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Pathomorphological and CT-angiographical characteristics of coronary atherosclerotic plaques in cases of sudden cardiac death

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Abstract:	<p>The goal of this study was to assess the localization and types of thrombosed plaques in cases of sudden cardiac death attributed to coronary artery disease, and to evaluate possible correlations with Body Mass Index (BMI) and increased heart weight. This retrospective study was performed on forensic cases for which the cause of death was attributed to coronary artery disease. A complete autopsy and a multi-phase post-mortem CT angiography (MPMCTA) were performed in all cases. 85 cases were selected (mean age 55.18±11.04 years; 72 men and 13 women). MPMCTA performed prior to autopsy enabled an evaluation of coronary artery perfusion before dissection of the body and helped therefore to guide sampling for histology. An acute coronary thrombosis was found in 57 cases, which included plaque erosion in 26 cases (mean age 46.73±8.33 years) and rupture or intraplaque hemorrhage in 31 cases (mean age 58.23±10.62 years). Erosions were most frequently found in the left anterior descending artery (61.5 %), while only 36.4% of ruptures were observed in this artery. Chronic coronary pathology was considered as the main cause of death in 28 cases (mean age 59.64±9.47 years). 62 of the cases (72.94%) had a BMI in the overweight category (BMI≥25), with the highest mean BMI in patients with chronic coronary pathology without acute thrombosis found at autopsy. The heart weight was above the predicted reference values in 52 cases (61.18%). Our results are in accordance with previously published studies on the spatial distribution of vulnerable plaques. We observed a higher percentage of eroded plaques than previously reported. Patients with coronary erosions were significantly younger than those with plaque rupture or those without an acute coronary thrombosis (p-values <0.0001). BMI and heart weight were significantly higher for cases without thrombosis in comparison to those with plaque rupture (p-values 0.023 and 0.003, respectively). Our results indicating that increased BMI and overweight hearts are associated with chronic ischemic heart disease are compatible with clinical studies. Performing more postmortem studies on forensic autopsies, including modern</p>

radiological examinations with MPMCTA, can enhance the detection of vulnerable plaques in living patients and prevent sudden cardiac death.

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Abstract

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pathology without acute thrombosis found at autopsy. The heart weight was above the predicted reference values in 52 cases (61.18%).

Our results are in accordance with previously published studies on the spatial distribution of vulnerable plaques. We observed a higher percentage of eroded plaques than previously reported. Patients with coronary erosions were significantly younger than those with plaque rupture or those without an acute coronary thrombosis (p -values <0.0001). BMI and heart weight were significantly higher for cases without thrombosis in comparison to those with plaque rupture (p -values 0.023 and 0.003, respectively). Our results indicating that increased BMI and overweight hearts are associated with chronic ischemic heart disease are compatible with clinical studies.

Performing more postmortem studies on forensic autopsies, including modern radiological examinations with MPMCTA, can enhance the detection of vulnerable plaques in living patients and prevent sudden cardiac death.

Keywords: postmortem CT-angiography, sudden cardiac death, coronary artery, ischemic heart disease, MPMCTA

Introduction

Ischemic heart disease remains the most important cause of sudden cardiac death (SCD) in the general population in western countries, and is nearly always associated with coronary atherosclerosis in the population over 35 years of age [1]. The information obtained from postmortem studies enriches the understanding of acute coronary syndrome, particularly in cases resulting in sudden death. Former studies on autopsy cases fuelled the current understanding of the pathophysiology and classification of coronary vulnerable plaques [2,3], although the term «vulnerable plaque» is still subject to debate among pathologists and clinicians [4,5]. Most cases of acute coronary syndrome are believed to result from luminal thrombosis, which have been described to be essentially associated with plaque rupture or erosion [2,3]. Intraplaque hemorrhage resulting from neo-vascularisation has also been recently recognized as an important cause of rapid plaque progression, playing a role in plaque enlargement and subsequent luminal narrowing [2].

The use of post-mortem coronary angiography on isolated hearts debuted in the mid-twentieth century [6,7], but the introduction of modern radiological technologies and changes in our understanding of acute coronary syndrome demand the need to revise and update our current knowledge and practice. At present, autopsy studies on sudden cardiac deaths are performed on forensic cases in many countries [8,9]. Over the past several years modern radiological examinations, like post-mortem computed tomography (PMCT), post-mortem computed tomography angiography (PMCTA) and post-mortem magnetic resonance imaging (PMMRI), were introduced into forensic practice. Radiological post-mortem evaluations performed for cardiovascular

pathologies have demonstrated a multitude of potential implications. It was reported that PMCTA, when correctly interpreted, is a reasonable tool to assess the patency of the coronary ostia, the degree of calcification, the dominance of vessels and the presence of significant stenosis, myocardial bridging and occlusive thrombi. PMCTA is also capable of evaluating the patency of stents and grafts [10-12].

The goal of this study was to assess the localization and types of thrombosed plaques in cases of sudden cardiac death attributed to coronary artery disease, and to evaluate possible correlations with Body Mass Index (BMI) and increased heart weight.

Materials and methods

Subjects: This retrospective study was carried out on forensic postmortem cases investigated between July 2010 and December 2013. To be included, at least one of the major coronary arteries had to have a histologically confirmed luminal thrombus or be narrowed by ≥ 75 % in cross-sectional area, and other causes of death had to be excluded.

All cases included in this study underwent multi-phase post-mortem CT angiography (MPMCTA) and a medico-legal autopsy, as was requested by the public prosecutor. The collection of samples for histological analyses was routinely performed during autopsy. Sampling of coronary arteries was guided by the results of the radiological and the macroscopic autopsy examination of the vessels. Sex, age, BMI, heart weight and its comparison with the predicted weight ranges were noted for every case [13].

Toxicological investigations were performed upon the demand of the inquiring authorities.

85 out of the 2180 cases examined during the study period met the selection criteria. The mean age was 55.18 ± 11.04 years, with 72 men and 13 women.

Radiological investigations

A unenhanced CT scan followed by MPMCTA was performed before the classical autopsy following the standard protocol of MPMCTA [14]. A native CT-scan was performed prior to any manipulation of the body with a 8-row CT-unit (CT LightSpeed 8, GE Healthcare, Milwaukee, WI, USA) using the following scan parameters: field of view (FOV) 50 cm, slice thickness 2.5 mm, interval of reconstruction 2 mm, 120 kVp, 280 mA and 150 second scan time. Post-mortem liquid samples were collected using CT-guidance for toxicological screening and the analysis of cardiac biomarkers. One sided femoral vessel cannulation was then performed under CT-guidance using cannulas (MAQUET GmbH & Co. KG, Rastatt, Germany) with a 16-French diameter for arteries and 18-French for veins. A recently developed pressure-controlled perfusion device (Virtangio®, Fumedica AG, Maquet®, Muri, Switzerland) was used to inject a mixture of contrast agent (Angiofil®, Fumedica AG, Muri, Switzerland) and paraffin oil. The arterial phase of MPMCTA was carried out using the following scan parameters: field of view 50 cm, slice reconstructed thickness 1.25 mm, interval of reconstruction 0.6 mm, 120 kVp, 280 mA, and a scan time of 140 seconds. Scan parameters of the venous and dynamic phases were: field of view 50 cm, slice reconstructed thickness 2.5 mm, interval of reconstruction 1.2 mm, 120 kVp, 280 mA, and a scan time of 140 seconds.

Radiological interpretation

A post-mortem radiological report, edited in consensus by one forensic pathologist specialized in forensic imaging and two radiologists with special training in forensic imaging, was established in all cases, describing all of the findings observed in the unenhanced CT and in each phase of MPMCTA as it is usual in our centre for all cases in which MPMCTA is mandated by the prosecutor. Concerning the description of coronary lesions, the main coronary arteries were divided into proximal, middle and distal segments, according to the nomenclature of the American Heart Association and the guidelines of the Society of Cardiovascular Computed Tomography [15-17]. In all cases, not only the main branches but also side branches such as diagonal and marginal arteries were evaluated on cross sectional images by comparing images of the different phases of MPMCTA, especially of the arterial and dynamic phase. In cases of suspected stenosis or occlusion of one or several of the vessels, Maximum Intensity Projection (MIP), curved reconstructions and multiplanar reconstructions (MPR) of concerned areas were performed in order to estimate the significance of stenosis. As this was a retrospective study, no exact calculation of stenosis was done but they were indicated in the radiological report as significant (≥ 75 % of the lumen) or non significant (≤ 75 % of the lumen) stenosis. Additionally, three-dimensional volume rendering (VR) reconstructions were made in order to give an overview of the coronary anatomy and to indicate the location of the stenosis to the forensic pathologist in charge of the case before carrying out the autopsy. The radiological reading and all reconstructions were performed on an Advantage Windows Workstation (ADW) using and ADW4.3 software (GE Healthcare, Milwaukee, WI, USA). We interpreted a finding as stenosis or vascular

occlusion when a filling defect was observed in the arterial phase that remained stable during the different phases of angiography, especially during the dynamic phase. Filling defects that disappeared during the different phases of MPMCTA were interpreted as artifact as proposed by Grabherr et al. [14] and were not taken into account for this study. For this study, all radiological reports established for medico-legal purposes, were reviewed in order to extract findings concerning coronary arteries (anatomy, permeability/stop of perfusion, stenoses and calcifications).

Autopsy, histological examination and toxicological analyses

Autopsies were performed according to international recommendations for the field of forensics and cardiovascular pathology for deaths considered to result from coronary artery disease [18-20]. Macroscopic and microscopic cardiac examinations, including evaluation of the myocardium and coronary arteries, were performed for all cases. Coronary arteries were transversally cut along the course of the main coronary arteries and branches, such as the diagonal and obtuse marginal branches, and their patency was verified. The labeled segments of coronary arteries were collected and examined histologically. As a detailed description of the radiological exam was available already before autopsy, the areas indicated as stenosis were already suspected before opening the body allowing the guidance of the macroscopic exam and histology sampling. The VR-images were especially useful to estimate the location of such regions of interests for the forensic pathologists. Labelled histological slides were systematically made from the anterior and posterior walls of the left ventricle, the right ventricular outflow tract and the interventricular septum. The slides were stained with H & E and according to the

case with a connective tissue stain (as van Gieson, Masson trichrome stain) and/or with an immunostaining according to the case.

Toxicological analyses were performed by GC-MS on the samples collected before radiological examination.

Statistical analyses

Data were summarized using mean values (SD) for continuous variables and number (percent) for categorical ones. The comparisons of the three categories of the coronary pathologies (cases with erosions, ruptures and without thrombosis) were compared for age, BMI and the heart weight using a one-way analysis-of-variance (ANOVA) model with the Bonferroni multiple-comparison tests. The comparison between gender and the numbers of hearts over the predicted weight ranges was tested using the Exact-Fisher test. Analysis was performed using the STATA software (*StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP*).

Ethical aspects

No consent was requested for this study performed retrospectively on codified data.

Results

Cases

Acute coronary thrombosis was found in 57 cases, which included plaque erosion in 26 cases (mean age 46.73 ± 8.33 years) and rupture or intraplaque hemorrhage in 31 cases

(mean age 58.23 ± 10.62 years). Considering that intraplaque haemorrhage may also provoke plaque rupture, the cases of haemorrhage of the plaque are presented in the group of plaque rupture. In 21 cases (3 cases of eroded plaques, 3 cases of intraplaque hemorrhage and 15 cases of plaque rupture) coronary thrombosis was associated with autopsy signs of chronic ischemic disease. Coronary pathology without coronary thrombosis was considered the cause of death in 28 cases (mean age 59.64 ± 9.47 years). For the 13 female cases (mean age 58.23 ± 11.24 years), eroded plaques were found in 4 cases (age range 47-56 years), ruptures in 7 cases (age range 47-89 years) and no thrombosis was found in 2 patients aged 51 and 65 years. Baseline characteristics are summarized in Table 1. Examples of postmortem radiological examination by PMCT and MPMCTA and during autopsy are presented in Figs 1-6.

Erosions were most frequently found in the left anterior descending artery (16/26; 61.5%), while ruptured plaques were more homogeneously distributed in all coronary arteries (see Table 2).

BMI and heart weight

The BMI was in the overweight category ($BMI \geq 25$) for 62 cases (72.3%), with the highest mean BMI in cases with chronic coronary pathology without an acute thrombosis at autopsy. After comparing the heart weight at autopsy with the predicted values, 55 hearts (61.8%) were above the predicted reference values. The highest mean heart weight was observed in the same group. Details are shown in Table 1.

Toxicological analyses

Toxicological analyses were performed for selected cases based on the decision of the district attorney. In two cases of eroded plaques in 24 and 46 year old men, cocaine or its metabolites were detected. Two 55 year old men, with no thromboses found at autopsy, were under methadone substitution with therapeutic and relatively low blood levels of this substance detected during postmortem analyses (290 and 410µg/l).

Statistical analyses

The results are summarized in Tables 1 and 2. Significant differences (p -value <0.0001) were observed for age between cases with coronary erosions and those with ruptured plaques, as well between cases with coronary erosion and those without an acute coronary thrombosis. BMI and heart weight were significantly higher for cases without thrombosis in comparison to those with plaque rupture (p -values 0.023 and 0.003, respectively). Box plots for age, BMI and heart weight for the different categories of coronary pathology are shown in Fig. 7.

Discussion

Pathological studies play a role in understanding the pathomechanisms of disease, and thus ultimately improve the clinical handling of affected patients. Knowledge of coronary artery thrombosis in post-mortem specimens obtained by different investigational methods (autopsy, histological examination, postmortem imaging) might help to improve the detection of vulnerable plaques and prevent sudden cardiac death [2]. In our study, an acute thrombus was found in 66% of cases, which is in accordance with previous

necropsy studies and suggests that a new thrombotic coronary event underlies 50–70% of sudden deaths caused by ischemic heart disease [21,22]. The most frequent underlying mechanism of sudden coronary death from thrombi reported in the literature is plaque rupture (55–65%), followed by plaque erosion (30–35%) and calcified nodules (2–7%) [23]. Plaque erosion is considered to be a common cause of thrombosis in young individuals, especially women less than 50 years of age [23]. In our study, the individuals with plaque erosions were younger than those with ruptures, which is consistent with the literature. The percentage of plaque erosion for all patients (45.61%) was higher than previously reported. This could be partially explained by the fact that victims of sudden coronary death autopsied in a forensic setting tend to be younger than those in studies of hospitalised patients [2,24]. Recently, an increase in sudden death from coronary artery disease in young adults was reported [25], which is in concordance with our findings.

Pathological studies on the spatial distribution of coronary lesions have indicated that vulnerable plaques are concentrated in the proximal portions of the LAD and the left circumflex coronary (CX) arteries, and are more uniformly distributed in the right coronary artery (RCA) [26,21]. According to Cheruvu et al, ruptured plaques and thin-cap fibroatheromas (TCFA) cluster in the proximal LAD and CX arteries [26]. An angiographic study performed by Wang et al showed that coronary occlusions tend to cluster within the proximal third of each of the vessels and that with each 10-mm increase in distance from the ostium the risk of an acute coronary occlusion decreases by 13% in the RCA, 30% in the LAD artery, and 26% in the CX artery [27]. In our study, 82% of ruptures and 77% of erosions were situated in the proximal segments of the

main coronary arteries. When including the first obtuse marginal artery, the percentages rise to 88% and 85%, respectively. Erosions were most frequently found in the LAD artery (61.5%), while only 36% of ruptures were observed in this artery.

According to recommendations for the field of forensic and cardiovascular pathology [18-20], a death can be certified as related to coronary artery disease in the presence of a stable atherosclerotic plaque with luminal stenosis $>75\%$, with or without a healed myocardial infarction, if no other cause of death is observed during autopsy and other complementary examinations [18-20]. Recently, Narula et al showed that stenoses with a cross-sectional area of more than 75% of the lumen were seen in 70% of ruptured plaques, and that only 5% of the ruptured plaques were associated with stenoses less than 50% in diameter [28]. Cardiologists have reported that the presence and extent of $\geq 50\%$ coronary stenoses at coronary angiography are closely associated with an increased risk of having a future cardiac event, and that although to a slightly lesser extent, even $< 50\%$ coronary stenoses are also strongly associated with future cardiac events [29,30]. This discordance between the degree of stenosis at autopsy and the degree noted in coronary angiography was already reported four decades ago. It is recognised that histological evaluation overestimates the degree of stenosis by 25-30% when compared to the angiographic method [4,31]. It was also demonstrated that the lack of concordance between the methods was not a function of the severity of stenosis [32].

In clinical practice, multi-detector computed tomography angiography (MDCTA) represents an important tool for the diagnosis of acute coronary syndromes and stable angina, and has a very important role in the measurement of the degree of coronary

stenosis. There are, however, limitations and potential errors in interpreting the degree of stenosis using coronary MDCTA [29]. The major limitations are coronary blurring and blooming artifacts caused by calcified plaques which are responsible for the false identification of stenoses over 50% of the lumen on coronary MDCTA [33,29]. Coronary artery calcification, although known as a well-established predictor of future cardiac events, is not a predictor of an unstable plaque. In a recent study, Otsuka et al showed that stable plaques show greater calcification than unstable plaques [34]. In clinical practice, many authors have underlined the importance of distinguishing vulnerable plaques from stable plaques with the use of imaging [2,35,36]. From the pathological point of view, the thickness of the fibrous cap is considered the best discriminator of plaque vulnerability before macrophage infiltration and necrotic core [28], but the spatial resolution of MDCT is too low to accurately determine cap thickness and differentiate between the lipid and fibrous plaque due to the overlapping of Hounsfield units [29]. It was recently reported that a ring-like enhancement observed in MDCTA might help assess of thickness of the fibrous cap [37].

Elevated BMI and increased heart weight are considered to be associated with unstable coronary artery disease [24,38], and our results are in accordance with these observations. Wolk et al reported that in a group of patients with established atherosclerosis, those with a BMI of 25.6 to 27.6 had a significantly greater risk of an unstable coronary syndrome than those with normal BMI (<25.6) [39]. Although the exact mechanisms remain unknown, the suggested underlying mechanism is that obesity, acting through hyperlipidemia and inflammation, may increase the vulnerability of the atheromatous plaque to rupture. The mean BMI in our cases was 28.20 ± 5.96 and

was highest for chronic ischemic heart disease cases (30.30 ± 6.9). An increased heart weight was reported for the advanced stages of ischemic heart disease [24,38]. When we compared the heart weight at autopsy in this study to the reference values [13], we found that the hearts which were the most over their references values were from individuals who had chronic ischemic heart disease.

In postmortem examination, Morgan et al evaluated the accuracy of targeted PMCTA compared to histological sections by the assessment of twenty-five vessels and 568 histological sections. They concluded that PMCTA is not a perfect replacement for the histological examination of coronary vessels as it has a sensitivity of 85.7% and specificity of 91.5% for the identification of critical stenoses and is not very reliable when evaluating dense calcifications [11]. Michaud et al evaluated the diagnostic value of MPMCTA for the investigation of sudden cardiac death related to atherosclerotic coronary artery disease, and suggested that MPMCTA is a reasonable tool to view the morphology of coronary arteries, rule out coronary artery stenosis and occlusion and evaluate coronary calcifications [40]. Although MPMCTA can perfectly visualize the coronary arteries, no guidelines exist yet concerning post-mortem radiological evaluation of coronary arteries and we had to learn how to interpret the radiological images. In MPMCTA, the most essential is to compare the different phases of angiography. Concerning the coronary arteries, a detailed correlation between the arterial and dynamic phase is essential. Any stenosis or occlusion of a coronary artery, visible in the arterial phase of MPMCTA has to be searched for and verified in the dynamic phase, as remaining blood in the vessels can mimic a real stenosis. Therefore, according to Grabherr et al. such artifacts have to be ruled out [14]. Although MPMCTA

seems to be an excellent tool to find and estimate the degree of a stenosis or occlusion, it cannot explain the exact pathomorphological lesion leading to it. Our first observations concerning radiological evaluation of eroded plaques suggest that the only visible sign in PMCTA is the presence of a focal stenosis, which doesn't have to be significant and which therefore doesn't catch the full attention during the radiological reading. In order to further investigate the use of MPMCTA, keys and guidelines for the radiological interpretation are needed. In this retrospective study, MPMCTA was therefore only used in order to better guide the histological sampling. However, in future, MPMCTA may represent a valuable tool for coronary-artery investigation. A prospective study to evaluate degree of stenosis compared to the results of autopsy and histology would be of interest in the near future in order to investigate the performance of the technique for this purpose.

In conclusion, our results are in accordance with previous studies on the spatial distribution of vulnerable plaques. We did, however, observe a higher percentage of eroded plaques than that previously reported, which could be explained by the changes in the epidemiology of acute coronary syndromes. Our findings are also compatible with the hypothesis indicating that increased BMI and overweight hearts are associated with chronic ischemic heart disease. In our opinion, more comparative studies of coronary artery thrombosis in post-mortem specimens, obtained by different investigational tools in the forensic context (autopsy, histology, modern postmortem imaging), will improve the detection and understanding of vulnerable plaques in living patients and help prevent sudden cardiac death. Post mortem coronary CT angiography is a relative new field in radiology, hence more comprehensive and larger studies are needed to

encourage the diffusion, the use and the evaluation of this technique.

Limitations

The limitations of the study are inherent to the retrospective design of the study.

References

1. Chugh SS, Reinier K, Teodorescu C, Evanado A, Kehr E, Al Samara M, Mariani R, Gunson K, Jui J (2008) Epidemiology of Sudden Cardiac Death: Clinical and Research Implications. *Progress in Cardiovascular Diseases* 51 (3):213-228. doi:10.1016/j.pcad.2008.06.003
2. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R (2013) Update on acute coronary syndromes: the pathologists' view. *European heart journal* 34 (10):719-728. doi:10.1093/eurheartj/ehs411
3. Giugliano RP, Braunwald E (2014) The Year in Acute Coronary Syndrome. *Journal of the American College of Cardiology* 63 (3):201-214. doi:10.1016/j.jacc.2013.10.041
4. Stone GW, Narula J (2013) The Myth of the Mild Vulnerable Plaques. *JACC: Cardiovascular Imaging* 6 (10):1124-1126. doi:10.1016/j.jcmg.2013.09.002
5. Friedewald VE, Ambrose JA, Stone GW, Roberts WC, Willerson JT (2008) The Editor's Roundtable: The Vulnerable Plaque. *The American Journal of Cardiology* 102 (12):1644-1653. doi:10.1016/j.amjcard.2008.09.001
6. Inokuchi G, Yajima D, Hayakawa M, Motomura A, Chiba F, Torimitsu S, Makino Y, Iwase H (2013) The utility of postmortem computed tomography selective coronary angiography in parallel with autopsy. *Forensic Sci Med Pathol* 9 (4):506-514. doi:10.1007/s12024-013-9473-z

7. Grabherr S, Djonov V, Yen K, Thali MJ, Dirnhofer R (2007) Postmortem angiography: review of former and current methods. *AJR American journal of roentgenology* 188 (3):832-838. doi:10.2214/AJR.06.0787
8. Oliva A, Brugada R, D'Aloja E, Boschi I, Partemi S, Brugada J, Pascali VL (2011) State of the Art in Forensic Investigation of Sudden Cardiac Death. *The American Journal of Forensic Medicine and Pathology* 32 (1):1-16
10.1097/PAF.1090b1013e3181c1092dc1096
9. Bajanowski T, Püschel K, Dettmeyer R (2012) Plötzlicher Herztod. *Pathologe* 33 (3):217-227. doi:10.1007/s00292-011-1556-6
10. Roberts ISD, Traill ZC (2014) Minimally invasive autopsy employing post-mortem CT and targeted coronary angiography: evaluation of its application to a routine Coronial service. *Histopathology* 64 (2):211-217. doi:10.1111/his.12271
11. Morgan B, Biggs MJ, Barber J, Raj V, Amoroso J, Hollingbury FE, Robinson C, Ruddy GN (2013) Accuracy of targeted post-mortem computed tomography coronary angiography compared to assessment of serial histological sections. *Int J Legal Med* 127 (4):809-817. doi:10.1007/s00414-012-0790-7
12. Michaud K, Grabherr S, Doenz F, Mangin P (2012) Evaluation of postmortem MDCT and MDCT-angiography for the investigation of sudden cardiac death related to atherosclerotic coronary artery disease. *The international journal of cardiovascular imaging* 28 (7):1807-1822. doi:10.1007/s10554-012-0012-x
13. Vanhaebost J, Faouzi M, Mangin P, Michaud K (2014) New reference tables and user-friendly Internet application for predicted heart weights. *Int J Legal Med* 128 (4):615-620. doi:10.1007/s00414-013-0958-9

14. Grabherr S, Doenz F, Steger B, Dirnhofer R, Dominguez A, Sollberger B, Gygax E, Rizzo E, Chevallier C, Meuli R, Mangin P (2011) Multi-phase post-mortem CT angiography: development of a standardized protocol. *Int J Legal Med* 125 (6):791-802. doi:10.1007/s00414-010-0526-5
15. Raff GL, Chair, Abidov A, Achenbach S, Berman DS, Boxt LM, Budoff MJ, Cheng V, DeFrance T, Hellinger JC, Karlsberg RP (2009) SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. *Journal of Cardiovascular Computed Tomography* 3 (2):122-136. doi:10.1016/j.jcct.2009.01.001
16. Kini S, Bis KG, Weaver L (2007) Normal and Variant Coronary Arterial and Venous Anatomy on High-Resolution CT Angiography. *American Journal of Roentgenology* 188 (6):1665-1674. doi:10.2214/AJR.06.1295
17. Sundaram B, Patel S, Bogot N, Kazerooni EA (2009) Anatomy and Terminology for the Interpretation and Reporting of Cardiac MDCT: Part 1, Structured Report, Coronary Calcium Screening, and Coronary Artery Anatomy. *American Journal of Roentgenology* 192 (3):574-583. doi:10.2214/AJR.08.1177
18. Brinkmann B (1999) Harmonisation of medico-legal autopsy rules. *Int J Legal Med* 113 (1):1-14. doi:DOI 10.1007/s004140050271
19. Basso C, Burke M, Fornes P, Gallagher PJ, de Gouveia RH, Sheppard M, Thiene G, van der Wal A, Association for European Cardiovascular P (2008) Guidelines for autopsy investigation of sudden cardiac death. *Virchows Archiv : an international journal of pathology* 452 (1):11-18. doi:10.1007/s00428-007-0505-5

20. Saukko P, Knight B (2004) Knight's Forensic Pathology. 3 edition edn. Hodder Arnold,
21. Farb A, Tang AL, Burke AP, Sessums L, Liang Y, Virmani R (1995) Sudden Coronary Death: Frequency of Active Coronary Lesions, Inactive Coronary Lesions, and Myocardial Infarction. *Circulation* 92 (7):1701-1709. doi:10.1161/01.cir.92.7.1701
22. Davies MJ (2000) The pathophysiology of acute coronary syndromes. *Heart* 83 (3):361-366. doi:10.1136/heart.83.3.361
23. Sakakura K, Nakano M, Otsuka F, Ladich E, Kolodgie FD, Virmani R (2013) Pathophysiology of Atherosclerosis Plaque Progression. *Heart, Lung and Circulation* 22 (6):399-411. doi:10.1016/j.hlc.2013.03.001
24. Roberts WC, Potkin BN, Solus DE, Reddy SG (1990) Mode of death, frequency of healed and acute myocardial infarction, number of major epicardial coronary arteries severely narrowed by atherosclerotic plaque, and heart weight in fatal atherosclerotic coronary artery disease: Analysis of 889 patients studied at necropsy. *Journal of the American College of Cardiology* 15 (1):196-203. doi:10.1016/0735-1097(90)90201-Y
25. Arzamendi D, Benito B, Tizon-Marcos H, Flores J, Tanguay JF, Ly H, Doucet S, Leduc L, Leung TK, Campuzano O, Iglesias A, Talajic M, Brugada R (2011) Increase in sudden death from coronary artery disease in young adults. *American Heart Journal* 161 (3):574-580. doi:10.1016/j.ahj.2010.10.040
26. Cheruvu PK, Finn AV, Gardner C, Caplan J, Goldstein J, Stone GW, Virmani R, Muller JE (2007) Frequency and Distribution of Thin-Cap Fibroatheroma and

- Ruptured Plaques in Human Coronary Arteries: A Pathologic Study. *Journal of the American College of Cardiology* 50 (10):940-949. doi:10.1016/j.jacc.2007.04.086
27. Wang JC, Normand S-LT, Mauri L, Kuntz RE (2004) Coronary Artery Spatial Distribution of Acute Myocardial Infarction Occlusions. *Circulation* 110 (3):278-284. doi:10.1161/01.cir.0000135468.67850.f4
28. Narula J, Nakano M, Virmani R, Kolodgie FD, Petersen R, Newcomb R, Malik S, Fuster V, Finn AV (2013) Histopathologic Characteristics of Atherosclerotic Coronary Disease and Implications of the Findings for the Invasive and Noninvasive Detection of Vulnerable Plaques. *Journal of the American College of Cardiology* 61 (10):1041-1051. doi:10.1016/j.jacc.2012.10.054
29. Kim H, Yoo S, Rho J, Lee H, White C (2014) MDCT evaluation of atherosclerotic coronary artery disease: What should radiologists know? *The international journal of cardiovascular imaging*:1-11. doi:10.1007/s10554-014-0411-2
30. Lin FY, Shaw LJ, Dunning AM, LaBounty TM, Choi J-H, Weinsaft JW, Koduru S, Gomez MJ, Delago AJ, Callister TQ, Berman DS, Min JK (2011) Mortality Risk in Symptomatic Patients With Nonobstructive Coronary Artery Disease: A Prospective 2-Center Study of 2,583 Patients Undergoing 64-Detector Row Coronary Computed Tomographic Angiography. *Journal of the American College of Cardiology* 58 (5):510-519. doi:10.1016/j.jacc.2010.11.078
31. Grondin CM, Dyrda I, Pasternac A, Campeau L, Bourassa MG, Lesperance J (1974) Discrepancies Between Cineangiographic and Postmortem Findings in Patients with

Coronary Artery Disease and Recent Myocardial Revascularization. *Circulation* 49 (4):703-708. doi:10.1161/01.cir.49.4.703

32. Mann JM, Davies MJ (1995) Assessment of the severity of coronary artery disease at postmortem examination. Are the measurements clinically valid? *Br Heart J* (74(5)): 528-530. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC484074/>
33. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, Rubin GD, Kramer CM, Taylor AJ, Berman D, Brown A, Chaudhry FA, Cury RC, Desai MY, Einstein AJ, Gomes AS, Harrington R, Hoffmann U, Khare R, Lesser J, McGann C, Rosenberg A, Schwartz R, Shelton M, Smetana GW, Smith Jr SC, Wolk MJ, Allen JM, Bailey S, Douglas PS, Hendel RC, Kramer CM, Min J, Patel MR, Shaw L, Stainback RF (2010) ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography. *Journal of Cardiovascular Computed Tomography* 4 (6):407.e401-407.e433. doi:10.1016/j.jcct.2010.11.001
34. Otsuka F, Finn AV, Virmani R (2013) Do vulnerable and ruptured plaques hide in heavily calcified arteries? *Atherosclerosis* 229 (1):34-37. doi:10.1016/j.atherosclerosis.2012.12.032
35. Camici PG, Rimoldi OE, Gaemperli O, Libby P (2012) Non-invasive anatomic and functional imaging of vascular inflammation and unstable plaque. *European heart journal* 33 (11):1309-1317. doi:10.1093/eurheartj/ehs067
36. Sadeghi MM, Glover DK, Lanza GM, Fayad ZA, Johnson LL (2010) Imaging Atherosclerosis and Vulnerable Plaque. *Journal of Nuclear Medicine* 51 (Supplement 1):51S-65S. doi:10.2967/jnumed.109.068163

37. Kashiwagi M, Tanaka A, Kitabata H, Tsujioka H, Kataiwa H, Komukai K, Tanimoto T, Takemoto K, Takarada S, Kubo T, Hirata K, Nakamura N, Mizukoshi M, Imanishi T, Akasaka T (2009) Feasibility of Noninvasive Assessment of Thin-Cap Fibroatheroma by Multidetector Computed Tomography. *JACC: Cardiovascular Imaging* 2 (12):1412-1419. doi:10.1016/j.jcmg.2009.09.012
38. Zhang M, Shields J, Zhang Y, Li L, Fowler D, Zhao Z, Burke A (2012) Correlation between coronary plaque burden and heart weight. *Pathology - Research and Practice* 208 (10):610-614. doi:10.1016/j.prp.2012.07.007
39. Wolk R, Berger P, Lennon RJ, Brilakis ES, Somers VK (2003) Body Mass Index: A Risk Factor for Unstable Angina and Myocardial Infarction in Patients With Angiographically Confirmed Coronary Artery Disease. *Circulation* 108 (18):2206-2211. doi:10.1161/01.cir.0000095270.85646.e8
40. Michaud K, Grabherr S, Doenz F, Mangin P (2012) Evaluation of postmortem MDCT and MDCT-angiography for the investigation of sudden cardiac death related to atherosclerotic coronary artery disease. *The international journal of cardiovascular imaging* 28 (7):1807-1822. doi:10.1007/s10554-012-0012-x

Legends:

Fig.1 Ruptured plaque of the proximal LAD in a 47 year old man: (a) axial image at the level of the LAD, reconstructed in the native PMCT showing several calcified plaques of arteriosclerosis (arrows) in its proximal and middle part without the possibility to evaluate the degree of stenosis or the presence of an eventual occlusion of the vessel. After contrast injection, the vascular lumen can be evaluated. The arterial phase of MPMCTA allows the visualization of a severe nearly completely occluding stenosis (arrows) in the proximal part shown in a coronal multi-intensity reconstruction (b) and in the 3D-volume rendering reconstructions, performed to orientate the forensic pathologist of the localization of findings before starting the autopsy (c). Histological examination, using H&E stain, confirms the sub-occlusion of the indicated region and allows for the diagnosis of a ruptured plaque.

Fig.2 Chronic atherosclerotic lesions without thrombosis in a 62 year old man who died while cycling: (a) axial image at the level of the LAD reconstruction after native PMCT shows multiple calcified arteriosclerotic plaques of all branches of the left coronary artery. The 3D-volume rendering reconstruction of the arterial phase of MPMCTA (b) shows massive calcifications of the vascular wall, but since the vascular lumen is only filiforme, an evaluation of stenosis could not be obtained using this reconstruction. Stenosis analysis software allows curved reconstructions and therefore the “unrolling” of each coronary artery and gives a better view on the vascular lumen (c: unrolled circumflex artery). Histological analysis confirms the presence of a permeable vascular lumen with a calcified vascular wall (d) H&E stain of the circumflex artery.

Fig.3 An eroded plaque of LAD in a 53 year old woman with multiple spots of arteriosclerosis on all branches of the coronary artery, visible in native CT-scan (a). A first reading of the radiological images by an inexperienced reader concluded that changes were due to artifact. Experienced readers should see the long and thin continuation of the perfusion at the level of the stenosis (arrows in b), that would lead to the diagnosis of an intra-vital occlusion. Autopsy and histology confirmed the presence of the partial occlusion and led to the diagnosis of an eroded plaque as its origin (c).

Fig 4 A 39 year old man found dead in the bathtub. Familial history of SCD; toxicology was negative. MPMCTA showed well perfused coronary arteries with the presence of a filling defect in the proximal part of the LAD (a). A zoom in the region inside the yellow box in (a) shows the “whole looking sign” (arrows in b and c) indicating an intra-plaque haemorrhage (b) which might correspond to the napkin ring sign. The same sign is visible in a 3D-volume rendering model of the arterial phase of MPMCTA (b). An axial reconstruction in the axes of the vessel (d) gives similar images to those seen histologically, (e) which confirmed the diagnosis. Axial image of the native CT-scan showing only one spotty calcification at the level of the proximal LAD (circle in a).

Fig.5 Old recannalised thrombosis in a 67 year old man found dead at home: native MDCT shows multiple coronary calcifications (a), MPMCTA did allow to find multiple stenosis of all three coronary arteries (b) and especially of the right coronary artery in its proximal part (arrow in b). The 3D-volume rendering reconstruction of the arterial phase of MPMCTA depicts the multiple stenosis of the coronary arteries (c) and a nearly complete occlusion in the proximal part of the RCA (arrow in c). The histological examination of this region identified an hemorrhage in a recannalised thrombus as cause of this subocclusion (d,e)

Fig.6 The 3D-reconstruction of the arterial phase of MPMCTA shows a significant stenosis in the distal part of LAD (arrow in b), leading to the suspicion of an intra-vital stenosis. Macroscopic investigation of the myocardium shows a red discoloration of the anterior wall of the left ventricle (d). Histology of the indicated part of the LAD confirms the intra-vital stenosis due to a fresh thrombosis of the vascular lumen (d).

Fig. 7 Box plots for age, BMI and heart weight for cases without thrombosis, and those with eroded and ruptured plaques.

Table1 Baseline characteristics of pathological findings; BMI body mass index, * exact Fisher test, **ANOVA test

Table 2 Spatial distribution of acute coronary thromboses in cases of sudden cardiac death (rupture versus erosion); LAD, left anterior descending artery; CX, left circumflex coronary artery; RCA, right coronary artery

Figure 1

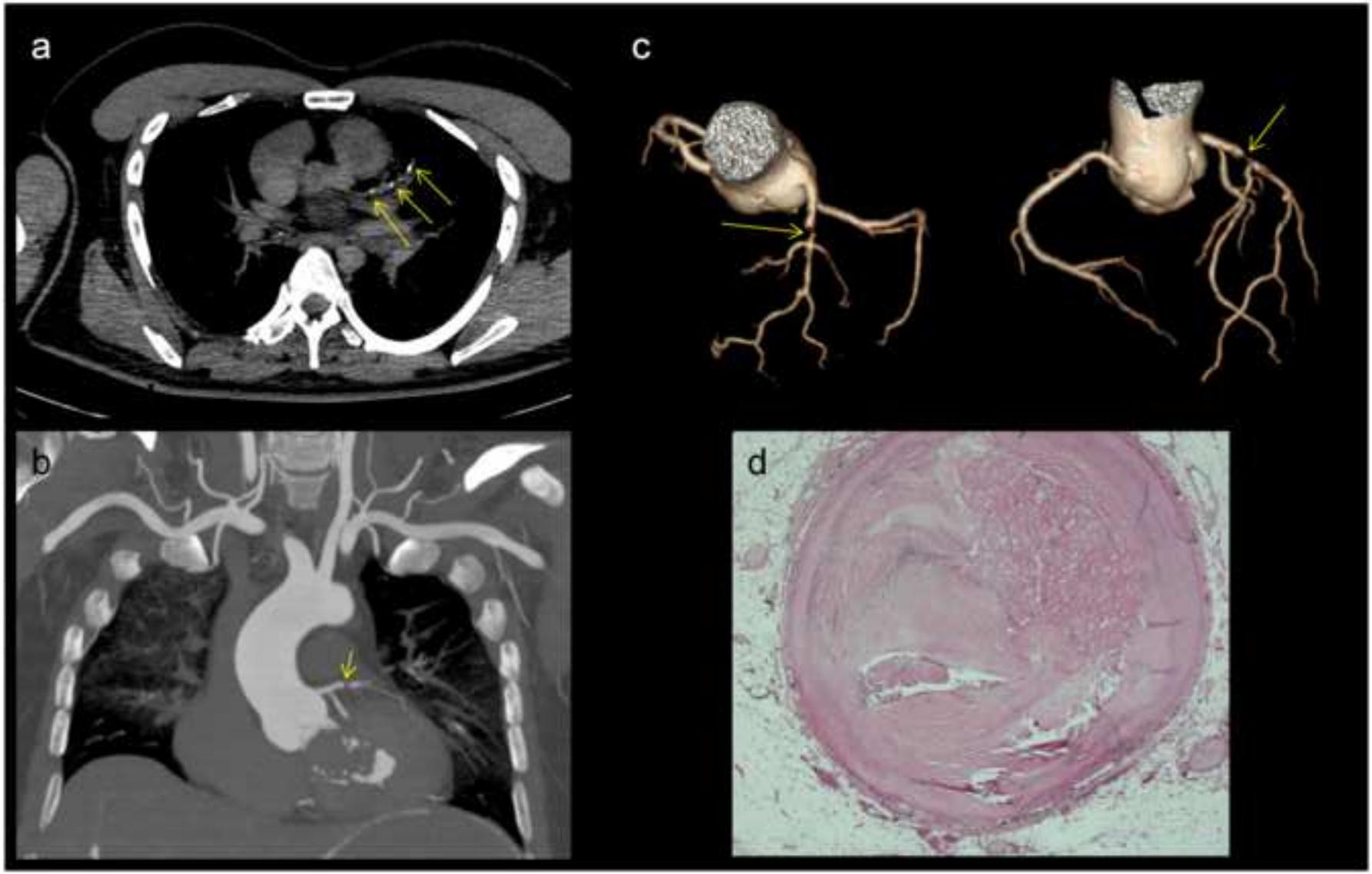


Fig. 1

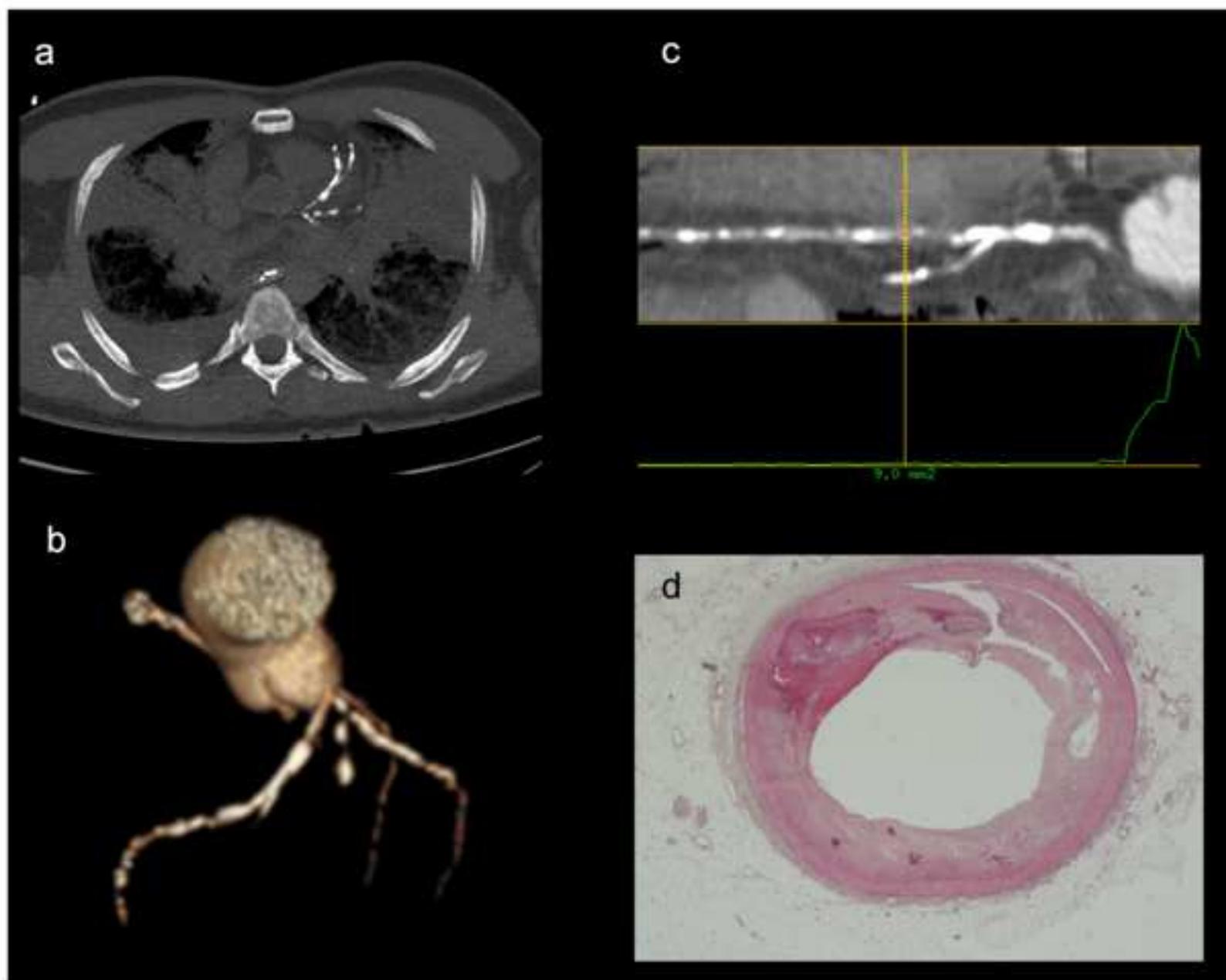


Fig. 2

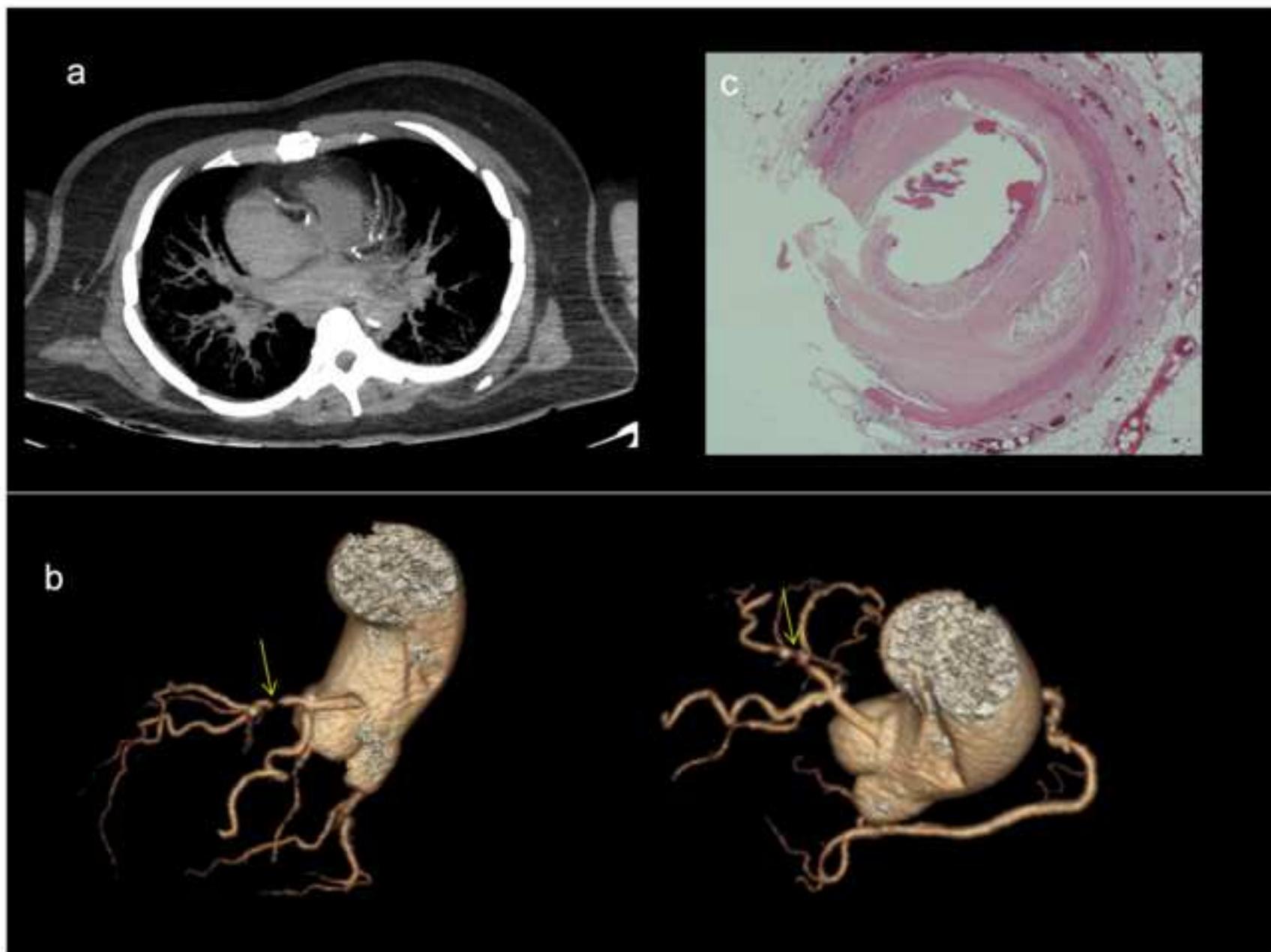


Fig. 3

Figure 4

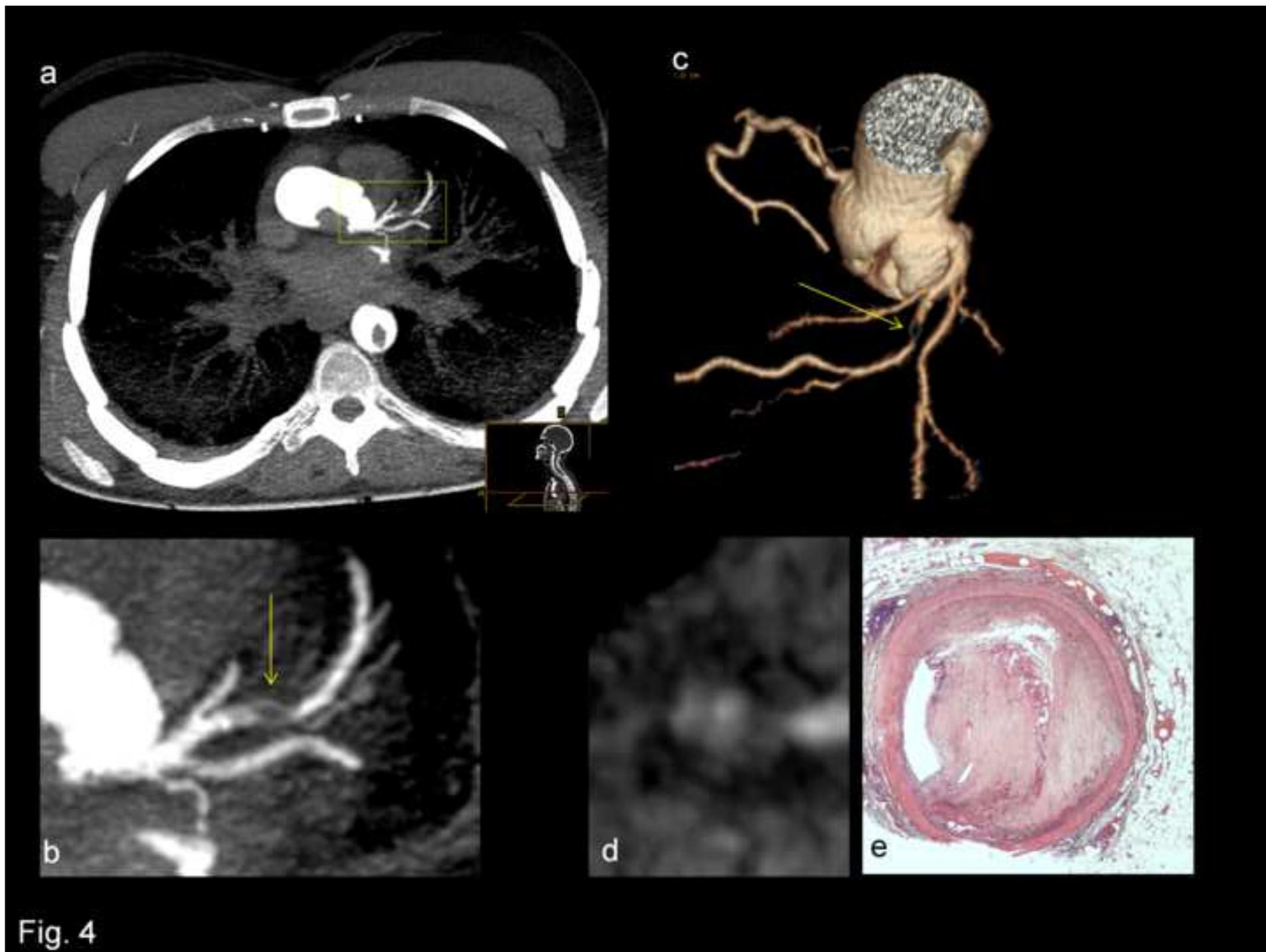


Fig. 4

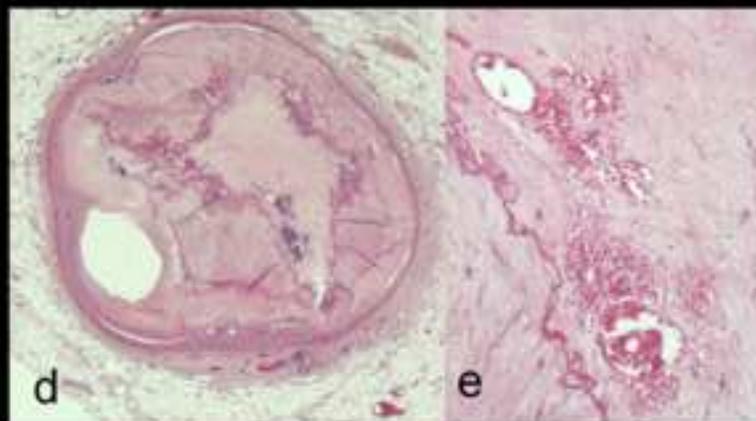
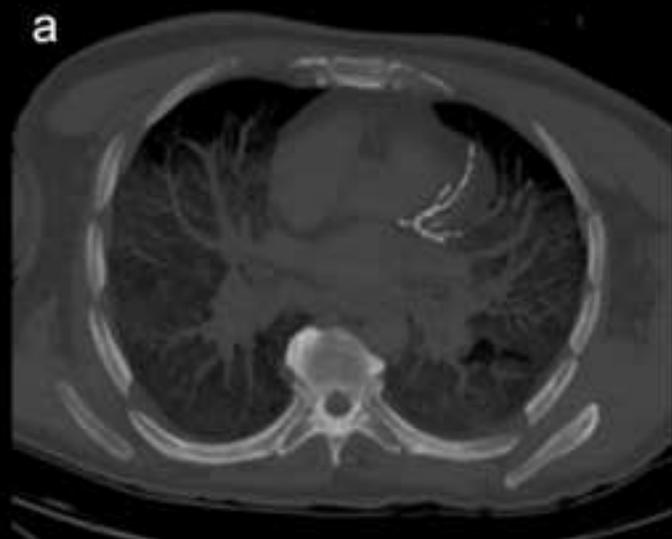


Fig. 5

Figure 6

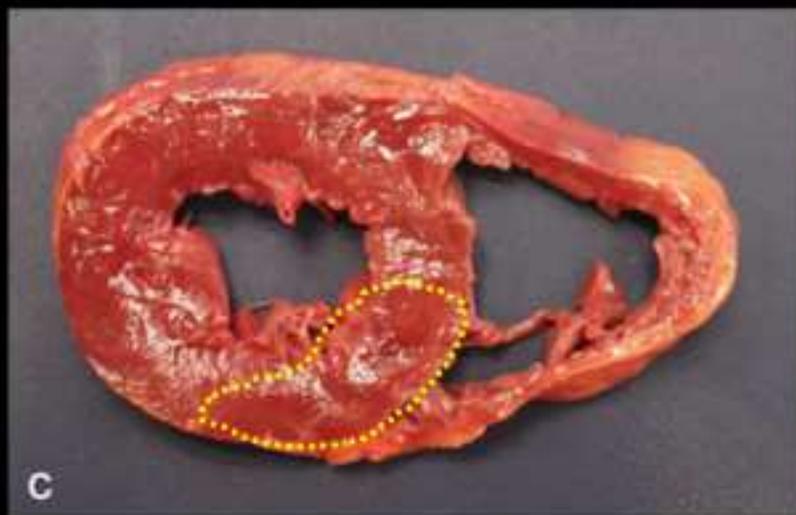


Fig. 6

Figure 7

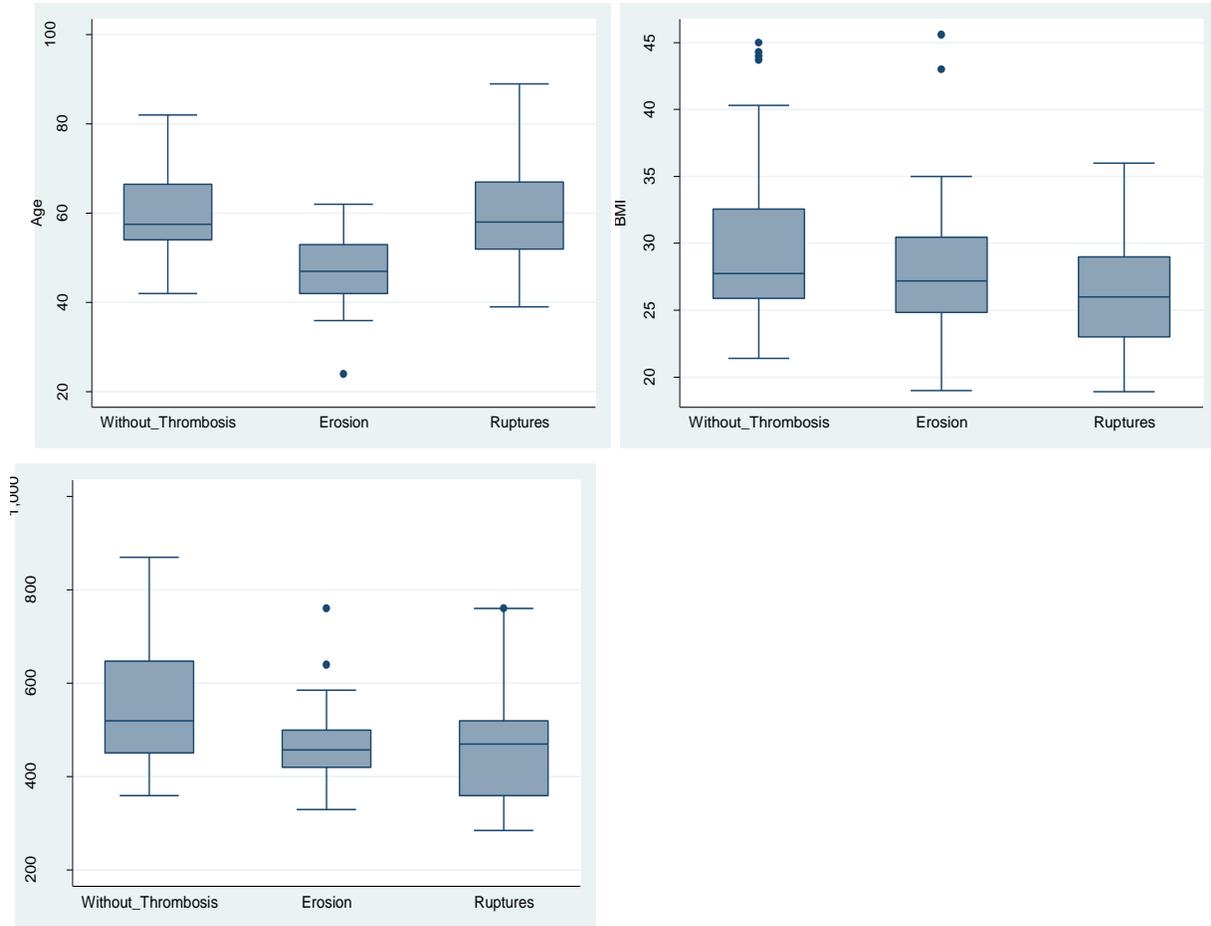


Fig. 7 Box plots for age, BMI and heart weight for cases without thrombosis, with eroded plaques and ruptured plaques

Table 1

	All cases N (%)	Ruptures N (%)	Erosions N (%)	Without thrombosis N (%)	<i>p</i> -value
Total	85 (100)	31(36.47)	26 (30.59)	28 (32.94)	
Sex (men)	72 (84.71)	24 (77.42)	22 (84.62)	26 (92.86)	*0.285
Hearts over predicted values range	52 (61.18)	16(51.61)	17(65.38)	19(67.86)	*0.461
	All cases mean (SD) [min, max]	Ruptures mean (SD) [min, max]	Erosions mean (SD) [min, max]	Without thrombosis mean (SD) [min, max]	<i>p</i> -value
Age	55.18 (11.04) [24,89]	58.23 (10.62) [39,89]	46.73 (8.33) [24.62]	59.64 (9.47) [42,82]	**<0.0001
BMI	28.20 (5.96) [18.90, 45.60]	26.18 (4.13) [18.90, 36.00]	28.34 (6.13) [19.00, 45.60]	30.30 (6.9) [21.40, 45.00]	**0.0278
Heart weight (g)	487.87 (114.96) [285, 870]	449.03 (102.03) [285, 760]	471.54 (92.01) [330, 760]	546.04 (127.33) [360, 870]	**0.0028

Table1 **Baseline characteristics of pathological findings**; BMI body mass index, * exact Fisher test, **ANOVA test

Table 2

	N (%)	coronary artery	N (%)	segment of coronary artery	N (%)
Erosions	26/57 (45.61)	LAD	16/26 (61.54)	proximal middle	14/16 (87.5) 2/16 (12.5)
		CX	4/26 (15.39)	proximal first obtuse marginal	1/4 (25) 3/4 (75)
		RCA	6/26 (23.08)	proximal middle	5/6 (83.3) 1/6 (16.7)
Ruptures	31/57 (54.39)	LAD	11/31 (35.48)	proximal middle	10/11 (90.91) 1/11 (9.09)
		CX	9/31 (29.03)	proximal first obtuse marginal	7/9 (77.78) 2/9 (22.22)
		RCA	11/31 (35.48)	proximal middle	9/11 (81.82) 2/11 (18.18)

Table 2 **Spatial distribution of acute coronary thromboses in cases of sudden cardiac death (rupture versus erosion);** LAD, left anterior descending artery; CX, left circumflex coronary artery; RCA, right coronary artery