Cortisol dynamics are associated with electrocardiographic abnormalities following the aneurysmal subarachnoid hemorrhage

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ABSTRACT

Context: Electrocardiographic (ECG) abnormalities are common following subarachnoid hemorrhage (SAH). It probably represents cardiovascular stress after SAH. **Aims:** The purpose of this study was to assess cortisol dynamics in relation to the ECG abnormality and disease course of SAH. **Settings and Design:** The study follows a consecutive cohort of aneurysmal SAH patients, who underwent surgery within 72 hours of onset, and they were followed up for 10 days. **Materials and Methods:** Serum cortisols, cortisol-binding globulin (CGB), adenocorticotropic hormone were measured (between 08.00-09.00 hours) preoperatively and then on postoperative days (PODs) 2, 4, 7, and 10. Electrocardiographs (ECG) were recorded on initial assessment and after surgery on daily basis in ICU. ECG abnormalities will be followed up by measurement of cardiac troponin T to quantify the myocyte necrosis. **Statistical Analysis Used:** Logistic regression analysis using commercial available software STATA 9. **Results:** A total of 44 patients (20 M and 24 F) were eligible for the cohort analysis. Average patient age is 52.02 years (52.02 ± 11.23), and 86% (6/44) arrived with World Federation of Neurosurgical Society Scale grade 3 or better. The ECG abnormality was found in 10 cases (22.7%), but the abnormal TnT (>1 µg/l) were found in eight cases, and two cases contribute to the mortality. The ECG abnormalities are significantly associated with total cortisol on day 4 ($P < 0.05$) and free cortisol on day 2 ($P = 0.0065$). **Conclusions:** Elevated levels of morning cortisol within the first four days after surgery are associated with the ECG abnormality.

Key words: Aneurismal subarachnoid hemorrhage, cortisol dynamic, Electrocardiographic abnormality, neurological deficits, outcome

INTRODUCTION

Electrocardiographic (ECG) abnormalities after subarachnoid hemorrhage (SAH) are a well-recognized phenomenon, but their significance is still unclear. The first report was in 1954, Burch described "cerebral T-wave" ECG abnormalities in patients with SAH.[1] Unfortunately, many reports also show that the ECG abnormalities were not always representing a myocardial infarct or injury.[2] This condition probably represents cardiovascular stress after SAH, and it might be associated with serum cortisol. It is interesting to study the cortisol dynamics in relation to the ECG abnormality and the disease course after aneurismal SAH.

MATERIALS AND METHODS

Study design

This is a prospective cohort study of SAH patients admitted to Siloam Hospital Lippo Village Neuroscience

Centre, conducted between January 2009 and June 2011. This study was designed to describe the cortisol dynamics in relation to the ECG abnormality after aneurismal SAH. The study follows a consecutive cohort of aneurysmal SAH patients, age > 18 years, who underwent clipping surgery within 72 hours of onset, and they were followed up until 10 days after surgery. The exclusion criteria were glucocorticoid medication during admission or treatment, sepsis, pregnancy, history of cardiomyopathy, or prior myocardial infarction. We also exclude patient who died on first postoperative day (POD).

Patient population and clinical data collection

Demographic data including age, sex, and history of coronary artery disease were collected. All patients underwent CT Angiography to identify the aneurysm location, and to reduce the bias, only patients who underwent clipping surgery were enrolled. The neurological status was assessed at the time of admission and graded according to WFNS Scale (World Federation of Neurosurgical Society Scale).[3]

Electrocardiographic study and laboratory study

Electrocardiographs (ECG) were recorded on initial assessment and after surgery on daily basis in ICU. ECG abnormalities include ST elevation, ST depression, and Negative T-wave. Only abnormal ECG will be followed by measurement of Cardiac Troponin T (TnT) to confirm and to quantify the myocyte necrosis. The samples were analyzed with immunoassay using TnT test kit (cat no. 942-940), that is intended for use only with the AQT90 Flex analyzer. The lowest detectable level was 0.01 µg/l, and maximum quantifiable level was 25 µg/l. In this study, the TnT level >1.0 µg/l was considered abnormal.

All patients or their next of kin provided consent for this study, which is approved by the Institutional Review Board of Universitas Hassanuddin Makassar. A ten-cc sample of venous blood was taken preoperatively, then every morning (08.00-09.00 hrs) on PODs 2, 4, 7, and 10. All serum and plasma were stored at -80°C until the completion of study. Serum cortisols, cortisol-binding globulin (CGB), and adenocorticotropic hormone (ACTH) were measured. Serum cortisol levels were measured with an immunoassay using Elecsys cortisol kit (cat no 11875116 122). CGB levels were measured with radioimmunoassay using transcortin RIA (cat no MG13061). ACTH levels were measured with an immunoassay using ALPCO immunoassay (cat 21-ACTHU-E01, lot 1391). Free cortisol were calculated according to Coolens' equation.[4] Daily clinical assessments were done by the investigator and another independent clinician.

Statistical analysis

Clinical data were compared between the patients with and without ECG abnormality. Logistic regression analysis between cortisol, free cortisol, and ECG abnormality were analyzed using commercial available software STATA 9.

RESULTS

A total of 44 patients (20 M and 24 F) were eligible for the cohort analysis. Average patient age is 52.02 years (52.02 ± 11.23), and 86% (6/44) arrived with WFNS grade 3 or better. The ECG abnormality was found in 10 cases (22.7%), and the abnormal TnT (>1 µg/l) were found in eight cases, and two of those eight cases contribute to the mortality. The ECG abnormality was not associated with initial assessment of WFNS grade ($P > 0.05$). One patient died on day 15 because of severe vasospasm and myocardial infarct. Another patient died on day 16 due to pneumonia and myocardial infarct. The distribution of mean serum cortisol [Figure 1] during the first four days showed higher level on patients with abnormal ECG. It is significantly associated with ECG abnormality on day two and day four ($P < 0.05$). It also shows a strong relationship ($P = 0.049$) [Table 1].

Table 1: Analysis of relationship between serum cortisol, free cortisol, and ECG

Variable	LR Chi2	OR	Std error	Z	P > |Z|	95% CI	Pseudo R2
Cortisol day 0	0.322	1.02	0.02	0.99	0.32	0.98;1.06	0.0208
Cortisol day 2	3.51	1.05	0.033	1.79	0.074	0.99;1.12	0.0761
Cortisol day 4	4.31	1.08	0.04	1.97	**0.049**	1.00;1.16	0.0915
Cortisol day 7	0.12	0.98	0.04	-0.34	0.732	0.90;1.07	0.0032
Cortisol day 10	0.05	0.98	0.047	-0.22	0.827	0.90;1.08	0.0019
Free cortisol day 0	1.52	1.55	0.56	1.23	0.219	0.76;3.16	0.033
Free cortisol day 2	6.54	2.56	1.01	2.39	**0.017**	1.18;5.55	0.1419
Free cortisol day 4	2.53	2.06	0.96	1.55	0.122	0.82;5.15	0.0536
Free cortisol day 7	0	0.98	0.29	-0.06	0.954	0.54;1.78	0.0001
Free cortisol day 10	0.3727	1.76	1.05	0.95	0.342	0.54;5.65	0.0306

Figure 1: The distribution of mean serum cortisol for the first 10 days after surgery, among the patients with normal and abnormal ECG
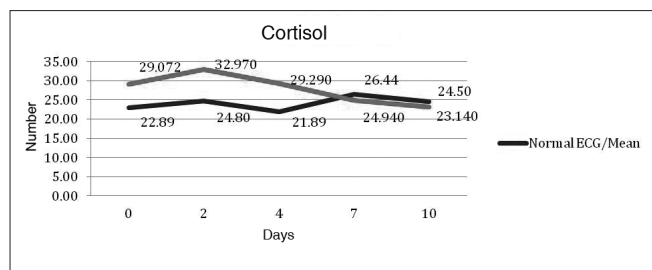

Figure 2: The distribution of mean free cortisol for the first 10 days after surgery, among the patients with normal and abnormal ECG

The distribution of mean free cortisol [Figure 2] also showed higher level on patients with abnormal ECG during the first four days after surgery. It is significantly associated with the ECG abnormality on day two ($P = 0.0065$). The Odd Ratio for day two free cortisol is 2.56 and the conversion to the risk is 72%. The cortisol dynamics of the two cases with normal TnT were not significantly different compared to the abnormal TnT patients ($P > 0.05$).

DISCUSSION

The significance of ECG abnormalities after SAH is still unclear. The first report was in 1954, Burch described "cerebral T-wave" ECG abnormalities in patients with SAH.[1] Unfortunately, many reports also show that the ECG abnormalities were not always representing a myocardial infarct or injury.[2] Such a case reported by Cropp and Manning, a patient with SAH and surgery was postpone because of ECG changes that was consistent with anterior myocardial infarction.[2] The patient died, and the autopsy findings included ruptured aneurysm and no cardiac abnormalities. In our series, we found two cases (2/10) with abnormal ECG that indicate a myocardial infarct, but the TnT level was normal (<1 μg/l). This present study showed that 20% of patient with abnormal ECG did not represent a myocardial infarct.

On the other hand, elevated cardiac enzyme levels, myocardial necrosis, and left ventricular (LV) systolic dysfunction have been described after SAH,[5-7] and the incidence of LV dysfunction could reach 10%.[8-10] In our series, we found eight (18%) patients with abnormal ECG and confirmed with abnormal TnT level.

There is an evidence that shows the role of abnormal sympathetic innervations that produce the LV dysfunction, although normal myocardial perfusion.[11] This condition probably represents cardiovascular stress after SAH, and it might be associated with serum cortisol. The cortisol secretion dynamics in the very acute phase in aneurysmal SAH is yet unclear. Sustained elevation of serum cortisol
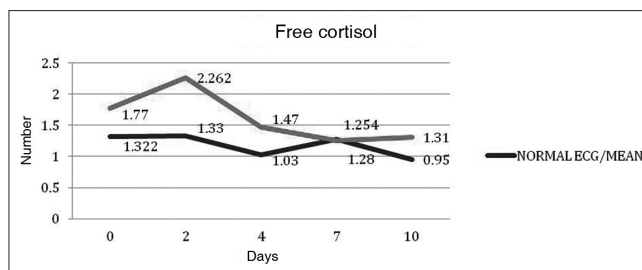
level have been proved to cause sensitization of coronary vasoconstricting responses.[12] In the present study, the first four days' morning serum cortisol levels were associated with ECG abnormality. It might represent cardiovascular stress following aneurysmal SAH. The morning free cortisol level was also associated with ECG abnormality. This fact suggests that the free cortisol might play some biological role, because 5 to 10% of unbound cortisol is biologically active and the rest of it is bound to CBG.[13]

CONCLUSIONS

Elevated levels of morning serum cortisol within the first four days after surgery are associated with the ECG abnormality. It might represent the cardiovascular stress or even play some biological role.

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REFERENCES

1. Burch GE, Meyers R, Abildskov JA. A new electrocardiographic pattern observed in cerebrovascular accidents. Circulation 1954;9: 719-23.
2. Cropp GJ, Manning GW. Electrocardiographic changes simulating myocardial ischemia and infarction associated with spontaneous intracranial hemorrhage. Circulation 1960;22:25-38.
3. Drake CG. Report of world federation of neurological surgeons committee on a universal subarachnoid hemorrhage grading scale. J Neurosurg 1988;68:985-6.
4. Coolens JL, Van BH, Heyns W. Clinical use of unbound plasma cortisol as calculated from total cortisol and corticosteroid-binding globulin. J Steroid Biochem 1987;26:197-202.
5. Fabinyi G, Hunt D, McKinley L. Myocardial creatine kinase isoenzyme in serum after subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 1977;40:818-20.
6. Horowitz MB, Willet D, Keffer J. The use of cardiac troponin-I (cTnI) to determine the incidence of myocardial ischemia and injury in patients with aneurysmal and presumed aneurysmal subarachnoid hemorrhage. Acta Neurochir (Wien) 1998;140:87-93.
7. Doshi R, Neil-Dwyer G, Stott A. Hypothalamic and myocardial lesions after subarachnoid hemorrhage. J Neurol Neurosurg Psychiatry 1977;40:821-6.
8. Kuroiwa T, Morita H, Tanabe H, Ohta T. Significance of ST segment elevation in electrocardiograms in patients with ruptured cerebral aneurysms.

Acta Neurochir (Wien) 1995;133:141-6.

9. Kono T, Morita H, Kuroiwa T, Onaka H, Takatsuka H, Fujiwara A. Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: Neurogenic stunned myocardium. J Am Coll Cardiol 1994;24:636-40.

10. Davies KR, Gelb AW, Manninen PH, Boughner DR, Bisnaire D. Cardiac function in aneurysmal subarachnoid haemorrhage: A study of electrocardiographic and echocardiographic abnormalities. Br J Anaesth 1991;67:58-63.

11. Banki NM, Kopelnik A, Dae MW, Miss J, Tung P, Lawton MT, *et al*. Acute neurocardiogenic injury after subarachnoid hemorrhage. Circulation 2005;112:3314-9.

12. Hizume T, Morikawa K, Takaki A, Abe K, Sunagawa K, Amano M, *et al*. Sustained elevation of serum kortisol level causes sensitization of Coronary vasoconstricting responses in pigs *in vivo*. A possible link between stress and coronary vasospasme. Circ Res 2006;99:767-75.

13. Siiteri PK, Murai JT, Hammond GL, Nisker JA, Raymoure WJ, Kuhn RW. The serum transport of steroid hormones. Recent Prog Horm Res 1982;38:457-510.