higher the score indicating the higher burden of posttraumatic stress disorder-related symptoms.
The RASS is a 10-points scale, ranging from -5 to +4, the lowest for the deeper sedation (-5: unarousable) and the highest indicating a major agitation (+4: combative).
NIV- associated discomfort, satisfaction and trauma have been assessed with a 0 to 10 numeric visual scale at ICU discharge and 0 to 10 numeric verbal scale at D90 (0: the absence of symptom – 10: the maximum level of symptoms).

Table 3: Secondary outcomes: respiratory discomfort and physiological variables across time

Evolution of the variables (units per hour)		First NIV session			All NIV sessions		
		Slope value	**Change compared with control Group**	***P*-value**	**Slope value**	**Change compared with control Group**	***P*-value**
Respiratory discomfort	**Control Group (n=39)**	-0.26 (-0.64;0.12)	-	-	-0.03 (-0.14;0.08)	-	
	Musical Intervention (n=36)	-0.45 (-0.83;-0.08)	-0.19	0.27	-0.14 (-0.27;-0.01)	-0.11	0.21
	Sensory Deprivation (n=38)	-0.23 (-0.68;0.22)	0.031	0.30	-0.17 (-0.31;-0.05)	-0.14	0.09
Respiratory rate	**Control Group (n=39)**	0.19 (-0.14;0.52)	-	-	0.02 (-0.20;0.24)	-	-
	Musical Intervention (n=36)	-0.12 (-0.62;0.38)	-0.31	0.31	-0.19 (-0.43;0.05)	-0.21	0.21
	Sensory Deprivation (n=38)	-0.21 (-0.75;0.32)	-0.40	0.21	-0.32 (-0.59;-0.05)	-0.34	0.049
Transcutaneous oxygen saturation	**Control Group (n=39)**	-0.18 (-0.78;0.41)	-	-	0.26 (-0.08;0.60)	-	-
	Musical Intervention (n=36)	-0.27 (-0.83;1.23)	-0.08	0.89	-0.09 (-0.48;0.30)	-0.35	0.18
	Sensory Deprivation (n=38)	0.20 (-0.83;1.23)	0.39	0.52	0.2 (-0.25;0.65)	-0.06	0.83
Exhaled tidal volume	**Control Group (n=39)**	4.61 (-9.01;18.24)	-	-	-1.76 (-7.09;3.57)	-	-
	Musical Intervention (n=36)	-6.99 (9.08;12.47)	-11.6	0.14	-9.42 (-15.70;-3.13)	-7.66	0.07
	Sensory Deprivation (n=38)	16.7 (-5.29;38.62)	12.1	0.58	4.23 (-4.01;12.47)	5.99	0.23

Heart rate	**Control Group (n=39)**	0.66 (-1.07;2.38)	-	-	-0.41 (-0.96;0.15)	-	-
	Musical Intervention (n=36)	-1.38 (-3.16;0.40)	-2.03	0.10	-0.19 (-0.78; 0.41)	0.22	0.59
	Sensory Deprivation (n=38)	-0.01 (-2.01;1.99)	-0.67	0.62	-0.47 (-1.11;0.17)	-0.07	0.87
Systolic arterial pressure	**Control Group (n=39)**	1.25 (-1.32;3.82)	-	-	-0.17 (-1.13;0.78)	-	-
	Musical Intervention (n=36)	-2.40 (-5.09;0.29)	-3.65	0.05	-0.69 (-1.73;0.33)	-0.53	0.45
	Sensory Deprivation (n=38)	1.63 (-1.57;4.83)	0.39	0.85	-0.91 (-1.98,0.33)	-0.75	0.30
Mean arterial pressure	**Control Group (n=39)**	0.80 (-0.55;2.15)	-	-	0.02 (-0.57;0.60)	-	-
	Musical Intervention (n=36)	-1.50(-3.00,0.003)	-2.30	0.02	-0.42 (-1.06;0.21)	-0.45	0.30
	Sensory Deprivation (n=38)	0.50 (-1.35;2.36)	-0.30	0.80	-0.47 (-1.14;0.20)	-0.50	0.27

Slope values were obtained using a linear mixed effects model fitted for each outcome. A positive slope means that the corresponding outcome increases over time, and a negative slope means that the corresponding outcome decreases over time. The slope value is indicated in mean units change per hour, with its 95%CI. The slope value of each intervention group (Musical and Sensory Deprivation) was compared with the slope value of the Control group using a Wald test.

Legends of the figures

Figure 1. Flow diagram of patients.

ICU: Intensive Care Unit; Other reasons for non-inclusion were: NIV refusal; NIV for pre-oxygenation; NIV interruption after a single session; legal impairment for inclusion; patient under the age of 18; patient already included in the study. The primary outcome could not be assessed for some of the subjects, as they were asleep under NIV after the first 30 minutes of therapy.

Figure 2. Median change in respiratory discomfort during the first non-invasive ventilation session in the 3 groups. The median difference was of -1 [-2-0] for the CG, 0 [-2-0] for the SD group; and -1 [-3-1.1] for the MI group (*P*=0.7 Wilcoxon rank sum test).

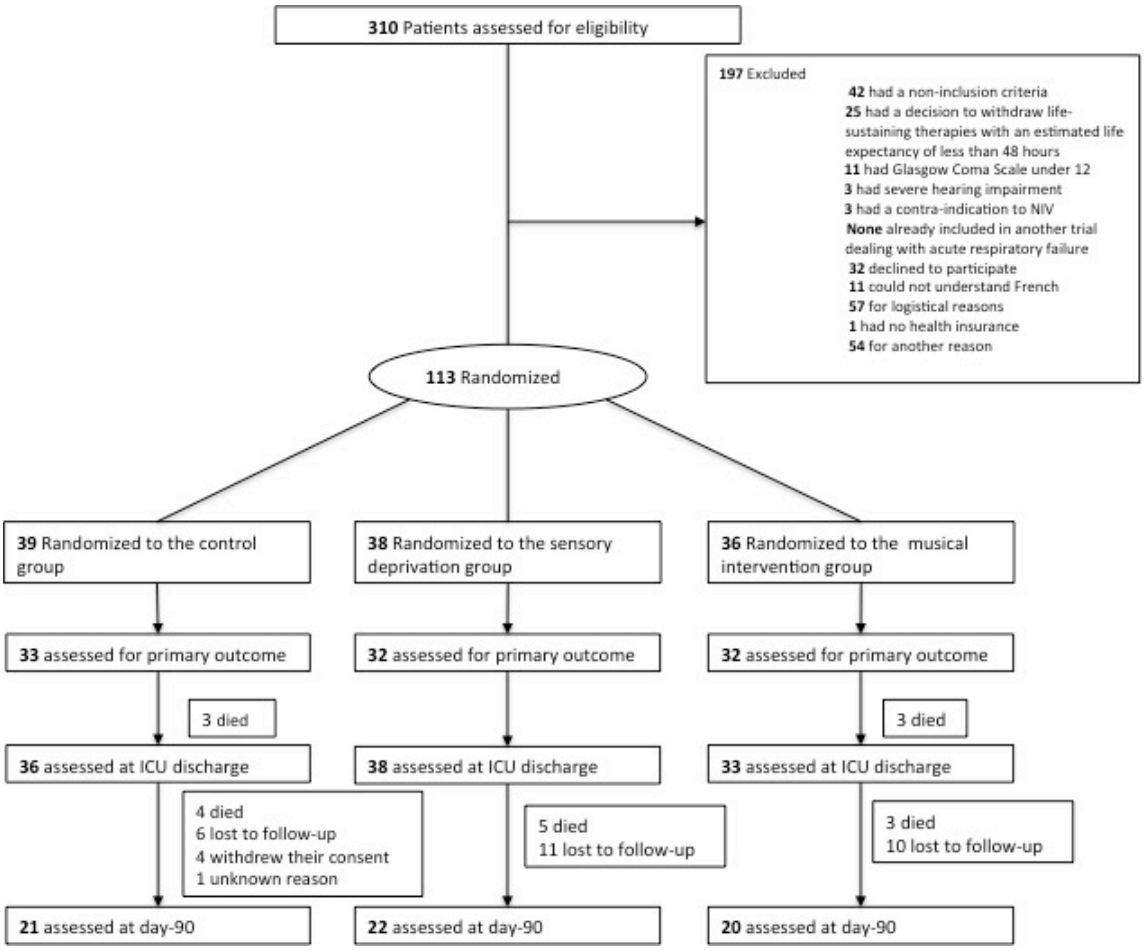
310 Patients assessed for eligibility
197 Excluded
42 had a non-inclusion criteria
25 had a decision to withdraw life-sustaining therapies with an estimated life expectancy of less than 48 hours
11 had Glasgow Coma Scale under 12
3 had severe hearing impairment
3 had a contra-indication to NIV
None already included in another trial dealing with acute respiratory failure
32 declined to participate
11 could not understand French
57 for logistical reasons
1 had no health insurance
54 for another reason
113 Randomized
39 Randomized to the control group
38 Randomized to the sensory deprivation group
36 Randomized to the musical intervention group
33 assessed for primary outcome
32 assessed for primary outcome
32 assessed for primary outcome
3 died
3 died
36 assessed at ICU discharge
38 assessed at ICU discharge
33 assessed at ICU discharge
4 died
6 lost to follow-up
4 withdrew their consent
1 unknown reason
5 died
11 lost to follow-up
3 died
10 lost to follow-up
21 assessed at day-90
22 assessed at day-90
20 assessed at day-90

Figure 1

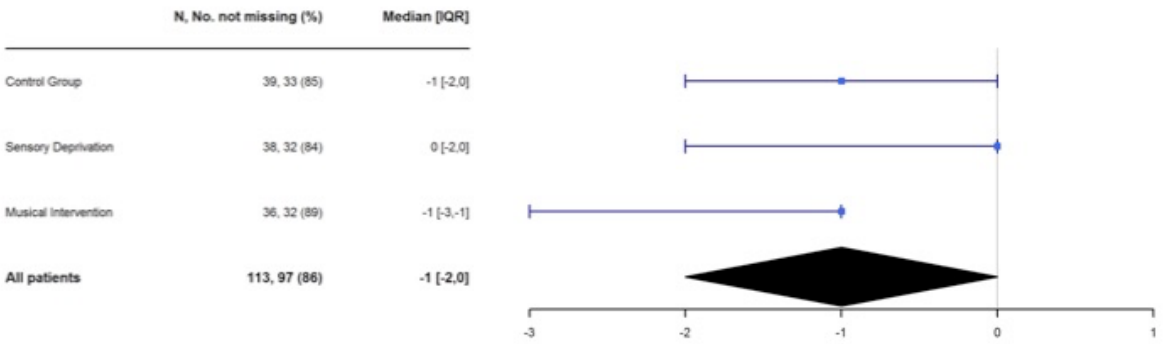
N, No. not missing (%)
Median [IQR]
Control Group
39, 33 (85)
-1 [-2,0]
Sensory Deprivation
38, 32 (84)
0 [-2,0]
Musical Intervention
36, 32 (89)
-1 [-3,-1]
All patients
113, 97 (86)
-1 [-2,0]
-3
-2
-1
0
1

Figure 2

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