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a proof of concept study

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Competing interests

Casper Falster has received personal fees from AstraZenica outside the submitted work. Gro Egholm has received personal fees from AstraZenica, Bayer and Bristol Myers Squibb outside the submitted work. Prof Jacob E Møller has received grants and personal fees from Abiomed, personal fees from Novartis, Orion Pharma, and Boeinger Ingelheim outside the submitted work. All remaining authors declare no competing interests.

Author contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by Casper Falster, Gro Egholm and Niels Jacobsen. The first draft of the manuscript was written by Casper Falster and all authors commented on all versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

Permission for initiation of the study was granted by The Regional Committees on Health Research Ethics of Southern Denmark. The study has therefore been performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1975 and its late amendments.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Abstract:

Purpose:
The purpose of this descriptive feasibility study was to assess the clinical impact and feasibility of conducting a multiorgan ultrasound examination of patients with pulmonary embolism at both time of diagnosis and at clinical follow-up.

Methods
Hemodynamically stable patients with pulmonary embolism verified by CT pulmonary angiography or ventilation perfusion scintigraphy were eligible for inclusion. Enrolled patients underwent multiorgan ultrasound investigation encompassing echocardiography supplemented with focused lung and deep venous ultrasound emphasizing right ventricular strain, subpleural consolidations and presence of deep venous thrombi. Identical investigations were conducted at 3 months follow-up. The presence of ultrasonographic findings at diagnosis and follow-up was compared and the clinical impact of any remaining pathology or strain was described.

Results
Twenty-one patients were enrolled in the study of whom 20 survived to attend follow-up. Mean age was 62 ± 15 years and 48% were female. At diagnosis, the most prevalent ultrasonographic findings were subpleural consolidations in 11 patients and right ventricular dilation in eight. At follow-up, signs of right ventricular strain had resolved in all patients. However, in one patient, no resolution was seen in a subpleural consolidation observed at the time of pulmonary embolism diagnosis, resulting in referral to a chest CT. Additionally, one patient exhibited residual deep venous thrombotic material, leading to prolongation of anticoagulative treatment.

Conclusion
In patients with pulmonary embolism, multiorgan ultrasound is feasible in follow-up and adequately powered studies should determine the clinical utility of such an approach.

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1. Introduction

The acute presentation of pulmonary embolism (PE) is heterogeneous and may encompass not only dyspnea and chest pain, but also hemoptysis, calf pain and syncope. These symptoms are unspecific and often lead to clinical suspicion of conditions such as acute coronary syndrome, exacerbation of chronic obstructive pulmonary disorder (COPD) or acute heart failure[1, 2]. As point-of-care ultrasound is becoming increasingly available, a growing number of patients are assessed with focused multiorgan ultrasound of the lungs, heart, and deep veins. This combination is especially valuable in the patient presenting with acute dyspnea or chest pain and may guide the physician towards suspicion of PE, leading to referral for confirmatory CT pulmonary angiography (CTPA) or even confirm PE by revealing a present source deep venous thrombus (DVT)[3, 4].

In the majority of patients with PE, complete reperfusion of the pulmonary arterial vasculature is attained within a few months following diagnosis and initiation of anticoagulative treatment[5]. However, a considerable proportion still experiences dyspnea or reduced physical performance in the following six months to three years, with as many as 47% exhibiting reduced maximal aerobic capacity[6, 7]. Furthermore, approximately 3% of patients surviving PE develop chronic thromboembolic pulmonary hypertension (CTEPH), a life-threatening obstructive vasculopathy in which thrombi have become persistent and organized[8]. As such, the European Respiratory Society (ERS) and the European Society of Cardiology (ESC) recommend routine clinical evaluation three to six months after the acute PE episode.

Echocardiography is a cornerstone of PE-follow up and is considered mandatory in patients with persisting symptoms or pronounced right ventricular (RV) strain at time of diagnosis. It allows probability assessment of persisting or newly developed PH, which should initiate further investigations of CTEPH[4].

Lung and deep venous ultrasound are both of use in diagnosis and prognostication in the acute phase, but the value of these modalities in PE follow-up has never been examined. While well-demarcated hypoechoic subpleural consolidations are often observed in relation to peripheral emboli due to the associated alveolar hemorrhage and infarction, these sonographic alterations may also represent distinct concomitant pathology, such as bronchogenic carcinoma[9]. While co-existing subpleural cancers in patients with PE are occasionally identified as incidental findings during the diagnostic work-up, they may be missed if the PE diagnosis is established via planar ventilation-perfusion scintigraphy (V/Q) or even CTPA if sufficiently small[4]. As such, for patients in whom subpleural consolidations were observed on lung ultrasound at time of PE diagnosis and interpreted as infarction, repeating the investigation at follow-up harbors the potential of identifying possible chest malignancy by referring for further diagnostic investigations in instances where the consolidation has not diminished in size.

Regarding the utility of deep venous ultrasound, recent guidelines from the European Society of Vascular Surgery recommend that extended anticoagulative treatment should be considered in patients with DVT if residual vein obstruction is observed three months after initiation of anticoagulation[10]. This raises the possibility that selected PE patients in whom initial anticoagulative treatment was scheduled for three months, due to major transient or reversible factors associated with increased risk of venous thromboembolism, may benefit from a control deep venous ultrasound investigation if a DVT was present at time of PE diagnosis.

In this prospective proof of concept study, we sought to appraise the clinical impact and feasibility of adding lung and deep venous ultrasound to the established follow-up investigation three months after PE-diagnosis in patients who had been subject to multiorgan ultrasound at time of diagnosis.

2. Method

2.1 Study setting

The study cohort is part of a larger descriptive validation trial, conducted as a single center prospective descriptive study. Patients were recruited as a convenience sample based on the availability of the study first author (CF). The study period spanned from June 2020 to May 2021 in the emergency department of a Danish tertiary referral center with approximately 65,000 annual emergency visits. Adult patients with clinical suspicion of PE are evaluated by emergency physicians in the outpatient clinic of the emergency department. All patients undergo clinical assessment with integrated Well's score, electrocardiography, arterial blood gas and a standard blood panel including high-sensitive D-dimer and troponin T. Chest X-ray is utilized based on physician preference. Patients in whom PE-suspicion persist are referred for diagnostic CTPA or V/Q.

2.2 Patients

Patients referred to diagnostic CTPA or V/Q were informed about the study protocol by CF and assessed for eligibility. All CTPAs were performed by a GE Revolution CT (GE Healthcare, Waukesha, Wisconsin, USA) and V/Q scans by a Discovery NM-CT 670 or Optima NM-CT 640 (General Electric, Boston, Massachusetts, USA). Patients with mental disability, known contrast allergy, renal failure (s-creatinine >200 µmol/L) or hemodynamic instability (two or more consecutive systolic blood pressure measurements <90 mmHg) were not eligible for inclusion. Included patients were subsequently subject to blinded multiorgan ultrasound. Interpreting radiologists or nuclear medicine physicians were blinded to multiorgan ultrasound findings. Patients who died between PE diagnosis and follow-up were excluded from further data-analysis.

2.3 Multiorgan ultrasound investigations

All multiorgan ultrasound investigations were performed within 24 hours of PE diagnosis by CF who had completed more than 300 echocardiographic exams and was certified in lung and deep venous ultrasound. At three-month PE follow-up, CF repeated the examinations.

A Vivid S5 (General Electric, Boston, Massachusetts, USA) was used for echocardiography and a LOGIQ E9 (General Electric, Boston, Massachusetts, USA) for lung and deep venous ultrasound.
Echocardiography was performed using a 1.5-4 MHz phased array probe with a cardiac preset. The patient was placed in the left lateral decubitus position with attached ECG-leads. Parasternal, apical and subxiphoid images were assessed for: The 60/60-sign (concomitant pulmonary valve acceleration time (PVAT) <60ms and tricuspid valve regurgitation

gradient (TRmax) <60 mmHg), D-sign (abnormal septal flattening or bulging towards the LV due to RV pressure overload), McConnell's sign (distinctive akinesia of the RV free wall with normal or hyperkinetic apical motion), intracardiac thrombi, basal right ventricular end diastolic diameter (RVEDD)/left ventricular end diastolic diameter (LVEDD)-ratio, pericardial effusion and tricuspid annular plane systolic excursion (TAPSE). The probability of present PH was assessed in accordance with table 8A and B of the collaborative guidelines by the ERS and ESC[11].

Focused lung ultrasound was performed with a 1-6 MHz curved array probe using an abdominal preset with cross-beam disabled. The patient was placed in a supine or sitting position. We used a protocol aimed at assessment of anterior, lateral and posterior scanning zones of each hemithorax[12–15]. The presence of subpleural hypoechoic consolidations of wedged, triangular, polygonal or rounded shape was noted in addition to consolidations suggestive of pneumonia, lung sliding, pleural effusion and B-lines.

Focused deep venous ultrasound was performed using a 4-15 MHz linear probe with a lower extremity veins preset. The patient was in the supine position. A protocol applied in several previous publications, comprising short axis visualization and compression of the common and superficial femoral veins and popliteal veins was utilized[16–22]. Visible intravascular thrombi or absence of total vein compression was noted. At time of follow up, emphasis was put on detection of residual thrombus material signifying chronic obstructive changes.

2.4 Statistics

All statistical analyses were performed in GraphPad Prism 9.0.0. (GraphPad Software, San Diego, California USA). 95% confidence intervals for proportions were calculated as Wilson Score intervals. Normality was assessed using the Shapiro-Wilk test. Normally distributed data is presented as mean ± standard deviation (SD). Non-normally distributed data is presented as median with interquartile range (Q1-Q3). Paired student t-test was used for comparison of normally distributed data and Wilcoxon Signed-Rank test was used when at least one group was not normally distributed. In instances where paired measurements could not be obtained for all patients, for instance TRmax, unpaired t-test or Mann-Whitney U-test was used based on normality. A P-value <0.05 was considered statistically significant.

3. Results

Of 75 patients with suspected PE, 21 had PE confirmed and were included in the study. Mean age was 62 ± 15 years and 48% were female. PE was confirmed by CTPA in 15 patients and V/Q in six. Six patients had a proximal PE. Baseline characteristics of enrolled patients are available in [TABLE 1]. One patient died before follow-up. Median time from PE diagnosis to clinical follow up for the remaining 20 patients was 94.5 (Q1-Q3: 91-105.5) days.

3.1 Echocardiography

At diagnosis, the most prevalent sign of RV strain was basal RVEDD/LVEDD >1 or an RV visibly larger than the LV which was observed in eight patients. Six patients exhibited the McConnell's sign. The 60/60-sign and D-sign were both seen in five patients. Signs of RV strain were most common in patients with proximal and lobar embolization. Present ultrasound signs in relation to PE localization are available in [TABLE 2]. At follow-up, McConnell's sign, D-sign, and 60/60-sign had resolved in all patients. PVAT had increased from 89msec (Q1-Q3: 66-126msec) to 133 ± 37msec (P=0.04) with no residual findings of the characteristic early systolic notch [FIGURE 1]. Mean TRmax of 22.75 ± 9.4mmHg at time of PE-diagnosis was not significantly different from 21.5 ± 6.7mmHg at follow-up (P=0.66). Right

ventricular dilation had resolved in all but one patient who had concomitant COPD. Mean TAPSE of 2.34 ± 0.5 cm at diagnosis did not differ significantly from 2.61 ± 0.4 cm at follow-up (P=0.07). No patients fulfilled the echocardiographic criteria for high suspicion of PH at follow-up.

3.2 Focused lung ultrasound

Eleven patients had one hypoechoic subpleural consolidation at the time of diagnosis, one patient had two and one had numerous consolidations with isoechoic centers and a diameter <0.5 cm, indicating active embolus resolution at time of PE diagnosis. Five patients had a simple pleural effusion with no other obvious cause. At follow-up, subpleural consolidations had resolved in all but three patients. Of these, two patients who both exhibited consolidations of significant sizes at PE diagnosis still had consolidations of similar morphology but with significantly reduced size and an isoechoic center, indicating active resolution. In the third patient, the consolidation was of similar size and echogenicity but had changed shape from triangular to rounded and seemed to involve more of the parietal pleura than at time of diagnosis [FIGURE 2]. A subsequent CT-scan did not raise suspicion of malignancy but revealed localized thickening of the parietal pleura. No patients had residual pleural effusion at follow-up. As such, follow-up lung ultrasound had clinical implications in one out of 11 patients with subpleural consolidations at PE diagnosis (9.1% (95%CI: 1.6-37.7%).

3.3 Focused deep venous ultrasound

Six patients had a DVT at the time of PE diagnosis of whom one died before follow-up. Two patients had thrombi encompassing both the femoral and popliteal veins. Three patients had DVT confined to the popliteal vein and in one patient DVT was located in the femoral vein. At follow-up, all signs of DVT had resolved except for one patient who still exhibited with intraluminal material in an incompressible vein, consistent with presence of residual thrombotic venous obstruction, leading to prolongation of anticoagulative treatment[23] [FIGURE 3]. Thus, abnormal findings were observed at follow-up in one out of five surviving patients with present DVT at time of PE diagnosis (20.0% (95%CI: 3.6-62.5%). No patients exhibited ultrasonographic findings at follow-up not observed at PE diagnosis.

4. Discussion

In our study on 20 patients reassessed 3 months following a PE diagnosis, supplementing echocardiography with ultrasound assessment of the lungs and deep veins in a multiorgan examination had clinical implications in two instances and implication for management in one case. Naturally, as this is a small proof of concept study, our findings and their potential clinical impact should be interpreted as hypothesis generating only.

4.1 Echocardiography

None of the surviving 20 patients had echocardiographic suspicion of PH at follow-up, which is expected considering that only 3% develops CTEPH[8]. That no patients exhibited right ventricular strain at follow-up, with the exception of a patient with COPD, highlights that anticoagulative treatment as an adjunct to the high fibrinolytic capacity of the pulmonary vessels allows complete vascular reperfusion within a few months in the majority of patients[5, 24]. However, it should be considered that this study did not include patients with hemodynamic instability. As both risk of

clinical deterioration during the acute PE episode and subsequent development of CTEPH correlates with the amount of thrombotic material, the risk of long-term cardiac sequelae in this study population might be more favorable compared to a population comprising all risk strata. In the patient who died prior to follow-up, echocardiography demonstrated a transit thrombus, which migrated through a persisting oval foramen due to pressure overload of the right-sided chambers, highlighting the importance of echocardiography during the acute phase of PE-diagnosis even in hemodynamically stable patients.

4.2 Focused lung ultrasound

While of modest size, the findings of our patient population support that the majority of subpleural infarctions observed in relation to PE have resolved prior to time of follow-up. Indeed, previous research has found that the majority of patients show complete radiographic clearance within three months[25]. As was the case in our study where only the more comprehensive consolidations were still present albeit of significantly reduced size.

As such, since even a complete focused lung ultrasound investigation may be conducted in five minutes in experienced hands, performing a follow-up scan of only the zones where subpleural consolidations were initially observed is feasible and barely time consuming. If a consolidation is still present and does not show signs of active resolution, have increased in size or altered in shape, a chest CT may be indicated for differential diagnostic considerations, as lung ultrasound is not able to reliably distinguish between infarctions, carcinomas and localized pleural thickening.

4.3 Focused deep venous ultrasound

As approximately 44% of patients with acute PE have residual thrombus material in the proximal deep veins of the lower extremities, assessing revascularization at follow-up may be of value. Indeed, recent guidelines from the European Society of Vascular Surgery recommend that extended anticoagulative treatment should be considered in patients with residual vein obstruction three months after initiation of anticoagulation[3, 10]. Furthermore, as studies on the natural history of iliofemoral DVT treated solely with anticoagulants have demonstrated that 15% of patients experience venous ulcerations or claudication, 40% restricted ambulation and 90% some degree of venous insufficiency, patients still experiencing symptoms such as calf pain or swelling while exhibiting persisting hyperechoic intraluminal material may be candidates for endophlebectomy or endoluminal recanalization[26]. As such, the addition of focused deep venous ultrasound at follow-up may be a possible adjunct to adjusting length of anticoagulative treatment and shortening time to referral for surgical evaluation.

4.4 Clinical utility of a multiorgan approach

Considering that none of the surviving ten patients with echocardiographic signs of right ventricular strain at time of PE diagnosis revealed signs of PH at follow-up, a number needed to scan for a clinically relevant finding of approximately 11 for subpleural consolidations and five for DVTs at follow-up seems feasible in comparison. As echocardiography is only indicated at follow-up in selected patients, ultrasound of the lungs and deep veins should also only be applied in patients with proven subpleural consolidation or DVT at time of diagnosis or in presence persisting symptoms encompassing pleural chest pain or symptoms suggestive of post-thrombotic syndrome. Naturally, this approach harbors a risk of unnecessary referral for radiation diagnostics and adequate competencies in all three ultrasound modalities should be a prerequisite to clinical utilization. Not all persisting subpleural consolidations or DVTs have clinical consequences and due to the small scale of this study, the number needed to scan to identify an actually clinical relevant

condition remains unclear. As such, when interpreting ultrasonographic findings at follow-up, the clinician must carefully correlate these with persisting or newly developed symptoms since PE diagnosis. For instance, observing pleural consolidations of diminishing size with a hyperechoic center should not initiate referral to radiation diagnostics but has value in reconciling the patient that resolution is ongoing.

As this proof-of-concept study encompasses only a modest patient population with considerable risk of type 2 error, further large-scale studies are needed to assess the clinical utility of this approach

4.5 Conclusion

In patients with PE, the addition of focused lung and deep venous ultrasound at 3 months follow-up is feasible and may be of clinical relevance if a subpleural consolidation or DVT was observed at time of diagnosis. Adequately powered studies are warranted to determine the clinical utility of such an approach.

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Figure Legends:

Table 1
Baseline characteristics of study population
Data are presented as n (%), mean ± SD or median with associated interquartile range

Figure 1
Examples of echocardiographic findings at PE-diagnosis and clinical follow-up. (A) The D-sign comprising septal flattening or bulging towards the left ventricle in both diastole and systole (arrow), representing right ventricular pressure overload in relation to present PE. (B) The same patient 3 months later. As the pulmonary pressure has normalized, the interventricular septum no longer bulges towards the left ventricle, which has regained its rounded shape. (C) Early systolic notching (arrow) due to mid-ventricular closing of the pulmonary valve observed in pulmonary hypertension by placing a pulsed wave doppler over the pulmonary valve. (D) The same patient at follow-up. As the pulmonary pressure has normalized, the patient now exhibits a normal bell-shaped spectral image and a normal pulmonary valve acceleration time >110ms. (E) The McConnell's sign, comprising akinesia of the free right ventricular wall with a concomitant normokinetic or hyperkinetic right ventricular apex (arrow). (F) A visibly dilated right ventricle with a thrombus (arrow) lodged in a persisting foramen ovale.

Table 2
An overview of PE-localization and related ultrasound signs. A † signifies that the patient was deceased prior to follow-up

Figure 2
Examples of pleural consolidations at time of PE-diagnosis and clinical follow-up. (A) A typical wedge--shaped well-demarcated wedge-shaped lesion, representing a pleural infarction. (B) The same patient and scanning zone 3 months later. Complete resolution is observed with no residual consolidation and an intact pleural line. (C) A sizeable triangular pleural infarction at time of PE-diagnosis. (D) The same patient 3 months later. The consolidation is still present, albeit reduced in size and isoechoic compatible with active resolution. (E) Wedge shaped pleural infarction at time of PE-diagnosis (F) The same patient 3 months later. The consolidation is still present but now involves the parietal pleura and a mended pleural line is visible below. A subsequent CT-scan revealed parietal thickening.

Figure 3
Examples of deep venous ultrasonographic findings at time of PE-diagnosis and clinical follow-up. (A) Deep venous ultrasound showing a non-compressible isoechoic formation in the femoral vein (arrow), compatible with a deep venous thrombus. (B) The same patient at follow-up three months later. No signs of residual intraluminal thrombotic material is observed and the vessel is completely compressible, compatible with complete thrombus resolution. (C) DVT present in the popliteal vein (arrow). (D) The same patient at follow-up. The vein was still incompressible and residual rigid intraluminal material was observed, consistent with chronic post thrombotic changes.

Baseline characteristics	
Age (years)	62 ± 15.0
Female sex	10 (47.6)
Body mass index (kg/m^2)	26.4 (Q1-Q3: 24.1-31.4)
Symptoms at presentation	
Dyspnea	18 (85.7)
Chest pain	7 (33.3)
Cough	6 (28.6)
Dizziness	3 (14.3)
Hemoptysis	3 (14.3)
Syncope	1 (4.8)
Calf pain	1 (4.8)
Vital signs	
Pulse (beats/min)	82.9 ± 17.2
Systolic blood pressure (mmHg)	140.3 ± 21.1
Diastolic blood pressure (mmHg)	84.1 ± 16.6
Oxygen saturation (%)	96.3 ± 2.6
Supplementary oxygen (n)	2 (9.5)
Supplementary oxygen (L/min)	6 (Q1-Q3: 4.0-8.0)
Respiratory rate	17.0 (Q1-Q3: 16.0-20.0)
Temperature (C^o)	36.9 ± 0.6
Ultrasonographic findings	
Hypoechoic pleural consolidations (total)	14
Hypoechoic pleural consolidations (median)	1 (Q1-Q3: 1-1)
Simple pleural effusion	5
60/60-sign	5
D-sign	5
McConnell's sign	6
Intracardiac thrombus	2
Basal RVEDD/LVEDD > 1	8
Pericardial effusion	0
TAPSE (mean)	2.3 ± 0.48
TAPSE <16mm	1
Deep venous thrombus	6

Lab results and Wells score	
D-dimer (mg/L)	6.5 (Q1-Q3: 2.0-8.9)
Troponin T (ng/L)	11.0 (Q1-Q3: 6.0-23.0)
Wells score for pulmonary embolism	3.5 ± 2.0
Comorbidities	
Hypertension	8
No known	5
COPD	2
Stroke	2
Asthma	1
Type II diabetes	1
Previous cancer	1
Valvular disease	1
Ischaemic heart disease	1
Obstructive sleep apnea	1

Data are presented as n (%), mean ± SD or median with associated interquartile range

PE localization	Diagnostic modality	Pleural consolidation	Simple pleural effusion	60/60-sign	D-sign	McConnell's sign	Basal RVEDD/LVEDD >1	RV thrombus	TAPSE (cm)	DVT
Proximal (saddle embolism)	CTPA	Yes	-	-	-	-	Yes	-	2.0	-
Proximal (saddle embolism)	CTPA	-	-	-	Yes	Yes	Yes	-	1.2	Yes
Proximal (both main arteries)	CTPA	Yes	-	-	-	-	-	-	2.6	-
Proximal (left main artery)	CTPA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	2.2	-
Proximal (right main artery)	CTPA	Yes	-	-	-	-	-	-	1.6	Yes
Proximal (right main artery)†	CTPA	Yes	-	Yes	Yes	Yes	Yes	Yes	2.0	Yes
Lobar (all arteries bilateral)	CTPA	-	-	-	Yes	-	-	-	2.9	-
Lobar (multiple)	CTPA	Yes	Yes	Yes	-	Yes	Yes	-	2.2	-
Lobar (single)	CTPA	Yes	-	-	-	-	-	-	2.9	-
Segmental (multiple)	CTPA	Yes	-	-	-	-	-	-	2.0	Yes
Segmental (multiple)	CTPA	-	-	-	-	-	-	-	2.5	-
Segmental (multiple)	CTPA	-	-	Yes	Yes	Yes	Yes	-	2.2	Yes
Segmental (multiple)	V/Q	Yes	-	-	-	Yes	-	-	2.9	Yes
Segmental (multiple)	V/Q	Yes	-	-	-	-	Yes	-	2.4	-
Segmental (two)	V/Q	Yes	-	-	-	-	-	-	2.1	-
Segmental (two)	V/Q	-	Yes	-	-	-	-	-	2.2	-
Segmental (single)	CTPA	Yes	-	-	-	-	-	-	2.2	-
Subsegmental (multiple)	V/Q	Yes	-	Yes	-	-	-	-	1.9	-
Peripheral (multiple)	CTPA	-	-	-	-	-	Yes	-	2.8	-
Peripheral (multiple)	CTPA	-	Yes	-	-	-	-	-	3.0	-
Peripheral (single)	V/Q	-	Yes	-	-	-	-	-	3.0	-