(67.9%) SSS patients and 10 of 13 (76.9%) AVB patients. As the side effects, palpitation, dry mouth, headache and other adverse symptoms were seen in 9 (18%) patients, but all these symptoms were clinically mild and tolerable.

Conclusion: Significant improvement of bradyarrhythmias was obtained by oral administration of AF-DX, indicating that this new agent can be used for long-term control of mild to moderate bradyarrhythmia and also as a temporary bridge until permanent pacemaker implantation.

1225-38 Aldosterone Causes Baroreceptor Dysfunction in Man

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Background: Baroreflex dysfunction is a key process leading to ventricular arrhythmias and mortality in chronic heart failure (CHF). Aldosterone has been shown to impair the baroreceptor response in animal models. This study is designed to test the hypothesis that aldosterone directly attenuates the baroreflex *in vivo* in man.

Methods: Fourteen healthy male volunteers [mean age (SD) 25 (9)] received iv d-aldosterone (12 pmol/kg/min) and placebo in a double blind cross-over fashion, confused with incremental doses of iv phenylephrine (PE) and sodium nitroprusside (SN).

Results: Baroreflex sensitivity was significantly blunted in the aldosterone group [8.4 (95%CI 7.5–9.2) vs 10.1 (95%CI 9.3–11.0) msec/mmHg; p = 0.01]. Reflex heart rate (HR) response to PE were impaired while BP responses were unaltered (Table 1). Aldosterone had no significant effect on the haemodynamic response to SN.

Table 1

PE Dose	PLACEBO		ALDO	
	ΔsBP (mmHg)	ΔHR (bt/min)	ΔsBP	ΔHR
0.6	12.5 (8.1, 16.9)	8.3 (6.1, 10.6)	13.5 (9.0, 17.9)	3.5 (1.3, 5.8)†
1.2	20.5 (14.4, 26.6)	13.9 (12.1, 15.8)	24.6 (18.7, 30.6)	9.0 (7.1, 10.8)†
2.4	43.1 (36.3, 49.8)	19.0 (17.5, 20.5)	44.1 (37.4, 50.9)	15.3 (13.8, 17)†
3.6	57.2 (51.7, 62.7)	22.1 (20.1, 24.2)	60.4 (53.9, 67.0)	18.8 (16.4, 21)†

Values are Mean (95% CI). †P < 0.05, ‡P < 0.01 compared with placebo.

Conclusion: This is the first study to show that aldosterone impairs baroreceptor function in man. High aldosterone levels causing baroreflex dysfunction may contribute to arrhythmogenesis and sudden cardiac death in conditions such as CHF.

1225-39 The Significance of Plasma Renin Levels in Patients With Dilated Cardiomyopathy on Therapeutic Doses of ACE Inhibitor

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To study interrelations between haemodynamics and renin-angiotensin system we measured BNP, ANP, renin, ACE and aldosterone (aldo) in plasma, LV long (LA) and short (SA) axes by M-mode echocardiography in 35 patients with dilated cardiomyopathy (DCM) taking therapeutic doses of ACE inhibitor.

In group I (15 pts) plasma renin was < 100 pg/ml (43.5 ± 23.1), and greater in group II (2474.6 ± 2579.4). LV ESD (5.0 ± 1.2 cm v 6.5 ± 1.5, p < 0.001) and EDD (6.2 ± 1.0 v 7.4 ± 1.4, p < 0.002), plasma aldo (284.6 ± 221.2 pmol/l v 674.9 ± 463.0, p < 0.001) were all greater in II gr while ACE level (35.3 ± 37.4 iu/l v 15.0 ± 19.3, p < 0.03). LVEF (20.2 ± 10.6 v 13.7 ± 4.7, p < 0.02) and peak shortening rates of LA (3.4 ± 1.8 cm/s v 2.3 ± 1.1, p < 0.04) were less. ANP and BNP did not differ between the groups (11.0 ± 7.4 pmol/l v 18.9 ± 23.1, p < 0.09 and 19.3 ± 18.4 v 24.3 ± 20.2, p < 0.24), but in II gr, but not I gr, were closely correlated with ACE level (r = 0.70 and 0.66). By contrast, in I gr, but not II gr, correlation was present between SA and LA peak shortening rates, r = 0.58 and lengthening rates, r = 0.67.

Thus in patients with DCM on therapeutic doses of ACE inhibitor, values of plasma renin < 100 pg/ml, but not ANP or BNP, are markers of larger cavity size, reduced shortening rates and lower ejection fraction. Consistent loss of normal coordination between SA and LA function in patients with high renin suggests advanced remodelling.

1225-40 Local Hyperinsulinemia Increases Endothelin Activity in the Human Forearm Circulation

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To investigate a potential mechanism linking hyperinsulinemia with hypertension and atherosclerosis, we examined whether insulin modulates the vasoactive effects of endothelin (ET-1), a vasoconstrictor and mitogenic peptide. To this purpose, we measured the forearm blood flow (FBF, strain-gauge plethysmography) responses to ET-1 receptor blockade during infusion of either saline or insulin in 8 healthy subjects on 2 separate days. During saline, intraarterial infusion of an ET_A-receptor blocker (BQ-123, 100 nmol/min for 60 min), alone and in combination with an ET_B-receptor antagonist (BQ-788, 50 nmol/min for further 60 min) did not significantly change FBF (2.9 ± 0.2 [mean ± SEM] mL/min/dL before, 2.9 ± 0.2 mL/min/dL after BQ-123 alone, 2.8 ± 0.2 mL/min/dL after the combination of BQ-123 and BQ-788; P = 0.29). Insulin administration (0.1 mU/kg/min for 2 hr) resulted in a marked increase in local insulin concentration (from 3 ± 1 to 295 ± 69 μU/mL; P = 0.004), but did not modify FBF (2.3 ± 0.1 mL/min/dL before and 2.2 ± 0.1 mL/min/dL after 2 hr of insulin infusion; P = 0.58). During hyperinsulinemia, ET-1 receptor antagonism caused a vasodilator effect, with a FBF increase of 25 ± 9% after 60 min of selective ET_A blockade and of 52 ± 7% after 60 min of combined ET_A and ET_B antagonism (P < 0.001). These findings suggest that insulin stimulates vascular production of ET-1, which may contribute to the hypertensive and atherogenic effects of hyperinsulinemia. The observation that insulin does not modify vascular tone in the absence of ET-1 receptor blockade is compatible with the concurrent activation of vasodilator mechanisms that physiologically balance the vasoconstrictor effect of increased ET-1.

1225-53 Effects of Dobutamine Administration on Timing of Atrial Contraction and Systolic Performance of the Left Atrium in Normal Subjects and in Patients With Heart Failure

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Background: Mechanical effects of atrioventricular interaction play an important role in ventricular filling during tachycardia. As heart rate increases, atrial contraction occurs earlier in diastole and thereby influence ventricular filling throughout a rate-limited diastolic period. The influence of dobutamine infusion on the left atrial (LA) systole was studied in 11 normal subjects and in 7 patients with heart failure who were atrially paced at a heart rate equal to that achieved by dobutamine infusion.

Methods: We have applied real-time two-dimensional echocardiographic imaging with automatic boundary detection (HP Sonos 2500) for the estimation of LA area changes. To obtain the LA pressure, a catheter-tip micromanometer was introduced retrogradely into the LA using a steerable cardiac catheter developed in our institution (Cordis Europa 5RE-699). The ratio of instantaneous LA pressure to LA area was calculated throughout the cardiac cycle and used as a measure of LA elastance [E(t)]. From the digitized data, PR electrocardiographic interval and the time interval from the onset of P wave to the maximum E_m (Δt) were also measured. Data were collected both before and after dobutamine infusion at a rate 5–20 μg/Kg/min.

Results: After dobutamine infusion maximum E_m increased from 1.43 ± 0.19 to 2.56 ± 0.30 mmHg/cm² in normals (p < 0.001 vs pacing) and from 0.73 ± 0.09 to 0.89 ± 0.10 mmHg/cm² in heart failure (p < 0.05 vs pacing). This increase however was larger in normals, p < 0.01. In all subjects the PR interval was significantly reduced (by 17.0 ± 2.7%) after dobutamine compared with atrial pacing (140.3 ± 16.2 vs 169.5 ± 22.7 msec, p < 0.001). Moreover, Δt was significantly reduced (by 22.1 ± 1.2%) after dobutamine compared with atrial pacing (125.5 ± 19.5 vs 161.2 ± 25.8 msec, p < 0.001). A positive correlation between per cent changes of PR interval and per cent changes of Δt interval was found (Δt = 0.33 PR + 0.16, r = 0.76).

Conclusions: An increased inotropic state in the same level of heart rate resulted in an increase of LA systolic elastance. However, response to inotropic stimulation was reduced in failing LA myocardium. Furthermore, ample time is left for the atrial 'kick' to boost ventricular filling in all subjects during the fairly short period that is defined by the PR interval after dobutamine infusion.

1225-54 Long-term Characterization of the Amiodarone-Warfarin Drug Interaction

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Background: The interaction between amiodarone (A) and warfarin (W) has only been described in small numbers of patients (pts) being followed for ≤ 8 weeks. The purpose of this study was to characterize this drug interaction over a longer time period in a larger cohort of pts.

Methods: We followed 35 pts receiving both A and W for ≥ 1 year; 22 were male and 13 female, aged 60 ± 14 years. The dosage of W was adjusted on a monthly basis to achieve an INR of 2–3.

Results: The magnitude of the interaction peaked at 7 weeks which resulted in a 42% mean maximum reduction in the W dose. The W dose