(mmol $L^{-1}$) calculated as $\Delta[NH_4^+]_i/\Delta pH_i$; $dpH_i/dt$ calculated from an exponential fit of the $pH_i$ recovery data.

| CONDITION | N | BASAL $pH_i$ | $\beta_{TOT}$ | $J_H$ |
|---|---|---|---|---|
| $HCO_3^-$ | 13 | 7.05 ± .01 | 69 ± 6 | 1.2 ± 0.4 |
| $HCO_3^-$/ EIPA | 9 | 7.02 ± .02 | 55 ± 7 | 0.6 ± 0.2 |
| HEPES | 14 | 6.98 ± .02 | 58 ± 5 | 0.5 ± 0.2 |
| HEPES / EIPA | 8 | 6.91 ± .02 | 43 ± 3 | < 0.1 |

At $pH_i$ 6.90 the $Na^+$-$H^+$ antiport and $Na^+$ and $HCO_3^-$-dependent acid extrusion each contribute approximately 50% to proton extrusion in this model. Intrinsic intracellular buffering capacity in HEPES / zero $Na^+$ was 37±2 mmol $L^{-1}$ and that in $HCO_3^-$ / zero $Na^+$ was 50±4 mmol $L^{-1}$. The contribution from $HCO_3^-/CO_2$ to buffering was therefore ~13mmol $L^{-1}$ which is substantially less than in single cells.

## 57 β-ADRENOCEPTOR DENSITY AND DISTRIBUTION IN THE CHRONICALLY FAILING TRANSPLANTED HUMAN HEART

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Redo heart & lung transplantation offers the opportunity to evaluate the effect of chronic right ventricular failure on β-adrenoceptor density (BARD) and distribution in the chronically denervated transplanted human heart.

**Method.** We used autoradiographic (AR) and radioligand binding (RLB) techniques in 4 unused normal donors and 5 chronically denervated hearts from patients undergoing redo heart & lung transplantation (redo). AR was performed on adjacent tissue sections using ICYP. Propranolol, CGP20712 A and ICI 118,511 were used to displace total, β1 and β2 receptors, respectively. Underlying tissue was stained for normal histology and fibrous tissue. Saturation isotherms were performed on adjacent tissue using $^{125}$I-iodopindolol in the presence of buffer (total), 200mMolar isoprenaline (nonspecific binding [NSB]) or 300nMolar CGP 20712A (B1 antagonist). Denervation was confirmed by HPLC with electrochemical detection on extracted tissue.

**Results.** High resolution AR demonstrated the presence of both β-adrenoceptor subtypes on cardiomyocytes. AR showed that receptors in the redo heart were unevenly distributed, with "islands" of receptor binding loci interspersed with largely non-binding fibrous material, producing a characteristic "crazed" appearance with the highest concentrations of receptors in the endocardial regions. RLB revealed that BARD was downregulated in the right ventricle compared to the left ventricle in the redo hearts whereas the BARD was evenly distributed between ventricles of the control heart Catecholamine levels in the redo heart were 1% of that seen in the control hearts.

**Conclusions.** 1. The redo heart is chronically denervated. 2. Both receptor subtypes are seen in the chronically transplanted human heart. 3. In the failing redo heart the β-subtypes appear to be differentially subject to chamber selective downregulation. 4. The chronically transplanted human heart has a characteristic "crazed" AR binding appearance, related to fibrous infiltration.

## 58 THE POTENTIAL IMPACT OF PATIENT SELF REFERRAL ON MORTALITY IN ACUTE MYOCARDIAL INFARCTION

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The need for early administration of thrombolytic treatment dictates audit of the admission policy for patients with acute myocardial infarction, but the impact of early presentation on improving survival due to inhospital resuscitation is not well addressed. Using details of all CCU admissions recorded prospectively onto a computer database, we have calculated median delays (mins) before thrombolytic treatment for a 24 month period to Dec 1991. General practitioner referral delayed arrival at the Emergency Department ($p<0.0001$) and was associated with similar inhospital delay:

| | Self Referral | GP Referral |
|---|---|---|
| Onset-Emergency Dept | 100 | 175 |
| Emergency Dept-Thrombolysis | 54 | 55 |

We have constructed a model to predict mortality, assuming: i) natural history of MI with minimal intervention is 50% of deaths by 2 hours and 32.7% total mortality at 28 days (Armstrong,1972) ii) 40% success rate for inhospital resuscitation for 48 hours only, and iii) a linear relationship between reduction in the odds of early death and delay to thrombolysis (31% for 0-3 hours, 22% for >3-6 hours). The predicted reduction in mortality (deaths prevented/100 patients) from successful inhospital resuscitation alone or in combination with thrombolytic treatment was calculated, along with the impact of telephoning for an ambulance after just 30 mins of symptoms ("early call"):

| | Onset-Emergency Dept | Resuscitation | Resuscitation & Thrombolysis |
|---|---|---|---|
| "Early call" | 60 mins | 4.5 | 8.3 |
| Self Referral | 100 mins | 4.1 | 7.4 |
| GP Referral | 175 mins | 3.5 | 6.2 |

Conclusions: Patients with chest pain should seek early medical assistance by calling for an ambulance. The potential impact of inhospital resuscitation on reducing early mortality in acute MI is comparable to the effect of thrombolytic treatment. A marked change in patient behaviour ("early call") would result in predicted reductions of only 0.9 and 2.1 deaths per 100 patients compared with the current self and GP referral patterns.

## 59 AN ANALYSIS OF HEART RATE VARIABILITY IN PATIENTS WITH CHRONIC HEART FAILURE

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Heart rate variability (HRV) is depressed in patients with chronic heart failure (CHF) but the important determinants of HRV and the influence of the aetiology of heart failure in these patients remain unclear. We have performed HRV analysis on 24 hour ambulatory recordings (Marquette Series 8000) on 73 patients (mean age 52, range 24-75 years) with CHF (38 ischaemic heart disease and 35 idiopathic dilated cardiomyopathy) and 24 normal controls (C, mean age 42, range 16-68 years). All measures of HRV were reduced in patients with CHF compared to normal controls (+$p<0.05$, *$p<0.001$);

| | mRR | SDRR | SD | rmSSD | PNN50 | TF | HF | LF |
|---|---|---|---|---|---|---|---|---|
| C (mean) | 852 | 132 | 67 | 39 | 16.7 | 49 | 19 | 33 |
| (SD) | 94 | 38 | 26 | 21 | 16 | 23 | 12 | 16 |
| CHF (mean) | 757+ | 105+ | 39* | 23* | 5.6* | 28* | 9* | 15* |
| (SD) | 136 | 44 | 17 | 12 | 8 | 11 | 5 | 8 |

Patients with CHF secondary to dilated cardiomyopathy showed a greater reduction in HRV compared to those with ischaemic heart disease (SDRR, $p<0.01$; SDANN, $p<0.01$). In the control group, parameters of HRV were highly dependant on age ($R=0.5$-$0.6$, $p<0.01$) with the exception of mRR, SDRR and SDANN (p=NS). In the CHF group, the effect of age was less pronounced, only reaching significance for mRR, SDRR and SDANN ($p<0.05$). Stepwise regression analysis however revealed that in patients with CHF, HRV was markedly influenced by left venticular systolic function (shortening fraction, $p<0.01$) and exercise capacity (maximal oxygen consumption, $p<0.05$). No difference was observed in HRV between patients with dilated cardiomyopathy and ischaemic heart disease by analysis of covariance (p=NS). This study demonstrates a marked reduction in HRV in patients with CHF. In these patients, HRV is strongly influenced by the patients exercise capacity and left ventricular function, but is less dependant on age. No differences in HRV were observed between patients with CHF secondary to ischaemic heart disease and dilated cardiomyopathy.

## 60 UPREGULATION OF $Na^+$, $K^+$ ATPase IN TISSUES OF RATS TREATED CHRONICALLY WITH DIGOXIN

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