

Introduction:

- Heart failure (HF) currently affects an estimated 6.5 million adults in the United States, of which approximately 50% have HF with preserved ejection fraction (HFpEF).
- Despite normal or near normal left ventricular ejection fraction, HFpEF is associated with increased morbidity and mortality.
- Sudden cardiac death is a major cause of death in patients with HFpEF.
- The complex pathophysiology of HFpEF remains incompletely understood.
- One of the most important findings across many epidemiological HFpEF studies is a distinct sex distribution with female : male ratio of 2:1.
- Also, sex strongly affects outcomes in HFpEF patients with males have higher morbidity and mortality compared to females.

Purpose:

- We examined the hypothesis that QT prolongation accounts for the increased risk of death in males compared to females rats with HFpEF.

Methods:

- Dahl salt-sensitive (DSS) rats of either sex were randomized into high salt (HS, 8% NaCl) or low salt (LS) diet (0.3% NaCl) at 7 weeks of age.
- The animals were monitored, for development of HFpEF, daily.
- After 6 weeks of LS or HS diets, ECG, echocardiogram and blood pressure measurements were performed.
- ECG parameters were analyzed in a blinded fashion.
- Logistic regression analysis was performed to identify independent predictors of mortality.

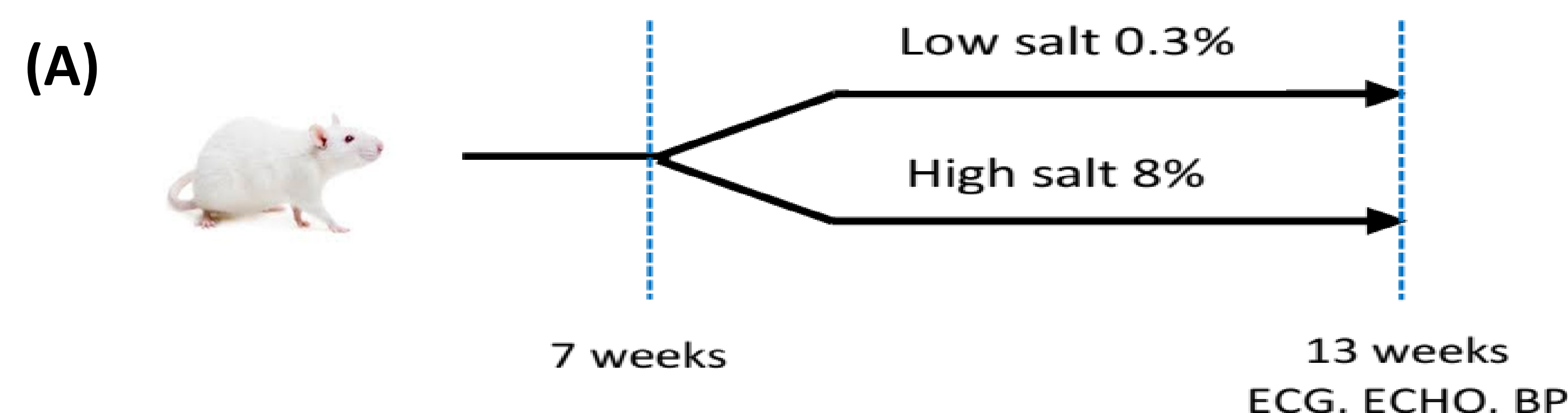


Figure (A). Study protocol

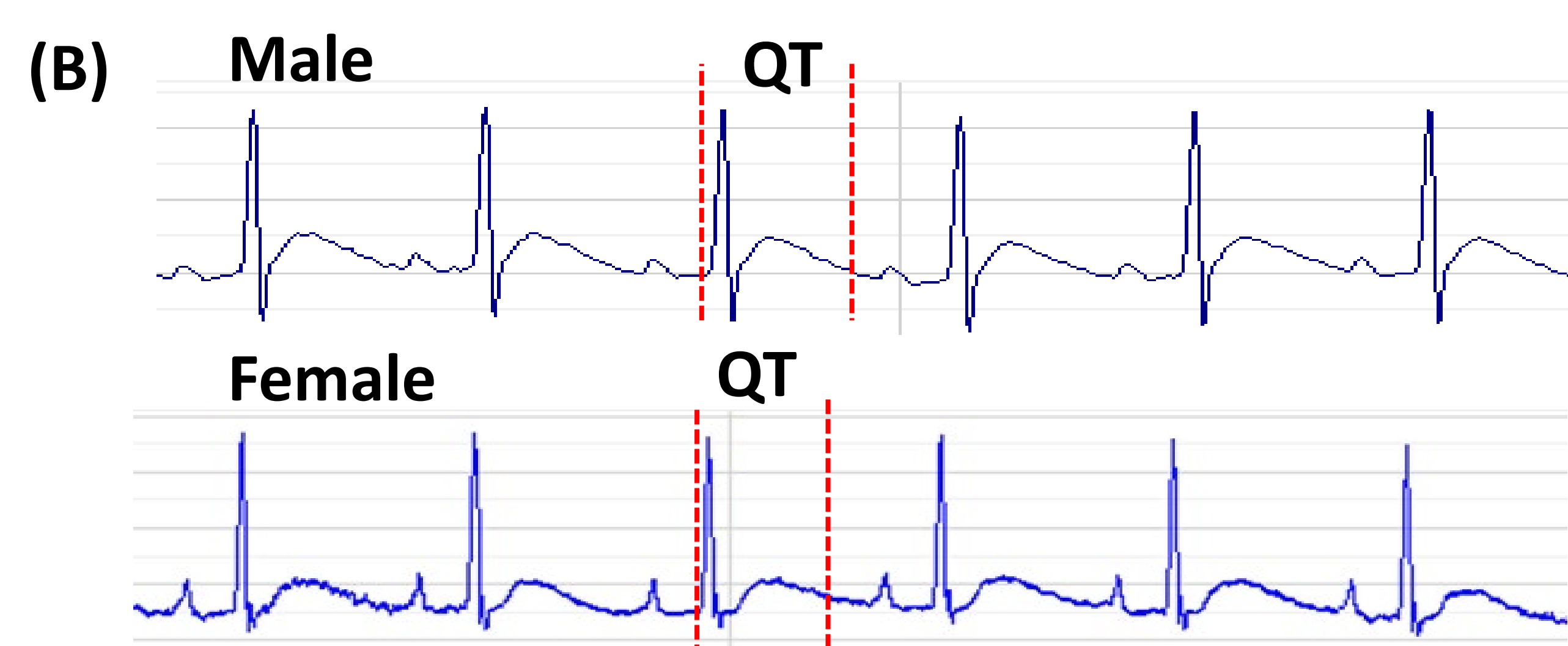


Figure (B). Representative ECGs from a male and a female rat demonstrating appreciable differences in QT interval despite similar heart rate. Corrected QT (QTc) was calculated as QT interval divided by the square root of RR interval.

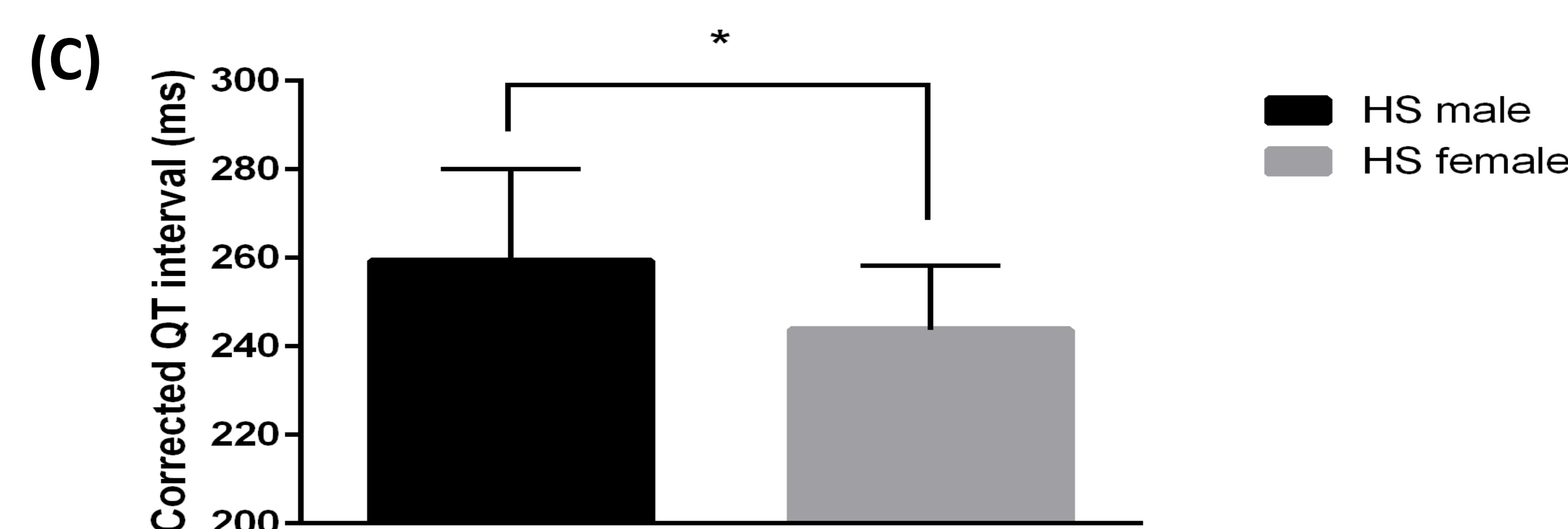


Figure (C). Comparison of corrected QT (QTc) interval between male and female rats at baseline. Male rats had a significantly longer corrected QT interval (*p=0.002).

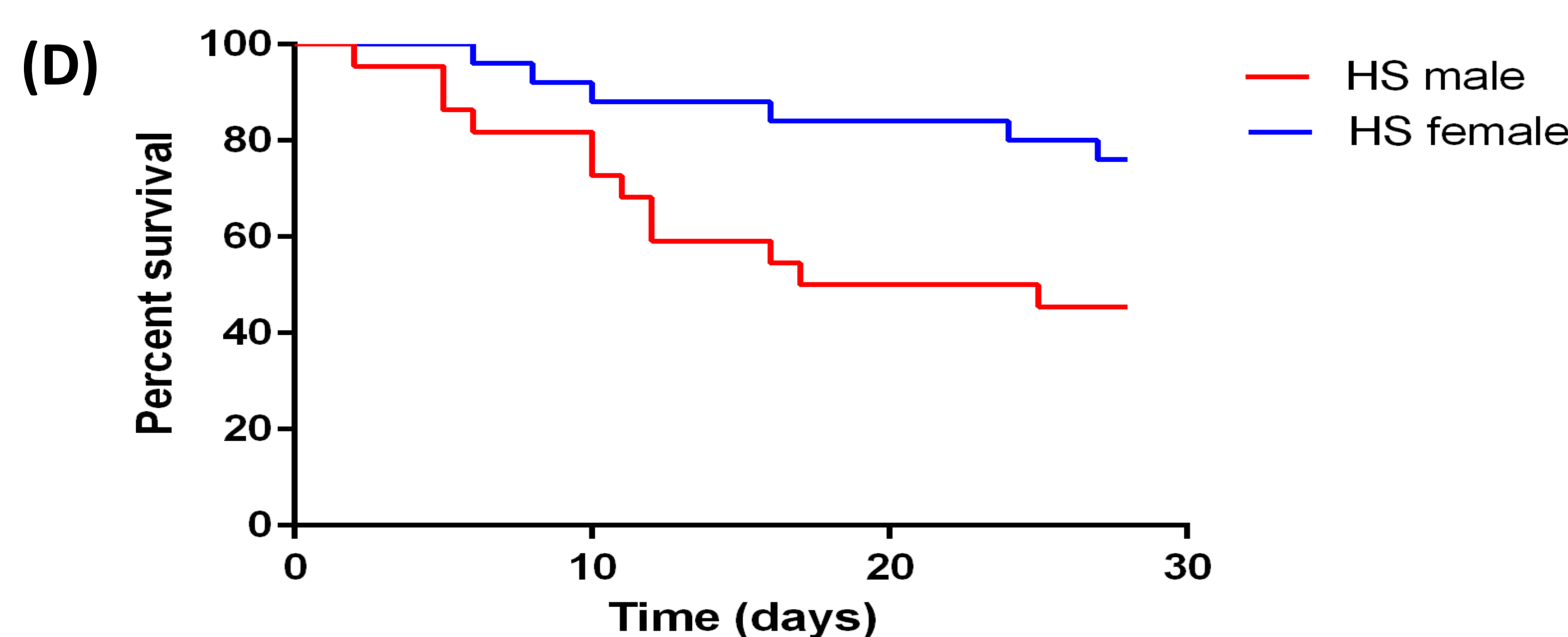


Figure (D). Survival of male rats was significantly less compared to female rats (p=0.004).

Results:

- A total of 81 rats were included (6 LS female, 5 LS male, 34 HS female, 36 HS male). Over 6 weeks of HS diet, rats developed significant hypertension and signs of HFpEF.
- 24% of females and 53% of males died (P=0.011). There were 4 sudden cardiac deaths in males (with ventricular tachycardia documented in 1 rat), whereas all the females died of HF or stroke.
- QTc was significantly prolonged in HS compared to LS rats (267.5±27.4 vs. 235.7±19.9 ms, respectively, p=0.0007), while all other ECG parameters did not differ significantly between groups.
- In HS rats, QTc prolongation was significantly more pronounced in males compared to females (280.4±30.8 vs. 259.1±21.5 ms, respectively, P=0.003).
- QRS and PR durations were significantly prolonged in males vs females (24.5±2.8 vs. 22.6±2.0 ms, p=0.002 and 51.5±2.8 vs. 49.0±4.0 ms, p=0.006, respectively).
- In univariate analysis, prolonged QTc (OR=1.04; 95% CI 1.01 to 1.06, p=0.003) and male sex (OR=3.21, 95% CI 1.19 to 8.66, p=0.016) predicted mortality.
- In multivariate analysis, QTc was the only significant predictor of mortality (OR=1.04; 95% CI 1.01 to 1.06, p=0.003).

Conclusions:

- Male rats with HFpEF exhibit worse survival compared to females and are at higher risk for sudden death**
- QTc prolongation accounts for the increased risk of sudden death in males compared to females**
- Further studies are required to examine the molecular mechanism of this difference**