Original Article

Correlating computed tomography pulmonary angiography signs of right ventricular strain in pulmonary embolisms to clinical outcomes

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Abstract:

INTRODUCTION: Right ventricular strain (RVS) in pulmonary embolism (PE) can be used to stratify risk and direct intervention. The clinical significance of computed tomography pulmonary angiogram (CTPA)-derived radiologic signs of RVS, however, remains incompletely characterized. We retrospectively analyzed a cohort of persons with acute PE to determine which, if any, findings of RVS on CTPA correlate with clinical outcomes.

METHODS: All patients with PE diagnosed on CTPA from March 2013 through February 2015 at Lyndon B. Johnson Hospital were identified. Their records were retrospectively reviewed to identify length of stay, intensive care unit (ICU) placement, hemodynamic failure, use of thrombolytics, vasopressor requirement, mechanical ventilation, and attributable mortality. Three radiologists, blinded to clinical outcomes, separately reviewed the cohort's CTPAs to identify signs of RVS – pulmonary trunk size, internal size of the right and left ventricles, paradoxical interventricular septal bowing, inferior vena cava (IVC) contrast reflux, and hepatic vein contrast reflux.

RESULTS: In our cohort of 102 persons, 12 demonstrated hemodynamic failure, 13 required ICU placement, 3 received thrombolysis, and 5 had death attributable to PE. The greatest interobserver agreement among radiologists existed for the presence of increased pulmonary trunk size (0.76 kappa by %agreement) and hepatic vein contrast reflux (0.92 kappa by %agreement). A multiple regression analysis found that when 100% radiologist agreement existed, presence of paradoxical intravenous septal bowing predicted thrombolytic usage ($P = 0.02$), and the presence of IVC reflux predicted attributable mortality ($P = 0.03$).

CONCLUSION: Only IVC contrast reflux was associated with increased mortality, and no other sign of RVS on CTPA correlated with clinical outcomes. This suggests that most signs of RVS on CTPA do not reliably predict PE severity. Therefore, RVS seen by CTPA should be used cautiously in weighing the decision to initiate thrombolytics.

Keywords:

Computed tomography pulmonary angiography, pulmonary embolism, right ventricular strain

In the United States, 500,000–600,000 patients are diagnosed each year with pulmonary embolism (PE); about 100,000 of those patients die as a result of this disease.[1] For this reason, urgent diagnosis and treatment of PE are essential. The gold standard for diagnosis is computed tomography pulmonary angiography (CTPA).[2] Echocardiographic or CTPA evidence of right ventricular strain (RVS) is an accepted sign of clinical severity in patients with PE.[3,4] The diagnosis of RVS has been correlated with greater success using thrombolytic therapy to

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re-establish pulmonary artery (PA) patency and reduce mortality.[5] Massive hemorrhage, the most serious side effect reported from thrombolysis, limits its benefit. Therefore, strict selection of candidates for this therapy is essential.

Several studies have shown that echocardiographic or CTPA findings of RVS predict mortality among normotensive patients with PE.[2,6,7] However, that association has not been fully studied with multiple radiologists blinded to outcome variables such as hemodynamic failure, use of thrombolysis, use of mechanical ventilation, use of vasopressors, use of intensive care unit (ICU), and mortality attributable to PE. The purpose of this study is to fill that gap of knowledge.

Methods

Subject population

The study was undertaken at Lyndon B. Johnson Hospital, a tertiary-care, county-based center in Houston, Texas, after waivered Institutional Review Board approval (HSC-MS-17-0983); patient consent requirements were obtained. We collected information from electronic medical records from March 1, 2013 to February 1, 2015. At the time, radiological signs of RVS were not customarily reported. Our intention was to avoid bias related to the existing reports of the evaluated CTPA.

Inclusion criteria

From the hospital radiology database, we reviewed all CTPAs from patients 18 years of age and older and selected all studies positive for acute PE. Of these identified patients, we enrolled those who were admitted to the hospital.

Exclusion criteria

Patients younger than 18 years of age and/or those with a nondiagnostic CTPA were excluded from the study. Patients transferred to other hospitals after the CTPA or those who left the hospital without adequate follow-up were also excluded from the study.

Data collection

From the examined medical records, we retrieved patients' age, gender, and date of the CTPA. We also recorded length of in-hospital stay and ICU placement, if applicable, coexistence of other pulmonary abnormalities (other masses, atelectasis, presumably infectious infiltrates, pleural effusion, and presumed primary or secondary malignant disease to the lungs). We also extracted whether they suffered hemodynamic failure, required use of thrombolytic therapy, vasopressors, mechanical ventilation, or if they died as a result of the PE. Hemodynamic failure was defined as the condition when systolic blood pressure was lower than 100 mmHg for more than an hour with a concomitant heart rate >100 beats/min during that same period. We documented alternative causes of hemodynamic failure when applicable.

From the selected CTPA patient data set, three separate board-certified radiologists, blinded to each other's observations, reported the presence or absence of the following signs of RVS, as reported in the literature: increased size of the PA trunk (>3 cm), increased ratio of the internal right to left ventricle size (maximum inner wall to inner wall diameter ratio >1), paradoxical interventricular septal bowing, inferior vena cava (IVC) contrast reflux, and hepatic vein contrast reflux.[8] Given that radiographic interpretations of CTPA imaging may be dependent on radiologist expertise and experience, we chose to utilize three radiologists in order to obviate any potential subjectivity in reporting.

Statistical analysis

MedCalc statistical software Version 18 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018) was utilized for the statistical analysis. Interrater reliability (IRR) of the five signs of RVS was calculated using average percent agreement and Cohen kappa.[9] We considered adequate IRR values 0.7 or above, as recommended. Categorical variables were analyzed using the Fisher exact test, and discrete variables were analyzed using the Student's *t*-test for unpaired samples. A multiple regression model was used to compare the association of the explored signs of RVS with the clinical outcomes. A two-sided $P < 0.05$ was considered indicative of statistical significance.

Results

Study cohort characteristics

One hundred and two patients fulfilled the inclusion criteria. Of them, 44 (45%) were men; the median age was 55 years (range 24–97). Clinical outcomes for our cohort are displayed in Table 1; hemodynamic failure was present in 12 persons (12%) and PE attributable death was present in five persons (5%). Of the patients considered

Table 1: Clinical outcomes in our cohort of 102 persons with acute pulmonary embolism

Variable	*n* (%)
Hemodynamic failure present	12 (12)
Intensive care unit placement	13 (13)
Requirement for vasopressor use	5 (5)
Requirement for mechanical ventilation	7 (7)
Requirement for thrombolytics	3 (3)
Death attributable to PE	5 (5)

PE=Pulmonary embolism

hemodynamically unstable, two had concomitant presumption of sepsis from pleural empyema, and one was suspected to have a major gastrointestinal bleed and died prior to obtaining an endoscopy.

Radiological signs of PE and RVS with associated IRR for each sign are presented in Table 2. The presence of hepatic vein contrast reflux was the variable with the highest interrater agreement.

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Correlation of RVS indicators with clinical outcomes was assessed for every individual radiologist first. Only one of them found that the risk for ICU admission was lower in the presence of pulmonary trunk >3 cm (3% vs. 18%, $P = 0.03$); all other signs of RVS were not associated with significantly different risk of evaluated clinical outcomes.

Table 3 shows that the correlation between the individual radiological indicators of RVS and the clinical outcome variables is poor. This occurred regardless of the strictness of the radiologist coincidence for the presence or absence of these signs: we accepted the variables when the three of them agreed or when two of them agreed. Table 4 depicts a multiple regression analysis to assess the impact of all radiological findings considered together (at 100% and 67% agreement) for each one of the evaluated clinical outcomes. When considered at 100% agreement, the presence of IVC contrast reflux predicted mortality and paradoxical interventricular septal bowing (the sign of RVS that in our cohort showed the lowest IRR) predicted thrombolytic use. Three patients received thrombolytic therapy; two of them required ICU care; none died.

Discussion

In our study, we found a poor correlation between RVS signs and negative clinical outcomes. The gold standard for the objective determination of RVS, a reliable determinant of clinical severity, is transthoracic echocardiography (TTE).[3-5] Unfortunately, TTE is limited by availability and a slow turnaround time.[10,11] On the contrary, CTPA can produce results in minutes but is limited to the analysis of static cardiac imaging.[7,8,10,11] Thus, the value of CTPA inappropriately and reliably determining clinically relevant RVS has been questioned.[12] Although several studies have investigated the degree of correlation between CTPA and TTE findings suggestive of RVS, the capacity of CTPA as a standalone predictor for clinically relevant outcomes

Table 2: Radiological signs of pulmonary embolism and right ventricular strain with associated interrater reliability for each sign

Variable	*n* (%)	Kappa by percent agreement	Kappa by Cohen
Occlusive embolism (vs. nonocclusive)	11 (11)	0.79	0.03
Peripheral embolism (vs. central and/or peripheral)	72 (71)	0.82	0.60
Unilateral embolism (vs. bilateral)	41 (40)	0.72	0.48
Pulmonary trunk size >3 cm (vs. smaller)	33 (32)	0.89	0.75
Paradoxical septal bowing	21 (21)	0.76	0.27
RV/LV ratio >1 (vs. less)	33 (32)	0.76	0.48
IVC contrast reflux	44 (43)	0.75	0.50
Hepatic vein contrast reflux	21 (21)	0.92	0.74

RV=Right ventricular, LV=Left ventricular, IVC=Inferior vena cava

Table 3: Univariate analysis correlating radiological signs of right ventricular strain with clinical outcomes

	Pulmonary Trunk >3cm		Paradoxical Septal Bowing		RV/LV Ratio >1		IVC Contrast Reflux		Hepatic Vein Contrast Reflux	
	100% (*n*=25)	67% (*n*=33)	100% (*n*=4)	67% (*n*=18)	100% (*n*=16)	67% (*n*=33)	100% (*n*=23)	67% (*n*=49)	100% (*n*=23)	67% (*n*=49)
Hemodynamic failure	1 (4%) *P*=0.28	1 (4%) *P*=0.28	1 (25%) *P*=0.40	2 (11%) *P*=1.00	2 (12%) *P*=1.00	4 (21%) *P*=1.00	4 (17%) *P*=0.46	5 (10%) *P*=0.76	2 (14%) *P*=0.67	3 (13%) *P*=1.00
ICU admission	1 (4%) *P*=0.18	1 (4%) *P*=0.28	2 (50%) *P*=0.08	3 (17%) *P*=0.70	3 (19%) *P*=0.42	6 (18%) *P*=0.34	4 (17%) *P*=0.48	5 (10%) *P*=0.56	1 (7%) *P*=0.67	2 (9%) *P*=0.73
Vasopressor Requirement	0 (0%) *P*=0.33	1 (4%) *P*=0.28	1 (25%) *P*=0.18	1 (6%) *P*=1.00	1 (6%) *P*=0.58	3 (9%) *P*=0.33	1 (4%) *P*=1.00	2 (4%) *P*=1.00	0 (0%) *P*=1.00	1 (4%) *P*=1.00
Mechanical Ventilation	1 (4%) *P*=1.00	1 (4%) *P*=0.28	1 (25%) *P*=0.25	2 (11%) *P*=0.60	2 (12%) *P*=0.30	4 (21%) *P*=0.21	2 (9%) *P*=0.65	3 (6%) *P*=1.00	1 (7%) *P*=1.00	1 (4%) *P*=1.00
Thrombolytic Use	0 (0%) *P*=1.00	0 (0%) *P*=0.55	1 (25%) *P*=0.11	0 (0%) *P*=1.00	1 (6%) *P*=0.40	0 (0%) *P*=0.55	2 (9%) *P*=0.13	0 (0%) *P*=0.24	1 (7%) *P*=0.36	0 (0%) *P*=1.00
Attributable death to PE	1 (4%) *P*=1.00	1 (4%) *P*=0.28	1 (25%) *P*=0.18	2 (11%) *P*=0.21	2 (12%) *P*=0.17	3 (9%) *P*=0.33	3 (13%) *P*=0.07	4 (8%) *P*=0.19	1 (7%) *P*=0.53	2 (9%) *P*=0.31

Table 4: Multiple regression correlating radiological signs of right ventricular strain to clinical outcomes

Dependent variables (clinical outcomes)	Radiological sign of RVS	Independent variables, with 100% agreement (*P*)	Independent variables, with 67% agreement (*P*)
Hemodynamic failure	PA trunk >3 cm	0.12	0.32
	Paradoxical septal bowing	0.60	0.48
	RV/LV ratio >1	0.94	0.93
	IVC contrast reflux	0.27	0.18
	Hepatic vein contrast reflux	0.69	0.88
ICU admission	PA trunk >3 cm	0.08	0.29
	Paradoxical septal bowing	0.14	0.35
	RV/LV ratio >1	0.64	0.43
	IVC contrast reflux	0.12	0.15
	Hepatic vein contrast reflux	0.16	0.98
Vasopressor requirement	PA trunk >3 cm	0.21	0.53
	Paradoxical septal bowing	0.14	0.28
	RV/LV ratio >1	0.90	0.15
	IVC contrast reflux	0.63	0.62
	Hepatic vein contrast reflux	0.46	0.55
Mechanical ventilation	PA trunk >3 cm	0.41	0.41
	Paradoxical septal bowing	0.31	0.75
	RV/LV ratio >1	0.52	0.32
	IVC contrast reflux	0.84	0.71
	Hepatic vein contrast reflux	0.92	0.36
Thrombolytic use	PA trunk >3 cm	0.18	0.58
	Paradoxical septal bowing	0.02*	0.47
	RV/LV ratio >1	0.78	0.55
	IVC contrast reflux	0.24	0.41
	Hepatic vein contrast reflux	0.90	0.75
Attributable death to PE	PA trunk >3 cm	0.38	0.65
	Paradoxical septal bowing	0.37	0.65
	RV/LV ratio >1	0.43	1.00
	IVC contrast reflux	0.03*	0.61
	Hepatic vein contrast reflux	0.17	0.33

PE=Pulmonary embolism, ICU=Intensive care unit, RV=Right ventricular, LV=Left ventricular, IVC=Inferior vena cava, PA=Pulmonary artery

has received less attention. Thus, the clinical thrust of this study was to determine if and how CTPA signs of RVS correlate to clinical outcomes in persons with acute PE.

We present data demonstrating that most radiological signs of RVS per CTPA have limited capacity in predicting short term clinical outcomes. This lack of clinical correlation is likely secondary to both the subjectivity of appropriately identifying radiological signs of RVS and the inability of these static signs to reflect hemodynamic patterns.[11-13] As shown in Table 2, there existed a wide range of IRR across the RVS variables (75%–92% kappa by percent agreement). This high degree of discordance amongst three radiologists seems to suggest that these radiological signs do not possess the reliability that may have otherwise been present if these parameters were clearly delineated to clinically correlate. Nevertheless, we demonstrate in Table 3 that even when variables are considered at a 100% agreement amongst radiologists, there is limited capacity for these parameters to predict clinical outcomes. However, we did find that the presence of paradoxical interventricular septal bowing correlated to thrombolytic use ($P = 0.02$) and that IVC reflux correlated to death attributable to PE ($P = 0.03$). Of note, however, both of these clinical outcomes – thrombolytic use and death due to PE – were rare events in our cohort and such, these findings may be underpowered. Similarly, per one radiologist's review of the CTPAs, increased pulmonary trunk size was also found to predict a lower ICU admission risk. Our cohort's being underpowered may also justify this seemingly contradictory finding. In effect, we were unable to find that CTPA findings could predict any clinically relevant measure. This novel information suggests that CTPA findings of RVS should be judiciously incorporated into patient management.

There exist several studies that have attempted to qualify the capacity of CTPA signs of RVS across numerous contexts including ability to correlate to echocardiography, appropriately risk-stratify patients, and predict clinical outcomes.[2,7,8,11,13] Unfortunately, these studies and the ability to incorporate CTPA findings risk stratification of persons with acute PE are limited by the inherent shortfalls of static imaging and the poor reliability of RVS radiological signs.[11,13]

As mentioned earlier, the images gathered from a CTPA are fixed and stationary. Consequently, the static nature of this modality poses numerous problems when analyzing for presence several RVS parameters, notably interventricular diameter ratios and increased PA size, both of which vary and are dependent on the phase of the cardiac cycle captured on imaging.[11,13,14] In essence, both these parameters may be quantified differently if the CTPA was captured during peak systole versus peak diastole versus any phase in between. Interestingly, both the interventricular diameter ratio and increased pulmonary trunk size were parameters found by others to demonstrate higher reproducibility compared to other RVS signs and have also been correlated with disease severity.[15-17]

The reproducibility and reliability of radiological signs of RVS has come into question in prior similar studies.[11,13] Similar to our own findings displayed in Table 2, others have also demonstrated that appropriately identifying paradoxical interventricular septal bowing and contrast reflux is highly radiologist dependent.[13,18] Regardless, studies have concluded that certain RVS signs on CTPA are able to predict certain clinical outcomes, including mortality.[7,8,12,18] Of note, despite the issue of IRR in identifying RVS being prevalent, to our knowledge, this is the only such study utilizing three blinded radiologists to survey the CTPAs in our study cohort; other studies utilized only 1 or 2 radiologists.[12,18-20] Incorporating radiological findings of RVS into patient management is further hindered by the fact that in clinical practice only one given radiologist analyses and reports on a CTPA study. Consequently, the limited utility demonstrated in our study of 100% radiologist agreement of RVS in correlating with short term clinical outcomes becomes further compromised with only one radiologist report in real-world practice. Incorporation of additional clinical data, namely TTE findings and hemodynamic parameters, are paramount in dictating patient management and deciding to initiate thrombolytic therapy.

Limitations

The major limitations of this study are secondary to our cohort having a limited sample size; our analysis incorporated only 102 persons with acute PE, of which only a small minority can be characterized as clinically severe cases (12% hemodynamic failure and 5% attributable death to PE). This limited power prevents findings from this study being fully and appropriately generalizable, in particular to those persons with more severe manifestations.

Conclusion

Only IVC contrast reflux is associated with increased mortality, and no other sign of RVS on CTPA correlates with short term clinical outcomes. This suggests that most signs of RVS on CTPA do not reliably predict the increased severity of PE. Evidence of RVS as determined per CTPA should be cautiously incorporated in weighing the decision to initiate thrombolytic therapy. We conclude that the ability of RVS findings on CTPA to predict clinical outcomes is limited.

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Conflicts of interest

There are no conflicts of interest.

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