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Definition of severity and compiling of entry criteria in patients undergoing ECLA: the use of a fuzzy logic expert system

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Extracorporeal lung assist (ECLA) has been proposed as an ultimate approach to treat patients with severe adult respiratory failure (1). Since the first successful extracorporeal membrane oxygenation (ELMO) performed by Hill et al. 1972, survival rate in these patients has not improved and mortality remains high (90%). Despite the discouraging results of the first multicenter ECMO study in adults, Kolobow and co-workers (2) started a new program of lung assist called extracorporeal CO₂ removal (ECCO₂-R) in addition to a low-frequency positive-pressure ventilation. By means of this new technique several European centers are able to show a significant increase in survival from 10% to 50%. However, because of a lack of uniformly accepted entry criteria, it is unclear whether the patients treated with ECLA can be compared. In a prospective randomized controlled study, Morris and co-workers investigated 40 patients with ARDS, 21 of this group with ECCO₂-R, 19 with pressure-controlled inverse-ratio ventilation. The authors found no significant difference in the survival rates of both groups (33% vs. 42%), but the survival rate was significant better than in the former randomized US trial. As a result the authors concluded that the use of an extracorporeal approach in patients with adult respiratory failure cannot be recommended.

In contrast to the most American centers, in Europe, the ECLA technique became more and more an accepted therapy and the

introduction of heparin-coated systems reduces the risk of bleeding, one of the major side effects. However, the use of uniformly accepted entry criteria in these patients should be the first step to increase the acceptance of ECLA world-wide. The goal of this multicenter study was therefore first to compare recently used entry criteria for inclusion of ARDS patients by means of a computerised protocol and secondly to design a patient state monitor on basis of uniformly accepted criteria.

Patients and methods:

The definition of the criteria as provided by the different centers is informal by nature and therefore not suited for direct implementation in an exact evaluation system. To overcome this inherent problem, we suggest replacing the classic logic (employing operators such as "AND" and "OR") which treats all operands equally by a general scoring system that allows weight to be given to certain criteria to reflect their importance, enabling compensation of diverging parameters at the same time. In addition, sharp boundaries as defined in the original criteria can be replaced by continuous transition from „ criterion not fulfilled“ to „criterion fulfilled“ through introduction of „fuzzy limits“.

While scoring as opposed to logical operators can indicate the number of criteria which are fulfilled, it cannot account for the case where one criterion is a near miss rather a clear deviation from the definition. For this purpose, the concept of fuzzy limits is introduced. A fuzzy limit may be regarded as a blurred boundary defined by two thresholds, one separating clear fulfilment from indecision/fulfilment (usually the original bound) and the other separating nonfulfilment from indecision/fulfilment. Fuzzy limits are denoted by a pair of numbers, the first representing the value below (or above, depending on the comparison operator) by which the condition is fully fulfilled; the second limit denotes the bound at which it is certainly not fulfilled (3).

Because most databases are incomplete in the sense that not all parameters have been entered, special measures must be taken to deal with so called "null" or nil values. A null value is not a special value (in particular, it must not be confused with zero!), it rather denotes the fact that the actual value simply is not known for any reason. For example, risk = null means that we do not know whether a risk factor is present or not. Null values required special treatment in the evaluation of conditions as employed in this study. Three-valued logics (comprising true, false, ill known) have been proposed and specified through respective truth tables for common logic operators such as "AND" or "OR".

General properties of the patient state monitor are first, the possibility to abstract from on-line parameters in two steps by calculating derived parameters such as paO₂/FIO₂ or scores and to determine the current state of the patient by taking both the actual and the previous state into account. This is in opposition to conventional monitors that cannot relate their variables to the patients history. Apart from automatically abstracting on-line information into a state that represents the result of an objective assessment of patient parameters, this approach allows also for context-specific interpretation of parameters such as paO₂/FIO₂ < 150 being a possible precursor for the ECLA state, while a rise to 250 does not necessarily indicate an improvement in the patients state, let alone imply his release. Secondly, this property is particularly useful in alarming, as thresholds on single parameters may vary depending on the actual stage of the disease

or the treatment of the patient. Thirdly, the monitor should provide an explicit definition of sequences of states and thus modelling of natural stages of a disease and give a implicit integration of time, as the current state always comprises the patients history.

The following variables are used for entry criteria: paO_2/FIO_2 , PEEP, peak inspiratory pressure, minute volume, mixed venous saturation, Morel score, compliance, Q_s/Q_t , extravascular lung water, Murray score, age, PCWP, mean pulmonary pressure, $paCO_2$, $AaDO_2$, tidal volume.

Results:

To provide preliminary data on the percentage of ECLA entry-criteria fulfilment, we investigated 88 patients with severe ARDS from two centers (Berlin and Vienna). Of these, 34 patients underwent ECLA therapy and 54 patients were conventionally treated. The degree of fulfilment of each phase of entry criteria is shown in table 1. Using the computerized protocol in patients from the center UKRV-Berlin, we found a fulfilment of entry criteria from center I (Marburg) in 56%, from center II (Milan) in 87%, from center III (Berlin) in 76%, from center IV (Paris) in 86%, from center V (USA ECMO trial) in 78% . Using the same protocol in Berlin, we found a fulfilment of 42% (center I), 66% (center II), 58% (center III), 70% (center IV) and 63% (center V). The survival was 67% in the ECLA -treated group and 89% in the control group.

Discussion:

These preliminary results from our pilot study show, that none of the entry criteria used in the 5 centers is able to differentiate between patients who should be treated with ECLA or extended conventional therapy. In addition, there was no uniform fulfilment of entry criteria from each center, indicating the use of different entry criteria and levels of variables in the 5 different centres. However, resulting percentages of fulfilment of criteria may be useful in a prospective randomized multicenter European study on patients treated with ECLA and compared to those with a conventional approach. Different therapeutic approaches and the use of technical advances (like heparin-coated systems) may be of disadvantage in case of a multicenter European study. Recently published excellent results (mortality 20% !) in these patients with a high mortality risk of more than 60% and a wide range of survival rates between 17% and 81 % points towards a certain role of the entry criteria therapeutic strategies and exact demographic information of these patients. To use a possible alternative to this very difficult and ethically problematic multicenter study, it may be possible to compare all relevant data of patients in a database (similar to the database of the US extracorporeal life support cooperation [ELSO registry]). By using all entry criteria it is possible to compare different centers and patients, and using the patient state monitor, it may be possible to perform an exact request (via "Internet", e.g.) to check the "international " recent status of the patients before and after fulfilment of entry criteria.

Traditional computer science offers a palette of formalism that

deal with such things as events, states and sequences. Among these, the concept of finite deterministic automata or finite state machines seems simple and powerful enough to be applied to the problem of monitoring. This concept of states accounts for the different stages of illness of a patient and this concept of transition accounts for the fact that a patients state changes over time based on events or conditions defined by the patients data. It was therefore decided to develop an intelligent monitoring system that combines both recording and displaying of on-line parameters with an expert-like objective evaluation of the observations. The goal was not only to present information at a higher level of abstraction, but also to enable the physician to base his decisions on objective conditions, which is not only necessary to increase quality and cost- containment of medical care but also a fundamental precondition for multicenter studies.

Further studies are necessary to develop uniformly accepted entry criteria for allowing a reliable decision as to which patients should be treated with this expensive therapy.

Table. Fulfilment of entry criteria from 5 different centers during 4 phases of evaluation.

	TP1	TP2	TP3	TP4	MP
a) patients with ECLA therapy from center Berlin (n=34)					
CNTR 1	56%	30%	27%	20%	34%
CNTR 2	87%	86%	87%	76%	84%
CNTR 3	76%	69%	67%	49%	66%
CNTR 4	86%	81%	78%	69%	79%
CNTR 5	78%	74%	74%	75%	75%
b) patients with ECLA therapy from center Vienna (n=6)					
CNTR 1	69%	39%	51%	42%	50%
CNTR 2	98%	86%	79%	67%	82%
CNTR 3	91%	73%	72%	62%	74%
CNTR 4	84%	80%	92%	78%	83%
CNTR 5	82%	65%	72%	68%	72%

CNTR1=Marburg, CNTR2=Milan, CNTR3=Berlin, CNTR4=Paris, CNTR5=USA
 TP1= 24 hsr before ECLA, TP2= 24 hrs after onset of the bypass, TP3= on day 7 on bypass, TP4= end of bypass, MP= Median value of all 4 phases

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