

Biyolojik “Pacemaker” ve Gen Tedavisi

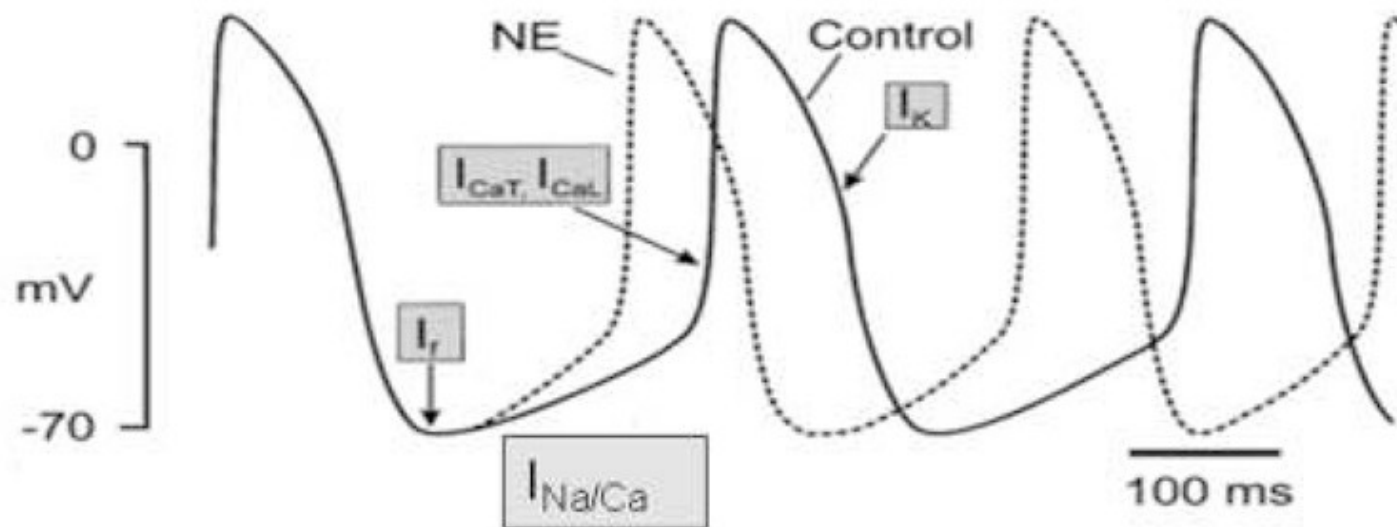
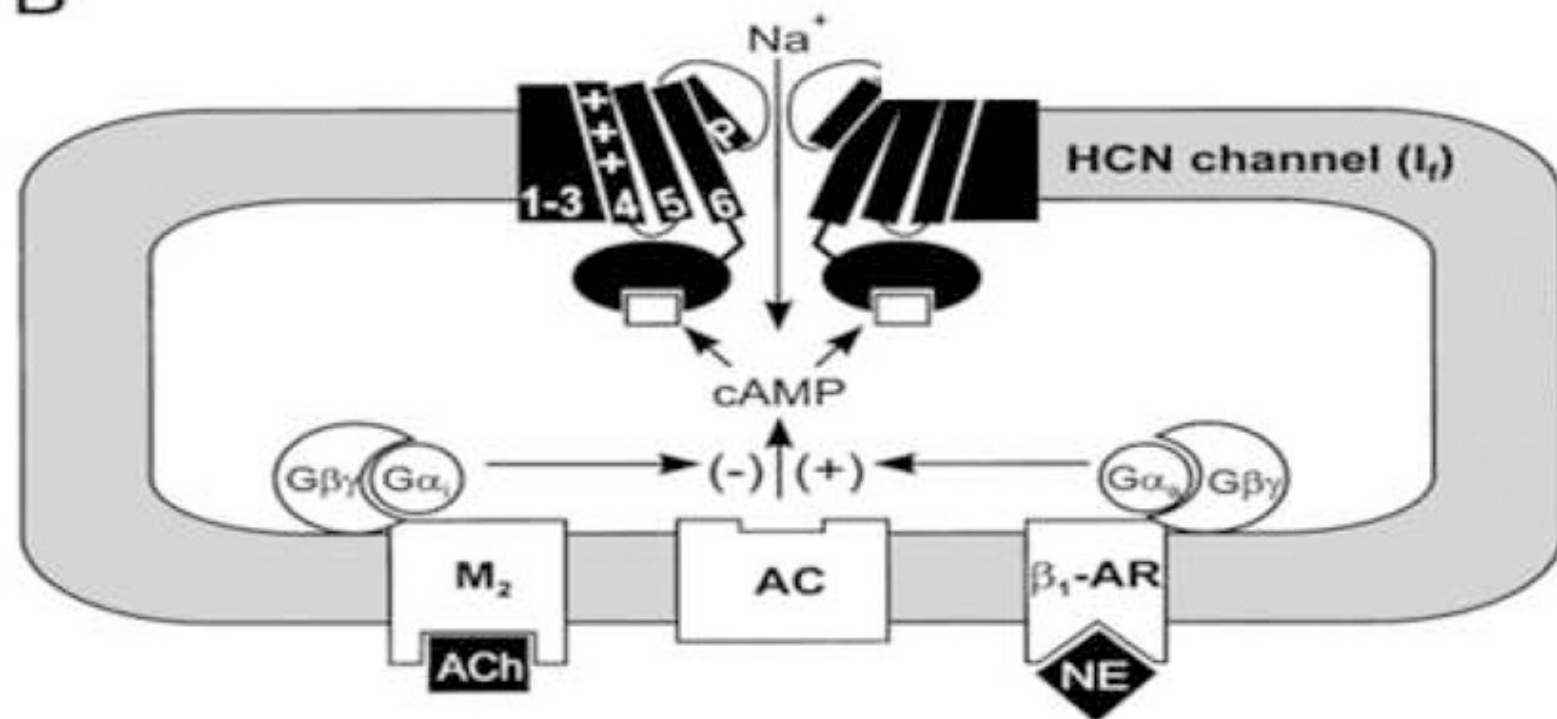
Prof.Dr.Enis Ođuz

Elektronik kalp pilinin kısıtlamaları

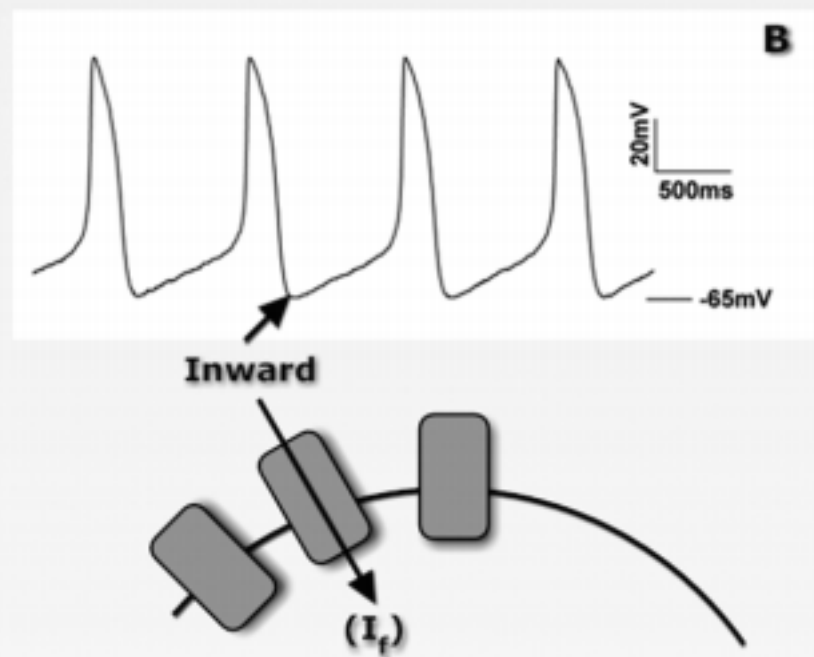
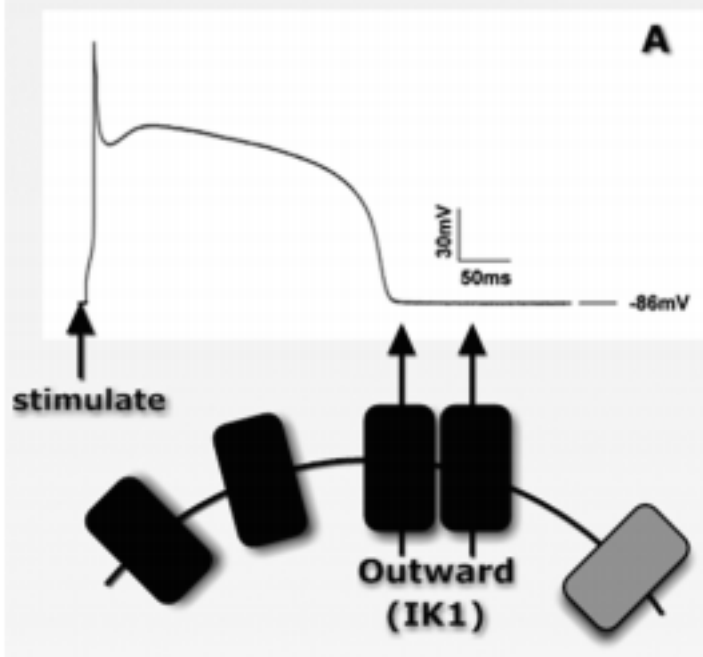
- Batarya ömrü
- Elektrot problemleri
- Fizyolojik uyarılara otonomik cevabın eksikliği
- Küçük çocuklarda gelişme-elektrot problemleri
- Uzun süre kullanımda kalp yetersizliği
- İnfeksiyon *

Biyolojik “Pacemaker” Yaklaşımları

- Gen temelli yaklaşımlar
- Hücre temelli yaklaşımlar
- Hibrid yaklaşımlar (Gen + Hücre)
- Somatik yeniden programlama

A**B**

Diastolic Depolarization



SAN da faz 4-diyastolik depolarizasyon

- I_f akımı (hücre içine doğru akım)
 - **HCN** : hiperpolarizasyon ile aktive-siklik nükleotid ile modüle olan kanallar
 - 4 izoform: HCN1,2,3,4
 - HCN kopyalanması en fazla SAN
 - Ventrikülde çok az
 - SAN da HCN4 dominant form

Ventrikül kası hücresinde faz 4 depolarizasyon

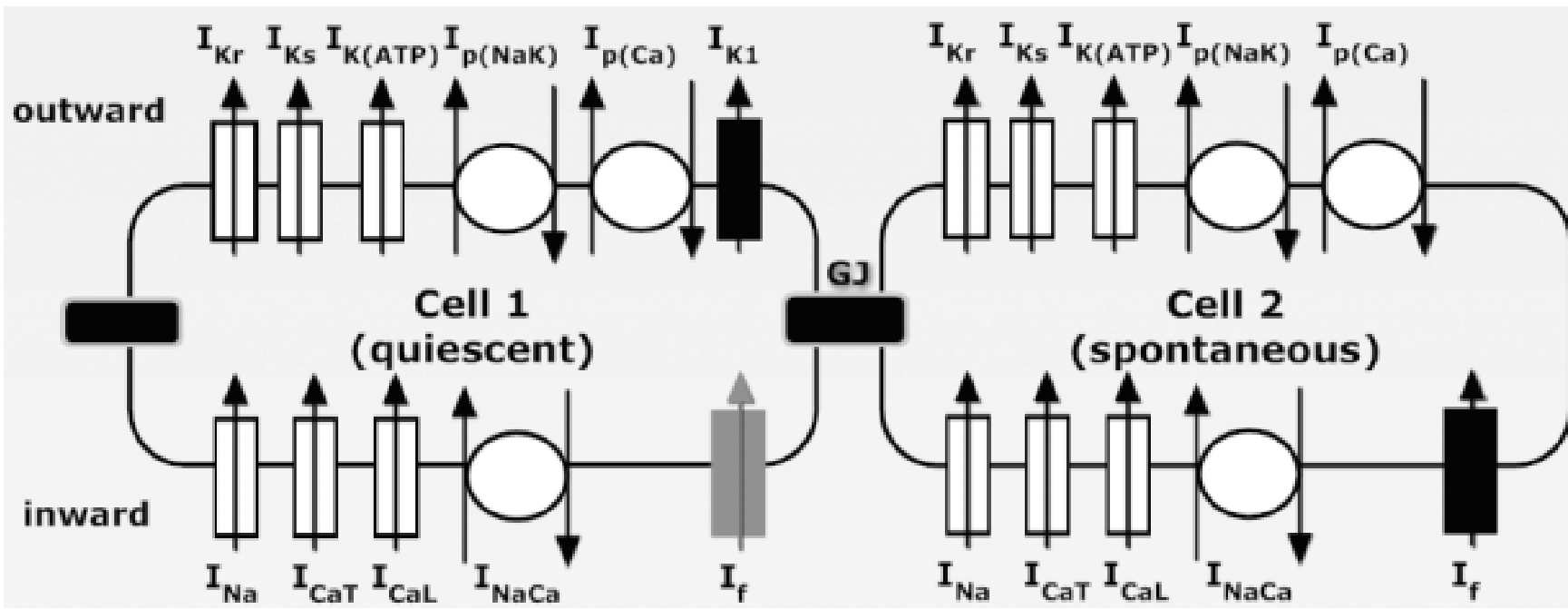
- I_{K1} akımı (dışa doğru K akımı)
 - Kir2.x kanalları
 - Kri2.1,2,3,4 izoformları
 - Ventrikülde Kir2.1 dominant
 - SAN çok düşük oranda

Bağlantı kanalları (“Gap Junctions”)

- İki hücre arasında elektrik iletkenliğini belirleyen kanallar.
- Bu kanallarda konneksin denen protein esas rolü oynar.
- Cx 40, Cx 43, Cx 45
- Ventrikül ve Purkinjede bağlantı kanallarında ileti hızlı
- “Pacemaker” hücrelerinde yavaş.

Bağlantı kanalları (“Gap Junctions”)

- Cx 43 Ventrikülde
- Cx 40 Atriyumda
- Cx 45 SAN,AVN
- Cx43,Cx40,Cx45 Purkinje hücreleri



Biyolojik “pacemaker”

- HCN kanal aktivitesini arttırmak
ve/veya
- Kir2.1 kanal aktivitesini azaltmak
- Son 10 yılda bu amaçla gen temelli yaklaşım ile HCN kanalları aktivasyonunu arttırmak ve dominant negatif Kir2.1 kanalları açığa çıkışını arttırmak yöntemleri ile biyolojik “pacemaker” oluşturulmaya çalışıldı.

Gen temelli yaklaşımlar

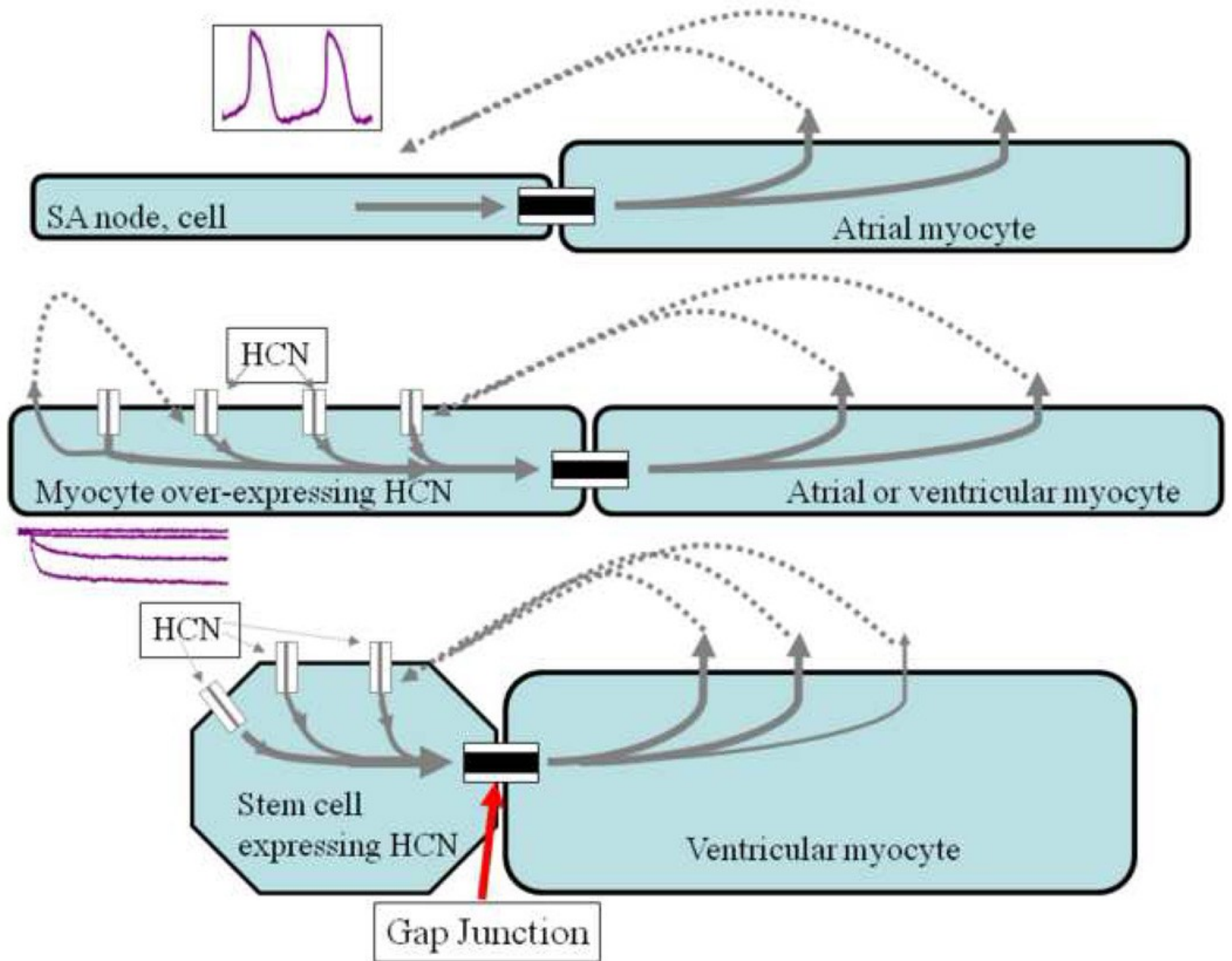
- Beta adrenerjik resptör fazla ekspresyonu
- Adenilat siklaz fazla ekspresyonu
- I_{k1} akımı inhibisyonu
- I_f akımının arttırılması
- Kv1.4 voltaj bağımlı K⁺ kanalının (sadece ventrikülde) hiperpolarizasyon ile aktive olan kanala çevrilmesi

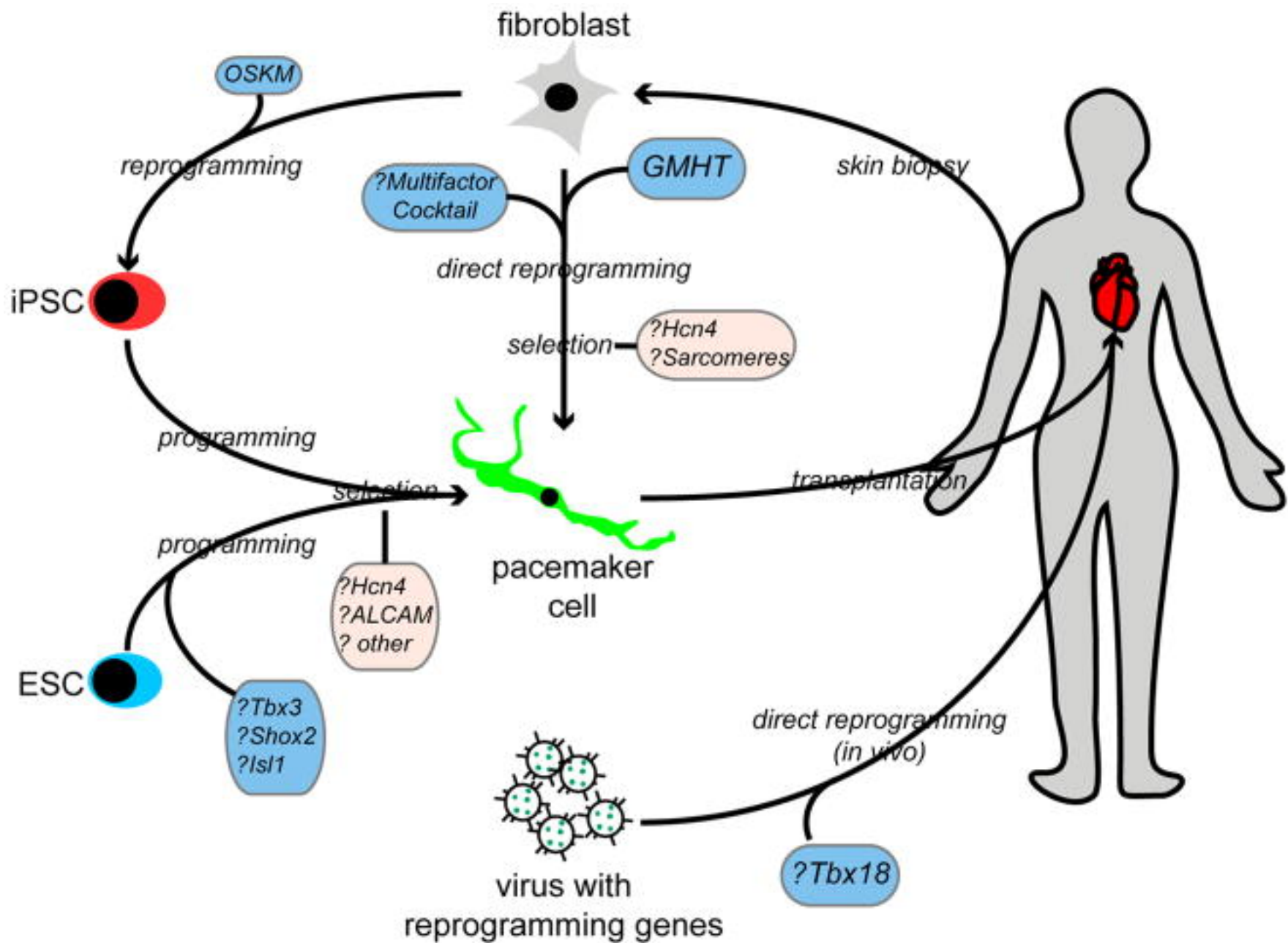
Hücre Temelli Yaklaşımlar

- Uyarı yapan doğal miyositler
- Kök hücre kaynaklı kardiyak miyositler
 - ESC ve iPSC “pacemaker” hücrelerine dönüşümü ve kısa süreli “pacemaker” aktivitesi gösterildi
 - Hibridleşme ve rejeksiyon problemi (immunoreaktivite)
 - Proaritmi – farklı elektriksel özelliklerde hücrelerin yarattığı repolarizasyon dispersiyonu

Hibrid Yaklaşımlar

- İyon kanalları ile ilgili genlerin yüklendiği mezenkimal kök hücreler
 - İmmunojenitesi düşük
 - Enjekte edildiği yerden migrasyonu ve çoklu ektopik odaklar oluşması





Somatik yeniden programlama

[Sci Transl Med](#). Author manuscript; available in PMC 2016 Jul 19.

PMCID: PMC4949602

Published in final edited form as:

NIHMSID: NIHMS799630

[Sci Transl Med](#). 2014 Jul 16; 6(245): 245ra94.

doi: [10.1126/scitranslmed.3008681](https://doi.org/10.1126/scitranslmed.3008681)

Biological pacemaker created by minimally invasive somatic reprogramming in pigs with complete heart block

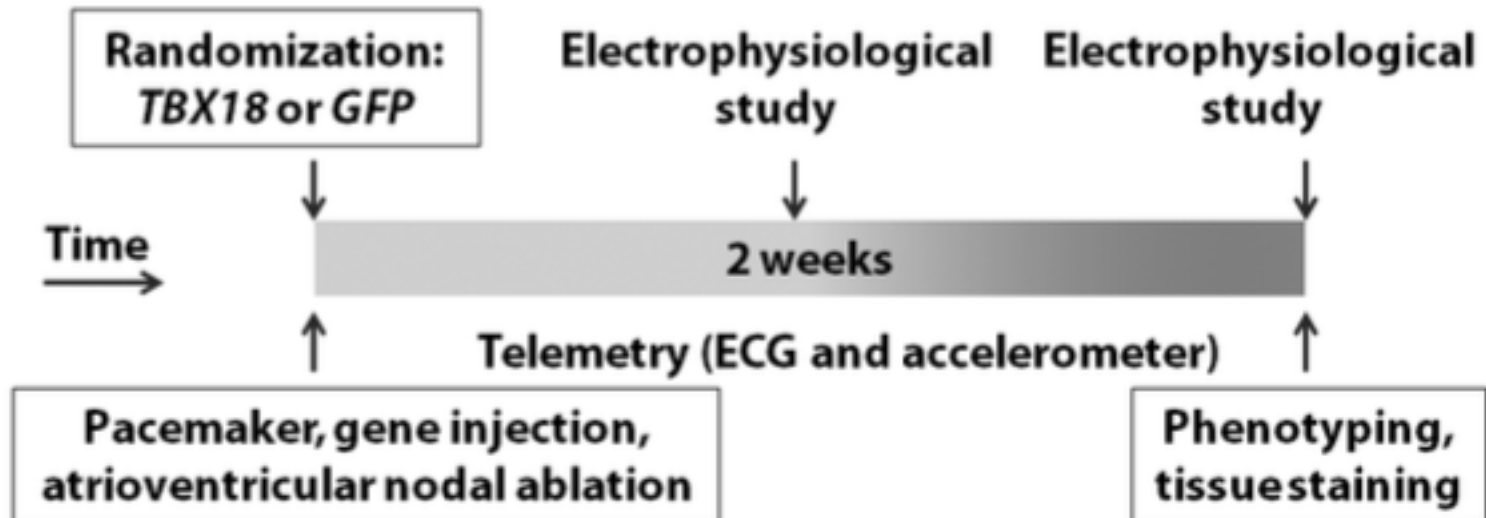
[Yu-Feng Hu](#),^{1,2} [James Frederick Dawkins](#),¹ [Hee Cheol Cho](#),¹ [Eduardo Marbán](#),^{1,*} and [Eugenio Cingolani](#)^{1,*}

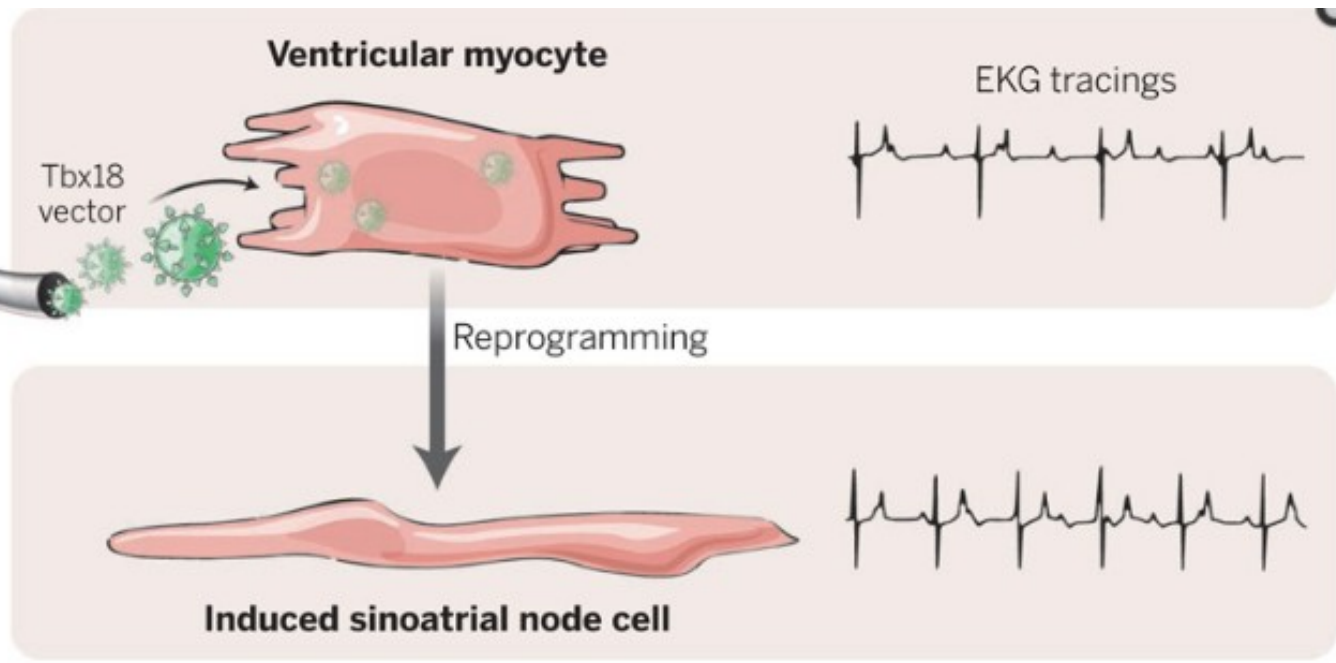
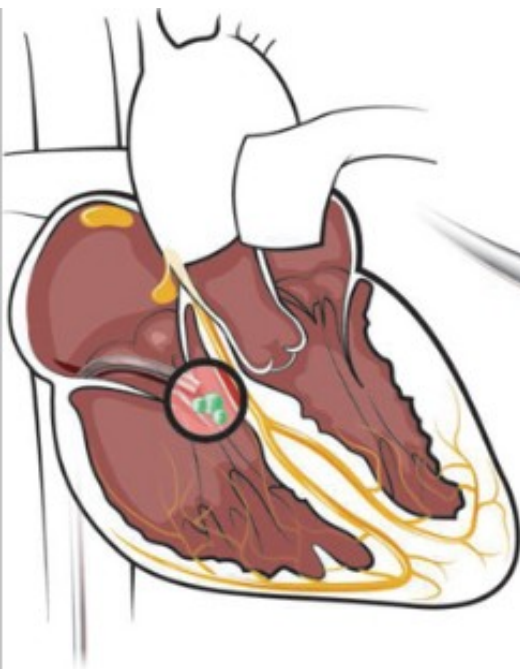
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Çalışma Dizaynı

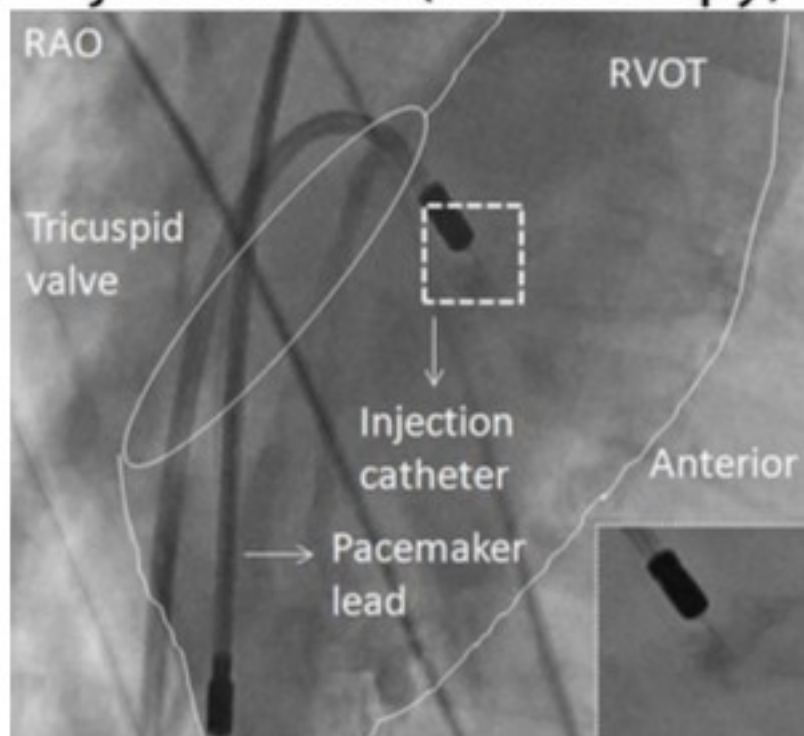
- Kontrol grup
- 5 domuz
- GFP

- Gen verilen grup
- 7 domuz
- TBX18 geni





Injection site (fluoroscopy)



Injection site (anatomic)

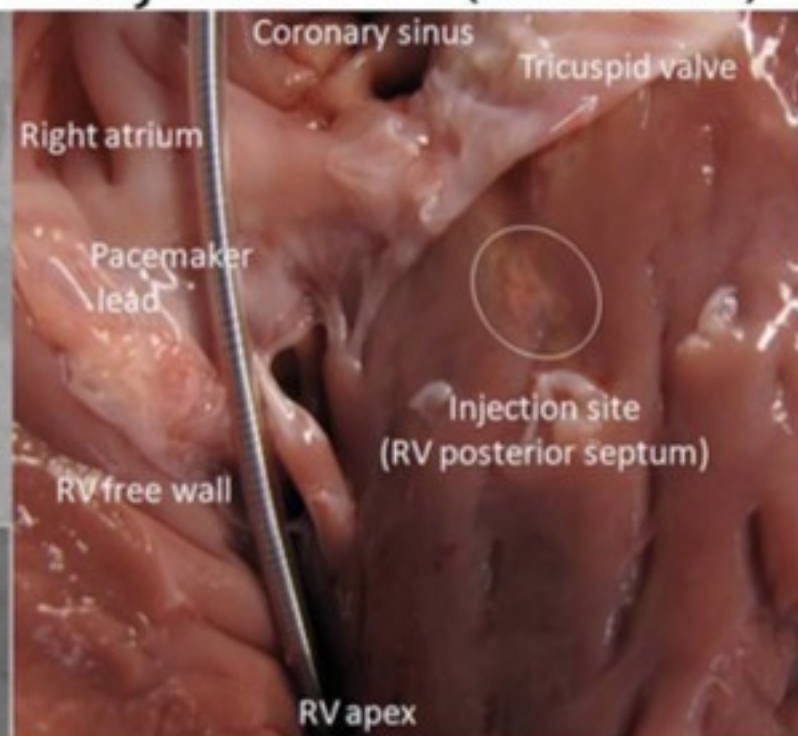
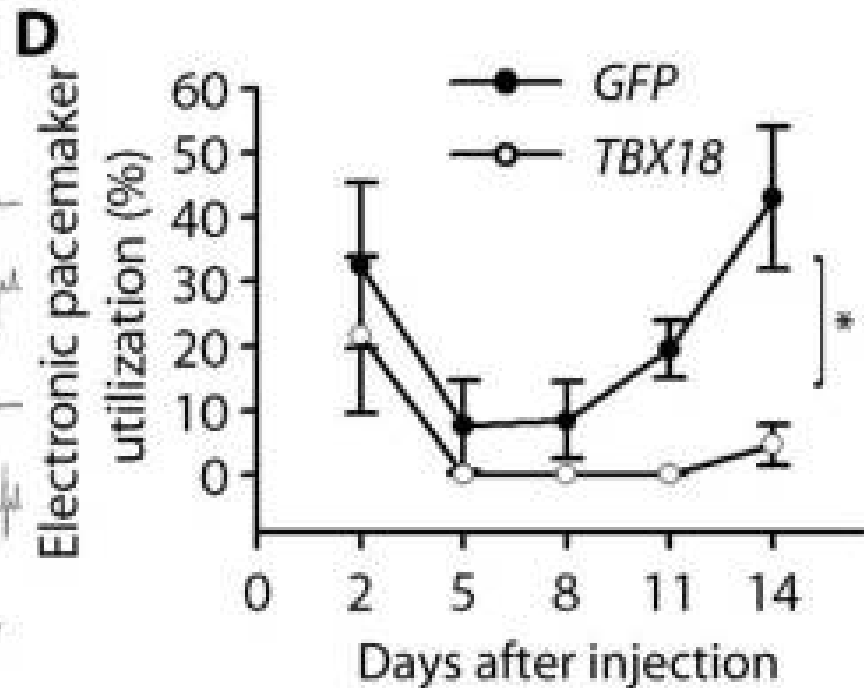
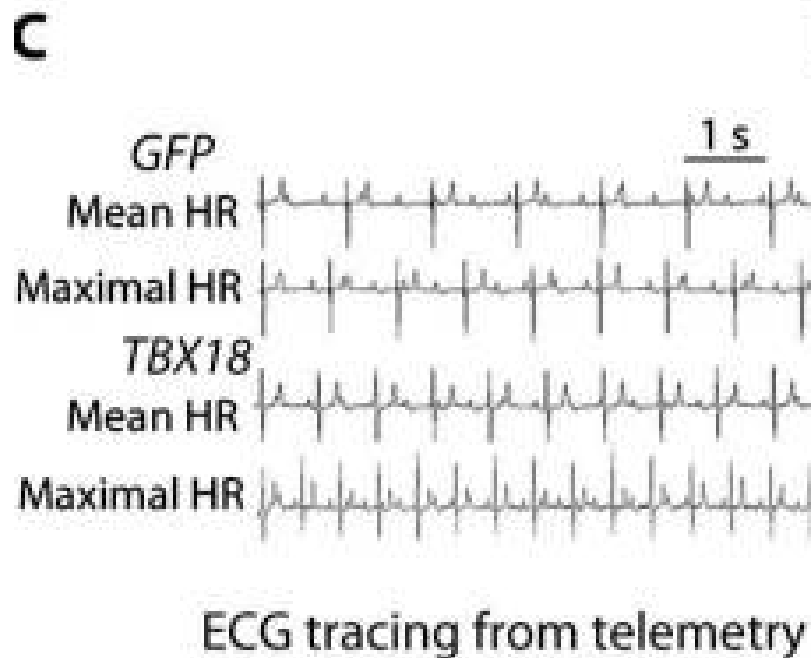
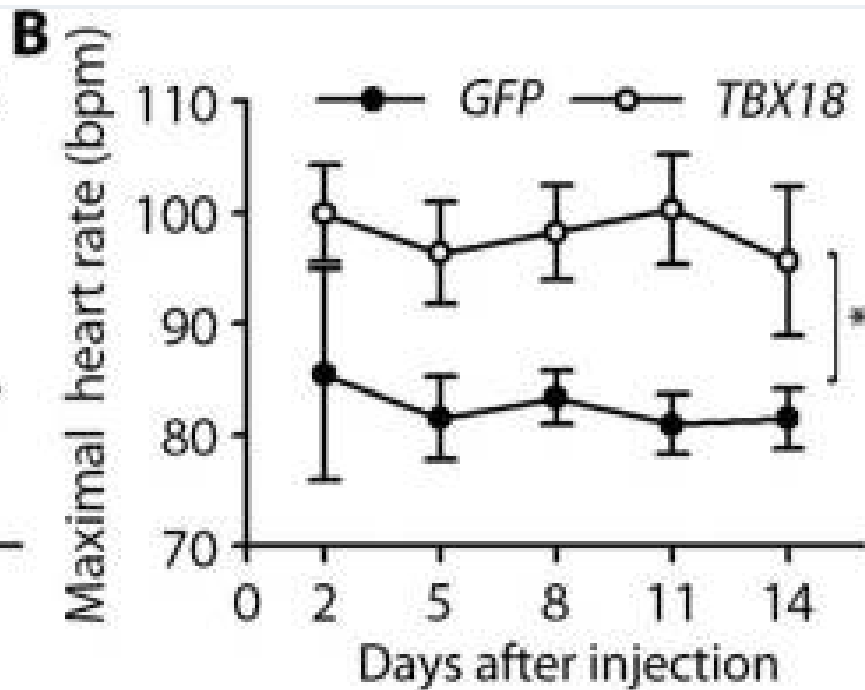
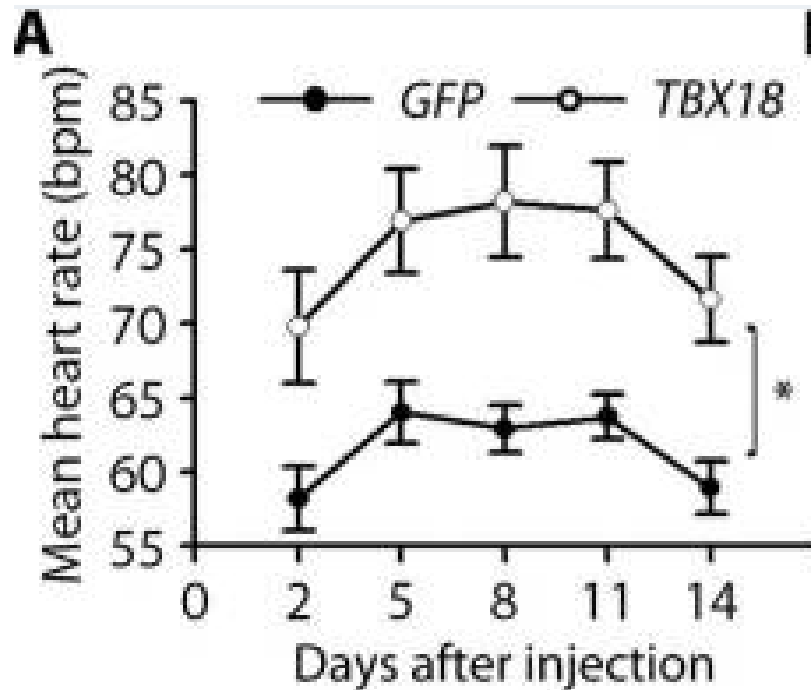
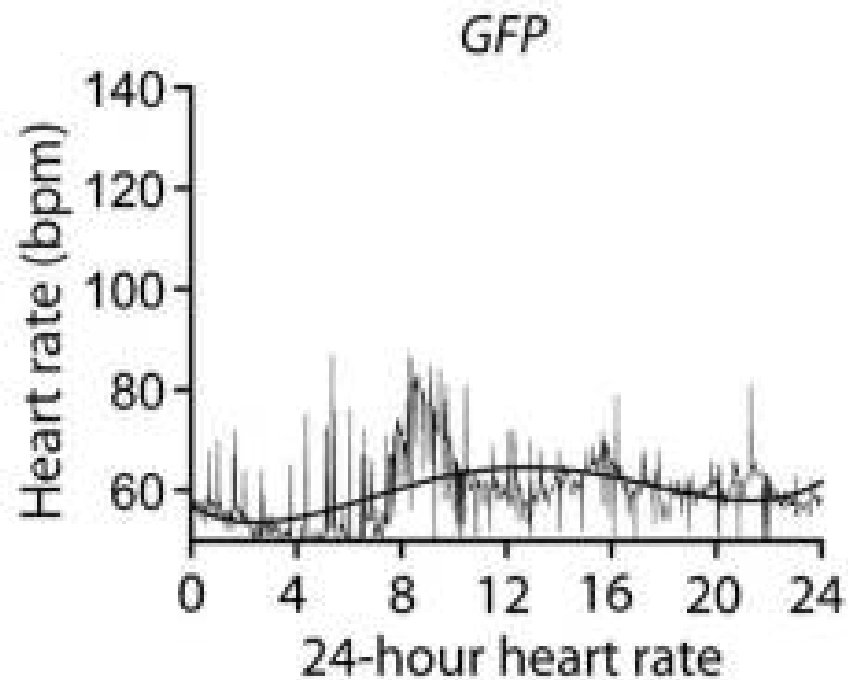
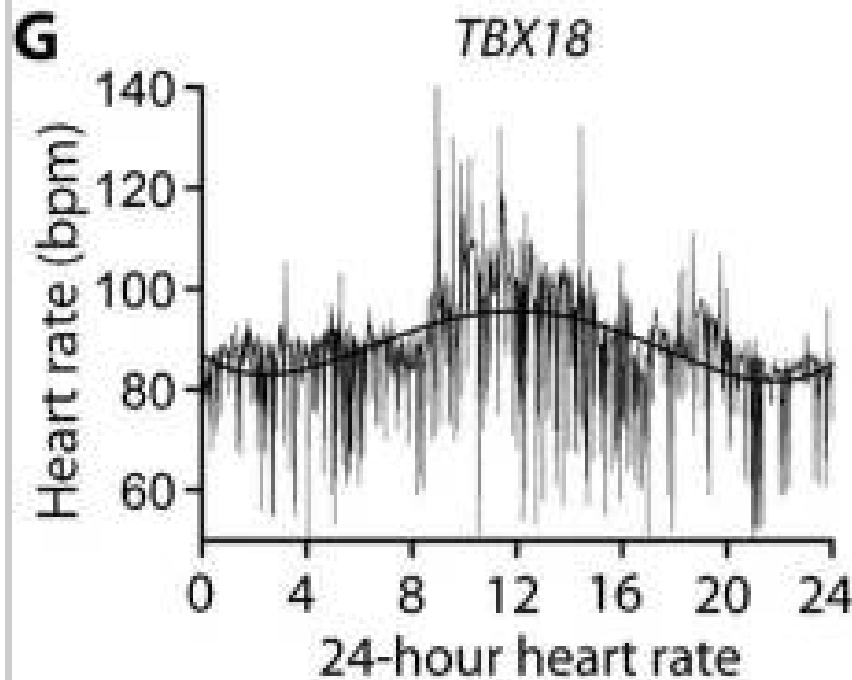
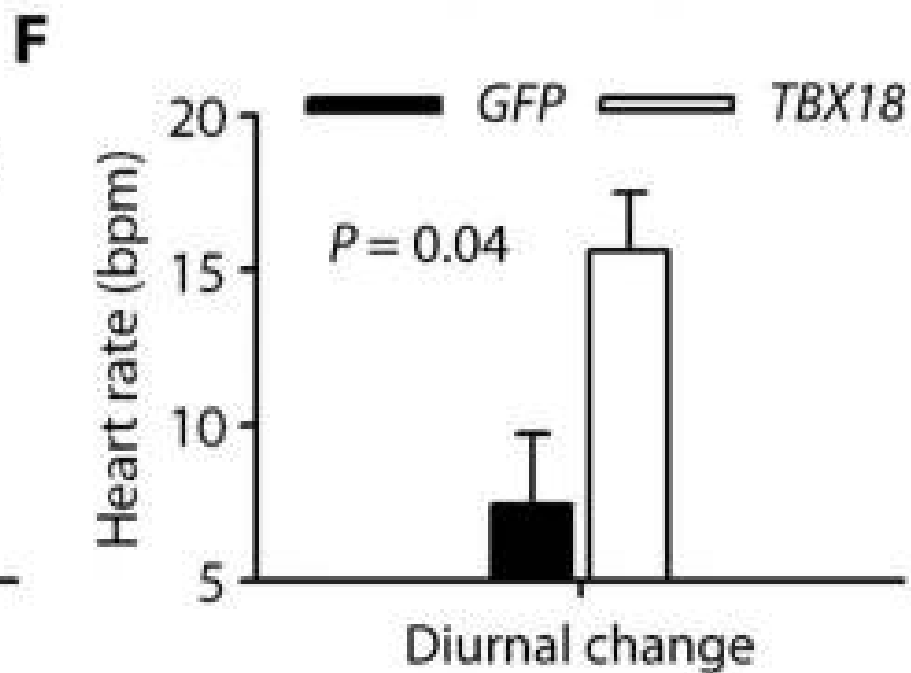
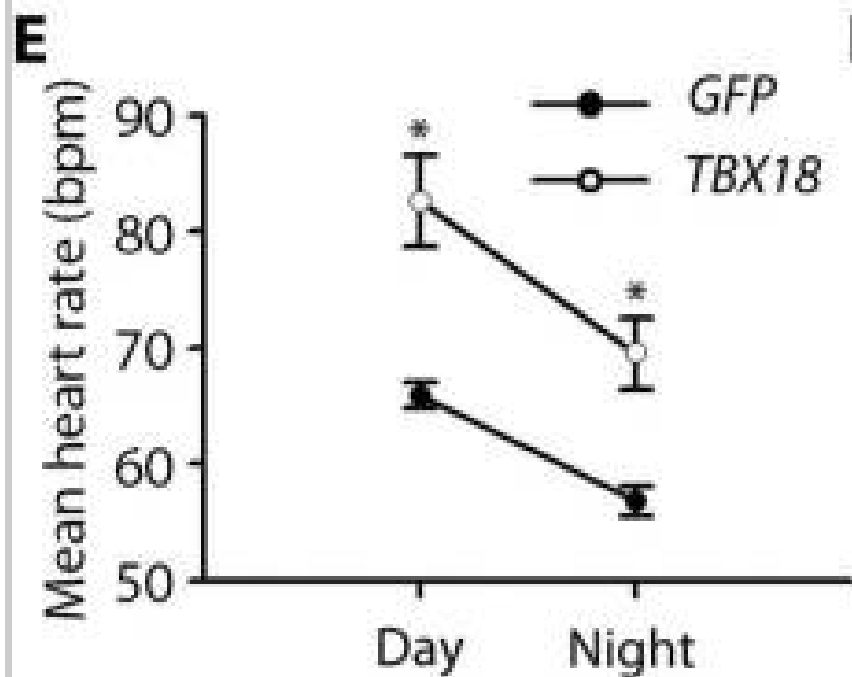
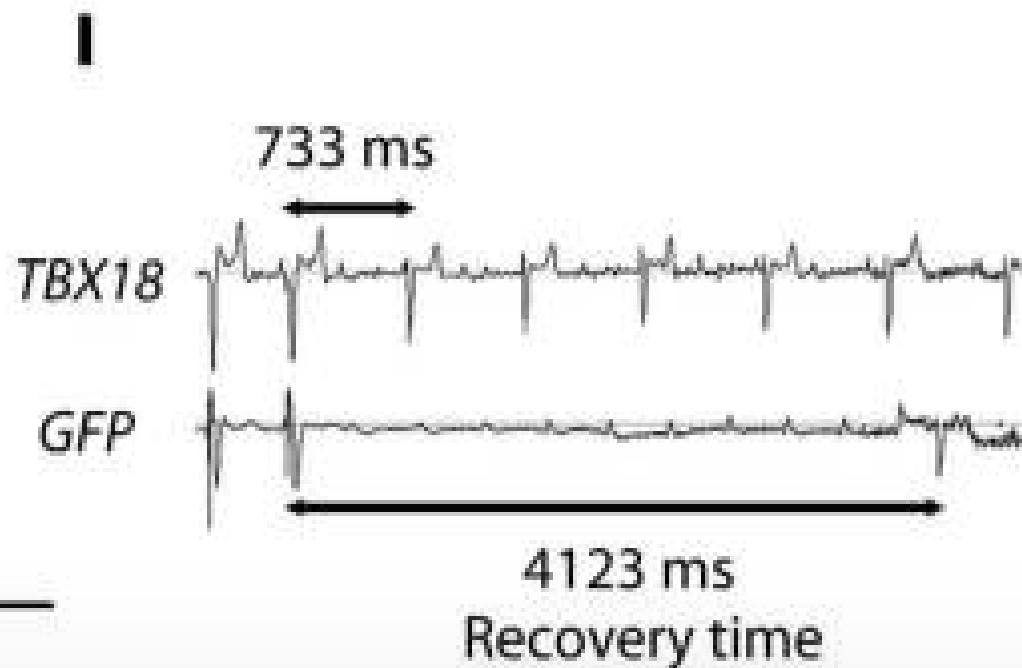
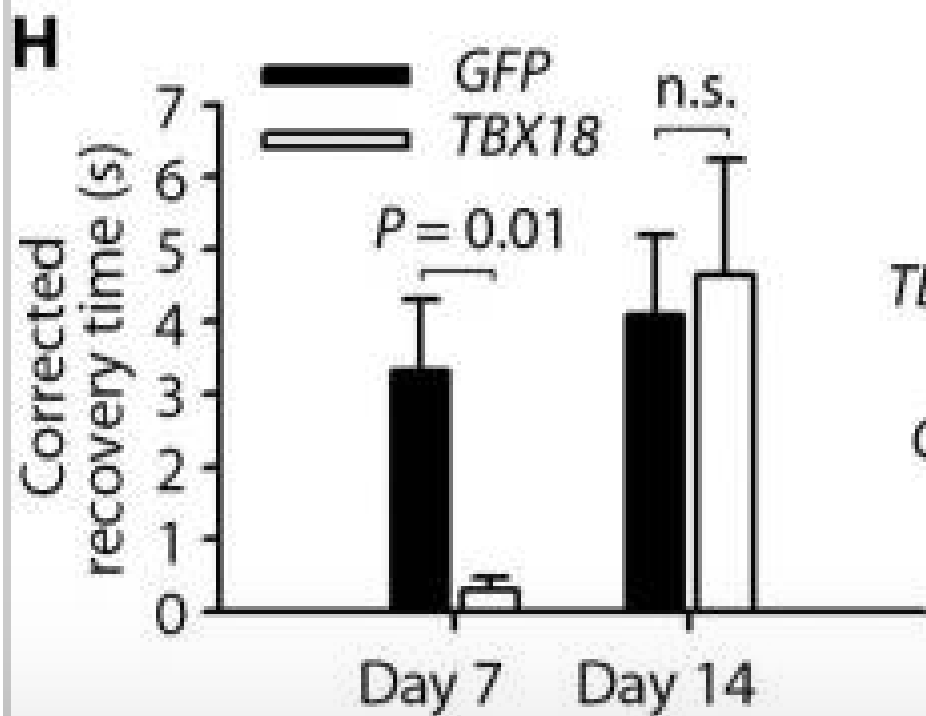
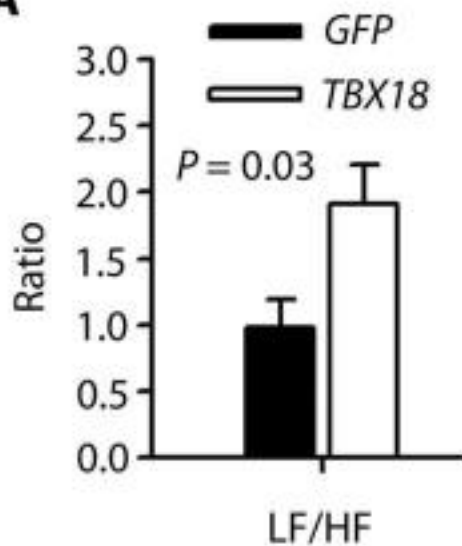
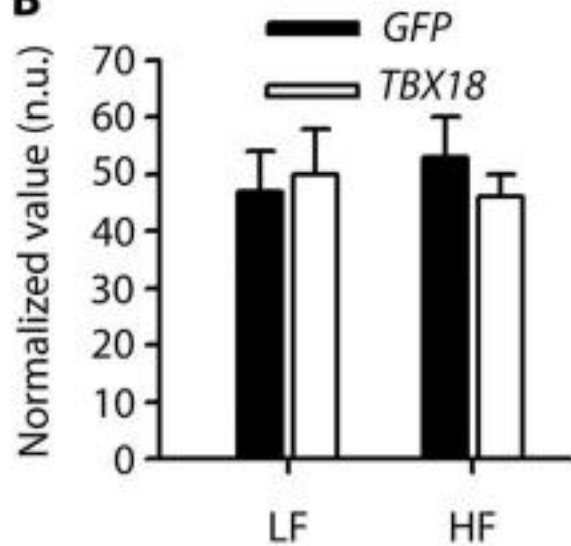
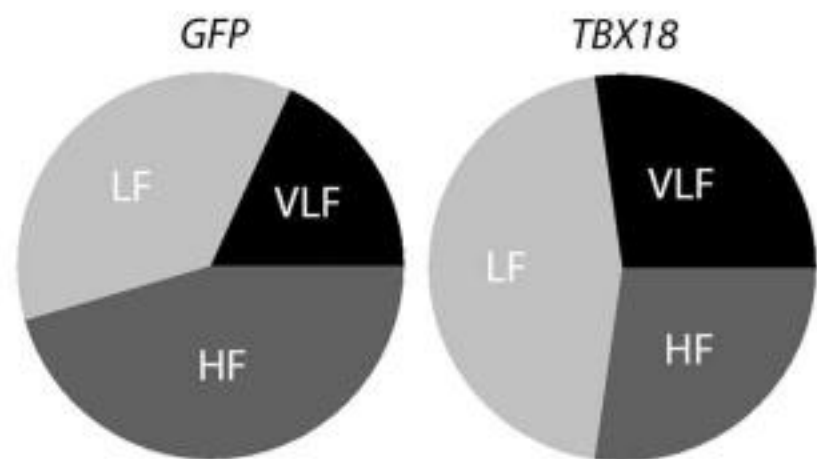
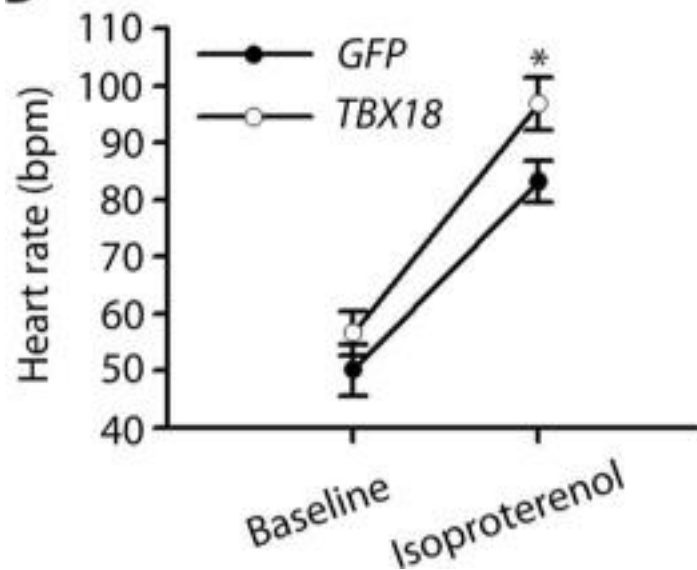
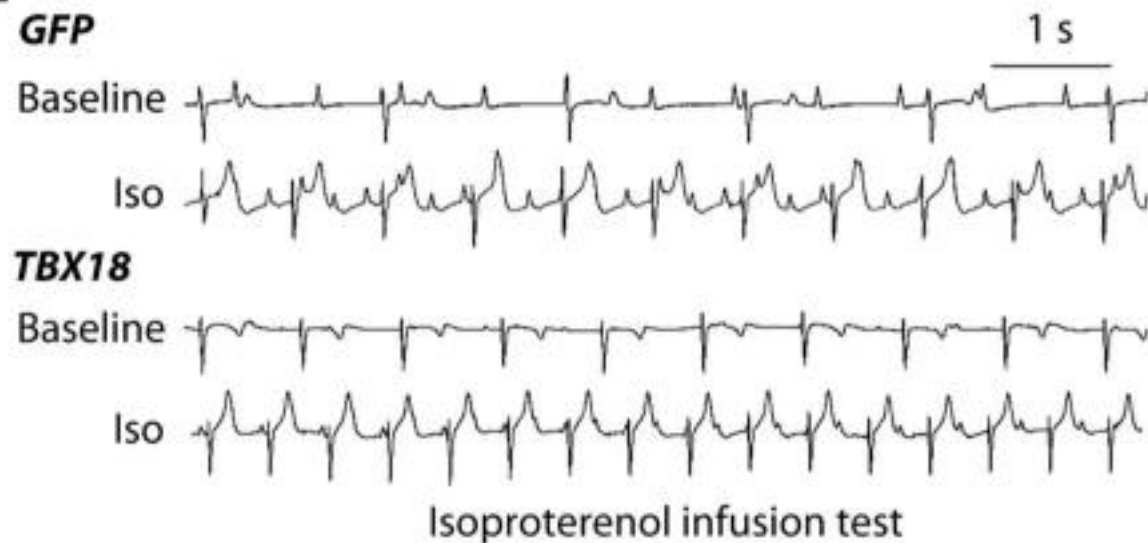


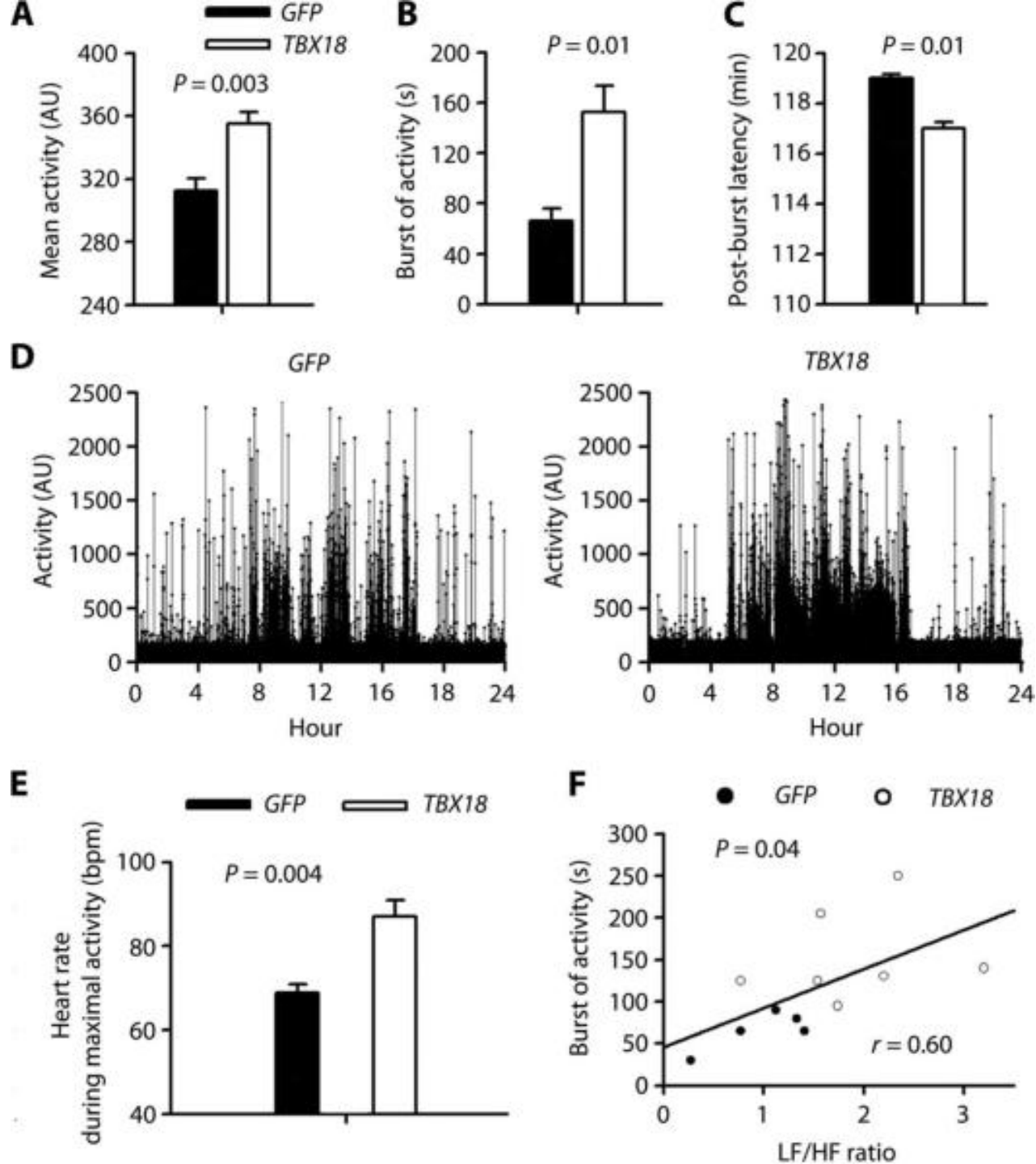
Fig. S5. Injection site images. RAO, right anterior oblique view; RV, right ventricle; RVOT, outflow tract of right ventricle.

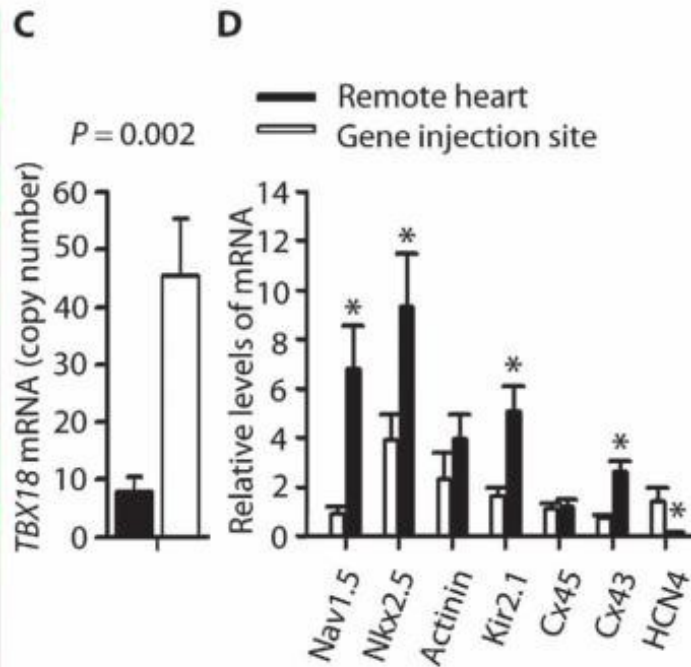
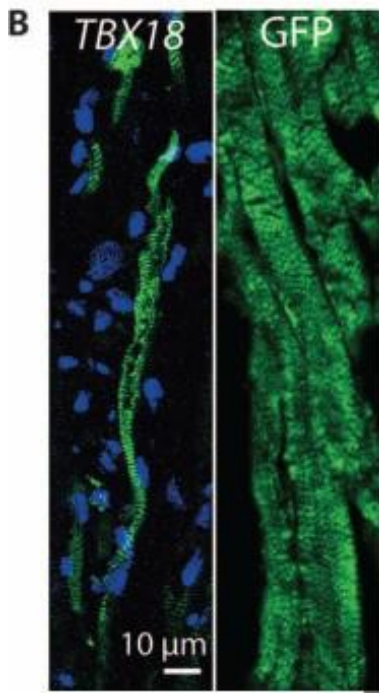
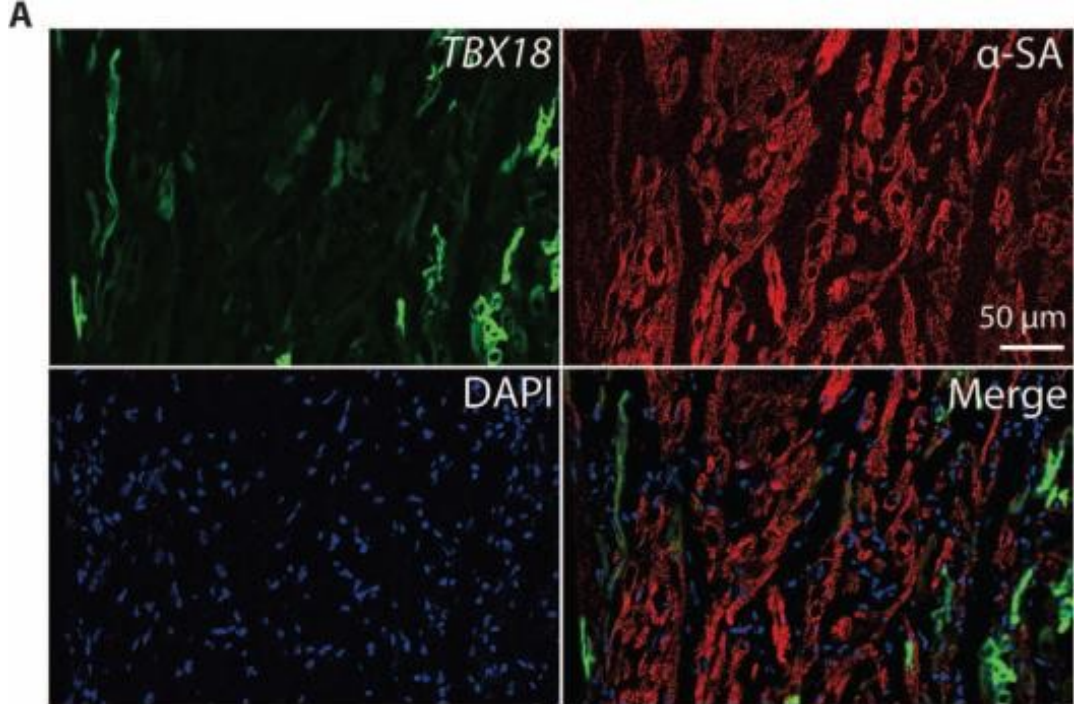


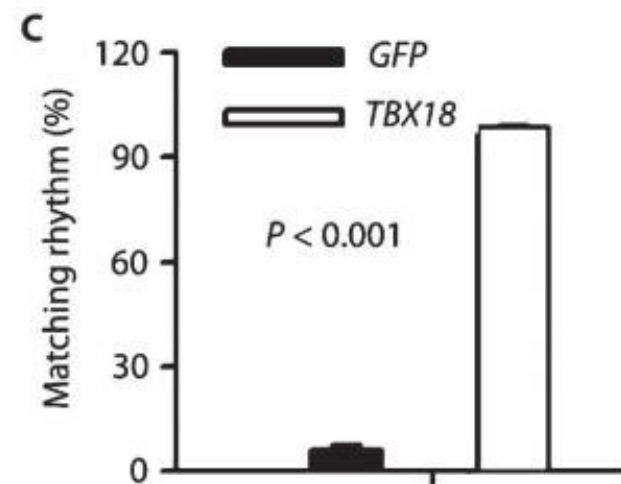
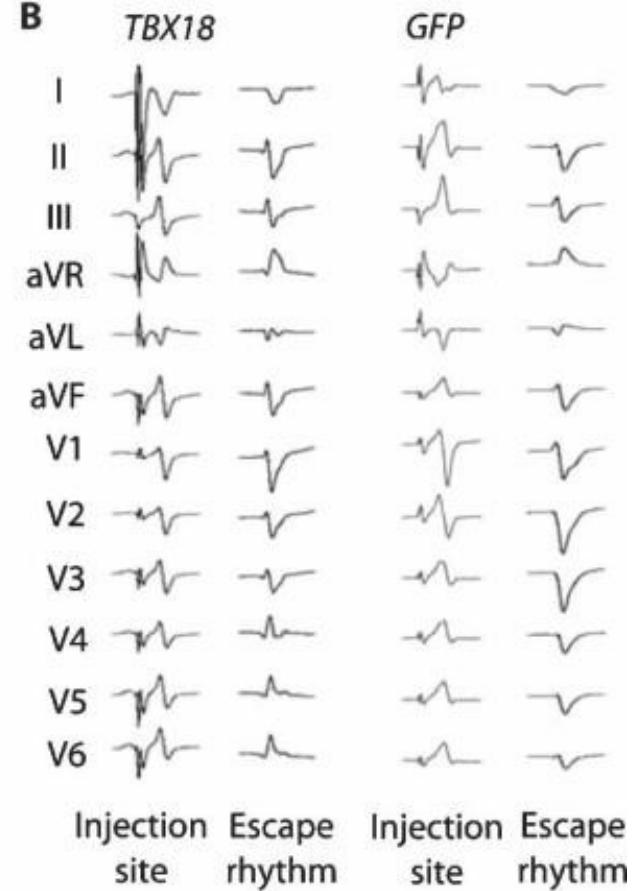
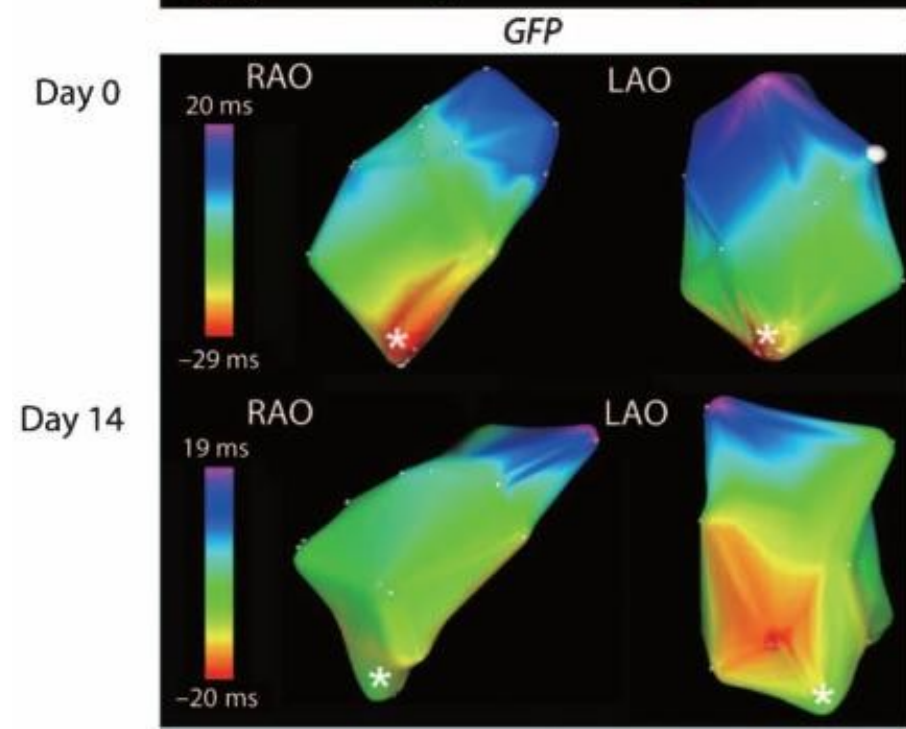
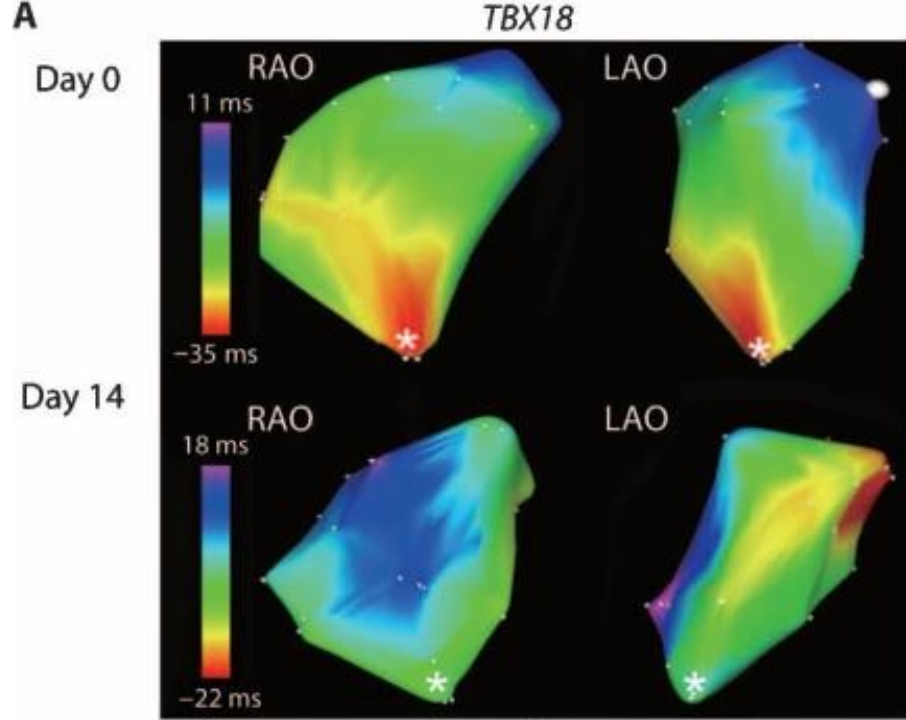




A**B****C****D****E**







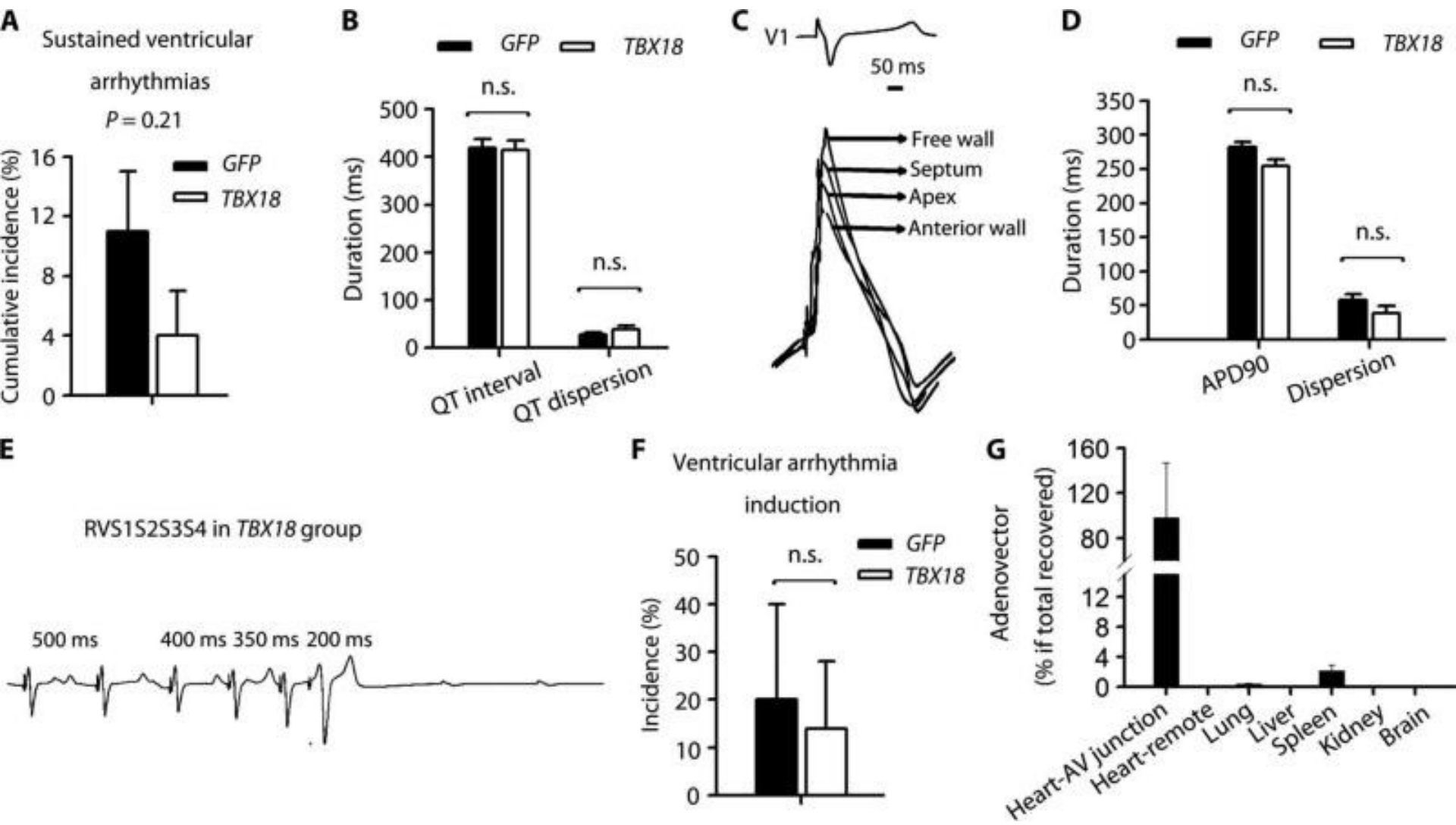


Table 1

Biochemistry profile of *TBX18*- and GFP-transduced animals 2 weeks after gene delivery

	GFP	TBX78	P
Liver function			
AST (IU/liter)	22.0 ± 2.6	23.6 ± 3.4	0.74
ALT (IU/liter)	21.8 ± 2.3	26.3 ± 2.8	0.28
Total bilirubin (mg/dl)	0.12 ± 0.02	0.11 ± 0.01	0.80
Alkaline phosphatase (IU/liter)	98.6 ± 22.1	107.0 ± 12.3	0.73
Renal function			
BUN (mg/dl)	9.6 ± 0.8	9.0 ± 0.4	0.48
Creatinine (mg/dl)	1.34 ± 0.08	1.39 ± 0.05	0.63
Pancreas function			
Amylase (IU/liter)	1304.4 ± 78.4	1112.1 ± 138.7	0.31

Mesajlar

- Biyolojik “pacemaker”
 - Henüz insan çalışması yok
 - Sorunlar
 - Proaritmi
 - Süreklilik ?
 - Tek odacıklı
 - Yeterli uyarı hızı ?