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Effects of chronic angiotensin II receptor antagonist and angiotensin-converting enzyme inhibitor treatments on neurohormonal levels and haemodynamics during cardiopulmonary bypass†

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Background. Chronic treatment with renin-angiotensin system (RAS) antagonists frequently causes deleterious hypotension during anaesthesia. We compared the effects of angiotensin II receptor antagonists (ARA) and angiotensin-converting enzyme inhibitors (ACEI) on neurohormonal levels and haemodynamics during cardiopulmonary bypass (CPB).

Methods. Forty-four patients undergoing mitral valvular surgery who were treated with either ARA (ARA group, *n*=14) or ACEI (ACEI group, *n*=15) over 12 weeks or who were not treated with any RAS antagonist (control group, *n*=15) were enrolled. The plasma levels of epinephrine, norepinephrine, arginine vasopressin (AVP) and angiotensin II, and haemodynamic variables were measured before (T1) and 15 min after (T2) the start of CPB, before aortic unclamping (T3) and at skin closure (T4). Mean arterial pressure (MAP) was maintained above 60 mm Hg with phenylephrine administration during CPB.

Results. The plasma epinephrine, norepinephrine, AVP and angiotensin II levels increased during CPB in all groups. Compared with the control group, the AVP level was lower at T1 in the ARA group and at T2 in the ARA and ACEI groups. The angiotensin II level was higher at T1, T2 and T3 in ARA group compared with ACEI and control groups. There were no significant differences in the epinephrine and norepinephrine levels among the three groups. The amount of administered phenylephrine during CPB was greater and MAP was lower in the ARA group compared with the ACEI and control groups.

Conclusions. Chronic ARA treatment resulted in more profound hypotension than ACEI treatment during CPB, and this may be associated with the blockade of angiotensin II receptors by ARA.

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Renin-angiotensin system (RAS) antagonists, such as angiotensin II receptor antagonists (ARA) and angiotensin-converting enzyme inhibitors (ACEI) have been increasingly used in hypertension, heart failure and even in the early stage of heart disease with reports of reduced mortality and morbidity.[1 2] However, long-term RAS inhibition with ARA and ACEI disable the RAS to compensate for reduced sympathetic tone, which can result in severe hypotension during anaesthesia.[3] Hypotensive episodes after the induction of anaesthesia have been known to occur more frequently in patients treated with ARA than in patients treated with ACEI.[4]

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Cardiopulmonary bypass (CPB) frequently causes hypotension as a result of tissue hypoxia and hypoperfusion, haemodilution and systemic inflammatory response.[5–8] It is usually transient and mild because of subsequent temporary elevation in several vasoconstrictive substances,[9 10] and temporary administration of low dose of vasopressor is usually sufficient to maintain perfusion pressure. However, deleterious vasodilatory shock may develop during CPB, requiring large amounts of vasopressors, which may be associated with difficulty in weaning from CPB and poor prognosis. Chronic treatment with ACEI is a known risk factor for vasodilatory shock associated with CPB.[11 12]

The aim of this study was to investigate the effects of long-term ARA and ACEI medications on vasoactive neurohormonal levels, such as epinephrine, norepinephrine, arginine vasopressin (AVP) and angiotensin II, and their haemodynamic consequences in patients undergoing CPB.

Methods

Patients

After obtaining the approval of the institutional review board and informed consent, 44 patients undergoing elective mitral valvular surgery between September 2004 and October 2005 were enrolled. The patients consisted of three groups; patients who had been treated with either ARA (ARA group, n=14) or ACEI (ACEI group, n=15) over 12 weeks, and patients who had not been treated with any RAS antagonists (control group, n=15). All patients had baseline systolic blood pressure below 130 mm Hg on three consecutive days. Patients with left ventricular ejection fraction <50%, New York Heart Association (NYHA) functional class III or IV, on calcium channel blocker medication, and/or with pre-existing endocrinal, renal, hepatic, neurological or coronary artery occlusive disease were excluded from this study.

Anaesthetic management

Cardiac medications were continued until the morning of surgery and all patients were premedicated with 0.05 mg kg^{-1} i.m. morphine 1 h before arriving in the operating room. Five ECG leads were attached, and leads II and V_5 were continuously monitored. A 20-G radial artery catheter was inserted under local anaesthesia. For continuous cardiac output monitoring, thermodilutional pulmonary artery catheter (Swan-Ganz, CCOmbo, Baxter Healthcare Co., Irvine, CA, USA) was inserted via the right internal jugular vein under local anaesthesia. After that, anaesthesia was induced with midazolam 0.05 mg kg^{-1}, sufentanil 1.5 μg kg^{-1} and rocuronium 50 mg, and maintained with continuous infusion of sufentanil 0.5 μg kg^{-1} h^{-1}, rocuronium 20–30 mg h^{-1} and low dose of isoflurane (under 0.5 vol%) in oxygen (50%) with air during the surgery. A transoesophageal echocardiographic probe was inserted to monitor myocardial contractility and wall motion abnormality. Arterial oxygen saturation, end-expiratory isoflurane concentration (ET-Isof, vol%), nasopharyngeal and rectal temperatures were monitored during the study. Mechanical ventilation was controlled to maintain normocarbia (4.7–5.0 kPa). The depth of anaesthesia was monitored with a bispectral index score (BIS) monitor (A-200 BIS monitor, Aspect Medical System Inc., Newton, MA, USA) and maintained at 50 (5). Any mean arterial pressure (MAP) below 60 mm Hg during the induction of anaesthesia or during surgery, was treated by 100 μg of phenylephrine.

CPB was instituted with a membrane oxygenator primed with 1.5 litre of crystalloid solution, and boluses of sufentanil 1.5 μg kg^{-1} and midazolam 0.05 mg kg^{-1} were administered through the venous reservoir. Body temperature was cooled to 32–33°C. After aortic cross-clamping, a hyperkalaemic cardioplegic solution was administered through the aortic root and repeated at 30 min intervals. A non-pulsatile pump flow rate was maintained at 2.0–2.5 litre min^{-1} m^{-2}. At the beginning of rewarming, additional boluses of sufentanil 1.5 μg kg^{-1} and midazolam 0.05 mg kg^{-1} were administered. After the completion of the surgical procedure and systemic rewarming (rectal temperature of at least 35°C), patients were weaned from CPB. During CPB, MAP was maintained above 60 mm Hg by the perfusionist who was blinded to the patients study group assignment. When the MAP decreased below 60 mm Hg during CPB, first the pump flow rate was increased up to 3.0 litre min^{-1} m^{-2}, thereafter phenylephrine (100 μg ml^{-1}) was infused until MAP increased to 60 mm Hg.

Measurements and calculations

Haemodynamic variables including cardiac index (CI), MAP, central venous pressure (CVP), heart rates (HR), mean pulmonary arterial pressure (MPAP), and systemic vascular resistance index (SVRI) were measured before (T1, baseline) and 15 min after (T2) the start of CPB, before aortic unclamping (T3) and at skin closure (T4). The number of patients and the frequency requiring phenylephrine bolus administration were recorded between induction and before skin incision, between skin incision and before CPB, and between termination of CPB and skin closure. During CPB, the dose of infused phenylephrine was recorded.

Arterial blood was sampled at T1, T2, T3 and T4 for measuring plasma epinephrine, norepinephrine, AVP and angiotensin II levels. Blood was collected in 5 ml polypropylene tube containing ethylenediaminetetraacetic acid and centrifuged in a refrigerated centrifuge at 3000 g for 10 min to separate the plasma. The decanted plasma was stored at −70°C until analysis. Plasma epinephrine and norepinephrine were measured by high-pressure liquid chromatography (SRL, Tokyo, Japan). Commercially available radioimmunoassay kits were used to measure the plasma

AVP (Yuka AVP RIA, Mitsubishi Kagaku Medical, Tokyo, Japan) and angiotensin II (angiotensin II kits, SRL) levels.

Statistical analysis

Data were analysed with SPSS (version 11.0, SPSS Inc., Chicago, IL, USA). Data were assessed for normal distribution of variance with Kolmogorov–Smirnov test. Results were expressed as number of patients or mean (SD). To assess differences in patient characteristics among three groups, one-way ANOVA with *post hoc* Tukey test and χ^2-test or Fisher's exact test were performed. To assess differences in plasma neurohormonal levels, haemodynamic variables, dose of administered phenylephrine during CPB among three groups, one-way ANOVA with *post hoc* Tukey test was performed. To assess differences in changes of neurohormonal levels within each group, repeated-measures ANOVA with respect to T1 was performed. To assess differences in the number of patients and the frequency requiring phenylephrine administration between induction and before skin incision, between skin incision and before CPB, and between termination of CPB and skin closure among three groups, χ^2-test or Fisher's exact test were performed. A *P*-value <0.05 was considered statistically significant.

Results

Patient characteristics

In the ARA group, candesartan (8 mg day^{-1} in 2 pts, 16 mg day^{-1} in 3 pts), losartan (25 mg day^{-1} in 2 pts, 50 mg day^{-1} in 3 pts), irbesartan (150 mg day^{-1} in 2 pts) and valsartan (80 mg day^{-1} in 2 pts) were taken. In ACEI group, lisinopril (10 mg day^{-1} in 3 pts, 20 mg day^{-1} in 3 pts), ramipril (2.5 mg day^{-1} in 1 pt, 5 mg day^{-1} in 4 pts) and cilazapril (1.25 mg day^{-1} in 1 pt, 2.5 mg day^{-1} in 3 pts) were taken. There were no differences in patient characteristic data, types of mitral valvular disease, types of operation, preoperative cardiac medications, preoperative echocardiographic findings, duration of CPB and ACC among three groups (Table 1).

Table 1 Patients characteristics. ACC, aortic cross-clamping; ACEI, angiotensin-converting enzyme inhibitors; ARA, angiotensin II receptor antagonists; CPB, cardiopulmonary bypass; LA, left atrial; LV, left ventricular. Data are presented as mean (range or SD) or number of patients. No significant differences were seen among the three groups

	Control group (*n*=15)	ACEI group (*n*=15)	ARA group (*n*=14)
Sex (male/female)	7/8	9/6	8/6
Age (yr)	59 (33–63)	55 (28–73)	60 (47–68)
Body surface area (m^2)	1.63 (0.16)	1.69 (0.12)	1.60 (0.11)
Mitral valve lesion (*n*)			
Regurgitation lesion	11	10	9
Stenotic lesion	5	5	5
Operation (*n*)			
Mitral valve repair	8	6	6
Mitral valve replacement	7	9	8
Medication (*n*)			
Digoxin	10	8	9
Diuretics	9	13	13
β-blockers	4	2	2
Echocardiography			
LV ejection fraction (%)	59 (7)	62 (9)	59 (9)
LV diastolic dimension (mm)	54 (5)	58 (7)	56 (10)
LV systolic dimension (mm)	36 (3)	40 (7)	42 (8)
LA volume index (ml m^{-2})	78 (40)	81 (23)	68 (32)
Intraoperative data			
CPB time (min)	137 (25)	123 (29)	130 (26)
ACC time (min)	103 (27)	90 (14)	95 (25)

Table 2 Neurohormonal changes during CPB. ACEI, angiotensin-converting enzyme inhibitors; ARA, angiotensin II receptor antagonists; AVP, arginine vasopressin. T1, before the start of CPB; T2, 15 min after the start of CPB; T3, before aortic unclamping; T4, skin closure. Data are presented as mean (SD). **P*<0.05 *vs* T1; †*P*<0.05 *vs* control group; ‡*P*<0.05 *vs* ACEI group

	T1	T2	T3	T4
Epinephrine (ng ml^{-1})				
Control	0.04 (0.02)	0.10 (0.05)*	0.08 (0.03)	0.10 (0.07)
ACEI	0.05 (0.04)	0.06 (0.04)	0.21 (0.18)*	0.29 (0.26)
ARA	0.05 (0.03)	0.12 (0.09)	0.20 (0.17)*	0.18 (0.15)
Norepinephrine (ng ml^{-1})				
Control	0.19 (0.15)	0.82 (0.64)*	1.24 (0.88)*	1.11 (0.89)*
ACEI	0.36 (0.22)	1.25 (0.90)*	1.76 (1.24)*	1.72 (0.91)*
ARA	0.32 (0.18)	1.76 (1.03)*	2.47 (0.93)*	2.03 (0.54)*
AVP (pg ml^{-1})				
Control	19.6 (11.5)	109.7 (45.7)*	48.9 (32.4)*	36.7 (22.1)*
ACEI	11.9 (8.9)	49.0 (38.6)*†	29.2 (19.5)*	29.1 (13.7)*
ARA	7.0 (3.7)†	32.2 (17.4)*†	30.9 (18.0)*	25.7 (20.5)*
Angiotensin II (pg ml^{-1})				
Control	30.7 (20.3)	61.4 (49.8)	169.1 (140.3)*	141.0 (96.5)*
ACEI	30.3 (16.4)	76.5 (52.6)	193.0 (170.9)*	90.3 (86.4)
ARA	140.7 (98.2)†‡	214.8 (149.7)†‡	507.7 (299.8)*†‡	185.3 (120.7)

Neurohormonal changes

Neurohormonal changes at each time point are presented in Table 2. The plasma epinephrine level increased at T2 in the control group and at T3 in the ARA and ACEI group compared with values at T1 without between-group differences. The plasma norepinephrine level increased at T2, T3 and T4 in all groups compared with values at T1 without between-group differences.

The plasma AVP level in all groups increased at T2, T3 and T4 compared with values at T1. It was significantly lower in the ARA group compared with that in the control group at T1, and lower in the ARA and ACEI group compared with that in the control group at T2. There was no difference in the plasma AVP level between the ARA and ACEI group.

The plasma angiotensin II level significantly increased at T3 in all groups and at T4 in the control group compared with values at T1. The plasma angiotensin II level was significantly higher in the ARA group compared with those in the ACEI and control group at T1, T2 and T3. There was no difference in the plasma angiotensin II level between the ACEI and control group.

Phenylephrine administration and haemodynamics

Between induction and before skin incision, and between skin incision and before CPB, the number of patients and

Table 3 Phenylephrine requirement during mitral valvular surgery. ACEI, angiotensin-converting enzyme inhibitors; ARA, angiotensin II receptor antagonists; CPB, cardiopulmonary bypass. Data are presented as mean (SD) or number. *$P<0.05$ *vs* control group; †$P<0.05$ *vs* ACEI group. No significant differences were seen between ACEI and control group

	Control group (n=15)	ACEI group (n=15)	ARA group (n=14)
Between induction and before skin incision			
No. of patients	2	4	10*†
Frequency	2	6	19*†
Between skin incision and before CPB			
No. of patients	0	1	6*†
Frequency	0	2	8*†
During CPB			
Total dose (mg)	3.3 (1.3)	5.1 (2.1)	10.7 (5.1)*†
Calculated infusion dose ($\mu g\ kg^{-1}\ min^{-1}$)	0.4 (0.2)	0.8 (0.4)	1.6 (0.9)*†
Between termination of CPB and skin closure			
No. of patients	0	0	2
Frequency	0	0	2

the frequency requiring phenylephrine administration were significantly higher in the ARA group than in the ACEI and control group (Table 3). There were no significant differences between the ACEI and control group. Preoperative haemodynamic variables were not different among the three groups (Table 4). After the induction of anaesthesia, MAP was significantly lower in the ARA group than in the control group. Haemodynamic variables were not different among the three groups at T1.

During CPB, all patients in the three groups required the administration of phenylephrine. The dose of administered phenylephrine was significantly greater in the ARA group than in the ACEI and control group. MAP was lower in the ARA group than in the control group at T2 and T3. SVRI was lower in the ARA group than in the ACEI group at T2. In conjunction with higher CI (pump flow), MAP and SVRI were lower in the ARA and ACEI group than in the control group at T3.

Table 4 Haemodynamic variables during mitral valvular surgery. ACEI, angiotensin-converting enzyme inhibitors; ARA, angiotensin II receptor antagonists; BIS, bispectral index score; CI, cardiac index; CVP, central venous pressure; ET-Isof, end-tidal isoflurane concentration; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; NA, not applicable; RT, rectal temperature; SVRI, systemic vascular resistance index. T1, before the start of CPB; T2, 15 min after the start of CPB; T3, before aortic unclamping; T4, skin closure. Data are presented as mean (SD). *$P<0.05$ *vs* control group; †$P<0.05$ *vs* ACEI group

	Pre-induction	Post-induction	T1	T2	T3	T4
MAP (mm Hg)						
Control	91 (13)	82 (11)	86 (10)	71 (9)	75 (6)	81 (12)
ACEI	89 (12)	80 (9)	86 (14)	70 (9)	70 (9)*	81 (8)
ARA	85 (10)	73 (10)*	78 (7)	62 (5)*	70 (7)*	77 (7)
CI (litre $min^{-1}\ m^{-2}$)						
Control	2.9 (0.7)	2.8 (0.6)	2.7 (0.8)	2.6 (0.5)	2.5 (0.2)	2.8 (0.4)
ACEI	3.2 (1.1)	3.1 (0.7)	2.6 (1.0)	2.4 (0.4)	2.8 (0.3)*	2.9 (0.7)
ARA	2.7 (1.0)	2.7 (0.8)	2.5 (0.6)	2.8 (0.5)	2.9 (0.3)*	3.2 (0.6)
HR ($beats\ min^{-1}$)						
Control	80 (23)	92 (21)	78 (15)	NA	NA	88 (16)
ACEI	84 (17)	84 (13)	81 (12)	NA	NA	88 (14)
ARA	81 (8)	80 (22)	82 (13)	NA	NA	96 (19)
MPAP (mm Hg)						
Control	28.9 (9.0)	26.5 (12.0)	30.8 (8.4)	NA	NA	20.6 (3.2)
ACEI	21.7 (7.8)	20.9 (7.1)	26.3 (7.4)	NA	NA	19.6 (3.9)
ARA	23.4 (11.1)	22.3 (5.4)	25.9 (5.8)	NA	NA	19.7 (5.6)
CVP (mm Hg)						
Control	7.6 (4.0)	7.3 (2.6)	8.6 (2.5)	NA	NA	9.5 (3.0)
ACEI	5.7 (2.7)	7.1 (2.6)	9.3 (2.1)	NA	NA	8.3 (2.9)
ARA	7.3 (1.6)	7.6 (1.3)	9.4 (2.7)	NA	NA	9.4 (3.0)
SVRI ($dyn\ s\ cm^{-5}\ m^{-2}$)						
Control	2480 (707)	2271 (717)	2501 (796)	2254 (587)	2340 (328)	2108 (584)
ACEI	2361 (1169)	2020 (545)	2724 (1157)	2417 (646)	1999 (364)*	2142 (712)
ARA	2595 (1064)	2130 (639)	2345 (493)	1774 (313)†	1935 (298)*	1696 (204)
Haematocrit (%)						
Control	36 (4)	34 (4)	33 (3)	24 (3)	26 (4)	28 (3)
ACEI	37 (6)	36 (5)	35 (5)	24 (5)	26 (3)	29 (4)
ARA	37 (4)	35 (3)	33 (4)	23 (3)	24 (4)	27 (3)
RT (°C)						
Control	NA	NA	36.5 (0.4)	34.4 (0.7)	35.3 (0.7)	36.4 (0.3)
ACEI	NA	NA	36.3 (0.5)	34.4 (0.5)	35.1 (0.5)	36.5 (0.5)
ARA	NA	NA	36.4 (0.4)	34.3 (0.4)	35.1 (0.5)	36.3 (0.3)
ET-Isof (vol %)						
Control	NA	0.4 (0.2)	0.3 (0.2)	0.2 (0.1)	0.3 (0.1)	0.4 (0.1)
ACEI	NA	0.3 (0.2)	0.3 (0.2)	0.2 (0.1)	0.3 (0.1)	0.4 (0.2)
ARA	NA	0.3 (0.1)	0.3 (0.1)	0.2 (0.1)	0.3 (0.1)	0.3 (0.1)
BIS						
Control	96 (5)	57 (6)	55 (7)	45 (5)	52 (9)	53 (6)
ACEI	96 (4)	55 (6)	53 (6)	47 (5)	54 (6)	52 (8)
ARA	97 (3)	57 (4)	53 (7)	44 (6)	55 (6)	52 (5)

Between termination of CPB and skin closure, there was no difference in the number of patients requiring phenylephrine administration, and in haemodynamic variables at T4 among the three groups. There were no differences in haematocrit, rectal temperature, ET-Isof and BIS at each time point of measurements among three groups (Table 4).

Discussion

In this study, the effects of long-term ARA and ACEI medication on changes in vasoconstrictive neurohormonal levels such as epinephrine, norepinephrine, AVP and angiotensin II, haemodynamic variables and vasoconstrictor requirement during CPB were evaluated. The results demonstrated that chronic ARA treatment resulted in a more profound hypotension and a greater need for vasoconstrictor treatment than ACEI treatment during CPB, and it may be associated with direct blockade of angiotensin II receptor by ARA.

Sympathetic nervous system, AVP and RAS are the main vasopressor systems for sustaining arterial blood pressure.[13] Each system may act as a compensatory mechanism whenever the other system is depressed. Angiotensin II exerts its effects through angiotensin II receptor subtype1 (AT1 receptor) and subtype2 (AT2 receptor).[1 13 14] Most physiological effects of angiotensin II, including vasoconstriction, renal salt and water retention, aldosterone and AVP release, and sympathetic facilitation, are mediated by the AT1 receptor. By contrast, AT2 receptor activation is associated with antiproliferation, cell differentiation and development, tissue degeneration and apoptosis. Theoretical advantage of ARA over ACEI is that it is more specific to the RAS. ARA selectively binds to AT1 receptor and acts independent of angiotensin II synthesis pathway, allowing more complete blockade of the RAS compared with ACEI. And, the compensatory increase of angiotensin II by ARA may cause the stimulation of the unblocked AT2 receptor, which could exert beneficial effects in terms of vascular and cardiac remodelling. In addition, ARA does neither elevate circulating bradykinin level nor elicit coughing.[15] In this study, angiotensin II level significantly increased during CPB compared with values before CPB in all three groups. This was consistent with the previous studies reporting increased plasma renin activity, aldosterone and angiotensin II concentrations during CPB as a result of CPB-induced RAS activation.[10 11 16] However, SVRI was significantly lower in the ARA group when compared with that in the ACEI group in spite of a greater amount of phenylephrine administered during CPB. In addition, the plasma angiotensin II level was significantly higher in the ARA group than that in the ACEI group during CPB. Therefore, these results suggest that ARA might have blocked vasoconstrictive action of angiotensin II on AT1 receptor during CPB, and caused the compensatory increase in plasma angiotensin II level.

It is well known that preoperative RAS antagonist medication blunts vasoactive response in anaesthetized patients not only by inhibition of RAS but also by modulating other vasoconstrictive neurohormones such as AVP. AVP as an antidiuretic hormone, modulates vascular tone via V_{1a} receptors on vascular smooth muscle. In humans, AVP release is stimulated by increase in the osmolality of the extracellular fluid compartment, decrease in the circulating blood volume, and a decrease in arterial blood pressure.[17 18] Several other stimuli for AVP release have been identified, including norepinephrine and angiotensin II. During CPB, increase in AVP level to more than six times, often exceeding 100 pg ml^{-1} has been reported.[9 19] In this study, AVP level increased during CPB in all three groups, especially about five times higher than before CPB value at 15 min after the start of CPB. Among three groups, AVP level was significantly lower in the ARA group than in the control group before and 15 min after the start of CPB. This might be associated with the direct blockade of the AT1 receptor, which is one of the stimulators for AVP release. In the ACEI group, although phenylephrine requirement during CPB was not different compared with the control group, MAP and SVRI were significantly lower than control group before aortic unclamping. These results suggest that lower AVP level in the ACEI group compared with the control group during CPB seemed to be responsible, and were compatible with a previous report of the association of AVP deficiency with deleterious hypotension during CPB.[12] However, angiotensin II level was not different between the ACEI and control group during the surgery. This may be attributable to generation of angiotensin II by other enzymes, such as chymase, chymostatin-sensitive angiotensin II generating enzyme, tissue plasminogen activator.[16 20] Licker and colleagues[11] also reported that there were no differences in catecholamine and angiotensin II levels between the ACEI and control group during cardiac surgery. Between induction and before CPB, phenylephrine was used more frequently in the ARA group than in other groups. Even though neurohormonal levels were not measured at anaesthetic induction time, similar changes in AVP and angiotensin II level might have occurred at this time because previous studies reported that there were no significant changes of neurohormonal levels between during the induction of anaesthesia and before the start of CPB.[11 21]

Catecholamines have been used as the first-line drug for treating hypotension associated with CPB. Our findings that phenylephrine administration was necessary in all patients during CPB in spite of marked increase in catecholamine levels indicate that sympathetic activation alone is not sufficient to maintain adequate blood pressure during CPB, and the activity of the AVP and RAS also play an important role on haemodynamics. The RAS antagonists have been increasingly used in patients with valvular heart disease for the purpose of attenuating pulmonary hypertension and pulmonary vascular remodelling.[22 23] In this study, considering the result that MAP could be barely maintained above 60 mm Hg in the ARA group during CPB despite administration of phenylephrine in doses beyond the clinically recommended upper limit,[24] preoperative long-term ARA

medication would be a serious challenge to anaesthesiologists during cardiac surgery. There was a report that vasodilatory shock during CPB in patients chronically treated with ACEI was successfully treated with angiotensin II.[25] However, our study showed that angiotensin II cannot be considered as an option in treating hypotension associated with long-term ARA medication during CPB. Therefore, we recommend the use of AVP as a second-line drug for treating hypotension. There were some reports that AVP has been successfully used in the treatment of deleterious vasodilatory shock associated with RAS antagonist during CPB.[12 26] Furthermore, discontinuing ARA medication before the surgery should be considered in patients on chronic ARA medication. Some investigators demonstrated that stopping ARA or ACEI therapy before surgery does not increase either hypertensive episodes or congestive heart failure perioperatively,[2 27] and also it decreases the risk of post-induction hypotension.[28] Yet further studies regarding these matters are warranted.

The limitations of this study are as follows: first, we did not include patients with left ventricular ejection fraction <50% or in NYHA functional class 3 or 4 in this study. Congestive heart failure itself is a risk factor of vasodilatory shock and is associated with alterations in many vasoconstrictive and vasodilatory neurohumoral factors.[12 17 29] Therefore, our results should not be extended to patients with congestive heart failure. Second, the authors had no knowledge of the patients' haemodynamic state before starting on ARA or ACEI medication, and this cannot be excluded as confounding factors. However, as the patient characteristic data and preoperative haemodynamic variables in all patients enrolled in this study were not different, the effects of these confounding factors should be minimal. Third, the differences in haemodynamic changes among three groups were elucidated by the changes in vasoconstrictive neurohormones. As potent vasodilatory substances such as complement, kinin–kallikrein, cytokine, bradykinin and prostaglandin were also activated during CPB,[7 8] the effects of ARA or ACEI medication on vasodilatory substance activities could not be excluded and further study is needed in this area.

In conclusion, chronic ARA medication resulted in more profound hypotension and needed greater dose of vasoconstrictor than ACEI medication during CPB, and it may be associated with the blockade of vasoconstrictive action of angiotensin II on AT1 receptor.

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