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TECHNICAL NOTE

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Reduction of Postmortem Angiography-Induced Tissue Edema by Using Polyethylene Glycol as a Contrast Agent Dissolver

ABSTRACT: Postmortem investigation is increasingly supported by computed tomography (CT) and magnetic resonance imaging, in which postmortem minimal invasive angiography has become important. The newly introduced approach using an aqueous contrast agent solution provided excellent vessel visualization but was suspected to possibly cause tissue edema artifacts in histological investigations. The aim of this study was to investigate on a porcine heart model whether it is possible to influence the contrast agent distribution within the soft tissue by changing its viscosity by dissolving the contrast agent in polyethylene glycol (PEG) as a matrix medium. High-resolution CT scans after injection showed that viscosities above *c.* 15 mPa s (65% PEG) prevented a contrast agent distribution within the capillary bed of the left ventricular myocardium. Thereby, the precondition of edema artifacts could be reduced. Its minimal invasive application on human corpses needs to be further adapted as the flow resistance is expected to differ between different tissues.

KEYWORDS: forensic science, postmortem angiography, forensic radiology, digital autopsy, virtopsy, minimally invasive autopsy, postmortem imaging, imaging autopsy, computed tomography, polyethylene glycol (PEG)

Postmortem investigations are increasingly supported by modern cross-section modalities such as multislice computed tomography (MSCT) and magnetic resonance imaging (MRI). Macromorphology can already be documented in osseous and gaseous findings using MSCT (1–3) and in soft tissue pathology to some extent using MRI (4–6). Otherwise, the assessment of vascular alterations was limited to major vessel injuries (7,8). The diagnostic lack of unenhanced imaging in vessel pathology was countered by implementing a minimal invasive angiography technique using iodinated contrast agents and MSCT (9). An excellent three-dimensional visualization of the arterial system was shown in a minimally invasive manner. As an artifact of the presented method, an increase in tissue edema signs in histological investigations was noted (9). It was assumed that the technique could even simulate edema signs in tissue regions with no signs of edema prior to angiography (9). We have suggested consulting appendant MRI data of the same body for signs of edema to discriminate between antemortem edema from angiography artifact. Otherwise, the comparison of the unenhanced (native) MSCT scan with the angiography scan can determine the tissue regions with increased contrast agent-caused enhancement. These are valuable solutions to overcome this artifact problem. Nevertheless, we aimed to modify the technique in order to reduce or even avoid the edema artifact.

The contrast medium used was an aqueous solution of an iodinated contrast agent. Reaching the capillary bed, it was able to enter and distribute within the interstitial space, causing edema signs at histology.

We wondered whether it is possible to increase the viscosity of the aqueous contrast agent solution. The subsequent increase of the flow resistance may prevent the entering of the contrast medium into the capillary bed under the advised intra-vascular pressure conditions (<60 mmHg) (9). To avoid lipophilic dissolving agents because of the described vessel wall interactions in regions with atheromatosis (10,11), we decided to use a polyethylene glycol (PEG) solution to increase slightly the viscosity of the hydrophilic contrast medium solution. PEGs are of increased intrinsic viscosity depending on the length of the PEG chains. We hypothesized that it might be possible to define a contrast medium viscosity that ensures a selective visualization of the arterial bed up to the precapillary arterioles, but on the other hand prevents the filling of the capillary bed and a possible consecutive tissue edema.

Material and Methods

Utilizing the coronary artery system in a porcine model already described in a previous publication (9), we investigated different PEG (PEG-200, Schärer und Schläpfer AG, Rothrist, Switzerland) concentrations as a contrast agent dissolver (Table 1) at 20°C ($\pm$ 0.5°C) room temperature. The viscosity of each solution was

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TABLE 1—*Investigated contrast agent solutions and their composition.*

Solution	Total Volume	Telebrix (mL) (8.7%)	Hemalum (mL) (4.35%)	H_2O (mL)	PEG (mL)	PEG (%)	Viscosity in mPa s at 20°C	Viscosity in mPa s at 25°C
1	460	40	20	400	0	0.0	1.1	1.1
2	460	40	20	350	50	10.9	1.4	1.3
3	460	40	20	300	100	21.7	1.8	1.6
4	460	40	20	250	150	32.6	3.0	2.7
5	460	40	20	200	200	43.5	6.0	5.0
6	460	40	20	150	250	54.3	11.0	8.5
7	460	40	20	100	300	65.2	18.0	14.0
8	460	40	20	50	350	76.1	28.5	23.5
9	460	40	20	0	400	87.0	41.0	33.5

PEG, polyethylene glycol.

analyzed using a conventional viscosimeter (Viscotester VT 01, Haake, Germany) at 20°C and at 25°C. Under defined pressure conditions, namely not exceeding 60 mmHG, the contrast medium solution was injected into the aortic root of the porcine hearts. With manual adaptation of flow, the pressure of 60 mmHg was maintained for 30 sec. After injection, a high-resolution MSCT scan of each specimen was performed (Emotion 6, Siemens Medical, Erlangen, Germany, collimation 6 × 0.5 mm, slice thickness 0.625 mm, increment of 0.3 mm, matrix 512). Hemalum (Mayer's hemalum solution, Merck KGaA, Darmstadt, Germany) was added to the contrast medium solution to determine in histological investigations the vessels that contain contrast medium. To reach preferably high PEG concentrations within the contrast agent solution, we limited the hemalum concentration to a comparably low 4.3%.

Results

Porcine Model

The measured concentration-dependent viscosities are displayed in Table 1. Measurements at 25°C showed decreased viscosities (Fig. 1).

MSCT and meglumine ioxithalamate provided a visualization of the coronary artery system. Figure 2 shows a series of short-axis CT images of each injected specimen with identical window settings (center 200 HU, width 400 HU). There was no obvious change in myocardial enhancement in lower viscosity solutions 1–5. From solutions 6–9, the visualization of the myocardium was distinctively lower, with a slight decrease in increasing PEG concentration and a consecutive increase in contrast medium viscosity. Figure 3 shows a representative histological specimen of injected specimens 1 (1.1 mPa s), 5 (6.0 mPa s), and 9 (41.0 mPa s). In solutions 1–4, the smallest measured contrast agent-filled vessel diameters were 7–8 µm. In solution 5, the smallest found diameter was 14.5 µm. From solution 6 onward, the filled vessels were more than 20–25 µm in diameter.

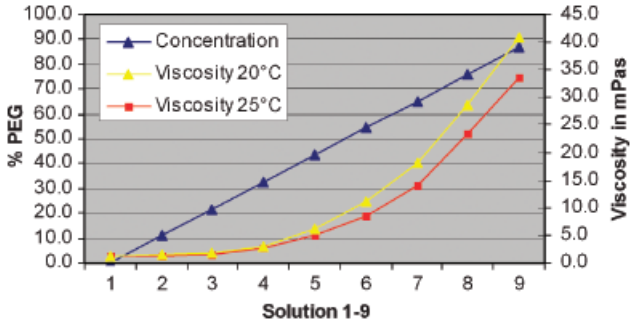

FIG. 1—*Polyethylene glycol (PEG) concentrations and graphical delineation of the resulting viscosities (at 20°C and at 25°C). At higher temperatures, the content of PEG needs to be increased to reach the same viscosity.*

Discussion

The intrinsic viscosity of vital blood is 4–5 mPa s (12). The major part of its viscosity is caused by the cellular components as the normal plasma viscosity is 1.3 mPa s (12). The injected contrast media do not contain particles with sizes comparable to erythrocytes. Therefore, the intrinsic viscosity of its solution has to be increased. We used a PEG solution with an intrinsic viscosity of 40–50 mPa s to increase the viscosity of the injected aqueous medium.

Our results have shown that the viscosity of injected media has to be increased up to at least threefold of vital blood levels to prevent a filling of the capillary system of the left ventricle myocardium under defined injection pressure conditions of 60 mmHg. Thereby, the angiography-induced tissue edema seems to be reducible with increasing contrast medium viscosity. Further studies with a series of human corpses are necessary to define an

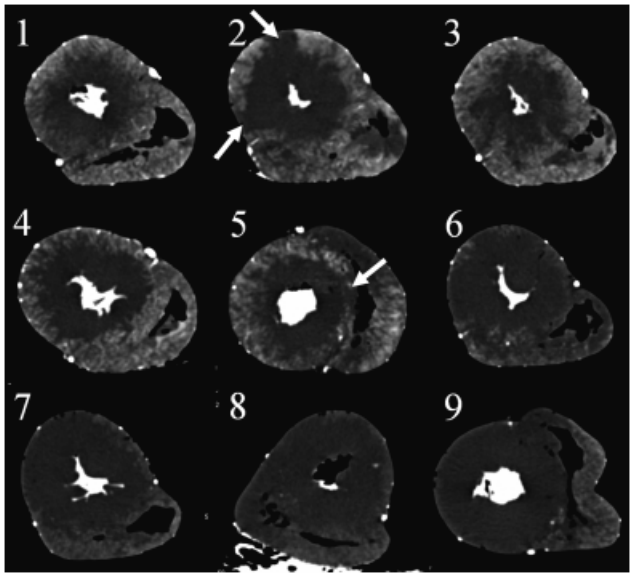

FIG. 2—*High-resolution short-axis images of the porcine hearts injected with solutions 1–9 (window settings: C 200 HU, W 400 HU). The enhancement of the left ventricle myocardium does not obviously reduce until solution 5. From solutions 6 and 7, the systematic visualization of the myocardium is prevented and the distribution of the contrast agent is limited to the coronary arteries. Note the filling defects due to air within the coronaries after slaughtering and consecutive unenhanced myocardial regions (2,5).*

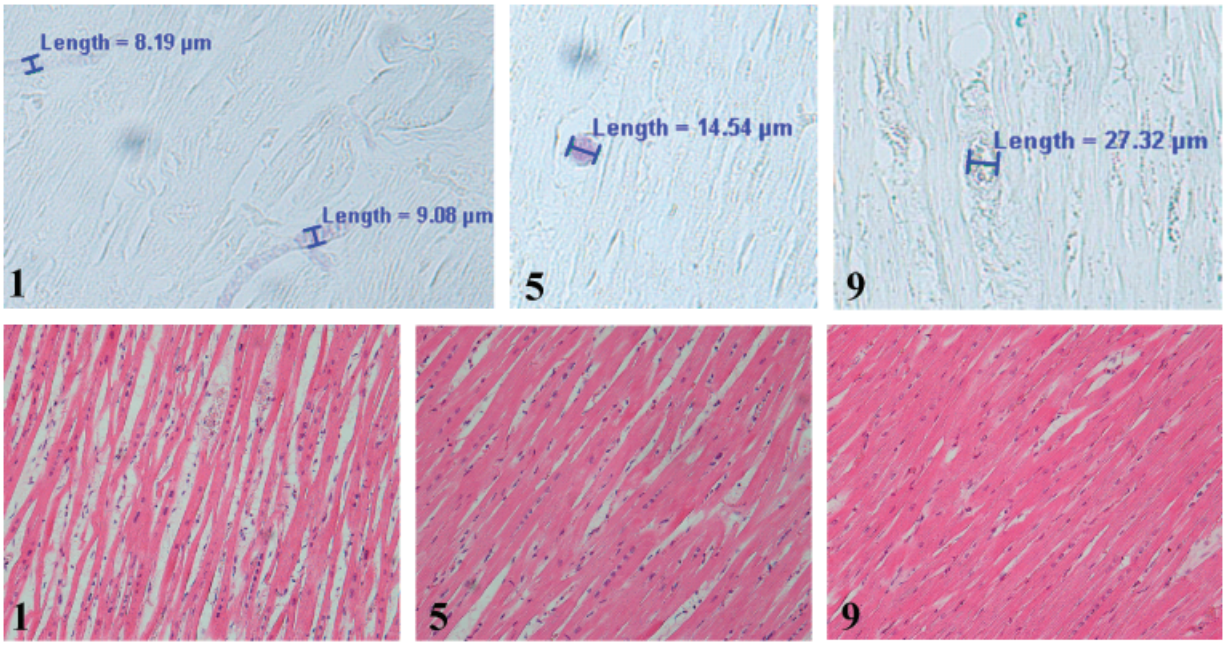

FIG. 3—*Unstained (upper) and HE-stained (lower) histological specimen with an injection of solution 1 (1.1 mPa s), solution 5 (6.0 mPa s), and solution 9 (41.0 mPa s). As the viscosity of the contrast solution increases, so does the smallest diameter of blood vessels into which the contrast agent is able to enter (the short blue lines represent the marked and measured vessel diameters). From 7–8 µm in solution 1, the minimal-stained vessel diameter slightly increases to 14.5 µm in solution 5, and in solution 9 only the terminal arterioles of 20–25 µm show intravascular hemalum. The HE-stained specimens are representative histological appearances of the injected porcine myocardium in solutions 1, 5, and 9. The obvious wide interstitial spaces between the myocardial fibers in solution 1 represent the so-called "angiography-induced tissue edema." This phenomenon is distinctively less obvious in solution 5 and completely absent in solution 9 when the contrast agent solution is not able to enter the capillary bed. Note the polynuclear porcine myocardial tissue.*

adequate contrast medium viscosity under consideration of all human soft tissues. We expect local differences in the flow resistance in different soft tissues. This is supported by the observation in our study that the visualization of the right ventricular myocardium was not obviously influenced by increasing viscosity within the investigated ranges. The viscosity probably has to be further increased to be valuable for use in a minimally invasive approach to prevent tissue edema in all soft tissues. PEGs with longer chains (e.g., PEG 400) may work comparably in larger viscosity ranges as an alternative.

It will be important to find an adequate compromise in increasing the contrast medium viscosity and still being able to detect small soft tissue injuries such as ruptures of the liver.

Its application on human corpses may be furthermore complicated due to the mixture of the contrast medium with the blood of the corpse during injection, which will also influence the viscosity. It is still required to turn the corpse several times before injection to redissolve the sedimented erythrocytes to prevent a distribution of the contrast medium only within the upper serum layer. However, in cases of severe blood loss, the arteries in the lacerated regions are expected to be almost devoid of blood, which facilitates the contrast agent filling.

PEG was used to influence the flow characteristic of this hydrophilic contrast agent solution. As PEGs are also used as solubilizers, they might have the ability to influence the intramural lipids of the vessel wall in atheromatosis. In systematic future experiments, we will gain more knowledge about possible PEG–vessel wall interactions or an aimed study will answer this question.

Our investigations were performed at 20°C room temperature. As can be seen in Table 1 and Fig. 1, especially the higher viscosities are strongly temperature dependent with a decrease in viscosity at a higher temperature. As a result, the PEG percentage of the solution needs to be adapted to the local temperature conditions of the scanning room and the corpse.

The major disadvantage of the used porcine heart model was the air within the coronaries after slaughtering that could not be totally drawn off and that caused local contrast agent-filling defects within the coronaries and consecutively unenhanced areas of the myocardium (Fig. 2).

Conclusion

The contrast agent distribution within the soft tissue can be influenced by increasing its viscosity using PEG. In the left ventricular porcine myocardium, 15 mPa s prevents a capillary distribution of the contrast agent at a 60 mmHg injection pressure.

The application of the technique on human corpses needs to be further adapted.

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