Computed tomographic pulmonary angiography procedures: Contrast media dilution from the venous to the systemic circulation

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Abstract:

Purpose
Computed tomographic pulmonary angiography (CTPA) is a clinically important imaging modality where data is acquired during the arterial phase of contrast media (CM) passage. Images from 33 patients who had undergone a CTPA procedure were reviewed in this retrospective study, in order to obtain knowledge about how CM is diluted through its way from the venous to the systemic circulation.

Method
Mass attenuation values were measured in Hounsfield Units (HU) at seven specific anatomical locations between the subclavian vein and the left atrium. At every measuring point the mass attenuation was measured in a region of interest (ROI), which was a cross section of the current blood vessel. Mean values with standard deviations (SDs) were calculated at every measuring point.

Results
45.8% of the mass attenuation value at the start of the subclavian vein was left in the right atrium. The largest decrease in mass attenuation was seen after the confluence of the brachiocephalic veins.

Conclusion
More than half of the image enhancing capabilities of the CM is lost before entering the pulmonary circulation, due to a high degree of CM dilution. The degree of dilution is probably underestimated because of the possibility that the whole contribution from the inferior vena cava is not reflected in the measurements, and that the first measuring point was in the subclavian vein and not just beyond the entry of the peripheral venous catheter (PVC).

Introduction:

Acute pulmonary embolism (PE)
Acute pulmonary embolism (PE) is a common and sometimes fatal disease with an increased estimated incidence in the general population since the introduction of D-dimer testing and computed tomographic pulmonary angiography (CTPA) in the 1990s (1). Most database analyses reported a doubling in the incidence of PE from the early 1990s to the early 2000s, with one database reporting an increase from 62 cases per 100,000 to 112 cases per 100,000 (1). In contrast, a Canadian database has reported a stable incidence rate of PE as 0.38 per 1000 person years between 2002 and 2012 (1). PE is accountable for 300,000 deaths amongst Europeans annually (1).

The clinical presentation of PE varies from no symptoms to sudden death, with dyspnoea as the most common presenting symptom (2). The severity of the PE however is not always related to the severity of the presenting symptoms. Diagnosing PE is thus crucial in order to avoid missing clinically relevant cases and to reduce mortality.

Computed tomographic pulmonary angiography (CTPA)
CTPA is the preferred diagnostic imaging modality to diagnose PE (2). Unlike computed tomography (CT), where parenchymal enhancement is what is desirable, a CTPA examination acquires data during the arterial phase of contrast media (CM) passage. If performed correctly, maximum contrast enhancement between the arterial vasculature and the surrounding structures is allowed to be displayed.

In order to achieve optimal vascular enhancement, knowledge of bolus geometry and the variables affecting it is essential. Bolus geometry is defined as the pattern of enhancement
after intravascular injection of CM (3). It is measured in a region of interest (ROI) and plotted on a time(s)/attenuation (Hounsfield Units (HU)) diagram (3). The attenuation value of an unenhanced baseline scan is subtracted from the attenuation values in the enhanced scans to calculate the enhancement (3).

An optimal bolus geometry is when the enhancement of the ROI increases immediately to a peak maximum level just before the start of data acquisition, and does not alter during the process (3). However, the actual bolus geometry is affected by several variables and does not take the shape of the optimal one. This is illustrated in figure 1. The bolus geometry is affected by age, weight, diseases that reduce cardiac output, timing of the scanning delay, and the use of a bolus chaser, as well as injection volume, injection rate, iodine concentration, viscosity and osmolality of the CM used (3, 4).

![Figure 1](image-url)

**Figure 1**: Adapted from Cademartiri F, van der Lugt A, Luccichenti G, Pavone P, Krestin GP. Parameters affecting bolus geometry in CTA: a review. Journal of computer assisted tomography. 2002;26(4):598-607.

CM is usually delivered through a peripheral venous catheter (PVC), and will be continuously diluted through its way to the central venous and pulmonary circulation. The amount of CM needed for a CTPA procedure should be normalized for body weight, and is determined by the injection rate, which in turn is determined by the scan time and the use of bolus timing techniques (3). Injection of saline after contrast injection increases the amount of contrast available and pushes the contrast bolus forward, with the potential to increase contrast enhancement and the efficiency of the CM, thus lowering the dose needed for the procedure (4). The degree of dilution from the PVC to the pulmonary circulation will also affect the dose of CM needed for the procedure, and the present study was performed to obtain knowledge about how CM is diluted through its way from the venous to the systemic circulation during CTPA procedures.

**Physiological effects of contrast media (CM)**

The use of CM is not without side effects. Mild, moderate and severe adverse events (AEs) reported for adults receiving CM include episodes of flushing, nausea, emesis, sneezing, vertigo, hives, headache, hypotension, bronchospasm, shock, convulsions, loss of consciousness, laryngeal oedema, pulmonary oedema, severe cardiac arrhythmias, and cardiovascular and pulmonary collapse (4).
One of the most serious AEs associated with CM use is contrast-induced nephropathy (CIN) (4). CIN is the most common cause of death after CM injection, and the third most common cause of hospital-acquired renal failure (4). The risk of developing CIN is related to underlying diseases, such as chronic renal failure, heart failure, diabetes, and the hydration state of the patient, but also to volumes and type of CM used in the examination (4).

To minimize the risk of AEs such as CIN, selecting the appropriate contrast agent and avoiding higher doses than needed for the actual procedure is essential. Careful consideration to the contrast enhancement capabilities of an agent and its potential for causing AEs must therefore be given prior to selection (4).

**Materials and methods:**

*The CT scanner*

A CT scanner consists of an x-ray tube and a diametrically opposed array of detectors. A CTPA is performed with a helical CT scan, where the x-ray tube rotates around the moving patient in a helical motion, generating an x-ray beam (5). The radiation that traverses the body is concurrently recorded by the detectors, while scattered radiation deriving from outside the area of the target of the x-ray tube is rejected with collimators on both the x-ray tube side, and the detector side (5). Analogue to digital converters digitize the data, which is then reconstructed into axial images using array processors and interpolation algorithms (5). The Toshiba Aquilion One and the GE VCT are the two different CT scanners used at OUS Rikshospitalet to perform a CTPA procedure.

**Helical CT scanning**

Schematic representation of the scanning geometry for helical CT.

*Adapted from Kalender, WA, Sissler, W, Klotz, E, Vock, P. Radiology 1990; 176:181.*

*Figure 2: Adapted from Stark, Paul. Principles of computed tomography of the chest. UpToDate. 2015*
**Injection techniques**

In order to achieve an optimal bolus form in the pulmonary arteries during CTPA procedures, several injection techniques have been developed for this purpose. In the present study, 10 patients had received Omnipaque 350 mg I/ml, 21 patients had received Iomeron 350 mg I/ml, and 1 patient had received Iomeron 300 mg I/ml as their CM. For one patient this information was not available. A mean CM volume of 78.8 ml had been used, with a mean injection rate of 5.8 ml/s. The volume ranged from 39 ml to 120 ml, and the injection rate ranged from 3 ml/s to 7.5 ml/s. The data had been acquired with a mean scanning delay time of 15.4 seconds, ranging from 12 s to 27 s. There was no documentation of saline injection, but according to the CTPA protocol (“e-håndboken”) at OUS Rikshospitalet, 50-110 ml of saline is used as a bolus chaser during CTPA procedures. In addition, a test bolus is used to time the scanning delay. Depending on which CT machine used, two different techniques are performed. Bolus tracking in the pulmonary trunk, with an automatic scanning initiation when the attenuation exceeds 220 HU, is used with the Toshiba Aquilion One. Single-slice scans in the pulmonary trunk four seconds after test bolus injection, with a new scan every two seconds until satisfying contrast enhancement is achieved in the pulmonary trunk, is used with the GE VCT. The scanning delay time is then calculated using the following formula:

\[
\text{Scanning delay time} = \text{picture number (with satisfying contrast enhancement)} \times 2 + 11 \text{ seconds.}
\]
Figure 4: The contrast injector with CM (orange) and saline (blue).

The venflon
BD Venflon™ Pro 18 GA (green) or BD Venflon™ Pro 16 GA (grey) are used at OUS Rikshospitalet for delivery of CM during CTPA procedures. They are designed to withstand a flow rate of 1.72 ml/s and 3.93 ml/s, respectively. The CTPA protocol at OUS Rikshospitalet specifically encourage insertion of the venflon into the right arm, and not to deliver CM through a central venous catheter (CVC). Figure 5 illustrates when CM is delivered through a PVC in the left arm instead of the right arm.
Finding the patients
48 patients were enrolled in this retrospective study. A personal dynamic working list was created in RIS/PACS, which is the clinical application used at OUS Rikshospitalet for patients who have undergone radiological procedures. Then the necessary filters to find the suitable patients were added. The NCRP-code SC0AE, which is the code for the CTPA procedure, was added to only include patients who had undergone the appropriate procedure. Being a pilot study, a limited amount of patients was desirable. It was therefore chosen to only include adults (≥ 18 year of age) who had undergone the appropriate procedure within a specific period of time. The time interval was set between 15.09.15-15.01.16. These filters gave 48 patients.

Acquiring the data
Since direct measurement of CM dilution is not available, mass attenuation values was selected as the measurement to assess dilution of CM from the venous to systemic circulation. Mass attenuation values give an indirect measurement of the dilution as they reflect the radio density of all elements in an image, and thus are influenced not only by the CM, but also by the blood that admixtures with it through its way in the blood stream.

Seven measuring points for measuring mass attenuation were established. These are listed in table 1, and illustrated in figure 6.
<table>
<thead>
<tr>
<th>Measuring point</th>
<th>Anatomical location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In the subclavian vein, just beyond the entry of the cephalic vein.</td>
</tr>
<tr>
<td>2</td>
<td>In the subclavian vein, just beyond the entry of the external jugular vein.</td>
</tr>
<tr>
<td>3</td>
<td>In the brachiocephalic vein, just beyond the entry of the internal jugular vein.</td>
</tr>
<tr>
<td>4</td>
<td>In the superior vena cava, just beyond the entry of the brachiocephalic vein.</td>
</tr>
<tr>
<td>5</td>
<td>In the right atrium, just beyond the entry of the superior vena cava.</td>
</tr>
<tr>
<td>6</td>
<td>In the pulmonary trunk, just after the departure from the right ventricle.</td>
</tr>
<tr>
<td>7</td>
<td>In the left atrium, just beyond the entry of the pulmonary veins.</td>
</tr>
</tbody>
</table>

*Table 1: Mass attenuation were measured at the listed anatomical locations.*

*Figure 6: Anatomical illustration of the measuring points.*
At every measuring point the mass attenuation was measured in a ROI of the current blood vessel. In order to allow proper admixture of blood and CM after each confluence, the ROI was chosen to be a cross section of the vessel/atrium 0.5-1.5 cm beyond the confluence. The ROI fulfilled the cross section of the vessel without touching its borders, as shown in figures 8-14. If there was not clear where the entry of a vessel was, no measurement was performed at that measuring point. When using the ROI-application in RIS/PACS, the outcome of each measurement in a ROI is a mean mass attenuation value in HU with a standard deviation (SD), as shown in figures 8-14. Normally, the measurements were performed with a normal window of 450/50. However, it was necessary to switch between different CT windows when measuring mass attenuation, especially in cases of high HU-values, as illustrated in figure 7.

Figure 7: Measurement of mass attenuation using a bone window of 2000/350.
Figure 8: Measurement of mass attenuation at the first measuring point. "Middelverdi" = Mean value. "Standardavvik" = Standard deviation.
Figure 9: Measurement of mass attenuation at the second measuring point. The ROI is a cross section of the subclavian vein, just beyond the entry of the external jugular vein.
Figure 10: Measurement of mass attenuation at the third measuring point. The ROI is a cross section of the brachiocephalic vein, just beyond the entry of the internal jugular vein.
Figure 11: Measurement of mass attenuation at the fourth measuring point. The ROI is a cross section of the superior vena cava, just beyond the entry of the brachiocephalic vein.
Figure 12: Measurement of mass attenuation at the fifth measuring point. The ROI is a cross section of the right atrium, just beyond the entry of the superior vena cava.
Figure 13: Measurement of mass attenuation at the sixth measuring point. The ROI is a cross section of the pulmonary trunk, just after the departure from the right ventricle.
Analysing the data
The measured mass attenuation values and their SDs at every measuring point were written in a protected Excel sheet file. Excel applications were used to calculate mean values and SDs of the data, and to create figures.

Results:
Of the 48 patients enrolled in the study, there were displayable images in RIS/PACS for 33 of them. Among the remaining 15 patients there were no images available due to several reasons; the patient had not met to the procedure, the procedure had been cancelled or there had been a second opinion of an investigation performed at another hospital, and the images were no longer available in the archive.

The demographics of the 33 patients investigated in the study are listed in table 2.
Table 2: Demographics of the patients investigated in the study.

<table>
<thead>
<tr>
<th>Total, n</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>14 (42.4%)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>19 (57.6%)</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>54.6 (26-82)</td>
</tr>
</tbody>
</table>

The first measuring point was given a mass attenuation value of 1. The percentage of the mass attenuation value of the first measuring point was calculated at the other measuring points. The mean mass attenuation value of all 33 patients and the standard deviation was calculated at each measuring point, as shown in figure 15. The mass attenuation value at the second measuring point was 86.4% of the value at the first measuring point, with a SD of 21%. At the third measuring point the value was 74% with a SD of 25%, at the fourth measuring point it was 56.7% with a SD of 23%, at the fifth measuring point it was 45.8% with a SD of 40%, at the sixth measuring point it was 44% with a SD of 32%, and at the seventh measuring point it was 30.7% with a SD of 27% of the value of the first measuring point. In 8 of the 33 patients the investigator was not able to determine the site of entry of the external jugular vein, and as according to protocol, no measurement was performed at this measuring point in these cases.

![Dilution of contrast media](image)

Figure 15: The mean mass attenuation value with standard deviations at each measuring point, shown as a percentage of the first measuring point. The measuring points are listed in table 1.

The mean alteration in mass attenuation with standard deviations between each measuring point was calculated and is shown in figure 16. From beyond the entry of the cephalic vein to beyond the entry of the external jugular vein, the mass attenuation value was reduced with
13.6 %, with a SD of 20.5 %. A 6.6 % reduction with a SD of 35.2 % was seen beyond the entry of the internal jugular vein, a 19.5 % reduction with a SD of 28.0 % was seen beyond the entry of the brachiocephalic vein, and another 15.7 % reduction with a SD of 58.7 % beyond the entry of the superior vena cava into the right atrium. There was a 0.7 % increase with a SD of 28.6 % in the mass attenuation value from the right atrium to the start of the pulmonary trunk, and a 27.7 % reduction with a SD of 31.5 % from the pulmonary trunk to the left atrium.

**Figure 16:** The alteration in mass attenuation between the measuring points with standard deviations, shown as a percentage reduction or increase between two neighbouring measuring points. 1: Between point 1 and 2. 2: Between point 2 and 3. 3: Between point 3 and 4. 4: Between point 4 and 5. 5: Between point 5 and 6. 6: Between point 6 and 7.

**Discussion:**

**Interpretation**
The mass attenuation value decreased between every measuring point from the entry of the cephalic vein towards the left atrium, except between the right atrium and the pulmonary trunk, where it increased. This is probably best explained by the nature of the CTPA examination, where vascular enhancement of the pulmonary arteries is desirable and the scan delay has therefore been timed thereafter, in order to achieve maximum contrast enhancement between the pulmonary arteries and the surrounding structures.

As a consequence, the interpretation of mass attenuation decrease as an expression of CM dilution through its way from the venous to the systemic circulation, is in the present study best to assess between the first and the fifth measuring point, which is between the start of the subclavian vein and the right atrium. Between these measuring points, there was seen a decrease of mass attenuation of 54.8 %. This means that more than half of the image enhancing capability of the CM is lost before entering the pulmonary circulation. It is reasonable to assume that the actual decrease in mass attenuation is even larger, since the CM is delivered through a PVC more peripheral than the first measuring point in the present study, and thus has been diluted through its way from the PVC to the first measuring point. In addition, the fifth measuring point was just beyond the entry of the superior vena cava, and
thus in the superior segment of the right atrium. The inferior vena cava contributes with approximately 70% of the venous return into the right atrium, and the highest degree of dilution is probably taking place after admixture with blood entering from here. The percent of venous return from the different veins of the upper body is not known to the author, but it is reasonable to believe that the right and the left brachiocephalic vein contributes with approximately 15% each under normal circumstances.

The largest decrease in mass attenuation was seen between the third and the fourth measuring point, with a 19.5% decrease in the mass attenuation value. Between these measuring points, the brachiocephalic veins confluence with each other, and as expected, a high degree of dilution is taking place. The 15.7% decrease between the fourth and the fifth measuring point is somewhat unexpectedly low, but could be due to the argument given in the previous paragraph, namely that the whole contribution from the inferior vena cava is not reflected in the measurement.

The standard deviations
Large SDs are seen in the presented results, implying a large variation in mass attenuation values between the patients, and thus in the degree of dilution of CM. One possible explanation is that the present study reviewed CTPA images that displayed the contrast enhancement at an instant moment of time. Even though the CTPA procedure is striving for maximal enhancement in the pulmonary arteries, the truth about bolus geometry will remain unknown until a continuous scan starting prior to the arrival of CM, and lasting until the iodine concentration diminishes, is performed. Since the execution of the CTPA procedure is based on knowledge of bolus geometry, this lack of knowledge gives rise to potentially large variations between patients undergoing CTPA procedures.

Other possible explanations to the large SDs could be the use of different bolus timing techniques, the use of different contrast agents, and the possibility that another procedure, such as an abdominal CT, was performed concurrently with the use of additional amounts of CM, thus influencing the bolus geometry at certain measuring points. At last, it is also possible that the large SDs simply reflects a true existence of a large variation in the degree of dilution between the patients.

Notifications
It is notable that the venflons used in CTPA procedures at OUS Rikshospitalet is designed to withstand a maximum flow rate of either 1.72 ml/s or 3.93 ml/s, while the CM in this study was delivered with a mean injection rate of 5.8 ml/s.

Applications and further investigations
A high degree of dilution of the CM was seen through its way to the central venous and pulmonary circulation in this study. The small number of patients enrolled in the study, and the large variations between them, indicate that further investigations are required to obtain more certain knowledge of how CM is diluted and distributed from the syringe towards the arrival at the ROI.

Nevertheless, several ADs are associated with the use of CM, including CIN. By reducing the amount of CM delivered to the patients, it is also possible to reduce the frequency of ADs. A possibility is CM delivery through a CVC, which have the potential of substantially reducing the amount of CM needed without compromising the contrast enhancement. This possibility
should at least be considered in patients with an already central venous access, or when renal function is too suppressed to receive normal amounts of CM.

**References:**