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Algorithmic distinction of ARDS and Heart Failure in ICU data from medical embedded systems by using a computer model ⋆

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Abstract: Acute Respiratory Distress Syndrome (ARDS) is a common cause for respiratory failure and has a high mortality rate of 30-40% in most studies. The current standard for the diagnosis of ARDS was proposed by the Berlin Definition from 2012. This article proposes an algorithmic classification to distinguish between patients with ARDS and those with heart failure (HF). Currently, the available database is not sufficient in regards to the necessary data quality to evaluate this classification. Therefore an approach of simulating data for patients with ARDS and HF by using a computer model was implemented. The model and classification are evaluated using selected patient data, which is recorded with medical embedded systems in intensive care units, as an input for the simulation. The included scores provide a retrospective assessment of whether or not a patient has developed an ARDS.

Keywords: Medical applications, Classification, Modeling, Diagnostic inference, Computer model, Simulation, ARDS

1. INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS), which was firstly mentioned in literature in the 1960s, is a serious disease with various causes (Ashbaug et al. (1967)). In an epidemiologic study, where Intensive Care Units (ICU) of 50 countries took part, about 10 percent of all patients admitted fulfilled the criteria for an ARDS (Bellani et al. (2016)). A late or even missed recognition of the syndrome might contribute to its high mortality (Bellani et al. (2020)). The most prominent definition of ARDS was presented by the Berlin Taskforce in 2012 and represents the current standard (Rubenfeld et al. (2012)). One criteria of the Berlin Definition defines the distinction or rather exclusion of a heart failure, which usually needs an objective assessment (e.g. echocardiography) by a physician. Echocardiograms or imaging results are not commonly available for every patient and their generation is associated with effort and time. Thus, we propose an algorithmic classification for the retrospective distinction of HF and ARDS. This classification is based on continuous vital signs, which are recorded by medical embedded systems, and laboratory results. Scores, that are calculated with recorded data, are widely adopted in the medical field and can support the physician during the diagnosis process, as p.e. the SOFA-score, which provides an degree of organ dysfunction of a patient (Lopes-Ferreira et al. (2001)). To validate this classification, a database, referred to as ICCA-DB, is provided by the University Hospital Aachen and comprehends 27,256 deidentified patients. As the average time between two datapoints of necessary vital signs in the ICCA-DB is about 170 minutes, a continuous evaluation of the patient status is difficult. Especially the arterial oxygen partial pressure P_aO_2, which is necessary to classify the severity of a possible ARDS, is only measured every 248 minutes on average. Therefore, we implemented a model of the cardiovascular and respiratory system to generate this data. As especially mathematical modeling has been widely established (Verma et al. (1981), Cobelli et al. (2014)), the implemented model addresses a systemic approach and relies on different models from literature, which will be described in the following section.

2. RELATED WORK

During the past decades, a variety of computer models have been proposed in literature adressing different fields

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in the medical context and providing solutions for prediction, classification, diagnostic support or simulation. To simulate physiological relations and test different settings, various computer models have been published over the years: (Grodins and Bart (1967), Fincham and Tehrani (1983), Francheteau et al. (1993), Sailors and East (1994), Winkler and Kaiser (1995), Wilson et al. (2009)). In the context of intensive care, computer models can be used for different purposes. Tehrani et al. for example worked on a model, that includes the mechanical ventilation (MV) for patients with a respiratory failure in order to test different ventilation settings and predict outcomes for the patient, so the best possible treatment can be assessed (Tehrani and Abbasi (2012)).

A different approach was proposed by Francheteau et al. who presented a simplified model which focusses on the cardiac physiology. The main objective is the prediction of hemodynamics in response to drug action on peripheral resistance (Francheteau et al. (1993)). In the book "Cardiovascular and Respiratory Systems" Batzel et al. describe a comprehensive physiological approach for modeling the cardiovascular and respiratory system (Batzel et al. (2007)). The models include differential equations to approximate physiological processes based on literature. The equations of Batzel et al. for the cardiovascular system were selected for this work, as they cover accurately all necessary relationships. Even though Batzel et al. presented a respiratory system as well, the Tehrani model is more suited for the described approach as ARDS patients are usually ventilated. Therefore, in order to generate patient data the models by Tehrani et al. for the respiratory system and the cardiovascular system by Batzel et al. are adapted and further described in Section 4 of this work. The resulting model was evaluated in Section 5 using a value range test for the simulated physiological parameters.

The classification of ARDS and HF patients can be based on various vital signs and laboratory results needed for the estimation. As we can only rely on ICU patient data, parameters, that are based on a physicians assessment of the patients health state and symptoms, are neglected (Ponikowski et al. (2016)). For the classification of patients with ARDS the previously mentioned Berlin Definition is used (Rubenfeld et al. (2012)). It includes four criteria for the recognition of an ARDS of which two criteria will be addressed. For the classification of HF patients the following scores are included. Fonarow et al. developed a score to guide clinicians in estimating the logarithmic mortality risk in patients with an acute decompensated heart failure (Fonarow et al. (2005)). Rajan et al. presented a score, which defines four risk classes for HF based on vital signs and laboratory parameters (Rajan and AlJarallah (2017)). Additionally, to determine a potential HF, various values of the cardiovascular system that correlate to a heart failure are considered. For instance, the ejection fraction for the left ventricle (EF_{LV}) qualifies as an important value to describe the degree of a HF, as an EF_{LV} below 50 percent indicates a cardiac failure (Ponikowski et al. (2016)). In a randomized controlled trial by Böhm et al., the risk for cardiac events, like hospital admission or death, was correlated with the heart rate (Böhm et al. (2010)). Already in moderate areas of heart rate (70 bpm), an increase of 5 beats per minutes resulted in a risk increase of 16%. Lastly, the brain natriuretic peptide (BNP) and the prohormone N-terminal proBNP (NT-proBNP) have proven to be a good indicator for the presence of a cardiac failure (Luchner et al. (2016)). In combination with the age of a patient, different thresholds for the probability of a HF are defined. The calculations for the different scores will be presented in the following section.

3. CLASSIFICATION

3.1 Berlin Definition

The two criteria for an ARDS, which were selected from the Berlin Definition:

1. Origin of pulmonary edema - The respiratory failure is not fully explained by cardiac failure or hypervolemia.
2. Oxygenation level - Horowitz-quotient in combination with ventilator settings positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP)

The first criterion is directly addressed as specific scores are included to rule out the cardiac reasoning for the failure of the lung. The oxygenation level for the second criterion is specified with the Horovitz-quotient:

$$Horovitz = \frac{P_aO_2}{F_iO_2}, \tag{1}$$

where P_aO_2 is the oxygen arterial partial pressure and F_iO_2 denotes the inspiratory oxygen fraction set in the mechanical ventilator. The Horovitz-quotient classifies an ARDS in four severity levels as seen in Fig. 1. Additionally, the PEEP or CPAP, which are common ventilator settings, have to be higher then 5 cmH_2O.

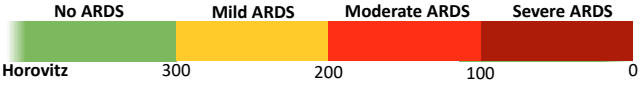

Fig. 1. Severity levels defined by Berlin Definition.

3.2 Rajan's Heart Failure risk score

The heart failure score R^{HF} by Rajan et al. is calculated with the following equation:

$$R^{HF} = \frac{EF \cdot eGFR \cdot Hb}{NTproBNP} \tag{2}$$

where EF denotes the ejection fraction of the left ventricel, Hb denotes hemoglobin and NT-proBNP is the biologically inactive part of brain natriuretic peptide (BNP). $eGFR$ stands for the estimated glomerular filtration rate. Depending on R^{HF} different HF risk levels for a patient are determined (see Fig. 2).

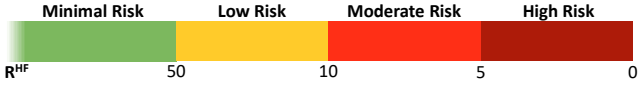

Fig. 2. Severity levels defined by Rajan et al.

3.3 Fonarow score

The score by Fonarow et al. estimates the logarithmic mortality using for the blood urea nitrogen value (BUN), the heart rate (HR) and the systolic blood pressure (SBP) as the most significant mortality risk predictors:

$$\begin{aligned} log\_Fon = 0.0212 \cdot BUN - 0.0192 \cdot SBP \\ +0.0131 \cdot HR + 0.0288 \cdot age - 4.72 \end{aligned} \tag{3}$$

The percentage probability of the patients mortality is then calculated with:

$$p_{Fon} = 10^{Log_{Fon}}. \tag{4}$$

3.4 Heart Failure score

To extend the classification we considered an additional score, referred to as P^{HF}, based on the EF_{LV}, the HR and the NTproBNP to determine the presence of a potential heart failure. Each of these three parameters is mapped to a score in the range of $[0, 1]$ where the arithmetic mean results in the P^{HF} score. A higher score implies a higher probability for the presence of a heart failure. Each score accomplishes a linear regression and is calculated as follows: For $V \in \{HR, NTproBNP\}$:

$$y_V : x \mapsto \begin{cases} 0, & \text{if } x < a_V \\ \dfrac{x - a_V}{b_V - a_V}, & \text{if } a_V \leq x \leq b_V \\ 1, & \text{if } x > b_V \end{cases}$$

and

$$y_{EF_{LV}} : x \mapsto \begin{cases} 0, & \text{if } x < 0 \\ 1 - \dfrac{x}{50}, & \text{if } 0 \leq x \leq 50 \\ 1, & \text{if } x > 50 \end{cases}$$

where for $V \in \{HR, NTproBNP\}$ the following thresholds a_V and b_V with $a_V < b_V$ are defined:

$$a_{HR} = 75min^{-1} \qquad b_{HR} = 200min^{-1}$$

$$a_{NTproBNP} = 300pg/mL$$

$$b_{NTproBNP} = \begin{cases} 450pg/mL, & \text{if } age < 50 \\ 900pg/mL, & \text{if } 50 \leq age \leq 75 \\ 1800pg/mL, & \text{if } age > 75 \end{cases}$$

With y_{HR}, $y_{EF_{LV}}$ and $y_{NTproBNP}$ the final score P^{HF} is calculated. In addition to the previously described scores it can be used to get an estimation for the presence of a heart failure and in accordance with the classification of the Berlin-Definition the exclusion of an ARDS. For a detailed analysis, high-resolution data would be useful, but is currently not available. To simulate such data, a corresponding model is presented.

4. MODELING

In this section the modeling process and underlying methods are described. These include a variety of physiological variables which can be found in table 1. The individual calculations and equations will be omitted as they can be found in the referenced literature. In this approach, the mathematical models of Batzel et al. (Batzel et al. (2007)) and Tehrani and Abbasi (Tehrani and Abbasi (2012)) were implemented, because the models are suitable to simulate ARDS and HF and could efficiently be connected. This model is not used for predictive simulation and is in this context only used for the evaluation of the classification.

Parameter	Description
HR	Heart rate
P_aO_2	arterial oxygen partial pressure
F_iO_2	inspiratory oxygen fraction
P_{as}, P_{ap}	systemic/pulmonary arterial blood pressure
P_{vs}, P_{vp}	systemic/pulmonary venous blood pressure
c_{as}, c_{ap}	systemic/pulmonary arterial compliance
c_{vs}, c_{vp}	systemic/pulmonary venous compliance
S_l, S_r	contractility (left/right)
σ_l, σ_r	derivatives of contractility
R_s, R_p	systemic/pulmonary vascular resistance
P_x, O_2, P_x, CO_2	O_2/CO_2 partial pressure without shunt
C_{vB,O_2}, C_{vB,CO_2}	O_2/CO_2 concentration in brain comp.
C_{vT,O_2}, C_{vT,CO_2}	O_2/CO_2 concentration in tissue comp.
ρ	shunted blood
Q	cardiac output

Table 1. Description of various variables of the cardiovascular and respiratory system.

4.1 ODE-System

To model the respiratory and cardiovascular system based on ordinary differential equations (ODE) the software Simulink/MATLAB by Mathworks was used as it allows an efficient way to model, simulate and analyze dynamic systems. In this implementation a vector x for the cardiovascular system and a vector y for the respiratory system are defined, which include all state variables of each system. For each of these variables exists one ODE $\dot{x}_i = F_i(x)$ and $\dot{y}_i = F_i(y)$ respectively. Additional values are omitted, because they depend on the state vector. To modularize these dependent values in the Simulink-model, an extented state vector $\hat{x}$ is calculated. The state vectors are combined in bus signals and passed on between subsystems in the model. In the highest layer of the model an additional subsystem contains an integration block for each variable of the vector. This structure is presented in Fig. 3 for the cardiovascular system, where $\hat{y}$ is the extended state vector of the respiratory system.

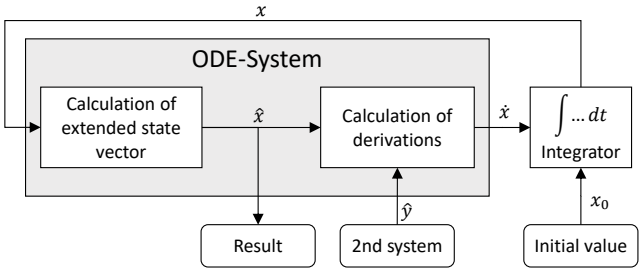

Fig. 3. Structure for the ODE-system of the system.

4.2 Cardiovascular system

In the following the physiological connections of the cardiovascular model based on Batzel et al.'s approach are described. The cardial system can be divided in two main compartments: the tissue compartment including the systemic blood cycle and the lung compartment including the

pulmonary blood cycle. For each compartment exists an overall resistance R_p and R_s. The blood pressure P and compliance c are considered for the arteries and veins in the pulmonary and systemic cycle separately.
The heart is divided into the left and right chamber with an individual contractility S. The heart functionality can be modeled using the frank-starling-mechanism (Asnes et al. (2006)). The overall structure of the compartments

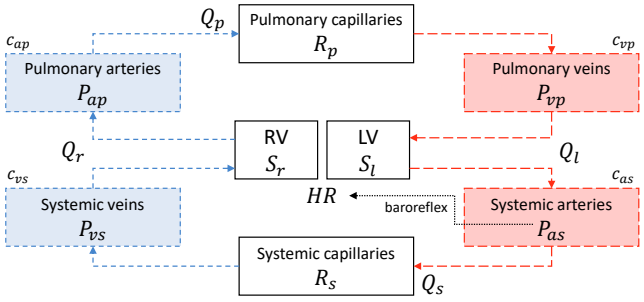

Fig. 4. Cardiovascular system structure. Red (long-dashed) / blue (short-dashed) depicts oxygen rich/poor blood.

and most important variables of the cardiovascular model can be seen in Fig. 4. The ODE-system consists of nine equations, where each of them determines the derivative value of one state variable. Conversely, the nine state variables define the state of the cardiovascular system.
Most relationships between hemodynamic values are based on physical connections. The heart rate however is dependent on neurological impulses of the autonomous nervous system, which is triggered by baroreceptors (Herring and Paterson (2018)). Batzel et al. describe the process of heart rate control by using a referenced blood pressure, which has to be matched with adjusting the heart rate. To simulate this, an approach from the optimal control theory is used, where an error term is continuously minimized to reach the referenced value (Kirk (2004)).
The state of the cardiovascular system is determined by the state vector x:

$$x = (P_{as}, P_{vs}, P_{ap}, P_{vp}, S_l, S_r, \sigma_l, \sigma_r, R_s, R_p, HR)^T \in \mathbb{R}^{10}. \quad (5)$$

4.3 Respiratory system

The respiratory system is split into three main compartments: the lung, tissue and brain compartment where the differing gas exchange is modeled. The tissue compartment describes the metabolism of the whole body. Depending on the parameters set for the MV the lung volume v is calculated. The cardiac output Q is assumed constant in both ventricles and blood flow in the systemic and pulmonary cycle. Similar to the model by Batzel et al. the relationships and coherences of the respiratory system are defined by differential equations. These define the gas diffusion in the lung, tissue and brain compartment.
Additionally, the model defines a lung shunt where a part of the blood ρ is adjusted which passes through the lung without being oxygenated. This component allows to simulate a intrapulmonary shunt, which appears when alveoli are perfused but not ventilated or the diffusion is impaired. The overall structure of the model can be seen in Fig. 5. The MV settings, like the F_iO_2 are also included, as most patients who develop an ARDS are mechanically ventilated. Altogether the respiratory model consists of six

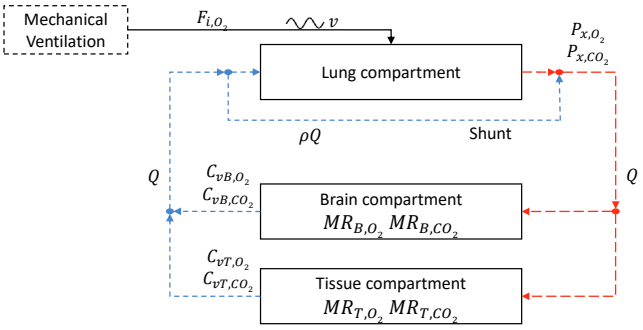

Fig. 5. Respiratory system structure. Red (long-dashed) / blue (short-dashed) depicts oxygen rich/poor blood.

differential equations. The state of the respiratory system is determined by the state vector y:

$$y = (P_{x,O_2}, P_{x,CO_2}, C_{vB,O_2}, C_{vB,CO_2}, C_{vT,O_2}, C_{vT,CO_2})^T \in \mathbb{R}^6. \quad (6)$$

Since the respiratory and cardiovascular system influence each other, the two models were connected. To achieve this, the cardiac output Q in the respiratory model is replaced by the pulmonary and systemic blood flow from the cardiovascular model. Additionally, the arterial oxygen concentration C_aO_2 of the respiratory system is considered in the calculation for the systemic vascular resistance in the cardiac system. The combined model is used to generate continuous data to evaluate the proposed classification.

To test the distinction of ARDS and HF the model needs to be able to simulate both diseases.

ARDS Typical for patients who have developed the condition is a reduced functionality of the lung, which can be simulated in the model by different settings. To simulate the loss of respiratory functions and missing gas exchange, the lung shunt in the respiratory system is set to 35%. Additionally, the dead space fraction λ is increased from 35% to 58% to simulate the higher dead space volume in the lungs. Due to the hypoxic pulmonary vasoconstricion the pulmonary vascular resistance of patients with ARDS usually increases, in the model increased from 1.6 to 2.8 mmHg min/L. With these adaptations most symptoms of an ARDS can be simulated and the model calculates the dependent variables accordingly.

Heart Failure (left) Additional to ARDS, heart failure needs to be simulated. Due to the fact that ARDS will inevitable lead to organ failure (in particular the right heart), it is necessary to differentiate between a left heart failure and a right heart failure. To simulate a left heart failure the contractility β_l of the left heart chamber is lowered by 70%. Because a heart failure also concerns the right heart the contractility for the right heart β_r is also reduced by 20%. With these settings, the model allows a simulation of both diseases. For the execution of the model different input parameters like: age, height, weight, HR, Mean blood pressures, respiratory rate, tidal volume and laboratory findings for the classification scores are used as an initial calibration of the model.

5. EVALUATION

The evaluation is split into two parts: the modelled respiratory and cardiovascular system and the implemented

classification. The latter will be discussed in Section 6. Firstly, we needed to evaluate the simulation of the implemented model in order to verify the results of the defined classification. To assess the model we used plausible thresholds that were initially defined based on literature and an algorithmic assessment of the available dataset (Burchardi et al. (2011), Striebel (2008)). Subsequently we executed the model with an exemplary data point and compared the simulation results with the defined value ranges. The simulation time was set to thirty minutes, as the model reaches equilibrium at this time. The results of the plausability check can be seen in Tab. 2.

Parameter	Unit	Interval	Result
Heart Rate	bpm	50-100	80
Mean art. b. p.	mmHg	65-110	101
Mean ven. b. p.	mmHg	2-8	4
Mean art. pul. b. p.	mmHg	10-20	14
Mean ven. pul. b. p.	mmHg	2-15	6
Q_l	L/min	3.5-5.5	5.2
Q_r	L/min	3.5-5.5	5.0
Flow (systemic cycle)	L/min	3.5-5.5	5.0
Flow (pulmonary cycle)	L/min	3.5-5.5	5.2
R_s	mmHg min/L	8.75-20	18
R_p	mmHg min/L	0.25-3.13	1.6
art. O_2 saturation	%	95-100	98
art. O_2 concentration	-	0.19-0.2	0.2
art. O_2 partial pressure	mmHg	80-100	98
ven. O_2 saturation	%	60-80	66
ven. O_2 concentration	-	0.12-0.16	0.13
Horovitz-quotient	mmHg	350-500	470

Table 2. Evaluation results for the model.

Overall, the model shows no inconsistencies, as all the simulated values were within the physiological intervals. Depending on whether ARDS or Heart failure was diagnosed for the patient, the according disease is simulated in the model using the belonging patient data as initial input. The results of the different simulations are shown for the most relevant parameters in Fig. 6 and Fig. 7. As seen

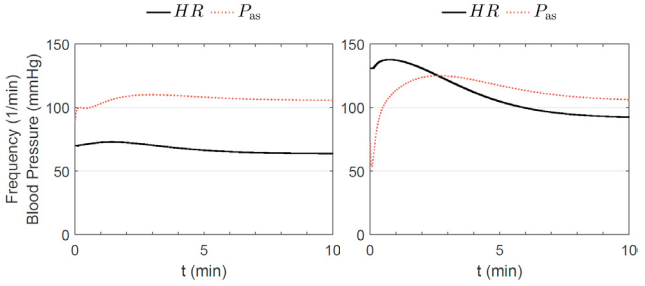

Fig. 6. Simulation of HR and P_{as} of a healthy patient (left) and patient with HF (right).

in Fig. 6, the blood pressure of a healthy patient reaches a stable state before the five minute marker. The blood pressure of a patient with a heart failure, however, drops in the beginning of the simulation and is then regulated due to an increase of the heart rate. Because of the baroreflex control, the referenced blood pressure is met resulting in a higher heart rate for the sick patient. For the ARDS patient, the most significant difference can be seen in the result of the arterial oxygen partial pressure, which is caused by the simulated non-functioning lungs and results

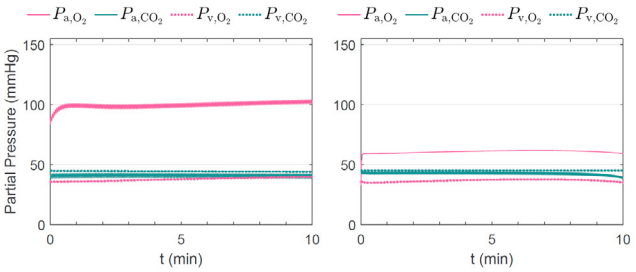

Fig. 7. Simulation of $P_{a,O_2/CO_2}$, $P_{v,O_2/CO_2}$ of a healthy patient (left) and a patient with ARDS (right).

in a lower Horovitz-quotient. For the evaluation of the classification, patient data from the database that were either diagnosed with ARDS or Heart Failure were used as initial parameters. Hereby, 175 patients that developed an ARDS and 688 patients that suffered an heart failure were found. To start a simulation for the different patients, it had to be ensured that sufficient data points were available in the database. Additionally, these data points should be measured simultaneously or in a short time interval. This fact is not always given in clinical datasets, as not all necessary values are measured at the same time. To continue to map a patient's condition appropriately, a time frame of one day has been established in which measurements for all required variables must be available. After filtering the patients accordingly, only ten patients were left, of which four patients were diagnosed with ARDS and six with HF. For these patients, the data points were used as initial input parameters for the model and the according disease was simulated and the classification scores calculated for the generated data (see Tab. 3).

ID	Disease	Horovitz	R^{HF}	p_{Fon}	P^{HF}
1	ARDS	moderate	low	0.00%	11%
2	ARDS	severe	moderate	0.04%	41%
3	ARDS	moderate	minimal	0.02%	11%
4	ARDS	severe	minimal	0.00%	41%
5	HF	moderate	low	0.02%	72%
6	HF	moderate	high	0.05%	62%
7	HF	normal	high	0.04%	72%
8	HF	moderate	moderate	0.06%	71%
9	HF	normal	high	27.92%	71%
10	HF	mild	low	0.11%	41%

Table 3. Evaluation results for Horovitz, R^{HF}, p_{Fon} and the P^{HF}-score.

6. DISCUSSION

The evaluation of the classification was executed on generated data of ten test patients as the used dataset did not contain more applicable data sets. The proposed parameters for a classification show mixed results. For example the classification of ARDS patients with the Horovitz-quotient indicates, that the distinction on the basis of the Berlin-Definition is not possible, as the heart failure patients with the IDs 5, 6, 8 and 10 fulfilled the oxygenation criterion, albeit mild to moderate (see Tab. 3). The heart failure score by Rajan et al. shows a similar result for the patients 5, 8 and 10, which is caused by the low NT-proBNP values belonging to this patients. Vice versa, the patients 1 and 2 with an ARDS were classified with

a low and moderate risk for heart failure as there was a high NT-proBNP value stored for them. The Fonarow score does not show a general assessment as only one patient had a score above 1%. The high value for patient 9 however indicates a high mortality risk because of a potential HF. Even though the heart rate and ejection fraction showed large differences between the ARDS and HF patients, the P^{HF} score for the previous mentioned patients is quite similar (around 40%), which is attributed to the high or low NT-proBNP. For the remaining patients the P^{HF} score displays a clear differentiation (approx. 10% vs. approx. 70%). These results show that the classification proposed for the retrospective distinction of ARDS and Heart Failure is very dependent on the NT-proBNP value, which is not measured frequently, as it is provided by laboratory analyses and restricts the basic patient data collection. This dependency should be addressed in future work.

7. CONCLUSION

In conclusion, we proposed a data based classification to distinguish between patients with ARDS and HF as imaging diagnostics are time consuming and costly and the imaging findings are not always available. With the included scores a retrospective assessment of patient data concerning ARDS and HF is possible. Because the available data set did not contain good enough data to evaluate the classification, we implemented a cardiovascular and respiratory model based on literature of modeling medical and physiological relations and processes. The model is used with actual patient data as initial input values and the according disease is simulated by adjusting different parameters in the model. In order to test the classification based on various parameters derived from literature, data points of ten test patients have been selected and the calculated results based on the simulated data evaluated. The overall results of the proposed classification look promising, but to validate the reliability high-resolution and well annotated patient data should be included in further studies.
It is needless to say, that such a classification should never replace the physicians decision, but the proposed P^{HF} score will hopefully help or simplify diagnostic processes and thus the treatment of patients. [1]

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