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Relationship between Catecholamines and Major adverse cardiovascular events

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An abstract of
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Abstract

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By Venkat Sanjay Reddy Manubolu

Background: Sympathetic nervous system hyperactivity has been reported as an important mechanism in ischemic heart disease. Some of the prior studies have indicated that higher catecholamine levels could be independent risk factor for cardiovascular events[1], although the prognostic role of catecholamine changes to emotional provocation in patients with coronary artery disease (CAD) has not been previously explored.

Methods: We studied 695 patients with CAD enrolled between June 2011 and August 2014 from Emory University affiliated hospitals and clinics. Plasma catecholamines were assayed during a rest period prior to stress, and mid-way through a speech stressor task. Follow-up assessments performed regularly, for up to 3 years after enrollment. We used Cox proportional hazard models to determine the relationship between baseline noradrenaline/adrenaline levels, as well as their changes with stress, and major adverse cardiovascular events (MACE).

Results: No statistical significance was achieved for the hazard ratio of catecholamines in predicting MACE except for the change in adrenaline from baseline to stress, which, in multivariate analysis, predicted decreased MACE risk; CAD patients whose change in adrenaline from stress to rest were above the median had a hazard ratio of 0.48 ($p=0.02$) for MACE compared to those below the median.

Conclusion: We found a statistically significant negative association between increases in adrenaline, but not noradrenaline, from baseline to stress, and MACE. This suggests that blunted adrenaline reactivity is a negative prognostic finding in CAD patients.

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CHAPTER 1

LITERATURE REVIEW

Sympathetic nervous system hyperactivity has been reported as an important mechanism in ischemic heart disease. The role of the sympathetic nervous system and catecholamines in relation to coronary artery disease has been explored in prior studies and found that it could catecholamines could be a independent risk factor for cardiovascular events[1]. A study on understanding the mechanism and role of catecholamines on in cardiovascular events showed the indirect relation of catecholamine's and cardiovascular events. Myocardial ischemia-reperfusion due to a micro vascular spasm or a direct cardiac effect of catecholamines might be a possible mechanism. A rat model for understanding mechanism of emotional stress and catecholamine induced heart attack was studied, which indicated activation of α-adrenoceptors or β-adrenoceptors is the primary trigger of emotional stress-induced molecular changes in the heart[2].

Study on sleep deprivation and subsequent changes in catecholamines related to heart problems was studied, it was hypothesized, chronic stress and elevated norepinephrine levels in relation to sleep deprivation could aggravate autonomic imbalance, which subsequently develops or triggers cardiovascular events (3).

Physiologic responses to emotional excitement were studied in the CAD patients and healthy subjects. Circulating catecholamines increased in a similar fashion in both groups in response to emotional excitement.[4] The prognostic implications of

autonomic function have been assessed; in stable angina patients, low heart rate variability (HRV) predicted increased risk for CV death. Baseline catecholamine concentrations, however, carried no prognostic information.[5]

CHAPTER 2

MANUSCRIPT

Abstract

Background: Sympathetic nervous system hyperactivity has been reported as an important mechanism in ischemic heart disease. Some of the prior studies have indicated that higher catecholamine levels could be independent risk factor for cardiovascular events[1], although the prognostic role of catecholamine changes to emotional provocation in patients with coronary artery disease (CAD) has not been previously explored.

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Conclusion: We found a statistically significant negative association between increases in adrenaline, but not noradrenaline, from baseline to stress, and MACE. This suggests that blunted adrenaline reactivity is a negative prognostic finding in CAD patients.

Introduction

Sympathetic nervous system hyperactivity has been reported as an important mechanism in ischemic heart disease. The role of the sympathetic nervous system and catecholamines in relation to coronary artery disease has not been well explored in prior studies. Some of the prior studies have indicated that higher catecholamine levels could be independent risk factor for cardiovascular events.[1]

The physiology of circulating catecholamines, adrenaline and noradrenaline, originate from two sources. Adrenaline is released by the adrenal medulla upon activation of preganglionic sympathetic nerves innervating the tissue. This activation occurs during times of stress (e.g., exercise, heart failure, hemorrhage, emotional stress or excitement, pain). Noradrenaline is also released by the adrenal medulla (about 20% of its total catecholamine release is noradrenaline). The primary source of circulating noradrenaline is spillover from sympathetic nerves innervating blood vessels. Normally, most of the noradrenaline released by sympathetic nerves is taken back up by the nerves (some is also taken up by extra-neuronal tissues) where it is metabolized. A small amount of noradrenaline, however, diffuses into the blood and circulates throughout the body. At times of high sympathetic nerve activation, the

amount of noradrenaline entering the blood increases dramatically. Both the hormones act on beta and alpha adrenergic receptors of autonomic nervous system and affect cardiac activity by altering heart rate and contraction and effects blood pressure by mediating vasodilation and vasoconstriction.

The purpose of the study is to assess the relationship between major circulating catecholamines, adrenaline and noradrenaline, and major adverse cardiovascular outcomes in a group of patients with pre-existing coronary artery disease.

Methods

Study Sample and patient enrollment

Patients enrolled between June 2011 and August 2014 from Emory University affiliated hospitals and clinics, including Emory University Hospital, Grady Memorial Hospital, Emory Midtown Hospital and the Atlanta VA Medical Center. Patients were enrolled if they were between 30 to 79 years of age and had documented CAD, which is described as per the inclusion criteria. Informed consent obtained prior to enrollment as per study protocol guidelines.

Inclusion criteria

Study group consist of a clinical diagnosis of CAD as follows (must have at least 1 of the criteria below):

- Angiographically proven disease including at least 1 major vessel with evidence of disease, but with no specific minimum lumen diameter criteria.

- Prior MI, documented by typical elevation of enzymes and typical pain or ECG changes.
- Abnormal coronary intravascular ultrasound exam (IVUS) demonstrating atherosclerosis of at least 1 vessel.
- Post bypass surgery or post PCI (percutaneous coronary intervention)

Exclusion Criteria

- Unstable angina, myocardial infarction, decompensated congestive heart failure in past week.
- Severe concomitant medical problems expected to shorten life expectancy to less than 5 years.
- Pregnancy. Women of childbearing age who are not postmenopausal will be screened by pregnancy test.
- Patients deemed to be unsafe to hold anti-ischemic medications for the 48 hours prior to the testing.
- Systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg on the day of the test
- History of current alcohol or substance abuse or dependence (past year); or history of severe psychiatric disorder other than major depression, such as schizophrenia or psychotic depression
- All anti-ischemic meds were stopped for 48 hours prior to the test with only use of nitroglycerin as needed. Patients for whom withholding medications is considered unsafe, based on the assessment of our study

cardiologist or the patients' physician, will not be included in the study as well.

Measurement of catecholamines

Blood samples were collected on the day of the mental stress study. Psychological stress induced by asking the patient to perform a difficult speech task. Plasma catecholamines, mainly adrenaline and noradrenaline were assayed prior to stress and mid-way through the speech task. The 2-CAT high sensitivity kit was used according to the manufacturer's protocol (Rocky Mountain Diagnostics, CO). This method has high sensitivity (limit of detection 25 pg/ml), specificity, and reproducibility.

Mental Stress Testing

While the participant rests for 30 minutes, baseline hemodynamics were assessed every 5 minutes. Subjects were then subjected to the stressor and instructed to perform the mental stress task by a trained actor in a lab coat, with several other participants. Subjects were asked to imagine a close relative had been mistreated in a nursing home. They were asked prepare a statement and think about their responses for 2 minutes and then present it in front of an audience and video camera for 3 minutes.

Follow up and recording of events

Follow-up assessments performed every 6 months after the initial studies. Patients were seen in clinic every year and queried by telephone 6 months after clinic visits.

Clinic assessments included a brief medical history, physical examination, and resting electrocardiogram (ECG) to detect otherwise unrecognized acute MI. Major adverse cardiovascular events were defined as myocardial infarction, revascularization for angina, and death.

Analysis

To determine the impact of catecholamines on MACE, univariate and multivariate analyses were performed using Cox proportional hazards models. Independent variables included pre-stress, baseline catecholamine levels, post-stress catecholamine levels, and the difference between pre and post- stress catecholamine levels (or delta catecholamine levels). Each independent variable was examined in separate models. Because of a possible non-linear relationship with MACE, predictors were considered both as continuous and binary variables. Binary variables were derived dividing the sample based on median catecholamine levels. The proportional hazards assumption was visually examined using log-log plots. The Statistical package SAS 9.4 was used to perform the statistical analysis.

Data Management, confidentiality

Data was entered and managed using Clinical DataFax Systems Incorporated client-server data management software (iDataFax, Ontario, Canada). The validity and quality of data were checked through regular data queries for out-of-range values and missing values. Omissions and errors are conveyed to the study staff for corrections on an ongoing basis. All data is on Emory university servers and is password

protected to ensure patient safety and confidentiality per HIPPA. The Emory IRB approved the study.

Results

Among 695 patients enrolled in study, the mean (standard deviation) age was 63 (9) with subjects' age ranging from 34 to 79 years. 72% of the study sample was male and 30% of the study sample was African American. Several other risk factors and medications that affect cardiovascular events and stress were considered as confounding factors and included in the study (Table1). All patients included in study had documented evidence of baseline coronary artery disease. Patients with prior history of myocardial infarction comprised 38% of the study sample and 34% of the study sample had a previous history of CABG.

Results of the univariate analysis are presented in table 2. No statistical significance was achieved for the hazard ratio in any of the univariate cox proportional hazard models. Multivariate analysis was conducted for same variables to control for confounding factors and to assess the individual effect of pre- and post-stress catecholamines on MACE are presented on Table3, with the predictors listed in the footnote. Only the change in adrenaline (Delta adrenaline) when used a binary predictor, was a statistically significant predictor, with hazard ratio of 0.48 (p=0.02).

As illustrated by Kaplan Meier curves (Fig1), there is trending difference between patients above and below median delta adrenaline values (p-0.05) in predicting MACE. In other Kaplan Meier curves, no significant differences were observed.

Discussion

This study evaluated the significance of relation between catecholamines and their change during emotional stress and MACE. We found a negative relationship between increases in adrenaline and MACE such that those who responded to stress with more increases in adrenaline had an approximately 50% reduced risk of MACE.

This study may provide important information about catecholamines and its relationship to adverse cardiovascular events in patients with CAD. The large sample size and ethnic diversity of cohort are unique features and major strengths of the study. Prior studies have showed no significant relationship of catecholamines with cardiovascular events, and also concluded that there is no prognostic value of catecholamines.[5] Although this study involved MI, non-fatal MI, and revascularization in the outcome, it will provide information to further research in the field of catecholamines and cardiovascular events. Unfortunately, few studies have evaluated the specific relationship of cardiovascular events and catecholamines as a individual predictor.

<u>Limitations</u>

In large patient samples, we are restricted to analyses in plasma or urine, since measurements of cardiac noradrenaline spillover require invasive techniques. Noradrenaline concentrations in venous plasma or urine reflect overall sympathetic nerve activity, which may correlate poorly with cardiac sympathetic nerve activity.

There is significant proportion of missing data for predictors, pre stress and post stress adrenaline and pre stress and post stress noradrenaline variables. Missing data during the analysis lead to exclusion of about 20% of the positive outcomes in the data.

Conclusion

We found a statistically significant negative association between increases in adrenaline, but not noradrenaline, from baseline to stress, and MACE. This suggests that blunted adrenaline reactivity is a negative prognostic finding in CAD patients.

CHAPTER 3

PUBLIC HEALTH IMPLICATIONS

Heart disease and stroke are the first and third leading causes of death in the United States, respectively. The estimated health care spending and lost productivity (direct and indirect costs) of total CVD exceed $400 billion. A healthy lifestyle pattern may prevent more than 50% of all deaths due to cardiovascular disease. The challenging circumstances we face today, in combination with significant advances in research, provide strong justification for encouraging behavioral modifications and healthy lifestyle changes at individual and community level to prevent heart disease and stroke.

As previous research and epidemiological studies have proven that smoking, hypertension, high cholesterol, diabetes, mental stress and sedentary lifestyle are significant risk factors for cardiovascular disease mortality. Thus by changing these risk factors in a healthier direction, a significant proportion of deaths can be preventable. This study shows that, mental stress induced changes in catecholamine levels are significantly associated with major adverse cardiovascular events in patients with underlying CAD. Modifying these risk factors would significantly reduce morbidity and mortality associated with cardiovascular disease

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Table1. Characteristics and clinical data of subjects enrolled in the study (n=695)

Demographics	
Age	63 (9)
Male	503 (72%)
African American	211 (30%)
Risk Factors	
Current smoker	102 (15%)
Past smoker	304 (44%)
Diabetes	226 (33%)
Chronic renal disease	17 (2%)
HFpEF[a]	34 (5%)
HFrEF[b]	50 (7%)
Cerebrovascular disease	74 (11%)
Peripheral vascular disease	50 (7%)
History of Myocardial Infarction	262 (38%)
History of CABG[c]	236 (34%)
Average SBP [d]	136 (18)
Average DBP[e]	79 (10)
Average HR[f]	63 (11)
Catecholamines	
Pre stress Adrenaline	25 (22)
Post stress Adrenaline	48 (49)
Pre stress Noradrenaline	585 (371)
Post stress Noradrenaline	582 (631)
Medications	
Beta Blocker	520 (75%)
ACE [lg]	315 (46%)
Antidepressant	58 (23%)

[a]HFpEF- Heart failure preserved ejection fraction
[b]HFrEF- Heart failure reduced ejection fraction
[c]CABG- Coronary artery bypass graft
[d]SBP- Systolic blood pressure
[e]DBP- Diastolic blood pressure
[f]HR- Heart failure

[g]ACEI- Angiotensin converting enzyme inhibitor

Table 2. Univariate analysis of continuous and binary predictors using COX proportional hazard model

Variable	Chi-Square	P- value	Hazard Ratio
Continuous			
Delta Adrenaline	2.01	0.16	0.99
Delta Noradrenaline	0.30	0.58	1.00
Pre stress Adrenaline	0.27	0.60	1.00
Post stress Adrenaline	0.61	0.44	1.00
Pre stress Noradrenaline	0.04	0.85	1.00
Post stress Noradrenaline	0.17	0.68	1.00
Binary			
Delta Adrenaline	3.55	0.06	0.57
Delta Noradrenaline	0.02	0.90	0.97
Pre stress Adrenaline	0.52	0.47	1.21
Post stress Adrenaline	0.01	0.98	0.99
Pre stress Noradrenaline	1.14	0.29	1.32
Post stress Noradrenaline	0.34	0.56	1.17

Table 3. Multivariate analysis of continuous and binary predictors using COX proportional hazard model

Variable	Chi-Square	P- value	Hazard Ratio
Continuous			
Delta Adrenaline	2.18	0.14	0.99
Delta Noradrenaline	1.22	0.27	1.00
Pre stress Adrenaline	0.33	0.56	1.00
Post stress Adrenaline	0.65	0.42	1.00
Pre stress Noradrenaline	0.01	0.97	1.00
Post stress Noradrenaline	0.41	0.52	1.00
Binary			
Delta Adrenaline	5.43	0.02	0.49
Delta Noradrenaline	0.59	0.44	0.81
Pre stress Adrenaline	0.25	0.62	1.15
Post stress Adrenaline	0.18	0.67	0.89
Pre stress Noradrenaline	0.49	0.48	1.21
Post stress Noradrenaline	0.05	0.82	1.01

Figure1. Survival curve for change in adrenaline

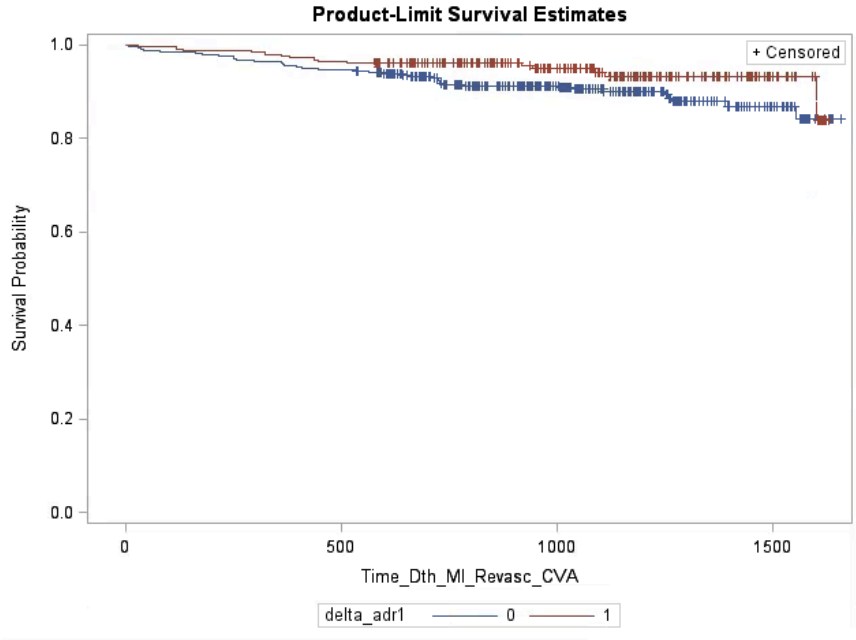

Figure2. Survival curve for pre stress adrenaline

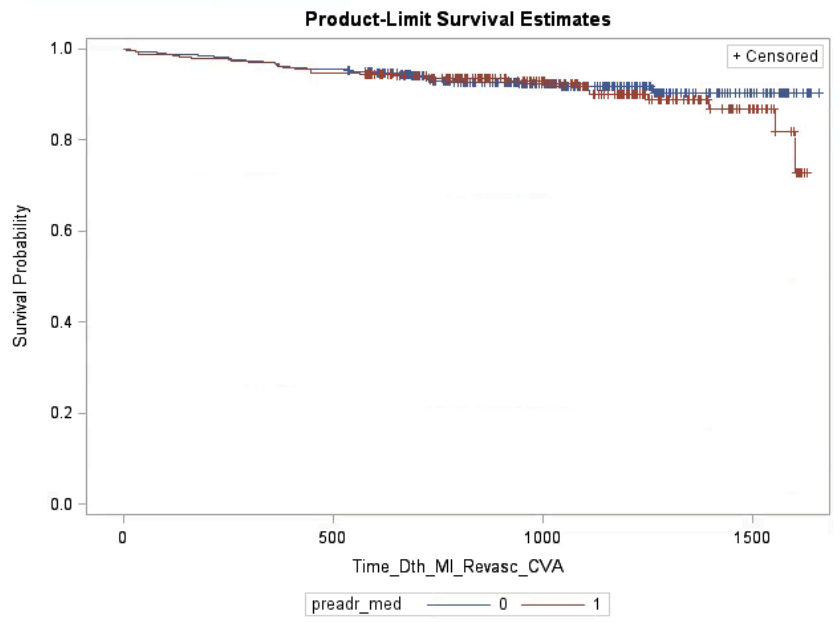

Figure3. Survival curve for post stress adrenaline

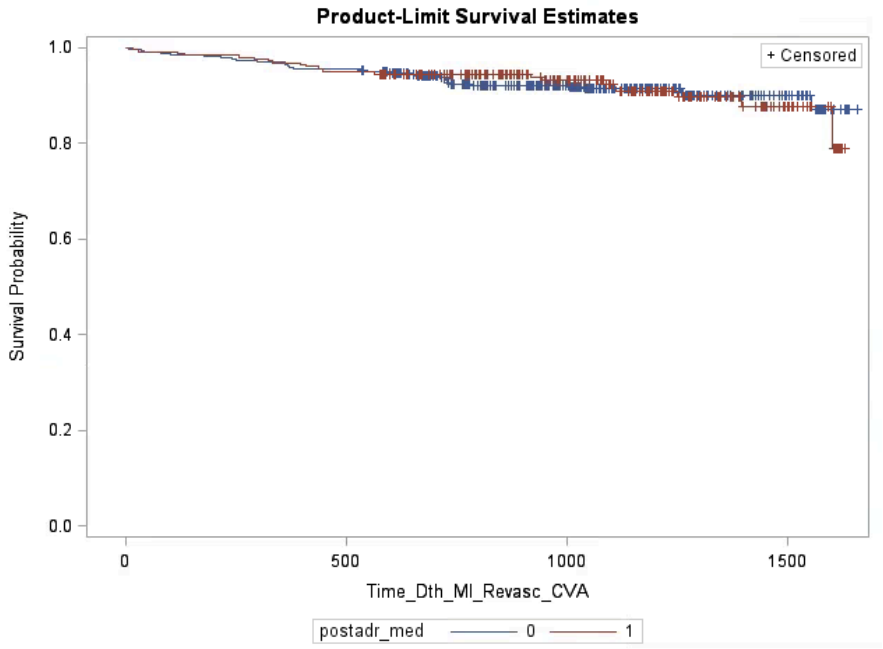

Figure4. Survival curve for change in noradrenaline

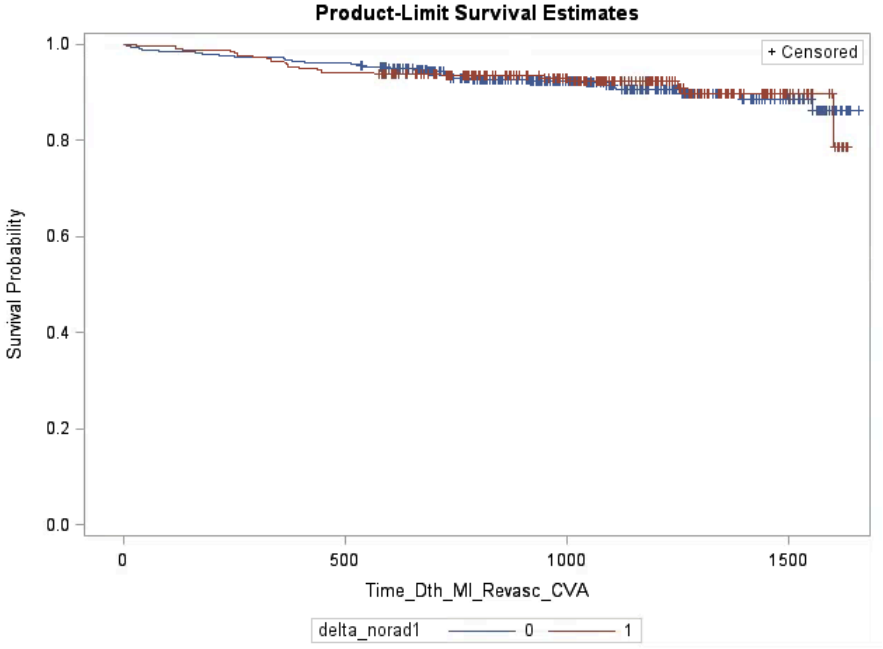

Figure5. Survival curve for pre stress noradrenaline

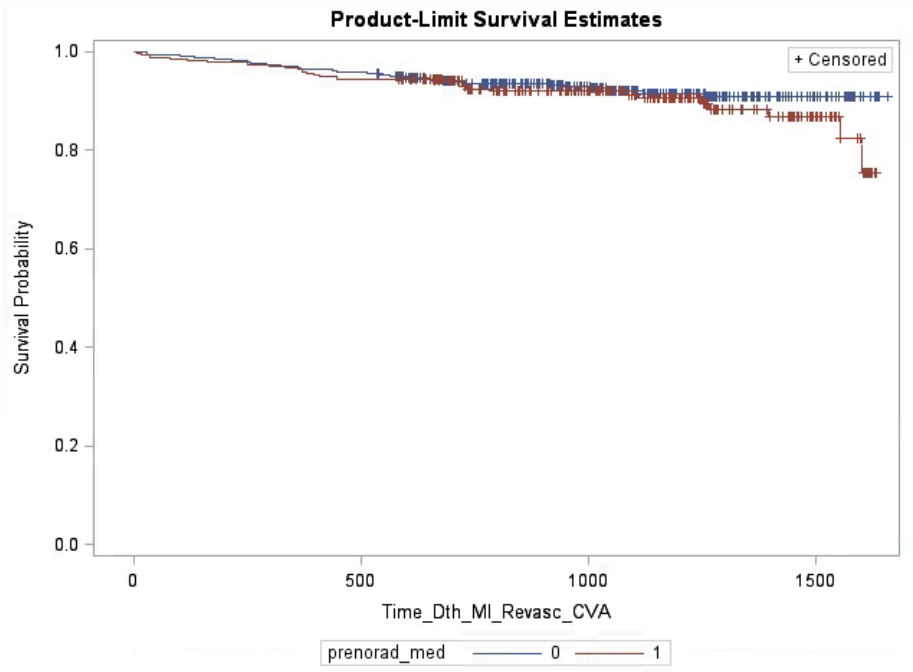

Figure 6. Survival curve for post stress noradrenaline