

Improved Neurohormonal Markers of Ventricular Function After Restoring Sinus Rhythm by the Maze Procedure

Anders Albåge, MD, Göran Kennebäck, MD, PhD, Jan van der Linden, MD, PhD, and Hans Berglund, MD, PhD

Departments of Cardiothoracic Surgery and Anesthesiology, and Cardiology, Karolinska Institute at Huddinge University Hospital, Stockholm, Sweden

Background. Clinical results of the Maze procedure for treatment of atrial fibrillation (AF) are excellent, suggesting improved ventricular function after restoring sinus rhythm. However, long-term corresponding effects on the release of cardiac natriuretic peptides and other vasoactive hormones are incompletely investigated after isolated Maze surgery.

Methods. Plasma levels of brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), antidiuretic hormone, aldosterone, and angiotensin II were measured in 15 patients (mean age, 52 ± 11 years) undergoing isolated surgical Maze (III) procedures for medically refractory AF, preoperatively and 6 months postoperatively. At the time of blood sampling, hemodynamic correlates were obtained at baseline and after 6 and 12 minutes of rapid ventricular pacing at 150 stimulations/minute.

Results. All patients were free of AF at 6-month follow-

up. The measured plasma levels of BNP, ANP, and angiotensin II were all significantly lower ($p = 0.03$) late after the isolated Maze procedure. Cardiac output was significantly higher postoperatively ($p < 0.01$). Other hemodynamic values and left atrial size were unchanged after surgery. Ventricular pacing caused almost identical hemodynamic changes in atrial pressures before and late after surgery, but the associated plasma ANP response was significantly attenuated postoperatively ($p < 0.001$).

Conclusions. Levels of cardiac natriuretic peptides and angiotensin II as markers of ventricular function are improved in the long term after clinically successful isolated Maze procedures. ANP response to hemodynamic challenge by ventricular pacing was attenuated postoperatively, possibly due to atrial scarring.

(Ann Thorac Surg 2003;75:790–5)

© 2003 by The Society of Thoracic Surgeons

Reports of clinical outcomes of the Maze procedure for surgical treatment of atrial fibrillation (AF) have been excellent in terms of freedom from arrhythmia, symptomatic and functional improvement, and return of atrial contraction on echocardiography [1–3]. These studies imply that return of sinus rhythm results in improved cardiac function. At present, there is a growing interest in cardiac natriuretic peptides as hormonal indicators of ventricular dysfunction [4]. Secreted mainly from the ventricles, brain natriuretic peptide (BNP) has recently been proposed as a potential “white count” of congestive heart failure (CHF) [5], possibly a simple and noninvasive tool to estimate both the severity and prognosis of CHF [6]. In addition, BNP has been shown to be an independent predictor of mortality in CHF [7]. In patients with AF, elevations in both BNP and atrial natriuretic peptide (ANP) have been reported, even when there is no underlying structural heart disease [8, 9]. However, return of sinus rhythm by cardioversion may reduce elevated plasma levels of both BNP and ANP [10, 11]. In a study of patients with poor left ventricular function undergoing

coronary artery bypass grafting, levels of BNP and ANP were markedly reduced postoperatively, in conjunction with observed improvements in left ventricular ejection fraction on echocardiography [12].

It is conceivable that the natriuretic peptide profile, as well as other vasoactive hormones involved in the compensatory mechanisms of CHF, would be reduced after restoring sinus rhythm and improving ventricular function by Maze surgery. Previous Maze-related studies have focused mainly on perioperative changes in ANP levels, associated with the frequently observed excessive postoperative fluid retention [13]. Reduction in levels of both ANP and BNP have been reported up to 1 month after combined valvular and Maze operations [14], but the patient group was not homogenous and postoperative invasive hemodynamic values were not measured. To our knowledge, long-term effects on levels of natriuretic hormones have not been studied after isolated Maze procedures.

As ANP secretion rapidly adjusts to variations in atrial pressure and atrial myocardial stretch [15], it is very important to include hemodynamic correlates in any attempt to compare hormone levels at various times. Furthermore, different protocols have been used to experimentally stimulate release of natriuretic hormones.

Accepted for publication Sept 27, 2002.

Address reprint requests to Dr Albåge, Department of Cardiothoracic Surgery and Anesthesiology, Huddinge University Hospital, SE-141 86 Stockholm, Sweden; e-mail: anders.albage@hs.se.

Table 1. Patient Characteristics

No. of patients	15
Male/female	13/2
Age (years)	
Mean	52
Median	53
Range	34–74
Atrial fibrillation, paroxysmal/chronic	3/12
Arrhythmia duration (years)	
Mean	7.5
Median	9
Range	2–14
Hypertension	2
Diabetes mellitus	2
Left ventricular ejection Fraction (%)	
> 50	8
40–50	4
35–40	3
Preoperative medication	
β -blockers	9
Ca channel blockers	2
ACE inhibitors	2
Amiodarone	2

Rapid ventricular pacing acutely increases right [16] and left (ie, pulmonary capillary wedge pressure [PCWP]) atrial pressures [15, 17], serving the purpose of release provocation of ANP. Less is known about release mechanisms of BNP, and responses to pacing in prior studies have been variable [17, 18].

The aim of the current study was to assess the baseline and stimulated response of BNP, ANP, antidiuretic hormone (ADH), aldosterone, and angiotensin II (Ang II), preoperatively and long-term postoperatively with hemodynamic correlates, in patients undergoing isolated surgical Maze procedures for medically refractory atrial fibrillation.

Patients and Methods

Fifteen nonconsecutive patients (2 women) with a mean age of 52 ± 11 years, who underwent the isolated surgical Maze (III) procedure between May 1995 and April 1999, constituted the study group. Patient characteristics are depicted in Table 1. They were all referred for surgery due to symptomatic and medically refractory AF. Patients scheduled for concomitant procedures were excluded from the study. Two patients had AF in association with hypertension and diabetes, respectively, and the remaining 11 patients had no associated significant cardiac or systemic disease. Left ventricular function was assessed by preoperative echocardiography or left ventricular angiogram. Approval of the study was obtained from the local hospital ethics committee (March 27, 1995), and each patient gave informed consent before being included in the study.

Operative Technique

The full surgical Maze III technique was used in all patients. In brief, the operation was performed through a median sternotomy with separate caval cannulation, total cardiopulmonary bypass, and mild systemic hypothermia (32°C). Incisions according to Cox and associates [1] were made in the right atrium on cardiopulmonary bypass but with the heart beating, whereas the incisions in the atrial septum and left atrium were performed with the heart arrested by cold intermittent blood cardioplegia, distributed in both antegrade and retrograde fashion. Cryo-ablations were made in areas close to the tricuspid and mitral valves, and the coronary sinus. All incisions were subsequently closed with running polypropylene sutures. Both atrial appendages were routinely excised during the procedure. Anesthetic management was customary for cardiac operations and similar in all patients. In general, the patients were treated 2 days in intensive care settings, monitoring heart rhythm, hemodynamics, and possible fluid retention, and 2 to 3 weeks in the ward for rehabilitation and rhythm evaluation.

Protocol

Hormone plasma levels with invasive hemodynamic correlates were measured in these patients preoperatively and 6 months (mean, 6.4 months; range, 4 to 12.5 months) after the Maze procedure. The measurements were done in conjunction with a heart catheterization study for electrophysiological evaluation, with the patient awake and resting in a supine position. The femoral vein was cannulated twice using the Seldinger technique. A pacing catheter was placed in the apex of the right ventricle. It was manipulated until a stable position with low stimulation thresholds was achieved. A Swan-Ganz catheter (Baxter-Edwards, Irvine, CA) was positioned in the pulmonary artery. A cannula was inserted in the left brachial artery. To attain a baseline situation, there was a 30-minute stabilization period with all catheters and electrodes in place before measurements were started. Hemodynamic variables recorded were heart rate, arterial and pulmonary systolic, diastolic and mean pressures, PCWP, right atrial pressure (RAP), and cardiac output (CO) through thermodilution technique. These values were measured and arterial blood samples drawn at baseline and after 6 and 12 minutes of right ventricular pacing at a rate of 150 stimulations per minute.

Arterial blood samples were drawn into ethylenediaminetetraacetic acid-treated 10-mL tubes, stored in ice, immediately refrigerator centrifugated to separate the plasma (P), and preserved at -70°C . Radioimmunoassay (RIA) analyses of ANP, ADH (vasopressin), aldosterone, and angiotensin II were then subsequently performed. BNP was analyzed using immunoradiometric assay (IRMA). Details concerning methods of analysis in our institution have been previously described [18].

Left atrial diameter was determined in the parasternal long-axis view by standard transthoracic echocardiography before the operation and postoperatively, in conjunction with the hospital admission period for the inva-

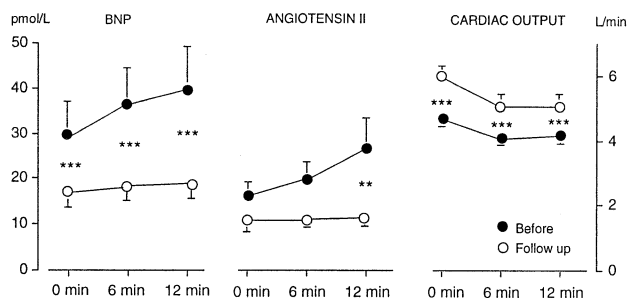


Fig 1. Effects on hormones and cardiac output of the isolated Maze procedure. Arterial plasma levels of brain natriuretic peptide (BNP) and angiotensin II, and measurement of cardiac output at baseline (0 minutes) and after 6 and 12 minutes of ventricular pacing (150 stimulations/min). Asterisks indicate significant differences at the various time points of measurement preoperatively as compared with follow-up 6 months postoperatively. The intended decrease in CO with rapid ventricular pacing was significant both before and after surgery. ** $p < 0.01$; *** $p < 0.001$.

sive electrophysiological study and the hormone analysis.

Statistics

Data are presented as means \pm SD. Pre- and postoperative differences in all measured variables were analyzed using repeated-measures analysis of variance (Super-ANOVA; Abacus Concepts, Inc., Berkeley, CA). In case of a significant main effect pre- versus postoperatively in the ANOVA, specific differences and change from baseline at various time points were tested with the appropriate contrasts. Differences in pre- versus postoperative plasma levels of ANP in response to pacing were tested in an analysis of covariance including RAP and PCWP as covariables in the model (ANCOVA). A p value of less than 0.05 was considered significant. Differences in left atrial diameter before and after surgery were analyzed using a paired Student's t test.

Results

There was no mortality in this study. All patients recovered well without long-term complications after surgery, except 1 patient who developed a moderately symptomatic pulmonary hypertension postoperatively. At 6 months or more after the operation, no patient was in atrial fibrillation. The postoperative rhythm at this point in time was regular sinus ($n = 11$), junctional ($n = 1$), ectopic atrial ($n = 1$), and permanent atrial pacing ($n = 2$). Postoperative pharmacological treatment included ACE inhibitors in 2 patients and calcium-channel blockers in 1 patient. The remaining patients were free from cardiac medication, and no patient was started on new ACE inhibitor therapy after the operation.

Plasma levels (main effect in the ANOVA pre- vs postoperative) of BNP (35 ± 32 vs 17 ± 13 pmol/L; F value, 5.47, $p = 0.03$), ANP (46 ± 46 vs 19 ± 18 pmol/L; F value, 6.02, $p = 0.03$), and Ang II (20 ± 19 vs 11 ± 8 pmol/L; F value, 6.93, $p = 0.02$) were all significantly

lower at 6 months postoperatively compared with preoperatively. Mean hormonal plasma levels at the various time points of measurement are presented in Table 2 and illustrated in Figures 1 and 2. Plasma levels of BNP were significantly lower both at baseline and during pacing at follow-up ($p < 0.001$). Correspondingly, cardiac output was significantly higher postoperatively (5.4 ± 1.4 vs 4.3 ± 1.0 L/min; F value, 10.23; $p < 0.01$). The difference in cardiac output was significant at baseline as well as during pacing ($p < 0.001$) (Fig 1). Other hemodynamic variables did not differ before and after surgery.

The responses to rapid ventricular pacing in ANP plasma levels and changes in atrial pressures are outlined in Figure 2. Pacing caused almost identical hemodynamic changes before and after the Maze procedure, with significant increases in PCWP and RAP (Fig 2), as well as a decrease in cardiac output (Fig 1). Accordingly, ANP levels rose acutely with increased PCWP preoperatively, but this response was significantly attenuated 6 months postoperatively ($p < 0.001$). There was also a significant rise in BNP levels during ventricular pacing before surgery ($p < 0.001$), but this was not reproduced at the follow-up evaluation. Plasma levels of antidiuretic hormone and aldosterone were not different before and after surgery.

There was no change in left atrial diameter before and after the Maze operation (44 ± 7 vs 43 ± 6 mm, NS).

Comment

The main finding in this cohort study was the reduced plasma levels of BNP 6 months after clinically successful isolated Maze procedures, as a possible hormonal marker of improved postoperative ventricular function.

The Maze procedure is an effective surgical treatment of AF, and restoration of sinus rhythm has been reported in 75% to 95% of cases by several authors [1-3]. However, corresponding data on natriuretic hormonal changes are scarce. There is now extensive documentation of the possible role of BNP as an indicator of ventricular dysfunction and as an evaluation tool of CHF, both in hospitalized patients and in out-patient practice [4, 5]. In fact, BNP has been found to be an independent predictor of mortality in association with CHF [6, 7]. ANP, or pro-forms of the hormone, has been reported to have a role in this setting as well [6]. Improved ventricular function after cardioversion of AF or coronary artery bypass surgery for ischemic heart disease has been associated with reductions in natriuretic peptide levels [10-12]. In addition, improvement in cardiac function after congenital heart surgery has been linked to decreased levels of plasma BNP [19]. In contrast to ANP, BNP's half-life is longer, and its regulation has been suggested to be mainly at the transcriptional and post-transcriptional level of gene expression [20]. Thus, BNP plasma levels may better reflect the prolonged and constant state of left ventricular function in a patient.

Nakamura and associates [14] examined plasma levels of ANP and BNP at rest and immediately after maximum exercise before and 1 month after combined valvular and

Table 2. Isolated Maze Procedure: Pre- and Postoperative Data on Hormone Variations and Hemodynamics

	Baseline		Pace 6 min		Pace 12 min	Main-Effect ANOVA Pre-vs Postoperative (<i>p</i> Value)
BNP (pmol/L)						
Pre	29.8 ± 28.7	—b—	36.4 ± 31.8	—c—	39.6 ± 37.3	
	c		c		c	
Post	16.4 ± 13.5		17.4 ± 12.6		18.5 ± 12.8	0.03
ANP (pmol/L)						
Pre	24.0 ± 13.4	—a—	46.7 ± 39.2	—c—	66.5 ± 62.4	
			b		c	
Post	13.5 ± 10.8	—a—	20.7 ± 19.8	—b—	22.6 ± 21.3	0.03
ADH (pmol/L)						
Pre	1.5 ± 1.4		3.1 ± 5.2		6.3 ± 13.2	
Post	1.4 ± 1.2		1.5 ± 1.0		5.3 ± 13.8	NS
Aldosterone (pmol/L)						
Pre	226 ± 140		245 ± 119		266 ± 117	
Post	169 ± 139		191 ± 182		203 ± 137	NS
Angiotensin II (pmol/L)						
Pre	15.9 ± 12.2		19.4 ± 15.8		26.1 ± 26.7	
					b	
Post	11.1 ± 10.8		11.1 ± 5.9		11.5 ± 7.9	0.02
HR (beats/min)						
Pre	75 ± 24		150		150	
Post	74 ± 11		150		150	NS
MAP (mm Hg)						
Pre	101 ± 19		98 ± 17		100 ± 18	
Post	99 ± 14		101 ± 17		97 ± 20	NS
RAP (mm Hg)						
Pre	4.8 ± 1.7		8.6 ± 3.3		8.9 ± 4.2	
Post	6.1 ± 3.2		8.9 ± 3.0		9.3 ± 3.1	NS
PCWP (mm Hg)						
Pre	11.1 ± 3.3		22.1 ± 6.6		22.3 ± 7.0	
Post	10.9 ± 4.0		20.7 ± 4.5		19.9 ± 4.1	NS
CO (L/min)						
Pre	4.7 ± 0.9	—b—	4.1 ± 0.9	—a—	4.2 ± 1.1	
	c		c		c	
Post	6.0 ± 1.2	—c—	5.1 ± 1.4	—c—	5.1 ± 1.4	0.01

The *p* value refers to main effect in the ANOVA regarding pre- versus postoperative differences in hormone levels and hemodynamic parameters.

Specific differences pre- vs postoperatively for different time points and differences baseline vs pacing are indicated as: ^a *p* < 0.05; ^b *p* < 0.01; ^c *p* < 0.001.

ANP = atrial natriuretic peptide; ADH = antidiuretic hormone; BNP = brain natriuretic peptide; CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure.

Maze surgery. They found the secretion of both natriuretic hormones to be reduced in the Maze group, but it could be argued whether this effect was attributed to the treated valvular problem or to the arrhythmia correction per se. The present study differs from previously reported work by assessing baseline and pacing-stimulated

release of ANP and BNP, as well as other vasoactive hormones, in patients without concomitant valvular disease undergoing isolated Maze procedures, with a longer follow-up time. In this study, the association of increased CO and significantly reduced levels of both BNP and ANP at 6 months postoperatively can be interpreted as a

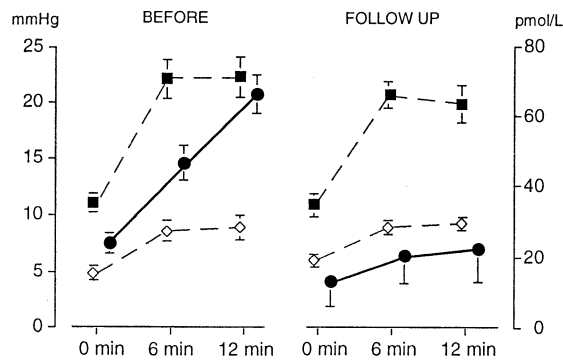


Fig 2. ANP and atrial pressure responses to rapid ventricular pacing before and 6 months after the isolated Maze procedure. Reactions in atrial pressures before and during ventricular pacing did not change after the operation, but the ANP response was significantly attenuated at follow-up ($p < 0.001$). Squares = PCWP; diamonds = RAP; circles = ANP. (ANP = atrial natriuretic peptide; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure.)

convincing indication of improved ventricular function after a successful Maze procedure per se, with the patient in regular sinus rhythm instead of AF. In addition, levels of Ang II were significantly reduced after surgery, which may reflect an attenuation of the neurohormonal response to cardiac incompensation, overt or not, caused by preoperative AF. This finding could also be consistent with an improved cardiac function after Maze surgery. These results could not be explained by differences in heart rate or atrial pressures, as all hemodynamic values except CO were equal before and after surgery at the time of measurement. Moreover, there was no significant change in left atrial size on echocardiography postoperatively, suggesting that this factor did not influence levels of natriuretic peptides.

There may be several reasons for improved post-Maze ventricular function that cannot be clearly separated by this study. First, a normalized and regular sinus or atrial rhythm will result in a more efficient ventricular performance, and add the component of atrial contraction to CO. Return of both left and right atrial contraction has been demonstrated after the Maze procedure [1, 2, 21], although the magnitude of the atrial contraction has been debated because of presumed postoperative atrial stiffness. Second, as some patients with long-standing and rapid AF may have a tachycardia-induced cardiomyopathy, myocardial function per se could be improved by restoring a normofrequent rhythm. In a study of patients with AF and reduced left ventricular function, ejection fraction was improved after normalizing heart rate by His bundle ablation and pacemaker implantation [22].

In the present study, there was a significantly attenuated ANP response to ventricular pacing 6 months postoperatively as compared with preoperatively, despite similar increases in atrial pressures. This is consistent with previous work of Yoshihara and associates [13], who noted a significantly reduced ANP response to supine bicycle ergometer exercise 2 months postoperatively in patients undergoing combined valvular surgery and

Maze. Because Rossi and coworkers have found AF to be an independent determinant of increased levels of N-terminal ANP (N-ANP) [8], it is feasible to believe that return of sinus rhythm would reduce ANP levels. However, there is also an anatomical and physiologic rationale for reduced ANP secretion after the Maze procedure, because it involves at least eight transmural incisions in both atria [1]. As quite extensive scarring should follow postoperatively, there is most likely a plain reduction in the amount of atrial cardiocytes containing ANP granules. Furthermore, both atrial appendages are removed with the operation. It has been suggested that up to 30% of the total amount of ANP in rats is contained in the atrial appendages combined [23], and Yoshihara and associates have demonstrated higher postoperative ANP levels in Maze patients in whom the right atrial appendage was preserved [24]. The long-term clinical implications of the decreased ability to release ANP are unknown.

In this study, levels of Ang II and BNP were affected by ventricular pacing preoperatively but not postoperatively. The reasons for this disparity are not clear, as we and other authors previously found no effect on release of these hormones by short time pacing [17, 18]. In fact, levels of tissue-derived Ang II from the heart were found not to increase even with longer-term pacing in experimental early heart failure [25]. Regarding BNP, however, recent studies have reported increased plasma levels in patients with lone AF [9, 26], and higher BNP levels in coronary sinus blood containing more atrial venous drainage than in the anterior interventricular vein, containing ventricular venous drainage [26]. In addition, other authors have found increased proBNP mRNA levels in the right atrial appendage in AF patients as compared with controls in sinus rhythm [27]. These findings suggest that part of the BNP secretion in patients with AF may be atrially derived. In view of this, it is possible that the pacing protocol in the present study, as well as the surgical atrial manipulation, could have had some influence on BNP release. Drug therapy could in theory have affected outcomes; however, no patient in this study had ACE inhibitor drugs initiated after the operation, which could otherwise clearly have influenced the results. Finally, design limitations of the present study can be attributed mainly to the small number of patients involved and the variability regarding age and preoperative left ventricular function.

In conclusion, there is a significant reduction in BNP and other important neurohormonal markers of ventricular function, as well as an improvement in CO, after clinically successful isolated Maze procedures. These findings add support to the view that the beneficial effects of the Maze procedure, in terms of restored sinus rhythm and cardiac function, outweigh the potential negative effects associated with post-Maze atrial stiffness. The impaired response of ANP to hemodynamic challenge after surgery may be caused by extensive atrial scarring, but the long-term implications of these findings are unknown.

This study was supported by grants from the Swedish Heart and Lung Foundation and the Swedish Society of Medicine. We would also like to thank research nurse Viveka Gustavsson for skillful processing of blood samples for hormone analysis, and Professor Elvar Theodorsson, Linköping, Sweden, for helpful assistance in the analysis of BNP.

References

- Cox JL, Boineau JP, Schuessler RB, Kater KM, Lappas DG. Five-year experience with the Maze procedure for atrial fibrillation. *Ann Thorac Surg* 1993;56:814–24.
- McCarthy PM, Gillinov AM, Castle L, Chung M, Cosgrove D III. The Cox-Maze procedure: the Cleveland Clinic experience. *Semin Thorac Cardiovasc Surg* 2000;12:25–9.
- Lonnerholm S, Blomstrom P, Nilsson L, Oxelbark S, Jideus L, Blomstrom-Lundqvist C. Effects of the maze operation on health-related quality of life in patients with atrial fibrillation. *Circulation* 2000;101:2607–11.
- Mair J, Hammerer-Lercher A, Puschendorf B. The impact of cardiac natriuretic peptide determination on the diagnosis and management of heart failure. *Clin Chem Lab Med* 2001;39:571–88.
- Maisel A. B-type natriuretic peptide levels: a potential novel white count for congestive heart failure. *J Card Fail* 2001;7: 183–93.
- Selvais PL, Donckier JE, Robert A, et al. Cardiac natriuretic peptides for diagnosis and risk stratification in heart failure: influences of left ventricular dysfunction and coronary artery disease on cardiac hormonal activation. *Eur J Clin Invest* 1998;28:636–42.
- Richards AM, Doughty R, Nicholls MG, et al. Plasma N-terminal pro-brain natriuretic peptide, and adrenomedullin: prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. Austral-New Zealand Heart Failure Group. *J Am Coll Cardiol* 2001;37: 1781–7.
- Rossi A, Enriquez-Sarano M, Burnett JC Jr, Lerman A, Abel M, Seward JB. Natriuretic peptide levels in atrial fibrillation: a prospective hormonal and doppler- echocardiographic study. *J Am Coll Cardiol* 2000;35:1256–62.
- Hirata Y, Matsumoto A, Aoyagi T, et al. Measurement of plasma brain natriuretic peptide level as a guide for cardiac overload. *Cardiovasc Res* 2001;51:585–91.
- Petersen P, Kastrup J, Vilhelmsen R, Schutten HJ. Atrial natriuretic peptide in atrial fibrillation before and after electrical cardioversion therapy. *Eur Heart J* 1988;9:639–41.
- Ohta Y, Shimada T, Yoshitomi H, et al. Drop in plasma brain natriuretic peptide levels after successful direct current cardioversion in chronic atrial fibrillation. *Can J Cardiol* 2001;17:415–20.
- Chello M, Mastroroberto P, Perticone F, et al. Plasma levels of atrial and brain natriuretic peptides as indicators of recovery of left ventricular systolic function after coronary artery bypass. *Eur J Card-thor Surg* 2001;20:140–6.
- Yoshihara F, Nishikimi T, Kosakai Y, et al. Atrial natriuretic peptide secretion and body fluid balance after bilateral atrial appendectomy by the Maze procedure. *J Thorac Cardiovasc Surg* 1998;116:213–9.
- Nakamura M, Niinuma H, Chiba M, et al. Effect of the Maze procedure for atrial fibrillation on atrial and brain natriuretic peptide. *Am J Cardiol* 1997;79:966–70.
- Berglund H, Edlund A, Theodorsson E, Vallin H. Haemodynamic and hormonal responses to cardiac pacing in humans: influence of different stimulation sequences and rates. *Clin Sci* 1995;88:165–72.
- Burnett JC Jr, Osborn MJ, Hammill SC, Heublein DM. The role of frequency of atrial contraction versus atrial pressure on atrial natriuretic peptide release. *J Clin Endocrinol Metab* 1989;69:881–4.
- Ylitalo K, Uusimaa P, Vuolteenaho O, Ruskoaho H, Peuhkurinen K. Vasoactive peptide release in relation to hemodynamic and metabolic changes during rapid ventricular pacing. *PACE* 1999;22:1064–70.
- Albåge A, van der Linden J, Bengtsson L, Lindblom D, Kennebäck G, Berglund H. Elevations in antidiuretic hormone and aldosterone as possible causes of fluid retention in the Maze procedure. *Ann Thor Surg* 2001;72:58–64.
- Ationu A, Singer DR, Smith A, Elliott M, Burch M, Carter ND. Studies of cardiopulmonary bypass in children: implications for the regulation of brain natriuretic peptide. *Cardiovasc Res* 1993;27:1538–41.
- Magga J, Martilla M, Mantymaa P, et al. Brain natriuretic peptide in plasma, atria and ventricles of vasopressin- and phenylephrine-infused conscious rats. *Endocrinology* 1994; 134:2505–15.
- Albirini A, Scalia GM, Murray RD, et al. Left and right atrial transport function after the Maze procedure for atrial fibrillation: an echocardiographic Doppler follow-up study. *J Am Soc Echocardiogr* 1997;10:937–45.
- Edner M, Caidahl K, Bergfeldt L, Darpo B, Edvardsson N, Rosenqvist M. Prospective study of left ventricular function after radiofrequency ablation of atrioventricular junction in patients with atrial fibrillation. *Br Heart J* 1995;74:261–7.
- Nishimura K, Saito Y, Hidaka T, et al. Does atrial appendectomy aggravate secretory function of atrial natriuretic peptide? *J Thorac Cardiovasc Surg* 1991;101:502–8.
- Yoshihara F, Nishimiki T, Sasako Y, et al. Preservation of the right atrial appendage improves reduced plasma atrial natriuretic peptide levels after the Maze procedure. *J Thorac Cardiovasc Surg* 2000;119:790–4.
- Luchner A, Stevens TL, Borgeson DD, et al. Angiotensin II in the evolution of experimental heart failure. *Hypertension* 1996;28:472–7.
- Inoue S, Murakami Y, Sano K, Katoh H, Shimada T. Atrium as source of brain natriuretic polypeptide in patients with atrial fibrillation. *J Card Fail* 2000;6:92–6.
- Tuinenburg AE, Brundel BJM, Van Gelder IC, et al. Gene expression of the natriuretic peptide system in atrial tissue of patients with paroxysmal and persistent atrial fibrillation. *J Cardiovasc Electrophysiol* 1999;10:827–35.