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ORIGINAL RESEARCH

Post-extrasystolic characteristics in the arterial blood pressure waveform are associated with right ventricular dysfunction in intensive care patients

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Abstract
Right ventricular dysfunction (RVD) is associated with end-organ dysfunction and mortality, but has been an overlooked condition in the ICU. We hypothesized that analysis of the arterial waveform in the presence of ventricular extrasystoles could differentiate patients with RVD from patients with a normally functioning right ventricle, because the 2nd and 3rd post-ectopic beat could reflect right ventricular state (pulmonary transit time) during the preceding ectopy. We retrospectively identified patients with echocardiographic evidence of moderate-to-severe RVD and patients with a normal functioning right ventricle (control) from the MIMIC database. We identified waveform records where ECG and arterial pressure were available in combination, simultaneously with echocardiographic evaluation. Ventricular extrasystoles were visually confirmed and the median systolic blood pressure (SBP) of the 2nd and 3rd post-ectopic beats compared with the median SBP of the ten sinus beats preceding the extrasystole. We identified 34 patients in the control group and 24 patients in the RVD group with ventricular extrasystoles. The mean SBP reduction at the 2nd and 3rd beat was lower in the RVD group compared with the control group [− 1.7 (SD: 1.9) % vs. − 3.6 (SD: 1.9) %, $p < 0.001$], and this characteristic differentiated RVD subjects from control subjects with an AUC of 0.76 (CI [0.64; 0.89]), with a specificity of 91% and sensitivity of 50%. In this proof-of-concept study, we found that post-extrasystolic ABP characteristics were associated with RVD.

Keywords Right ventricle · Right ventricular function · Hemodynamics · Arterial blood pressure · Extrasystole · Intensive care

1 Introduction

While left heart failure has been extensively characterized and studied, only relatively recently has right heart failure been the subject of more rigorous investigation. In the last decade, efforts have been made to accurately define and characterize right ventricular dysfunction (RVD). Previously considered as a secondary actor to the left heart, right ventricular (RV) function has now been found to play an important role in determining prognosis, mortality, and end organ dysfunction. Early awareness of RVD can influence treatment decisions, including fluid administration, which is particularly relevant in the intensive care unit (ICU) population [1]. Currently, we rely on specialist-requiring methods to identify RVD such as echocardiography or right heart catheterization, which logistically cannot be performed on every patient [1]. To screen patients for RVD who might warrant additional workup, we propose a novel method of analyzing ventricular extrasystoles identified in the electrocardiogram

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(ECG) and arterial blood pressure (ABP) waveform, which is routinely monitored in ICU patients.

Pulse pressure variation (PPV) is one of the validated methods to predict fluid responsiveness [2]. However, due to various limitations to PPV, other methods have been proposed [3] of which one is based on extrasystoles. An extrasystole's post-ectopic beat is associated with a brief increased volume load to the heart, and by applying the same physiological principle as for PPV, an extrasystole may be used to assess fluid responsiveness [4–6].

PPV is limited in patients with RVD because preload responsiveness requires biventricular preload responsiveness. In case of RVD, the RV is often preload unresponsive, even when the left ventricle (LV) is preload responsive [7] as possibly indicated by PPV. As such, RVD may create false-positive classification of fluid responsiveness based on PPV [8], a clinical case that should merit RV echocardiographic workup [9, 10]. In theory, RVD should also be a limitation to the use of the extrasystolic method to predict fluid responsiveness, because the post-ectopic beat characteristics are predominantly indicating LV function—just like PPV. Yet, the ABP morphologic configuration of the heart beats *following* the post-ectopic beat may reflect RV function, because the LV senses RV flow reductions 2–3 heart beats after they occurred on the right side [11]. The physiologic rationale is that LV stroke volume (SV) and RV SV are both related in a curvilinear fashion to preload [12] (i.e. the Frank–Starling curve, see Fig. 1). In a normally functioning RV, an extrasystole would lead to a markedly lower RV SV (if not completely abolished) at the ectopic beat (see Fig. 1). Typically, a slightly increased SV is seen at the post-ectopic beat, although this increase does not completely compensate for the decreased SV at the ectopic beat [13]. In the presence of RVD, the RV function curve is attenuated and baseline RV SV is lower, and so the reduction in SV at the ectopic beat would be less pronounced compared to a normally functioning RV (see Fig. 1). The RV output changes, which theoretically may be more pronounced when RV function is normal, are affecting LV preload approximately 2–3 heart beats later [7, 11] and in turn affecting LV SV, which may be reflected in the ABP waveform (visualized in Figs. 2, 3). That is to say, in a healthy heart, an extrasystole will typically cause a reduction in RV flow that can be indirectly observed 2–3 beats later; but in the case of RVD, the RV is doing less of the work to begin with, and so this effect may be lessened or absent.

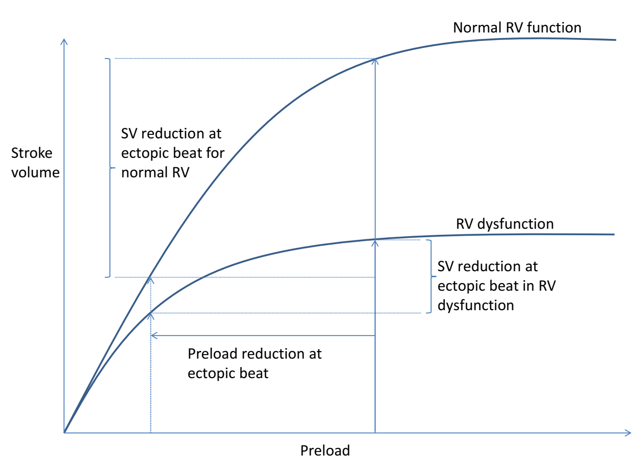

Fig. 1 Theoretical RV function curves and the impact of ectopic beat on stroke volume in a normally functioning right ventricle and a dysfunctional right ventricle

In our experience, the reduced SV encountered at ectopic beats is most pronounced for ventricular ectopy compared with atrial ectopy. Based on these *theoretical* considerations of biventricular interaction, we propose that systolic blood pressure (SBP) at the second and third heart beats following ventricular ectopic beats is less affected in the case of RVD compared with patients with normal RV function.

We therefore hypothesize that these post-extrasystolic ABP characteristics could differentiate patients with RVD from patients with a normally functioning RV. We tested this hypothesis retrospectively in an ICU cohort using a database where echocardiographic evaluation of cardiac function and ECG and ABP waveforms were available.

2 Methods

The Medical Information Mart for Intensive Care III (MIMIC-III) is a large database that is freely available in the public domain and includes information from electronic medical records of patients admitted to the ICUs at Beth Israel Deaconess Medical Center since 2001 [14]. The creation and use of the MIMIC database was approved by the institutional review boards of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology (IRB protocol 2001-P-001699/3). Physionet is also freely available in the public domain and contains a wealth of information including physiological waveforms for a portion of patients in MIMIC-III. A fraction of the MIMIC-III patient admissions are matched with captured hemodynamic waveform monitoring, i.e. the *matched subset* of the MIMIC database, which was used for this retrospective study.

The study is reported in alignment with the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines [15].

2.1 Patient selection and data extraction

All patients in MIMIC-III with an echocardiography report were identified. All patients with normal LV function, normal tricuspid valve, and no tricuspid stenosis or

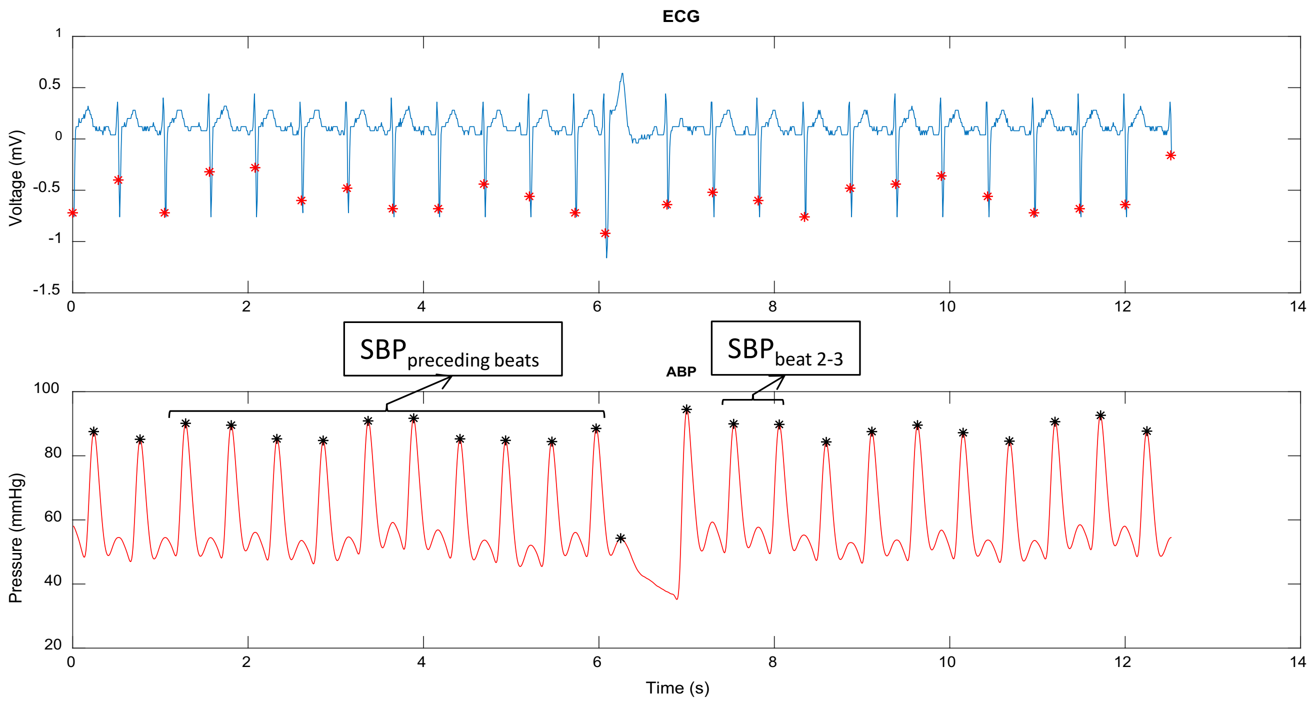

Fig. 2 Conceptual visualization of the features extracted for a patient from the right ventricular dysfunction group. Curly brackets indicate the heart beats defining each of the variables in boxes as described in Sect. 2

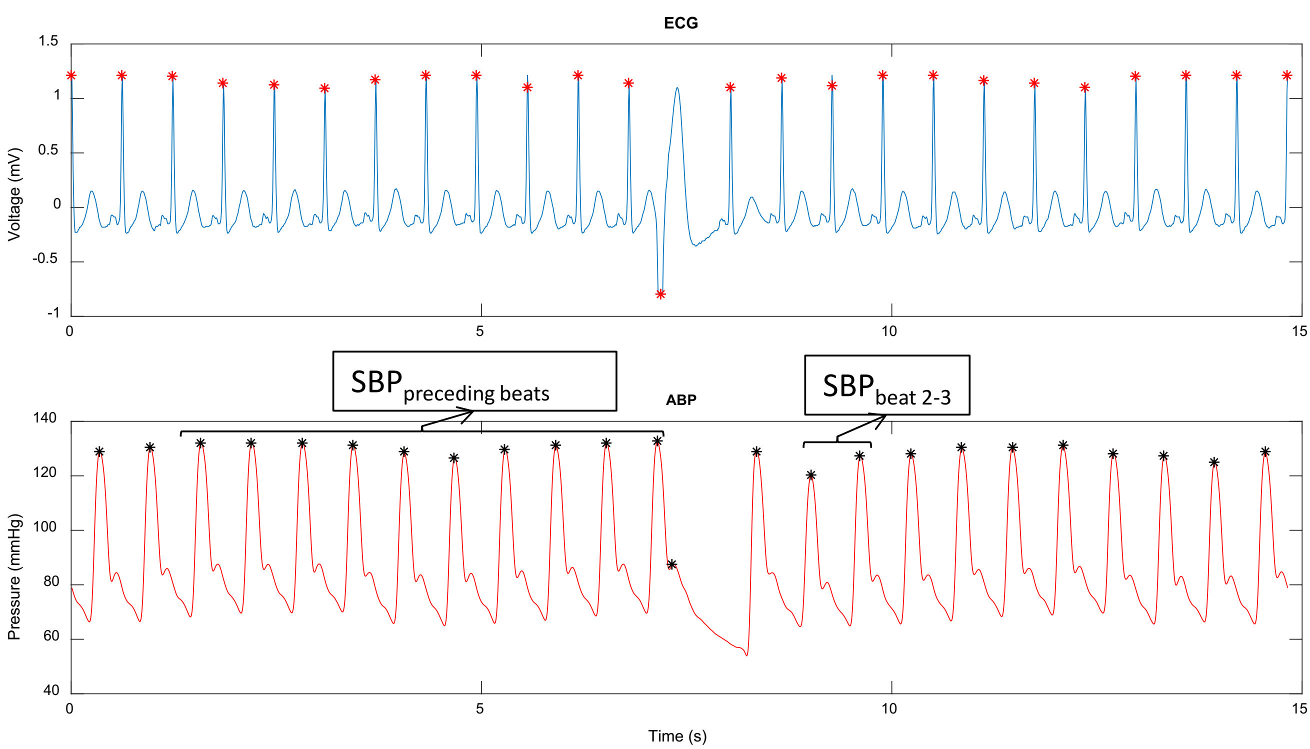

Fig. 3 Example of the post-extrasystolic ABP waveform morphology for a patient from the control group. Curly brackets indicate the heart beats defining each of the variables in boxes as described in Sect. 2

regurgitation were selected. From this cohort, two groups were defined: patients with normal RV function (control group) and patients with moderate or severe RVD (RVD group). A list of echocardiographic descriptions identified in echocardiographic reports defining normal as well as moderate-to-severe RV dysfunction is presented in supplemental data, S1. All echocardiographic reports were automatically labeled using natural language processing methodology previously developed in our lab [16].

For the RVD and control groups, the ECGs with annotated heartbeats (including beats annotated as ventricular ectopy) and ABP waveform data were obtained from the *matched subset* waveform database. A waveform was analyzed if parts of it were recorded within ± 12 h of the echocardiographic examination, and the extracted ECG and ABP waveforms (both sampled at 125 Hz) were truncated at these temporal limits with respect to the echocardiographic examination. Patients without these data were excluded from analyses. In cases of more than one record per subject, we looked at the first admission within the database. A portion of the patients had beat annotations (including identification of extrasystoles) from the Philips monitoring system.

For patients in the RVD group who did not have readily available beat annotations from the Philips monitoring system, a simple algorithm based on Kubios HRV-derived RR intervals was used to identify potential ventricular ectopy in ECGs (Kubios HRV, University of Eastern Finland, Kuopio, Finland).

This resulted in the dataset of potential ventricular ectopy that requires visual inspection/verification in both the RVD and control groups. Ahead of the visual inspection, RR intervals were automatically evaluated to ensure that the ten heartbeats preceding the potential ectopic beat and the ten heart beats succeeding the potential post-ectopic beat were sinus beats, i.e. none of the RR intervals differed more than 10% with respect to the median RR interval among these heartbeats. To verify identified ventricular extrasystoles, visual inspection was initially carried out by one researcher (STV). In uncertain cases, the ectopic morphology was discussed with another researcher (CC) for decision on ectopic origin and CC finally confirmed all ventricular extrasystoles initially verified by STV. In cases of more than 100 annotated ventricular extrasystoles, only 100 were inspected. These were equally distributed across the ECG recording, i.e. if a patient had 500 annotated ventricular extrasystoles, every fifth was inspected for eligibility.

Descriptive variables such as demographics, comorbidity, and clinical characteristics were extracted from the MIMIC database for the RVD and control cohorts with confirmed ventricular ectopy.

2.2 ABP waveform characteristics

All ABP waveform analyses was carried out in Matlab (version R2017b, MathWorks Inc., MA, USA). Based on the verified ventricular extrasystoles, the following characteristic based on the 2–3 heart beats after the ectopic beat and the ten sinus beats preceding the extrasystole was derived for each identified ventricular extrasystole (see also Figs. 2, 3 for visual explanation of the specific heart beats used).

The median SBP from the two heartbeats following the post-ectopic beat, $SBP_{beat\ 2-3}$, were compared with the median SBP at the ten sinus beats preceding the ectopic beat, $SBP_{preceding\ beats}$:

$$\Delta SBP_{beat\ 2-3} = 100\% \times \left(SBP_{preceding\ beats} - SBP_{beat\ 2-3}\right)/SBP_{preceding\ beats}$$

In cases where more than one ventricular extra systole was identified and confirmed for a patient, a summary $\Delta SBP_{beat\ 2-3}$ characteristic was defined by the median value of the $\Delta SBP_{beat\ 2-3}$ values obtained from all confirmed ventricular extrasystoles.

2.3 Statistics

Data accommodating the inclusion criteria for the two study groups was used and a power calculation was not considered feasible. When extracting the *reference standard* (RV function category), the *index test* ($\Delta SBP_{beat\ 2-3}$) was not available. The calculation of $\Delta SBP_{beat\ 2-3}$ was an automated process after the visual confirmation of ventricular extrasystoles in the ECG and therefore blinded to the reference standard.

Student's *t* test was used to compare characteristics for continuous data and Chi square test for categorical variables between the two groups. The ability to classify RVD with the above stated ABP characteristics was analyzed with receiver operating characteristic (ROC) statistics with deLong method for estimation of confidence intervals (CI). Given the screening nature of the method, optimal threshold was assessed with emphasis on high specificity and secondarily reported according to the Youden index. In addition, a *grey zone* approach was applied, where the grey zone was defined as the threshold zone for $\Delta SBP_{beat\ 2-3}$, where neither sensitivity nor specificity were beyond 90% as previously described by Cannesson et al. [17].

A logistic regression including the derived $\Delta SBP_{beat\ 2-3}$ characteristic, age, gender, and comorbidity (Elixhauser score) was applied to investigate whether ABP characteristics independently were associated with RV dysfunction. All data is reported as mean (standard deviation, SD) or mean [CI] unless otherwise indicated. Statistics was performed in *R* (version 3.5.0 using R studio version 1.1.453 and package 'pROC' for ROC statistics with DeLong method used for ROC area CIs).

3 Results

Based on the echocardiographic criteria, there were 2086 echocardiographic reports meeting the echocardiographic control group criteria, and 876 echocardiographic reports meeting the echocardiographic RV dysfunction criteria. Waveform availability (ECG and ABP) in the matched subset waveform database fulfilling the ± 12 h echocardiographic temporal proximity criteria resulted in 93 unique beat annotated ECG and ABP waveforms from the control group subjects and 66 ECG and ABP waveforms from the RVD group. 22 required manual beat annotations. The inspected waveform windows were on average 6.9 (SD: 5.3) h in the control group and 9.1 (SD: 6.7) h in the RVD group.

In these windows, we identified, visually confirmed and derived the $\Delta SBP_{beat\ 2-3}$ waveform characteristics from at least one ventricular extra systole for 34 patients in the control group and 24 patients in the RV dysfunction group. Representative examples of the ABP post-extrasystolic morphologic characteristics are shown in Fig. 2 for an RVD subject and in Fig. 3 for a control subject.

Demographics, comorbidity, severity of illness, service, and hemodynamic vital signs are reported in Table 1.

The $\Delta SBP_{beat\ 2-3}$ characteristic was − 1.7 (1.9) % in the RVD group and − 3.6 (1.9) % in the control group ($p < 0.001$) and $\Delta SBP_{beat\ 2-3}$ classified RV dysfunction with a ROC curve area of 0.76 [0.64; 0.89] with optimally high specificity of 91% and corresponding sensitivity of 50%, respectively, at a threshold of − 1.5%, (reduction) in SBP see Fig. 4. Maximizing the Youden Index, the optimal specificity of 71% and sensitivity of 75% were found at a threshold of − 2.85%. Using a grey zone approach, the threshold interval between 90% sensitivity and 90% specificity was [− 4.1%; − 1.5%], see Fig. 5.

In the logistic regression, $\Delta SBP_{beat\ 2-3}$ remained independently associated with RVD ($p = 0.007$).

Table 1 Demographics, comorbidity, severity of illness, ICU service and hemodynamic vital signs of the two groups

	RV dysfunction (n = 24)	Control (n = 34)	p-value
Age	63 (15)	62 (14)	0.79
Male gender	15 (63%)	24 (71%)	0.85
Diabetes	8 (32%)	15 (44%)	0.62
Hypertension	4 (16%)	7 (21%)	0.91
Elixhauser	10.7 (8.0)	4.0 (6.6)	0.001
qSOFA, admission	1.96 (0.54)	1.88 (0.59)	0.607
Inotropes	3 (12%)	1 (2.9%)	0.40
Vasopressors	18 (72%)	20 (59%)	0.44
Ventilated	20 (80%)	28 (82%)	1
Renal failure	4 (16%)	6 (18%)	1
HR	87 (16)	84 (15)	0.45
MAP	76 (11)	81 (11)	0.13
SBP	112 (15)	121 (18)	0.06
Service			0.13
CMED	1 (4.2)	4 (11.8)	
CSURG	7 (29.2)	16 (47.1)	
GU	1 (4.2)	0 (0.0)	
MED	8 (33.3)	4 (11.8)	
NMED	0 (0.0)	3 (8.8)	
NSURG	0 (0.0)	1 (2.9)	
SURG	5 (20.8)	3 (8.8)	
TRAUM	1 (4.2)	1 (2.9)	
TSURG	1 (4.2)	0 (0.0)	
VSURG	0 (0.0)	2 (5.9)	

RV right ventricular, *HR* heart rate, *MAP* mean arterial pressure, *SBP* systolic arterial blood pressure, *CMED* non-surgical cardiac ICU admission, *CSURG* surgical cardiac ICU admission, *GU* reproductive organs/urinary system ICU admission, *MED* internal medicine ICU admission, *NMED* neurologic ICU admission, *NSURG* neurosurgical ICU admission, *SURG* general surgical ICU admission, *TRAUM* trauma ICU admission, *TSURG* thoracic surgery ICU admission, *VSURG* Vascular surgery ICU admission

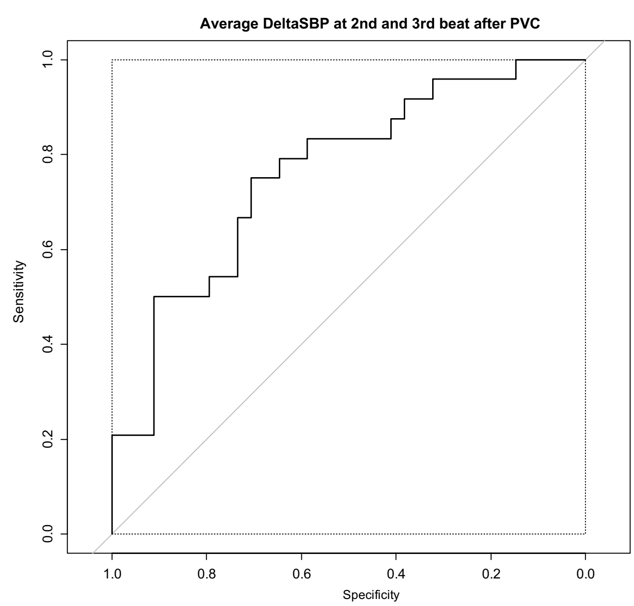

Fig. 4 Receiver operating characteristics curve for classification of right ventricular dysfunction based on the arterial blood pressure waveform morphology at the 2nd and 3rd heart beat after a ventricular extrasystole

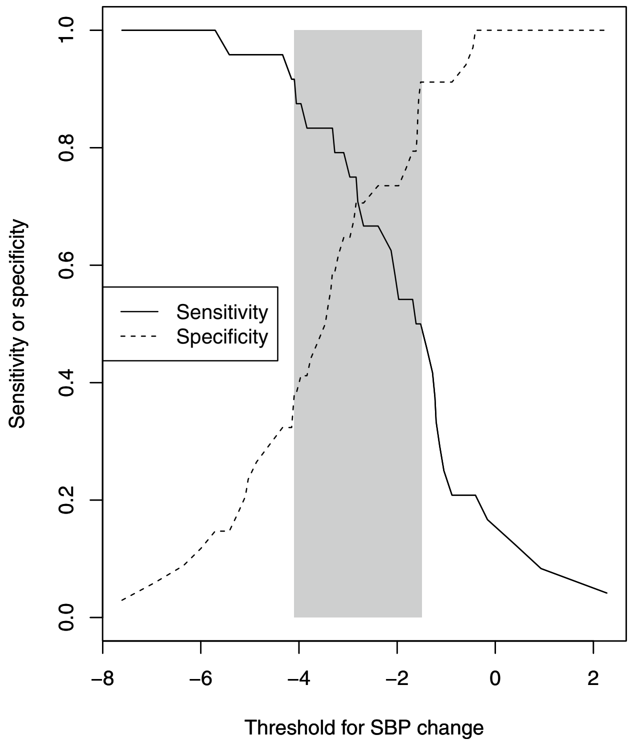

Fig. 5 Visualization of the grey zone, where neither sensitivity nor specificity are exceeding 90%. The grey zone was between − 4.1 and − 1.5% for $\Delta SBP_{beat\ 2-3}$

4 Discussion

In this proof-of-concept study, we found that the post-extrasystolic ABP characteristics induced by ventricular extrasystoles could separate patients with RVD from patients with normal RV function (AUC = 0.76 [0.64; 0.89]). Logistic regression analyses that included patient demographic information and comorbidity further revealed that the post-extrasystolic ABP characteristic was independently associated with RVD.

The optimal threshold associated with a high specificity (91%), i.e. the upper limit of the identified grey zone ($\Delta SBP_{beat\ 2-3}$ of − 1.5%) was at the expense of sensitivity (50%). A high specificity is of great importance since RVD is not a common finding among ICU patients [8]. On the other hand, we consider the threshold limit defined by the Youden Index (− 2.85%) and, in particular, the lower limit of the grey zone (− 4.1%; i.e. high sensitivity on the expense of specificity) to be of less significant clinical value given the relatively low prevalence of RVD in a general ICU population. Yet, we are not aware of exact numbers for the prevalence of RVD in ICU patients. Our method is indeed suggested as a screening tool for early identification of patients with possible RVD where additional echocardiographic workup could be merited. An important aspect of this method is therefore also the availability of ventricular extrasystoles, which the present study does not address in an adequately systematic way. However, we recently showed that in septic ICU patients, 76% of patients (32 out 42) with analyzable ECGs had at least one ventricular extrasystole in their 24 h ECG recording, of which most were recorded on the first day of ICU admission [18]. In subjects with atrial fibrillation or other frequent arrhythmias such as trigemini, this method cannot be considered.

Our study has relevant limitations. We selected patients with a normal LV and valve function and then subdivided that group into normal RV function and moderate/severe RV function. The results may not generalize to those with an abnormal LV function. Since the echocardiographic reports were analyzed retrospectively (i.e. the echocardiographers were not instructed to focus specifically on RV function), there could be errors in classification between the RVD and the control groups. In addition, patients with affected valve or LV function was not investigated in this preliminary study and the obvious next step is to investigate this hypothesis prospectively, i.e. involving clear and quantifiable echocardiographic definitions of RV and LV function. Another relevant limitation is that the identification and calculation of $\Delta SBP_{beat\ 2-3}$ has to be done by monitors, because spontaneous ventricular extrasystoles rarely occur every minute and because the associated SBP changes of just a few mmHg cannot be accurately estimated on the hemodynamic monitor by clinicians at the bedside.

In conclusion, RV dysfunction affects post-extrasystolic blood pressure differently compared with normal RV function. Future prospective studies are needed to measure the value of the suggested method in assessing RV function. RVD is associated with worse mortality, and early identification of this condition may improve patient outcomes in the ICU.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was exclusively observational and based on retrospective analysis of data from the MIMIC III database, which is a public database available for researchers worldwide.

Informed consent This type of study does not require informed consent from study subjects.

Research involving human participants The MIMIC database is a public database approved by the US authorities waiving consent from patients, whose data is in the database. The patients are de-identified in this public database.

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