Comparative effects of angiotensin II on Doppler parameters of left and right heart systolic and diastolic blood flow

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- 1 The purpose of the study was to investigate the effects of angiotensin II on Doppler parameters of right ventricular systolic and diastolic blood flow, and to compare these with effects on the left heart, in normal subjects.
- 2 Pulsed-wave Doppler measurements were made in eight normal volunteers: after a 30 min control i.v. infusion of dextrose, after 30 min stepwise infusions of angiotensin II (2, 4 and 6 ng kg⁻¹ min⁻¹), and finally 30 min after stopping the 6 ng kg⁻¹ min⁻¹ dose of angiotensin II. Aortic (Ao) and pulmonary (Po) systolic ejection parameters, as well as mitral (Mi) and tricuspid (Tc) diastolic filling parameters were measured.
- 3 Ao and Po maximal velocity were both significantly reduced by angiotensin II, whereas there were significant opposite effects on Ao (reduced) and Po (increased) mean acceleration. There was a dose-related fall in Po acceleration time with angiotensin II, whilst Ao acceleration time remained unchanged.
- 4 Mi and Tc early diastolic filling velocities were not significantly altered by angiotensin II compared with baseline, although there was a significant rebound increase in both Mi and Tc early filling after cessation of angiotensin II infusion. Mi and Tc pressure half-times were not significantly changed.
- 5 In conclusion, angiotensin II produced changes in Po ejection parameters consistent with a pressor response in the pulmonary vascular bed. Neither right nor left ventricular diastolic filling were directly affected by angiotensin II. The differential effects of angiotensin II on Po and Ao ejection parameters might be due to inherent differences in basal pulmonary and systemic vascular tone.

Keywords angiotensin II Doppler parameters systolic blood flow
diastolic blood flow

Introduction

Activation of renin-angiotensin system (RAS) results in release of angiotensin II which produces systemic pressor effects in addition to sodium and water retention via aldosterone. In the intact-chest cat, it has recently been shown that angiotensin II is a potent pulmonary vasoconstrictor, with reversal of pulmonary pressor effects by an angiotensin II antagonist [1]. Studies in rats have also suggested that angiotensin II may have an additional facilitatory role in terms of sensitising the pulmonary vascular bed in the vasoconstrictor effects of hypoxaemia [2, 3]. However, relatively little is known regarding the

effects of angiotensin II on right heart and pulmonary blood flow in humans. The latter may be of relevance in that RAS activation with raised levels of angiotensin II occurs in patients with pulmonary hypertension due to cor pulmonale [4, 5, 6]. It is therefore interesting to consider whether elevated levels of angiotensin II might in part account for the altered haemodynamic status in cor pulmonale, in terms of producing raised right ventricular after-load and impaired left and right ventricular diastolic filling [7, 8]. The purpose of this study was to investigate the effects of angiotensin II in normal subjects

on Doppler parameters of right ventricular systolic and diastolic blood flow, and to compare these with effects on the left heart.

Methods

Subjects

Eight normal volunteers (age 24 ± 3 years) were studied after giving written consent to a protocol approved by the Tayside Health Board Committee for medical ethics. All subjects were required to be normotensive and receiving no medical treatment. Prior to inclusion into the study, subjects were required to have a normal screen including physical examination, 12 lead ECG, Doppler echocardiographic evaluation, full blood count as well as urea and electrolytes.

Protocol

Subjects attended the laboratory at the same time of the morning (09.00–10.00 h). On arrival at the laboratory, subjects were placed supine and remained in this position for the duration of the study period. An indwelling i.v. cannula was placed in each antecubital fossa, one for infusion and the other for venous sampling for angiotensin II. Baseline Doppler measurements were made after an initial 30 min resting period during which a control infusion of 5% dextrose was given. Following this, sequential stepwise 30 min infusions of angiotensin II (2, 4 and 6 ng kg⁻¹ min⁻¹) (Clinalfa, Laufelfingen, Switzerland) were given, with Doppler measurements being made at the end of each dose. A final set of measurements was recorded 30 min after stopping the last dose of angiotensin II (Off).

Measurements

Pulsed-wave Doppler measurements were made during the last 10 min of each 30 min period at baseline, at each dose of angiotensin II, and at Off. A Vingmed SD-50 (Vingmed Sound, Horten, Norway) was used in conjunction with a 2.0 MHz probe. All measurements were recorded onto videotape and analysed at the end of the study. The mean of five consistent waveforms was used for each parameter, for the purpose of analysis.

Ascending aortic (Ao) systolic blood flow was recorded from the suprasternal notch with measurement of the following parameters: maximal velocity (AoV_{max}), acceleration time (AoAT), ejection period (AoEP), and mean acceleration (AoAcc). The systolic velocity integral (AoSVI) was also measured and represents the linear analogue of stroke volume (SV), since the aortic cross-sectional area (CSA) is a constant ($SV = AoSVI \times AoCSA$) [9]. Pulmonary (Po) arterial systolic blood flow was recorded from the second or third left intercostal space, in order to measure: PoV_{max}, PoAT, PoEP and PoAcc.

Diastolic blood flow across the tricuspid (Tc) and mitral (Mi) valves was recorded from the apex, with measurement of maximal early (E_{max}) and late (A_{max}) filling velocities, as well as the pressure half-time ($t_{1/2}$) for early diastolic filling.

Venous blood samples for angiotensin II were collected into chilled plain glass tubes containing 0.5 ml of a solution comprising 0.05 mmol l⁻¹ *o*-phenanthroline, 0.2 g neomycin l⁻¹, 0.125 mol l⁻¹ EDTA (disodium salt) and 2% (v/v) ethanol. Samples were spun in a cooled centrifuge, separated and stored at -70° C. The assays were performed in batches at the completion of the study and were analysed in duplicate. Angiotensin II was measured after extraction on an Amprep C8 column (Amersham International, Bucks, UK) using a commercially available radio immunoassay kit (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The within and between assay values for analytical imprecision were 2.2% and 12.0% respectively.

Statistical analysis

All data were analysed using a 'Statgraphics' software package. The intraindividual short-term variability was calculated for Doppler parameters measured before and after the 30 min control infusion. One way analysis of variance was used to obtain the mean sum of squares for within subject variation (s.d.²), where s.d. is the standard deviation. The coefficient of variation (CV) for within subject variability was then calculated as s.d./global mean $\times 100\%$.

Comparisons between time-points were made by analysis of variance followed by Duncan's multiple range test [10]. A probability value of $P < 0.05$ (two-tailed) was considered to be of significance. For the sake of clarity, individual P values are not given in the text where a result is said to be of significance. Data are shown in the text as means and 95% confidence intervals (95% CI).

Results

The coefficients of variation (CV) for systolic Doppler parameters were: PoV_{max} 3.0%, AoV_{max} 4.4%, PoAT 1.7%, AoAT 6.4%, PoEP 2.0%, AoEP 1.6%, PoAcc 4.4%, AoAcc 12.5%, AoSVI 1.2%. The CV values for diastolic parameters were: TcE_{max} 12.2%, MiE_{max} 9.3%, TcA_{max} 13.7%, MiA_{max} 19.3%, Tct_{1/2} 7.6%, Mit_{1/2} 6.6%.

There were dose-related increases in plasma levels of angiotensin II (pmol l⁻¹): baseline 32.9(16.6–49.1), 2 ng kg⁻¹ min⁻¹ 71.0(54.8–87.3), 4 ng kg⁻¹ min⁻¹ 112.3(96.1–128.5), 6 ng kg⁻¹ min⁻¹ 148.4(132.2–164.7). There were significant differences between levels at baseline and all three doses of angiotensin II.

Numerical data for ejection systolic parameters and diastolic filling parameters are shown in Tables 1 and 2 respectively.

Both Ao and Po V_{max} were significantly attenuated by all doses of angiotensin II, with values returning to baseline after stopping angiotensin II (Figure 1). For Ao but not Po V_{max}, there was a significant difference between the 2 and 4 ng kg⁻¹ min⁻¹ doses of angiotensin II. In contrast, Ao and Po Acc showed significant opposite responses to angiotensin II with a significant increase in PoAcc and a decrease in AoAcc (Figure 1).

There were significant dose-related falls in PoAT in response to angiotensin II with an almost complete return to baseline levels after cessation of angiotensin

Table 1 Ejection systolic parameters

	Baseline	Angiotensin II ($\text{ng kg}^{-1} \text{min}^{-1}$)				Off
		2	4	6		
PoV _{max} (cm s^{-1})	82.4 (78.5–86.3)	76.4 (72.5–80.3)*	74.3 (70.4–78.1)*	76.4 (72.5–80.3)*	82.5 (78.6–86.4)	
AoV _{max} (cm s^{-1})	112.4 (108.4–116.3)	105.5 (101.6–109.5)*	96.6 (92.7–100.6)**	93.4 (89.4–97.3)**	112.8 (108.8–116.7)	
PoAT (ms)	148 (142–155)	138 (131–144)*	117 (110–123)**	107 (100–113)**	143 (137–150)	
AoAT (ms)	63 (59–67)	66 (62–70)	66 (62–70)	65 (61–70)	64 (61–68)	
PoEP (ms)	309 (303–316)	303 (297–310)	296 (289–302)*	296 (289–302)*	311 (305–318)	
AoEP (ms)	305 (296–314)	305 (296–314)	303 (293–312)	300 (291–309)	304 (295–314)	
PoAcc (cm s^{-2})	558 (508–608)	556 (506–606)	645 (595–695)*	711 (661–761)*	576 (526–626)	
AoAcc (cm s^{-2})	1790 (1627–1953)	1613 (1450–1776)	1474 (1311–1637)*	1575 (1412–1738)	1820 (1657–1983)	
AoSVI (cm)	18.3 (17.5–19.1)	16.9 (16.1–17.7)*	16.5 (15.7–17.3)*	16.1 (15.3–16.9)*	18.5 (17.7–19.3)	

Ejection parameters for pulmonary (Po) and aortic (Ao) systolic blood flow: at baseline; after 2, 4 and 6 $\text{ng kg}^{-1} \text{min}^{-1}$ of angiotensin II; and after stopping angiotensin II (Off). V_{max} (maximal velocity), AT (acceleration time), EP (ejection period), Acc (mean acceleration), SVI (systolic velocity integral). Values shown are means and 95% CI. * $P < 0.05$ vs baseline, ** $P < 0.05$ vs 2 $\text{ng kg}^{-1} \text{min}^{-1}$ angiotensin II, *** $P < 0.05$ vs 4 $\text{ng kg}^{-1} \text{min}^{-1}$ angiotensin II.

Table 2 Diastolic filling parameters

	Baseline	Angiotensin II ($\text{ng kg}^{-1} \text{min}^{-1}$)				Off
		2	4	6		
TcE _{max} (cm s^{-1})	59.4 (56.3–62.4)*	59.0 (55.9–62.1)*	57.9 (54.8–60.9)*	58.4 (55.3–61.4)*	64.3 (61.2–67.3)	
MiE _{max} (cm s^{-1})	73.3 (69.3–77.2)	69.3 (65.3–73.2)*	69.5 (65.6–73.4)*	68.2 (64.3–72.2)*	76.6 (72.7–80.6)	
TcA _{max} (cm s^{-1})	36.8 (32.0–41.5)	38.6 (33.8–43.4)	35.5 (30.7–40.3)	32.9 (28.1–37.7)	36.8 (32.0–41.5)	
MiA _{max} (cm s^{-1})	44.5 (40.5–48.5)	43.5 (39.5–47.5)	40.8 (36.8–44.7)*	39.6 (35.7–43.6)*	48.6 (44.7–52.6)	
Tct _{1/2} (ms)	63.8 (61.2–66.3)	61.9 (59.4–64.4)	63.1 (60.6–65.7)	61.9 (59.4–64.4)	64.4 (61.9–66.9)	
Mit _{1/2} (ms)	58.1 (54.2–62.0)	54.4 (54.2–58.3)	55.6 (51.7–59.5)	53.8 (49.9–57.6)	58.1 (54.2–62.0)	

Filling parameters for tricuspid (Tc) and mitral (Mi) diastolic blood flow: at baseline; after 2, 4 and 6 $\text{ng kg}^{-1} \text{min}^{-1}$; and after stopping angiotensin II (Off). E_{max} (early maximal filling velocity), A_{max} (late maximal filling velocity), $t_{1/2}$ (pressure half-time for early diastolic deceleration). Values are shown as means and 95% CI. * $P < 0.05$ vs Off. There were no significant effects of angiotensin II compared with baseline.

Figure 1 a) Pulmonary (Po) and b) aortic (Ao) maximal velocity (V_{max}) measured at baseline (O), after angiotensin II (2, 4 and 6 $\text{ng kg}^{-1} \text{min}^{-1}$), and after stopping angiotensin II (Off). c) Pulmonary and d) aortic mean acceleration (Acc). * $P < 0.05$ vs baseline, ** $P < 0.05$ vs 2 $\text{ng kg}^{-1} \text{min}^{-1}$ angiotensin II.

Figure 2 a) Effects of angiotensin II on a) pulmonary and b) aortic acceleration time (AT). c) Pulmonary and d) aortic ejection period (EP). * $P < 0.05$ vs baseline, ** $P < 0.05$ vs 2 ng kg⁻¹ min⁻¹ angiotensin II, *** $P < 0.05$ vs 4 ng kg⁻¹ min⁻¹ angiotensin II, NS: not significant.

II (Figure 2). However, AoAT unlike PoAT, was not significantly altered by any of the angiotensin II doses. There was also a significant fall in PoEP but not AoEP with angiotensin II (Figure 2). Dose-dependent attenuation of AoSVI occurred in response to angiotensin II which was significant at all doses with a return to baseline after stopping angiotensin II (Figure 3).

Right ventricular (Tc) and left ventricular (Mi) early and late diastolic filling velocities ($E_{\max}$) were not significantly attenuated by angiotensin II in comparison with baseline values. However, there was a significant rebound increase in both RV and LV early filling after stopping the angiotensin II infusion (Figure 3). There was also a significant rebound increase in late LV but not RV filling ($A_{\max}$) after cessation of angiotensin II. Mi and Tc $t_{1/2}$ were not significantly altered by angiotensin II and there was no rebound effect after stopping angiotensin II.

Discussion

In discussing the results, it seems appropriate to consider separately effects of angiotensin II on ejection systolic and diastolic filling parameters. The falls in Ao and Po $V_{\max}$ are a reflection of respective effects of angiotensin II on left and right ventricular stroke volume. This is because $V_{\max}$ is a major determinant of the area under the velocity-time curve (SVI) and hence stroke volume [9]. In this respect the measurement of $V_{\max}$ has been shown to mirror changes in stroke volume with posture and exercise [11]. Thus, it is perhaps not surprising that

the effects of angiotensin II on Ao $V_{\max}$ and AoSVI were similar. The fall in stroke volume probably occurs as a reflex response to the increase in systemic vascular resistance with angiotensin II, and also as a result of venodilatation and associated reduction in left ventricular end diastolic volume [12].

It was interesting to find that angiotensin II produced a dose-related reduction in PoAT whereas AoAT was not significantly attenuated. Several previous studies have shown that PoAT correlates closely with mean pulmonary arterial pressure and pulmonary vascular resistance [13–15]. Thus, it can be inferred that angiotensin II produced a rise in right ventricular afterload due to pressor effects on the pulmonary circulation. The unchanged AoAT with angiotensin II probably reflects the greater systemic vascular resistance, as evidenced by the difference between basal values of PoAT and AoAT. In other words, it is possible to detect vasoconstrictor effects by measuring the AT in a vascular bed where there is a low resistance. There were also significant reductions in PoEP but not to AoEP in response to angiotensin II. However, changes in PoEP were of small magnitude suggesting that PoEP is not a sensitive parameter of changes in pulmonary vascular resistance.

Angiotensin II produced significant opposite effects on PoAcc and AoAcc. The measurement of AoAcc has been shown to be a sensitive index of inotropic response to β -adrenoceptor stimulation, although it is also known to be affected by loading conditions [16–18]. It is possible that effects of angiotensin II on myocardial contractility may have affected PoAcc independent from its effects on right ventricular afterload. This conclusion tends to

Figure 3 a) Effects of angiotensin II on aortic systolic velocity integral (SVI)—stroke distance. * $P < 0.05$ vs baseline. b, c) Effects of angiotensin II on tricuspid (Tc) and mitral (Mi) early diastolic filling velocity ($E_{\max}$). * $P < 0.05$ vs Off. There were no significant effects of angiotensin II compared with baseline.

be supported by *in vitro* data showing that angiotensin II produces positive inotropic effects in the isolated heart [19, 20]. Since angiotensin II also produces right ventricular preload reduction by venodilatation [12], the net effect on PoAcc is probably a summation of responses. Another possible explanation to account for divergent effects of angiotensin II on Ao and Po Acc, is that angiotensin II reduced PoAT but not AoAT, whilst producing falls in both Po and Ao $V_{\max}$. Hence, acceleration (dv/dt) measured in Ao would fall, but would increase in Po.

There was no significant change in left or right ventricular diastolic filling with angiotensin II, although there was a rebound increase in filling after stopping angiotensin II. The most likely explanation is that a rebound overshoot of venoconstriction occurs after stopping angiotensin II, following the venodilatation which occurs during angiotensin II infusion [12]. The overshoot in venoconstriction would result in increased venous return and hence increased right ventricular filling. Our results therefore suggest that angiotensin II does not acutely reduce ventricular compliance, the inference being that angiotensin II is not directly involved in producing diastolic dysfunction which occurs in patients with cor pulmonale.

On the basis of our findings with angiotensin II one might predict that ACE inhibitors would reduce pulmonary vascular resistance and increase stroke volume in patients with cor pulmonale. Although at first sight these sequelae might appear to be beneficial, it is also conceivable that an increase in pulmonary perfusion to underventilated alveoli might ensue as a result of these effects. This would produce a worsening of the ventilation-perfusion mismatch and hence an increase in pulmonary venous oxygen desaturation. Single-dosing studies with ACE inhibitors have shown variable effects on pulmonary arterial pressure in patients with cor pulmonale [21–23]. However, it is probably more meaningful to investigate chronic-dosing effects of ACE inhibitors in terms of haemodynamics, gas exchange and survival [24, 25]. In this respect, the use of Doppler ultrasound may prove to be a valuable non-invasive tool for evaluating serial effects of ACE inhibitors on pulmonary haemodynamics in cor pulmonale [26–28], without having to resort to repeated right heart catheterisation.

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