Journal of Geriatric Cardiology (2016) 13: 855–865

Case Report · **Open Access** ·

Multi-phase post-mortem CT-angiography: a pathologic correlation study on cardiovascular sudden death

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Abstract

Multi-phase post-mortem CT-angiography (MPMCTA) has the great potential to increase the quality of the post-mortem investigation, especially in the area of sudden death; however, its role as routine complement to the pathology toolbox is still questioned as it needs to be further standardized. The aim of this study is to investigate the contribution of MPMCTA in cases of sudden unexplained death in adults and in particular in sudden cardiovascular death. Sixty-eight sudden unexpected deaths of adults were investigated at our institution between 2012 and 2013. Ten cases underwent MPMCTA and autopsy and were included in the study. Before the angiographic step by complete filling of the vascular system, prior to any manipulation of the body, a non-contrast CT-scan was carried out. Image reconstructions were performed on a CT workstation (Vitrea) and two radiologists experienced with post mortem imaging interpreted the MPMCTA findings. In all 10 cases, we could state a good correlation between combination of post-mortem CT and MPMCTA and autopsy procedures, confirming a high diagnostic sensitivity. With this case series we want to illustrate the advantages offered by performing MPMCTA when facing a sudden death, regardless of specific suspicion for acute coronary syndrome or other vascular or ischemic disease.

J Geriatr Cardiol 2016; 13: 855–865. doi:10.11909/j.issn.1671-5411.2016.10.003

Keywords: Angiography; Imaging; Sudden death

1 Introduction

Cardiovascular diseases are a frequent cause of sudden death and they can be challenging to recognize during autopsy.[1,2] A large number of sudden death cases still remain unexplained even when conventional autopsy with macroscopic and histological investigation is thoroughly performed; consequently the search for and identification of the cause of death still remain a heavy challenge for pathologists. Post-mortem imaging is a new tool to explore sudden death.[3] Computed tomography (CT) and magnetic resonance imaging (MRI) has been offered as a concomitant or alternative method to conventional autopsy in such cases.[4,5] A further added value in post-mortem imaging is the introduction and the implementation of Multi-Phase Post-Mortem CT-Angiography (MPMCTA) that has the great potential to increase the quality of the post-mortem investigation because this technique shows a high ability to enhance the visualization of the cardiovascular system.[6,7] MPMCTA is very promising in the area of sudden death; however the role of MPMCTA as routine complement to the pathology toolbox is still questioned as it needs to be further investigated and standardized.[8,9] Among the different post-mortem CT- angiography techniques and methods, only targeted coronary angiography (TCA) is being investigated in a structured and well-defined manner containing clear morphological comparison between a standardized technique and macro- and microscopic findings while the other techniques are still missing such basic studies.[8] In addition, exploring sudden death is a very thorny field since data from different sources, including clinical, autopsy, histological and laboratory genetic and molecular investigation, are pivotal in ascertain the cause of death in such cases.[3]

The aim of this study is to investigate the contribution of

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Received: May 1, 2016 **Revised:** October 16, 2016
Accepted: October 22, 2016 **Published online:** October 28, 2016

MPMCTA in cases of sudden unexplained death in adults and in particular in sudden cardiovascular death.

2 Case series

Between 2012 and 2013, 68 sudden unexpected deaths of adults were investigated at our institution. Ten cases underwent MPMCTA and autopsy were included in the study. This study did not require informed consent from the relatives of the deceased to perform imaging investigations.

Before the angiographic step by complete filling of the vascular system, prior to any manipulation of the body, a non-contrast CT-scan without contrast agent injection was carried out, taking care to wrap the body in an artifact-free bag. In all presented cases the non-contrast CT-scan was performed with a 16-row CT-unit (CT BrightSpeed 16, GE Healthcare, Milwaukee, WI, USA) using the following scan parameters: field of view (FOV) 50 cm, slice thickness 0.625 mm, interval of reconstruction 1.25 mm, 120 kVp, 112 mA and 48 s scan time. According to in-house standards, specimens of peripheral blood and urine were taken before angiographic procedures for toxicological screening and analyses.

The following angiographic phases were performed introducing only one modification to the standardized protocol, the cannulation of the axillary vessels on one side (but not in the second and in the fourth presented case), using cannulas (MAQUET Gmbh & Co. KG, Rastatt, Germany) with a diameter of 16-French for the artery and 18-French for the vein.[10] The minimally invasive post-mortem CT-angiography technique is based on perfusion of vascular system performed using a pressure-controlled perfusion device (Virtangio®, Fumedica AG, Maquet®, Muri, Switzerland) that pumps up the contrast agent, a mixture of oily contrast agent (Angiofil®, Fumedica AG, Muri, Switzerland) and paraffin oil (liquid paraffin obtained from the local pharmacy).[11] The highly radiopaque iodized oil is transported in paraffin oil through the vascular system in analogy to the delivery of contrast agent by the circulating blood in clinical angiography. The oily contrast agent is an iodized oil (Angiofil) and it is mixed with paraffin oil in 6% concentration (220 mL of Angiofil in 3500 mL of paraffin oil).

The arterial phase of MPMCTA was carried out using the following scan parameters: FOV 50 cm, slice thickness 0.625 mm, interval of reconstruction 1.25 mm, 120 kVp, 112 mA and 48 s scan time. The same scan parameters were used also in the venous and dynamic phases. Image reconstructions were performed on a CT workstation (Vitrea) and two radiologists experienced with post mortem imaging interpreted the MPMCTA findings.

A complete autopsy was systematically performed within 36–72 h after death by our forensic pathologists; histological investigations were performed according to our standardized protocols.

2.1 Case No. 1

A 72-year old man during a violent quarrel with his wife complained of thoracic pain. An attempt at cardiac massage was unsuccessful and the man was declared dead by the rescue team. No known pre-existing disease was reported. An autopsy was arranged by the local prosecutor. Prior to the autopsy, a non-contrast CT-scan was performed, showing diffuse calcification of both the aorta and the coronary arteries, and massive hemopericardium. At MPMCTA, left ventricle posterior wall rupture was clearly visualized and a better definition of the pericardial clot was obtained. The autopsy confirmed the presence of a blood clot (approximately 300 g) within the pericardial sac. The heart was excised, fixed in formalin solution, and then examined. Cardiac size was mildly increased (13 cm × 12 cm × 4.5 cm), with conical shape; heart weight was increased (525 g). A darkish and stiff area (8.5 cm × 8 cm) was observed at the posterior wall of the left ventricle. Cross-section of coronary arteries revealed diffuse advanced atherosclerotic lesions with occlusive thrombus formation of the left circumflex artery (LCX). A large area of pale myocardium diffused to the lateral and posterior free wall of the left ventricle with cardiac rupture was evident at axial section of the heart. Elongation of the sarcomeres and nuclei with polymorphonuclear leukocyte margination at the periphery of the infarct necrosis were observed at histological examination. Myocardial hemorrhage, and edema were the histological features of the ruptured ventricular wall.

The cause of death was cardiac tamponade following rupture of the free left ventricular wall associated with transmural infarct due to occlusive thrombosis of LCX.

2.2 Case No. 2

A 38-year old man was admitted to the local hospital due to severe pain on the right side of the neck. During the clinical examination, he presented multiple episodes of hematemesis and suddenly died. A previous traumatic event and a suspect about medical malpractice were alleged; a post-mortem examination was arranged by the local prosecutor. A non-contrast CT-scan revealed large hemorrhagic infiltration of cervical soft tissue and muscles. The MPMCTA showed a ruptured pseudoaneurysm of the right common carotid artery, and the contrast agent leaked through the rupture passing onto the mouth.

At autopsy, all the cervical organs were fixed in formalin solution. The subsequent observation allowed the easy identification and localization of the source of bleeding as a 1cm tear in the wall of the right common carotid artery penetrating into the pharynx. The diagnosis of hemorrhagic shock for acute rupture of a pseudoaneurysm of the right common carotid artery was established as cause of death.

2.3 Case No. 3

A 67 year-old woman was found dead in her home. Medical history was unremarkable. A clinical autopsy was arranged since the cause of death was unknown. Prior to autopsy, a MPMCTA was performed; it showed massive hemothorax, and the partial and irregular opacification of aortic lumen with associated dilatation of the aorta. Volume rendering and maximum intensity projection reconstructions allowed a better visualization of the massive left hemothorax and of the starting point and the presence of an aortic wall tear that was easily visualized at autopsy (Figure 1 & 2). The section of the thoracic aorta confirmed the aortic dissection of the wall with the false and the true lumen (Figure 3 & 4).

2.4 Case No. 4

A 53 year-old man felt sick and died suddenly while working in the fields, and no specific disease was known by his relatives. The external examination was unremarkable. Before the autopsy examination, a post-mortem-CT angiography was performed which showed a filling defect in the right pulmonary artery; no abnormalities were arising from CT-scan images of the limb. In the course of the autopsy examination an embolus was detected in the right pulmonary artery and the research of the exact site of the thrombus in the peripheral vessels was performed. The subsequent histological investigations confirmed the causal relationship with pulmonary thromboembolism as cause of death and allowed to assess the age of the thrombosis.

2.5 Case No. 5

A 73-year old man was found lying in a public street near a car with blood around. He was conscious but unable to communicate with the rescue team. It was assumed that he had been hit by a vehicle and then abandoned on the road. He was immediately transported to the local Emergency Department to be treated for the injuries received. He was

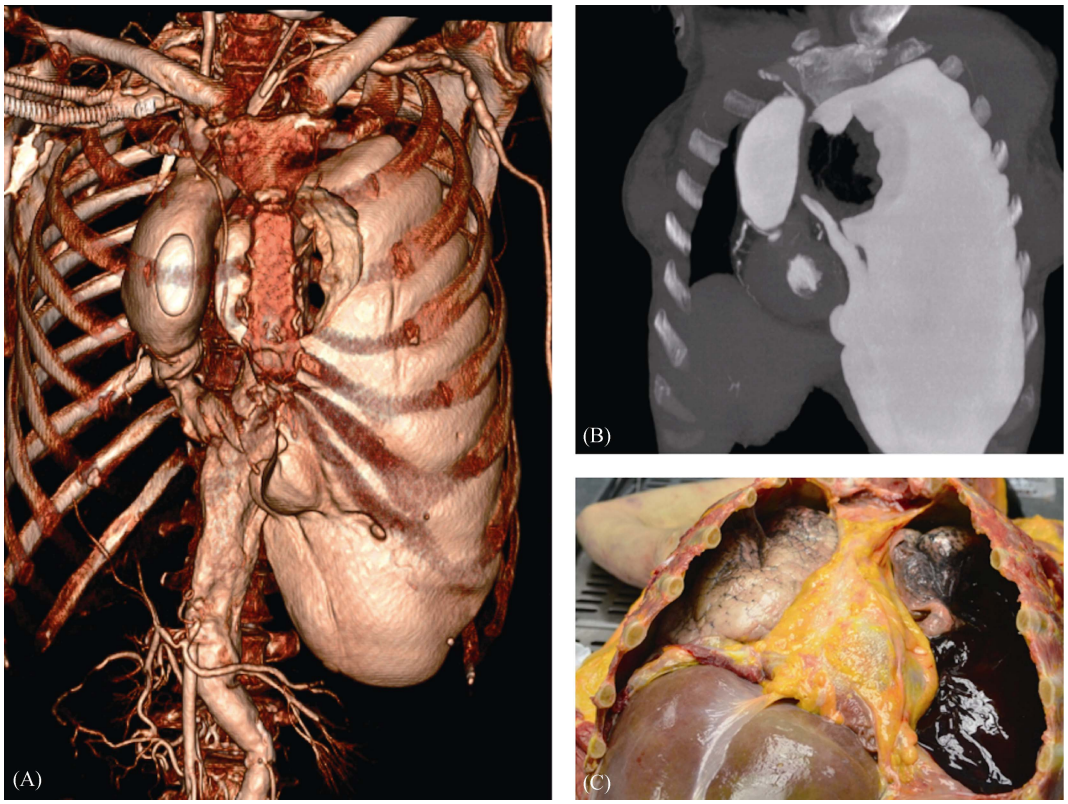

Figure 1. Volume rendering (A) and maximum intensity projection (B) reconstructions showed the massive left hemothorax, also confirmed by the post-mortem examination (C).

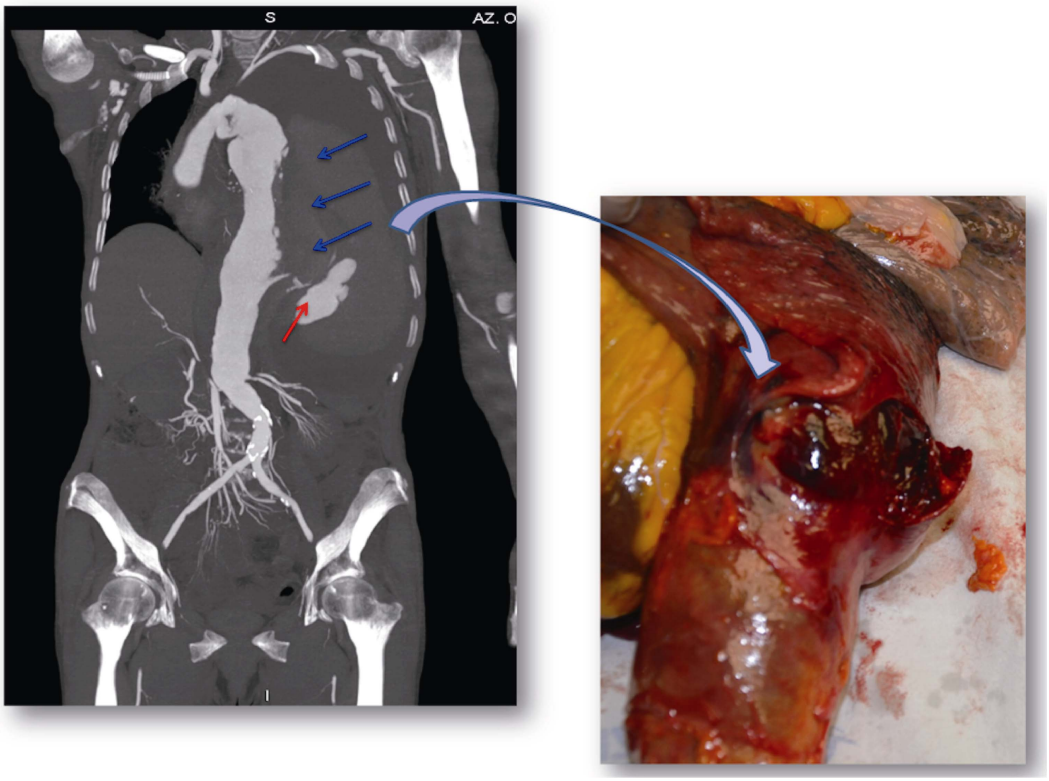

Figure 2. Maximum intensity projection reconstruction revealed the irregularity of aortic lumen, the leakage of contrast agent from the aortic wall tear. Note the starting and end point of lumen irregularity.

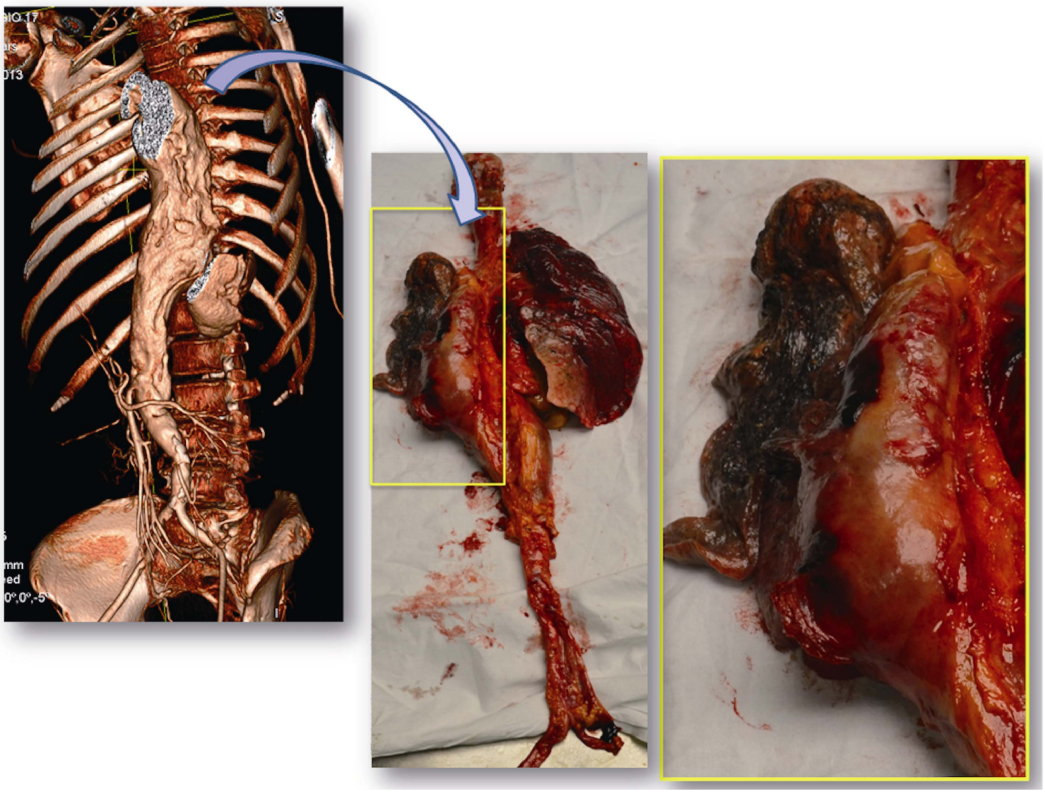

Figure 3. Volume rendering reconstruction revealed the irregular opacification of aortic lumen, and on the right we show the autopsy findings that confirmed the ruptured thoracic aortic wall.

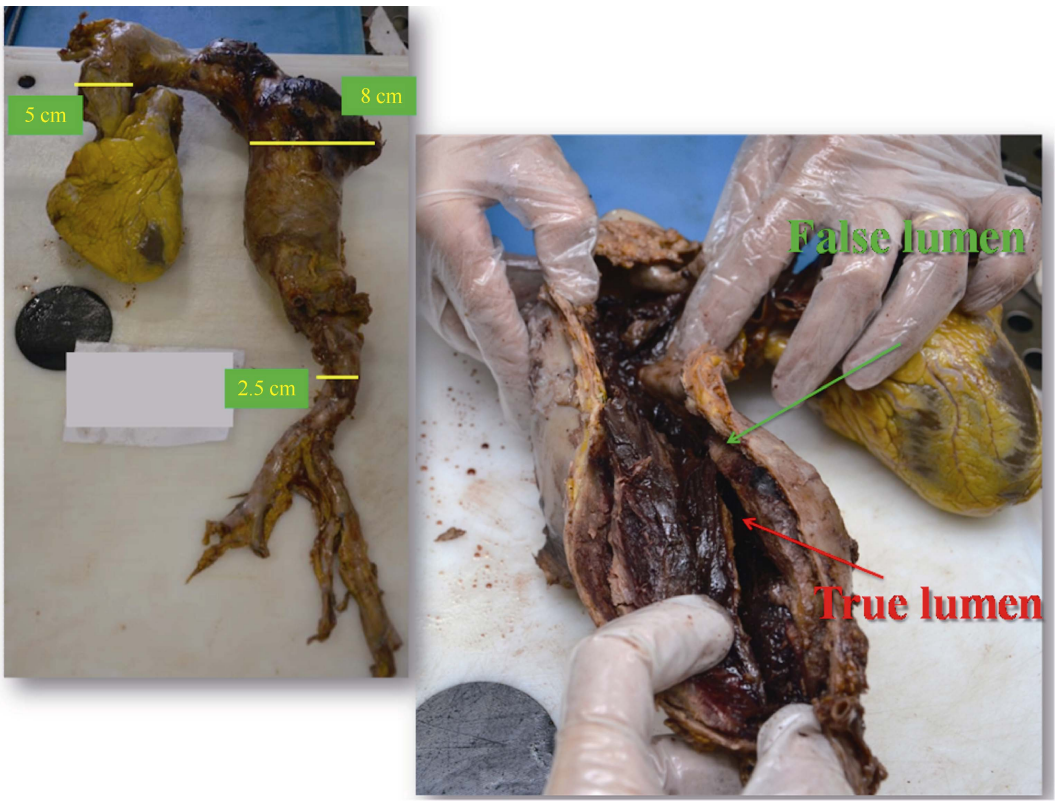

Figure 4. The ascending aorta appeared dilated, over the valvular plane, with the diameter of 5 cm, and it showed also the descending thoracic aorta ectasia (with a maximum diameter of 8 cm). The section of the thoracic aorta confirmed the aortic dissection of the wall with the false and the true lumen.

conscious, the blood pressure was 190/100 mmHg. Right hemiplegia and aphasia were detected by physicians. A total body CT scan showed large left cerebral hemorrhage, shift of septum pellucidum, bilateral intraventricular hemorrhage, and massive perilesional edema. A sagittal linear fracture of the right frontal bone with hemosinus was detected. One hour later, the man became unconscious; he experienced a severe bradycardia and suddenly died. An autopsy was arranged. Prior to autopsy, a non-contrast CT-scan confirmed all the findings described *in vivo*. When the MPMCTA arterial phase was performed, a large left intraparenchymal and intraventricular hemorrhage was better visualized. At autopsy, massive intraventricular hemorrhage was detected; the subsequent observation of the formalin fixed brain showed a large (4 cm × 5 cm × 6 cm) left intraparenchymal hemorrhage extending to basal ganglia, internal capsule and to subcortical white matter in the frontal lobe.

2.6 Case No. 6

A 51 years old man was found dead in a public place; his medical history was unremarkable. Since the cause of death was unknown, a clinical autopsy was disposed. Prior to autopsy, the non-contrast CT-scan visualized calcification of the left anterior descending coronary artery. MPMCTA performed by cannulation of the axillary vessels, revealed thickening of the left anterior descending coronary artery at the level of an advanced plaque (Figure 5A).

The right coronary artery showed a diffuse narrowing of the lumen through the initial tract (Figure 5B).

The examination of the formalin fixed heart confirmed the severe stenosis of the lumen (85%–90%). At histological investigation of heart samples areas of focal fibrosis, foci of hyper-contracted myocardial cells with markedly short sarcomeres, extreme thickening of Z lines and rexis of the myofibrillar apparatus into cross-fiber, diffuse fragmentation of the myocells with square nuclei, and small areas of reflow characterized by infiltrates of erythrocytes between the myocells were detected.

2.7 Case No. 7

A 73 years old man was struck by a car, than he was immediately transported to the local Emergency Department by ambulance. A total body CT scan showed the thoracic T4 spine fracture and the right hemi-pelvis fracture. In

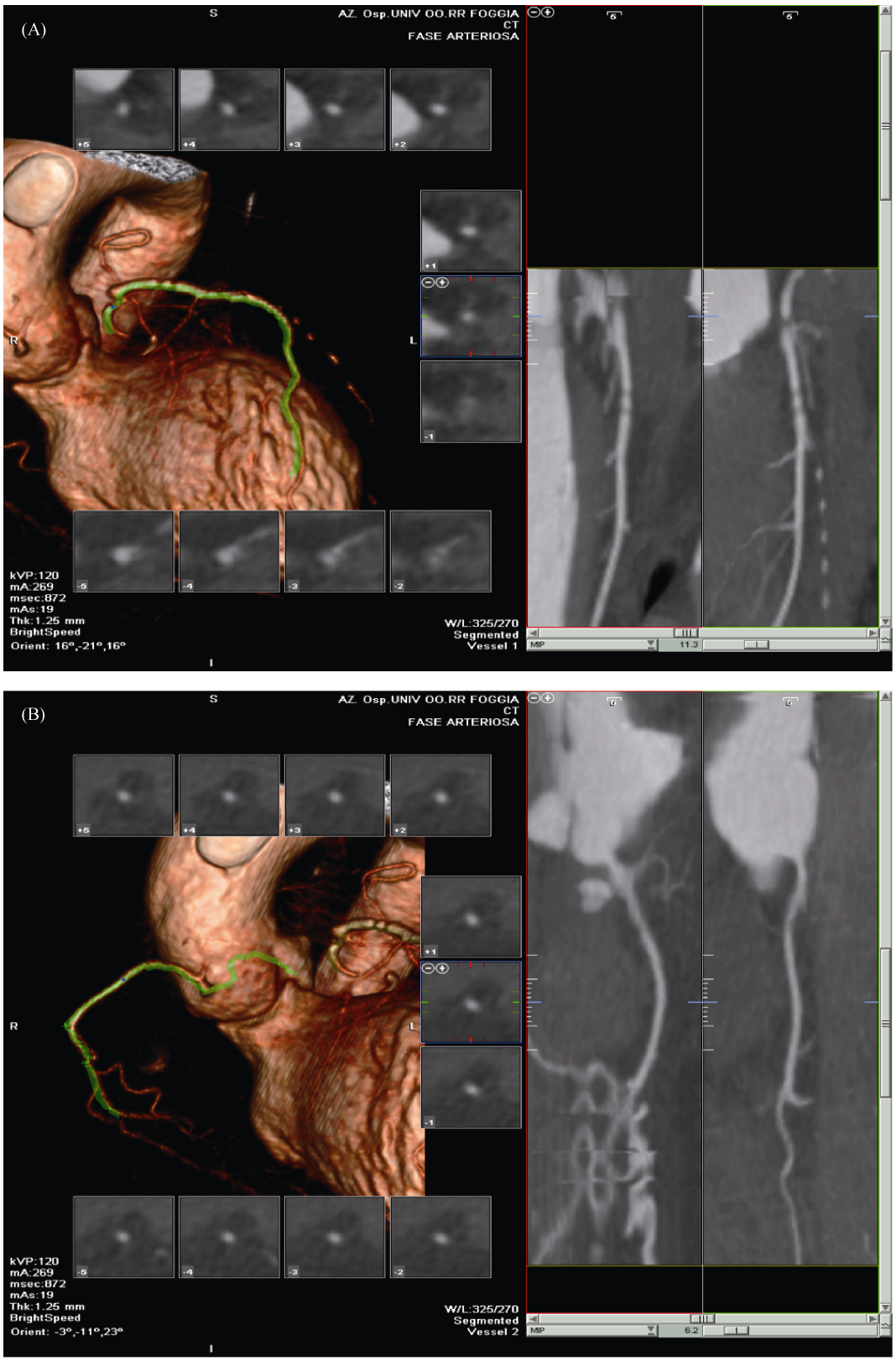

Figure 5. MPMCTA results of case No. 6. MIP reconstruction showed the calcified plaque at the left anterior descending coronary artery (A) and right coronary artery (B). Volume rendering reconstruction enabled a better visualization of the stenosis of the left anterior descending coronary artery and of the right coronary artery, respectively. MIP: maximum intensity projection; MPMCTA: multi-phase post-mortem CT-angiography.

the following days, he suddenly referred dyspnea and the thorax CT scan showed a filling defect in the left pulmonary artery, later he suddenly died. A post-mortem non-contrast CT-scan confirmed the spine and the right hemi-pelvis fractures, and it visualized the diffuse calcification of aorta and coronary arteries. The venous phase of the MPMCTA, performed by cannulation of the axillary vessels, showed a luminal filling defect of the left pulmonary artery, of the inferior vena cava, beneath renal veins' origin and of the left femoral vein. The autopsy revealed a suspicious embolus in the proximal left pulmonary artery formed from the bifurcation of the main trunk. The dissection of the inferior vena cava and of the deep veins of the legs confirmed the presence of suspicious thrombotic material both in the vena cava as in the left femoral vein. The histological examination confirmed that they were embolus and thrombus in the left femoral vein.

2.8 Case No. 8

A 37 years old man was found dead in a farmland, no specific disease was known. No findings arising from the non-contrast CT-scan post-mortem and from MPMCTA. The autopsy and histological examination allowed to asses that the cause of death was acute heart failure due to massive colliquative myocytolisis.

2.9 Case No. 9

A 48 years old man, was found dead in a public place, no clinical history was known. The MPMCTA showed a large intraparenchymal mid-brain hemorrhage. The external examination and the autopsy showed no findings; the gross examination of the brain after formalin fixation, confirmed the intraparenchymal hemorrhage, while it wasn't possible to highlight the exact source of bleeding.

2.10 Case No. 10

A 47 years old man was found unconsciouos in a public place and transported to the local Emergency Department where he arrived dead. The MPMCTA showed a right intraparenchymal brain ischemic area and luminal defect of the right middle cerebral artery. The examination of the brain after formalin fixation confirmed the cerebral ischemic area and a significative occlusion of the lumen.

3 Discussion

The idea of studying hollow anatomical structures in a post-mortem setting comes from quite a long time ago. In the 15th century, Leonardo da Vinci produced wax casts of heart chambers and cerebral ventricles inducing maceration of soft tissue applying maggots.[9] At the end of the 19th century, this purpose started to be crossed with imaging technologies and it was focused on the vascular tree; in 1899 Walter Baumgarten published an extensive review on myocardial infarction in which he injected a radio-opaque contrast in the coronary arteries of isolated hearts. Since then approaches of this kind have been passing through continuous technical renovation, but they still imply a difficult and long procedure with too many inconveniencies for a routine application.

Only in the last decade, as multi-detector CT scans have become quite common in forensic medicine institutes, the use of intraluminal contrast medium gained a new foothold. Among reports and series recently published, PMCTA has been evaluated in specific cases, like deaths by falling from a height,[12] peculiar stab wounds,[13,14] transposition of great arteries in a newborn.[15] The standardized protocol developed by the Virtopsy study group in Lausanne allows a quite quick, easy and economically affordable procedure to obtain a whole body CT angiography; this whole body approach is a milestone in the widespread promotion of post-mortem imaging in the routine work.[11] It has the advantage of better standardizing the procedure and sparing lots of time rather than a single-excised organ or block vascular study.

Non-contrast total-body post-mortem CT also gives precious information about cause of death, eventual traumatisms, or bones fractures. Nevertheless, one of the main limitations for medical professionals to accept it as a support in conventional autopsies has been its poor sensitivity for natural death mechanisms involving vascular pathology, coronary syndromes and ischemic heart disease above all.[5] Implementation of CT with three contrast-enhanced angiographic phases is supposed to be able to overcome this limit, allowing to better visualize the cardiovascular system.[16–18] In a recent trial, Roberts, *et al.*,[19] showed a significant reduction in number of invasive autopsies needed when a coronary angiography was added to the post-mortem CT.

Among those who are studying and publishing their experiences with post-mortem application of imaging techniques and other diagnostic tools there are some who try to test them as alternatives to conventional autopsies, reviewing such feasibility.[20] This is not our aim as we still consider autopsy undeniable.

Strong input to this exploitation is coming from devel-

opments in clinical medicine, both in understanding pathogenesis of diseases and in improving diagnostic tools and procedures. This should induce even the context of legal medicine to shift paradigm about post-mortem assessment of cause of death. Especially when dealing with natural death, it is common to face cases of no obvious pathological findings at autopsy. Nowadays, autopsies can reach an acceptable diagnostic accuracy only if implemented with organ and lesions sampling for later processing and histological assessment. At the same time, we know that in most legal medicine institutes there is a general tendency to avoid histopathological tests for clinical autopsies because of time and costs needed. Another requirement which is considered to be essential for the correct interpretation of autopsy findings should be the deceased's medical history and the circumstances of death. Unfortunately, this information is often unknown, unavailable or unremarkable. It is clear, then, that common conventional autopsies, conducted without preliminary information or further histopathology, cannot be considered any longer a gold standard in determining cause of death. However, high incidence of autopsy-negative cases is reported in sudden unexpected death.

It was demonstrated how the combination of MPMCTA and conventional autopsies should be considered a new gold standard in the assessment of cause of death in case of suspected vascular lesion and lethal hemorrhage. With this case series, we want to illustrate the advantages offered by performing MPMCTA before dissection when facing a sudden death, both for judicial and clinical autopsies, regardless of specific suspicion for acute coronary syndrome or other vascular or ischemic disease. Definition of sudden death varies greatly. The most widely accepted definition is an unexpected death that occurs within 1 h of symptom onset; for unwitnessed cases, victims observed alive within 24 h before death meet the definition.[21]

In case of suspected hemopericardium due to ventricle rupture, forensic pathologist could plan in advance the excision of the whole heart (without thoracic aorta) and a complete examination after fixation. Post-mortem non contrast CT-scan has already been studied in the diagnosis of pericardial tamponade even as an alternative to invasive autopsy.[22] However, the same authors affirm that hemopericardium alone it's not sufficient to establish definitely a diagnosis of death mechanism by tamponade. In our case, the association of non-contrast CT scan with contrast angiography ascribed directly the hemopericardium to the ventricular wall breech so that it was easy to provide a complete evaluation of cause, mechanism and manner of death.

In one case, we dealt with a lethal hemorrhage originating from a common carotid artery-oropharyngeal fistula.[23] The MPMCTA exam allowed us to find in the first hypothesis the correct diagnosis; otherwise it would have been much more complicated to solve the case. Generally extracranial carotid artery aneurysms are rare; sudden death caused by spontaneous rupture of such lesion or pseudoaneurysm have been described only in a few reports. During the autopsy, cervical dissection was consequently conducted more precisely and carefully. As expected, a large subfascial hemorrhagic clot was found extending from the sternocleidomastoid muscle to the pharynx and larynx and also to the posterior mediastinum. During the following observation of formalin fixed organs, it was really easy to identify the carotid breech and the fistula tunnel. This is a patent example of how adequate post-mortem imaging can give early useful indications on which dissection technique to prefer and on how to plan all the tests needed for a complete medico-legal investigation. We could call it "tailored" autopsy in analogy to the modern clinical tailored medicine.

In case of aortic dissection, we would expound considerations similar to the previous one; but an important difference lays in the greater incidence of a lethal rupture of the aorta compared with that of the common carotid artery. By the way, MPCTA immediately provided a presumptive cause of death which was quickly confirmed after thorax incision and examination of the excised thoracic aorta. MPCTA is a sensitive exam both for aorta and smaller vessel rupture, which allows to visualize clearly a diffuse hemorrhagic infiltration as well as a fluid blood collection in a cavity. Another concern about small vessels is to get them damaged during dissection, so that it would be useful to assess whether they are intact before autopsy starts.

In case of cerebral injury, sometimes circumstantial data suggested a violent death from a vehicle collision; on the contrary clinical imaging showed an intracranial lesion pattern not compatible with the skull fracture. Post-mortem CT-scan implemented with angiographical phases confirmed in vivo findings and better depicted the cerebral injury as the result of a spontaneous hemorrhagic ictus centered in the left frontal lobe. This finding indicated the advisability of an in situ dissection of ventricular cavities at autopsy which revealed blood in both sides; afterwards, sections of the fixed brain led decisively to the correct localization of the lesion to the left frontal lobe. MPMCTA following non-contrast CT as a single standard procedure allows vessel opacification as well as parenchymal contrast-enhancement covering a wide pathological variety. In this case, in-

direct imaging was more sensitive than direct fresh organ observation.

Very useful is to study typical lethal acute coronary syndrome in healthy adults. Sudden cardiac death (SCD) is the most common sudden death and remains itself the major cause of death in the developed world.[24] Ischemic heart disease accounts for approximately 80% of SCD.[21] Because of short latency from acute myocardial infarction to time of death, in this case there wasn't any macroscopic pathological finding about the myocardium. Histology provided diffuse and multiple signs suggesting ischemic myocardium injury but not conclusive "*per se*" for such a definitive cause of death. This was attributed matching the evidence of a severe stenosis of the coronary lumen, based on "the balance of probability".[25] This finding had already been found during the MPMCTA and it was observed also in the fixed organ and on histological samples. We know that measuring the narrowing degree in the absence of blood flow can lead to an overestimation because of lack of coronary wall distension. The use of a vascular contrast filling and dynamic phase scans provides one more parameter to assess the stenosis which comes closer to *in vivo* pathogenesis. Some authors, using water soluble contrasts too, hypothesized a correlation between "myocardial blushing" patterns and underlying coronary artery disease.[25,26] By the way, we agree with the others who consider unreliable non-invasive technique for the identification of ischemic myocardium,[27] so that we didn't mind eventual medium extravasation or wall-enhancement at the PMCTA but we exploited it for better volume-rendering reconstructions of morphology of the coronary arteries and respective lumens.

Again, is very important to study cases in which the clinical examination immediately led to the diagnosis of suspected pulmonary thromboembolism. These cases make for a good proof for high sensitivity of the MPMCTA in ascribing a filling defect in the pulmonary artery to an embolism rather than to an artifact or a post-mortem clot. In these cases it was even possible to find the original thrombosis in the deep venous system of the inferior limb by post-mortem imaging. Obviously many more observations are needed to definitely state its diagnostic accuracy in this specific field, but our experience goes to strengthen other authors' considerations. In cases of suspected lethal pulmonary embolism, a full autopsy dissection should be always mandatory, including deep veins of the legs, as it is considered the diagnostic gold standard. Nevertheless, implementation of MPMCTA could help selecting cases which will undergo autopsy, with the purpose of better define the epidemiology of this lethal condition, especially in hospitalized cohorts. Furthermore, it makes easier to check the correct source of the embolism along the whole inferior limb venous system. In some situations, in fact, this identification can be time-consuming or even unsuccessful, for example when vessels of small caliber or located in poorly accessible areas are involved.

In a retrospective report of more than 50 consecutive cases, authors affirmed that a pathological finding had never been interpreted as an artifact.[28] We can assume that radiologists' consciousness of further autoptical confirmation provided a bias advantageous for a pathological rather than a normal interpretation of findings. In any case, we can state a good correlation between combination of post-mortem CT and MPMCTA and autopsy procedures.

This case series investigates the contribution of MPMCTA in cases of sudden unexplained death in adults. While this procedure gains wider and wider diffusion,[29] we will be able to define better some open questions, such as the whole range of artifacts encountered, especially in the histo-pathological investigation following MPMCTA,[30] or the convenience of preliminary imaging-guided biopsies,[31] or the specific requirements to consider a radiologist as a forensic expert one. Indeed post-mortem imaging should be a field of strict collaboration among different specialists as it has been evaluated in most studies.[8]

It is fundamental to highlight the utility of this approach that furnishes higher anatomical detail and analysis of pathological changes, to offer high-quality standards to the results of the report written by the pathologists and possible re-evaluations through a "second look".[32] Lastly, we mention the usefulness of post-mortem imaging for providing standard records re-evaluable in the future but also for generating spectacular images to illustrate and document injuries.[33–35]

Conflict of interest

The authors declare they have not competing commercial interests in relation to the submitted work.

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