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Institutional report - Arrhythmia

Brain natriuretic peptide elevation and the development of atrial fibrillation following coronary artery bypass surgery☆

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Abstract

The study was designed to determine whether the development of atrial fibrillation is associated with post-operative left ventricular dysfunction and subsequent left atrial stretch. We recruited 133 patients with well preserved pre-operative left ventricular function undergoing bypass surgery. Brain natriuretic peptide was measured at baseline, 24 and 48 h after the onset of cardiopulmonary bypass, and patients were monitored for 72 h after surgery. Atrial fibrillation occurred in 65 patients. Median 48 h brain natriuretic peptide levels were greater in the atrial fibrillation group (440 pg/ml (AF) and 319 pg/ml (non AF) $P=0.001$). As atrial fibrillation can cause an elevation in brain natriuretic peptide we divided the subjects into early atrial fibrillation (<48 h) and late (>48 h). In those with early atrial fibrillation there was no difference in the 24 h brain natriuretic peptide levels (381 pg/ml and 365 pg/ml $P=0.73$). In those with late atrial fibrillation the median 48 h brain natriuretic peptide level was greater than in the control group (405 pg/ml and 319 pg/ml, respectively, $P=0.02$). Brain natriuretic peptide levels rise significantly following bypass surgery. This increase was more evident in those who develop late atrial fibrillation which may suggest a role for atrial stretch in this arrhythmia.

Keywords: Atrial fibrillation; Brain natriuretic peptide; Coronary artery bypass surgery

1. Introduction

Atrial fibrillation occurs in up to 40% of patients having coronary artery bypass and in over 50% of those undergoing valve surgery [1]. There has been major progress in the understanding of the pathogenesis of atrial fibrillation in the non-surgical setting, but factors related to coronary artery bypass surgery associated atrial fibrillation are not well understood [2,3].

Brain natriuretic peptide (BNP) is produced by ventricular myocardium in response to elevation in end-diastolic pressure [4,5]. Levels correlate closely with pulmonary capillary wedge pressure in left ventricular systolic dysfunction and it is used as a screening tool for the presence of ventricular dysfunction [6,7]. It has been demonstrated to be elevated in the immediate post-coronary artery bypass surgery period, with levels elevated up to 24 h following the operation [8–10].

Changes in left atrial pressure secondary to left ventricular dysfunction may cause left atrial stretch alter the refractory period and hence have a role in the genesis of post-operative atrial fibrillation. The objective of this study was to determine whether there was a relationship between the degree of post-operative brain natriuretic peptide elevation (a surrogate marker for left ventricular end diastolic pressure) and the development of post-operative atrial fibrillation.

2. Materials and methods

The study complies with the Declaration of Helsinki and was approved by the Hospital Ethics Committee in July 2001; written informed consent was obtained from all patients. Patients in sinus rhythm undergoing first time non-emergent on pump coronary artery bypass grafting were enrolled. Exclusion criteria included impaired ventricular function (ejection fraction $<40\%$), renal impairment (creatinine 200), malignancy, diabetes mellitus and concurrent infection. One hundred and thirty-three patients were recruited (65 cases and 68 controls). The control population consisted of selected patients that remained in sinus rhythm following surgery. Subjects were recruited the night before surgery and were followed throughout their hospital stay and reviewed six weeks post surgery.

Telemetry which was performed for 72 h following surgery was reviewed on a daily basis. The telemetry system has a

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24 h recall capacity facilitating review of the cardiac rhythm in the preceding 24 h. The primary endpoint was defined as new onset atrial fibrillation prior to hospital discharge which persisted for at least one hour or required urgent therapy due to clinical instability.

As atrial fibrillation usually develops 48–72 h following surgery we measured the brain natriuretic peptide levels prior to anaesthetic induction and 24 and 48 h following the onset of cardiopulmonary bypass [11]. Samples were centrifuged within 1 h and stored at −70 °C pending analysis. Brain natriuretic peptide levels were measured with a fluorescence immunoassay on freshly thawed samples (Biosite Diagnostics, San Diego, California). This assay has a detection range from 5 to 1300 pg/ml; in the setting of cardiac failure a decision threshold of 100 pg/ml is usually recommended.

Standard cardiac anaesthetic technique was used and cardiopulmonary bypass was achieved with a single right atrial cannulation technique using a Jostra HL 20 heart lung machine with an arterial multiflow roller pump connected to a Cobe Optima microporous hollow fibre oxygenator with a Cobe Sentry arterial filter.

3. Statistical analysis

Descriptive statistics are presented for the baseline characteristics of patients in the study. Means and standard deviations are presented for normal data, medians and inter-quartile ranges (IQR) for non-normal data, and proportions for categorical data. The Brain Natriuretic peptide data were non-normal, neither a square root transformation nor a log transformation was able to normalise the data. Comparison was made between the two groups using a Wilcoxon rank sums test for the non-normal data and Chi-squared analysis for the descriptive data. A P-value <0.05 was considered significant with two-sided tests. All analyses were performed using the JMPin software (SAS Institute Inc.).

4. Results

Baseline demographics are presented in Table 1. Atrial fibrillation occurred in 65 of the 133 subjects. Apart from being older the subjects and controls were similar for baseline demographic and clinical parameters. The hospital stay was longer in the atrial fibrillation group [7 days (IQR 6–9) and 6 days (IQR 5–7), respectively $P=0.005$]. Most patients (84%) were on beta-blockers, which were given the morning of surgery and as soon as possible following surgery.

4.1. BNP data

Baseline median brain natriuretic peptide was 44.7 pg/ml (IQR 17.9–101 pg/ml) consistent with a selected group of patients with good left ventricular function. Following cardiopulmonary bypass, the median level rose to 379 pg/ml (IQR 253–548 pg/ml) at 24 h and 366 pg/ml (IQR 223–482 pg/ml) at 48 h.

The pre-operative brain natriuretic peptide levels were similar in the 2 groups ($P=0.07$) (Fig. 1). There was a rise in brain natriuretic peptide in both the atrial fibrillation and non-atrial fibrillation groups, with similar median levels at 24 h in both ($P=0.29$). The median brain natriuretic peptide at 48 h was greater in the atrial fibrillation group, [440 pg/ml (IQR 250–606 pg/ml) and 319 pg/ml (IQR 169–443 pg/ml), respectively, $P=0.001$]. The mean time to onset of atrial fibrillation (measured from the onset of cardiopulmonary bypass) was 60 ± 27 h.

As atrial fibrillation itself may impact on the brain natriuretic peptide level the patients who developed atrial fibrillation were divided into those who developed atrial fibrillation before or after 48 h [12]. Thirty patients (46%) developed atrial fibrillation in the first 48 h and 35 (54%) after the 48 h time period.

In those who developed atrial fibrillation in the first 48 h baseline brain natriuretic peptide levels were similar to those who remained in sinus rhythm [44.9 pg/ml (IQR 13.8–134 pg/ml) and 40.15 pg/ml (IQR 14.2–80.75 pg/ml), respectively, $P=0.54$] (Table 2). At 24 h the levels remained similar in both groups [381 pg/ml (IQR 246–516 pg/ml) and 365 pg/ml (IQR 252–517 pg/ml), respectively, $P=0.73$]. At 48 h there was an increase in brain natriuretic peptide levels in the atrial fibrillation group, 454 pg/ml (IQR 248–661 pg/ml) compared with 319 pg/ml

Table 1
Demographic data, mean values and standard deviations are presented for normal data, medians and IQR for non normal data. For categorical data percentages are presented with the difference between the groups analysed with a Chi-squared test

	AF $N=65$	No AF $N=68$	P-Value
Age (years)	65 (60–71)	62 (54–69)	0.007
Hypertension	56% (36)	51% (35)	0.919
Smoker	14% (9)	11% (7)	0.769
Ex Smoker	47% (30)	66% (45)	0.276
Aspirin	89% (58)	92% (63)	0.981
Preop B-blocker	85% (55)	83% (56)	0.982
Postop B-blocker	79% (51)	81% (55)	0.989
Statin	70% (46)	82% (56)	0.658
ACE inhibitor	47% (31)	41% (28)	0.754
Ca channel blocker	40% (26)	37% (25)	0.927
Nitrate	57% (37)	62% (42)	0.885
Diuretic	10% (7)	13% (9)	0.902
No. of grafts	3.0 ± 0.7	3.08 ± 0.8	0.541
Bypass time (min)	91.3 ± 23	92.97 ± 29.6	0.718
Cross clamp (min)	51.01 ± 15	53.41 ± 16.2	0.378
Core temperature	32.9 ± 1.16	33.0 ± 1.09	0.609
Hospital stay (days)	7 (6–9)	6 (5–7)	0.005

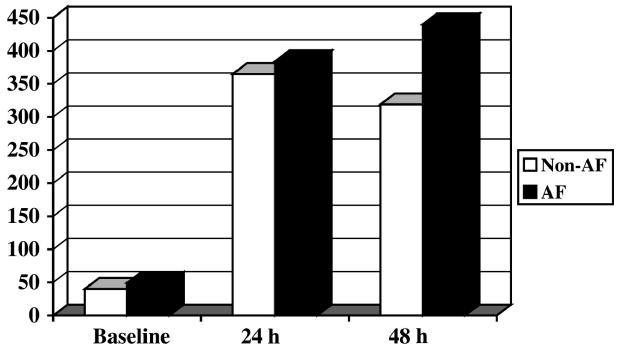

Fig. 1. Median BNP pg/ml levels non AF vs. AF.

(IQR 169–443 pg/ml) in those who remained in sinus rhythm, $P=0.004$. This increase was seen after the onset of atrial fibrillation and may have been influenced by the arrhythmia itself.

In those who developed atrial fibrillation after 48 h the baseline median brain natriuretic peptide was higher than in those who remained in sinus rhythm ($n=68$) [53.2 pg/ml (IQR 32.6–138 pg/ml) and 40.15 pg/ml (IQR 14.2–80.75 pg/ml), respectively, $P=0.056$]. The 24-h levels were similar, 440 pg/ml (IQR 252–691 pg/ml) compared with 365 pg/ml (IQR 252–517 pg/ml), $P=0.19$. The 48-h level, which was before the onset of the atrial fibrillation, was increased in the atrial fibrillation group, 405 pg/ml (IQR 248–583 pg/ml) compared with 319 pg/ml (IQR 169–443 pg/ml) for those who remained in sinus rhythm, $P=0.02$. As the baseline median brain natriuretic peptide was higher in those who developed atrial fibrillation after 48 h this difference was controlled for. The 48-h brain natriuretic peptide value in this later onset atrial fibrillation group remained elevated following correction for the baseline level ($P=0.05$) (Table 3).

5. Discussion

We have demonstrated that patients with well preserved pre-operative systolic function have a significant post-operative brain natriuretic peptide elevation and that the degree of elevation at 48 h post surgery was greater in those who developed subsequent atrial fibrillation. We postulated that the threshold for the development of atrial fibrillation might be lowered by atrial stretch secondary to left ventricular dysfunction and used brain natriuretic peptide as a surrogate marker of left ventricular function.

As almost half of the patients developed atrial fibrillation prior to the 48-h time-point this difference could occur as a result of the atrial fibrillation rather than being causative [12]. The patients who developed atrial fibrillation within 48 h of surgery did not have significantly different brain natriuretic peptide levels to the control group apart from the 48 h value, which could be secondary to the arrhythmia. In those who developed atrial fibrillation after 48 h, the baseline brain natriuretic peptide values were marginally different and the 48-h levels were increased in those who developed atrial fibrillation.

These data suggest that the etiology of atrial fibrillation may be multifactorial. Perhaps in those who develop ‘early atrial fibrillation’, i.e. less than 48 h, atrial trauma from cannulation or the inflammatory response caused by the bypass circuit may be the primary stimuli for arrhythmia onset. In those who develop atrial fibrillation later, atrial stretch may be an important feature in the pathogenesis of atrial fibrillation either directly or as facilitator for other triggers.

Our results demonstrate that despite having normal left ventricular function pre-operatively most patients undergoing coronary artery bypass surgery develop left ventricular dysfunction, which is often sub-clinical and in this study occurred up to 48 h after the operation. The aetiology of this dysfunction is unclear. It may be a residual effect of cardioplegia and cardiopulmonary bypass or it may be caused by ongoing ischaemia or myonecrosis. We excluded patients with systolic dysfunction and valvular surgery as we felt that in both these groups baseline brain natriuretic peptide may be elevated and this may obscure the significance of the post-operative elevation. Also in valve surgery the procedures are more complex and the atria undergo different haemodynamic stresses. Accordingly we recruited a homogenous group in order to reduce any potential confounding variables.

There are limited data on brain natriuretic peptide elevation following cardiac surgery. In a study of 178 patients with varying clinical diagnoses admitted to intensive care, the 52 patients who had undergone cardiopulmonary bypass had significantly higher brain natriuretic peptide levels at 24 h than the other patients and also a control group [8]. Mair et al. studied 19 patients, some with poor left ventricular function, undergoing elective coronary artery bypass surgery. They demonstrated myocardial release of brain natriuretic peptide by comparing coronary sinus and peripheral arterial levels up to 20 min after aortic cross clamp release. The levels were higher in 3 patients with the highest lactate levels, which suggested a relationship to ischaemic time [9]. In another study of 29 patients undergoing coronary artery bypass surgery, brain natriuretic peptide levels were elevated compared to baseline at 2 h following the end of cardiopulmonary bypass. This study also showed no difference between brain natriuretic peptide levels measured from the radial artery and the pulmonary artery [10]. Hakala et al. studied the relationship of pre- and post-coronary artery bypass surgery brain natriuretic peptide levels to the development of atrial fibrillation in 88 patients [13]. They measured brain natriuretic peptide at baseline and 18 and 28 h following surgery. They found no correlation between brain natriuretic peptide and atrial fibrillation at any of the time points. The mean time to onset of atrial fibrillation was 56 h. Brain natriuretic peptide has a short half-life and perhaps their negative result was due to sampling at an inappropriate time point unrelated to the development of atrial fibrillation.

Table 2
Median BNP levels (pg/ml) in control group vs. Group I (AF < 48 h) vs. Group II (AF > 48 h)

	Baseline	24 h	48 h
Control	40.2 (14.2–81)	365 (252–517)	319 (169–443)
AF < 48 h	44.9 (13.8–134)	381 (246–516)	454 (248–661)
AF > 48 h	53.2 (32.6–138)	440 (252–691)	405 (248–583)

Table 3
Age and peri-operative variables of the three groups, Group I AF occurs < 48 h ($n=30$), Group II AF occurs > 48 h ($n=35$) and the non-AF group ($n=68$)

	AF < 48 h $N=30$	AF > 48 h $N=35$	Non AF $N=68$	P-Value
Age	65 (59–72)	64 (60–72)	62 (53.3–69)	0.08
No. of grafts	2.96 ± 0.75	3.02 ± 0.79	3.08 ± 0.8	0.766
Bypass time (min)	89.2 ± 25	93.2 ± 22	92.97 ± 29.6	0.787
Cross clamp (min)	50.3 ± 15	51.7 ± 14.8	53.41 ± 16.2	0.642
Core temperature	32.97 ± 1	32.8 ± 1.24	33.0 ± 1.09	0.68
Hospital stay (days)	6 (5–7)	6.5 (5–9.25)	7 (6–10)	0.001

A more recent paper in Circulation examined the pre-operative brain natriuretic peptide level in 187 patients undergoing a variety of cardiac surgical procedures [14]. They found that after adjusting for a number of factors that the preoperative brain natriuretic peptide level predicted postoperative atrial fibrillation. The group that developed atrial fibrillation were older and more likely to have undergone valvular surgery and higher brain natriuretic peptide levels correlated with age, depressed left ventricular function and a history of hypertension. Unlike our paper this interesting study enrolled a heterogenous group with a significant elevation in preoperative brain natriuretic peptide levels (444 ng/ml in the non AF group and 615 ng/ml in the atrial fibrillation group).

Identifying patients most at risk for the development of atrial fibrillation remains difficult. Predictors of atrial fibrillation following coronary artery bypass surgery include age, a previous history of atrial fibrillation, *P* wave duration on signal averaged electrocardiogram and withdrawal of preoperative beta-blockade. The ability to accurately predict a group at increased risk of post-coronary artery bypass surgery atrial fibrillation would facilitate targeting prophylactic therapies, such as amiodarone, biatrial overdrive pacing or potentially a diuretic to decrease left ventricular end-diastolic pressure.

6. Conclusion

Patients with normal pre-operative systolic function have a significant brain natriuretic peptide rise following surgery. This elevation is associated with the development of atrial fibrillation after 48 h, suggesting that left ventricular dysfunction and subsequent left atrial stretch may have a role in its pathogenesis.

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