- AC_{VI} Gene Transfer for CHF -

- Rationale
- Preclinical Data
- Proposed Clinical Trial

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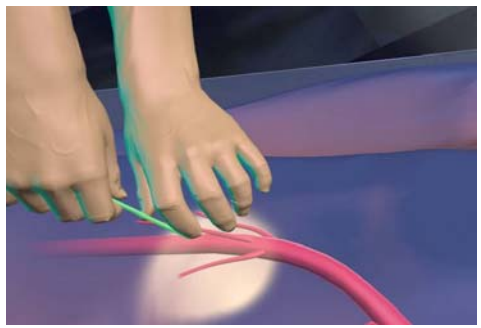
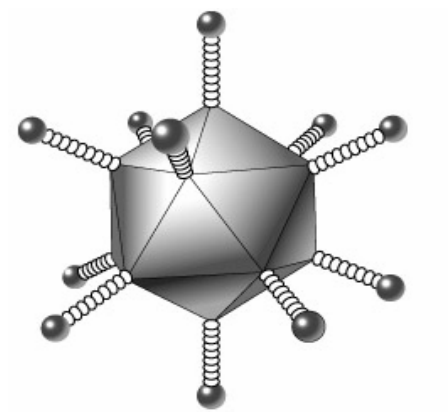
- AC_{VI} Gene Transfer for CHF -

Unmet Medical Need, Reduced Morbidity

Intracoronary Delivery



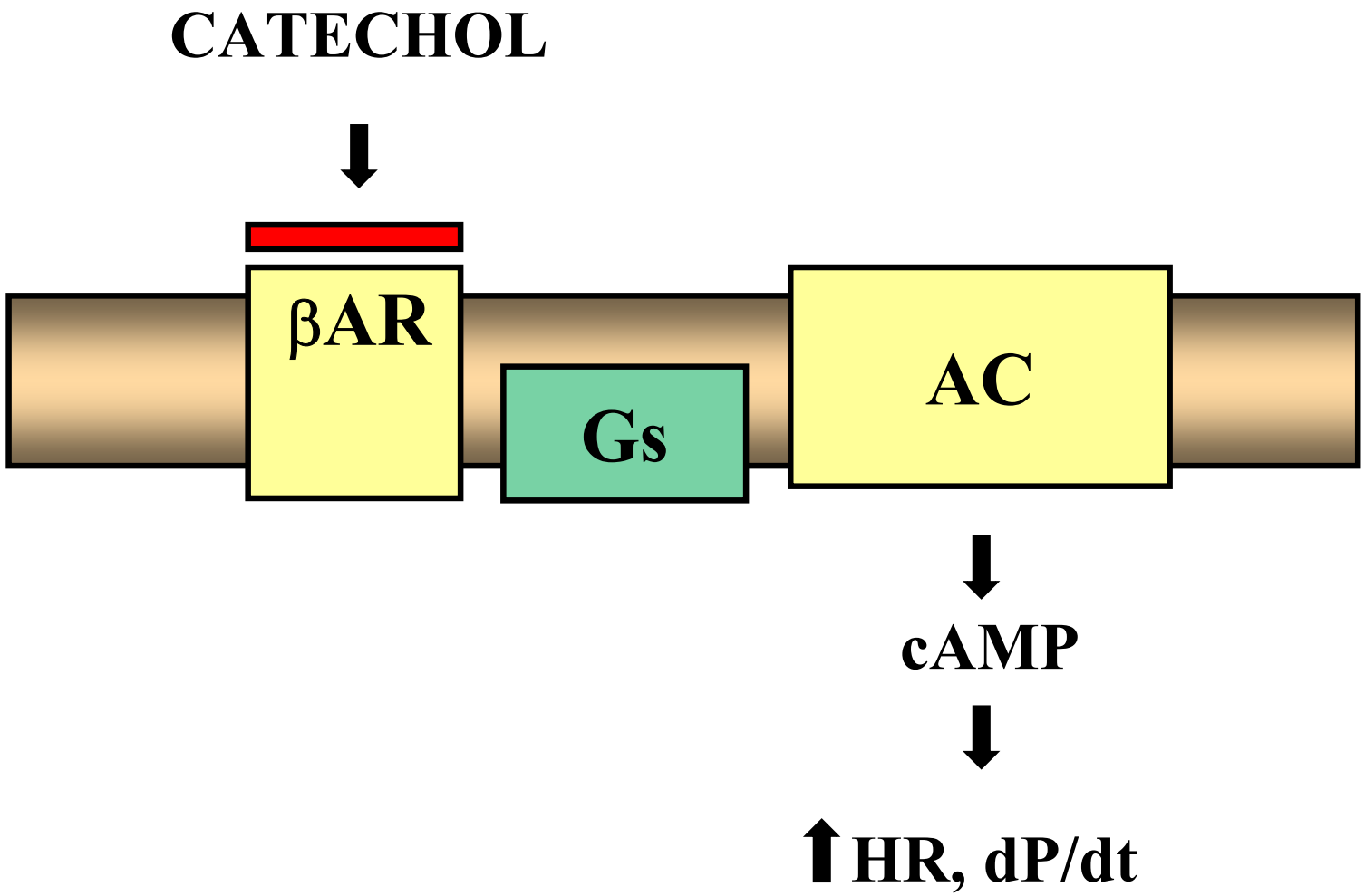
- **Prevalent disease — most common non-elective admitting diagnosis in patients >60 years old**
- **Current therapy — 40% mortality 3 yr after onset of Class III/IV symptoms**
- **Current therapy has substantial side-effects**
- **No thoracotomy — reduced morbidity & mortality vs strategies that require invasive procedures**
- **New strategy would provide an option for patients not suited for CABG, PCI or other therapies**



Adenovirus Encoding AC_{VI}

- Heart Failure -

Can we safely increase LV contractility ?



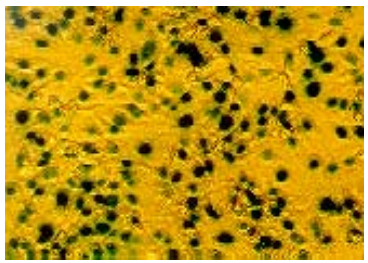
- AC_{VI} Gene Transfer -

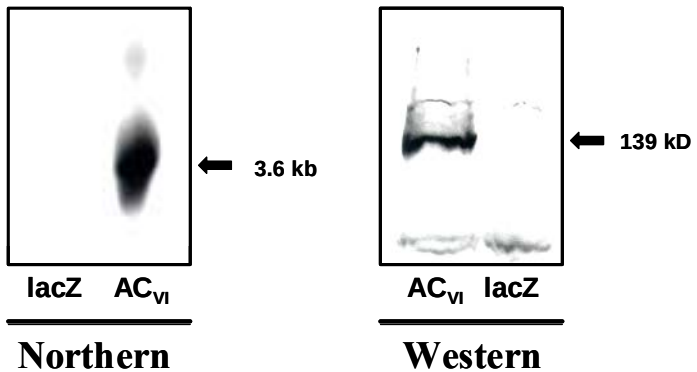
Neonatal Rat Cardiac Myocytes

- Stoichiometry -

ßAR : Gs : AC

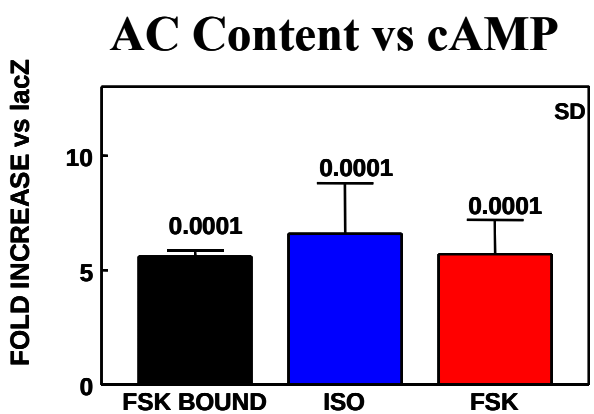
1 : 200 : 3





Hypothesis

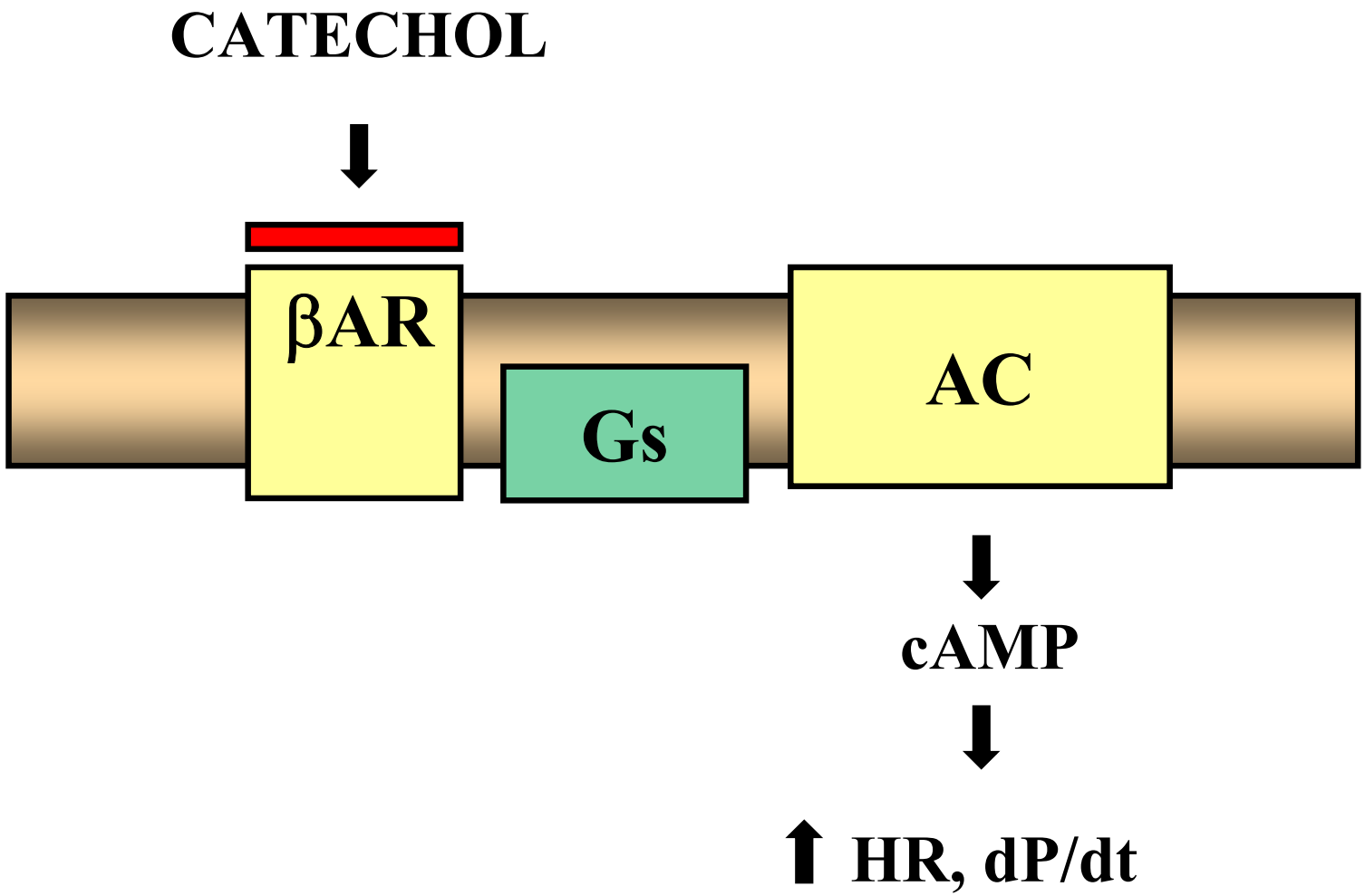
AC content limits cardiac myocyte adrenergic responsiveness



- PNAS 95: 1038-1043, 1998

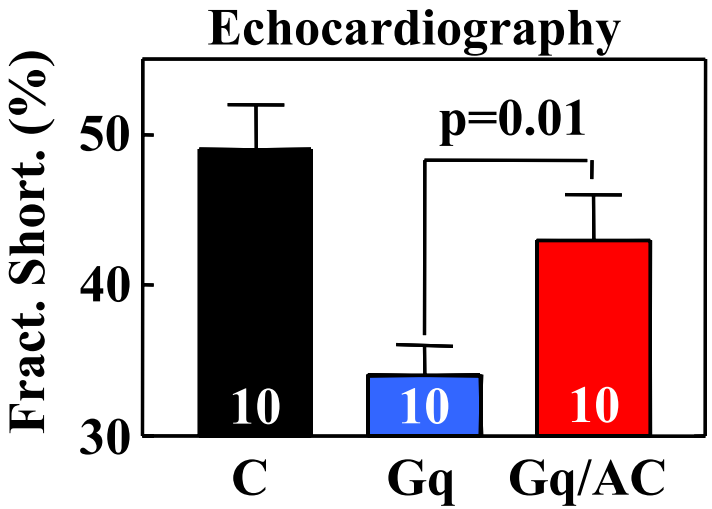
- Cardiac-Directed AC_{VI} Expression -

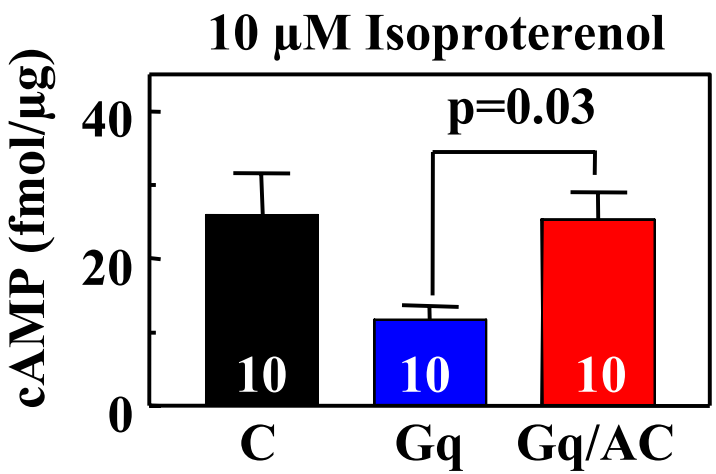
Murine Cardiomyopathy

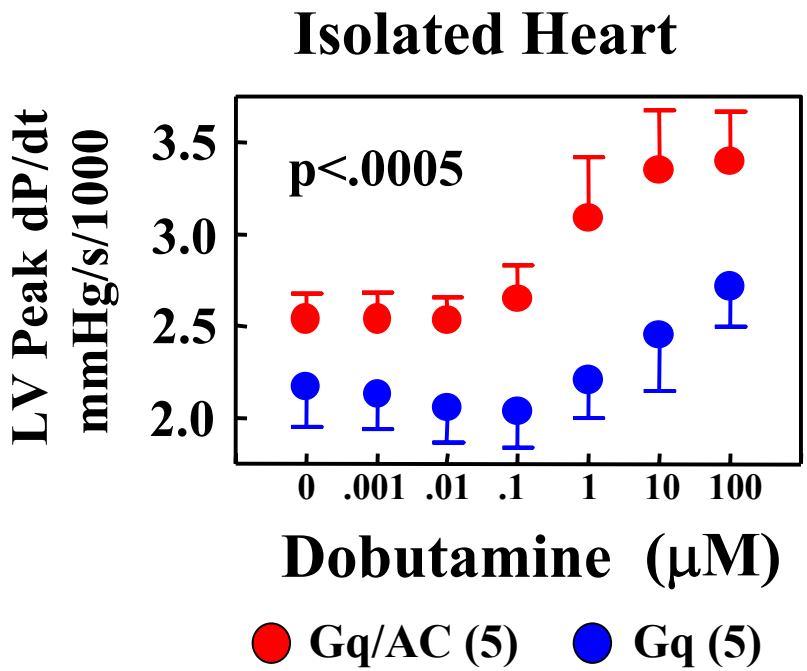


- AC_{VI} in Cardiomyopathy -

LV Function and cAMP





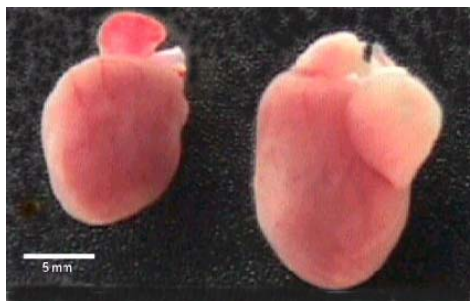


- Circulation 99: 3099-3102, 1999

- AC_{VI} in Cardiomyopathy -

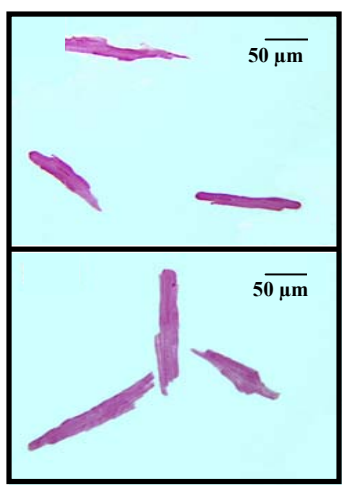
Effect on Hypertrophy & Mortality

p<0.004



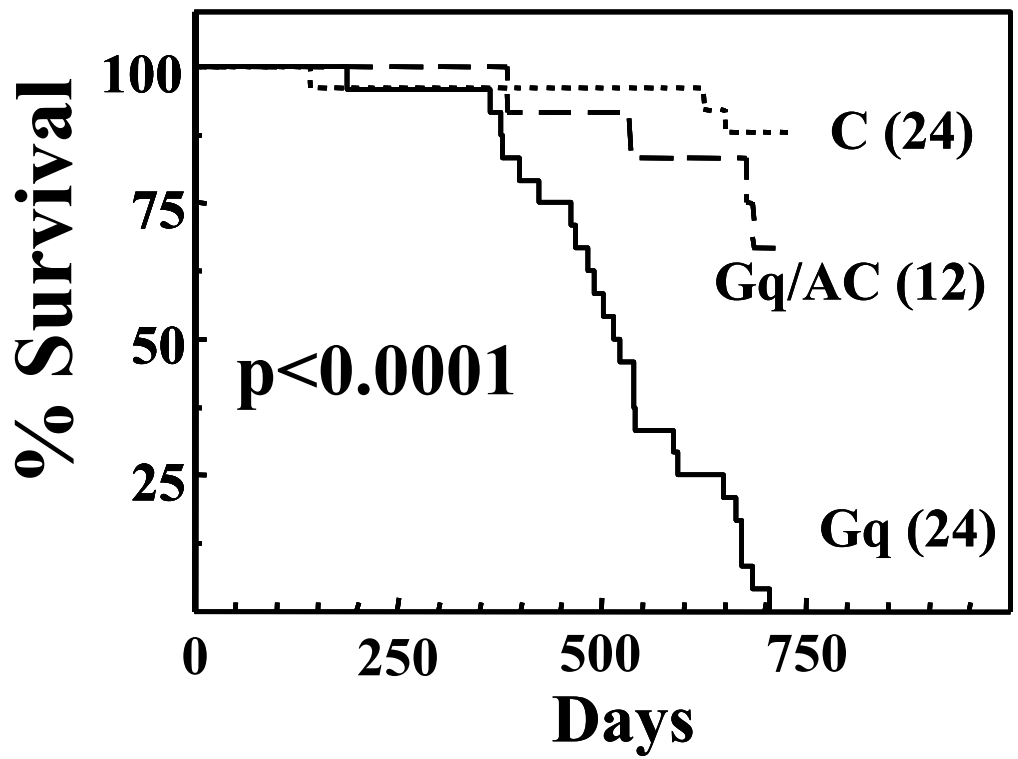
Gq/AC Gq

Gq/AC



Gq

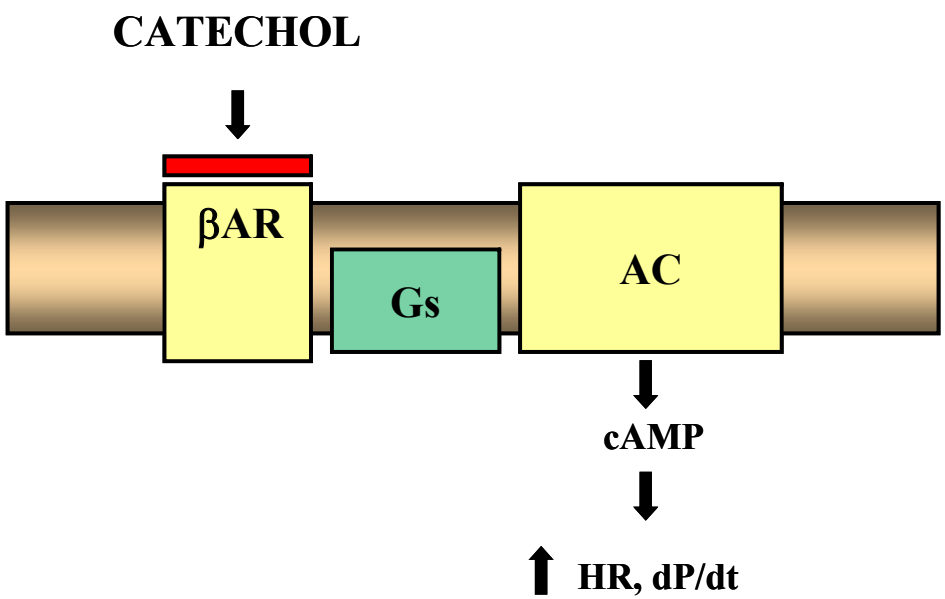
p<0.0075

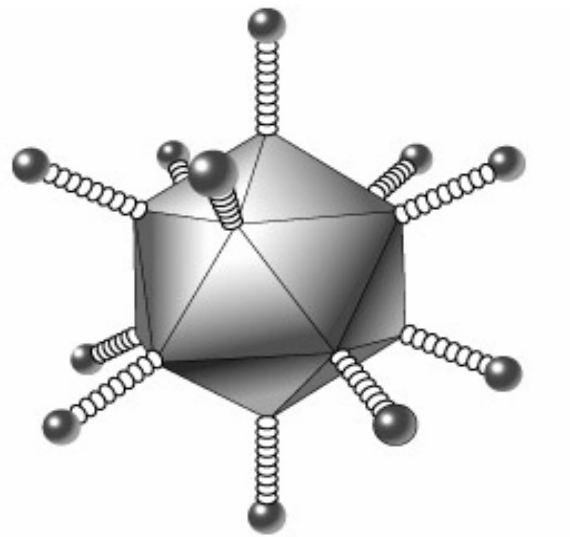


- Circulation 105: 1989-1994, 2002

- Intracoronary Gene Transfer -

Adenovirus Encoding AC_{VI} in Pigs with CHF

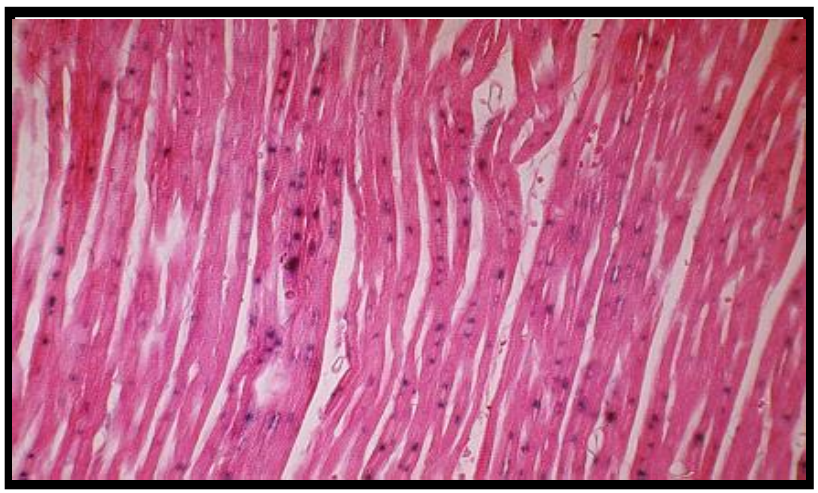




AC_{VI} Gene Transfer

Adenovirus Vector

- Intracoronary Delivery of Adenovirus -

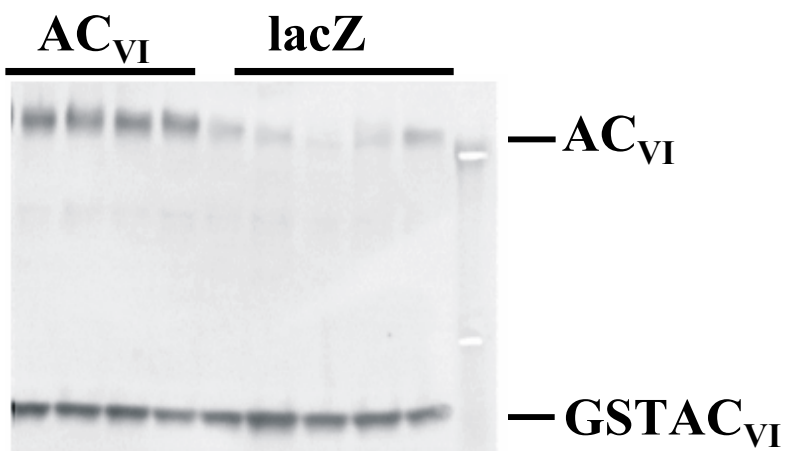


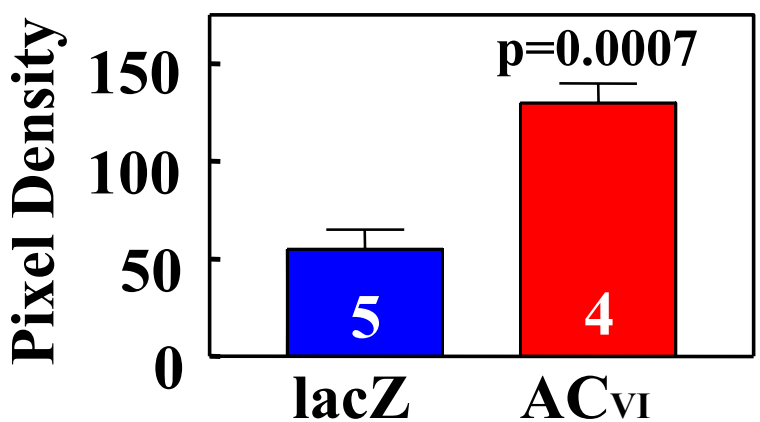
1.4 x 10^{12} vp adenovirus encoding nuclear-tagged lacZ. Five days after coronary delivery, substantial gene transfer was seen in the heart, without inflammation. Blue color indicates gene transfer. LV Transmural sections. Left panel, 30X; Right Panel, 200X.

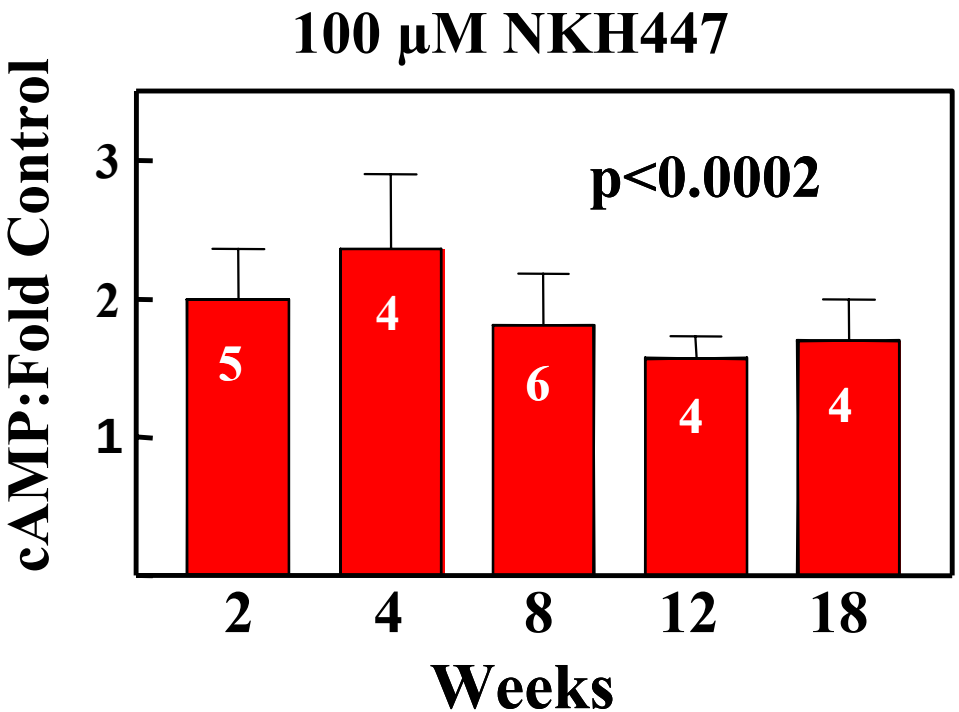
- Circulation 102: 2396-2401, 2000

- Intracoronary Ad.AC_{VI} -

LV AC_{VI} Expression & Duration of Effect



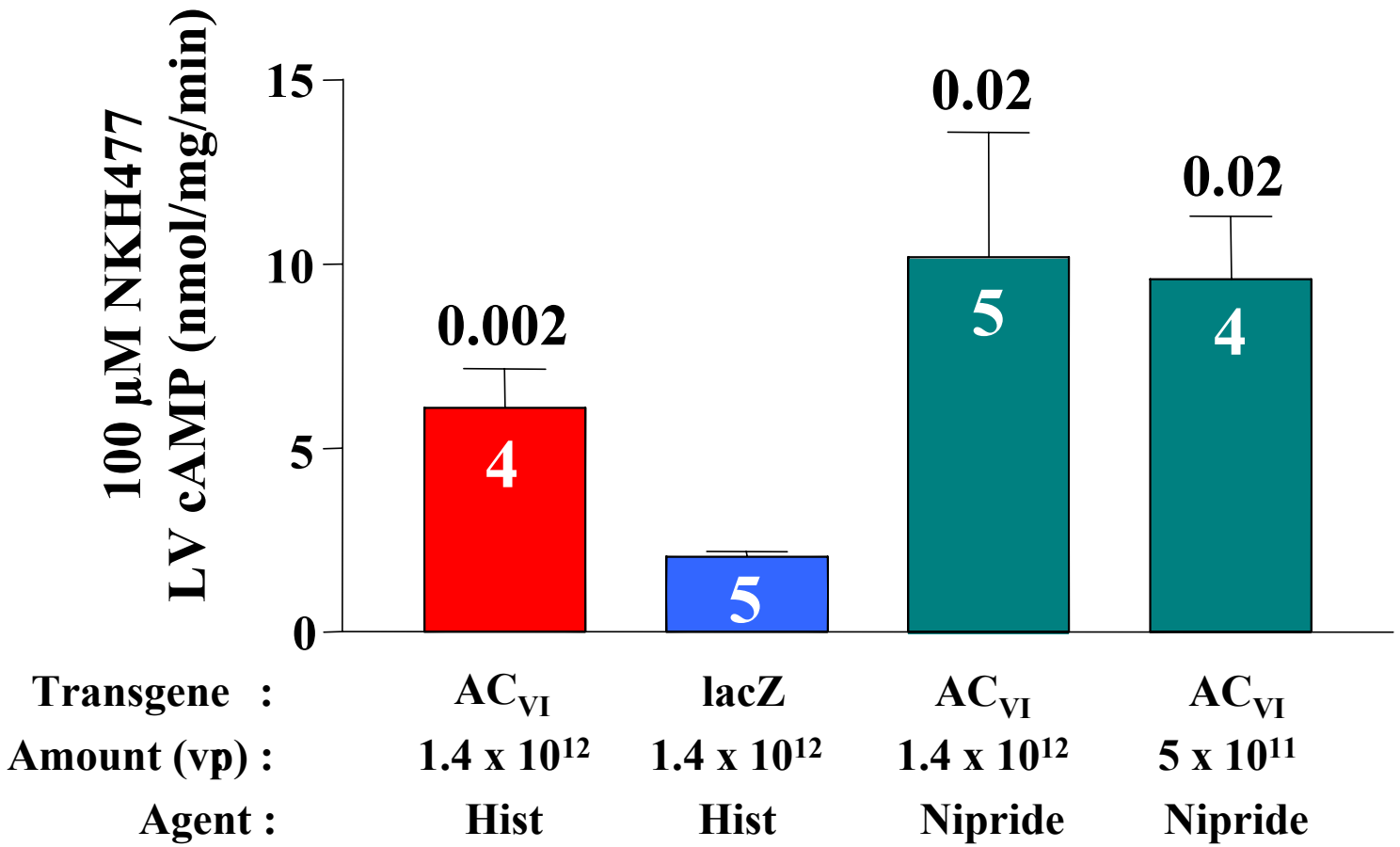




- Circulation 102: 2396-2401, 2000

- Intracoronary Delivery of Adenovirus -

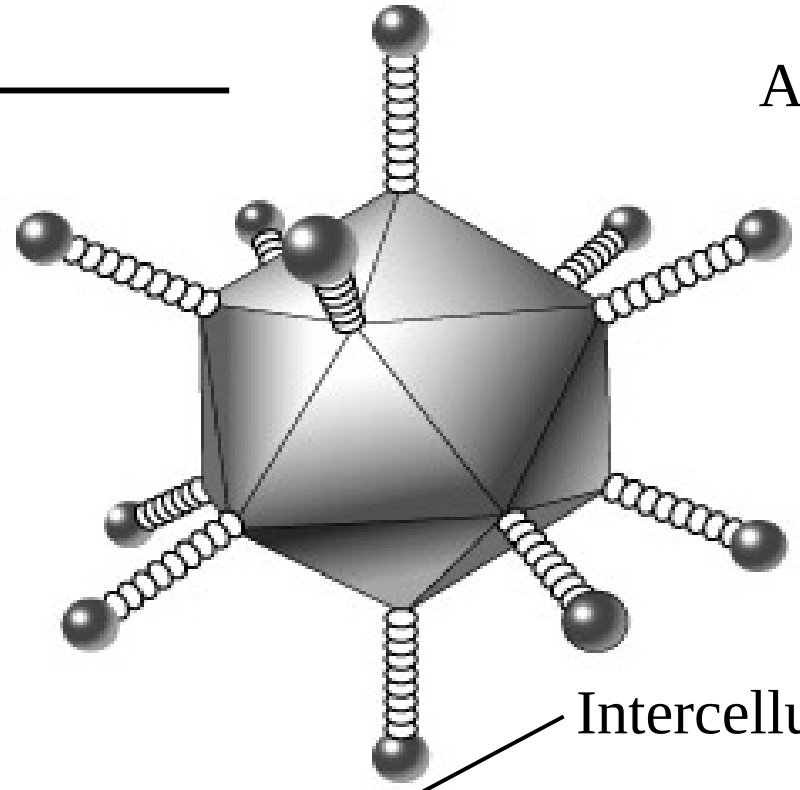
Effect of Nitroprusside



- Intracoronary Gene Transfer -

Transcytosis of Adenovirus ?

Adenovirus = 80 nm



Intercellular gap = 5 nm

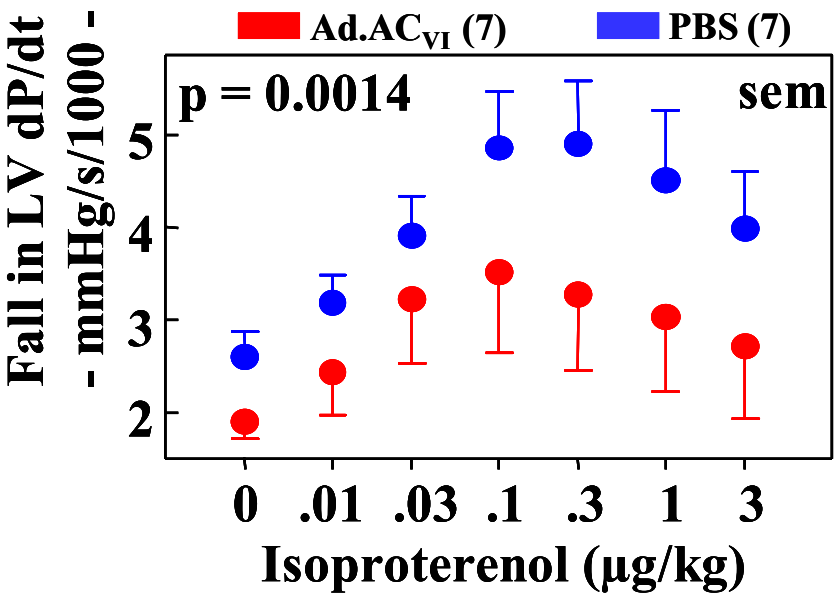
Luminal Side

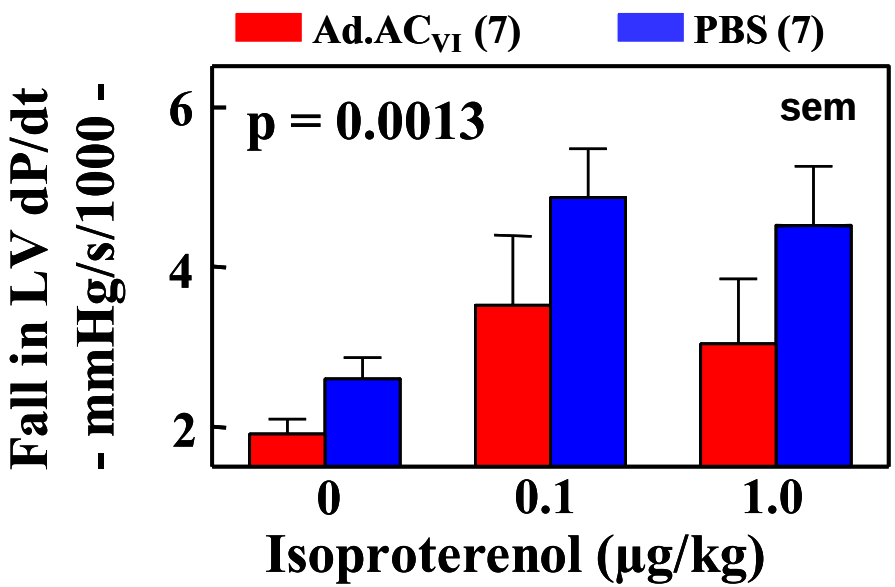
Endothelial Cell

Endothelial Cell

- Intracoronary Ad.AC$_{VI}$ in CHF -

Increased Contractility 14d after Gene Transfer

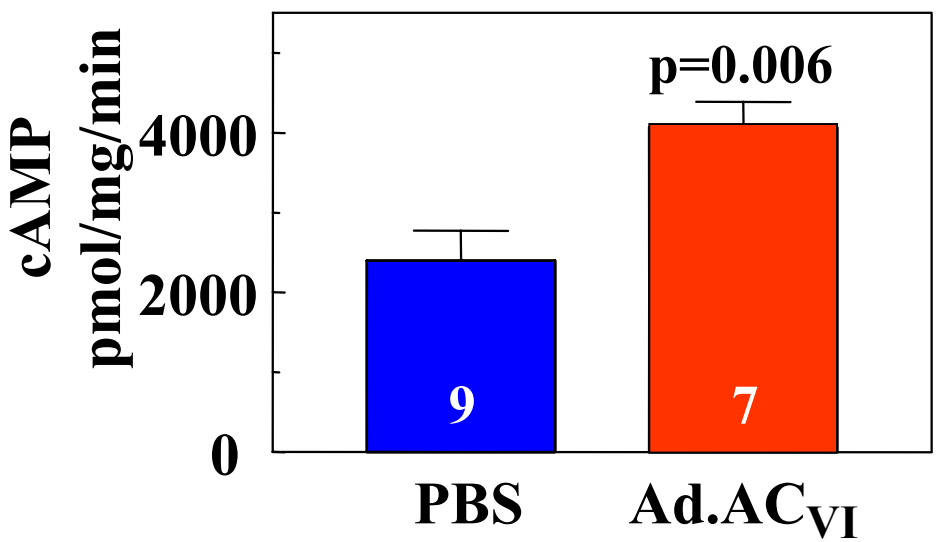




- Ad.AC_{VI} in Pacing-Induced CHF in Pigs -

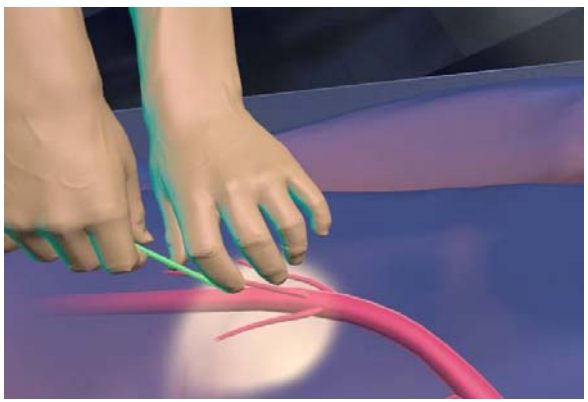
Improved LV Geometry, Function and cAMP Generation

Pre vs 21d	PBS n=9	AC_{VI} n=6	p
EDD Increase - mm -	18±2	13±2	0.04
FS Decrease - % unit -	29±2	23±3	0.03
Vcf Decrease - circ/s -	1.1±0.1	0.7±0.1	0.008

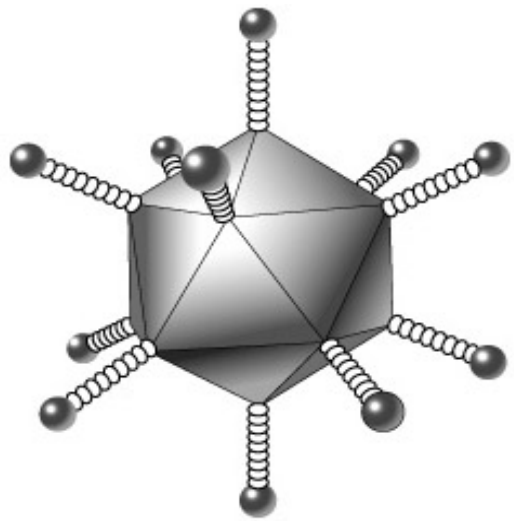


- Data obtained before and after 21d of continuous LV pacing
- Gene transfer on Day 7 (CHF present)
- Blinded study

- AC_{VI} Gene Transfer for CHF -
Clinical Trial Design

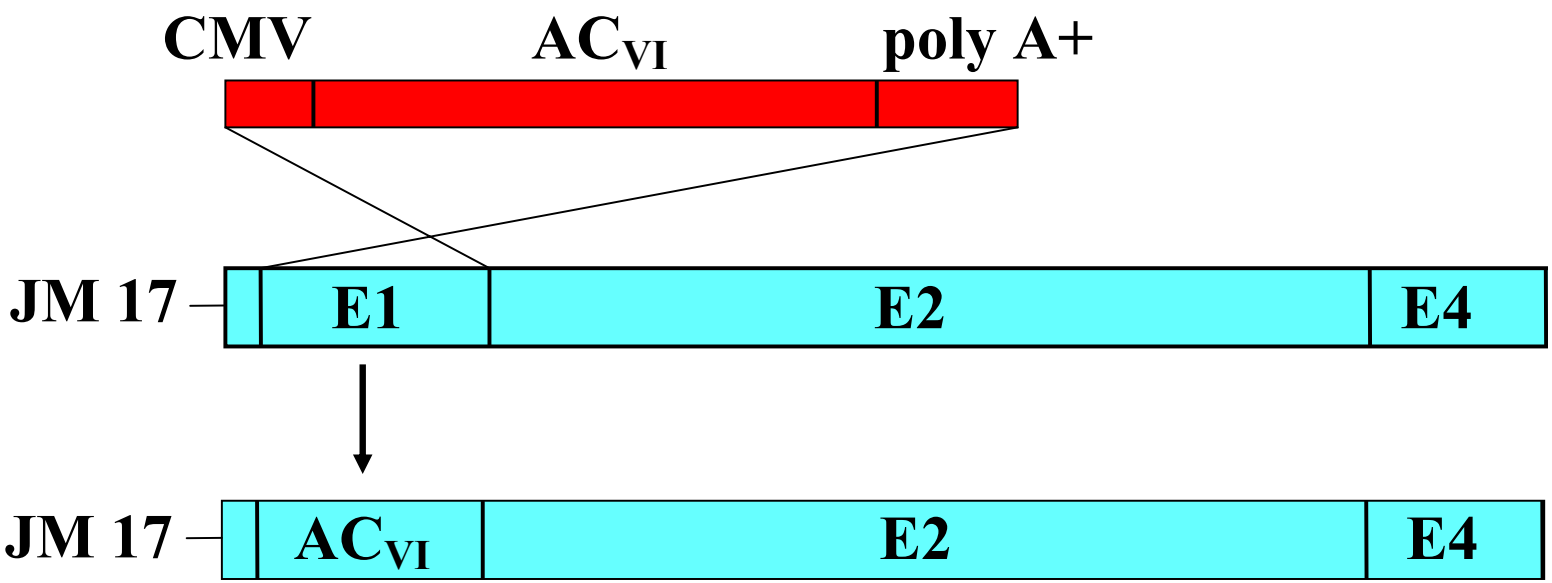


Intracoronary Delivery



Adenovirus Encoding Human AC_{VI}

- Recombinant Adenovirus Encoding AC_{VI} -



E1/E3- Deleted Recombinant Adenovirus Encoding Human AC_{VI}

- Gene Transfer for CHF -

Intracoronary Ad5.AC$_{VI}$

Objective

Examine safety and identify dose(s) that warrant further study in larger trials

End Point

6 minute walk test before and 4 and 12 weeks after treatment

Follow-Up

Careful monitoring, visits for 12 weeks, interviews at 6 and 12 months

- AC_{VI} Gene Transfer for CHF -

Enrollment And Exclusions

Enrollment

- Stable CHF, Class III/IV
- ≥ 1 yr history of CHF
- LVEF ≤35%
- 6-min walk: 25–300 meters
- 21-75 years of age

Exclusions

- Decompensated CHF, iv inotropes
- CAD: Severe 3 vessel or LM
- Angina ≥ Class 2 or unstable
- Immune suppressive agents
- Creatinine >2.5 mg/dL
- Liver disease
- VT/VF with syncope unless AICD
- Women of child-bearing potential

- AC_{VI} Gene Transfer for CHF -

Protocol

Double-blind, 3:1 randomization (Ad5.AC_{VI} : Placebo)

Intracoronary infusion (40% RCA, 60% LCA) with intracoronary nitroprusside (50 µg/min, 3 min)

5 Doses @ 0.5 log increments: 3×10^9 to 3×10^{11} vp

In-hospital observation (overnight)

Follow-up (Weeks 1, 2, 4, 8, 12; Months 6, 12)

Exercise testing (Weeks 4 and 12)

Safety Monitoring

Adenovirus Surveillance

- Pulmonary artery (during administration)
- Venous blood (1 hr after administration)
- Urine (first 6 hours after administration)
- Antibody titers (baseline and 12 weeks)

Holter Monitoring (baseline and Week 2)

PE, ECG & Blood Samples (Weeks 1,2,4,12; Months 6,12)

- Liver function (SGOT, SGPT, LDH, alkaline phosphatase, bilirubin, albumin)
- Cardiac (CPK, CPK-MB, Troponin)
- CBC, electrolytes, BUN, creatinine, urinalysis
- BNP, norepinephrine, epinephrine

- AC_{VI} Gene Transfer for CHF -

Clinical Testing & Procedures

	Screen	D 1	W 1	W 2	W 4	W 12	M 6	M 12
6 Minute Walk Test	XX				X	X		
Interview	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X
Urine Sample	X		X	X	X	X		
Blood Sample	X	X	X	X	X	X	X	X
Chest Radiogram	X					X		
ECG	X	X	X	X	X	X		
24 Hour Holter	X	X*		X				
Echocardiogram	X				X	X		
Coronary Angiogram		X						
Ad5.AC_{VI} or PBS		X						
Right Heart Catheterization		X			X			

Dose Escalation, Termination of Trial

- The NHLBI DSMB will monitor the trial & manage randomization; members periodically will be unblinded to evaluate safety & efficacy.
- Adverse events will be reported to the DSMB and other agencies.
- The DSMB will make decisions regarding advancing to the next dose or ending the trial due to toxicity.
- The DSMB may ask that additional patients be recruited in a dose-group to evaluate toxicity or efficacy (limit 16 patients: 12 Ad5.AC_{VI}, 4 placebo).
- Otherwise, the study will be completed as proposed.

- AC_{VI} Gene Transfer for CHF -

Dose Groups and Potential Outcome

Dose Group	*vp*	*Ad5.AC_{VI} - n -*	*Placebo - n -*
1	3.2×10^{9}	3	1
2	10^{10}	3	1
3	3.2×10^{10}	9	3
4	10^{11}	9	3
5	3.2×10^{11}	21 (9+12)	7 (3+4)
Dose 5 Comparison		21	15
Total Patients		45	15

- **Placebo group is proposed**
- **15 patients will receive placebo and 45 will receive Ad5.AC_{VI}**
- **DSMB may recruit additional patients in groups of 8 (6:2) if trend for efficacy seen**
- **In example, 16 additional patients recruited in Dose Group 5**
- **Comparison: 21@ 3.2×10^{11} vs 15 Placebo**

- Placebo Group -

Ethical Considerations

- **Data (safety & efficacy) will interpretable only if collected & analyzed in a double-blinded manner.**
- **Coronary angiography is recommended for patients with CHF. Whether patients enroll in the trial or not, they should undergo coronary angiography.**
- **The consent form indicates patients will undergo coronary angiography with a 1 in 4 chance of receiving placebo. The risks are clearly presented — no duress will be placed on patients to enroll.**

Helsinki Declaration — "Biomedical research involving human subjects must conform to generally accepted scientific principles…"

Funding

- National Institutes of Health (NHLBI PEGT)
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- American Heart Association

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