2:45

850-4 Radiofrequency Catheter Ablation Using High Power

F. Philippon, L. Blier, G. O'Hara, M. Gilbert. *Quebec Heart Institute, Quebec, Canada*

Radiofrequency (RF) catheter ablation requires a tissue temperature (T°) ≥52°C. Some substrates require either higher T° or more energy to achieve a successful ablation and most generators are limited to a maximum of 50 W. We studied 904 consecutive ablations performed in our laboratory. 544 ablations were done using a standard RF generator (50 W max., non thermistor). 360 ablations were performed with a high power generator (EPT1000XP, 0–150 W, thermistor) using T° monitoring (set at 60–70 °C). Of these 360 ablations (all successful), 135 required >50 W to achieve the targeted T°. The substrates were AVNRT: 75, WPW: 35 (posteroseptal (PS): 12, right sided: 5, left sided: 18), AVN: 18 and atrial flutter in 8 pts. Five PS pathways were recurrences and 2 right anterior and 1 PS pathways were prior unsuccessful ablations. The mean fluoro. time was 19 ± 14 min with a median number of RF applications of 9. The effective lesion required a mean of 67 ± 11 W (mean power set at 84 ± 12 W) for 50 ± 17 sec to achieve a mean T° of 51 ± 4 °C (mean max. T° achieved 62 ± 7 °C, median 60 °C) with a mean impedance of 126 ± 14 Ω. When the mean effective lesion T° was <60 °C, a "bonus" lesion was applied increasing the power until the targeted T° was obtained during all the RF application (bonus: mean: 62.5 ± 16.4 W with median power set at 85 W). All procedures were successful and no coagulum formation was noted. In comparison, a 14% failure rate was observed in the 544 ablations done with the standard RF generator. There was no arrhythmia recurrence at a mean follow-up of 9 months.

In Conclusions: High power was required to obtain the desired T° in 38% of cases. Since T° monitoring is required to use more than 50 W (otherwise the output is locked at 50 W), it should be beneficial to use T° monitoring in all cases with this generator. The initial success rate is higher and prior ablation failures can be done successfully. The influence of this technology on the recurrence rate will need further studies.

3:00

850-5 Electroanatomic Mapping of Atrial and Junctional Tachycardia

E. Hoffmann, C. Reithmann, P. Nimmermann, T. Remp, S. Ben-Haim[1], G. Steinbeck. *Med. Klinik I, Klinikum Großhadern, LMU Munich, Germany, [1]Technion, Haifa, Israel*

Catheter ablation of atrial and junctional tachycardia (AT/JT) can be complex and time consuming. The aim of this study was to determine the feasibility and safety of nonfluoroscopic electroanatomic mapping and ablation in 21 consecutive patients (pts) with AT or JT (5 men, 16 women, mean age 47 ± 15 years).

Results: electrophysiologic study and CARTO mapping of the right atrium was performed in 24 tachycardias and the mechanism determined as: junctional in 3 pts, incisional in 3 pts, reentrant in 4 pts, focal in 14 pts (4 left atrial). We created 24 maps with a mean of 79 ± 48 different catheter positions within the right atrium. The mapping procedure took 47 ± 16 min. CARTO mapping criteria for focal tachycardia could be defined as radial impulse propagation away from the site of earliest activation, clearly distant earliest and latest activation and a different tachycardia cycle length (CL) and activation time (366 ± 115 ms vs 94 ± 30 ms). Reentry tachycardias were characterized as close proximity of earliest and latest activity and a comparable tachycardia CL and activation time (236 ± 44 ms vs 240 ± 56 ms). The ablation of the 4 left AT was not attempted in the first ablation session. In 15 of 17 (88%) right AT and 2 of 3 JT, ablation was performed successfully. No complications occurred.

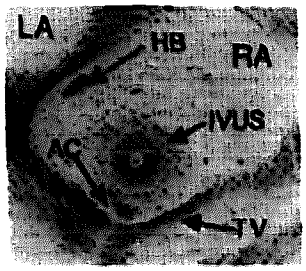
Conclusions: the visualization and 3D presentation of the atrial activation sequence with the CARTO system allows the differentiation of tachycardia mechanisms and the determination of the successful site of ablation in right atrial focal and junctional tachycardias.

3:15

850-6 True Anatomic Ablation of AV Nodal Reentry Using Radiofrequency Current Guided by Intravascular Ultrasound

W.W. Wassynger, D.D. Hodgkin, T.W. Simmons, W.K. Haisty, Jr., G.H. Crossley, D.M. Fitzgerald. *Bowman Gray School of Medicine, Winston-Salem, N.C., USA*

Radiofrequency (RF) ablation of the slow pathway of AV Nodal Reentry (AVNRT) is usually guided by fluoroscopic anatomy which shows the relative location of a mapping catheter to reference catheters. Intravascular ultrasound (IVUS) provides precise anatomic detail of the tricuspid annulus and coronary sinus and may be useful for mapping and ablation procedures requiring anatomic lesions. Accordingly, in sixteen consecutive patients with typical AVNRT, an IVUS probe (6.2F, 12 MHz) was placed along the tricuspid annulus. RF current was applied through an ablation catheter (AC) placed using IVUS, in front of the os of the coronary sinus on the tricuspid annulus (see Figure). In all 16 pts, slow pathway conduction was eliminated. Successful ablation was achieved with 1–7 RF pulses (median, 2). Fluoroscopic location of RF pulses was mid-septal in 4 pts and postero-septal in 6 pts despite IVUS location of the AC in the posteroseptal region in 16 pts.



Conclusions: Selective slow pathway ablation of AVNRT can be achieved using IVUS to place anatomic RF lesions. Fluoroscopic location of the AC is less accurate than IVUS. Once validated, this technique could reduce radiation exposure and the number of RF lesions.

851 Molecular Mechanism of Heart Failure

Tuesday, March 31, 1998, 2:00 p.m.–3:30 p.m.
Georgia World Congress Center, Room 255W

2:00

851-1 Adenosine Inhibits Cardiac Expression of Tumor Necrosis Factor-alpha in the Failing Human Heart

D.R. Wagner, C. McTiernan, A.M. Feldman. *University of Pittsburgh, Pittsburgh, PA, USA*

Background: Tumor necrosis factor-alpha (TNF) has been implicated in the pathogenesis of CHF. We have previously shown that adenosine inhibits the lipopolysaccharide (LPS)-induced expression of TNF in rat cardiomyocytes and rat papillary muscle. The aim of this study was to determine whether adenosine has the same effect in the failing human heart muscle.

Methods: Trabecular muscles were isolated from the hearts of cardiac transplant recipients and stimulated with LPS (10 μg/ml). TNF release was measured with enzyme linked immunosorbent assay. Muscle sections were analyzed immunchistochemically for the presence of TNF.

Results: In contrast to healthy rat papillary muscles, trabecular muscles from failing human hearts released TNF in the absence of LPS (287 ± 91 pg/ml/g wet weight). However, addition of LPS induced a further 10-fold increase in TNF. The adenosine A2 receptor agonist DPMA (10 μM) inhibited the ability of LPS to activate myocardial TNF by 94% (n = 7, p < 0.05). Iodotubercidin (10 μM), which increases endogenous adenosine concentration, also inhibited TNF expression in trabecular muscle by 99% (n = 7, p < 0.05). Immunohistochemistry identified the myocyte as a primary source of TNF in the failing human heart.

Conclusion: Adenosine can significantly diminish TNF levels in the failing human heart and may provide a new pharmacologic approach in CHF.

2:15

851-2 Increased Protein Kinase C Expression in Failing Human Heart

N. Bowling, T. Estridge, R. Fouts, G. Song, R. Roden, M. Bristow, R. Walsh, H. Sabbah, G. Sandusky, J. Mizrahi, G. Gromo, C. Vlahos. *Lilly Research Labs, Indianapolis, IN, USA*

Background: The aim of the study was to determine protein kinase C (PKC)-β1 and β2 expression in failing and nonfailing myocardium to ascertain if re-expression of PKC-β is a marker of heart failure.

Methods: Explanted hearts of patients with idiopathic dilated cardiomyopathy (DCM) or coronary artery disease (CAD) were examined for PKC-β content by Western blot, *in situ* hybridization, immunostaining, and enzymatic activity, and compared with nonfailed (NF) left ventricle (LV) from hearts rejected for transplant.

Results: Western blots showed that PKC-β was significantly increased in membrane fractions of failed hearts (n = 12) compared to NF (n = 11) (β1: 76 ± 7 vs. 49 ± 9 units, P < 0.04; β2: 78 ± 9 vs. 52 ± 4 units, P < 0.02); there were no differences between DCM and CAD failed hearts. Immunostaining

with antibodies to PKC-β1 and -β2 was slight in NF myocyte, but intense in the myocytes of failed LV. *In situ* hybridization revealed increased expression of PKC-β1 and β2 mRNA in cardiomyocytes of failed human heart tissue. Total PKC activity was increased in membrane fractions from failed hearts (1219 ± 188 vs. 609 ± 171 pmol/min/mg protein; failed vs. NF; $P < 0.05$). LY333531, a selective inhibitor of PKC-β, significantly decreased PKC activity from failed hearts by 24%.

Conclusions: PKC-β1 and -β2 are elevated in failed human heart, and inhibition of PKC-β may represent a novel therapeutic approach to heart failure.

2:30

851-3 Growth Hormone Resistance in Chronic Heart Failure

S.D. Anker, M. Volterrani, C.-D. Pflaum, P.A. Poole-Wilson, C.J. Strasburger, A.J.S. Coats. *Cardiac Medicine, NHLI London, UK; Dept of Cardiology, Gussago, Italy*

Acquired growth hormone (GH) resistance occurs in severe illness and cachexia, and may explain the different responses to GH in recent studies of patients with chronic heart failure (CHF).

In 72 CHF patients (age 61 ± 1y, peak VO_2 16.5 ± 0.7 ml/kg/min) and 20 healthy controls ([Con] 58 ± 2y, $p = 0.07$) the GH - IGF-I axis was studied in relation to IGF binding protein 3 (IGFBP-3) and GH-binding protein (GH-BP) (controls vs CHF: differences = NS). The CHF patients were sub-devided according to cachectic ([c], >7.5% weight loss over >6 months) or non-cachectic (nc) state. The logIGF-I/GH ratio (9 AM) was calculated as index of GH sensitivity, and was found to correlate well with mean GH overnight levels (11 CHF patients: blood samples for 8 hrs, every 20 min, $r = -0.60$, $p = 0.05$), and mean overnight logIGF-I/GH ratio ($r = 0.72$; $p = 0.01$).

	Con n = 20	ncCHF n = 51	cCHF n = 21	ncCHF vs Con (p)	cCHF vs Con (p)	cCHF vs ncCHF (p)
total GH (ng/ml)	1.2±0.3	1.2±0.3	5.3±1.3	NS	<0.0001	<0.0001
intact GH (ng/ml)	0.5±0.1	0.4±0.1	1.6±0.5	NS	0.0073	0.0017
IGF-I (ng/ml)	151±9	150±8	124±9	NS	0.09	0.06
log IGF-I/GH	2.7±0.2	2.0±0.1	1.7±0.2	NS	0.0002	0.0001
IGFBP-3 (μg/ml)	3.8±0.1	3.7±0.1	3.1±0.2	NS	0.012	0.012
GH-BP (pmol/l)	852±83	950±84	607±64	NS	0.06	0.0047

mean ± SEM; NS = p > 0.20. Sample time: 9 AM

Correlations: log IGF-I/GH *vs* %ideal weight (Con: $r = 0.23$, p = NS; CHF: $r = 0.54$, $p < 0.0001$), and *vs* GH-BP (Con: $r = 0.79$; CHF: $r = 0.61$, both $p < 0.0001$; nc: $r = 0.50$, $p < 0.01$; c: $r = 0.68$, $p < 0.001$).

Cachectic patients with CHF show the biochemical features of acquired GH resistance possibly due to a down regulation of GH receptors. The presence of GH resistance may influence the response to GH therapy and should be assessed prior to treatment.

2:45

851-4 The Growth Hormone Secretagogue Hexarelin Improves Cardiac Function in Rats After Experimental Myocardial Infarction

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Background: Accumulating evidence indicate that growth hormone (GH) can enhance cardiac performance both in rats after experimental myocardial infarction (MI) and in patients with congestive heart failure. Hexarelin is one of several synthetic compunds with capacity to stimulate GH secretion in animals and humans. The aim of the present study was to investigate if administration of Hexarelin could improve cardiac function in rats after experimental MI.

Methods: Male rats were treated for two weeks with either Hexarelin in a dose of 5 or 50 $\mu g \cdot kg^{-1}$, recombinant human GH (rhGH) in a dose of 1 $mg \cdot kg^{-1}$ or saline injected s.c twice daily four weeks after ligation of the left coronary artery. Intact rats were used as controls. Transthoracic echocardiography was performed before and after the treatment period.

Results: Stroke volume (SV) was increased 49% ± 10% by rhGH, 53% ± 16% by Hexarelin 10 $\mu g\,kg^{-1} \cdot day^{-1}$, and 55% ± 21% by Hexarelin 100 $\mu g \cdot kg^{-1} \cdot day^{-1}$, ($p < 0.05$ vs baseline). Cardiac output (CO) was increased 62% ± 21% by rhGH, 48% ± 19% by Hexarelin 10 $\mu g \cdot kg^{-1} \cdot day^{-1}$ and 51% ± 13% by Hexarelin 100 $\mu g \cdot kg^{-1} \cdot day^{-1}$. There were no effects on SV and CO in the saline treated groups.

Conclusion: Hexarelin improves cardiac performance to a similar extent as exogenously administered rhGH in rats after experimental myocardial infarction. This may have clinical implications if beneficial effects can also be obtained in patients with congestive heart failure.

3:00

851-5 Renal and Hemodynamic Effects of Growth Hormone Treatment in Experimental Heart Failure

R. Willenbrock, I. Pagel, M. Scheuermann, K.-J. Osterziel, R. Dietz. *Franz-Volhard-Klinik, Berlin, Germany*

Chronic growth hormone (GH) treatment is a new approach for the therapy of heart failure. We analyzed whether cardiac and renal function could be improved by chronic application of GH in experimental heart failure. Manifest heart failure was induced by a large aortocaval shunt in male Wistar rats which were treated with recombinant human GH (2 mg/day s.c.) for 30 days. We anylazed renal excretory function by using metabolic cages and measured cardiac pressures and contractility.

Rats treated with GH developed a significant higher body weight already after 6 days of treatment. After 30 days, the GH treated rats weighed 333 ± 9 vs. 305 ± 6 g in placebo treated shunted rats ($p < 0.01$). The relative heart weight increased in shunted rats from 319 ± 7 to 583 ± 40 mg/100 g, compared to sham operated controls, but was not influenced by GH treatment. Cardiac enddiastolic pressures were elevated in shunted rats compared to sham-operated controls, but were not modified by GH. Similarly, cardiac contractility (dP/dt) was lower in shunted rats (4820 ± 210 vs. 5400 ± 433 mmHg/sec, $p < 0.05$) and was not improved by GH therapy. Water intake was not different between GH- and placebo treated shunted animals. Water and sodium excretion, however, was enhanced by GH: natriuresis increased from 1.54 ± 0.06 to 2.01 ± 0.10 mmol/d ($p < 0.05$) and diuresis from 17.4 ± 2.0 to 23.1 ± 3.0 ml/d ($p < 0.05$).

Our results suggest that chronic treatment with growth hormone might not improve cardiac function in this model of heart failure but seems to have a beneficial effect on water and sodium homeostasis.

3:15

851-6 17β-Estradiol Protects Against the Development of Pressure Overload Cardiac Hypertrophy in Rats

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Cardiac hypertrophy shows gender-based differences with markedly higher mortality in men. The influence of estrogens on cardiac hypertrophy is poorly understood. This study examined the protective effect of 17β-estradiol (E2) against the development of cardiac hypertrophy induced by abdominal aortic banding for 6 weeks. One hundred 8-wk old male (M) and ovariectomized female (F) Sprague Dawley rats were randomized to sham-operated (S), banding + placebo (P) and banding + E2 (E2, 10 mg slow release pellets implanted 48 h before surgery) groups. We measured carotid and left ventricular systolic (CSP, LVSP, mmHg) and diastolic pressure (CDP, LVDP), ratio of left ventricular weight to body weight (LVW/BW, mg/g), LV ± dp/dt (mmHg/s) and LV wall thickness (LVW-T, mm), and cardiac myosin heavy chain (MHC) mRNAs by Northern blot analysis.

Group	LVW/BW	CSP	LVSP	LV ± dp/dt	LVW-T
P (M)	2.8 ± 0.1	177 ± 11	127 ± 7	4573 ± 169	4.4 ± 0.2
E2 (M)	2.3 ± 0.1*	117 ± 4*	95 ± 4*	3372 ± 201*	3.6 ± 0.1*
P (F)	3.0 ± 0.1	155 ± 3	99 ± 5	4406 ± 232	5.1 ± 0.2
E2 (F)	2.5 ± 0.0*	118 ± 3*	79 ± 3*	3624 ± 148*	3.7 ± 0.1*

Mean ± SEM. * $p < 0.05$ compared with group P

E2 significantly attenuated hypertension and reduced left ventricular muscle mass in both male and ovariectomized female rats. Further, E2 but not P decreased expression of β-MHC mRNA. (14.3% in male; 15.2% in female; both $P < 0.05$) but increased α-MHC mRNA (9.8% in male; 11.3% in female; both $P < 0.05$).

Conclusions: 17β-Estradiol prevents the development of hypertension and cardiac hypertrophy in rats with experimental hypertension.

TUESDAY ORAL