Published in final edited form as:

Anesthesiology. 2017 April ; 126(4): 643–652. doi:10.1097/ALN.0000000000001531.

High-sensitivity Cardiac Troponin Elevation after Electroconvulsive Therapy (ECT):

A prospective, observational cohort study

Andreas Duma, M.D., M.Sc.^{*,†}, Swatilika Pal, MBBS, MS^{*}, Joshua Johnston, D.O., Mohammad A. Helwani, M.D., Adithya Bhat, M.D., Bali Gill, M.D., Jessica Rosenkvist, M.D., Christopher Cartmill, B.S., Frank Brown, B.S., J. Philip Miller, A.B., Mitchell G Scott, Ph.D., Francisco Sanchez-Conde, Michael Jarvis, M.D., Ph.D., Nuri B. Farber, M.D., Charles F. Zorumski, M.D., Charles Conway, M.D., and Peter Nagele, M.D., M.Sc.

Division of Clinical and Translational Research, Department of Anesthesiology (AD, SP, JJ, MH, FB, FSC, PN), Division of Biostatistics (JPM), Department of Pathology & Immunology (MGS), Department of Psychiatry (JR, MJ, NBF, CFZ, CC), Taylor Family Institute for Innovative Psychiatric Research (CFZ, NBF, CC, PN), Washington University School of Medicine in St. Louis

Abstract

Background—While electroconvulsive therapy (ECT) is widely regarded as a life-saving and safe procedure, evidence regarding its effects on myocardial cell injury are sparse. The objective of this investigation was to determine incidence and magnitude of new cardiac troponin elevation after ECT using a novel high-sensitivity cardiac troponin I (hscTnI) assay.

Corresponding Author: Peter Nagele, MD, MSc, Division of Clinical and Translational Research, Dept of Anesthesiology, Washington University School of Medicine, 660 S. Euclid Ave, Box 8054, St. Louis, MO 63110, nagelep@wustl.edu; phone: 314-362-5129; fax: 314-362-1185.

^{*}Both authors contributed equally to the manuscript

[†]Current institution: Dept. Of Anesthesiology and Critical Care, Medical University of Vienna, Austria

Conflicts of Interest and Source of Funding:

Nagele: Dr. Nagele has filed for intellectual property protection related to the use of nitrous oxide in major depression. He has received research funding and speaker fees from Roche Diagnostics (Indianapolis, IN) and research funding from Abbott Diagnostics (Abbott Park, Illinois). He is currently supported by the Stanley Medical Research Institute (SMRI, Chevy Chase, MD), the National Institute for Mental Health (1R21MH108901), by a NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation (New York, NY), by a grant from the McDonnell Center for Systems Neuroscience at Washington University (St. Louis, MO).

Scott: Research Support - Siemens Healthcare Diagnostic (Malvern, PA); Abbott Diagnostics (Abbott Park, Illinois), Instrumentation Laboratories (Orangeburg, NY); Consulting - Instrumentation Laboratories (Orangeburg, NY); Becton-Dickinson (Franklin Lakes, NJ) Zorumski: Dr. Zorumski serves on the Scientific Advisory Board of Sage Therapeutics (Cambridge, MA).

Conway: He has received research funding from Bristol-Myers Squibb (New York, NY), Cyberonics (Houston, TX), the Sidney Baer Foundation (Clayton, MO) and is currently supported by the Stanley Medical Research Institute (SMRI, Chevy Chase, MD), the National Institute for Mental Health (1R21MH108901), by a NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation (New York, NY), by a grant from the McDonnell Center for Systems Neuroscience at Washington University (St. Louis, MO).

All others: No conflicts of interest.

This study was primarily funded by the Departments of Anesthesiology and Psychiatry as well as the Taylor Family Institute for Innovative Psychiatric Research at Washington University School of Medicine. Abbott provided the hscTnI assay for free and covered the costs of running the tests. Dr. Gill received an ASPIRE summer research stipend via the Washington University Institute of Clinical and Translational Sciences (UL1 RR024992). Dr. Bhat received a Medical Student Anesthesia Research Fellowship from the Foundation for Anesthesia Education and Research (FAER, Schaumburg, IL). Dr. Duma was supported by a Max Kade Research Fellowship from the Max Kade Foundation, New York.

Role of the funding sources: The sponsors had no role in the collection, management, and interpretation of the data; or preparation, review, or approval of the manuscript.

Methods—This was a prospective cohort study in adult patients undergoing ECT in a single academic center (up to three ECT treatments per patient). The primary outcome was new hscTnI elevation after ECT, defined as an increase of hscTnI >100% after ECT compared to baseline with at least one value above the limit of quantification (10 ng/L). 12-lead ECG and hscTnI values were obtained prior to and 15–30 minutes after ECT; in a subset of patients an additional 2-hour hscTnI value was obtained.

Results—The final study population was 100 patients and a total of 245 ECT treatment sessions. Eight patients (8/100, 8%) experienced new hscTnI elevation after ECT with a cumulative incidence of 3.7% (9/245 treatments; one patient had two hscTnI elevations), two of whom had a non-ST-elevation myocardial infarction (incidence 2/245, 0.8%). Median hscTnI concentrations did not increase significantly after ECT. Tachycardia and/or elevated systolic blood pressure developed after approximately two thirds of ECT treatments.

Conclusions—ECT appears safe from a cardiac standpoint in a large majority of patients. A small subset of patients with pre-existing cardiovascular risk factors, however, may develop new cardiac troponin elevation after ECT, the clinical relevance of which is unclear in the absence of signs of myocardial ischemia.

Introduction

Electroconvulsive therapy (ECT) is used in the treatment of severe or otherwise refractory psychiatric conditions, such as bipolar disorder, refractory psychosis and treatment-resistant major depression.¹ ECT involves administration of an electrical current to the head of the patient to initiate a generalized seizure. In spite of general anesthesia, ECT results in significant cardiovascular stress and carries the rare risk of more serious adverse cardiac events, including myocardial infarction (MI)^{2–8} and stress-induced cardiomyopathy (Takotsubo).^{9–12} While serious adverse cardiac events are rare, a recent report showed that isolated cardiac troponin elevations after ECT may occur as frequently as one in ten patients.¹³

Until recently, a systematic evaluation of cardiac risk after ECT was hampered by the relative insensitivity of contemporary cardiac troponin assays and predominantly relied on clinical observations.¹⁴ The recent introduction of high-sensitivity cardiac troponin (hscTn) assays^{15,16} offered an opportunity to determine a better estimate of incidence and magnitude of cardiac troponin release after ECT, because these assays allow the detection of baseline cardiac troponin values in most adult patients and thus a quantification of before-and-after changes. HscTn assays – currently not available in the U.S., but approved in many other countries – measure the same cardiac troponin (I or T), but with markedly increased sensitivity. Indeed, the definition of high sensitivity troponin assays is that the assay can detect circulating levels of cardiac troponin above the limit of detection in >50% of healthy subjects.¹⁵ Numerous studies have shown that previously undetectable elevations of cardiac troponins are predictive of future cardiovascular risk.¹⁶

Methods

Study Design and Oversight

We conducted a prospective cohort study in 100 evaluable patients who underwent ECT at Barnes-Jewish Hospital, St. Louis, MO. The study was approved by the Institutional Review Board (IRB) of Washington University, St. Louis, MO, and written informed consent was obtained from each patient.

Patients and Treatment

Adult patients scheduled to undergo ECT were eligible for recruitment. Patients with baseline cognitive impairment were excluded. ECT and anesthesia were provided according to departmental standards. For anesthesia, etomidate (0.1–0.2 mg/kg body weight) and succinylcholine (0.5–1 mg/kg body weight) were administered intravenously and patients were ventilated with 100% oxygen. No beta-blockers or other antihypertensive drugs were administered per institutional practice. Typically, patients received either right unilateral, bifrontal or bitemporal ECT treatment according to a standard institutional ECT regimen using a Thymatron System IV Electroconvulsive Therapy Unit (Somatics, LLC, Venice, FL), and trains of 0.3 ms pulses at 6.0 times the seizure threshold for right unilateral (d'Elia position) and 1.0 ms pulses at 2.0 times the threshold for bitemporal and bitemporal treatments. Seizure thresholds were estimated at the initial treatment for all patients using a method of limits approach.

Assessment and Outcomes

The goal of this study was to quantify the incidence and magnitude of new cardiac troponin elevation after each ECT visit for a series of up to three treatments in each patient. Patient demographics, cardiovascular risks, and home medications were assessed at enrollment. For each treatment, high-sensitivity cardiac troponin I (hscTnI) and a 12-lead ECG were obtained within two hours before and within 15–30 minutes after ECT in all patients. After study initiation, the study protocol was amended to allow the acquisition of an additional hscTnI sample two hours after ECT to determine if hscTnI kinetics may reveal delayed troponin changes that were not present shortly after ECT. ECGs were analyzed for signs of ischemia (such as new ST-segment depression or elevation; T-wave inversion; presence of new Q-waves or left bundle branch block) by a blinded expert. Periprocedural heart rate, blood pressure, and pulse oximetry were recorded in 2- to 5-minute intervals, and clinical signs of myocardial ischemia were monitored and until two hours after ECT.

Primary outcome was the incidence of new hscTnI elevation after ECT, defined as an hscTnI increase >100% combined with at least one value above the limit of quantification (LOQ; 10 ng/L). In addition, we determined new hscTnI elevations above the sex-specific 99th percentile upper reference limit (URL).¹⁷ We investigated up to three ECT treatments per patient to determine the variability of hscTnI elevation after each ECT visit. Additional outcomes included MI defined as an hscTnI increase above the LOQ plus clinical or ECG signs of myocardial ischemia according to the Third Universal definition of MI¹⁸, hypertensive episode defined as periprocedural peak systolic blood pressure >160 or >200 mmHg, and tachycardia defined as a peak heart rate >100 or >150 beats per minute.

Laboratory Analyses

Samples were collected in lithium heparin tubes, immediately put on ice and centrifuged within 30 minutes of collection. Plasma was transferred into cryogenic tubes and stored at -70°C . Biomarker measurements were performed in batches and by study personnel unaware of clinical outcomes. Grossly hemolyzed samples were excluded from analysis. hscTnI (reported as ng/L) was measured on an Abbott Architect STAT $\text{\textcircled{C}}$, Abbott Laboratories, Abbott Park, IL, platform (limit of blank 0.7 – 1.3 ng/L; limit of detection 1.1 – 1.9 ng/L; LOQ: 10.0 ng/L; 99th percentile URL female: 15.6 ng/L; male: 34.2 ng/L).¹⁹ Imprecision of the assay at the 99th percentile concentrations is <6% coefficient of variation.¹⁵

Statistical Analysis

Only ECT treatment visits with available before-and-after hscTnI levels were included for analysis. The cumulative incidence of new hscTnI elevation, as well as hypertensive episodes and tachycardia after ECT was calculated per patient and per whole cohort. Sample size was not based on a formal sample size calculation, but chosen based on our previous experience with using hscTn and its ability to reliably detect even small hscTn changes.²⁰ HscTnI values are presented as median and interquartile range. Friedman's ANOVA for paired hscTnI data was used to test for statistically significant changes in hscTnI levels over three treatments for all patients as well as in the subgroup with an additional hscTnI sample available two hours after ECT. Linear correlation was analyzed by calculation of Spearman's correlation coefficient. All p-values are two-sided and a $p < 0.05$ was considered statistically significant (IBM $\text{\textcircled{R}}$ SPSS $\text{\textcircled{R}}$ version 22, IBM, Armonk, NY; JMP Pro 12.2, SAS Institute, Cary, NC). Plots were produced using GraphPad Prism $\text{\textcircled{R}}$ version 6.07 (GraphPad Software Inc, La Jolla, CA) and JMP 12.2. (SAS Institute, Cary, NC).

Results

Patients

Between June 2011 and September 2012 115 patients were recruited into the study. After withdrawal of 15 patients the final study population was 100 patients (Figure 1), of which 58 patients had three ECT visits, 29 patients had two ECT visits, and 13 patients had one ECT visit analyzed. In total, complete before-and-after hscTnI data were available for 245 ECT treatment visits ($58 \times 3 + 29 \times 2 + 13 \times 1 = 245$). In the final 14 of 100 (14%) patients (35 of 245 ECT treatments) an additional hscTnI level was obtained 2 hours after ECT. Table 1 presents patient characteristics. The majority of patients received ECT for major depressive disorder or bipolar disorder. Table 2 provides details about the ECT treatments. In 38% ($n=38$), the first study ECT visit coincided with the first ECT treatment the patient received during which initial seizure threshold determination was made.

Study Outcomes

Figure 2 shows the absolute and relative changes in hscTnI after ECT. HscTnI levels did not change significantly after ECT treatments both immediately after ECT ($n=72$; $P=0.4$), as well as in the subgroup with an additional hscTnI sample available two hours after ECT ($n=10$; $P=0.6$) (Figure 3). Most patients did not experience an increase in hscTnI after ECT,

but a subset had a marked increase (maximum hscTnI: 731.6 ng/L). Patients who developed new hscTnI elevation after ECT tended to be older and had more cardiovascular risk factors

Eight patients (8/100, 8%) experienced new hscTnI elevation after ECT with a cumulative incidence of 3.7% (9/245 treatments; one patient experienced two hscTnI elevations after separate ECT visits) (Table 3, Figure 4). A detailed description of the eight patients who developed a new hscTnI increase is provided in Table 3. Two patients (patients A and C in Table 3 and Figure 4) met definitive criteria for non-ST-elevation myocardial infarction (NSTEMI) (incidence 2/245, 0.8%). In a total of ten ECT visits (10/245, 4.1%) of six patients (6/100, 6%) hscTnI was already elevated >99th percentile URL prior to ECT, and they did not experience a subsequent new hscTnI elevation.

Patients who had their initial ECT treatment with seizure threshold determination did not experience significantly different absolute or relative hscTnI changes after ECT compared to patients who had subsequent ECT treatments (absolute difference: -0.1 ng/L [$-0.9, 0.8$] median [IQR], vs. -0.1 [$-1.1, 0.9$], $p=0.74$; relative difference: -1.8% [$-16.9, 9.8$], median [IQR], vs. -2.4% [$-16.9, 14.4$], $p=0.95$). Four patients with initial ECT and seizure threshold determination experienced an hscTnI increase >100% (4/37, 10.8%) compared to four patients undergoing subsequent ECT treatments (4/62, 6.5%); this corresponded to a non-significant unadjusted odds ratio of 1.68 (95% CI 0.40 – 7.11, $p=0.48$). Neither central seizure duration nor convulsion duration were correlated with absolute hscTnI change after ECT ($r=-0.10$ and -0.13 , respectively). Among the eight patients with hscTnI elevation, seven received right unilateral and one bifrontal ECT treatment.

In approximately two thirds of ECT visits tachycardia (HR >100/min) and/or elevated systolic blood pressure (>160 mmHg) after ECT developed (Table 4). In approximately 17% of ECT visits, peak systolic blood pressure was elevated > 200 mmHg with maxima reaching up to 250 mmHg. Neither peak heart rate ($r = -0.06$) nor systolic blood pressure ($r = 0.19$) were correlated with absolute hscTnI change.

Discussion

This prospective cohort study of 100 patients undergoing ECT demonstrated that: (1) most patients did not develop a hscTnI elevation after ECT; (2) median hscTnI values did not change after ECT, both when measured immediately as well as 2 hours after ECT; (3) a small subset of patients developed new hscTnI elevation after ECT, indicative of myocardial injury. Because we obtained hscTnI values in up to three ECT treatments per patient, we were able to determine if some patients always develop hscTnI elevation after ECT. Unexpectedly, there was no consistency between ECT treatments, e.g. patients may develop hscTnI elevation after one ECT treatment but none after another.

New cardiac troponin elevation

Cardiac troponin, a myocardial protein, is a very sensitive and specific cardiac and standard biomarker for the diagnosis of MI.¹⁸ Cardiac troponin is released when myocardial cells are injured and the magnitude of cardiac troponin elevation correlates with the damaged or necrotic myocardial cell mass. The newly developed high-sensitivity cardiac troponin assays

(not available in the U.S. at present) measure the same cardiac troponin molecule, but have significantly increased analytic sensitivity that allows detection of circulating cardiac troponin in >50% of healthy subjects.¹⁵

Cardiac troponin elevations in the absence of clinical symptoms, such as chest pain or ischemic ECG changes, have recently been referred to as “myocardial injury” or “myocardial damage”.^{21,22} However, there are currently no accepted guidelines as to which absolute or relative cardiac troponin elevations and changes constitute myocardial injury.²¹ Short-term within individual biologic variability of cardiac troponin concentrations in healthy subjects has been reported to be 4–14% and when combined with analytic variability the positive reference change value for hscTnI is 45–52%.^{23–25} The biologic and analytic variability of hscTnI levels may therefore result in intra-individual increases and decreases of up to 52%. The RCV is the change that exceeds normal biologic variability and analytic variability and represents a physiologic change. Thus, in the rapid rule in/rule out diagnosis of MI in patients with chest pain, a relative increase of >50% is often interpreted as a positive test.¹⁵ Little evidence is available for clinical scenarios in which a “true” baseline can be obtained, such as patients undergoing ECT or cardiac stress test. Taking into account the uncertainty around “significant” cardiac troponin elevations and analytical and biological variability, we opted for a conservative cutoff of a >100% hscTnI increase compared to the pre-ECT sample to identify patients with a new significant cardiac troponin elevation after ECT in order to decrease the likelihood of false positives.^{17,24,26–28}

Clinical relevance

New cardiac troponin elevations without definitive signs of myocardial ischemia have recently been referred to in the cardiology literature as “myocardial injury” or “myocardial damage”.²² Although the criteria for defining and diagnosing myocardial injury or damage are lacking, there is evidence that even small cardiac troponin elevations after major stress may have prognostic significance for subsequent cardiovascular morbidity and mortality.²⁹ The cause for the observed new hscTnI elevations in our patient population is unclear: in some patients, particularly those with pre-existing coronary artery disease, the cause may be stress-induced myocardial ischemia via supply-and-demand mismatch. In other patients, stress-induced catecholamine release may directly cause myocardial cell damage. The latter mechanism is possibly related to stress-induced cardiomyopathy (Takotsubo), which has been described in patients undergoing ECT.^{9–12} Investigations focused on electro- and echocardiographic evidence for ECT-induced myocardial ischemia found incidence rates of new regional wall motion abnormalities (indicative of ischemic myocardium in the distribution of a coronary artery) in 4 – 45% of patients.^{4,30} The largest population-based study of mortality after ECT found 78 deaths within 30 days after ECT among 99,728 ECT treatments in the Danish National Patient Register (mortality rate: 0.08%). Six of these deaths occurred on the day of ECT treatment. The most prevalent attributed cause of deaths was cardiopulmonary.³¹

Using contemporary cardiac troponin assays, Martinez and coauthors found an 11.5% incidence rate of new abnormal cardiac troponin elevations after ECT.^{13,32} Integrating case report series, cardiac biomarker studies, and echocardiographic evidence it appears that a

small subset of patients – probably those with chronic heart and/or lung disease – are at higher risk of developing adverse cardiac events after ECT. It is beyond the scope of this article, but efforts have been made to use preventive strategies to mitigate the cardiac risk associated with ECT in high-risk patients, such as improved identification¹⁴ or therapeutic strategies, such as beta-blockers.^{33,34} It should be pointed out that patients who did not develop new hscTnI elevation after ECT, but had already elevated baseline hscTnI values, may be at increased long-term cardiovascular risk even if they did not experience myocardial injury during ECT.

Strengths and Weaknesses

The use of a novel high-sensitivity cardiac troponin assay is a strength of the study for two main reasons. First, these novel assays have increased the sensitivity for detection of cardiac troponin by an order of magnitude over traditional cardiac troponin assays. The increased sensitivity allows for the detection of small cardiac troponin concentration differences with a high degree of precision. Second, the use of these hscTn assays allows for the detection of circulating cardiac troponin at “baseline” and in absence of an acute cardiac event. Thus, they allow before-and-after measurements and thereby a rigorous quantification of delta or change values which correspond to the amount of injured myocardium. However, there is overwhelming evidence in other populations that increased cardiac troponin predict future cardiovascular risk.^{15,16}

The fact that this study did not follow patients for long-term cardiovascular outcomes precludes the determination if observed cardiac troponin elevations had any long-term clinical relevance. Second, we were unable to obtain pre- and post ECT hscTnI values for all patients and all three planned ECT treatment measurements, which limited the power of the study. Third, the study was not designed to obtain robust incidence rates for hard clinical outcomes, such as NSTEMI. Thus the observed incidence rate of NSTEMI (2%) may substantially under- or overestimate the true incidence.

Conclusions

In the overwhelming majority of patients, ECT appears to be safe from a cardiac standpoint. A small subset of patients develops cardiac troponin elevation after ECT, suggestive of myocardial injury. Lacking long-term outcome data, however, the clinical relevance of an isolated new cardiac troponin elevation after ECT, in the absence of evidence of myocardial ischemia, is presently unclear and should be determined in a larger prospective study that follows cardiovascular outcomes.

Acknowledgments

We thank the Taylor Family Institute for Innovative Psychiatric Research at Washington University School of Medicine in St. Louis for their support. We also thank the clinical staff from the Washington University/Barnes-Jewish Hospital Electroconvulsive Therapy (ECT) service who provided tremendous help during this study. We would like to thank Allan Jaffe, M.D., Professor of Medicine, Cardiovascular Division, Department of Internal Medicine and Division of Core Clinical Laboratory Services, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota for valuable comments related to the interpretation of high-sensitivity cardiac troponin elevations.

References

1. Greenberg RM, Kellner CH. Electroconvulsive therapy: a selected review. *Am J Geriatr Psychiatry*. 2005; 13:268–81. [PubMed: 15845752]
2. Stoudemire A. Cardiovascular morbidity and ECT. *Am J Psychiatry*. 1995; 152:1697–8.
3. Steiner LA, Drop LJ, Castelli I, Alfille PH, Schouten R, Welch CA. Diagnosis of myocardial injury by real-time recording of ST segments of the electrocardiogram in a patient receiving general anesthesia for electroconvulsive therapy. *Anesthesiology*. 1993; 79:383–8. [PubMed: 8342848]
4. Messina AG, Parancas M, Katz B, Markowitz J, Yao FS, Devereux RB. Effect of electroconvulsive therapy on the electrocardiogram and echocardiogram. *Anesth Analg*. 1992; 75:511–4. [PubMed: 1530163]
5. Webb MC, Coffey CE, Saunders WR, Cress MM, Weiner RD, Sibert TR. Cardiovascular response to unilateral electroconvulsive therapy. *Biol Psychiatry*. 1990; 28:758–66. [PubMed: 2257285]
6. Knos GB, Sung YF, Cooper RC, Stoudemire A. Electroconvulsive therapy--induced hemodynamic changes unmask unsuspected coronary artery disease. *J Clin Anesth*. 1990; 2:37–41. [PubMed: 2310579]
7. Dec GW Jr, Stern TA, Welch C. The effects of electroconvulsive therapy on serial electrocardiograms and serum cardiac enzyme values. A prospective study of depressed hospitalized inpatients. *JAMA*. 1985; 253:2525–9. [PubMed: 3981780]
8. Gould L, Gopalaswamy C, Chandy F, Kim B. Electroconvulsive therapy-induced ECG changes simulating a myocardial infarction. *Arch Intern Med*. 1983; 143:1786–7. [PubMed: 6615101]
9. Celano CM, Torri A, Seiner S. Takotsubo cardiomyopathy after electroconvulsive therapy: a case report and review. *J ECT*. 2011; 27:221–3. [PubMed: 21673587]
10. Beach SR, Wichman CL, Canterbury RJ. Takotsubo cardiomyopathy after electroconvulsive therapy. *Psychosomatics*. 2010; 51:432–6. [PubMed: 20833943]
11. Go O, Mukherjee R, Bhatta L, Carhart R Jr, Villarreal D. Myocardial stunning after electroconvulsive therapy in patients with an apparently normal heart. *J ECT*. 2009; 25:117–20. [PubMed: 19225404]
12. O'Reardon JP, Lott JP, Akhtar UW, Cristancho P, Weiss D, Jones N. Acute coronary syndrome (Takotsubo cardiomyopathy) following electroconvulsive therapy in the absence of significant coronary artery disease: case report and review of the literature. *J ECT*. 2008; 24:277–80. [PubMed: 18955900]
13. Martinez MW, Rasmussen KG, Mueller PS, Jaffe AS. Troponin elevations after electroconvulsive therapy: the need for caution. *Am J Med*. 2011; 124:229–34. [PubMed: 21396506]
14. Tess AV, Smetana GW. Medical evaluation of patients undergoing electroconvulsive therapy. *N Engl J Med*. 2009; 360:1437–44. [PubMed: 19339723]
15. Sandoval Y, Smith SW, Apple FS. Present and Future of Cardiac Troponin in Clinical Practice: A Paradigm Shift to High-Sensitivity Assays. *Am J Med*. 2016; 129:354–65. [PubMed: 26743351]
16. Landesberg G, London MJ. The Enigma of Postoperative Troponin Elevation. *Anesth Analg*. 2016; 123:5–7. [PubMed: 27192474]
17. Wildi K, Twerenbold R, Mueller C. How acute changes in cardiac troponin concentrations help to handle the challenges posed by troponin elevations in non-ACS-patients. *Clin Biochem*. 2015; 48:218–22. [PubMed: 25218832]
18. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Joint ESCAAHAWHFTfUDoMI. Third universal definition of myocardial infarction. *Circulation*. 2012; 126:2020–35. [PubMed: 22923432]
19. Krintus M, Kozinski M, Boudry P, Capell Nuria E, Köller U, Lackner K, Lefèvre G, Lennartz L, Lotz J, Herranz Antonio M, Nybo M, Plebani M, Sandberg Maria B, Schratzberger W, Shih J,

- Skadberg Ø, Chargui Ahmed T, Zaninotto M, Sypniewska G. European multicenter analytical evaluation of the Abbott ARCHITECT STAT high sensitive troponin I immunoassay. *Clinical Chemistry and Laboratory Medicine (CCLM)*. 2014;1657. [PubMed: 24897400]
20. Nagele P, Brown F, Gage BF, Gibson DW, Miller JP, Jaffe AS, Apple FS, Scott MG. High-sensitivity cardiac troponin T in prediction and diagnosis of myocardial infarction and long-term mortality after noncardiac surgery. *Am Heart J*. 2013; 166:325–332. e1. [PubMed: 23895816]
 21. Nagele P. The Case for a Revised Definition of Myocardial Infarction-Resolving the Ambiguity of Type 2 Myocardial Infarction. *JAMA Cardiol*. 2016; 1:247–8. [PubMed: 27438099]
 22. Alpert JS, Thygesen KA, White HD, Jaffe AS. Diagnostic and therapeutic implications of type 2 myocardial infarction: review and commentary. *Am J Med*. 2014; 127:105–8. [PubMed: 24462011]
 23. Vasile VC, Saenger AK, Kroning JM, Klee GG, Jaffe AS. Biologic variation of a novel cardiac troponin I assay. *Clin Chem*. 2011; 57:1080–1. [PubMed: 21519039]
 24. Wu AH, Shea E, Lu QT, Minyard J, Bui K, Hsu JC, Agee SJ, Todd J. Short- and long-term cardiac troponin I analyte stability in plasma and serum from healthy volunteers by use of an ultrasensitive, single-molecule counting assay. *Clin Chem*. 2009; 55:2057–9. [PubMed: 19729470]
 25. Schindler EI, Szymanski JJ, Hock KG, Geltman EM, Scott MG. Short- and Long-term Biologic Variability of Galectin-3 and Other Cardiac Biomarkers in Patients with Stable Heart Failure and Healthy Adults. *Clin Chem*. 2016; 62:360–6. [PubMed: 26546635]
 26. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, Bassetti S, Steuer S, Winkler K, Peter F, Meissner J, Haaf P, Potocki M, Drexler B, Osswald S, Mueller C. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation*. 2011; 124:136–45. [PubMed: 21709058]
 27. Giannitsis E, Becker M, Kurz K, Hess G, Zdunek D, Katus HA. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. *Clin Chem*. 2010; 56:642–50. [PubMed: 20167697]
 28. Jaffe AS, Moeckel M, Giannitsis E, Huber K, Mair J, Mueller C, Plebani M, Thygesen K, Lindahl B. In search for the Holy Grail: suggestions for studies to define delta changes to diagnose or exclude acute myocardial infarction: a position paper from the study group on biomarkers of the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care*. 2014; 3:313–6. [PubMed: 25009249]
 29. Chew DP, Briffa TG, Alhammad NJ, Horsfall M, Zhou J, Lou PW, Coates P, Scott I, Brieger D, Quinn SJ, French J. High sensitivity-troponin elevation secondary to non-coronary diagnoses and death and recurrent myocardial infarction: An examination against criteria of causality. *Eur Heart J Acute Cardiovasc Care*. 2015; 4:419–28. [PubMed: 25505224]
 30. O'Connor CJ, Rothenberg DM, Soble JS, Macioch JE, McCarthy R, Neumann A, Tuman KJ. The effect of esmolol pretreatment on the incidence of regional wall motion abnormalities during electroconvulsive therapy. *Anesth Analg*. 1996; 82:143–7. [PubMed: 8712391]
 31. Ostergaard SD, Bolwig TG, Petrides G. No causal association between electroconvulsive therapy and death: a summary of a report from the Danish Health and Medicines Authority covering 99,728 treatments. *J ECT*. 2014; 30:263–4. [PubMed: 25166734]
 32. Briggs MC, Pasculli RM, Bryson EO, Aloysi AS, Popeo DM, Kellner CH. Troponins and electroconvulsive therapy (ECT): caution in reporting results. *Am J Med*. 2011; 124:e11. author reply e13.
 33. Boere E, Birkenhager TK, Groenland TH, van den Broek WW. Beta-blocking agents during electroconvulsive therapy: a review. *Br J Anaesth*. 2014; 113:43–51. [PubMed: 24942714]
 34. van den Broek WW, Leentjens AF, Mulder PG, Kusuma A, Bruijn JA. Low-dose esmolol bolus reduces seizure duration during electroconvulsive therapy: a double-blind, placebo-controlled study. *Br J Anaesth*. 1999; 83:271–4. [PubMed: 10618942]

Figure 1. CONSORT diagram – study flow

Of 115 patients enrolled, 100 patients had at least one pair of analyzable hscTnI levels before and 15–30 minutes after an ECT treatment. ECT = electroconvulsive therapy; hscTnI = high-sensitivity cardiac troponin I.

Figure 2.
Histogram of absolute (A) and relative (B) changes in hscTnI after ECT

Figure 3. HscTnI before and after ECT visits

Boxplots with Tukey's whiskers represent hscTnI levels (median [IQR]) at ECT visit one, two, and three. Panel A shows hscTnI levels before and 15–30 minutes after ECT of all patients: Before ECT one: 5.4 [4.6 – 7.5]; 15–30 minutes after ECT one: 5.3 [4.2 – 7.9]; before ECT two: 5.4 [4.6 – 8.1]; 15–30 minutes after ECT two: 5.4 [4.2 – 7.8]; before ECT three: 5.2 [4.1 – 7.0]; 15–30 minutes after ECT three: 5.3 [4.3 – 6.9]. Panel B shows hscTnI levels before, 15–30 minutes, and 2 hours after ECT of the subgroup with an additional blood sample obtained 2 hours after ECT: Before ECT one: 6.1 [4.6 – 8.2]; 15–30 minutes after ECT one: 6.1 [4.2 – 7.4]; 2 hours after ECT one: 6.4 [3.8 – 9.5]; before ECT two: 5.3 [5.0 – 7.8]; 15–30 minutes after ECT two: 6.1 [4.9 – 7.7]; 2 hours after ECT two: 5.5 [4.0 – 13.1]; before ECT three: 6.0 [4.2 – 10.1]; 15–30 minutes after ECT three: 6.3 [4.5 – 9.5]; 2 hours after ECT 3: 6.4 [4.1 – 9.2]. ECT = electroconvulsive therapy, hscTnI = high sensitivity cardiac troponin I.

Figure 4. Patients with new hscTnI elevation after ECT

The dashed line indicates the >99th sex-specific percentile URL. Individual patients (Graphs A–H) were followed for up to three visits. Clinical and numeric hscTnI data are shown in table 4. # = number of patient's ECT treatment, ECT = electroconvulsive therapy; hscTnI = high-sensitivity cardiac troponin I.

Table 1**Baseline Characteristics**

	No Elevated hscTnI N=92	Elevated hscTnI N=8	Total N=100	Stand. Diff
Patient Characteristics				
Age, years, mean (SD)	45 (14)	53 (19)	46 (14)	0.55
Male, N, %	49 (53)	4 (50)	53 (53)	0.05
Race, N (white / black / other)	82/7/3	8/0/0	90 / 7 / 3	0.34
Smoking history, N, %	53 (58)	6 (75)	59 (59)	0.25
Primary Indication for ECT, N, %				
Major depressive disorder	75 (82)	7 (88)	82 (82)	0.17
Bipolar disorder	14 (15)	1 (13)	15 (15)	
Posttraumatic stress disorder	1 (1)	0	1 (1)	
Severe eating disorder/OCD/depression	1 (1)	0	1 (1)	
Co-morbidities, N, %				
Hypertension	37 (40)	1 (13)	38 (38)	0.46
Hypercholesterolemia	20 (22)	4 (50)	24 (24)	0.75
Atrial fibrillation	3 (4)	0	3 (3)	0.30
Coronary artery disease	3 (3)	1 (13)	4 (4)	0.84
Previous MI	2 (2)	1 (13)	3 (3)	1.23
Congestive heart failure	2 (2)	0	2 (2)	0.26
Diabetes	11 (12)	2 (25)	13 (13)	0.51
Insulin-dependent diabetes	4 (4)	0	4 (4)	0.34
Chronic kidney disease	4 (4)	0	4 (4)	0.34
Stroke/TIA	2 (2)	0	2 (2)	0.26
Medication, N, %				
Aspirin	14 (15)	2 (25)	16 (16)	0.31
Beta-Blocker	16 (17)	0	16 (16)	0.52
Clopidogrel	1 (1)	0	1 (1)	0.19
Warfarin	2 (2)	0	2 (2)	0.26
ACE-Inhibitor	11 (12)	0	11 (11)	0.47
Statin	11 (12)	3 (38)	14 (14)	1.09
Angiotensin II receptor blocker	4 (4)	0	4 (4)	0.34
Calcium channel blocker	10 (11)	0	10 (10)	0.46
Diuretics	14 (15)	1 (13)	15 (15)	0.09

ACE – angiotensin-converting enzyme; ECT – electroconvulsive therapy; MI – myocardial infarction; OCD – obsessive compulsive disorder; SD – standard deviation; TIA – transient ischemic attack;

Table 2

ECT treatment details

Electro-convulsive Therapy (n=100), count, n	
At ECT visit 1	
Initial ECT titration and treatment #1	38
Treatment #2 – #5	38
Treatment #6 – #10	10
Treatment > #10	13
Unknown	1
Lead Placement	
Right unilateral	89
Bilateral	6
Bifrontal	4
Unknown	1
Required >1 stimulus	2
Duration of convulsion, seconds, median [IQR]	37 [27–50]
Duration of central seizure, seconds, median [IQR]	57 [37–80]

Count equals percent. ECT data were missing for one patient. # = number of patient's ECT treatment; ECT = electroconvulsive therapy; IQR = interquartile range.

Table 3

Patients with post-ECT hscTnI elevation >100%

Panel in Fig. 5	Sex Age, years	ECT visit 1 hscTnI, ng/L		ECT visit 2 hscTnI, ng/L		ECT visit 3 hscTnI, ng/L		Adverse Events	Ischemic ECG Signs	Adjudication	Other findings
		before	after	before	after	before	after				
		Treatment Nr, #	Treatment Nr, #	Treatment Nr, #	Treatment Nr, #	Treatment Nr, #	Treatment Nr, #				
with new hscTnI elevation after ECT											
A	Female, 40	2.5	19.7	2.7	2.9	2.5	2.1	bradycardia, bigeminus, hypertensive episode	ST-depression	NSTEMI	She developed bradycardia and new RBBB during ECT #2. Clinical cTnI peaked at 1.04 mcg/L and she received emergent CAG that showed stress-induced CMP (acute heart failure, LVEF 40%, no CAD), which resolved over a few days. After a pause of 3 month an uneventful course of 29 ECTs followed with prior beta-blocker.
	#2		#3		#4						
B	Female, 55	4.6	22			n/a		none	negative	negative	She had no adverse events or clinical symptom of MI at ECT #1 and an uneventful course of 28 ECTs.
	#1										
C	Male, 29	8.8	34.7	189.8	173.9			chest pain	negative	NSTEMI	He had chest pain with unspecific ECG changes after ECT #1, brief new atrial fibrillation during ECT #2, and urgent cardiology consult. Psychiatrist decided to discontinue ECT treatment.
	#1			#2		n/a					
D	Male, 62	4.4	10.2	10.8	10.2	11.2	12.5	hypertensive episode	negative	negative	He had no clinical symptom of MI at ECT #4 and an uneventful course of 49 ECTs.
	#4			#5		#6					
E	Male, 83	10	27.6	7.5	9.7	32.7	166.9	bradycardia, hypertensive episode	negative	negative	He had no clinical symptom of MI at ECT #3 and an uneventful course of 31 ECTs.
	#1			#2		#3					
F	Female, 29	5.1	10.5	18.7	17.4	13.6	11.4	hypertensive episode	negative	negative	She had no clinical symptom of MI at ECT #1 and an uneventful course of 13 ECTs.
	#1			#2		#3					
G	Male, 73	8.8	9.8	8.4	15.2	13.0	365.0	none	negative	negative	He had no clinical symptom of MI at ECT #3 and an uneventful course of 10 ECTs. He had a history of MI and coronary stent (CAG prior to ECT showed patent stent and no obstructive CAD).
	#1			#2		#3					
H	Female, 51	6.1	33.9	13.6	15.1	6.2	6.7	none	negative	negative	She had no clinical symptom of MI at ECT #2 and an uneventful course of 10 ECTs.
	#2			#3		#5					

Data in boxes show events of hscTnI increase >100% combined with >LOQ compared to before the respective ECT visit. Numbers in red are hscTnI values >99th sex-specific percentile URL. Patients were followed for up to three visits. HscTnI data of cases is plotted in the corresponding panel A – G of Figure 5. # = number of patient's; AE = adverse event; CAD = coronary artery disease; CAG = coronary angiography; CMP = cardiomyopathy; cTnI = cardiac Troponin I; ECG = electrocardiogram; ECT = electroconvulsive therapy; LOQ = limit of quantification (10 ng/L); LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; RBBB = right bundle branch block; URL = upper reference limit (female: 15.6 ng/L; male: 34.2 ng/L).

Table 4

ECT visits with elevation of hscTnI, blood pressure, and heart rate

	No hscTnI elevation	hscTnI elevation >100% and >LOQ		Missing BP and HR data	Total
		with elevation >99 th percentile URL	without elevation >99 th percentile URL		
Count, n (%)	235 (95.9)	6 (2.4)	3 (1.2)	1 (0.4)	245 (100)
Hypertensive Episode					
Systolic BP > 160, n (%)	152 (62.0)	5 (2.0)	2 (0.8)	1 (0.4)	159 (64.9)
Systolic BP > 200, n (%)	42 (17.1)	3 (1.2)	1 (0.4)	1 (0.4)	46 (18.8)
Tachycardia					
HR > 100, n (%)	152 (62.0)	3 (1.2)	2 (0.8)	1 (0.4)	157 (64.1)
HR > 150, n (%)	4 (1.6)	0 (0.0)	0 (0.0)	1 (0.4)	4 (1.6)

This table shows hemodynamic data of ECT visits where before-after samples of hscTnI were available. Reported proportions are percent of the total n=245. Periprocedural peak blood pressure and heart rate were used to calculate incidence of hypertensive episodes and tachycardia in ECT visits with and without new hscTnI elevation. Of 9 ECT visits with new hscTnI elevation >100% and >LOQ, 6 were with an elevation > 99th percentile URL and 3 were not. BP = blood pressure (mmHg); HR = heart rate (beats per minute); LOQ = Limit of Quantification (10ng/L); 99th percentile URL = upper reference limit (female: 15.6 ng/L; male: 34.2 ng/L).