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Sudden Aortic Death - proposal for a comprehensive diagnostic approach in forensic and in clinical pathology practice

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Abstract:	Aortic rupture or dissection as immediate cause of sudden death is encountered in forensic and clinical autopsy practice. Despite a common denominator of "Sudden Aortic Death" (SAD), we expect that in both settings the diagnostic workup, being either primarily legal or primarily disease related, differs substantially, which may affect the eventual diagnoses. We retrospectively reviewed case records of deceased persons who fitted a diagnosis of SAD in the continuous autopsy cohorts in a forensic (Suisse) and a clinical setting (The Netherlands). Clinical characteristics, data from post-mortem imaging, tissue blocks for histological analysis and results of ancillary studies were reviewed for its presence and outcome. SAD was found in 7.7% in the forensic versus 2.2% in the clinical autopsies. In the forensic setting, autopsy was always combined with post-mortem imaging, showing variable outcome on detection of aortic disruption and/or pericardial bleeding. Histology of aorta was performed in 12/35, mostly in the natural deaths. In the clinical setting, histology of the aorta was available in all cases, but post-mortem imaging in none. In both settings, underlying aortic disease was mostly cystic medial degeneration, atherosclerosis or a combination of both, with occasional rare unexpected diagnosis. Also in both, a genetic cause of aortic dissection was revealed in a minority (three cases). Sudden aortic death (SAD) is more commonly encountered in a forensic than in a clinical setting. Major differences in the approach of SAD between these settings coincide with similarities in causes of death and underlying diseases. To ensure a correct diagnosis, we recommend that the investigation of SAD includes a study of the medical history, a full autopsy with histology of major organs including aorta, and

	storage of material for toxicological and genetic testing. Post-mortem radiological examination, useful for documentation and screening purposes, is feasible as non-invasive alternative when autopsy is not possible but cannot substitute a full autopsy.

Sudden Aortic Death- proposal for a comprehensive diagnostic approach in forensic and in clinical pathology practice

ABSTRACT

Backgrounds Aortic rupture or dissection as immediate cause of sudden death is encountered in forensic and clinical autopsy practice. Despite a common denominator of "Sudden Aortic Death" (SAD), we expect that in both settings the diagnostic workup, being either primarily legal or prim arily disease related, differs substantially, which may affect the eventual diagnoses.

Methods We retrospectively reviewed case records of deceased persons who fitted a diagnosis of SAD in the continuous autopsy cohorts in a forensic (Suisse) and a clinical setting (The Netherlands). Clinical characteristics, data from post-mortem imaging, tissue blocks for histological analysis and results of ancillary studies were reviewed for its presence and outcome.

Results SAD was found in 7.7% in the forensic versus 2.2% in the clinical autopsies. In the forensic setting, autopsy was always combined with post-mortem imaging, showing variable outcome on detection of aortic disruption and/or pericardial bleeding. Histology of aorta was performed in 12/35, mostly in the natural deaths. In the clinical setting, histology of the aorta was available in all cases, but post-mortem imaging in none. In both settings, underlying aortic disease was mostly cystic medial degeneration, atherosclerosis or a combination of both, with occasional rare unexpected diagnosis. Also in both, a genetic cause of aortic dissection was revealed in a minority (three cases).

Conclusion Sudden aortic death (SAD) is more commonly encountered in a forensic than in a clinical setting. Major differences in the approach of SAD between these settings coincide with similarities in causes of death and underlying diseases. To ensure a correct diagnosis, we recommend that the investigation of SAD includes a study of the medical history, a full autopsy with histology of major organs including aorta, and storage of material for toxicological and genetic testing. Post-mortem radiological examination, useful for documentation and screening purposes, is feasible as non-invasive alternative when autopsy is not possible but cannot substitute a full autopsy.

Keywords: aorta; dissection; rupture; sudden death; forensic autopsy

1. INTRODUCTION

Forensic and clinical pathologists are regularly confronted with sudden unexpected death. In case of an aortic rupture, perforation or dissection, the immediate cause of death is usually easily recognized at autopsy or post-mortem imaging. Examples are cerebral hypoxia due to massive internal haemorrhage or a cardiac tamponade due to retrograde extension of a dissection of the thoracic aorta. The onset of an aortic disruption can be purely traumatic. However, when also natural underlying aortic disease is involved, these may vary to a great extent, ranging from age-related and acquired disorders of the aortic wall to distinct hereditary syndromes [1, 2].

As such, sudden death due to aortic rupture, dissection or perforation shows analogies with sudden cardiac death [3]. In both, a similar clinical presentation of sudden unexpected death, being witnessed or unwitnessed, can be initiated by a wide range of undering diseases. Also in both, the recognition of a hereditary/genetic component has important implications for the relatives of the deceased and can only be identified by a thorough diagnostic workup. In order to study the relation between aortic diseases and sudden death we therefore propose the concept of 'Sudden Aortic Death' (SAD). This includes all sudden and unexpected, natural or unnatural deaths due to aortic rupture, perforation or dissection. In contrast to the definition of sudden *cardiac* death, which is limited to natural deaths, our definition of sudden aortic death includes unnatural deaths as well. This is because in some cases of SAD an apparent unnatural death (e.g. a traffic accident) may be initiated by a natural cause (e.g. aortic rupture due to a hereditary connective tissue disease).

As stated above, SAD can be encountered in either a forensic or clinical setting [4-8]. Since the former primarily focuses on findings pertaining to possible misconduct and the latter focuses more on disease, the scope and extent of an autopsy in case of SAD may differ between the two settings. These differences might subsequently result in either missing an unnatural cause of death in a clinical setting or, on the other hand, lack of reporting important underlying diseases in a forensic setting. An example of the latter would be the presence of a hereditary connective tissue disease such as Marfan's syndrome or Ehlers-Danlos, which predispose for SAD due to aortic dissection and/or aortic rupture.

Currently it is not known to what extent the occurrence or the diagnostic approach of SAD differs between a forensic and clinical setting. The first part of this paper is therefore dedicated to a retrospective survey of the differences between a) the cases and b) the used diagnostic methods in two representative series of SAD, one from a forensic, and one from a clinical setting. This comparison will give insight in to what extent the current clinical and forensic diagnostic methods are sufficient to study all aspects of SAD.

The second part of the manuscript uses the results of our retrospective survey to propose a recommendation that advises the pathologist on how to approach a case of SAD, be it in clinical or in forensic autopsy pathology. Surely there are certainly several guidelines/national recommendations available on how to perform a proper autopsy in case of sudden death, but at present they are hampered by a lack of updated knowledge on how to deal with SAD specifically.

2. Material and Methods

We defined SAD as a sudden, unexpected, natural or unnatural death, directly related to aortic rupture, perforation or dissection. For our retrospective comparison, we included all cases of SAD that were autopsied at the University Center of Legal Medicine (CURML) in Lausanne between January 2013 and December 2014 were compared to the cases of SAD that were autopsied at the Academic Medical Center (AMC) in Amsterdam between January 2010 and July 2015. For the purpose of this article, the subset from the CURML will be referred to as the 'forensic subset' and the cases from the AMC as the 'clinical subset'. The clinical subset covers a longer time period to have two groups of similar size. All cases were retrospectively reviewed for basic demographic and clinical information, for the used diagnostic methods, for differences between radiological and autopsy results, and for the eventual cause, mechanism and manner of death. All cases were autopsied within 72 hours after death.

3. RESULTS

3.1. Demographics

A total of 57 cases were included. The forensic subset from the CURML consisted of 35 cases from a total of 453 autopsies (7.7%). 31 of them were male, 4 were female. Age ranged from 1 to 84 years old, with a mean of 52.1 (Standard Deviation (SD) 24.0). The clinical subset from the AMC included 22 cases from a total of 902 autopsies (2.4%). 14 were male, 8 were female. Age ranged from 17 to 83 years old, with a mean of 63.7 (SD 16.9). These results are summarized in Table 1.

3.2. Diagnostic methods

3.2.1. Forensic subset

In the forensic setting, 14 autopsies were preceded by post-mortem computed tomography without contrast medium injection (PMCT). In 21 cases (60%) multiphase PMCT-angiography (MPMCTA) was performed according to the protocol published by Grabherr *et al.* [10]. MPMCTA was used in 11 cases of the 12 natural deaths and 10 cases of the 23 unnatural deaths.

All forensic cases were autopsied in full, according to the internationally accepted recommendations by Brinkman [11]. Each autopsy included the histological examination of the major organs (brain, heart, liver, kidneys, and lungs) with standard Haematoxylin and Eosin (HE) stained sections. In 12 cases (34.3%), the aortic wall was examined histologically, in all cases with HE stained sections, and in 11 cases with additional stains including Elastic von Gieson (EvG) to visualize the connective tissue skeleton of the aortic media. Of the 23 cases in which the aorta was not examined histologically, 21 were unnatural deaths. 18 of these were accidents or suicides, mostly traffic accidents and falls or jumps from heights, whilst 3 of them were homicides. The two natural deaths in which the aorta was not examined histologically included a patient with a ruptured atherosclerotic aneurysm and a patient who died due to loosening of the sutures two weeks after aortic valve replacement. Material for toxicological and genetic test analyses was collected in all cases in the forensic setting.

To determine the value of post-mortem radiology, we compared the outcomes of PMCT and MPMCTA with autopsy findings for the presence of an aortic lesion, the location of the aortic lesion defect and the presence of pericardial fluid (in keeping with hematopericardium). For all three items, but especially in the identification and localisation of the aortic lesion, MPMCTA was superior to PMCT. However, both modalities did not reach perfect agreement with the autopsy. PMCT missed the presence or the location of an aortic lesion in 10 out of 14 cases (71.4%). For MPMCTA this was in 3 out of 21 cases (14.3%). The presence of pericardial fluid was missed in 7.5% of cases by PMCT, and in none by MPMCTA. PMCT was false positive for the presence or location of aortic lesions in none of the cases, whilst MPMCTA was false positive in one case (4.8%). For the presence of pericardial fluid, PMCT was false positive in 2 cases (14.3%) and MPMCTA in one (4.8%). These results are summarized in Table 2. Figure 1 illustrates MPMCTA imaging in a case of aortic dissection.

3.2.2. Clinical subset

In the clinical subset, none of the cases underwent post-mortem imaging. All cases were autopsied in full, using the guidelines for Sudden Cardiac Death as proposed by the Association for the European Cardiovascular Pathology (AECVP) as a basis for the investigation [9]. This protocol, although not primarily aimed at SAD, propagates a full autopsy, including extensive sampling for histology, toxicology and genetic testing. With the

exception of four older cases, all cases included histological analysis of the aortic wall. This consisted of multiple standard HE stained sections in combination with additional stains, including EvG or Movat's stain. No material for toxicological analysis was collected, but tissue samples for genetic testing (as recommended in [9]) were taken in all autopsies.

The differences and similarities in used diagnostic modalities between the forensic and clinical subset are summarized in Table 3.

3.3 Diagnoses

3.3.1 Forensic subset

Of the 35 cases, 23 of deaths were deemed unnatural: 16 accidental deaths, of which 3 post-operative; 4 suicides (jumps from heights); and 3 homicides. In the accidental deaths, 10 were traffic-related, with the individuals mostly being either car drivers or pedestrians. The direct cause of death was commonly typical acceleration-deceleration trauma with rupture of the aortic root. Two individuals fell accidently from heights, all suicides jumped from heights; in all these cases with resultant aortic rupture. The homicides' victims died from perforation of the aortic wall by a knife or a bullet. The three accidental post-operative cases included a 74-year old women who died one post-operatively due to iatrogenic perforation of an aortic valve cusp after thermo-ablation of the AV-node; a 59-year old woman who did not survive surgery for an aortic abdominal 'false' aneurysm following surgery for colon cancer five weeks earlier; and a 75-year old man who died two weeks after aortic valve replacement due loosening of the stitches with subsequent rupture of the ascending aorta.

Information of underlying aortic disease in the unnatural deaths was limited. One case reportedly had cystic medial degeneration (CMD), diagnosed histologically. Three cases were reported to have atherosclerosis, of which one confirmed histologically. In the 19 remaining cases, the reports do not comment on underlying aortic disease.

The twelve natural deaths in the forensic subset included four ruptured aortas and eight dissections, either with or without subsequent total rupture. Two of the natural cases were post-operative ones; a 76-year old male who died eight days after surgery for a bladder tumour due to a ruptured atherosclerotic aneurysm, and a 75-year old male who died whilst receiving orthopaedic surgery of his foot, due to a ruptured aortic dissection with hemato-pericardial tamponade.

Histologically, CMD was diagnosed in three cases, including a 22-year old male who was found dead next to his bicycle. This particular case is of additional interest, since the circumstances initially suggested an unnatural death (i.e. a traffic accident) but full autopsy and histology eventually resulted in the diagnosis of a ruptured aortic wall due to the hereditary connective tissue disease Loeys-Dietz syndrome. Atherosclerosis was identified in six cases; a combination of CMD and atherosclerosis was identified in two cases. In a 45-year old male, a fatal dissection of the ascending aorta was found in combination with a bilateral adrenal adenoma. The latter allegedly caused hypertension; and could therefore be a major contributory factor to the individuals' death. Use of cocaine or other abusive drug that could potentially relate to onset of aortic dissection was not found in any of the cases.

3.3.2. Clinical subset

In the clinical subset, all 22 deaths were natural. Ten individuals died due to aortic dissection, either with or without subsequent total rupture of the aortic wall. Histology identified previous/older dissection in two individuals (Fig. 2). The remaining twelve cases presented with ruptured aortic walls, often with concomitant abdominal aneurysms.

With respect to underlying aortic disease, four individuals had only CMD. In one case, the CMD appeared to be related to longstanding hypertension due to fibromuscular dysplasia of the renal arteries (Fig. 3). In two cases, a 17-year old female (Fig. 3) and a 46-year old male, the severity of CMD prompted further genetic investigation. In both, a hereditary connective tissue disease was confirmed. The male was diagnosed with Marfan syndrome, the female with Loeys-Dietz syndrome. Seven cases were diagnosed with atherosclerosis alone, whilst nine cases had a combination of CMD and atherosclerosis. In all cases, the underlying diseases were directly linked to the eventual cause of death, i.e. CMD in case of (ruptured) dissections and extensive atherosclerosis in case of ruptured aortic abdominal aneurysms. Two cases were diagnosed with a ruptured mycotic aneurysm, with positive stains for microorganisms, i.e. a Gram-stain and a Periodic-acid Schiff Diastase (PAS-D) stain, confirming the infectious nature.

The underlying aortic diseases per subset are listed in Table 4.

4. DISCUSSION

Our survey on SAD victims who were submitted to either a clinical or a forensic pathology institute reveals that there are not only marked differences in their prevalence (7,7% or 35 per 453 autopsies in forensic, versus 2,4%,

or 22 per 902 autopsies in clinical practice), but also in the diagnostic approach of SAD when both settings are compared.

In the forensic setting, the autopsy was generally preceded by radiological examination, whilst histological analysis was relatively limited, especially in unnatural deaths. In the clinical setting, with natural deaths only, the autopsy generally included extensive histological examination, but radiological examination was not performed.

Over the past years, post-mortem radiography has quickly gained popularity as a post-mortem diagnostic technique. The non-invasive imaging of the complete body (including those areas less accessible during autopsy), and the possibility to store the images indefinitely, made it a valuable diagnostic adjunct in autopsy pathology [12-15]). Our survey shows that in case of SAD, it may give information on the presence of aortic lesions, the location of aortic wall defects and the presence of pericardial fluid. MPMCTA was superior to PMCT for all these purposes, although both were not as sensitive or specific as full body autopsy. Still, post-mortem radiology may provide a feasible alternative in those cases in which no consent for autopsy is given. In such cases, post-mortem can also be used to assessing the extent of aortic atheroma [16].

The different diagnostic approach in both settings coincides with marked similarities in the underlying diseases that we found. In the natural deaths, both settings report a substantial amount of CMD, atherosclerosis or a combination of the two. Also in both settings, previously unknown hereditary connective tissue diseases were diagnosed. In addition, both settings reported rather unconventional underlying diseases, i.e. bilateral adrenal adenomas in the forensic setting, and fibromuscular dysplasia of the renal arteries in the clinical setting. For the recognition of all these diseases and its relation to the SAD, a full body autopsy and histological examination of the major organs, normal aorta and lesional aorta is necessary [1, 2]. Histology is also essential to objectify the effects of longstanding systemic hypertension on organs including the aorta. Moreover, histological determination of the timing of aortic dissection is essential to evaluate potential repetitive dissections or suspicion of medical negligence [17]. Our survey identified at least two cases of repetitive (healed) dissections (Fig. 2). As a result we recommend that histology of all major organs, including the aorta should be taken in any case of SAD. The tissue blocks from the aorta should include normal and lesional aorta and the major aortic branches.

For the purpose of this study, we paid particular attention to potential use of cocaine, because of its reported association with the onset of aortic dissection. In a recent survey of 3584 patient in the International Registry of Acute aortic Dissection (IRAD), use of cocaine appeared to be implicated in only 1.8% of victims [8]. Most of

these patients were enrolled at US sites (86.4%) rather than at European sites (13.6%) and were typically of young age. Cocaine abuse was not detected in any of the forensic cases, whilst no material for toxicological analysis was sampled in the clinical setting. The latter contrasts with the used guidelines of Basso et al. and suggests that clinical pathologists should be more aware of the necessity to store material for toxicological testing in case of sudden death. Despite the negative results in the forensic subset in our own study, we recommend to sample material for toxicological analysis, even more since cocaine abuse relates not only to SAD but also to sudden cardiac death [18].

The relation between hereditary connective tissue disease, aortic dilatation and sudden death is well known [19], and circa 20% of patients with thoracic aortic aneurysms have an identifiable monogenic disease [20]. Also in our series, both settings presented cases of hereditary connective tissue disease with fatal outcome. The many reports on similar cases illustrate that pathologists are likely to come across such a case sooner or later in their career [6, 21-24]. Currently over 15 types of hereditary connective tissue disease that may affect the aorta are known [25]. The most well known are Marfan syndrome, Loeys-Dietz syndrome and Ehlers-Danlos syndrome type IV, which all have an autosomal dominant inheritance pattern [25]. As a matter of fact, up to 29% of patients with hereditary connective tissue disease have an affected first-degree relative [26], which emphasizes the potential impact of a correct diagnosis on the siblings of the deceased. We therefore recommend that in each case of SAD, material is stored for genetic analysis.

All in all, our survey has revealed important differences in the diagnostic approach of SAD in a forensic and medical setting, whilst a correct diagnosis of the cause of death and underlying disease requires a thorough post-mortem investigation. To aide pathologists in future cases of SAD, we recommend to obtain a full medical history, perform a full body autopsy (including the aorta, its main branching arteries) with histology (of all major organs, normal and lesional aorta and the major aortic branches) and to store material for toxicological and DNA analysis. Post mortem imaging is not deemed necessary, but can be very helpful for documentation reasons or when an autopsy is not possible. Our recommendations are summarized in Table 5.

For the purposes of this study, the concept of SAD enabled us to comprehensively study all deaths related to aortic perforation, dissection of rupture. The definition of SAD should not be limited to immediate deaths, since our survey, in analogy with the current definition of sudden cardiac death, also included cases that survived for several days after medical intervention. Also, the definition should not be limited to natural deaths, as our survey has shown that also in cases that seem unnatural initially, an underlying natural aortic disease should be

considered as the cause of death. For the purpose of further study, the concept of Sudden Aortic Death should therefore be defined as any sudden, unexpected death directly related to aortic rupture, perforation or dissection.

We think that although the described series of cases stem from two centers, they can be taken as representative for the situation in many medical and forensic centers. Both centers used internationally accepted, peer-reviewed guidelines as a basis for their diagnostic approach [9, 11], which makes their approach comparable to similar centers elsewhere. Also, both centers are typical in their size, staffing and equipment for their specific types of institutes, have cardiovascular expertise and reflect the current state of the art in their respective fields. Underlying disease that are related to SAD, such as hypertension, atherosclerosis, inflammatory disease and hereditary connective tissue disease are found all over the world [2, 27].

Conclusion

Sudden aortic death (SAD) is a commonly encountered cause of death in forensic and medical settings. There are major differences in the approach of SAD between these two settings, but the causes of death and aortic diseases show striking similarities. To ensure a correct diagnosis, we recommend that each investigation of SAD includes; a) a full medical history; b) full body autopsy with examination of all major organs and aorta, plus its major branches; c) histological examination of all major organs, normal aorta plus its main branches, and the aortic lesion; d) storage of tissue for toxicological; and e) genetic testing. Post-mortem computed tomography, preferably extended with contrast-angiography, is valuable for documentation purposes and initial assessment of the body and may be a valuable solution if there is no consent for a full body autopsy. However, it currently cannot be used as a substitute for full body autopsy and histology in case of SAD.

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Figure captions

Fig. 1 Transversal (**a, b**) and sagittal (**c**) images of the arterial phase of multiphase post-mortem computed tomography angiography (MPMCTA) according to Grabherr *et al*., in an individual who died from an acute dissection of the thoracic and abdominal aortic wall. The use of contrast readily reveals the true (T) and false (F) lumen of the dissected aorta, and indicates the location of an intimal entry or exit lesion (arrow)

Fig. 2 Micrographs of a healed aortic medial dissection. **a)** full thickness view of the aortic wall, showing an old dissection channel (*) filled up with fibrous scar tissue (red). The periadventitial area (A) also shows extensive fibrosis (M= media, IL= intimal layer). Elastica von Giesson stain, magnification x25. **b)** detail of the healed dissection channel showing emedding of fragments of elastic lamellae in the scar tissue (red). Elastica von Giesson stain, magnification 200x

Fig. 3 Macroscopy and histology of a fatal rupture of an aneurysm of the ascending aorta due to a hereditary connective tissue disease (Loeys-Dietz syndrome), in a 17 year old female. **a+b)** The aortic root is severely dilated, with a longitudinal tear in the ascending aorta (arrow). **c)** Micrographs of the aortic wall shows severe loss of smooth muscle cells and accumulation of glycoproteins. Haematoxylin and eosin stain, magnification x25. **d)** The same are as shown in panel **c**, now stained with Elastica von Gieson stain. There is near-total destruction of the elastin fibres in the aortic wall. The findings in panel **c** and **d** indicate severe cystic medial degeneration, which, in combination with the age of the patient, is highly suggestive of a hereditary connective tissue disease

Figure captions

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Figure 1

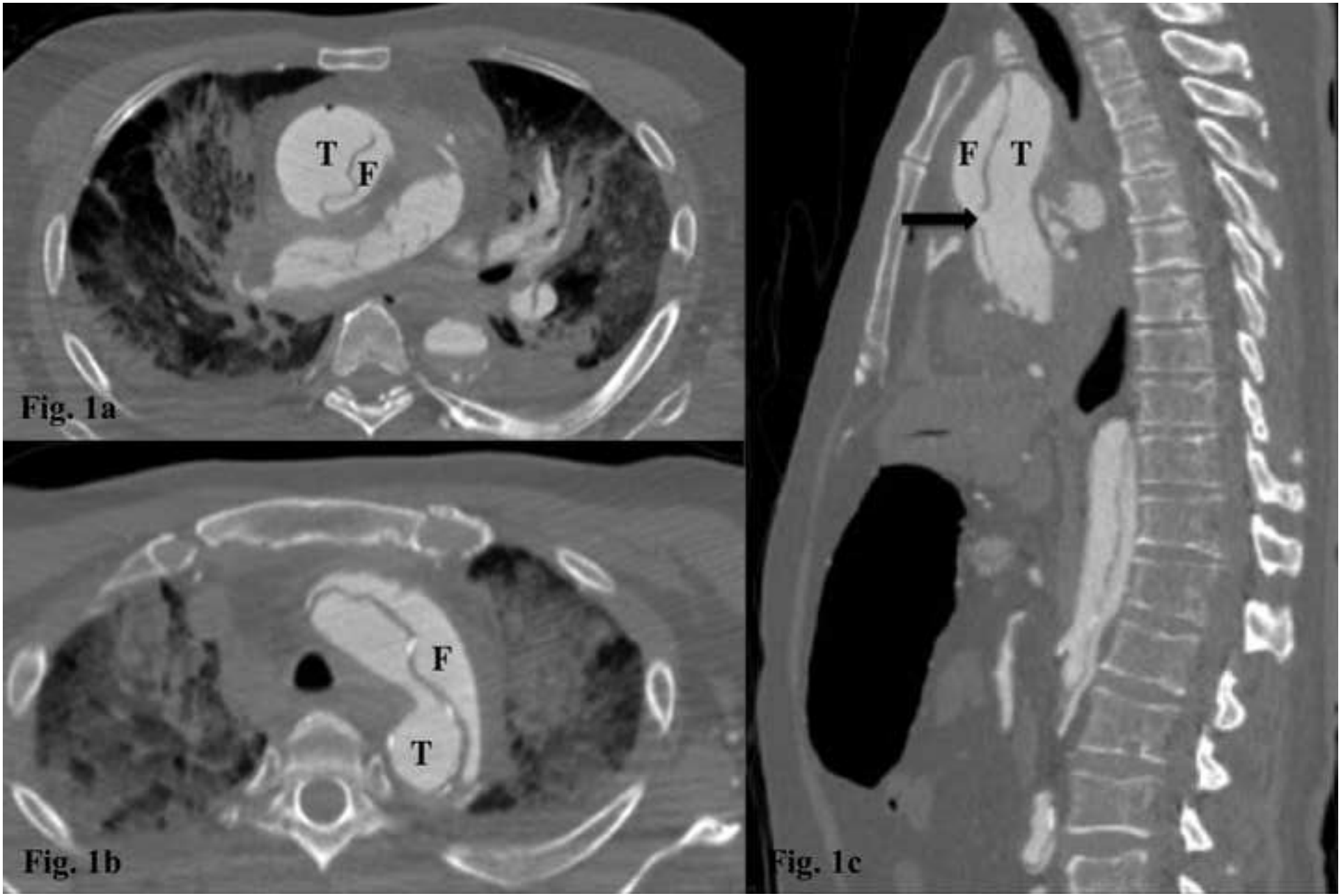

Figure 2

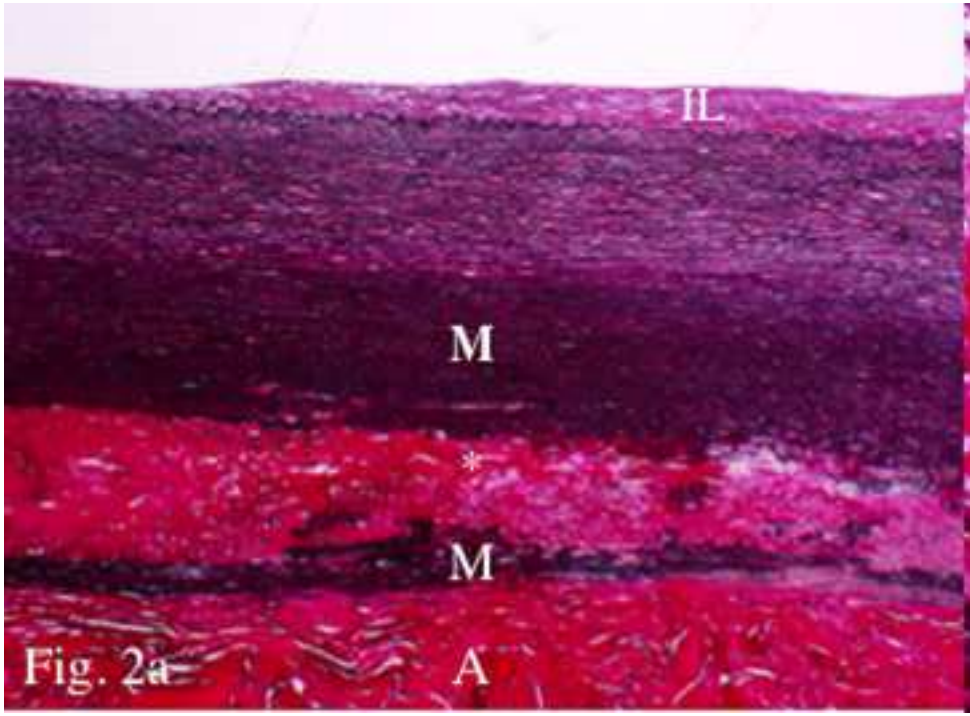

Fig. 2a

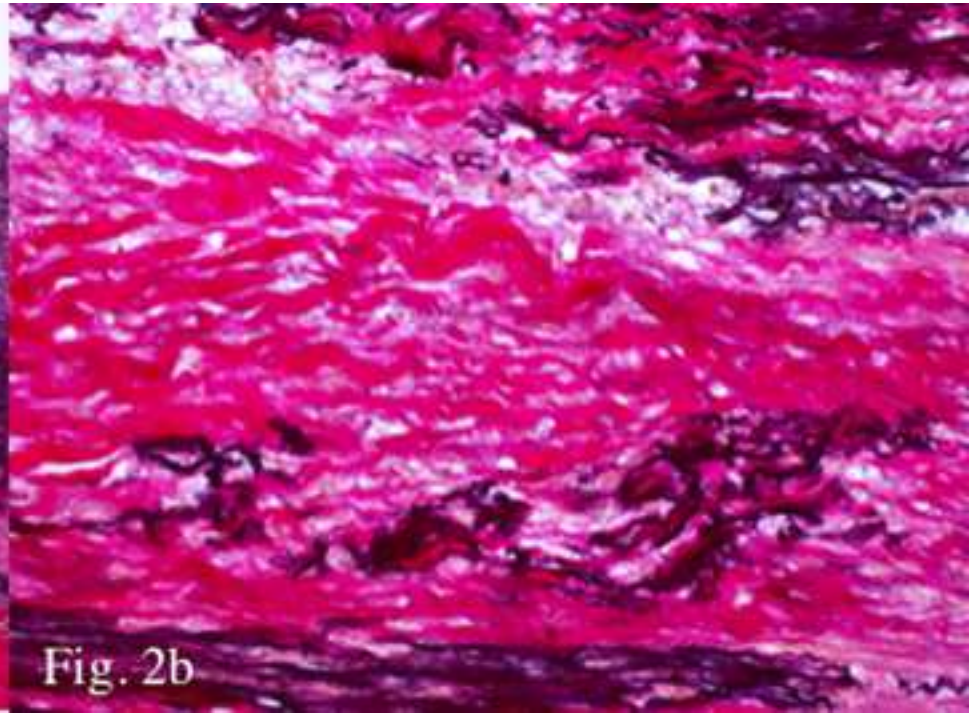

Fig. 2b

Figure 3

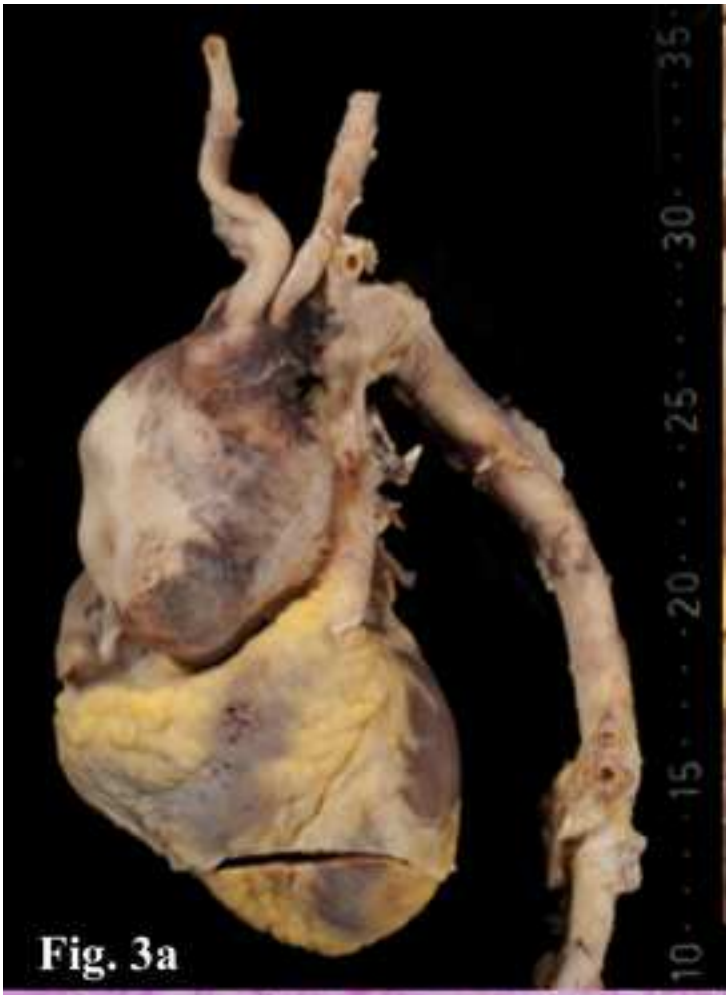

Fig. 3a

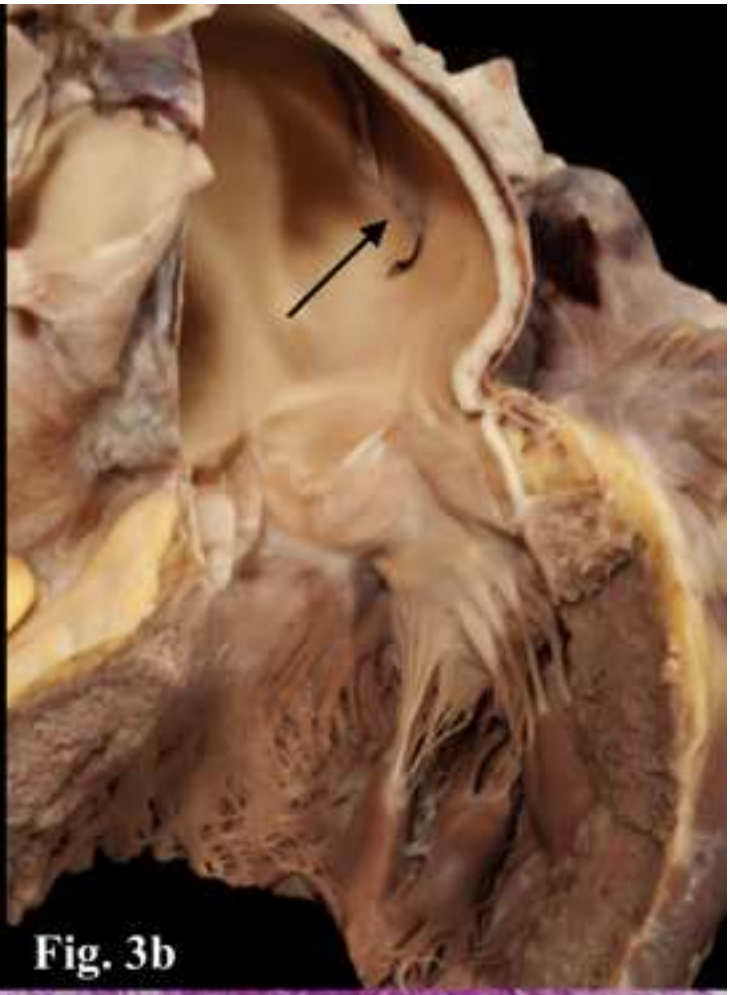

Fig. 3b

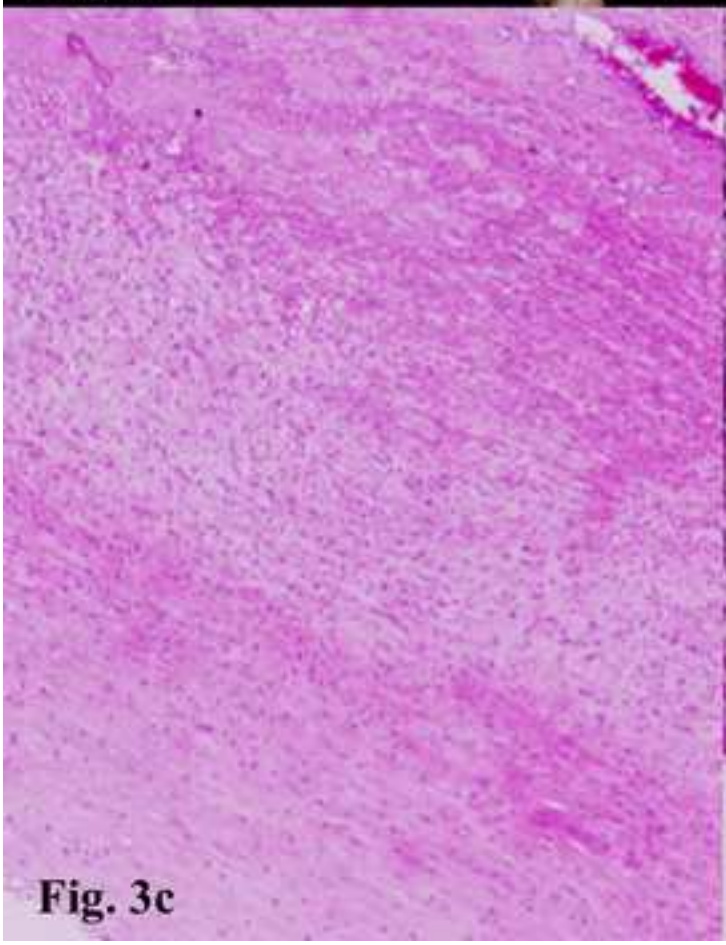

Fig. 3c

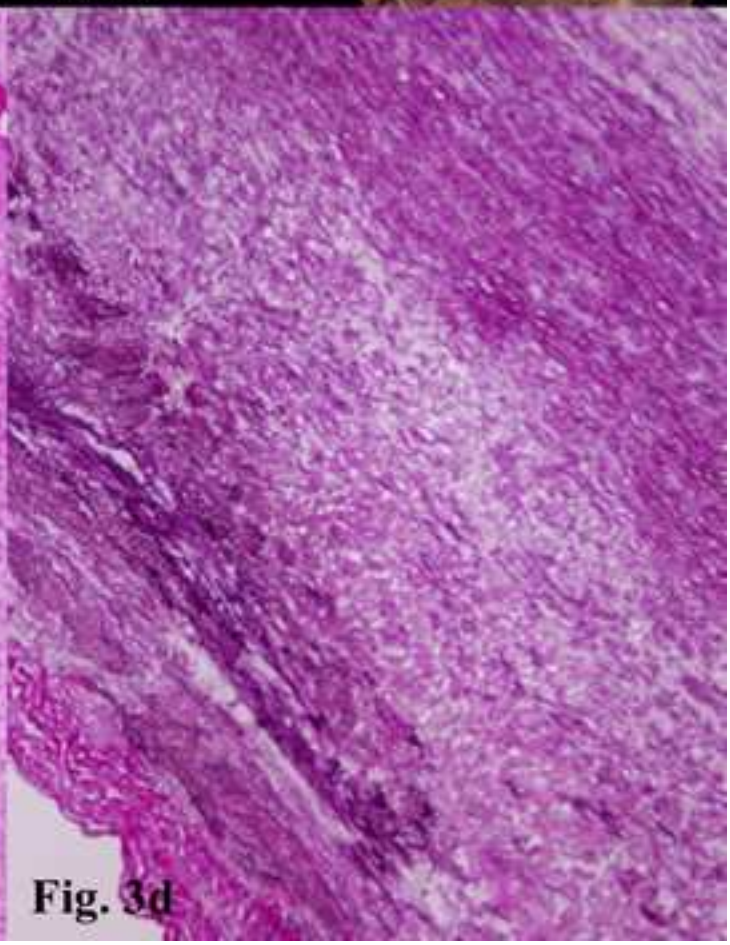

Fig. 3d

Table 1. Demography of the study group

		Forensic subset	Clinical subset	Total
No. of individuals		35	22	57
Sex	Male (%)	31 (88.6)	14 (64)	45 (79)
	Female (%)	4 (11.4)	8 (36)	13 (22)
Age (years)	Mean (SD)	54.2 (22.6)	63.7 (16.9)	57.9 (20.9)
	Min-Max	1-84	17-83	1-84
SAD / total autopsies*	N / N (%)	35/453 (7.7)	22/902 (2.4)	57/1355 (4.2)

Abbreviations: N=number of individuals; SD= standard deviation; SAD=sudden aortic death.

* Total number of autopsies in the forensic subset in the period January 2013–December 2014, and total number of autopsies in the clinical subset in the period January 2010-July 2015.

Table 2. Comparison of post-mortem radiology with autopsy findings

	The presence of the aortic lesion		**The localisation of the aortic lesion**		**The presence of pericardial fluid**	
	PMCT N (%)	MPMCTA N (%)	PMCT N (%)	MPMCTA N (%)	PMCT N (%)	MPMCTA N (%)
Full agreement with autopsy results	4/14 (28.6)	18/21 (85.7)	4/14 (28.6)	18/21 (85.7)	11/14 (78.6)	20/21 (95.2)
Type 1 disagreement with autopsy results	9/14 (64.3)	2/21 (9.5)	9/14 (64.3)	2/21 (9.5)	1/14 (7.1)	0/21 (0)
Type 2 disagreement with autopsy results	0/14 (0)	1/21 (4.8)	0/14 (0)	1/21 (4.8)	2/14 (14.3)	1/21 (4.8)
Type 3 disagreement with autopsy results	1/14 (7.1)	0/21 (0)	1/14 (7.1)	0/21 (0)	0/14 (0)	0/21 (0)

Abbreviations: N = number of individuals; PMCT = post-mortem computed tomography; MPMCTA = multiphase post-mortem computed tomography angiography.

Type 1 disagreement: post-mortem radiology is only false negative, i.e. post-mortem radiology has missed a lesion that was revealed by autopsy.

Type 2 disagreement: post-mortem radiology is false negative and false positive, i.e. post-mortem radiology and autopsy identify a different lesion.

Type 3 disagreement: there is agreement between post-mortem radiology and autopsy on one lesion, but post-mortem radiology is false negative in another lesion, i.e. when post-mortem radiology and autopsy identify the same lesion, but autopsy reveals an additional lesion.

Table 3. Used diagnostic modalities.

Diagnostic modality		**Forensic subset**	**Clinical subset**
		N (%)	**N (%)**
Radiology	PMCT	35 (100)	0 (0)
	PMCTA	21 (60)	0 (0)
Autopsy		35 (100)	22 (100)
Histology of the aorta	None	23 (66)	4 (18)
	Basic[1]	1 (3)	0 (0)
	Extensive[2]	11 (31)	18 (82)
Sampling for genetic testing		35 (100)	22 (100)
Total		35	22

Abbreviations: N= number of individuals. PMCT= post-mortem computed tomography; MPMCTA= multiphase post-mortem computed tomography angiography.

[1] Haematoxylin and Eosin stained sections only.

[2] Additional (immuno)histochemical staining methods.

Table 4. Underlying diseases per subset.

Aortic pathology	**Forensic subset**		**Clinical subset**
	Unnatural deaths	**Natural deaths**	
	N (%)	**N (%)**	**N (%)**
CMD	1 (4)[1]	3 (25)	4 (18)[2]
Atherosclerosis	3 (13)	6 (50)	7 (32)
CMD + Atherosclerosis	0 (0)	2 (17)	9 (41)[3]
Aortitis	0 (0)	0 (0)	2 (9)
Other	0 (0)	1 (8)[4]	0 (0)
Unknown/not investigated	19 (83)	0 (0)	0 (0)
Total	23 (100)	12 (100)	22 (100)

Abbreviations: N= number of individuals; CMD=cystic medial degeneration.

[1] Subsequently diagnosed with Loeys-Dietz syndrome.

[2] Including two cases in which a hereditairy connective tissue disease was diagnosed, namely syndrome of Marfan and Loeys-Dietz syndrome.

[3] Including one case of fibromuscular dysplasia of the renal arteries.

[4] Diagnosed with an adrenal adenoma.

Table 5: Recommendations for the diagnostic approach in case of Sudden Aortic Death

Diagnostic modality	Comment
Medical history	Recommended to acquire in full. Of special notice are hypertension, use of medication or drugs (e.g. cocaïne) and a family history of sudden death.
Post-mortem radiology	Useful for general documentation purposes, may provide information on presence and location of aortic lesions, and/or pericardial fluid. MPMCTA is superior to PMCT for all these purposes. Cannot substitute a full body autopsy, but is a feasible non-invasive alternative when autopsy is not possible.
Full body autopsy	Recommended in each case, should include examination of all organs including aorta and its major branching arteries.
Histological analysis	Of all major organs, normal and lesional aorta wall and major aortic branches. We recommend use of connective tissue stains (Elastica von Gieson, Movat) on arterial sections.
Toxicological analysis	Recommended to identify drugs of abuse, especially cocaine. For this, collect at least peripheral blood and urine.
Genetic testing	Tissue sampling (e.g. frozen splenic tissue or EDTA blood) for eventual cytogenetic analysis is recommended in each case.