



Original Contribution

Prehospital non-invasive ventilation in acute respiratory failure is justified even if the distance to hospital is short



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ABSTRACT

Aims: Evaluation of the efficacy of prehospital non-invasive ventilation (NIV) in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) and cardiogenic pulmonary edema (CPE).

Material and methods: Consecutive patients who were prehospitally treated by Emergency Physicians using NIV were prospectively included. A step-by-step approach escalating NIV-application from continuous positive airway pressure (CPAP) to continuous positive airway pressure supplemented by pressure support (CPAP-ASB) and finally bilevel inspiratory positive airway pressure (BiPAP) was used. Patients were divided into two groups according to the prehospital NIV-treatment-time (NIV-group 1: ≤ 15 min, NIV-group 2: > 15 min). In addition, a historic control group undergoing standard care was created. Endpoints were heart rate, peripheral oxygen saturation, breathing rate, systolic blood pressure, and a dyspnea score.

Results: A total of 99 patients were analyzed (NIV-group 1: $n = 41$, NIV-group 2: $n = 58$). The control group consisted of 30 patients. The majority of NIV-patients (90%) received CPAP-ASB, while CPAP without ASB was conducted in 8% and BiPAP-ventilation in 2% of all cases. Technical application of NIV lasted 6.1 ± 3.8 min. NIV-treatment-time was as follows: NIV-group 1: 13.1 ± 3.2 min, NIV-group 2: 22.8 ± 5.9 min. Differences between baseline- and hospital admission values of all endpoints showed significantly better improvement in NIV-groups compared to the control group ($p < 0.001$). The stabilizing effect of NIV in terms of vital parameters was comparable between both NIV-groups, independent of the duration of treatment (n.s.).

Conclusion: Prehospital NIV-treatment should be performed in patients with COPD-exacerbation and CPE, even if the distance between emergency scene and hospital is short.

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1. Introduction

Non-invasive ventilation (NIV) has been shown to be effective in the treatment of various forms of acute respiratory failure (ARF) such as exacerbation of chronic obstructive pulmonary disease (COPD) and cardiogenic pulmonary edema (CPE) [1, 2]. The term NIV covers different forms of non-invasive ventilatory support which can be provided as continuous positive airway pressure (CPAP), continuous positive airway pressure supplemented by pressure support (CPAP-ASB) or as positive pressure ventilation such as bilevel inspiratory positive airway pressure (BiPAP) [3]. CPAP and CPAP-ASB are spontaneous breathing modes,

whereas BiPAP is mostly used to perform assisted or controlled ventilation [4]. It has been shown that the application of NIV leads to significant improvement of vital signs like respiratory rate, heart rate, blood pressure, and peripheral capillary or arterial oxygen saturation [3, 5–7]. Furthermore, it is known that using these techniques, early initiation is important for successful treatment of ARF [3, 8, 9]. Accordingly, it seems to be apparent that patients can benefit from initiation of non-invasive treatment already in the prehospital setting to avoid intubation and to improve patient outcome. However, while in-hospital evidence for the benefit of NIV in treating COPD-exacerbation and CPE is robust, there is a lack of knowledge about the out-of-hospital use of NIV, particularly in terms of outcome parameters such as length of intensive care unit stay, length of hospital stay or survival rate [10]. An important issue regarding the prehospital application of NIV is the additional time required to establish the equipment and to adapt the NIV-mask to the face of the patient, when avoiding a significant leakage [7]. This raises the question as to whether the considerable extra effort associated with a prolonged on-scene time is justified out-of-hospital, in

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particular when the ambulance transport time is short, as in most metropolitan areas [10–12].

Therefore, in this study we investigated the effect of prehospital applied NIV on vital functions of patients suffering from exacerbation of COPD or CPE, while paying particular attention to the impact of on-scene time, transport time and, in particular, NIV-treatment time. It was our hypothesis that prehospital application of NIV is justified in aiming to improve vital functions, even in a metropolitan area with short times from arrival at scene to hospital handover.

2. Methods

2.1. Study design

This prospective observational study was conducted in a prehospital setting to investigate the efficacy of NIV used in patients with COPD-exacerbation or CPE with particular reference to the impact of the duration of prehospital NIV-treatment. Patient data from the Emergency Medical Service (EMS) in Hamburg (Germany) were collected over a 4-year period (from January 2012 to December 2015) and divided into two groups, according to the duration of prehospital NIV-treatment which resulted from both: on-scene time and transport time (NIV-group 1: ≤ 15 min, NIV-group 2: > 15 min). In order to create a similar comparison group (control group) of patients with ARF undergoing standard care, we included historical data from the EMS database collected prior to introduction of NIV (October 2011 to December 2011). In any case treatment of ARF requires the presence of an Emergency Physician. In the present study data four Emergency Physician-based ambulance stations were considered. The study was approved by the local Ethics Committee (ÄK-Hamburg/PV3217).

2.2. Study population

Patients with ARF who were prehospitally treated by an Emergency Physician using NIV were included in the study. Further inclusion criteria were age ≥ 18 years, acute dyspnea, breathing rate (BR) > 25 , pulse oxymetric oxygen saturation (SpO_2) $< 90\%$, COPD-exacerbation or CPE as presumed cause of ARF (diagnostic criteria: obstructive pulmonary disease or chronic heart failure in medical history, permanent medication, auscultatory findings, percussion sound). Patients with asthma exacerbation, pneumonia or other respiratory pathologies were not considered. Exclusion criteria were hemodynamic instability (systolic blood pressure < 90 mm Hg) and a reduced level of consciousness (Glasgow Coma Scale < 12).

2.3. Treatment protocol

Standard prehospital care for ARF (historical control group) consisted of convenient positioning of the patient, high flow oxygen administered by mask (with oxygen at a flow of $15 \text{ l} \cdot \text{min}^{-2}$) and, depending on the presumed etiology, salbutamol inhalation, intravenous furosemide, sublingual nitroglycerine spray and/or intravenous morphine. For NIV-treatment, we used an empirically chosen step-by-step approach. Treatment was started using CPAP with an end-expiratory positive pressure of $5 \text{ cmH}_2\text{O}$, which could be gradually increased to $7.5 \text{ cmH}_2\text{O}$ and $10 \text{ cmH}_2\text{O}$. With respect to the effectiveness of this treatment and the patient's condition, NIV could be intensified using assisted spontaneous breathing (ASB) or in a final step BIPAP. The decision to escalate NIV to the next supporting level was made by an Emergency Physician if dyspnea (shortness of breath, dizziness, wheezing), tachypnea (breathing rate > 25 per minute), hypoxia ($\text{SpO}_2 < 90\%$), agitation and/or anxiety persisted without any tendency to improve. At each therapy step, patients were treated for about 1 min, before the next supporting level was aspired.

To implement NIV, we used the “Weimann Medumat Elektronik” (Weimann Medical Technology, Hamburg, Germany). Once started, NIV was performed until hospital admission in each case.

2.4. Data collection

All data for the study were obtained from standardized electronic patient records (Emergency Care Protocol for Physicians, German Society of Intensive Care and Emergency Medicine; version 5.1). Prior to analysis patient records were checked in terms of completeness and credibility. Records with missing data and those with inconclusive diagnosis were excluded. Heart rate (HR) and peripheral oxygen saturation (SpO_2) were monitored continuously (CORPULS, GS Elektromedizinische Geräte, G. Stemple GmbH, Kaufering, Germany), while breathing rate (BR) and systolic blood pressure (SBP) were recorded at an interval of 5 min. Additionally, a subjective dyspnoe score (DS, 1 = no dyspnea, 10 = maximum dyspnea) and the Glasgow Coma Scale (GCS) were determined at the beginning and at the end of the treatment. Furthermore, the on-scene time, the transport time, and the NIV-treatment time were recorded. The on-scene time was defined as the time from arrival of the ambulance at the scene to departure. The transport time was defined as the time from departure of the ambulance at the scene to arrival at the hospital. The NIV-treatment time included the period from the beginning of effective airway support to handover of the patient at the hospital.

2.5. Statistical analysis

Statistical analysis was performed with the support of the asklepios ProResearch institute. Data are shown as mean plus standard deviation of the mean if normally distributed and otherwise as median plus 25th and 75th percentile. Group comparisons were conducted using Chi^2 test and Fisher's exact test or ANOVA and Kruskal-Wallis test when appropriate. Sample size estimation was based on values obtained from a retrospective data analysis that included 16 patients (8 standard care, 8 NIV). We found a difference in dyspnoe score of 30% between standard care and NIV in favor of the latter technique. Accordingly, a power analysis (level of power: 80%, probability of error: 0.05, test: Chi-square test) was performed to determine the number of patients required. A difference in dyspnoe score of 10% was considered as clinically relevant.

3. Results

3.1. Patients

A total of 103 consecutive patients with ARF receiving prehospital NIV-treatment by Emergency Physicians were primarily included in the study. While data of 99 patients were statistically analyzed, 4 patients were excluded afterwards: In three patients NIV failed to improve respiratory failure due to persistent hypoxemia and endotracheal intubation with subsequent mandatory ventilation had to be performed. One patient did not tolerate NIV and asked to discontinue the treatment. In 41 patients the duration of NIV-treatment lasted 15 min or less. In 58 patients NIV-treatment lasted > 15 min. The control group consisted of 30 patients who received standard care from Emergency Physicians. Demographic data as well as presumed etiology of ARF are shown for all patients in Table 1. Patient characteristics such as sex, age, and body mass index as well as presumed diagnosis showed no statistically significant differences between groups. All included patients survived until hospital admission.

3.2. Noninvasive ventilation

The majority of NIV-patients (90/99, 90%) received CPAP-ASB at the time of hospital admission (92% in presumed CPE, 87% in presumed COPD). CPAP without ASB was conducted in 8% (7/99) of all cases.

Table 1
Demographic data and presumed etiology of ARF.

	Control n = 30	NIV-1 n = 41	NIV-2 n = 58
Sex (female/male), n (%)	16/14 (53/47%)	23/18 (56/44%)	27/31 (47/53%)
Age (years)	74.6 ± 9.6	75.8 ± 9.0	74.1 ± 10.4
COPD/CPE	15/15 (50/50%)	19/22 (46/54%)	26/32 (45/55%)
Body-mass-index (kg·m ⁻²)	27.5 (22.5, 31.3)	27.6 (22.4, 31.8)	27.4 (23.1, 30.7)

ARF = acute respiratory failure, Control = standard oxygen therapy by face mask, NIV-1 = non-invasive-ventilation (duration ≤ 15 min), NIV-2 = non-invasive-ventilation (duration > 15 min), COPD = chronic obstructive pulmonary disease, CPE = cardiogenic pulmonary edema, results are presented as mean (±SD) or as median (IQR), if the data were not normally distributed.

Only 2% (2/99) of all included patients needed BIPAP-ventilation (2× COPD). No significant differences were seen between NIV-groups in this regard. The same applies to PEEP (positive end-expiratory pressure) level (NIV-1: 5.0 [5.0, 10.0], NIV-2: 5.0 [5.0, 10.0]) and ASB (airway pressure) support (NIV-1: 10.0 [5.0, 12.0], NIV-2: 10.0 [5.0, 15.0]). The fraction of inspired oxygen was at the same level in both NIV-groups and the control group (1.0 [0.5, 1.0]).

3.3. Treatment times and physiological effects

Fig. 1 shows the average *on-scene time* as well as the *transport time* for all groups. In NIV-groups, adjustment of the device and adaptation to the individual need of the patient lasted 6.1 ± 3.8 min. In the control group, oxygen masks were placed within just a few seconds. *NIV-treatment time* was as follows: NIV-1: 13.1 ± 3.2 min, NIV-2: 22.8 ± 5.9. There were no significant differences between groups in terms of baseline values of physiological parameters like dyspnoe score, breathing rate, SpO₂, blood pressure, and heart rate, including the control group. Physiological effects of both prehospitally applied NIV and standard prehospital care on vital functions are presented as differences (Delta) between the baseline values measured when the ambulance arrived (initial) and the values measured immediately before handing over the patient in the hospital (end) (Figs. 2 and 3). Analysis of differences of baseline and admission values revealed significantly better improvement of all physiological parameters in NIV-groups compared to the control group. No significant difference was seen in direct

comparison of NIV-groups in this regard. Vital parameters at hospital admission are presented in Table 2.

4. Discussion

Our results indicate that prehospital NIV-treatment should be performed in patients with COPD-exacerbation and CPE, even if the distance between the scene of emergency and the hospital is short. We have shown that prehospitally applied NIV can normalize disturbed vital functions very quickly. This effect was seen in short-term as well as in longer-term application of NIV. The comparison with standard care showed that shorter on-scene time associated with standard therapy cannot compensate the superiority of NIV in stabilization of vital functions. Hence, refraining from the application of NIV already prehospitally is difficult to justify if there is a clear medical indication. For that reason we decided to use a historical control group rather than a prospective cohort for comparison with NIV-groups.

4.1. NIV therapy in ARF

Non-invasive ventilation strategies have been used with increasing frequency since the nineteen-nineties [5, 13]. NIV improves ventilation and oxygenation, prevents endotracheal intubation, and decreases the mortality rate in selected patients with ARF [12]. Patients with hypercapnic ARF such as COPD-exacerbation can in particular benefit from this type of airway support [1]. In hypoxemic ARF such as cardiogenic pulmonary edema, NIV prevents alveolar collapse and helps redistribute intra-alveolar fluid, improving pulmonary compliance and reducing the pressure of breathing [18]. It remains to be seen whether the out-of-hospital use of NIV is a viable and effective treatment option as well as in-hospital use, especially in an urban setting. The data on this issue are unclear or even contradicting. It seems to be certain that prehospital NIV given as a supplement to medical therapy improves vital signs such as breathing rate, heart rate, blood pressure, and oxygenation when compared to standard care alone [3, 14–16]. Based on these findings, we used the aforementioned physiological parameters as clinical endpoints for our study.

In terms of outcome parameters, the available data are contradictory. Some authors could not find any benefit from NIV in their prehospital setting with respect to endotracheal intubation rate, intensive care unit (ICU) admission, ICU length of stay, hospital mortality, and length of hospital stay [10, 17]. In contrast, other research groups reported a reduction in the number of intubations and mortality in patients with ARF who received NIV in the prehospital setting [18].

Another important aspect is the uncertain cost-effectiveness of out-of-hospital NIV, which will presumably be crucial for the establishment of this method in routine care [19]. There are findings that prehospital NIV is more expensive than standard care [20].

A major problem when comparing out-of-hospital care studies stems from the fact that results cannot simply be transferred to other health care contexts because of the inherent differences in the organization and staffing of the EMS systems [18].

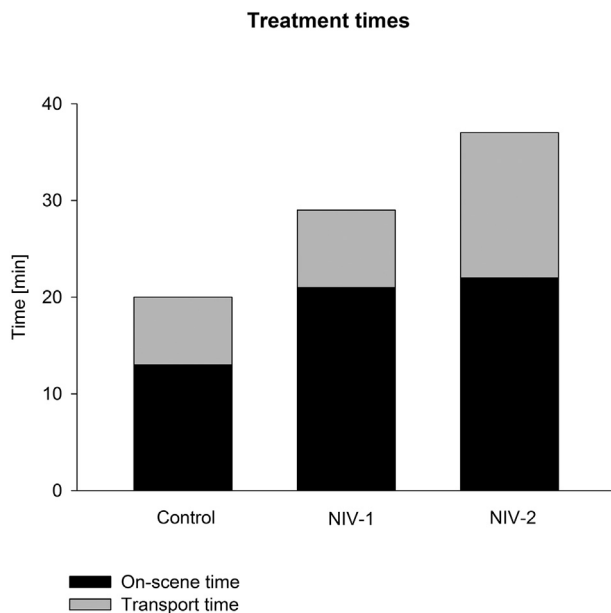


Fig. 1. Treatment times. Combined presentation of average on-scene time (black columns) and transport time (gray columns) for all study groups (NIV-treatment time is included in both times), on-scene time: Control vs. NIV ($p < 0.001$).

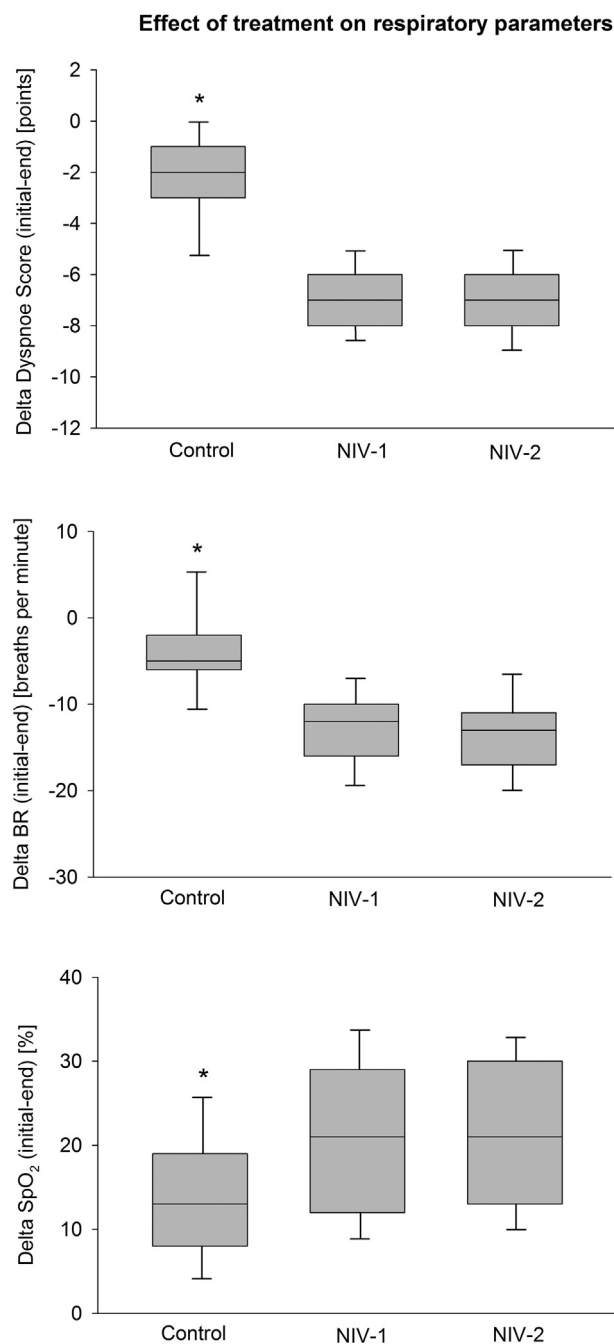


Fig. 2. Effect of treatment on respiratory parameters. Effects of prehospitally applied standard therapy or NIV on respiratory parameters are presented as differences (Delta) between the baseline values measured when the ambulance arrived (initial) and the values measured immediately before handing over the patient in the hospital (end), Control = standard oxygen therapy by face mask ($n = 30$), NIV-1 = non-invasive-ventilation (duration ≤ 15 min, $n = 41$), NIV-2 = non-invasive-ventilation (duration > 15 min, $n = 58$), BR = breathing rate, SpO₂ = peripheral capillary oxygen saturation, (*) $p < 0.001$ (Control vs. NIV).

4.2. Selection of NIV-mode

Currently, there are no reliable findings about which NIV-mode is the most effective in treating acute respiratory failure. CPAP and CPAP-ASB as well as BIPAP have been shown to be efficient in prehospital stabilization of vital functions in patients with COPD-exacerbation and CPE [21]. Studies in patients with COPD indicate that CPAP decreases inspiratory work of breathing [22]. The addition of pressure support ventilation to positive end-expiratory pressure increases the tidal volume in proportion to the

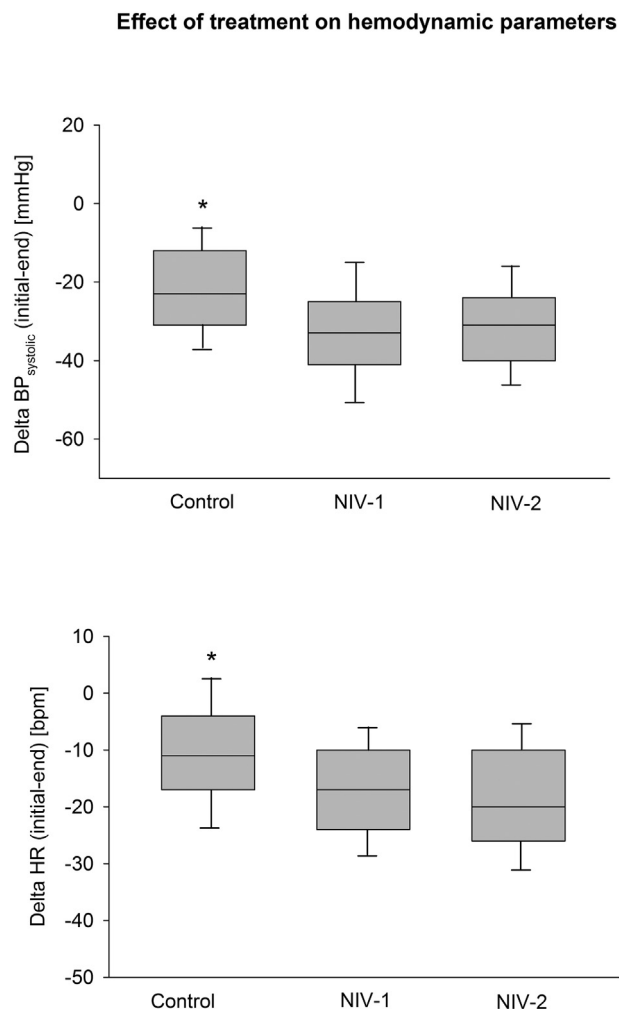


Fig. 3. Effect of treatment on hemodynamic parameters. Effects of prehospitally applied standard therapy or NIV on hemodynamic parameters are presented as differences (Delta) between the baseline values measured when the ambulance arrived (initial) and the values measured immediately before handing over the patient in the hospital (end), Control = standard oxygen therapy by face mask ($n = 30$), NIV-1 = non-invasive-ventilation (duration ≤ 15 min, $n = 41$), NIV-2 = non-invasive-ventilation (duration > 15 min, $n = 58$), BP_{systolic} = systolic blood pressure, HR = heart rate, (*) $p = 0.018$ (Control vs. NIV).

amount of pressure applied and can relieve inspiratory muscles [23]. In this sense, the application of BIPAP, used as the pressure controlled ventilation mode (CMV-BIPAP), represents another escalation level. However, this step-by-step approach is only a theoretical consideration, because there is no proof that BIPAP leads to better results in comparison with CPAP or CPAP-ASB [3]. From a practical point of view CPAP has been shown to be cheaper and easier to use and implement in clinical practice, so it should be the preferred intervention [24]. The equipment necessary to apply CPAP-ASB and BIPAP is technically more sophisticated than the equipment necessary to deliver CPAP [3]. To be able to apply CPAP, only a breathing gas source, a face mask and a turbulent flow valve are necessary (Boussignac) [24]. In our study, we used a portable ventilator to create all three NIV-modes. As this clinical investigation was conducted in a physician-based EMS, the decision to intensify NIV to the next level was only made by physicians based on the criteria described in the Methods section.

4.3. On-scene time, transport time, NIV-treatment time

Total prehospital time consists of response time (the time from ambulance call receipt to arrival of the ambulance at the scene), on-scene

Table 2

Vital functions at the end of prehospital treatment (at hospital admission).

	Control n = 30	NIV-1 n = 41	NIV-2 n = 58
Dyspnea score _{HA} (points)	7.0 (5.0, 8.0)*	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)
Breathing rate _{HA} (breaths·min ⁻¹)	24.0 (21.0, 26.0)*	16.0 (14.0, 18.0)	17.0 (15.0, 18.0)
SpO ₂ _{HA} (%)	91.0 (89.0, 94.0)*	97.0 (96.0, 99.0)	97.0 (96.0, 99.0)
Blood pressure _{systolic HA} (mm Hg)	158.0 ± 25.6*	130.0 ± 19.4	131.5 ± 18.8
Heart rate _{HA} (beats·min ⁻¹)	105.4 ± 19.2*	96.3 ± 15.3	95.7 ± 12.7

Control = standard oxygen therapy by face mask, NIV-1 = non-invasive-ventilation (duration ≤ 15 min), NIV-2 = non-invasive-ventilation (duration > 15 min), SpO₂ = peripheral capillary oxygen saturation, HA = hospital admission (patient transfer between EMS-team and ER-team), results are presented as mean (±SD) or as median (IQR), if the data were not normally distributed.

* p < 0.001.

time, and transport time. While response time and transport time can only be influenced by organizational measures that concern the entire EMS, the duration of on-scene time is directly affected by the activity of the emergency team. Several authors have shown that a prolonged on-scene time, and thus the prolongation of total prehospital time, is associated with negative effects on the outcome of critically ill patients [25–27]. Taking these findings into account, Nielsen et al. stated that distance and transport time to hospital are important factors when deciding how to treat patients with ARF at the scene as well as during ambulance transport [6]. These authors describe the difficult balance between time used to initiate a prehospital treatment and a faster arrival to definitive treatment at hospital. It was shown in their study, that NIV was effective in an EMS-system with a mean treatment time of 35 min, reflecting a relatively long transport time in a rural area. In our study, a significantly shorter treatment time between 10 and 30 min was seen, associated with similarly good results. Accordingly, we agree with the view that early initiation of NIV-treatment is important for success [3].

Essential preconditions for a successful out-of-hospital use of NIV are special training programs for Emergency Physicians and Emergency Medical Technicians as well as appropriate equipment. Our data show that only a minimal additional time of about 6 to 7 min is necessary to apply NIV using a transport ventilator. Considering the demonstrated high efficacy of NIV, this additional time is well justified.

4.4. Limitations

Our study has some limitations that need to be discussed. First of all, we can only speculate as to whether the improvements in vital functions caused by NIV-treatment can lead to a better patient outcome as well. Secondly, another weakness is the inclusion of a retrospective data collection from a historical control group that was treated with standard care. However, as already mentioned above, we have ethical concerns about denying effective therapy to seriously ill patients. Thirdly, the step-by-step approach escalating the NIV-application from CPAP to CPAP-ASB and finally BIPAP – if vital signs did not show substantial improvement – was based on a partially subjective assessment made by the Emergency Physician. However, 90% of the patients included received CPAP-ASB anyway. And finally, our results are considered to be useful with regard to big cities and metropolitan areas in Germany, but our findings cannot simply be transferred to rural districts or other countries.

5. Conclusion

Prehospital use of NIV in patients with ARF results in a fast and significant improvement of vital functions such as blood pressure, heart rate, breathing rate, and oxygenation. This stabilizing effect seems to be largely independent of the duration of NIV-treatment. As used in our study, NIV-treatment was effective even when applied only for a short period of time. Prehospital NIV-treatment should be performed

in patients with COPD-exacerbation and CPE, even if the distance between scene of emergency and hospital is short. Provided that NIV-treatment will be performed by a well-trained emergency team, only a minimal additional time is necessary to apply non-invasive ventilation. CPAP should be considered as first line intervention, because it is cheap and easy to implement in clinical practice. The question as to whether prehospital NIV-treatment also results in a better patient outcome must be definitively answered in future studies.

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In memoriam Mike Sebastian Strunden.

Conflicts of interest

None.

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