2:30

CAN ACUTE HEMODYNAMIC STUDIES IN HEART FAILURE BE USED TO PREDICT THE OPTIMAL DOSE OF A NEW DRUG DURING LONG-TERM THERAPY?

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Physicians commonly select a dose of a new drug for heart failure (CHF) based on the results of acute hemodynamic studies, but it is unknown whether such short-term studies predict the best long-term dose. To investigate this question, we compared the effects of 1st doses of 75, 100, 125 and 150 mg of flosequinan (FSQ) with the effects of long-term (1-3 months) therapy with 75 mg qd, 100 mg qd, 150 mg qd and 75 mg bid in 73 CHF pts. Stroke volume index (SVI, ml/m^2), pulmonary wedge pressures (PCW, mmHg), heart rate (HR, bpm), systemic vascular resistance (SVR, d-s-c) & plasma renin activity (PRA, ng/ml/hr) were measured both during short- and long-term therapy. Shown below are changes from pre-FSQ, where * = p < .05 vs pre-FSQ:

		SVI	PCW	HR	SVR	PRA
Short-term	75mg	+5.9*	-11.3*	0	-23%*	+0.9
	100mg	+4.2*	-11.9*	0	-20%*	+0.1
	125mg	+5.2*	-11.2*	+2	-23%*	+2.3
	150mg	+6.3*	-12.1*	+4*	-32%*	+0.4
Long-term	75mg qd	+5.5*	-9.6*	+1	-28%*	+6.6
	100mg qd	+4.4*	-11.8*	+6*	-30%*	+0.6
	75mg bid	+3.7*	-8.2*	+12*	-25%*	+1.1
	150mg qd	+2.6	-10.1*	+16*	-32%*	+8.5*

150 mg produced the best 1st-dose effects, but during long-term therapy, 150 mg ↑ HR & PRA and produced no ↑ in SVI. In contrast, 100 mg (which ↓ SVR the least initially) produced the largest long-term ↓ in PCW and the smallest ↑ in PRA. Symptoms ↓ in 31% of pts treated with 75mg bid, in 41% on 75mg qd, in 55% on 150mg qd & 65% on 100mg qd.

In conclusion, the "best" dose of a new drug identified from the results of short-term studies may not be the optimal dose to be used during long-term therapy of pts with CHF.

3:00

DIFFERENCES IN THE DEVELOPMENT OF NITRATE TOLERANCE AND IN ITS REVERSAL WITH N-ACETYLCISTEINE BETWEEN ARTERIAL AND VENOUS VESSELS IN MAN.

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To assess the relative susceptibility to the development of nitroglycerin (NTG) tolerance in arterial and venous vessels in man and to evaluate the interactions between NTG and N-acetylcisteine (NAC), we studied 18 pts with coronary artery disease. All pts underwent a continuous 24h NTG infusion (mean 172 µg/min) followed by a bolus administration of 5g of NAC. Forearm blood flow (ml/100ml/min) and venous volume (ml/100ml) were measured by strain gauge plethysmography under control conditions, at the end of NTG titration, at 24h and after NAC; vascular resistance was calculated as cuff blood pressure/ flow. After 24h continuous infusion, the acute effects of NTG were reduced in venous vessels of 13/18 pts and in arterial vessels of 5/15 pts (p<.03). NAC restored NTG action in all tolerant veins but only in 2/5 tolerant arteries (p<.01). No potentiation of NTG was observed in non-tolerant arteries and veins.

In conclusion, after 24h NTG infusion, tolerance developed more frequently in venous than in arterial vessels. NAC restored NTG action in tolerant veins but proved to be less effective in tolerant arteries and did not potentiate NTG effects in non-tolerant vessels.

2:45

REDUCED RENAL RESPONSIVENESS TO ATRIAL NATRIURETIC FACTOR IN END-STAGE HEART FAILURE.

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To determine the renal effects of atrial natriuretic factor (ANF) in heart failure, we infused 0.01, 0.03 and 0.1 ug/kg/min ANF for 45 min at each dose in 5 class IV heart failure patients (CHF) and 5 normal (N1) subjects. All subjects received a 10 ml/kg water load orally, had steady-state infusions of PAH and inulin, and urine flow was replaced with D5 1/2 NS i.v.

CHF patients had higher plasma ANF (117±22 vs 24±5, p<0.001) and lower renal plasma flow (294±18 vs 459 ± 57 ml/min, p<0.05) at baseline than N1 subjects. At the highest dose of ANF infusion, plasma ANF (N1: 1105±147, CHF: 1470± 158 pg/ml P=NS) and cGMP (N1: 22.8±1.1, CHF: 50.2±7.6 pmol/ml P=NS), and urinary cGMP rose significantly. Urine flow rate increased from 2.2±0.6 to 7.1±3.4 ml/min in CHF and 6.6±1.2 to 25.7±6.3 in N1 (p<0.05). Sodium excretion rose from 17±4 to 232±163 uEq/min in CHF and 211±19 to 1367±179 in N1 (p<0.05) and fractional sodium excretion rose from 0.5±0.1 to 1.3±0.9 in CHF vs 0.9±0.1 to 5.8±1.8 in N1 (p<0.05). ERPF, GFR and filtration fraction did not change.

We conclude that severe CHF patients exhibit renal responses to ANF which are similar in proportion, but reduced in absolute magnitude when compared with normal subjects. The renal changes seen in CHF are similar to those noted in N1 subjects following a mild oral water load.

3:15

HEMODYNAMIC BENEFIT OF NITRATE THERAPY IN PATIENTS WITH HEART FAILURE ALREADY TREATED WITH ANGIOTENSIN CONVERTING ENZYME INHIBITION

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Nitrates are commonly used in treatment of chronic heart failure (CHF). However, their hemodynamic effect when given concomitantly to angiotensin converting enzyme inhibition (ACEI), has not been investigated. We studied the effect of 40 mg oral isosorbide dinitrate (ISDN) in 11 patients (pts) with CHF chronically treated with captopril (CAP) 89±32mg/ day. Mean pulmonary arterial (PA), pulmonary wedge (PAW) and right atrial (RA) pressures (mm Hg) were studied on CAP alone and 24 hrs later on CAP+ISDN. Hemodynamic values were as follows: (*p<0.05 vs CAP)

		Baseline	2 hrs	4 hrs	6 hrs
PA	CAP	38±8	37±8	37±10	38±9
	C+ISDN	38±7	30±8*	32±8*	33±8*
PAW	CAP	24±6	22±6	24±7	25±7
	C+ISDN	24±7	16±6*	18±9*	20±9*
RA	CAP	11±6	11±5	12±6	12±5
	C+ISDN	12±5	8±3*	10±4	9±4*

Addition of ISDN to CAP resulted in no significant change in blood pressure (BP).

CONCLUSIONS: 1) ISDN potentiates hemodynamic effect of captopril on RA, PA and PAW without change in BP. 2) The reduction of right and left ventricular filling pressures and pulmonary hypertension demonstrates the therapeutic potential of combination therapy with nitrates + ACEI in pts with chronic CHF.