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Cardiac and noncardiac, particularly neuromuscular, disease with troponin-T positivity

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ABSTRACT

Objectives: Although elevated cardiac troponin T is caused by myocardial damage in the vast majority of the cases (primary cardiac causes), noncardiac disease with secondary damage to the myocardium (secondary cardiac causes) is being increasingly recognised. The present study aimed to retrospectively evaluate the frequency of primary cardiac and secondary cardiac causes of troponin-T positivity, in particular how often troponin-T positivity is associated with neuromuscular disorders.

Results: Of 16,944 troponin-T determinations in a secondary centre between April 2004 and April 2005, troponin T was positive in 1408 of them (8.3%). Of these, 622 were included for evaluation. Troponin-T positivity was associated with elevated creatine kinase in 54.5% and with creatinine >2 mg/dl (177 μmol/l) in 16.6% of the tests. The most frequent primary cardiac causes of troponin-T positivity were myocardial ischaemia (59%), atrial fibrillation (23%), and heart failure (22%). The most frequent secondary cardiac causes of troponin-T positivity were renal insufficiency (22%), chronic obstructive lung disease (10%), and acute stroke (4%). There was one cause for troponin-T positivity in 249 cases and more than one in 373 cases. A neurologist saw patients with troponin-T positivity in 9.5% of the cases. Troponin-T positivity was associated with a neuromuscular disorder in 6.3% of the cases. Causes of troponin-I positivity were also frequently causes of troponin-T positivity.

Conclusions: Ischaemic heart disease is the most frequent cause of troponin-T positivity, followed by heart failure and renal insufficiency. Many causes previously described to be only responsible for troponin-I positivity also cause troponin-T elevation. Troponin-T positivity is frequently associated with neuromuscular disorders, most likely due to cardiac involvement of these conditions.

KEYWORDS

Cardiac involvement, cardiomyopathy, myocardial infarction, myocardial ischaemia, skeletal muscle, troponin

INTRODUCTION

Cardiac troponin T was introduced in the routine laboratory diagnostic work-up in 1989[1] and was conceptualised to sensitively indicate acute myocardial ischaemia, even in the absence of angina pectoris, creatine kinase (CK), or CK-MB elevation.[2] Meanwhile, it turned out that, in addition to primary cardiac causes of troponin-T positivity, various extracardiac disorders are associated with troponin-T positivity due to secondary damage to the myocardium (secondary cardiac causes).

The aim of the present study was 1. To retrospectively evaluate how often troponin T is positive in a secondary centre; 2. How often troponin-T positivity is associated with elevated CK or elevated creatinine; 3. Which are the primary cardiac or secondary cardiac causes of troponin-T positivity in these patients; 4. How often patients with troponin-T positivity are seen by a neurologist; and 5. How often troponin-T positivity is attributable to a neuromuscular disorder (NMD).

METHODS

From all patients who attended an inpatient unit of the general hospital Krankenanstalt Rudolfstiftung in Vienna, Austria between April 2004 and April 2005 (13 months) with the initials A to P and in whom troponin T was determined as positive during this period, the electronic

records were reviewed for 19 previously reported causes of troponin-T positivity and 27 previously reported causes of troponin-I-positivity (*table 1*). Patients with the initials Q to Z were excluded because frequency distribution of troponin-T positivity no longer varied with progression of the data acquisition. We did not look for the diagnoses cardiac tamponade, rhabdomyolysis, hypovolaemia or cirrhosis because they were not recognised to be associated with troponin elevation before completion of the data acquisition. Also registered were the CK and creatinine values in case the patient was seen by a neurologist, as well as the number of causes of troponin-T positivity found per admission. If the patient was seen by a neurologist, the neurological diagnosis was registered, in particular in case an NMD was responsible for the troponin-T positivity. Causes of troponin-T positivity were classified as primary cardiac or secondary cardiac (*table 1*). If a patient was admitted several times during the study period and had a positive troponin T at some or all of these admissions, each admission was regarded as a distinct entity. If troponin T was determined several times during a single hospitalisation, only one positive determination was used for statistical analysis. If there was more than one single cause to explain troponin-T positivity, all possible causes were registered. If there was disagreement on the cause of troponin-T positivity, the investigators discussed the case until agreement was reached.

Troponin T was measured with the qualitative analytical troponin-T test TROP sensitive Rapid Assay (Roche Diagnostics). All assays were performed according to the manufacturer's instructions. Venous whole blood from patients anticoagulated with EDTA was used in all assays. The cut-off for troponin-T positivity in this assay is 0.08 ng/ml. The results are expressed as troponin-T negative or positive. The sensitivity of the assay is >95% for acute myocardial infarction and subacute infarction with an analytical specificity of >92%. All determinations with a positive or slightly positive result were initially considered. Heterophilic antibodies, which may cause a minor release of troponin, were not determined. Creatinine was measured with the Creatinine Jaffe Gen.2 test (Roche Diagnostics) on a COBAS INTEGRA 700/800 system. The test relies on the buffered kinetic Jaffé reaction without deproteination. Zero point of the creatinine reaction to picrate acid was measured at 512 nm, which is directly proportional to the serum creatinine concentration.

RESULTS

Between April 2004 and April 2005, 16,944 determinations of troponin T were carried out in the hospital's laboratory. Among them, 1408 determinations were troponin-T positive (8.3%). Of these 190 were only slightly positive (*table 2*). After exclusion of patients with

Table 1. *Causes of troponin-T and troponin-I positivity*

	Troponin T	Troponin I
Primary cardiac causes		
Myocardial ischaemia, unstable coronary heart disease	[27]	[28]
Myocarditis	[29]	[30]
Pericarditis	NR	[31,32]
Dilated cardiomyopathy	[33]	NR
Hypertrophic cardiomyopathy	[29]	[32]
Uraemic cardiomyopathy	[8]	NR
Atrial fibrillation	NR	[34]
Tachycardia	NR	[31,32]
Congestive heart failure	[35]	[9,31,32,36]
Increased left ventricular mass	NR	[13]
Severe aortic valve disease	NR	[32]
Coronary vasospasm	NR	[32]
Takotsubo phenomenon	[37]	[12]
Cardiac contusion	NR	[32]
Cardiac tamponade	NR	[38]
Hypertensive crisis	NR	[32]
Hypotonia, hypovolaemia	[3]	NR
Implantable cardioverter defibrillator shocks	NR	[39]
Electrical cardioversion	NR	[10]
Percutaneous coronary intervention, ASD closure	[40]	[41]
Radiofrequency ablation	NR	[42]
Cardiac transplantation	NR	[43]
Pacemaker implantation	NR	[44]
Secondary cardiac causes*		
Pulmonary		
• Pulmonary embolism	[45]	[32,46]
• Chronic pulmonary hypertension	[47]	NR
• Chronic obstructive pulmonary disease	NR	[48]
Neuromuscular		
• Duchenne muscular dystrophy	[7,49]	NR
• Dermatomyositis	[2,7,18-20,49]	NR
• Polymyositis	[2,49]	NR
• Inclusion body myositis	[17]	NR
• Rhabdomyolysis	NR	[50]
• Physical exertion	NR	[31]
Other		
• Sepsis, systemic inflammatory respons	NR	[51]
• Acute stroke	[52]	[49]
• Subarachnoid haemorrhage	NR	[26]
• Amyloidosis	NR	[53]
• Chemotherapy	NR	[54]
• Lymphoma	[17,55]	NR
• Chronic renal insufficiency	[7,8,56,57]	[7]
• Scorpion or jellyfish envenoming	NR	[58,59]
• Eclampsia, pre-eclampsia	NR	[60]
• Rheumatoid arthritis	NR	[61]
• Epileptic seizures	NR	[62]
• Diabetic ketoacidosis	[63]	[16]
• Noncardiac surgery	[64]	NR
• Gastrointestinal bleeding	NR	[32]
• Electrical trauma	NR	[32]
• Cirrhosis	NR	[65]

NR = not reported so far. *Disorders with secondary cardiac damage as an explanation for troponin-T or troponin-I positivity.

Table 2. *Stratification of troponin-T tests carried out between April 2004 and April 2005 (13 months)*

Stratification	Absolute number (n)
Total number of troponin-T tests	16,944
Total number of positive troponin-T tests	1408
Number of slightly positive troponin-T tests	190
Total number of positive troponin-T tests after exclusion of the patients with initials Q to Z	1008
Number of positive troponin-T tests after exclusion of repeated determinations per admission	729
Number of positive troponin-T tests with insufficient data on the electronic records (excluded)	107
Number of admissions (cases) with at least one positive test	622
• Cases with 1 cause	249
• Cases with >1 cause	373
• Cases with 2 causes	211
• Cases with 3 causes	103
• Cases with 4 causes	44
• Cases with 5 causes	14
• Cases with 6 causes	1
Number of patients with at least one positive test	595

the initials Q to Z, 1008 positive troponin-T determinations remained for further analysis (*table 2*). Of these, all multiple determinations per admission were excluded. Additionally, 107 admissions were discarded because the electronic files no longer contained the information required. Thus, altogether 622 admissions (cases) were finally used for statistical analysis (*table 2*). The 622 cases were attributable to 595 patients since 23 were admitted twice, 3 three times, and 1 five times during the observational period. CK was elevated, >144 U/l in women and >170 U/l in men, in 337 of 618 determinations (54.5%). Creatinine was elevated >1.1 mg/dl (97.4 µmol/l) in 303 of 604 determinations (50.2%) but a creatinine value (177 µmol/l) was only found in 100 of 604 determinations (16.6%).

The frequencies of the various other causes of troponin-T positivity are listed in *table 3*. The most frequent causes of troponin-T positivity were myocardial ischaemia, followed by heart failure, renal insufficiency, and atrial fibrillation (*table 3*). A single cause of troponin-T positivity was found in 249 cases, two causes in 211 cases, three causes in 103 cases, four causes in 44 cases, five causes in 14 cases, and six causes in a single case (*table 2*). If only patients with a single cause were considered, the most frequent causes of troponin-T positivity were myocardial ischaemia, renal insufficiency, and atrial fibrillation (*table 3*). In 24 cases no plausible cause, as listed in *table 1*, could be detected (*table 3*). Causes of troponin-T positivity previously attributable only to troponin-I-positivity were found in 34 cases (*table 3*). The most frequent single causes of troponin-T positivity, previously only observed together with troponin-I positivity, were atrial fibrillation, chronic obstructive lung disease, tachycardia, and electrical cardioversion (*table 3*). Causes of troponin-T positivity previously described but not found in the present cohort were Duchenne muscular dystrophy, polymyositis, and

Table 3. *Frequency of causes for troponin-T positivity*

Cause	Multiple causes	Single causes
Myocardial ischaemia	369	134
Atrial fibrillation*	140	11
Congestive heart failure	137	9
Chronic renal insufficiency	135	19
Percutaneous cardiac interventions	70	1
Chronic obstructive pulmonary disease*	60	6
Tachycardia*	57	5
Acute stroke	26	2
Electric cardioversion*	24	0
Dilated cardiomyopathy	20	2
Increased left ventricular mass*	19	3
Sepsis*	16	2
Epileptic seizures*	16	1
Pulmonary embolism	13	8
Aortic valve disease*	13	1
Hypertensive crisis*	12	1
Gastrointestinal bleeding*	12	0
Noncardiac surgery	8	4
Pacemaker implantation*	7	1
Chronic pulmonary hypertension	6	0
Myocarditis	5	1
Subarachnoid haemorrhage*	4	2
Chemotherapy*	4	0
Hypertrophic cardiomyopathy	3	0
Pericarditis*	3	1
Septic shock*	3	0
Systemic inflammatory response*	3	0
Lymphoma	2	0
Implantable cardioverter defibrillator shocks*	2	0
Uraemic cardiomyopathy	1	0
Takotsubo phenomenon	1	1
Inclusion body myositis	1	1
Dermatomyositis	1	0
Coronary vasospasm*	1	0
Radiofrequency ablation*	1	0
Physical exertion*	1	0
Amyloidosis*	1	0
Polymyositis	0	0
Diabetic ketoacidosis	0	0
Duchenne muscular dystrophy	0	0
Cardiac contusion*	0	0
Cardiac transplantation*	0	0
Scorpion or jellyfish envenoming*	0	0
(Pre)eclampsia, gestational hypertension*	0	0
Rheumatoid arthritis*	0	0
Electrical trauma*	0	0
No cause	0	24

*Diagnosis so far only associated with troponin-I positivity.

ketoazidosis (*table 3*). Causes of troponin-I positivity previously described, but absent in the present cohort, were cardiac contusion, heart transplantation, scorpion envenoming, eclampsia, rheumatoid arthritis, and electrical trauma (*table 3*). Among the 33 patients who were repeatedly admitted during the observational period the cause or causes of troponin-T positivity changed in nine, remained unchanged in three, and partially changed in 15 patients. The departments with the highest prevalence of troponin-T positivity were the cardiology, endocrinology/oncology, and the nephrology departments (*table 4*).

Table 4. *Frequency of troponin-T positivity in the different hospital departments*

Department	Frequency (n)
Cardiology	388
Oncology, endocrinology	89
Nephrology	41
Gastroenterology	15
Neurology	14
Neurosurgery	13
1. Surgery	10
Oto-rhino-laryngological	7
2. Surgery	4
Urology	3
Dermatology	3
Ophthalmology	2
Gynaecology	0
Paediatrics	0

Table 5. *Definite neurological diagnoses among 39 patients and suspected neurological diagnoses among all patients with troponin-T positivity*

Neurological diagnoses	Definite (n)	Suspected (n)
Neuromuscular disorder	14	25
Metabolic myopathy	4	22
Polyneuropathy	4	0
Myopathy of unknown aetiology	3	3
Limb girdle muscular dystrophy	1	0
Dermatomyositis	1	0
Rhabdomyolysis	1	0
Ischaemic stroke	10	0
Epilepsy	5	0
Subrachnoidal bleeding	4	0
Encephalitis/meningitis	3	0
Unknown	3	0
Dementia	2	0
Parkinson's syndrome	2	0
Neurologically normal	2	0
Apallic syndrome	1	0
Gait disturbance	1	0
Depression	1	0
Syncope	1	0
Carotid artery stenosis	1	0
Intracerebral bleeding	1	1
Subdural haematoma	1	0
Confusional state	1	0
Multiple sclerosis	1	1
Cerebral metastasis	1	0
Tremor	0	1
Lumbago, disc herniation	0	1
Acute deafness	0	1

Altogether, a neurologist saw 59 of the 622 cases (9.5%). The most frequent neurological diagnoses in these cases were NMD, stroke, or epilepsy (*table 5*). An NMD was detected in 14 of the 595 patients (*table 5*). The most frequent NMDs were metabolic myopathies, polyneuropathy, and myopathy of unknown aetiology. An NMD was responsible for troponin-T positivity as the single cause in four cases. From the retrospective study of the records additional neurological diagnoses were found or suspected (*table 5*). Among these, the most frequent were metabolic myopathies and myopathies of unknown aetiology. Altogether, an NMD was found in 39 of 622 cases (6.3%).

DISCUSSION

This study shows that troponin T is positive in 8.3% of the troponin-T determinations in a secondary centre, that troponin-T positivity is associated with elevated CK in 54.5% and with elevated creatinine in 50.2% of the determinations, that the most frequent primary cardiac causes of troponin-T positivity are myocardial ischaemia, heart failure, and atrial fibrillation, that the most frequent secondary cardiac causes of troponin-T positivity are renal insufficiency, chronic obstructive lung disease and stroke, that patients with troponin-T positivity are seen by a neurologist in 9.5% of the cases, and that troponin-T positivity is associated with an NMD in 6.3% of the cases.

Troponins are regulatory proteins which control the interaction of actin and myosin.[3] Troponins consist of three subunits, troponin T, I, and C. Troponin T binds to tropomyosin and facilitates contraction, troponin I binds to actin and inhibits actin/myosin interaction, and troponin C binds to calcium ions, which mediate the interaction of actin and myosin.[4] Troponins are not only expressed in myocardiocytes, but also in skeletal striated muscle and smooth muscle cells. In the three muscle cell types they occur as three different isoforms. Since the amino-acid sequence of the skeletal and cardiac isoforms of troponin T and I are dissimilar, they are differentiable by monoclonal antibody-based assays.[3] Since the number of false-positive results may be different between the various tests, it is generally recommended to interpret troponin-T test results only in the clinical context and not as

a test result alone.[5] The high number of causes of troponin-T positivity in the present investigation previously reported only for troponin-I positivity can be explained by the fact that troponin-T determination was not performed in most of these studies or that the applied test also recognises troponin I. That troponin T is more frequently elevated than troponin I in patients with chronic renal disease is attributable to the fact that elimination of troponin T is more dependent on renal function than is the elimination of troponin I.[6]

In accordance with the present investigation, troponin T is derived from the myocardium in almost all cases. Cardiac troponins are released from cardiomyocytes in case of irreversible cell damage or reversible membrane permeability dysfunction.[3] In the latter case myocardial damage is transient and not associated with necrosis of cardiomyocytes. Nonspecific troponin-T elevation is a common finding among hospitalised patients and associated with a worse prognosis. High troponin-T levels are significant predictors of death or rehospitalisation in patients with heart failure. Troponin-T positivity is also associated with a poor outcome in patients with ST-segment elevation acute myocardial infarction. Troponin-T levels are also independent predictors of long-term mortality, cardiovascular events, or death, and of noncardiovascular death in patients with chronic peritoneal dialysis. The most frequent cardiac condition resulting in troponin-T positivity is acute myocardial infarction, where troponin T is elevated in up to 97% of the cases.[7] In stable angina pectoris cardiac troponin remains normal but in unstable angina pectoris cardiac troponin T is elevated in 33 to 41% of the cases.[7] Troponin T may also be increased in 43% of the patients with heart failure.[8,9] In these patients troponin T is a predictor of decreased survival.[8] Contrary to the present findings, electrical cardioversion has so far only been reported to increase troponin I.[10] Troponin-T positivity in patients undergoing percutaneous coronary interventions is most likely due to irreversible myocardial injury as assessed by periprocedural delayed-enhancement MRI.[11] Also the Takotsubo phenomenon, which is triggered by emotional or physical stress, gastrointestinal infection, or surgical intervention,[12] may be associated with troponin-T positivity (*table 1*).[12] There is no evidence to support an association between cardiac troponin T and increasing left ventricular mass,[8] but troponin I has been found positive in this condition.[13] Primary cardiac causes of troponin-T positivity previously only found in association with troponin-I positivity are pericarditis, atrial fibrillation, tachycardia, increased left ventricular mass, severe aortic valve disease, coronary vasospasm, cardiac contusion, cardiac tamponade, hypertensive crisis, ICD shocks, pacemaker implantation, radiofrequency ablation, or cardiac transplantation (*table 1*). Other primary cardiac causes of troponin-T positivity are listed in *table 1*. That a neurologist saw 9.5% of the troponin-T positive patients is most likely due to the polymorbidity of these patients.

Secondary cardiac causes of troponin-T positivity are variable and include a number of disorders (*table 1*). As confirmed by the present investigation, the most frequent secondary cardiac cause of troponin-T positivity is chronic renal failure, where troponin T is elevated in up to 39% of the cases.[7,14] The mechanism by which renal failure causes troponin-T positivity is unknown, but there are indications that it is due to secondary myocardial thickening or myocardial ischaemia.[15] In patients with chronic kidney disease troponin T is a marker of poor survival[8] and predicts an increased mortality.[7] In these cases the blood pH correlates negatively with serum troponin T.[16] Secondary cardiac causes of troponin-T positivity previously only found in association with troponin-I positivity are chronic obstructive pulmonary disease, rhabdomyolysis, physical exertion, sepsis, subarachnoid haemorrhage, amyloidosis, chemotherapy, scorpion envenoming, eclampsia, rheumatoid arthritis, epileptic seizures, gastrointestinal bleeding, electrical trauma, or cirrhosis (*table 1*). Other secondary cardiac causes of troponin-T positivity are listed in *table 1*. In all these conditions myocardial involvement in the underlying disease is held responsible for the troponin positivity. Because of the high frequency of multicausality of troponin-T positivity in most of the presently investigated cases, it was difficult to identify a single or major cause of troponin-T positivity in the majority of the cases.

Only single studies attribute elevated troponin T to skeletal muscle disorders. So far, troponin-T positivity has been found in association with dermatomyositis, polymyositis, inclusion body myositis, and Duchenne muscular dystrophy (DMD) (*table 1*).[2,17-20] Troponin-T positivity was also reported in DMD carriers.[21] Troponin T may be also elevated in 75% of the patients with Becker's muscular dystrophy.[7] Additionally, cardiac troponin-T mRNA has been found in patients with sarcoglycanopathies.[22] Other studies, however, did not find elevated levels of troponin T or troponin I in DMD patients.[23] The present study additionally suggests that also patients with metabolic myopathy may present with troponin-T positivity. In NMD patients, troponin-T positivity is most likely due to cardiac involvement in myopathy, a frequently observed finding in the majority of the NMDs. Expression of the cTnT gene in skeletal muscle cells, however, cannot be definitively excluded as an additional explanation for troponin-T positivity in these patients, although there is currently no evidence that upregulation of cTNT genes is related to troponin-T or troponin-I levels.

Generally, troponin-T positivity without evident myocardial damage is attributable to a number of different causes. First, it may be explained by a low specificity of the applied tests, due to the presence of heterophilic antibodies, which may not only recognise cardiac troponin T but, to a variable degree, also troponin T derived from the skeletal muscle or even the smooth muscle. An argument

against this assumption, however, is that second to fourth generation cTnT tests show hardly any cross-reactivity with the skeletal muscle and are highly cardiospecific. Another reason for secondary cardiac troponin-T positivity in extracardiac disease may be the fact that various disorders are associated with secondary cardiac disorders. This may be the case with sepsis/SIRS, which is accompanied by myocardial depression and a supply/demand mismatch, intake of sympathomimetic agents, which have a direct adrenergic effect, chemotherapy, which is cardiotoxic in the majority of the cases, pulmonary embolism or pulmonary hypertension, or strenuous exercise, which all cause right ventricular strain.[3] A third reason could be the production of cardiac troponin T by tissues other than the myocardium. However, there is currently no evidence that upregulation or re-expression of the appropriate cTnT genes or post-transcriptional modifications of mRNAs result in the production of cardiac troponin T by noncardiac cells.[22,24,25] A fourth mechanism by which noncardiac disease might cause troponin-T positivity could be the release of norepinephrine from sympathetic nerves, resulting in damage to both myocytes and nerve terminals in the autonomic nervous system.[26] This mechanism may explain why intracranial haemorrhage is sometimes associated with troponin-T positivity. Which of these hypotheses is the most plausible remains speculative.

Limitations of the study were that it was retrospective, that patients with the initials Q to Z were excluded, that the electronic records were not available in a number of cases, the occurrence of multiple causes of troponin-T positivity in a number of patients, and the difficulty to identify a single cause of troponin-T positivity in the majority of the cases.

CONCLUSION

This study shows that troponin-T positivity is most frequently associated with ischaemic heart disease, followed by atrial fibrillation and heart failure. Many previously described causes of troponin-I positivity are also responsible for troponin-T elevation. NMDs are frequently associated with troponin-T positivity, most likely due to cardiac involvement of NMDs. Neurologists should be more frequently involved in the diagnostic work-up of troponin-T positive patients and clinicians should be aware of the large variety of causes and multicausality of troponin-T positivity.

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