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Predictors of respiratory function deterioration after transfer of critically ill patients

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Abstract *Objectives*: Critically ill patients are often transferred due to the growing number of diagnostic procedures required to be performed outside the intensive care unit. These transfers have proved to be very critical. The aim of this study was to evaluate predictors for the deterioration of respiratory function in critically ill patients after transfer.
Design: Prospective, clinical, observational study.
Setting: 1800-bed university teaching hospital.
Subjects: 98 mechanically ventilated patients were investigated during transfer.
Measurement and main results: Before transfer, all patients were classified according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Therapeutic Intervention Scoring System (TISS). Haemodynamics and arterial blood gases were measured at 11 different times. Arterial oxgen tension (PaO_2), fractional inspired oxygen (FIO_2), PaO_2/FIO_2 ratio, lowest PaO_2/FIO_2 ratio, minimal PaO_2 and maximal FIO_2, APACHE II score, TISS before transfer, age and duration of transfer were analysed as potential predictors for deterioration of respiratory function after transfer. Variables were analysed using Classification and Regression Trees and Clustering by Response. In 54 transports (55 %) there was a decrease in the PaO_2/FIO_2 ratio, and a decrease of more than 20 % from baseline was noted in 23 of the transferred patients (24 %). Age > 43 years and $FIO_2 > 0.5$ were identified as predictors for respiratory deterioration.
Conclusions: Our predictors were able to indicate deterioration after transfer correctly in 20 of 22 patients (91 %), combined with a false-positive rate in 17 of 49 (35 %).

Key words Transportation of patients · Critical illness · Mechanical ventilation · Critical care · Predictors

Introduction

Critically ill patients often need diagnostic and therapeutic procedures performed outside the intensive care unit (ICU) for optimal patient care. This results in a growing number of transfers within or between hospitals [1]. These transfers appear to be among the most critical phases in intensive care therapy, showing a high incidence of complications [2, 3] and deterioration of respiratory function during and after transfer [4].

Because the possibilities for treatment are reduced during the transfer period, it is difficult to maintain ICU levels of therapy and monitoring. It is as yet impossible to continue the up-to-date ventilatory modes available on the modern ICU ventilator while using simple portable ventilators [5]. It has been demonstrated that no matter how short the transfer distance or time pa-

Table 1 Haemodynamics and arterial blood gas values were measured in all 98 patients at 11 predetermined times over 48 h

Times	
t 1	24 h before transfer
t 2	12 h before transfer
t 3	4 h before transfer
t 4	Before changing ventilator on the ICU
t 5	Arrival at the transfer destination
t 6	Departure from the transfer destination
t 7	After changing ventilator on the ICU
t 8	1 h after arrival
t 9	4 h after arrival
t 10	12 h after arrival
t 11	24 h after arrival

tients are at a greater risk during transfer than on the ICU [6].

Taking these risks into account, the potential consequences or benefit of the diagnostic investigation for a change in patient management have to be considered carefully [7, 8]. Therefore, it would be useful to have predictors to identify the patients whose conditions might deteriorate. Predictors would be valuable for weighing the benefit of the diagnostic procedure to the patient against the hazards of transfer before it takes place. This study was designed to determine predictors for the potential deterioration of respiratory function in critically ill patients after transfer.

Materials and methods

After we obtained the permission of the local ethics committee, 98 patients were investigated. All data were collected prospectively during scheduled transfer from an ICU for diagnostic reasons; 74 transfers were performed within the hospital and 24 outside the hospital. All patients were mechanically ventilated throughout study period and were accompanied during transfer by a physician, usually an anaesthesiologist. All physicians were senior registrar or consultant level. Neuromuscular blockade and sedation were used as appropriate.

The patients were classified according to the Acute Physiology and Chronic Health Evaluation (APACHE) II [9] and the Therapeutic Intervention Scoring System (TISS) [10] from data obtained immediately before transfer. Arterial blood pressure, heart rate and electrocardiography were monitored continuously during transfer with a portable device. Additionally, oxygen saturation, respiratory rate and end-tidal CO_2 were monitored in the transfer period by pulse oximetry and capnometry in most patients. Arterial blood gases were measured at 11 different times (4 during transfer) in a period of 48 h (Table 1). All arterial blood samples were stored immediately in ice water or a cool pack [11] for a maximum of 30 min [12]. Analyses were performed under standard conditions with a Radiometer ABL 300 blood gas analyser. During transfer, all patients were ventilated with a time-cycled, volume-constant portable ventilator (Oxylog, Drägerwerke, Lübeck, Germany). A suction device was available during transfer and at the destination. Most patients needed a fractional inspired oxygen (FIO_2) < 0.5 on the ICU and were ventilated during transfer with the fixed position "air mix" ($FIO_2 = 0.6$). Patients needing an $FIO_2 > 0.5$ on the ICU were ventilated with the position "no air mix" ($FIO_2 = 1.0$). Positive end-expiratory pressure (PEEP) was maintained at the same level as on the ICU. After transfer the same level of arterial oxygen tension (PaO_2) was maintained if possible as before. The FIO_2 was set to produce an arterial saturation of 95 to 99 %. The following variables were examined as potential predictors of deterioration of respiratory function after transfer: PaO_2, FIO_2, PaO_2/FIO_2 ratio, lowest PaO_2/FIO_2 ratio, minimal PaO_2 and maximal FIO_2 at four times in the 24 h period before transfer (t1–t4, Table 1), age, APACHE II score, TISS and duration of transfer. As criteria for deterioration of respiratory function we regarded: a PaO_2/FIO_2 ratio below 250 after transfer, or a reduction in the PaO_2/FIO_2 ratio of more than 20 % 1 h after transfer compared to the pretransfer level (t8:t4).

As statistical procedures, Classification and Regression Trees (CART) [13] and Clustering By Response (CBR) [14] were applied in order to identify predictors and specific constellations of predictor values that are typically associated with deterioration. CART was applied to the original versions of the potential predictors, while in CBR all variables were dichotomised before the analysis. Cut-points were chosen according to known critical values of clinical variables; for the variable "age", the result of CART analysis was used. Validation of the results was performed by permutation tests in the CBR analysis and by cross validation in CART.

CART or CBR analysis was preferred to standard procedures like multiple or linear logistic regression because of two specific features that are relevant for the present study. Firstly, the result of a CART or CBR analysis is the division of the population into distinct subgroups related to different levels of deterioration. Thus, instead of finding a regression equation, such an analysis will directly produce a selection rule to identify subgroups at low and high risk. Secondly, for both procedures the identification and inclusion of interaction effects among the predictors are an integral part of the analysis. CART, as a tree-structured method, sequentially splits the study population into subgroups (called "nodes") of growing homogeneity with respect to the distribution of the criterion variable, the deterioration. Therefore, for each node of the growing tree all possible splits of the form "$(X \leq c)$ versus $(X > c)$" for any predictor X and any cut-point c are checked to provide the best further split. Thereby, an incorporated cross-validation procedure essentially prevents the generation of invalid trees that would otherwise occur due to overfitting the sample data in a complex model. In contrast to this "locally optimal" splitting process, CBR analyses series of different segments of the populations and finally selects the best one globally. However, in contrast to CART, only binary predictors are allowed for this procedure.

Results

In all of the 98 patients all measurements were complete. None of the patients died during transfer or in the observation period; 29 female and 69 male patients with a mean age of 46 ± 18 years (range 16–89) were transferred (Table 2). Mean transfer time was 84 ± 51 min (range 22–275). Admission diagnoses were: multiple injuries (28 %), severe head trauma (19 %) or intracerebral pathology (21 %), transplantation surgery (11 %), cardiothoracic surgery (11 %), intra-abdominal pathology (8 %) or other (2 %). Indication for computed tomography was the main reason for transfer

Table 2 Demographic data before transfer in all 98 investigated patients. Data are given as mean ± standard deviation and range. (*APACHE* Acute Physiology and Chronic Health Evaluation, *TISS* Therapeutic Intervention Scoring System)

Sex	Female	29 (30 %)
	Male	69 (70 %)
Age (years)		46 ± 18 16–89
Duration of transfer (min)		84 ± 51 22–275
APACHE II score		13 ± 5 3–29
TISS score		41 ± 6 31–64

(61 %); other reasons were radiological investigations such as angiography (9 %), positron emission tomography (4 %), magnetic resonance imaging (3 %) or sintigraphy (3 %). The mean APACHE II score was 13 ± 5 (range 3–29) and the mean TISS was 41 ± 6 (range 31–64) (Table 2). Six months after transfer the overall mortality for the 98 patients was 27 %. The relationship between the APACHE II score and hospital mortality was significant. No statistically significant difference was found in haemodynamics during the transfer period compared with the pretransfer level.

Baseline data for predictors investigated are given as mean ± SD or as frequencies in Tables 2 and 3. In 54 transfers (55 %) the PaO_2/FIO_2 ratio was impaired 1 h after arrival on the ICU (t8) compared to baseline measured directly before transfer (t4). A decrease of 20 % or more (t8:t4, t4 = 100 %) was noted in 23 patients (24 %). After 24 h this deterioration of respiratory function continued in 18 patients (18 %).

For both criteria of deterioration defined above, CART analysis proved the pretransfer PaO_2/FIO_2 ratio was the most significant prognostic variable. According to the results of the CART analysis we created two subgroups of main interest: 27 patients with a pretransfer PaO_2/FIO_2 ratio below 250 (group 1) and 71 patients with a pretransfer PaO_2/FIO_2 ratio above 250 (group 2).

A PaO_2/FIO_2 ratio below 250 after transfer was found in 20 of 27 (74 %) patients in group 1, compared with 13 (18 %) of the 71 patients in group 2. The critical value of 250 of the pretransfer PaO_2/FIO_2 ratio that separates groups 1 and 2 was not predefined but was revealed by the CART program. When all patients were analysed, the criteria for deterioration were studied separately. For patients in group 2 deterioration was assumed if one or two of the criteria were fulfilled. A decrease of 20 % or more in the PaO_2/FIO_2 ratio compared to the pretransfer level (t4) was less frequent in group 1 (3/27 = 11 %) than in group 2 (20/71 = 28 %). Thus, group 1 had a low pretransfer PaO_2/FIO_2 ratio (< 250) that was stable against a further decrease; in 75 % of the patients it remained below the 250 limit (Fig. 1), whereas in 25 % of group 1 patients it increased to over 250 after transfer compared to the pretransfer level. For patients in group 2, either of the two criteria of deterioration was regarded as clinically relevant. Using these criteria, 22 of 71 (31 %) patients deteriorated in group 2.

CART identified 43 years of age in a patient as a cut-point as the best predictor for deterioration: in group 2, 18 of the 22 patients who deteriorated were older than 43 years and 4 were younger than 43 years (Table 4).

CBR showed the same result. Additionally, it identified FIO_2 as a second valid predictor: all five patients

Table 3 Levels of PaO_2, FIO_2 and PaO_2/FIO_2 ratio during the study period in group 1 (n = 27) and group 2 (n = 71). Data are given as mean ± standard deviation and range

	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11
FIO_2											
Group 1	0.44 ± 0.13 0.3–0.7	0.5 ± 0.22 0.3–1.0	0.49 ± 0.19 0.3–1.0	0.55 ± 0.18 0.3–0.91	0.69 ± 0.17 0.6–1.0	0.69 ± 0.17 0.6–1.0	0.54 ± 0.2 0.3–1.0	0.5 ± 0.17 0.3–0.8	0.46 ± 0.15 0.3–0.8	0.46 ± 0.16 0.3–0.8	0.46 ± 0.18 0.3–0.8
Group 2	0.35 ± 0.07 0.21–0.5	0.33 ± 0.06 0.21–0.6	0.34 ± 0.12 0.21–1.0	0.35 ± 0.13 0.21–1.0	0.61 ± 0.07 0.6–1.0	0.61 ± 0.07 0.6–1.0	0.42 ± 0.19 0.25–1.0	0.36 ± 0.13 0.21–1.0	0.33 ± 0.06 0.21–0.5	0.33 ± 0.06 0.21–0.5	0.32 ± 0.04 0.21–0.4
PaO_2 (mmHg)											
Group 1	104 ± 31 50–203	90 ± 27 48–166	98 ± 20 74–145	94 ± 28 52–170	144 ± 59 64–293	150 ± 69 55–302	129 ± 70 58–291	98 ± 33 61–222	105 ± 31 59–207	106 ± 21 76–148	110 ± 26 78–160
Group 2	118 ± 36 45–241	112 ± 26 32–182	116 ± 30 55–185	130 ± 69 71–515	212 ± 69 72–428	216 ± 77 70–525	141 ± 75 62–440	113 ± 29 67–178	112 ± 27 66–192	111 ± 22 62–176	110 ± 26 47–177
PaO_2/FIO_2											
Group 1	258 ± 90 83–413	209 ± 79 76–377	224 ± 82 89–440	182 ± 55 57–249	212 ± 77 73–410	224 ± 97 75–460	245 ± 107 69–469	208 ± 62 78–357	247 ± 92 98–414	251 ± 90 111–467	266 ± 93 111–497
Group 2	344 ± 100 90–610	346 ± 90 106–607	352 ± 98 155–610	371 ± 76 251–563	346 ± 107 120–606	356 ± 130 117–875	354 ± 143 83–753	334 ± 104 82–593	348 ± 90 181–557	344 ± 77 221–540	351 ± 91 155–590

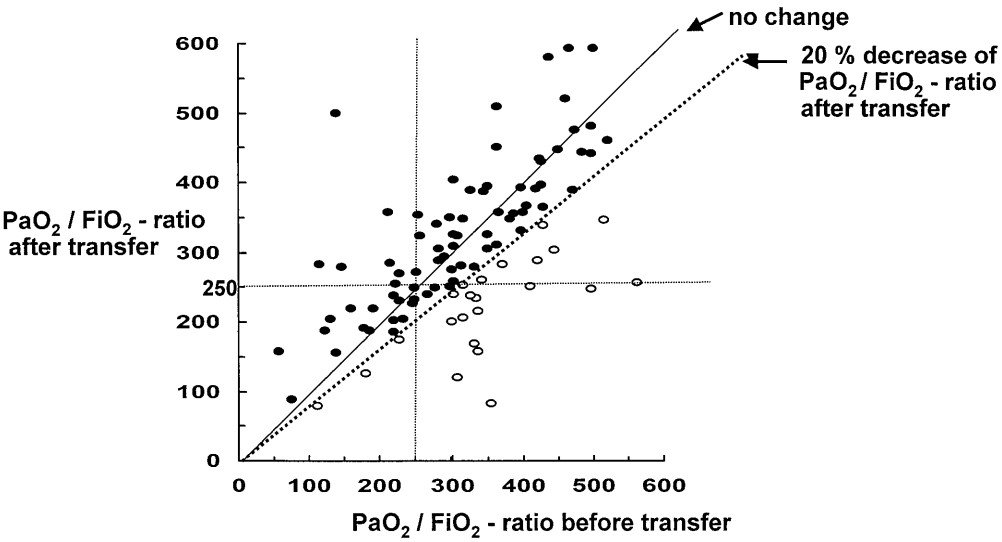

Fig. 1 Individual data for change in PaO_2/FIO_2 ratio after transfer compared to pretransfer levels [t4] in patients with no deterioration > 20 % *closed circles* and patients with deterioration > 20 % *open circles*

Table 4 FIO_2, age and FIO_2 and age combined analysed as predictive variables by CART and CBR in the 71 patients with a PaO_2/FIO_2 ratio > 250 before transfer (group 2). Data are given as numbers and percentages (*CART* Classification and Regression Trees, *CBR* Clustering by Response)

Variables	No deterioration *n* (%)	Deterioration *n* (%)	Total *n* (%)
$FIO_2 > 0.5$	0 (0)	5 (100)	5 (7)
$FIO_2 < 0.5$	49 (74)	17 (26)	66 (93)
Total	49 (69)	22 (31)	71
Age > 43 years	17 (49)	18 (51)	35 (49)
Age ≤ 43 years	32 (89)	4 (11)	36 (51)
Total	49 (69)	22 (31)	71
Age > 43 years, $FIO_2 > 0.5$ or both	17 (46)	20 (54)	37 (52.1)
Age ≤ 43 years and $FIO_2 \leq 0.5$	32 (94.1)	2 (5.9)	34 (47.9)
Total	49 (69)	22 (31)	71

who needed an FIO_2 of more than 0.5 deteriorated after transfer, compared with 17 of 66 (26 %) patients with an FIO_2 equal to or less than 0.5 (Table 4). According to the 5 % significance permutation test of CBR, a combination of both predictors resulted in an additional improvement of the prediction: the deterioration rate was 2 of 34 (6 %) for younger patients (43 years) who needed an FIO_2 0.5 compared to 20 of 37 (54 %) patients with one or both predictors positive (Table 4). If used as a prognostic classification, this corresponds to a sensitivity of 20 of 22 (91 %) and a specificity of 32 of 49 (65 %). Cross-validation results for CART indicate that only a slight decrease in these numbers, due to the overfitting phenomenon, has to be assumed.

Discussion

In the 71 patients with a pretransfer PaO_2/FIO_2 ratio above 250 in our study we could identify age > 43 years and $FIO_2 > 0.5$ immediately before transfer as predictors of deterioration of respiratory function after transfer. These findings may help to weigh the potential benefits of performing the diagnostic procedure against the potential for complications during transfer. The importance of accurate prediction to avoid inappropriate transfers has been emphasized previously [15, 16]. It has been demonstrated that the subsequent management was changed in only 39 and 24 % of patients within 48 h after transfer [7, 8], but 68 % of the patients underwent potentially serious physiological changes during transfer.

Changes in arterial blood gases are common during transfer, especially when ventilator-dependent patients are ventilated manually during this period [17]. Braman et al. [18] demonstrated that using portable mechanical ventilators for intrahospital transport resulted in a significant improvement in arterial blood gas values. Although in our study all patients were ventilated with a time-cycled, volume-constant, portable ventilator during transfer, a decrease in the PaO_2/FIO_2 ratio afterwards was noted in 55 % of the patients.

One hour after arrival on the ICU a reduction of 20% or more in the PaO_2/FIO_2 ratio compared to the pretransfer level occurred in 23 patients (24%): in 3 of 27 patients in group 1 (11%) and in 20 in 71 patients of group 2 (28%). Thus implies that the PaO_2/FIO_2 ratio remained low in 74% of group 1 patients and improved in 26% of group 1 patients. The reason for this might be that it is accepted that caring for an unstable critically ill patient requires extensive services or participation of more senior staff, although all physicians in the present study were at least senior registrar level. The significance of the training and expertise of the staff as the most important determinant of quality of care during transfer has been pointed out frequently [15, 19].

Five patients needed up to 24 h for recovery, however in 18 patients the deterioration persisted longer than 24 h. An interval of 1 h was chosen to exclude transitory changes in respiratory function but to detect changes in respiratory function, which were transfer related. No further medical intervention, e.g., bronchoscopy, occurred in this period. None of the patients had any invasive medical or surgical interventions even within the first 24 h after transfer.

These results were confirmed by Waydhas et al. [4]. They reported a decrease in the PaO_2/FIO_2 ratio in nearly 84% of their transfers, and in 43% an impairment in the PaO_2/FIO_2 ratio of more than 20% compared to the pretransfer levels occurred 1 h after arrival on the ICU. In 20% of their patients this major deterioration of respiratory function after transfer lasted for over 24 h.

The reasons for the deterioration of respiratory function are not easy to identify considering all the potential influences on and risks of deterioration of the patient's condition caused by the transfer itself. In the present study the predictors analysed should help to identify patients at risk for deterioration of respiratory function after transfer. The objective of the present study was not to evaluate data to clarify underlying pathophysiologic mechanisms and reasons for deterioration. However, changes in the patient's posture, sedation or pulmonary blood flow may cause changes in shunt. Additionally, the use of portable ventilators might be an important factor. None of the ventilators used at present are capable of continuing the sophisticated ventilatory support of modern ICU ventilators, e.g. decreased gas flow or accurate inverse ratio ventilation (IRV), which build up intrinsic PEEP, although the recently introduced Oyxlog 2000 (Dräger, Lübeck) has more facilities than most [20]. The pre-existing intrinsic PEEP is even lost by disconnection in changing ventilators. This can be prevented by clamping the endotracheal tube during this manoeuvre. The importance of this is supported by the fact that neither Waydhas et al. nor we have found a relation between duration of transfer and respiratory deterioration indicating the early transfer period, including changing of ventilators, as the determinant. Waydhas et al. tried to evaluate APACHE II, transfer time, PEEP, age of patient, initial PaO_2/FIO_2 ratio, initial PaO_2 and absence from the ICU as predictors for deterioration of respiratory function after intrahospital transfer [4]. The use of PEEP as a predictor seems to be questionable, because predictors ideally should be independent variables and we regard PEEP as an important part of the therapy [21]. We admit that FIO_2, one of our predictors, is a therapeutic modality like an administered PEEP. But an increase in a required FIO_2 is mandatory rather than therapeutic to prevent hypoxemia, when all the therapeutic modalities like IRV, setting of respiratory rate, setting of peak inspiratory pressure or kinetic therapy fail to normalize oxygenation. Furthermore accurate measurement and maintenance of PEEP during transfer is difficult in respect of changes in the position of the patient, analgesia/sedation, pulmonary blood flow and the use of portable ventilators [15].

Using CART and CBR to analyse the 71 patients age > 43 years and $FIO_2 > 0.5$ were identified as predictors for deterioration of respiratory function after transfer. The predictor $FIO_2 > 0.5$ was analysed as a very specific variable (100%), but this subgroup consisted of only 5 patients. The need for an $FIO_2 > 0.5$ might be because of trauma to the thorax – lung contusion, ARDS or pneumonia. Pneumonia is a frequent problem in patients who require mechanical ventilation for more than 48 h [22]. Furthermore, the incidence of pneumonia is related to the underlying lung injury, prolonged preoperative hospitalisation and a thoracic or upper abdominal incision. The elderly are particularly at risk for pneumonia [23, 24]. Szem et al. [25] demonstrated that the length of stay on an ICU for the patient who required transfer was three times that in the APACHE-matched control group, indicating that the patient who needed intervention outside the ICU is a more severely ill patient. In consequence this may result in more invasive ventilatory therapy and a greater need for FIO_2.

The age of a patient is well documented as an important factor that affects morbidity and hospital mortality [26–28]. Age is one of the pretreatment determinants helping to predict outcome of critical illness before treatment starts. The cut-point of 43 years in our study seems to be low, but has to be interpreted in relation to our patient population with a mean age of 46. In contrast to our results, Szem et al. [25] reported a mean age of 65 years in 175 transferred patients, whereas Gentleman reported a mean age of 33.2 years in 600 neurosurgical patients requiring interhospital transfer [29]. However, it has to be assumed that the cross-validation results of CART indicate only a slight decrease in the classification results, due to the overfitting phenomenon.

Several investigators tried to evaluate the usefulness of measuring the severity of illness to predict the risk of

complications during transfer. In our study we did not find a correlation for the APACHE II score as a predictor for deterioration of respiratory function, but we showed a correlation between hospital mortality and the APACHE II score. Similar to our results, Bion et al. [19] reported a significant correlation between APACHE II and hospital mortality in a study of 50 transferred patients. However, it seems questionable whether the evaluation of a severity illness score is helpful in identifying the risk of complications during an ICU transfer. As such, its use as a predictor is doubtful.

In conclusion, the decision to transfer a ventilated patient must be made carefully. The analysed variables of age > 43 years and required $FIO_2 > 0.5$ as predictors for respiratory deterioration after transfer were easy to achieve and correct in 20 out of 22 patients (91 %). In 2 patients they did not predict deterioration (false-negative rate) and were inaccurate in 17 patients (35 %) (false-positive rate), indicating that the combined use of our predictors is sensitive (91 %), but not very specific (65 %). This missing specificity is explained considering all the potential influences and risks for the patient caused by the transfer. Our predictors allow the physician to identify patients at risk before transfer and to assess the benefit of a diagnostic procedure in each individual case against the hazards of transfer.

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