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Electrocardiographic Right Ventricular Strain Precedes Hypoxic Pulseless Electrical Activity Cardiac Arrests: Looking Beyond Pulmonary Embolism

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Abstract

Aim: The role of the right ventricle (RV) in pulseless electrical activity (PEA) is poorly defined outside of pulmonary embolism. We aimed to 1) describe the continuous electrocardiographic (ECG) manifestations of RV strain (RVS) preceding PEA/Asystole in-hospital cardiac arrest (IHCA), and 2) determine the prevalence and clinical causes of RVS in PEA/Asystole IHCA.

Methods: In this retrospective cross-sectional study, we evaluated 140 patients with continuous ECG data preceding PEA/Asystole IHCA. We iteratively defined the RVS continuous ECG pattern using the development cohort (93 patients). Clinical cause determination was blinded from ECG analysis in the validation cohort (47 patients).

Results: The overall cohort had mean age 62.1 ± 17.1 years, 70% return of spontaneous circulation and 30% survival to discharge. RVS continuous ECG pattern was defined as progressive RV depolarization delay in lead V1 with at least one supporting finding of RV ischemia or right axis deviation. Using this criterion, 66/140 (47%) cases showed preceding RVS. In patients with RVS, no pulmonary embolism was found in 9/13 (69%) autopsies and 8/10 (80%) CT chest angiograms. The positive and negative predictive value of RVS pattern for diagnosing a

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Conflicts of Interest:

Noel Boyle has received speaking honoraria from Janssen Pharmaceutical; Jason Bradfield has received speaking honoraria from Abbott and Boston Scientific; Xiao Hu is an inventor on patent application US20170046499 “Recognizing predictive patterns in the sequence of superalarm triggers for predicting patient deterioration” and patent US9600990B2 “System and methods for generating predictive combinations of hospital monitor alarms”; Duc Do, Noel Boyle, Alan Kuo, Xiao Hu are coinventors on patent application US2019036850 “Risk prediction of in-hospital cardiac arrest using continuous electrocardiographic monitoring data”; other authors have nothing to disclose.

respiratory cause of PEA/Asystole in the validation cohort was 81% [95% CI 64–98%] and 58% [95% CI 36–81%], respectively.

Conclusion: RVS continuous ECG pattern preceded 47% of PEA/Asystole IHCA and is predictive of a respiratory cause of cardiac arrest, not just pulmonary embolism. These suggest that rapid elevations in pulmonary pressures and resultant RV failure may cause PEA in respiratory failure.

Background

In-hospital cardiac arrests (IHCA) affect over 292,000 patients in the United States annually, with fewer than 30% surviving to discharge[1]. Our understanding of the pathophysiology of cardiac arrests, particularly from pulseless electrical activity (PEA), remains very limited.

PEA is defined as a syndrome with the absence of a palpable pulse in an unconscious patient with organised electrical activity that is not ventricular tachycardia/fibrillation[2]. Two subtypes of PEA, those with and without residual left ventricular (LV) contraction (frequently referred to as pseudo-PEA vs. true PEA), have been described[2]. However, the role of the right ventricle (RV) in the pathophysiology of PEA is often overlooked and not well-defined outside of acute pulmonary embolism, a well-recognised, potentially reversible, cause of PEA[3].

RV failure from acute pulmonary embolism manifests a variety of well-known 12-lead electrocardiogram (ECG) findings, including the $S_1Q_3T_3$ pattern or new right bundle branch block (RBBB)[4]. Many patients at risk of IHCA are monitored with continuous ECG and thus this serves as an excellent modality to understand the role of the RV leading up to PEA arrest. In this study we aimed to: 1) describe the continuous ECG manifestations of RV strain (RVS) preceding IHCA due to PEA/Asystole, and 2) determine the prevalence and associated causes of the RVS ECG pattern preceding IHCA from PEA/Asystole.

Methods

We conducted a retrospective cross-sectional study at the University of California, Los Angeles (UCLA) Ronald Reagan Medical Center and the University of California, San Francisco (UCSF) Medical Center at Parnassus, both tertiary care hospitals. Telemetry data was obtained by General Electric (GE) bedside patient monitoring systems (GE Healthcare, Waukesha, WI), and pooled on a remote data server via BedmasterEx (Excel Medical Electronics, Jupiter, FL). Signals were sampled at 240 Hz with 12-bit representation. Continuous ECG was obtained using a standard 5 electrode configuration providing 4 ECG leads (I, II, III and precordial lead). At UCLA, a total of 200/520 beds, including all 130 adult intensive care unit (ICU) beds, and 70 medical–surgical unit beds were monitored with the BedmasterEx system at any one time. At UCSF, all 77 adult ICU beds (of 600 total beds) were monitored with BedmasterEx. This study received approval from UCLA IRB 10–000545 and UCSF IRB 14–13262.

We evaluated all ‘code blues’ between April 2010 and August 2014 at UCLA and ICU ‘code blues’ between March 2013 and December 2017 at UCSF. We included IHCA cases (defined

as lack of central pulse, apnea, and unresponsiveness) due to PEA/asystole in patients age ≥18 years, with telemetry data available for at least 3 consecutive hours prior to and including the onset of IHCA. We excluded patients with baseline pulmonary hypertension (WHO Class I, III, IV, V), baseline RV hypertrophy/enlargement by ECG, a do-not-resuscitate order at time of 'code blue', ventricular-paced rhythm, left ventricular assist device or extracorporeal membranous oxygenation support at time of arrest, out-of-hospital cardiac arrest leading to current admission, IHCA in a procedural or operating room, and IHCA within the first 24 hours of a trauma admission. Cases where a precordial lead in the V1 or V2 position (henceforth referred to as V1 for simplicity) was not present or had excessive artefact were excluded (E-Figure 1). Only the first IHCA in any patient was included.

We extracted telemetry data for up to 24 hours preceding IHCA. All ECG analysis was performed using LabChart Reader v.8.1.13 (AD Instruments, Colorado Springs, CO). The time of cardiac arrest was determined by ECG review and marked at onset of asystole or initiation of chest compressions as visualised by chest compression artefact in PEA.

We separated cases into a development cohort (all 67 UCLA cases, 26 UCSF cases) and validation cohort (47 UCSF cases, Table 1). UCSF cases were divided into development and validation cohort based on timing of data extraction. Using the development cohort, we defined the full range and sequence of ECG findings consistent with RVS using an iterative process starting with cases where RVS was most apparent and expected (including autopsy and computed tomography (CT) -confirmed massive/submassive pulmonary embolism). We evaluated for lead V1 morphological changes (Table 2), development of ST elevation in lead V1, development of ST segment elevation in limb leads (with focus on the ST elevation vector, documented as lead with the highest ST segment elevation or least ST segment depression), development of progressive right axis deviation, and pattern of new intraventricular conduction delay (none, delay in intrinsicoid deflection, post-intrinsicoid deflection (ie. terminal) delay, delay in both). These features were used to define what continuous ECG changes constituted 1. Definite, 2. Possible, and 3. Not RVS pattern. Additionally, we also evaluated for the development of notable features including 1. $S_1Q_3T_3$/$S_1rSR'_3T_3$, 2. Pseudo-Brugada pattern[5], 3. Peaked T waves.

Clinical cause of IHCA was determined by chart review of medical history, resuscitation records and notes, pre- and post-arrest vital signs, lab, imaging, and autopsy data. The level of confidence in the diagnosis was rated on a scale of 1–4 (1: no cause clearly identified, 2: possible cause identified but the certainty in diagnosis was low, 3: most likely cause identified though other less likely competing causes were present, 4: cause clearly identified). For the development cohort, the clinical cause was determined in conjunction with ECG analysis by a single physician (DD). For the validation cohort, clinical cause and level of certainty was determined by two physicians (DD, AK) independently, both blinded to the results of ECG analysis, with discrepancies resolved by discussion or adjudication by a third physician (NB). ECG analysis for the validation cohort was performed by a single physician (DD), with blinding to clinical cause through use of de-identified study identification numbers. Unblinding was performed only after clinical cause determination was finalised.

Normally distributed variables were reported as mean ± SD. Non-normally distributed variables were reported as median (IQR). Comparisons between categorical variables were performed using Chi-square test. Two-sided $p< 0.05$ was considered statistically significant. Statistical analysis was performed using R v 3.5.0 (R Foundation, Vienna, Austria).

Results

We included 67 patients (mean age 63.7 ± 17.7, 54% male) at UCLA and 73 patients (mean age 60.6 ± 16.4, 59% male) at UCSF (Table 1, E-Figure 1, E-Table 1–2).

Right Ventricular Strain ECG Pattern

The QRS morphological changes in lead V1 followed the same sequence of gradual delay in RV depolarization (Figure 1; E-Figures 3 through 5). RBBB was the most common terminal morphology (occurring in 44/66 (67%), Table 2).

We defined definite RVS as having the above V1 morphological change sequence, either no intraventricular conduction delay or terminal intraventricular conduction delay (ie. not delay in the intrinsicoid deflection) with 2 or more of the following supporting changes occurring simultaneously with the V1 morphological changes:

1. ST elevation in V1
2. Rightward directed ST elevation vector in limb leads (ie. towards lead III)
3. Rightward axis deviation in limb leads

Possible RVS was defined as having only 1 of the above supporting features. Using this criterion, 39/93 (42%) and 5/93 (5%) in the development cohort and 18/47 (38%) and 4/47 (9%) in the validation cohort had definite and possible RVS, respectively.

In patients with definite or possible RVS compared to those without, the $S_1Q_3T_3$/$S_1rSR'_3T_3$ and pseudo-Brugada (Figure 1B) patterns were significantly more common but not peaked T waves (E-Table 3).

The first ECG change suggestive of RVS was observed at a median 7.2 [IQR 3.6 – 24.8] minutes prior to arrest (median 7.2 [IQR 3.0 – 21.1] in those with a normal baseline QRS). In 3/5 (60%) cases of acute respiratory distress syndrome (ARDS), ECG changes suggestive of RVS were present more than 24 hours prior to arrest (E-Figure 5).

Causes of IHCA

When considering only cases where the level of confidence in clinical diagnosis was rated 3 or 4, all 4 patients with PEA/asystole caused by pulmonary embolism (including 2 each in the development and validation cohorts) demonstrated a definite or possible RVS ECG pattern (Table 3). In the development cohort, respiratory causes of cardiac arrest were much more common in those with any preceding RVS ECG pattern compared to those without (28/35 vs. 13/38, 80% [95% CI 67–93%] vs 34% [95% CI 51–81%], $p < 0.001$). Similar findings were seen in the validation cohort (17/21 vs. 8/19, 81% [95% CI 64–98%] vs. 42%

[95% CI 36–81%], p < 0.001) (chi-square goodness of fit to development cohort distribution p = 0.843).

There was similar performance when evaluating the validation cohort regardless of level of confidence in the clinical diagnosis: sensitivity 68% [95% CI 50–86%], specificity 77% [95% CI 60–95%], positive predictive value 77% [95% CI 59–95%], negative predictive value 68% [95% CI 50–86%] (E-Table 5). The distribution of clinical causes for definite and possible RVS ECG pattern were similar (E-Table 6).

Clinical/Imaging correlation of RVS

Of patients with any preceding RVS ECG pattern, 8 patients had a CT angiogram of the pulmonary arteries which ruled out pulmonary embolism as the cause; 2 were known to have massive/submassive pulmonary embolism by CT angiogram within the 24 hours prior to cardiac arrest. Of the 13 patients with RVS ECG pattern and an autopsy, 4 (31%) had a large burden of pulmonary embolism that was deemed the cause of cardiac arrest and death (Table 4). No patients without RVS ECG pattern had pulmonary embolism by CT angiogram (3 patients) or autopsy (10 patients). In patients without pulmonary embolism by autopsy, 1 patient each with and without RVS ECG pattern was given thrombolytics; no patients with negative CT angiogram were given thrombolytics.

New isolated right ventricular dysfunction (new enlargement, decrease in systolic function, or volume and/or pressure overload) in an echocardiogram done within 24 hours post-IHCA was seen in 9/22 (41%) patients with RVS ECG pattern compared to 1/14 (7%) without. No patients with RVS ECG pattern showed new isolated left ventricular dysfunction (Table 4).

Discussion

Survival from PEA/Asystole arrests remains poor, whether in-hospital or out-of-hospital. A better understanding of the underlying mechanism is necessary to improve outcomes beyond that achievable by rigorous improvement in systems of care. IHCA represents a unique opportunity to gain insights into the mechanisms of PEA arrest, particularly the early phases, taking advantage of available laboratory and imaging data, direct observation by clinical staff, and continuous ECG. Though high-quality continuous ECG data is currently difficult to obtain for careful retrospective review, it continuously reflects patients' underlying physiologic processes and serves as an excellent modality to better understand the pathophysiologic mechanisms that precede and lead to PEA arrest. With the current revolution in cloud storage, cloud computing, and automation through deep learning, this type of continuous temporal data will be increasingly available and important to consider in clinical management[6–9].

In this study, we: 1. Defined the continuous ECG changes that constitute RVS (Figure 2), 2. showed that the RVS ECG pattern preceding IHCA is associated with new isolated RV dysfunction by echocardiogram obtained after return of spontaneous circulation (ROSC), 3. found the prevalence of RVS in IHCA patients without preexisting right ventricular hypertrophy who are continuously monitored pre-arrest was 47%, and 4. that RVS preceding PEA/Asystole IHCA was highly suggestive of a hypoxic respiratory etiology, not just due to

pulmonary embolism. This is the first study to demonstrate that continuous ECG changes preceding PEA/Asystole arrests can provide insights into the underlying pathophysiologic mechanisms leading to cardiac arrest.

Defining RVS Continuous ECG Pattern

It has long been known that patients with large pulmonary emboli may show several different signs of RVS on 12-lead ECG. However, prior studies have largely considered such findings as independent of each other due to a lack of temporal understanding by only using single or intermittently collected 12-lead ECGs [5, 10–14]. By defining the RVS continuous ECG pattern in patients who suffered cardiac arrest, we ensured our findings were representative of the entire sequence of progression towards severe RV failure. As such, we were able to unify these prior findings through a single definition for RVS pattern: progressive delay in right ventricular depolarization with associated right ventricular injury pattern.

In normal ventricular depolarization, the left and right ventricles depolarise nearly simultaneously[15]. As RV pressures elevate acutely, there is progressive RV dilation and transmural ischaemia, manifesting as a rightward ST segment elevation vector. Shortly thereafter or simultaneously, RV depolarization gradually delays due to ischaemia of the right bundle. Depending on the baseline relative timing of LV/RV depolarization, this can initially manifest as decreasing amplitude of the V1 S wave, a notch in the upstroke of the V1 S wave, or a terminal r/r'. Hence, RBBB in this setting is due to progressive right bundle branch conduction delay resulting in a QRS duration greater than 120ms, rather than true conduction block.

RVS pattern in PEA/Asystole

Determining the precise cause of IHCA retrospectively is difficult, with no gold standard method. Furthermore, review of telemetry data to aid in the determination of IHCA cause is also currently not standard in clinical practice due to a lack of understanding of how to incorporate this information into clinical diagnosis and management. Hence, we designed our study with a validation cohort where only data available in the electronic medical records were used to determine clinical cause with blinding to the results of the ECG analysis, avoiding the potential bias of incorrectly correlating RVS with a particular clinical cause.

In our cohort, we found a 47% prevalence of RVS ECG pattern preceding PEA/Asystole arrests; 80% of these cases had a respiratory cause of cardiopulmonary arrest. While all 4 cases of confirmed pulmonary embolism as the aetiology of cardiac arrest (by CT angiogram or autopsy) manifested the RVS pattern, most cases with RVS pattern and post-arrest CT angiogram or autopsy showed no pulmonary embolus. Electrocardiographically, no morphological characteristics could distinguish RVS from pulmonary embolism from that of other causes of hypoxic respiratory failure (eg. ARDS, pneumonia, mucus plug, or aspiration). This suggests that RV failure plays at least a substantial, if not a primary role, in the early stages of PEA/Asystole due to hypoxic respiratory failure in general. Echocardiographic demonstration of normal LV systolic function with severely reduced RV

function and dilation has been well-described in PEA due to pulmonary embolism, but not from other causes of respiratory failure[3].

In pulmonary embolism, RV failure results from direct obstruction of the pulmonary vasculature and pulmonary vasoconstriction from the release of vasoconstrictive substances such as thromboxane and serotonin[16]; in ARDS through microvessel occlusion and hypoxic vasoconstriction[17]. In other types of respiratory failure, RV failure likely results from elevated pulmonary vascular resistance through similar mechanisms: pulmonary vascular bed compression (eg. mucus plug and massive aspiration) and acute hypoxic vasoconstriction. Netzer *et al.* showed that acutely subjecting unacclimated normal volunteers to normobaric hypoxia led to rapid rise in pulmonary vascular resistance and increase in echocardiographic RV size without any significant effect on the LV; these RV changes also rapidly reversed with correction of hypoxia [18]. This may explain why patients with PEA due to hypoxic respiratory failure can frequently obtain ROSC within 1 round (2 minutes) of cardiopulmonary resuscitation with successful ventilation/oxygenation.

It is likely that hypercarbia and the resultant acidemia, rather than hypoxia, was the main driving factor in those cases of clear respiratory failure without preceding RVS pattern (E-Table 7). This, however, is difficult to objectively quantify using just blood gases obtained pre- and post-arrest given the numerous confounding factors. Further investigation of the heart rate and respiratory dynamics preceding cardiac arrest, which is beyond the scope of the current investigation, may provide more clues given the differential effect of hypercapnia/acidemia and hypoxia on cardiovascular physiology[19].

Myocardial infarction due to a proximal right coronary artery occlusion causing RV injury can also potentially manifest an RVS pattern, which may be difficult to distinguish using only a limited set of ECG leads[20, 21]. However, in our IHCA population, we found only one patient with myocardial infarction who met criteria for possible RVS ECG pattern.

Clinical Implications

Our findings have several implications in the management of patients who are at risk for or develop PEA/Asystole arrests in the hospital. In current clinical practice, identification of the RVS ECG pattern in a monitored patient who obtains ROSC after PEA/Asystole can help guide workup and management focused on causes of hypoxic respiratory failure, not limited to only pulmonary embolism. In patients with progressive respiratory failure, recognition of progressive RVS may also prompt escalation of management to potentially avert cardiac arrest. In the future, development of automated algorithms to detect development of the RVS pattern can help not only guide management of a patient suffering PEA/Asystole arrest in real-time, but potentially predict *impending* cardiac arrests and allow for earlier targeted interventions[6, 22]. Furthermore, this study suggests that different clinical causes and pathophysiologic mechanisms can lead to the same clinical manifestation of PEA/Asystole, and it is possible that they can be distinguished through their preceding ECG manifestations.

Limitations

Our study has several limitations. All included patients had to be monitored in an acute care bed uninterrupted for at least 3 hours prior to cardiac arrest; hence, patients who were unmonitored or required off-floor tests and procedures were excluded. There is also no established method to determine the actual cause of cardiac arrest when several possible causes co-exist (ie. ARDS with end organ damage in several other organs, or massive upper GI bleed with aspiration of blood). Hence, it is possible that the positive predictive value of RVS for a respiratory cause of arrest is higher than was reported. Our echocardiographic correlation with ECG only included those performed after ROSC was achieved, hence limited to patients who survived cardiac arrest. Future studies evaluating ECG findings and routine peri-arrest bedside echocardiography are necessary to better understand the correlation of these modalities.

Conclusion

In this study, we defined the continuous ECG RVS pattern as progressive RV depolarization delay in lead V1 with at least one supporting finding: development of ST elevation in V1, rightward-directed limb lead ST elevation vector, right axis deviation. RV strain ECG pattern preceded 47% of PEA/asystole IHCA, predominantly due to hypoxic respiratory failure, not limited to pulmonary embolism. RV strain ECG pattern was also associated with isolated RV dysfunction by echocardiogram post-IHCA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

IHCA	in-hospital cardiac arrest
RV	right ventricle
LV	left ventricle
RVS	right ventricular strain
PEA	pulseless electrical activity
ECG	electrocardiogram
CT	computed tomography
RBBB	right bundle branch block
iRBBB	incomplete right bundle branch block

ARDS	acute respiratory distress syndrome
ROSC	return of spontaneous circulation

References

[1]. Holmberg Mathias J, Ross Catherine E, Fitzmaurice Garrett M, Chan Paul S, Duval-Arnould J, Grossestreuer Anne V, et al. Annual Incidence of Adult and Pediatric In-Hospital Cardiac Arrest in the United States. Circulation: Cardiovascular Quality and Outcomes. 2019;12:e005580. [PubMed: 31545574]

[2]. Myerburg RJ, Halperin H, Egan DA, Boineau R, Chugh SS, Gillis AM, et al. Pulseless Electric Activity Definition, Causes, Mechanisms, Management, and Research Priorities for the Next Decade: Report From a National Heart, Lung, and Blood Institute Workshop. Circulation. 2013;128:2532–41. [PubMed: 24297818]

[3]. Hernandez C, Shuler K, Hannan H, Sonyika C, Likourezos A, Marshall J. C.A.U.S.E.: Cardiac arrest ultra-sound exam—A better approach to managing patients in primary non-arrhythmogenic cardiac arrest. Resuscitation. 2008;76:198–206. [PubMed: 17822831]

[4]. McGinn S, White PD. Acute cor pulmonale resulting from pulmonary embolism: its clinical recognition. Journal of the American Medical Association. 1935;104:1473–80.

[5]. Wynne J, Littmann L. Brugada electrocardiogram associated with pulmonary embolism. International Journal of Cardiology. 2013;162:e32–e3. [PubMed: 22664370]

[6]. Do DH, Kuo A, Lee ES, Mortara D, Elashoff D, Hu X, et al. Usefulness of Trends in Continuous Electrocardiographic Telemetry Monitoring to Predict In-Hospital Cardiac Arrest. The American Journal of Cardiology. 2019;124:1149–58. [PubMed: 31405547]

[7]. Do DH, Hayase J, Tiecher RD, Bai Y, Hu X, Boyle NG. ECG changes on continuous telemetry preceding in-hospital cardiac arrests. J Electrocardiol. 2015;48:1062–8. [PubMed: 26362882]

[8]. Faust O, Hagiwara Y, Hong TJ, Lih OS, Acharya UR. Deep learning for healthcare applications based on physiological signals: A review. Computer Methods and Programs in Biomedicine. 2018;161:1–13. [PubMed: 29852952]

[9]. Xiao R, King J, Villaroman A, Do DH, Boyle NG, Hu X. Predict In-Hospital Code Blue Events using Monitor Alarms through Deep Learning Approach. 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) 2018 p. 3717–20.

[10]. Digby GC, Kukla P, Zhan Z-Q, Pastore CA, Piotrowicz R, Schapachnik E, et al. The Value of Electrocardiographic Abnormalities in the Prognosis of Pulmonary Embolism: A Consensus Paper. Annals of Noninvasive Electrocardiology. 2015;20:207–23. [PubMed: 25994548]

[11]. Zhan Zq, Wang Cq, Nikus KC, He Cr, Wang J, Mao S, et al. Electrocardiogram Patterns during Hemodynamic Instability in Patients with Acute Pulmonary Embolism. Annals of Noninvasive Electrocardiology. 2014;19:543–51. [PubMed: 24750207]

[12]. Zhan Z-Q, Wang C-Q, Baranchuk A. Acute pulmonary embolism with ST-segment elevation in the inferior leads. International Journal of Cardiology. 2014;177:718–9. [PubMed: 25456693]

[13]. Zhong-qun Z, Chong-quan W, Nikus KC, Sclarovsky S, Chao-rong H. A new electrocardiogram finding for massive pulmonary embolism: ST elevation in lead aVR with ST depression in leads I and V4 to V6. The American Journal of Emergency Medicine. 2013;31:456.e5–e8.

[14]. Kucher N, Walpoth N, Wustmann K, Noveanu M, Gertsch M. QR in V1 – an ECG sign associated with right ventricular strain and adverse clinical outcome in pulmonary embolism. European Heart Journal. 2003;24:1113–9. [PubMed: 12804925]

[15]. Schamroth L, Myburgh D, Schamroth C. The early signs of right bundle branch block. Chest. 1985;87:180–5. [PubMed: 3967525]

[16]. Smulders YM. Pathophysiology and treatment of haemodynamic instability in acute pulmonary embolism: the pivotal role of pulmonary vasoconstriction. Cardiovascular Research. 2000;48:23–33. [PubMed: 11033105]

[17]. Lahm T, Douglas IS, Archer SL, Bogaard HJ, Chesler NC, Haddad F, et al. Assessment of Right Ventricular Function in the Research Setting: Knowledge Gaps and Pathways Forward. An

Official American Thoracic Society Research Statement. American Journal of Respiratory and Critical Care Medicine. 2018;198:e15–e43. [PubMed: 30109950]

[18]. Netzer NC, Strohl KP, Högel J, Gatterer H, Schilz R. Right ventricle dimensions and function in response to acute hypoxia in healthy human subjects. Acta Physiologica. 2017;219:478–85. [PubMed: 27332955]

[19]. Clowes GH Jr., Hopkins AL, Simeone FA. A comparison of the physiological effects of hypercapnia and hypoxia in the production of cardiac arrest. Ann Surg. 1955;142:446–59. [PubMed: 13249341]

[20]. Robalino BD, Whitlow PL, Underwood DA, Salcedo EE. Electrocardiographic manifestations of right ventricular infarction. American Heart Journal. 1989;118:138–44. [PubMed: 2662727]

[21]. Melgarejo-Moreno A, Galcerá-Tomás J, García-Alberola A, Valdás-Chavarri M, Castillo-Soria FJ, Mira-Sánchez E, et al. Incidence, clinical characteristics, and prognostic significance of right bundle-branch block in acute myocardial infarction: a study in the thrombolytic era. Circulation. 1997;96:1139–44. [PubMed: 9286941]

[22]. Hu X. An algorithm strategy for precise patient monitoring in a connected healthcare enterprise. npj Digital Medicine. 2019;2:30. [PubMed: 31304377]

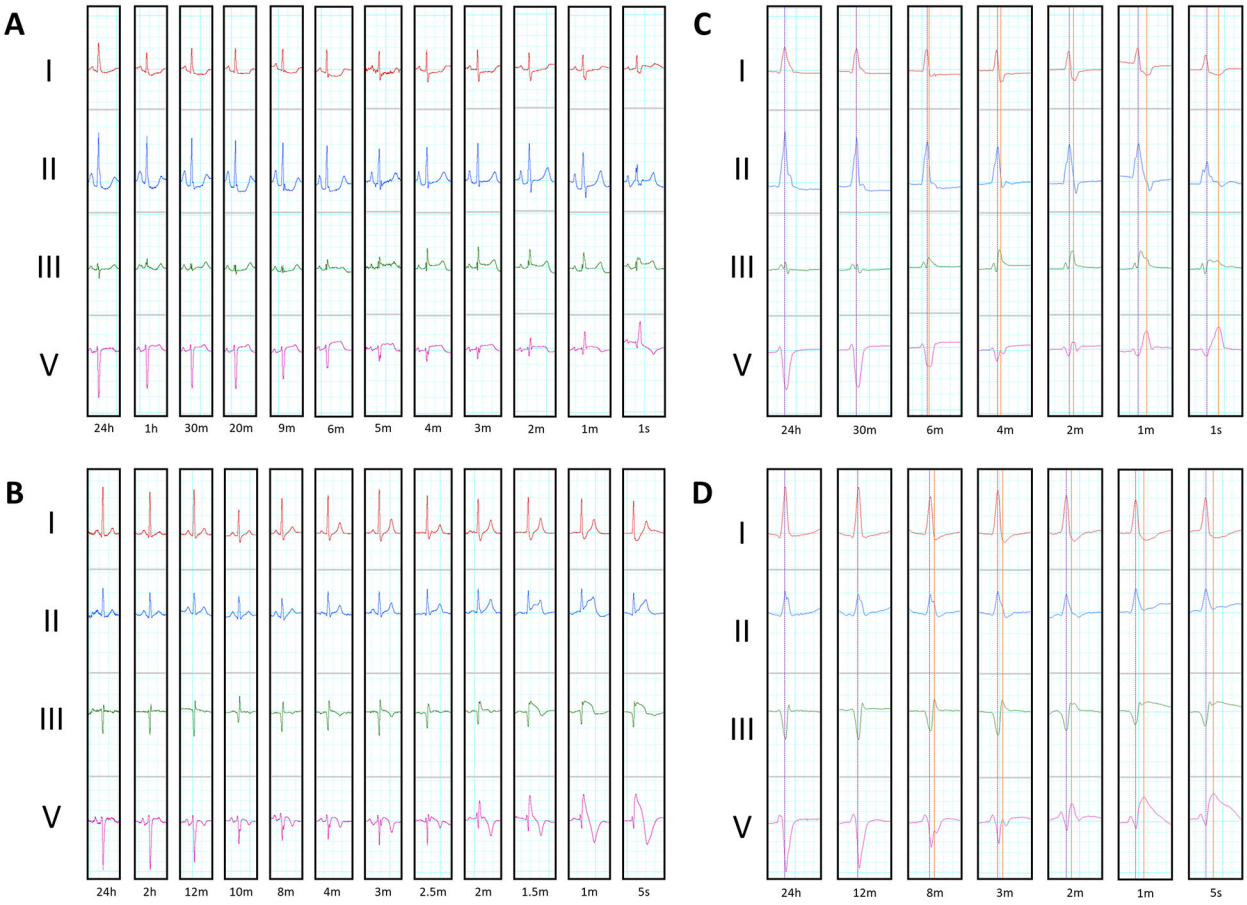

Figure 1: Right ventricular strain pattern by continuous electrocardiogram.

Leads I, II, III, and precordial lead in the V1 position are shown. Times noted are time prior to onset of chest compressions for PEA arrest. Panels A and B are in 25mm/s speed. Panel A shows the progression of ECG changes associated with RV strain in an 83 year old male patient with PEA arrest from hypoxic respiratory failure due to hospital-acquired pneumonia. The baseline QRS morphology is normal. By 30 minutes prior to arrest, in lead V1 there are notable increase in ST elevation; a notch in the S wave is noted 20 minutes PTA with associated decrease in S wave amplitude. The notch becomes progressively later in the QRS complex and gradually grows into a terminal R wave reflecting delayed RV activation, which is clearly noted by 2 minutes PTA. There is progressive RV conduction delay with widening of the terminal R wave as the patient gets closer to PEA arrest. The limb leads simultaneously show a rightward axis shift and rightward-directed ST elevation vector, which is most positive in lead III. Panel B shows a 63 year old male with metastatic adrenal carcinoma being treated for pneumonia and altered mental status with sudden worsening of hypoxia leading to PEA arrest. Continuous ECG shows decrease in lead V1 S wave amplitude and S wave notch with rightward directed ST elevation vector starting at 10 minutes PTA. There is progressive delay in RV depolarization which eventually manifests as a terminal R wave. The terminal R wave fuses with the ST segment elevation by 1 minute PTA, mimicking a Brugada Type 1 ECG pattern. Note the simultaneous development of the S1Q3T3 pattern and peaked T waves. Panels C and D show select time points from Panels A

and B, respectively, in 100mm/s. Reference dotted lines in purple mark the intrinsicoid deflection as measured in lead II; dotted red lines mark the peak of the S wave notch in lead V1 as it eventually becomes a terminal R wave. In Panel C and D, the intrinsicoid deflection time remains 46ms and 50ms, respectively, throughout the entire 24 hour period, whereas there is gradual terminal RV conduction delay with increase in QRS duration from an initial 92ms to 142ms and 104ms to 178ms, respectively. Abbreviations. PEA: pulseless electrical activity, PTA: prior to arrest, RV: right ventricular.

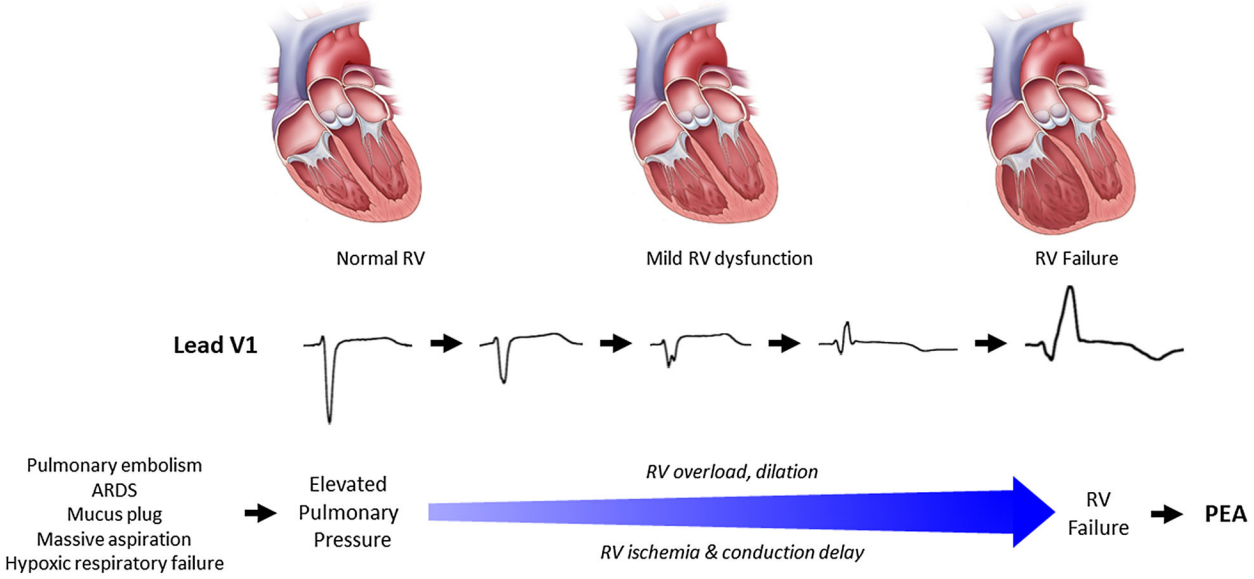

Figure 2: Proposed mechanism of hypoxia-mediated pulseless electrical activity arrest.

Hypoxic respiratory failure, whether from pulmonary embolism or other causes, leads to elevated pulmonary pressures, RV dilation, RV ischaemia and conduction delay, and eventually PEA due to RV dysfunction/failure. RV ischaemia and conduction delay can be clearly tracked on lead V1. Abbreviations. ARDS: acute respiratory distress syndrome, RV: right ventricle, PEA: pulseless electrical activity.

Table 1:

Patient population

	Overall Cohort (n = 140)	UCLA Cohort (n = 67)	UCSF Cohort (n = 73)
Age, mean ± SD	62.1 ± 17.1	63.7 ± 17.7	60.6 ± 16.4
Male, n (%)	79 (56)	36 (54)	43 (59)
ICU, n (%)	133 (95)	60 (90)	73 (100)
PEA, n (%)	120 (86)	53 (76)	67 (92)
HR > 100 bpm, n (%)	8 (6)	3 (4)	5 (7)
HR 60 – 100 bpm, n (%)	39 (28)	14 (21)	25 (34)
HR < 60 bpm, n (%)	73 (52)	36 (54)	37 (51)
Asystole, n(%)	20 (14)	14 (21)	6 (8)
Sinus arrest, n (%)	10 (7)	8 (12)	2 (3)
AV block, n (%)	10 (7)	6 (9)	4 (5)
ROSC, n (%)	104 (74)	47 (70)	57 (78)
Survive to Discharge, n (%)	38 (27)	20 (30)	18 (25)
Primary Etiology of Cardiac Arrest			
Respiratory - Nonintubated, n(%)	38 (27)	17 (25)	21 (29)
Respiratory - Intubated, n(%)	19 (14)	11 (16)	8 (11)
Acute Respiratory Distress Syndrome, n(%)	10 (7)	6 (9)	4 (5)
Pulmonary Embolism, n(%)	5 (4)	1 (1)	4 (5)
Metabolic Acidosis, n(%)	21 (15)	6 (9)	15 (21)
Distributive Shock, n(%)	1 (1)	1 (1)	0 (0)
Hemorrhagic Shock, n(%)	11 (8)	5 (7)	6 (8)
Cardiogenic Shock, n(%)	4 (3)	3 (4)	1 (1)
Obstructive Shock, n(%)	2 (1)	0	2 (3)
Multiorgan Failure, n(%)	11 (8)	7 (10)	4 (5)
Myocardial Infarction, n(%)	3 (2)	1 (1)	2 (3)
Conduction disorder (primary), n(%)	2 (1)	1 (1)	1 (1)
Vagal, n(%)	1 (1)	0	1 (1)

	Overall Cohort (n = 140)	UCLA Cohort (n = 67)	UCSF Cohort (n = 73)
Other, n(%)	2 (1)	0	2 (3)
Unknown, n(%)	10 (7)	8 (12)	2 (3)

Abbreviations. ICU: intensive care unit, PEA: pulseless electrical activity, ROSC: return of spontaneous circulation

Table 2:

Lead V1 QRS morphological changes in right ventricular strain pattern

End QRS morphology* / Starting QRS morphology*	Normal	SV1 decreased amplitude	SV1 notch	QR†	iRBBB	RBBB	Total Patients
Normal	0	3	7	4	6	25	45
SV1 decreased amplitude		0	0	0	0	1	1
SV1 notch			0	1	1	7	9
QR†				0	0	1	1
iRBBB					0	7	7
RBBB						3‡	3
Total Patients	0	3	7	5	7	44	66

*Each combination of row and column denotes the number of patients with starting QRS morphology (row) and end QRS morphology prior to chest compression (column) in lead V1 (eg. 6 patients with normal initial lead V1 QRS morphology had iRBBB just prior to chest compression)

†QR was defined only when QRS duration < 100 ms

‡These cases showed progressive widening of the R'

Abbreviations. iRBBB: incomplete right bundle branch block, RBBB: right bundle branch block

Table 3:

Causes of cardiac arrest with and without right ventricular ECG strain pattern

	Development Cohort		Validation Cohort	
Clinical Cause*	**RV Strain (n = 35)**	**No RV Strain (n = 38)**	**RV Strain (n = 21)**	**No RV Strain (n = 19)**
Respiratory, n (%)	28 (80)	13 (34)	17 (81)	8 (42)
Un-intubated, n(%)	15 (42)	8 (21)	7 (33)	5 (26)
Intubated, n(%)	9 (35)	1 (3)	5 (24)	2 (11)
ARDS, n(%)	2 (6)	4 (10)	3 (14)	1 (5)
Pulmonary embolism, n(%)	2 (6)	0	2 (10)	0
Non-Respiratory, n (%)	7 (17)	25 (66)	4 (19)	11 (58)
Metabolic acidosis, n(%)	3 (9)	8 (21)	0	7 (37)
Distributive shock, n(%)	0	1 (3)	0	0
Haemorrhagic shock, n(%)	1 (3)†	5 (13)	2 (10)†	2 (11)
Cardiogenic shock, n(%)	0	1 (3)	0	0
Obstructive shock, n(%)	0	1 (3)	0	1 (5)
Multiorgan failure, n(%)	2 (6)	7 (18)	1 (5)	0
Myocardial infarction, n(%)	0	1 (3)	1 (5)‡	1 (5)
Conduction disorder (primary), n(%)	0	1 (3)	0	0
Vagal, n(%)	0	0	0	0
Other, n(%)	1 (3)	0	0	0

*Only cases where the level of confidence in diagnosis of the clinical cause was rated as 3 (most likely cause identified though other less likely competing causes were present) or 4 (cause clearly identified)

†assive upper gastrointestinal tract bleeding with aspiration of blood clearly documented

‡Patient with known coronary artery disease with cardiac arrest in post-operative setting. Probable diagnosis based on elevated troponin with subsequent fall, no coronary angiogram or autopsy performed

Abbreviations. ARDS: acute respiratory distress syndrome

Table 4:

Imaging and Autopsy correlation of right ventricular strain ECG pattern

	Development Cohort		Validation Cohort		Entire Cohort	
	RV Strain by ECG (n = 35)	**No RV Strain by ECG (n = 38)**	**RV Strain by ECG (n = 21)**	**No RV Strain by ECG (n = 19)**	**RV Strain by ECG (n = 56)**	**No RV Strain by ECG (n = 57)**
Chest CT Angiogram for Pulmonary Embolism*, n	5	2	5	1	10	3
Positive, n (%)	0	0	2 (40)	0	2 (20)	0
Negative, n (%)	5 (100)	2 (100)	3 (60)	1 (100)	8 (80)	3 (100)
Autopsy - Pulmonary embolism†, n	7	5	6	5	13	10
Positive, n (%)	2 (29)	0	2 (33)	0	4 (31)	0
Negative, n (%)	5 (71)	5 (100)	4 (67)	5 (100)	9 (69)	10 (100)
Echocardiogram - post arrest‡, n	14	7	8	7	22	14
New isolated RV dysfunction§, n(%)	5 (36)	0	4 (50)	1 (14)//	9 (41)	1 (7)
New isolated LV dysfunction, n(%)	0	1 (14)	0	2 (29)	0	3 (21)
New biventricular dysfunction, n(%)	2 (14)	2 (29)	1 (13)	0	3 (14)	2 (14)
No change, n(%)	7 (50)	4 (57)	3 (37)	4 (57)	10 (45)	8 (57)

*Positive result denote studies showing evidence of massive or submassive pulmonary embolus. Negative results denote studies showing no pulmonary embolism, segmental or subsegmental embolus without evidence of right ventricular strain by CT. Positive studies include those performed up to 24 hours pre-arrest, and those post-arrest. Negative studies must be performed post-arrest

†Positive autopsy shows large burden of pulmonary embolism deemed to be the likely cause of cardiac arrest

‡Performed within 24 hours post-cardiac arrest

§Enlargement, decrease in systolic function, or volume and/or pressure overload not previously present

//his patient developed possible R strain C pattern post-arrest

Abbreviations. CT: computed tomography, LV: left ventricle, RV: right ventricle