Body Sensing Network – The Case for Integration

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Body Sensing Network – The Case for Integration

Monitoring biological structure and function

Levels

- Systems
- Organs
- Tissue
- ECM
- Cells
- DNA
- Other

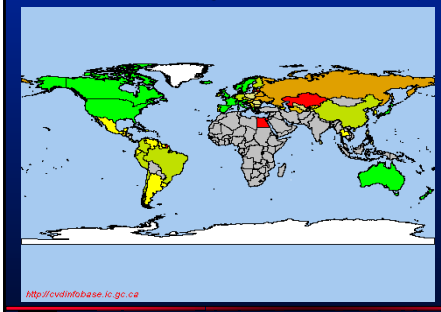
Body Sensing Network – The Case for Integration

Chronology

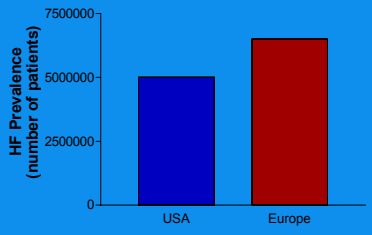
- Biology is dynamic
- Continuous monitoring of biological functions has major diagnostic and therapeutic value
- Medical devices need feedback
- Heart failure as a model

MORTALITY RATE

(Age Standardized Death Rates)



Prevalence of HF in the USA and Europe



New Medicine, Inc. 1997:1-40
CHF worldwide markets, clinical status and product dev. opportunities

Severe heart failure – bridging to recovery

Working hypothesis
myocardium as a target

Susceptibility factors
↓
Trigger
↓
Remodelling
↓↑
Progression
↓
Death

Severe heart failure – bridging to recovery

Target = myocardium
major players

- **cardiomyocytes**
- **matrix**
- **fibroblasts**
- **endothelial cells**

Severe heart failure – bridging to recovery

Effector mechanisms
?secondary phenomena

- **genetic**
  polymorphisms and mutations
- **environmental**
  e.g. neurohormonal, activation of innate immune systems, metabolic and nutritional, skeletal muscle system

Severe heart failure – bridging to recovery

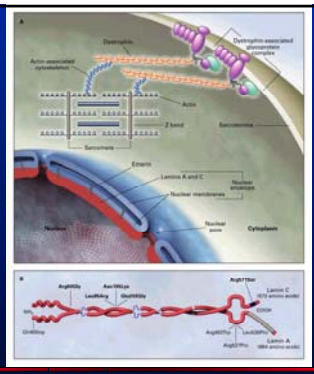
Reverse remodelling - the major players

1) Myocytes
2) Endothelial cells and capillaries
3) Fibroblasts
4) Matrix (MMP, MMPI)

Severe heart failure – bridging to recovery

Possible Cellular Changes

I) Myocardial
a. change in size and shape (slippage)
b. cytoskeletal changes (force, transduction)
c. B_1 & B_2 receptors
d. G proteins
e. Cytokine expression (TLR-4, TNF alpha, IL-6, IL-1, IL-18)
f. Ca handling proteins and ion channels
g. metabolic enzymes
h. apoptotic pathways



Severe heart failure – bridging to recovery

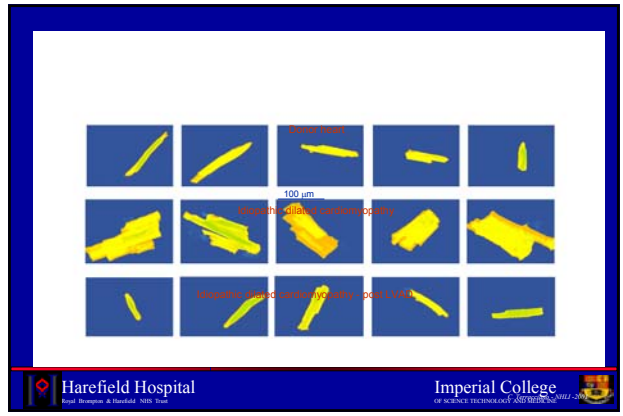
Possible Cellular Changes

II) Endothelial
a. NO, PGI2 ➡ flow reserve
b. angiogenesis
III) Fibroblasts
a. ⬇ mitogenesis
d. ⬇ collagen synthesis

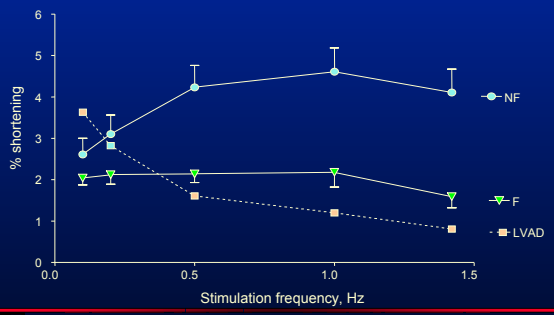
Severe heart failure – bridging to recovery

Possible Changes in matrix

1) Altered MMP & MMP1 → ↓ stiffness
2) Crosstalk with myocytes & fibroblasts

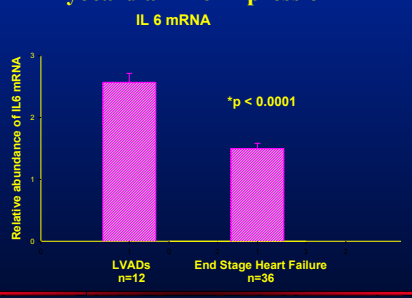


Severe heart failure – bridging to recovery

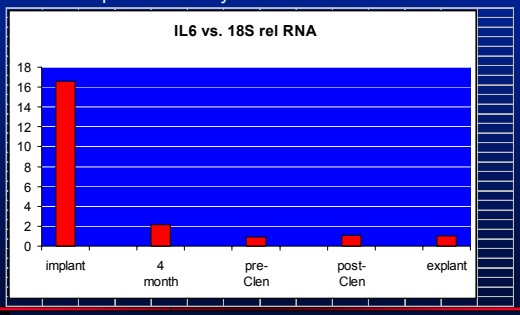


Severe heart failure – bridging to recovery

Myocardial IL 6 Expression

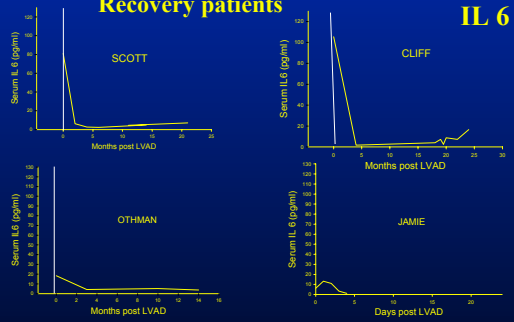


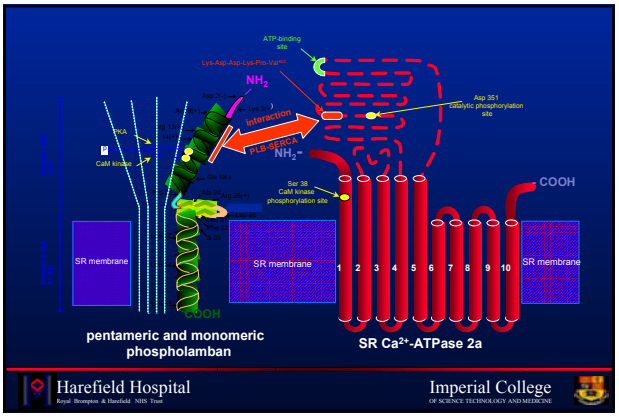
Molecular remodelling in a LVAD patient: expression of Myocardial Interleukin-6



Recovery patients

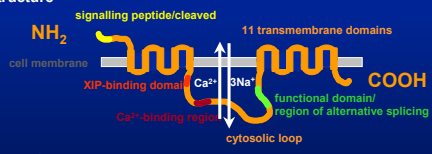
IL 6





The cardiac sarcolemmal Na^+-Ca^{2+}-exchanger

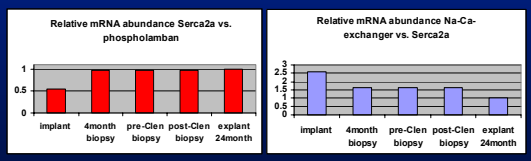
A) Protein Structure



B) Putative Gene Structure

Severe heart failure – bridging to recovery

Time course of molecular remodelling in a LVAD patient: Expression of Ca^{2+}-handling proteins in sequential biopsies



Severe heart failure – bridging to recovery

Confocal microscopy

Microelectrodes

Cell volume

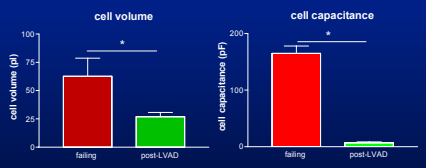
Cell capacitance

SR Ca content

Ca entry

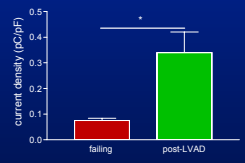
Severe heart failure – bridging to recovery

Cell size



Severe heart failure – bridging to recovery

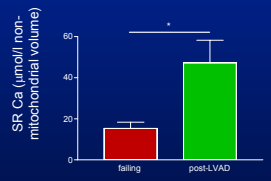
Ca entry during the action potential



Ca entry via sarcolemmal Ca channels during action potential using action potential voltage-clamping before and after rapid cadmium application

Severe heart failure – bridging to recovery

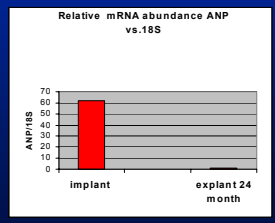
SR content

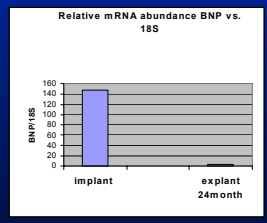


SR Ca content assessed by integrating the Na/Ca exchanger transient inward current induced by rapid application of caffeine

Severe heart failure – bridging to recovery

Molecular remodelling in a LVAD patient:
expression of natriuretic peptides



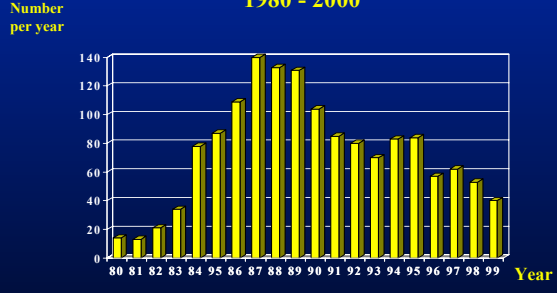


Severe heart failure – bridging to recovery

Options for the Treatment of Severe HF

1) Medical - poor prognosis
2) Surgical a. Transplantation
   b. Non transplant options
3) Evolving strategies

Royal Brompton and Harefield Heart Transplants 1980 - 2000



Severe heart failure – bridging to recovery

Novel therapies - evolution of a concept

Regeneration I (revive or grow again)

- **Induction maximal reverse remodeling by combination of LVAD & pharmacological agents**
- ***Followed by* induction 'physiological' hypertrophy using clenbuterol**

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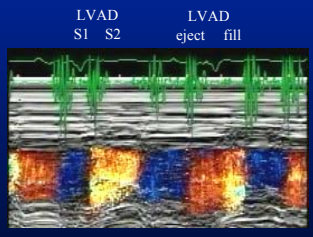
Severe heart failure – bridging to recovery



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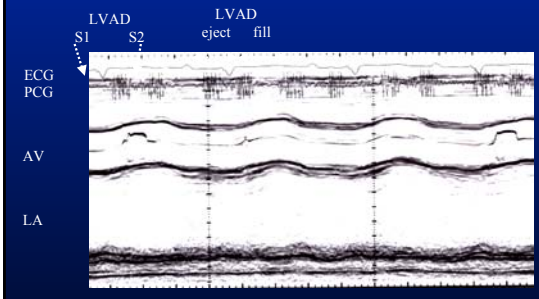
Severe heart failure – bridging to recovery



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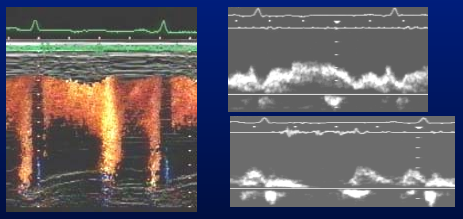
LVAD - Continuous pump
slow speed

Apex

Base

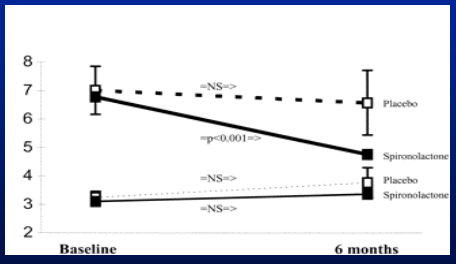


Severe heart failure – bridging to recovery

Pharmacological agents used for reverse remodeling

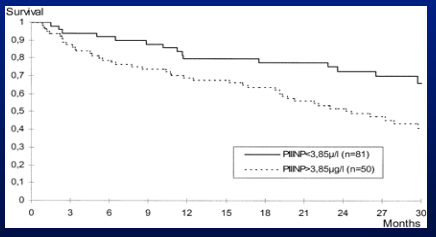
- Digoxin
- B blockade (Carvedilol & Bisoprolol)
- ACE inhibition – SAVE, SOLVD, HOPE (Lisinopril)
- Angiotensin II inhibition - RESOLVD (Losartan)
- Aldosterone receptor blockade - RALES (Spironolactone)

Severe heart failure – bridging to recovery



Zanad et al, Ciculation 2000; 102:2700

Severe heart failure – bridging to recovery



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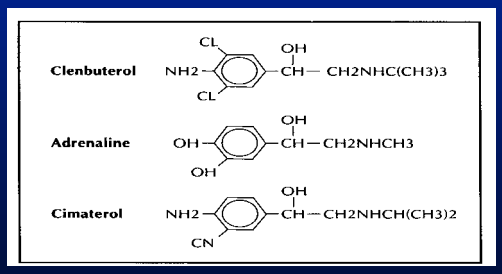
Severe heart failure – bridging to recovery



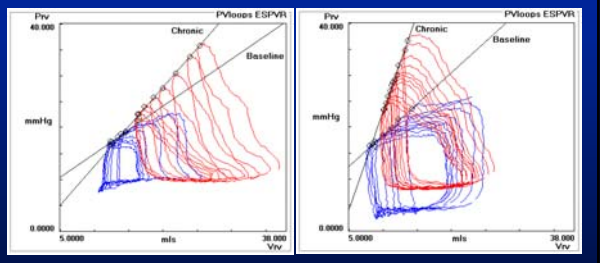
Severe heart failure – bridging to recovery

Clenbuterol & its actions

1) On skeletal muscle
- 'Physiological' hypertrophy
- Increased power – Petrou 1999, Maltin 1993
- Faster contraction & relaxation – Petrou 2000
- Induction of IGF1 – *Cell* 2002

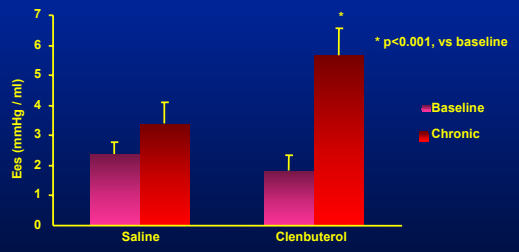
2) On cardiac muscle
- 'Physiological' hypertrophy – Wong 1998, Petrou 1995
- Enhancement of systolic & diastolic function in small & large animal models – Wong 2000, Hon 2001, 2002
- Prevents fibrosis following banding of the aorta & PA – Hon 2001
- Gene expression (physiological hypertrophy) – Bhavsar 2002

RV Pressure-Volume Loops



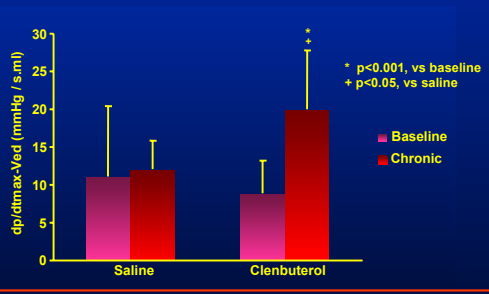
Hon et al.JTCVS 2001; 122:767

Ees



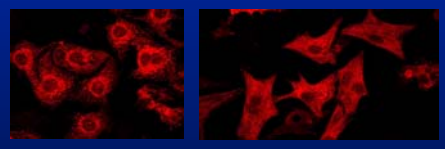
Hon et al.JTCVS 2001; 122:767

Dp/dpmax - Ved



Hon et al.JTCVS 2001; 122:767

Clenbuterol Induces Myofibrillogenesis



Untreated

Clenbuterol 10µM

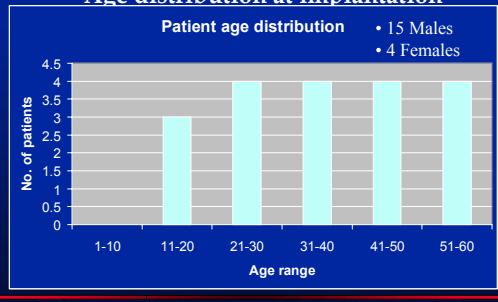
Severe heart failure – bridging to recovery

Patient demographics

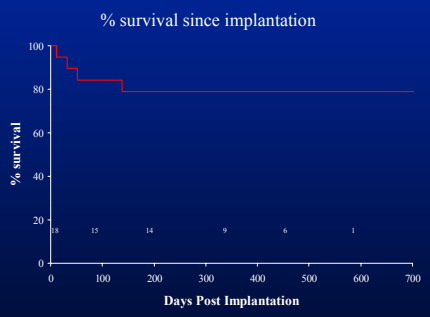
- 19 patients (15 males)
- 15 – 56 years
- Deteriorating end stage dilated cardiomyopathy, NHYA class IV, all inotrope dependent, 5(26%) IABP
- 16 idiopathic DCM, 1 post-chemo, 2 post partum, 0 myocarditis
- Mean interval from diagnosis to treatment 44 months (1-156)
- Emergency implantation with 18 HeartMate 1 & 1 HeartMate II

Severe heart failure – bridging to recovery

Age distribution at implantation

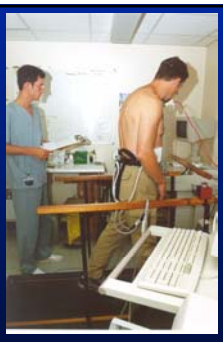


Severe heart failure – bridging to recovery



Monitoring

- TTE - LV dimensions, function and wall thickness
  - 4/52 - off pump echo (after heparinisation) at 5, 10, 15 mins & after 6 min walk (haemodynamics monitored)
  - if TTE stable after 6 min walk >150m, measure mVO2
- MVO2, VE/VCO2 (LVAD on / off)
- MUGA (if LV function maintained off VAD for 15 mins)
  - LV & RV ejection fractions & response to exercise
- Cardiac catheterisation
  - pressures / cardiac output /LV angiography on and off
  - LV Biopsies : RT-PCR, proteomics, single cell physiology
- PET - myocardial blood flow & CFR on and off
- Humoral changes



Severe heart failure – bridging to recovery

Explantation criteria

- LV dimensions *with device off* EDD <60mm, ESD <50mm, EF >45%
- LVEDP <12mmHg
- Resting CI >2.8L/min/m^2
- mVO2 >20ml/kg/min & VE/VCO2 slope <34

Harefield Recovery Study

Outcome

19 Patients

4 Deaths (21%)
(3 Periop, 1 Late Infection)

15 Survivors (79%)

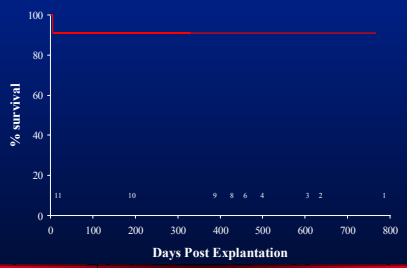
3 Transplanted
(1 Subsequent Death)

11 Explanted (73%)

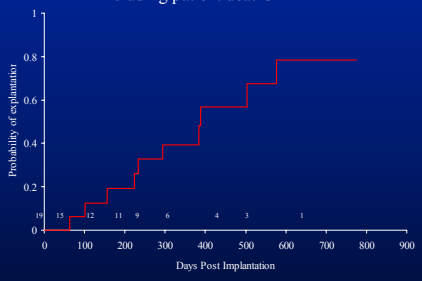
1 Ongoing

1 Periop Death (7%)

% survival since explantation



Including patient deaths



Explanted patient follow-up

- **Mean follow up *since explantation* 596 days (303-842)**
- **9/10 asymptomatic with unrestricted activities, 5 in full-time & 4 in part-time employment**
- **1 developed inoperable lung carcinoma**
- **At current follow-up:**
  - **mean EF 66% (53-80)**
  - **mean mVO2 27ml/kg/min (18-36)**
  - **mean *resting* PAP 17mmHg (8-34)**
  - **mean PCWP 8.4mmHg (2-17)**
  - **mean *resting* CO 5.0 L/min (4.5-6)**

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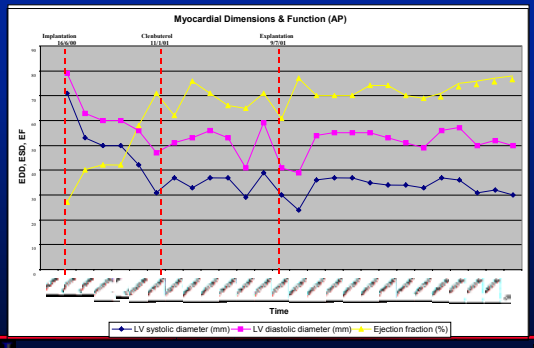
Clinical follow-up - addendum

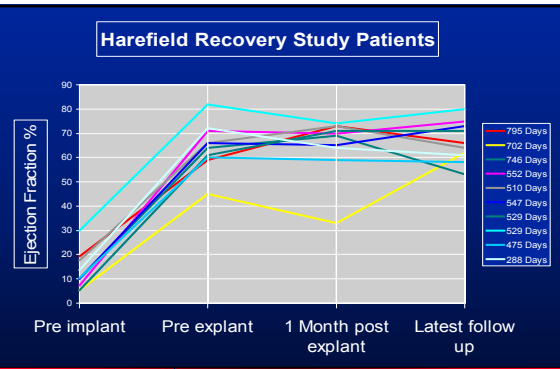
One patient developed progressive dilatation of the left ventricle following alcohol abuse 21 months after explantation but remains asymptomatic with a VO2 max of 24

Severe heart failure – bridging to recovery

Complications

Driveline infections 15 (79%)
Reexploration for haemorrhage 11 (58%)
Systemic infections 8 (42%)
Arrhythmia requiring chemical/electrical cardioversion 3(16%)
Device malfunction in 3 (16%)
Inlet valve regurgitation 2 (11%)
TIA 2(11%)
Fatal septic embolus (5%)





Severe heart failure – bridging to recovery

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Severe heart failure – bridging to recovery

Conclusions

- **Induction of R.R. followed by physiologic hypertrophy gives promising intermediate results in "Class V" DCM**
- **Acceptable survival ?improved further by patient selection**
- **High explantation rate**
- **Safe explantation (mini-invasive)**
- **Low post-explant mortality with preserved LV function to date**

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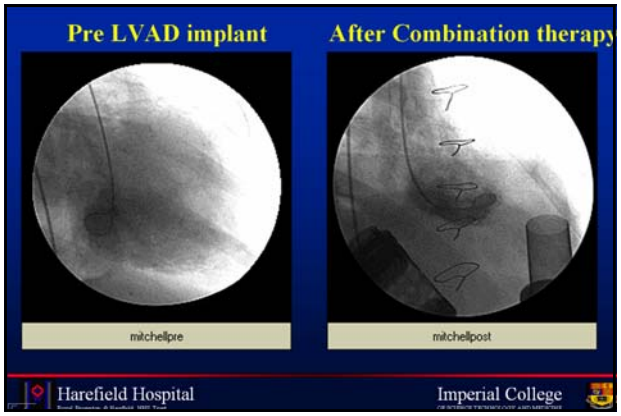
Pre LVAD implant
After Combination therapy
mitchellpre
mitchellpost
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