Ruling out PE: a novel approach using end-tidal CO2 with compression Ultrasonography and transthoracic Echocardiography in Pulmonary Embolism Diagnosis (CUEPED)

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ABSTRACT

Diagnosis of pulmonary embolism (PE) remains a challenge in clinical practice, especially in emergency setting despite availability of various diagnostic tools. It is desirable to have a rapid and accurate bedside test to rule out PE.

The aim of this study is to evaluate the diagnostic accuracy of CUEPED, a novel method of ruling out pulmonary embolism using a combination of end-tidal CO_2 (ETCO2), Compression Ultrasonography (CUS) and Transthoracic Echocardiography (TTE).

In this pilot study, patients who presented to the Emergency Department at University Malaya Medical Centre with suspected acute PE from December 2013 to October 2014, who fulfilled the inclusion and exclusion criteria, were assessed using CUEPED. CUEPED was considered positive if the measured ETCO2 was less than 35 mmHg, or if there was presence of venous incompressibility in lower limb ultrasonography or if tricuspid annular plane systolic excursion (TAPSE) in transthoracic echocardiography was less than 1.6. All patients received a computed tomography pulmonary angiography (CTPA) for confirmation of diagnosis. Data obtained was analyzed to determine if a negative CUEPED has the potential to accurately rule out a PE.

30 patients (mean age = 48 years [SD = 13.6]) were involved with an equal distribution between gender. The incidence of PE was 56.7%. CUEPED had a sensitivity of 100% for PE. Negative CUEPED ruled out PE with a negative predictive value of 100%. Positive CUEPED ruled in PE with a low specificity of 53.8% and moderate positive predictive value of 73.9%.

This diagnostic study showed that a negative CUEPED is potentially accurate in ruling out PE.

Keywords: pulmonary embolism, End-tidal CO2, compression ultrasound, transthoracic echocardiography

INTRODUCTION

Pulmonary embolism (PE) is a common illness with substantial morbidity and mortality.[1-2] D- dimer testing is time consuming and may delay further tests in suspected PE. CTPA is a non-invasive highly sensitive and highly specific imaging tool in PE. However, CTPA is associated with its complications including contrast media-induced nephropathy and radiation exposure.[9-10] Use of CTPA requires the transport of potentially unstable patient to the radiological department and is not feasible for unstable patients. CTPA may be overused in the evaluation of PE diagnosis.[11-12]

Studies on the diagnostic accuracy of transthoracic echocardiography (TTE) in PE showed it is neither sensitive nor specific as a stand-alone tool in the diagnosis of PE.[13].Sensitivity of TTE in detecting the indirect signs of PE is low, ranging from 56% to 73% and increases in combination with compression ultrasonography (CUS) to 87%,[14-15] since 90% of the pulmonary emboli arise from the lower limbs.[3] ETCO2 has a reported sensitivity of 87.2-92.6% and a specificity of 53-83% in the diagnosis of PE.[5, 16] ETCO2 is an indirect marker of the alveolar dead space, which will be reduced in PE.

It is desirable to have a rapid and accurate bedside test to rule out PE. We piloted a study on the use of a combination of ETCO2, CUS and TTE in pulmonary embolism diagnosis (CUEPED) as a potential tool for ruling out PE.

METHODS

Participants

This was a pilot study conducted between 1st December 2013 and 31stOctober 2014 at the University of Malaya Medical Centre (UMMC), Kuala Lumpur. Patients ≥ 18 years old who presented to the Emergency Department at UMMC with symptoms suggestive of PE were screened for suitability for the study. Patients were enrolled based on clinical suspicion by the treating physician, and if they matched any criteria described in the simplified Geneva score for PE. Patients were excluded if they had history of or known to have severe cardiovascular or pulmonary diseases including severe cardiac hypokinesia, obstructive cardiomyopathy, cor pulmonale, chronic PE and congenital valvular heart disease. Patients were also excluded if they were on mechanical ventilation and if they were pregnant.

Index Test - CUEPED

CUEPED consisted of measurement of end tidal CO2 (ETCO2), compression ultrasonography (CUS) of the lower limbs and transthoracic echocardiography (TTE). ETCO2 was measured using Drager quantitative capnometer. An uptake nasal cannula which was connected to the capnometer was placed over patient's nostrils. Patients were asked to breathe following their own rate and tidal volume. Measurement of ETCO2 was done after 60 seconds of breathing to allow a period of stabilization by the patients using the device. Three readings were taken with 30 seconds interval between each reading. The average value was used as the ETCO2 for the data analysis. 35mmHg was selected as the optimal cut-off value.[5] An ETCO2 of less than 35mmHg was considered positive.

2-point compression ultrasonography (CUS) test was performed using GE LOGIQ BOOK XP ultrasound machine with linear transducer (8L-RS probe, 4-11 MHz). The common femoral and popliteal veins of both lower limbs were examined. CUS was considered positive in venous incompressibility.[17]

TTE was performed using GE LOGIQ BOOK XP ultrasound with microconvex transducer (3S-RC probe, 2-5 MHz). Apical 4 chamber view was obtained and tricuspid annular plane systolic excursion **(TAPSE)** was measured. TTE was considered positive if **TAPSE** was less than 1.6.[18]

Both the CUS and TAPSE were done by a single trained investigator who had undergone WINFOCUS BASIC ECHO training and 2 months echocardiography and lower limb vascular ultrasound training under

a board certified cardiologist and emergency physician. Inter-rater agreement between the investigator, and the cardiologist and emergency physician on measurement of TAPSE and CUS was performed using Fleiss Kappa analysis. Kappa values of 0.77 (95% CI 0.56 – 0.98) and 0.8 (95% CI 0.54 – 1.0) were achieved for TAPSE and CUS respectively.

CUEPED was considered positive if any of its component tests (ETCO2, CUS or TTE) was positive. A positive result in any single component could be a result of a multitude of clinical causes including PE. Therefore a negative CUEPED was hypothesized to be able to rule out Pulmonary Embolism.

Reference test

Diagnosis of PE was confirmed based on gold standard CTPA findings [6, 19] as reported by radiologists who were blinded to the result of the index test.

Data collection

CUEPED data was documented as either positive or negative. Demographic data, presenting complaints, co-morbidities and risk factors of thromboembolism were recorded before the index test and the reference test were performed.

Statistical analysis

All statistical analyses were done using SPSS 21.0. For demographic characteristic and clinical profile data, categorical data are presented as percentage and numerical data are presented as mean (SD). Diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CUEPED were calculated with 95% confidence interval.

RESULTS

Participants

After exclusion, a total of 30 patients were recruited in the study. Mean age of the patients was 48 years old (SD = 13.6), with 50 % of them were male. Demographic data and PE risk profile of the patients are summarised in **Table 1**.

TABLE 1: Demographic Characteristic of the Study Population (N = 30)

	PE (n = 17) n (%)	Non PE (n = 13) n (%)	All n (%)
Age (years)[a]	45.0 (12.9)	51.8 (14.2)	48.0 (13.6)
Females n	9 (52.9)	6 (46.2)	15 (50.0)
Race			
Malay	9 (52.9)	4 (30.8)	13 (43.3)
Chinese	2 (11.8)	3 (23.0)	5 (16.7)
Indian	2 (11.8)	6 (46.2)	8 (26.7)
Other	4 (23.5)	0	4 (13.3)
Comorbidities			
None	9 (52.9)	3 (23.0)	12 (40.0)
Diabetes	5 (29.4)	5 (38.4)	10 (33.3)
Hypertension	5 (29.4)	6 (46.2)	11 (36.7)
Other	4 (23.5)	2 (15.4)	6 (20.0)
PE Risk Factors			
None	8 (47.1)	1 (7.7)	9 (30.0)
Post Operative	5 (29.4)	9 (69.2)	13 (43.3)
Cancer	1 (5.8)	3 (23.0)	4 (13.3)
Post Partum	1 (5.8)	2 (15.4)	3 (10.0)
Immobilised	8 (47.1)	8 (61.5)	16 (53.3)
Multiple	5 (29.4)	10 (76.9)	15 (50.0)

PE = pulmonary embolism; SBP = systolic blood pressure; DBP = diastolic blood pressure
[a]mean (SD)

The presenting features and clinical profiles of the patients are summarized in **Table 2**. Dyspnoea was the most common presenting complaint among all patients (100% in PE group and 92.3% in non-PE group). Mean Simplified Geneva Score were 2.3 (SD = 0.8) and 2.7 (SD = 0.8) in PE and non-PE group respectively.

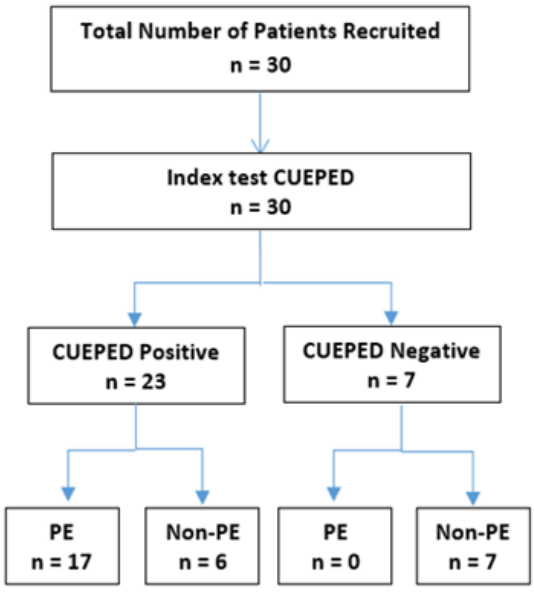
TABLE 2: Clinical Profiles of Subjects in the Study (N = 30)

	PE (n = 17) mean (SD)	Non PE (n = 13) mean (SD)	All mean (SD)
Chief Complaints, n (%)			
Dyspnoea	17 (100)	12 (92.3)	29 (96.7)
Chest Pain	5 (29.4)	1 (7.7)	6 (20.0)
Haemoptysis	1 (5.8)	0	1 (3.3)
Syncope	3 (17.6)	0	3 (10.0)
Leg Swelling/Pain	2 (11.8)	0	2 (6.7)
Palpitation	0	2 (15.4)	2 (6.7)
Simplified Geneva Score	2.3 (0.8)	2.7 (0.8)	2.5 (0.8)
Heart Rate	107.7 (21.0)	101.8 (17.3)	105.2 (19.4)
SBP mmHg	123.2 (14.9)	123.7 (15.5)	123.4 (14.9)
DBP mmHg	70.4 (10.3)	70.0 (9.8)	70.2 (9.9)
Respiratory Rate	22.2 (3.7)	23.2 (2.8)	22.7 (3.3)

PE = pulmonary embolism; SBP = systolic blood pressure; DBP = diastolic blood pressure

Figure 1 shows the flow chart of enrolment and outcomes of CUEPED in PE. Patients are categorised into PE (56.7%) and non-PE group (43.3%) based on CTPA. 47.1 % of the patients in PE group had no risk of developing PE.

Figure 1: Enrolment and outcome of suspected PE and CUEPED test



PE = pulmonary embolism, CUEPED = ETCO2 combined with compression ultrasound of lower limb and transthoracic echocardiography

Test results

CUEPED was cross-tabulated against diagnosis of PE by CTPA (**Table 3**). CUEPED was positive in all PE patients, resulting in a sensitivity of 100% (**Table 4**). 7 out of 13 patients without PE had negative CUEPED test, with a specificity of 53.8%. CUEPED had a PPV for PE of 73.9%. None of the patients with negative CUEPED test result had PE, resulting in a NPV of 100%. TTE as a stand-alone test had a sensitivity of 58.8% and a specificity of 92.3%. CUS alone had a sensitivity of 29.4% and a specificity of 100%. ETCO2 as stand-alone test for PE had a sensitivity of 94.1% and a specificity of 61.5%. Combination of TTE and CUS had a sensitivity of 64.7% and a specificity of 92.3%.

TABLE 3: CUEPED cross-tabulation against CTPA diagnosis of PE

	PE (n =17) n (%)	**non PE (n = 13) n (%)**
CUEPED positive	17 (100)	6 (46.2)
CUEPED negative	0	7 (53.8)

PE = pulmonary embolism, CUEPED = ETCO2 combined with compression ultrasound of lower limb and transthoracic echocardiography

TABLE 4: Diagnostic Values of CUEPED, CUSTTE, TTE, CUS and ETCO2

	Sensitivity (95% CI)	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
CUEPED	100.0 (80.3 - 100.0)	53.8 (25.2 - 80.6)	73.9 (51.5 - 89.7)	100.0 (58.9 - 100.0)
CUSTTE	64.7 (38.3 – 85.7)	92.3 (63.9 – 99.8)	91.6 (61.5 – 99.7)	66.6 (40.9 – 86.6)
TTE	58.8 (32.9 – 81.5)	92.3 63.9 – 99.8)	90.9 (58.7 – 99.7)	63.2 (38.3 – 83.7)
CUS	29.4 (10.3 – 55.9)	100 (75.2 – 100)	100 (47.8 – 100)	52 (31.3 – 72.2)
ETCO2	94.1 (71.3 – 99.8)	61.5 (31.5 – 86.1)	76.1 (52.8 – 91.7)	88.8 (51.7 – 99.7)

CI = confidence interval, PPV = positive predictive value, NPV = negative predictive value, CUEPED = ETCO2 combined with compression ultrasound of lower limb and transthoracic echocardiography, CUSTTE = Compression ultrasound of lower limb combined with transthoracic echocardiography; TTE = Transthoracic echocardiography, CUS = Compression ultrasound of lower limb, ETCO2 = End-tidal CO2

DISCUSSION

Clinical presentation, risk factors of thromboembolism or clinical probability of PE may not reliably help in predicting the diagnosis. Dyspnoea was present in all PE patients and almost all non PE patients (92.3%) in our study. Majority of the PE patients had no risk factors of thromboembolism. There was no statistically significant difference in simplified Geneva score between PE and non PE group.

Although there are professional society guidelines using well-validated clinical prediction rules such as Well's score, Geneva score, Pulmonary Embolism Rule Out Criteria (PERC) and D-dimer exist to determine whether further work up for suspected PE is necessary, clinician does not comply with guidelines. [20] Wide variation in use and familiarity of rules presents among clinicians. [21]

CUEPED was designed as potentially a rapid and noninvasive bedside test which helps in ruling out PE in emergency department. We used TAPSE in CUEPED as it is a more simplified and quantitative echocardiographic evaluation as compared to other echocardiographic measurement for PE such as measurement of right ventricular end diastolic diameter (RVEDD) /left ventricular end diastolic diameter (LVEDD) or McConnell's sign.[22, 23]. TAPSE is preferably used in normotensive patient. TAPSE is a parameter for global RV function and is proven as a good modality to determine the prognostic factor in PE patient. [24] Our study showed TAPSE and compression ultrasonography of lower limbs yielded a sensitivity of 58.8% and 29.4% respectively in the diagnosis of PE. Combination of TTE and CUS increased sensitivity to 64.7% with specificity of 92.3%. This result was comparable with other studies. Mansencal et. al. showed TTE in combination with CUS has a sensitivity of 87-89% and specificity of 71-100% in diagnosis of PE[15]. et. al. also demonstrated a sensitivity and specificity of triple point-of-care ultrasound (lung, heart and leg vein) of 90% and 86% respectively [25]. In our study, CUS or TTE or CUS combined with TTE had PPV and specificity of 90-100%, making it a potentially accurate ruling-in test. PPV and specificity of 90-100%, making it a potentially accurate ruling-in test.

Data in our study also showed comparable findings with ETCO2-based diagnosis of PE with a sensitivity of 94.1% and a specificity of 61.5%.[5, 16] A study published in 2014 by Riazand Jacob, using a lower ETCO2 cut-off value of 32 mmHg yielded a sensitivity of 100% and a specificity of 68% in the diagnosis of pulmonary embolism.[26] However, in their study, ETCO2 was measured by oral capnography using a mouth cannula which may alter patient's breathing effort and thus the lower ETCO2 value.

This study showed that CUEPED had a high sensitivity (100%) and high NPV (100%) making it a better screening tool to rule out PE compared to TTE, CUS or ETCO2 alone. CUEPED can be performed as a point-of-care test which can rule out PE particularly in the emergency setting and expedite other diagnosis workout and appropriate treatment. Positive CUS or TTE or CUS and TTE is also useful as a guide for further management such as thrombolysis in patient with suspected PE but who is unstable to go for CTPA.

LIMITATION

In this study, patients were enrolled only when the investigator was present. Small sample size and convenience sampling method may lead to selection bias in the study and the demographic and clinical characteristic may not be representative of general population. CUEPED is useful so far as only for patients without pre-existing cardiovascular or pulmonary pathology in ruling out PE.

CONCLUSION

This diagnostic study showed that CUEPED has the potential as a good diagnostic bedside tool in ruling out PE. It provides another avenue of ruling out PE besides the commonly used D-Dimer. Larger studies are needed to confirm our findings and to study the feasibility of incorporating CUEPED into the diagnostic algorithm.

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