行政院國家科學委員會專題研究計畫　成果報告

腦類排鈉肽胜血清濃度對於全身麻醉病患處理的應用價值

計畫類別： 個別型計畫
計畫編號： NSC92-2314-B-002-257-
執行期間： 92 年 08 月 01 日至 93 年 07 月 31 日
執行單位： 國立臺灣大學醫學院麻醉科

計畫主持人： 葉惠敏

報告類型： 精簡報告

處理方式： 本計畫可公開查詢

中　華　民　國 93 年 8 月 5 日

附件一

行政院國家科學委員會補助專題研究計畫 ■ 成 果 報 告 □期中進度報告

腦類排鈉肽血清濃度對於全身麻醉病患處理的應用價值

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計畫主持人：葉惠敏
共同主持人：
計畫參與人員：

成果報告類型(依經費核定清單規定繳交)：■精簡報告　□完整報告

本成果報告包括以下應繳交之附件：
□赴國外出差或研習心得報告一份
□赴大陸地區出差或研習心得報告一份
□出席國際學術會議心得報告及發表之論文各一份
□國際合作研究計畫國外研究報告書一份

處理方式：除產學合作研究計畫、提升產業技術及人才培育研究計畫、列管計畫及下列情形者外，得立即公開查詢
□涉及專利或其他智慧財產權，□一年□二年後可公開查詢

執行單位：國立臺灣大學醫學院麻醉科

中　華　民　國　93　年　8　月　5　日

中文摘要及關鍵詞
背景：血漿 N 端原腦類排鈉肽胜(NTproBNP)是心臟衰竭的重要指標，本研究探討 NTproBNP 在非心臟手術病患中，預測術後心臟併發症的價值。
方法：本研究共納入 190 名患者，除一般術前評估外，我們在麻醉前測量 NTproBNP 的數值。而心臟併發症則定義為心因性死亡，急性冠心症，心衰竭及危及血行動力學的心律不整。
結果：在 190 名患者中，15 人有心臟併發症，其中有四名急性冠心症，13 名心臟衰竭。這 15 名患者的 NTproBNP 數值明顯高於其他患者，我們並發現，NTproBNP 大於 450 ng/L 將可以預測心臟併發症的發生，其敏感度為 100%而特異度為 82.9%，本研究中，ASA 分類，年齡及臨床的心功能不全皆可以預測心臟併發症，若將這些因素及 NTproBNP 納入多變數分析，其結果顯示，唯有 NTproBNP 是獨立的預測因子。
結論：NTproBNP 可預測非開刀手術患者的預後心臟併發症。
關鍵詞: N 端原腦類排鈉肽胜，非心臟手術，心臟併發症

英文摘要及關鍵詞
Background: Plasma level of N-terminal pro-brain natriuretic peptide (NTproBNP) is a sensitive marker for heart failure. We tested the hypothesis that the plasma level of NTproBNP is a predictor of cardiac complications in patients undergoing non-cardiac surgery.
Method: We included 190 consecutive patients who underwent elective non-cardiac surgery requiring general anesthesia. In addition to routine pre-operative evaluations, serum NTproBNP level was measured before anesthesia. Cardiac complications were defined as cardiac death, acute coronary syndrome, heart failure, and hemodynamic compromising cardiac arrhythmias.
Results: Among the 190 patients, 15 had cardiac complications, including 4 with acute coronary syndrome and 13 with congestive heart failure. Serum NTproBNP levels were significantly higher in patients with cardiac complications than in those without. NTproBNP greater than 450 ng/L was predictive of cardiac complications with a sensitivity of 100% and a specificity of 82.9%. A higher ASA class, aging, and clinical cardiac impairment were also significantly associated with cardiac complications. In the multivariate analysis, NTproBNP level was the only independent factor associated with cardiac complications.
Conclusion: Plasma NTproBNP level is an independent predictor of cardiac complications in patients undergoing non-cardiac surgery. Pre-operative measurement of NTproBNP may contribute to the identification of patients at risk for such complications.

Key words: pro-brain natriuretic peptide, cardiac complications, surgical risk

前言:

Brain natriuretic peptide (BNP) is one of the cardiac natriuretic peptides. It was initially discovered in porcine brain and was therefore named.[1] It is now known, however, that the left ventricle instead of the brain, is the major source of BNP.[2] It is secreted by the left ventricle in response to wall stress. BNP is synthesized as a pro-hormone called proBNP. Upon secretion, it is cleaved into the N-terminal proBNP (NTproBNP) and the bioactive BNP.[3,4] NTproBNP has been demonstrated to be useful in the clinical assessment of left ventricular dysfunction, heart failure, and risk stratification of patients with acute coronary syndromes.[5-9] Furthermore, it has been shown that serum NTproBNP is elevated in patients with asymptomatic left ventricular dysfunction before their symptoms become overt.[10,11]

Cardiac complications are a major cause of mortality and morbidity in patients undergoing non-cardiac surgery.[12] Among the many predictors of cardiac complications, heart failure is an important one.[13-15] Patients with a history of heart failure tend to be intolerant of hemodynamic changes and are prone to pulmonary congestion. The underlying causes of ventricular dysfunction may also contribute to cardiac complications. However, the diagnosis of heart failure is difficult in some cases because some patients with left ventricular dysfunction may remain asymptomatic.[16] Furthermore, patients with left ventricular diastolic dysfunction may have normal cardiac size and normal left ventricular ejection fraction. Because NTproBNP is a sensitive marker of left ventricular dysfunction, we tested the hypothesis that the plasma level of NTproBNP is useful in predicting cardiac complications in patients undergoing non-cardiac surgery.

方法

Patients

The study included 190 consecutive ASA class I-IV patients undergoing elective non-cardiac surgery requiring general anesthesia. ASA classification was applied as previously described.[17] The study was approved by the Institutional Review Board and written consents were obtained. Pre-operative evaluations included history taking, physical examination, and laboratory

studies. Patients were considered clinically as having cardiac impairment if they had one or more of the followings: 1) a history of coronary artery disease or heart failure; 2) appropriate symptoms and signs of heart failure; 3) on treatment for heart failure with appropriate responses; or 4) objective signs of impaired left ventricular function or lung congestion, such as cardiomegaly and lung congestion, documented in chest X-ray or reduced left ventricular ejection fraction in echocardiography or ventriculography.

Measurement of serum NTproBNP levels

Serum NTproBNP levels were measured using a chemiluminescent immunoassay kit (Roche Diagnostic, Indianapolis, IN, USA). Blood samples were obtained before anesthesia and were anti-coagulated with EDTA. The blood samples were then centrifuged and the plasma portions were stored in a freezer at -70^{o}C. Commercial controls (PreciControls) were provided by Roche Diagnostics. NTproBNP was measured on an Elecsys 2010 analyzer (Roche Diagnostic, Indianapolis, IN, USA).

Cardiac complications

Cardiac complications were documented by the study physicians and were validated by two independent investigators who were blinded to the clinical and NTproBNP results. When the two investigators disagreed, the decision was made by a third independent investigator. Cardiac complication was defined as (1) death from a cardiac cause; (2) acute coronary syndrome, including myocardial infarction and unstable angina; (3) congestive heart failure; and (4) serious cardiac arrhythmia. Cardiac death was defined as death caused by myocardial infarction, dysrhythmia, or congestive heart failure. Diagnosis of myocardial infarction required an elevation of the cardiac enzymes (creatine-kinase MB isoenzyme or troponin-I) and ECG evidence of myocardial infarction (new Q waves or ST-T wave changes) in at least two adjacent leads.

Unstable angina was defined as anginal chest pain that was not responsive to rest and nitroglycerin, associated with transient ST-segment and T-wave changes without the development of Q waves or elevated enzyme levels. Diagnosis of congestive heart failure required one or more of the following: 1) the development of symptoms or signs of pulmonary edema (shortness of breath, basal rales, arterial desaturation); 2) evidence of left ventricular failure (cardiomegaly, ventricular gallop sound, jugular venous distention); or 3) abnormal results on chest radiography (vascular redistribution and interstitial or alveolar edema). Serious cardiac tachycardia was defined as sustained arrhythmia lasting longer than 30 second, with hemodynamic compromise.

Statistical analysis

Data were expressed as mean ± standard deviation except for NTproBNP measurements, which were expressed as median and range because the values were not normally distributed. Wilcoxon signed-sum test (for NTproBNP) or Student's *t* test (for variables other than NTproBNP) was used for comparing continuous variables while Chi-square test was used for comparing dichotomous data. Logistic regression analysis was used for correlation between cardiac complications and ASA classes. Linear regression was used for correlation between NTproBNP and age, and ASA classes. The receiver operative characteristic (ROC) curve and its area under the curve were calculated to evaluate the accuracy of NTproBNP in predicting cardiac complications. Multivariate analysis was performed to determine independent factors associated with cardiac complications. Only variables with a $p < 0.1$ in the univariate analysis were placed in the multivariate model. A $p < 0.05$ was considered as significant.

結果

Characteristics of the study patients

There were a total of 190 patients (96 men and 94 women) included in the present study with a mean age of 57.2±17.8 years. There were 37 (19.5%) patients in ASA class I, 47 (24.7%) in ASA class II, 77 (40.5%) in ASA class III, and 29 (15.3%) in ASA class IV. Among the 190 patients, 158 patients underwent a major surgery (intra-abdominal surgery in 94, thoracic surgery in 29, craniotomy in 30 and major vascular surgery in 5) while 32 underwent a minor surgery. There were 26 patients with cardiac impairment as judged by clinical evaluation. None of the patients had angina before the operation. Coronary revascularization had been performed to relieve angina before surgery in 2 patients. The mean plasma NTproBNP level was 1200±4560 ng/L (median 107.7, range 5-35000).

Comparison between patients with and without cardiac complications (Table 1)

Among the 190 patients, 15 (7.9%) had cardiac complications. Among these, there was 1 cardiac death (death due to myocardial infarction), 4 with acute coronary syndrome (all had myocardial infarction, including the one who died), and 13 with congestive heart failure. Patients with cardiac complications were significantly older than those without (67.7±13.8 years vs 55.6±17.8 years, p<0.018). The serum creatinine level was not significantly different between the two groups (1.10±0.86 mg/dL vs 1.26±1.38 mg/dL, for patient with and without cardiac complications, p<0.871). The incidences of cardiac complications were 2.7%, 6.4%, 6.5%, and

20.1% for ASA classes I, II, III, and IV patients, respectively, indicating that a higher ASA class had a higher association with cardiac complications (p<0.027). The incidence of having a cardiac complication was not significantly influenced by whether the patient underwent a major surgery or not (12/158 vs 3/32, p<0.733). Patients with clinical evidences of cardiac impairment had a higher incidence of developing cardiac complications [5/26(19.2%) vs 10/164(6.1%), p<0.021].

NTproBNP level and cardiac complications

The serum NTproBNP level was significantly higher in patients with cardiac complications than in patients without (median 1217, range 462-35000 vs median 94.6, range 5-35000 ng/L, p<0.001). Figure 1 shows NTproBNP levels in patients with and without cardiac complications. If a cut-off value of 450ng/L was used for the elevation of NTproBNP, all of the patients with cardiac complications would have an elevated NTproBNP level. We also found that NTproBNP elevation had a sensitivity of 100% and a specificity of 82.9% in predicting cardiac complications. We also performed an ROC analysis to evaluate the accuracy of NTproBNP in predicting cardiac complications. The area under the ROC curve was 0.934 with a 95% confidence interval of 0.897 to 0.971 (Fig. 2).

Factors influencing NTproBNP level

Plasma NTproBNP level was significantly influenced by serum creatinine level, age, ASA class, and clinical cardiac impairment. In linear regression analysis, plasma NTproBNP level positively correlated with serum creatinine level, with a correlation co-efficiency of 0.34 and a regression co-efficiency of 1204 $ng*L^{-1}*mg^{-1}*dL$ (p<0.001). Plasma NTproBNP level also positively correlated with age, with a correlation co-efficiency of 0.178 and a regression co-efficiency of 45.5 $ng*L^{-1}*year^{-1}$ (p<0.014). NTproBNP level also positively correlated with ASA class (r=0.222, p<0.002). Patients with clinical cardiac impairment had a higher NTproBNP level (median 663.1, range 15.3-35000 ng/L vs median 91.9 range 5-29207 ng/L, p<0.001). Plasma NTproBNP level was not significantly different between patients undergoing a major surgery and those undergoing a minor surgery (p<0.127). The distribution of major and minor surgery was not significantly different between patients with NTproBNP greater or less than 450 ng/L (p < 0.270).

Multivariate and subgroup analysis

In the univariate analysis, we found that age, ASA class, cardiac impairment, and NTproBNP were all significantly associated cardiac complications. Multivariate analysis was performed to evaluate whether these factors were independently associated with cardiac complications. In a logistic regression model including all of these four factors, NTproBNP was the only factor independently associated cardiac complications. The p values for age, ASA class, and clinical cardiac impairment were 0.181, 0.307, and 0.959, respectively, in the multivariate logistic regression analysis. In a subgroup of patients with NTproBNP greater than 450ng/L (n=45), age, ASA class, and clinical cardiac impairment were no longer significant predictors for cardiac complications.

討論

In the present study, we found that the plasma level of NTproBNP is a sensitive predictor for cardiac complications. Congestive heart failure has been identified in several studies as a risk factor for a poor outcome in patients undergoing non-cardiac surgery. The plasma NTproBNP level, however, is a new marker for heart failure. Its value in pre-operative risk assessment has not yet been reported before. To the best of our knowledge, this is the first study to investigate the association between NTproBNP and surgical risk. We found that patients with cardiac complications had a higher NTproBNP level. When a cut-off value of 450 ng/L was used, cardiac complications happened almost exclusively in patients with an elevated NTproBNP level.

NTproBNP as an early marker of heart failure

Patients with compensated heart failure may have no symptom or signs on clinical assessment. During anesthetic and surgical processes, there might be large fluctuations in vascular tone and effective volume, and overt heart failure might occur. It is a diagnostic challenge to identify these patients. The plasma level of NTproBNP is a sensitive marker for heart failure and can be used to screen for heart failure before clinical symptom signs are overt.[10-11] In the present study, 15 patients had cardiac complications. Among them, 10 had no clinical evidence of cardiac impairment. Elevated NTproBNP was the only hint that the patient had heart failure.

Cut-off value for NTproBNP

The cut-off value for NTproBNP is controversial. When using the chemiluminescent kit from Roche Diagnostic, the 97.5 percentile level is 155 ng/L and 84 ng/L for women and men, respectively, under the age of 50 years. For women and men aged between 50-65 years, the 97.5 percentile level is 222 ng/L and 194 ng/L, respectively (Roche Diagnostic, proBNP kit pamphlet). In clinical practice, there is no consensus cut-off value. The reported cut-off value ranged from below 100 ng/L to above 1000 ng/L.[5-8, 11, 18-22]

In a ROC analysis, we found that a cut-off value of 450 is associated with good sensitivity and reasonable specificity. With this cut-off value, cardiac complications happened almost exclusively in patients with elevated NTproBNP (sensitivity 100%) although patients with high NTproBNP did not necessarily develop cardiac complications (specificity 82.9%). In patients with elevated NTproBNP, necessary pre-operative work up and treatment are advised. Adequate intra-operative monitoring and judicious drug selection should likewise be considered.

NTproBNP or BNP

Both BNP and NTproBNP levels have been reported to be markers for congestive heart failure because both were secreted in response to ventricular wall stress. BNP is the bioactive peptide while NTproBNP do not have action. A comparison between the two has been made.[21-23] NTproBNP is more stable than BNP and has a longer half-life, while BNP is rapidly degraded within minutes. Therefore, BNP is suitable for measurement of acute changes in the cardiac filling state while NTproBNP may reflect ventricular filling pressure for a longer time period. From a technical point of view, measurement of the NTproBNP using the chemiluminescent kit from Roche Diagnostic is more precise and had a smaller co-efficiency of variation than BNP.[23] The process of measurement is automated and has been approved by the American Food and Drug Administration (FDA). This NTproBNP chemiluminescent kit is more likely to be used in a routine biochemical laboratory.

Other diagnostic tests for CHF

Heart failure has long been regarded as a risk factor for anesthesia and surgery. However, current clinical and laboratory assessments of heart failure are not satisfactory. Echocardiography and radionuclide studies have been evaluated for pre-operative left ventricular function assessment.[24-27] It is generally agreed that depressed left ventricular function detected by echocardiography or radionuclide ventriculography is associated with a higher risk for cardiac complications. However, it is still controversial whether these tests provide any extra benefit when compared to routine clinical evaluation.[28] For instance, Halm *et al* reported that an ejection fraction less than 40% was associated with cardiac complications, especially heart failure. However, when adjusted for history of congestive heart failure, ejection fraction was no longer a predictor for cardiac complications.[24]

In contrast, measurement of NTproBNP is biochemical marker of heart failure It is objective with little operator variation.[23] Furthermore, it is sensitive, convenient, and less expensive. Its value as a routine pre-operative evaluation item deserves further large-scale investigation.

Limitations

We did not perform troponin I or 24 hour ECG in all patients. The patients were monitored as in usual clinical practice. Clinical tests were performed when needed as decided by the physician in charge. Subclinical problems could have been missed. On the other hand, they were missed because they did not result in serious morbidity in the operative or postoperative period.

The present investigation was a retrospective analysis. We found that an NTproBNP level greater that 450 ng/L was a good cutoff value for predicting cardiac complications. The usefulness of this cut-off value should be evaluated in future prospective trials.

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Table 1. Clinical characteristics and plasma NTproBNP levels of the study patients

	Patient with CC (n=15)	Patient without CC (n=175)	*p*
Gender (M/F)	7/8	89/86	0.755
Cardiac impairment	5 (33.3%)	21 (12%)	0.021
ASA class			0.027
I	1 (6.7%)	36 (20.6%)	
II	3 (20.0%)	44 (25.1%)	
III	5 (33.3%)	72 (41.1%)	
IV	6 (40.0%)	23 (13.1%)	
NTproBNP (ng/L)			
Median (range)	1217(462-35000)	94.6(5-35000)	<0.001
Mean±SD	6686±10856	729±3207	
NTproBNP >450 ng/L	15 (100%)	30 (17.1%)	<0.001

ASA = American Society of Anesthesiologists; CC = cardiac complications; F = female; M = male; NTproBNP = N-terminal pro-brain natriuretic peptide; SD = standard deviation.

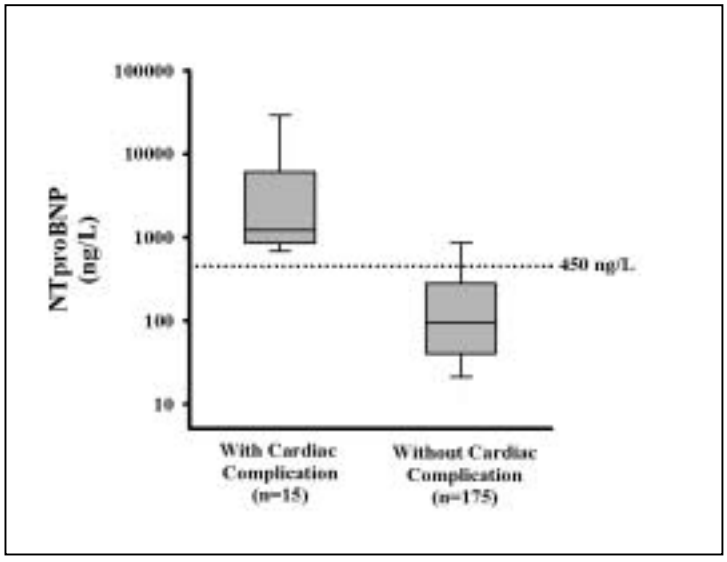

Figure 1. Box plot showing the plasma NTproBNP level in patients with and without cardiac complication. The central lines represent the median levels while the gray boxes represent 25 to 75 percentile levels and error bars represent 10 to 90 percentile levels. A cut-off value of 450 ng/L is also shown in the figure.

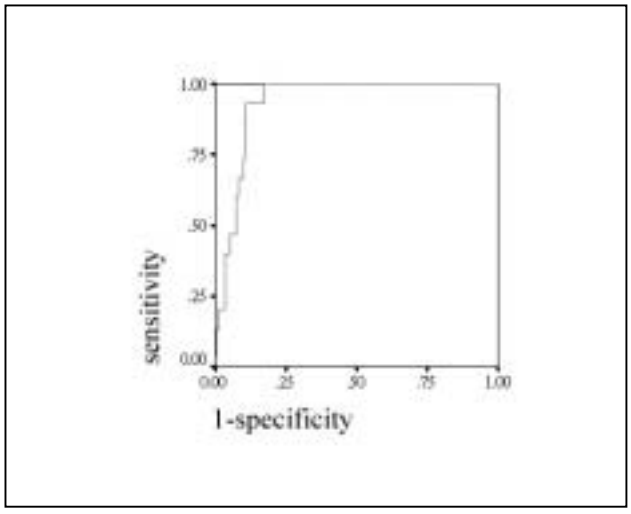

Figure 2. The receiver operative characteristic (ROC) curve for evaluating the accuracy of NTproBNP in predicting cardiac complications. The area under the curve was 0.934 with a 95% confidence interval of 0.897 to 0.971.