# SUPPLEMENTAL MATERIALS

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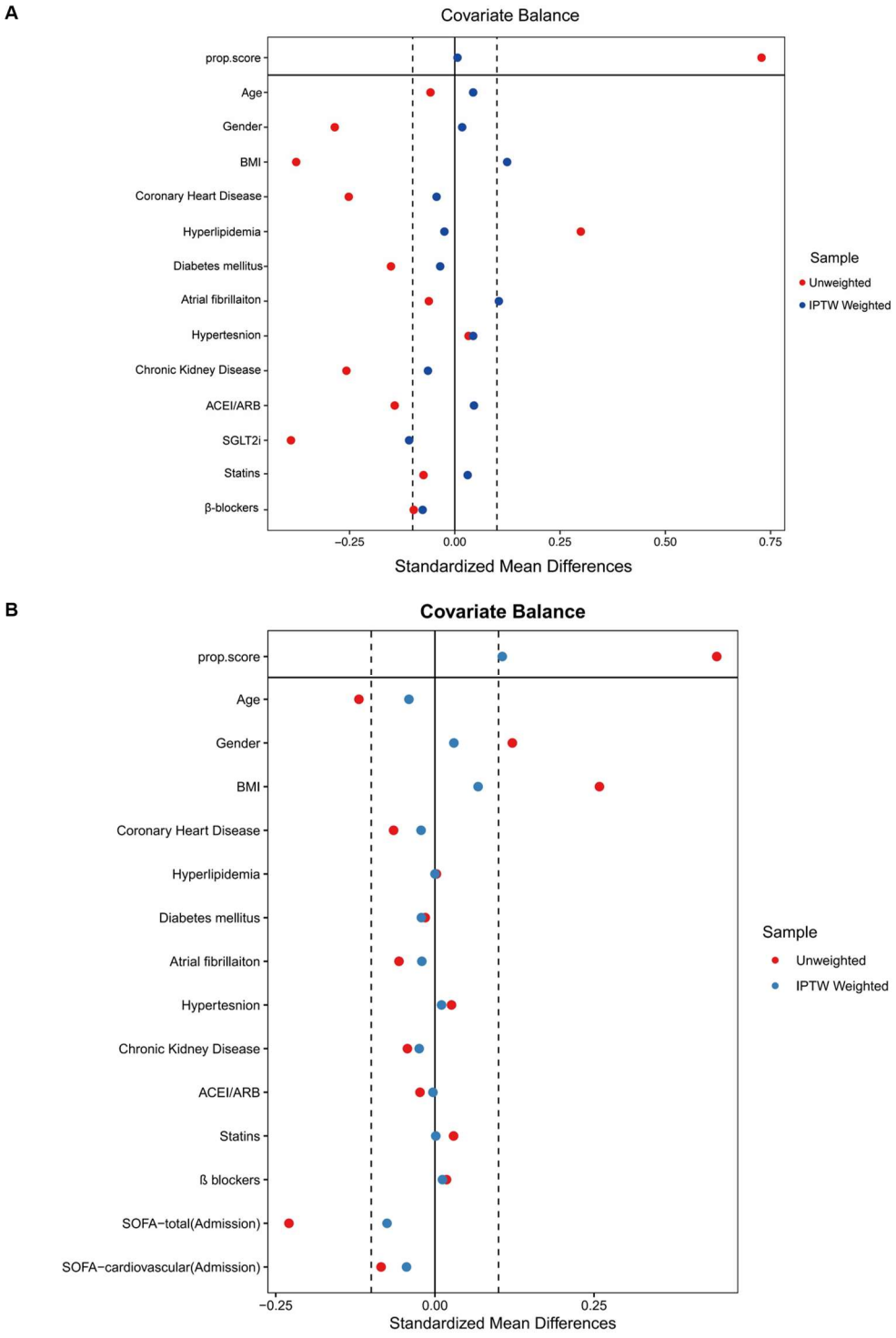



**Figure S1. A,** Standardized Mean differences of covariates before and after weighting in clinical cohort. **B**, Standardized Mean differences of covariates before and after weighting in MIMIC database.

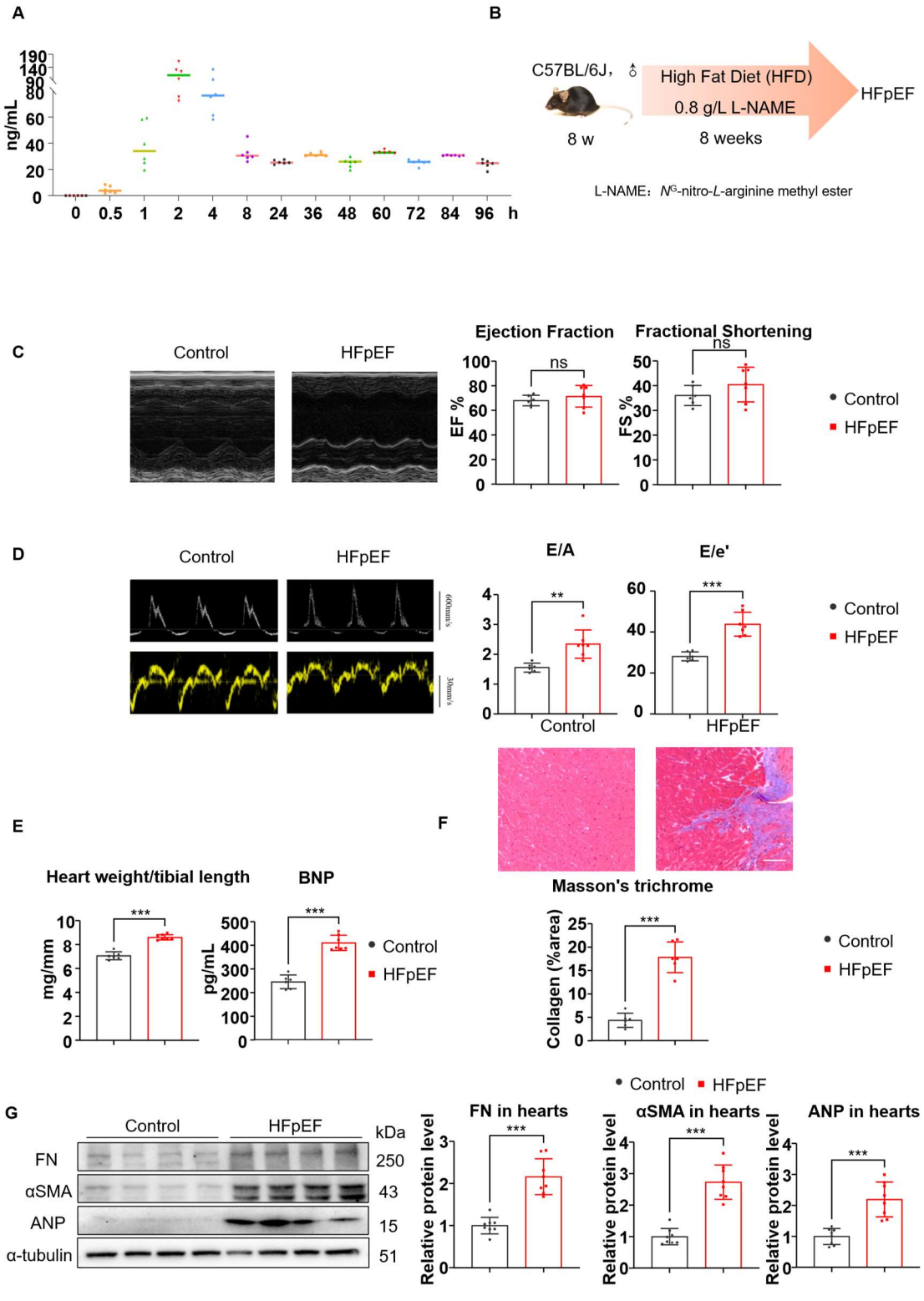



**Figure S2. Establishment and evaluation of the HFpEF mouse model. A**, Mass spectrometry measuring the concentration of fluvoxamine in mouse plasma, n = 6. **B**,

Schematic diagram of the experimental protocol for generating the HFpEF mouse model. **C**, Representative M-mode echocardiography images (showing end-systolic and end-diastolic volumes) and quantitative analysis of ejection fraction (EF) and fractional shortening (FS) in HFpEF and wild-type control (Control) mice. n = 6-7 mice per group. Statistical significance was assessed by unpaired 2-tailed Student t test. **D**, Representative transmitral flow and tissue Doppler echocardiography images, E/A ratio, and E/e′ ratio in HFpEF and Control mice. n = 6-7 mice per group. Statistical significance was assessed by unpaired 2-tailed Student t test. **E**, Heart weight-to-tibia length ratio and Serum BNP levels in HFpEF and Control mice. n = 6-7 mice per group. Statistical significance was assessed by unpaired 2-tailed Student t test. **F**, Representative images of Masson's trichrome staining and the percentage area of Masson's trichrome staining. Scale bar = 100μm. n = 6-7 mice per group. Statistical significance was assessed by unpaired 2-tailed Student t test. **G**, Representative Western blot and quantitative data showing protein levels of fibronectin (FN), alpha-smooth muscle actin (α-SMA), and atrial natriuretic peptide (ANP) in heart tissues. n = 8 mice per group. Statistical significance was assessed by unpaired 2-tailed Student t test.

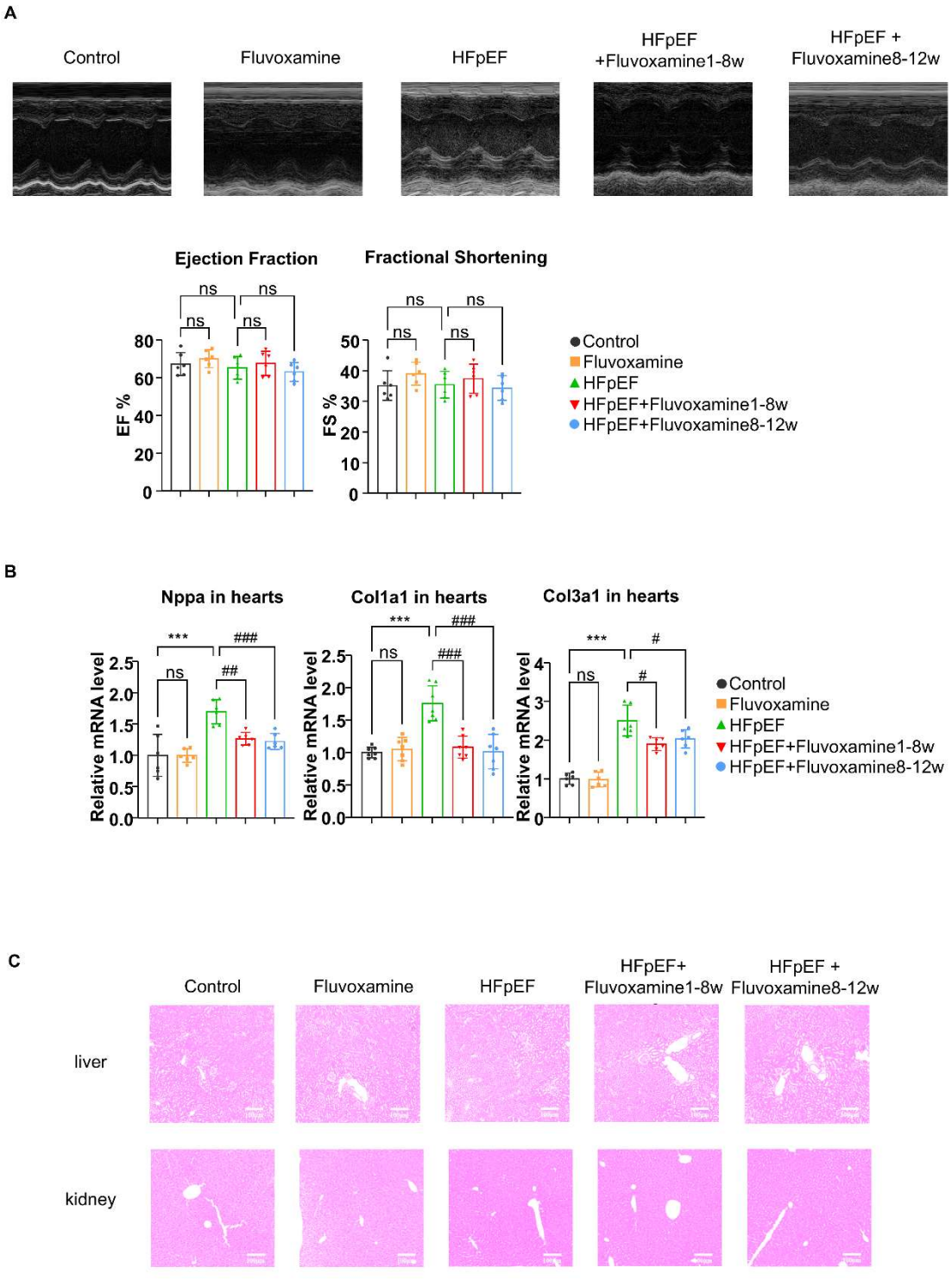



**Figure S3 A**, Representative M-mode echocardiography images (showing end-systolic and end-diastolic volumes) and quantitative analysis of ejection fraction (EF) and

fractional shortening (FS) in HFpEF mice treated with fluvoxamine or DMSO. n = 6 mice per group. Two-way ANOVA with Bonferroni's post-test was used to analyze the effects of treatment group and time. **B**, Quantitative real-time PCR analysis of NPPA, collagen type I, and collagen type III mRNA levels in heart tissues from HFpEF mice treated with fluvoxamine or DMSO. n = 6 mice per group. Two-way ANOVA with Bonferroni's post-test was used to analyze the effects of treatment group and time. **C**, Representative images of hematoxylin and eosin (H&E) staining of liver and kidney tissues. Scale bar = 100μm.

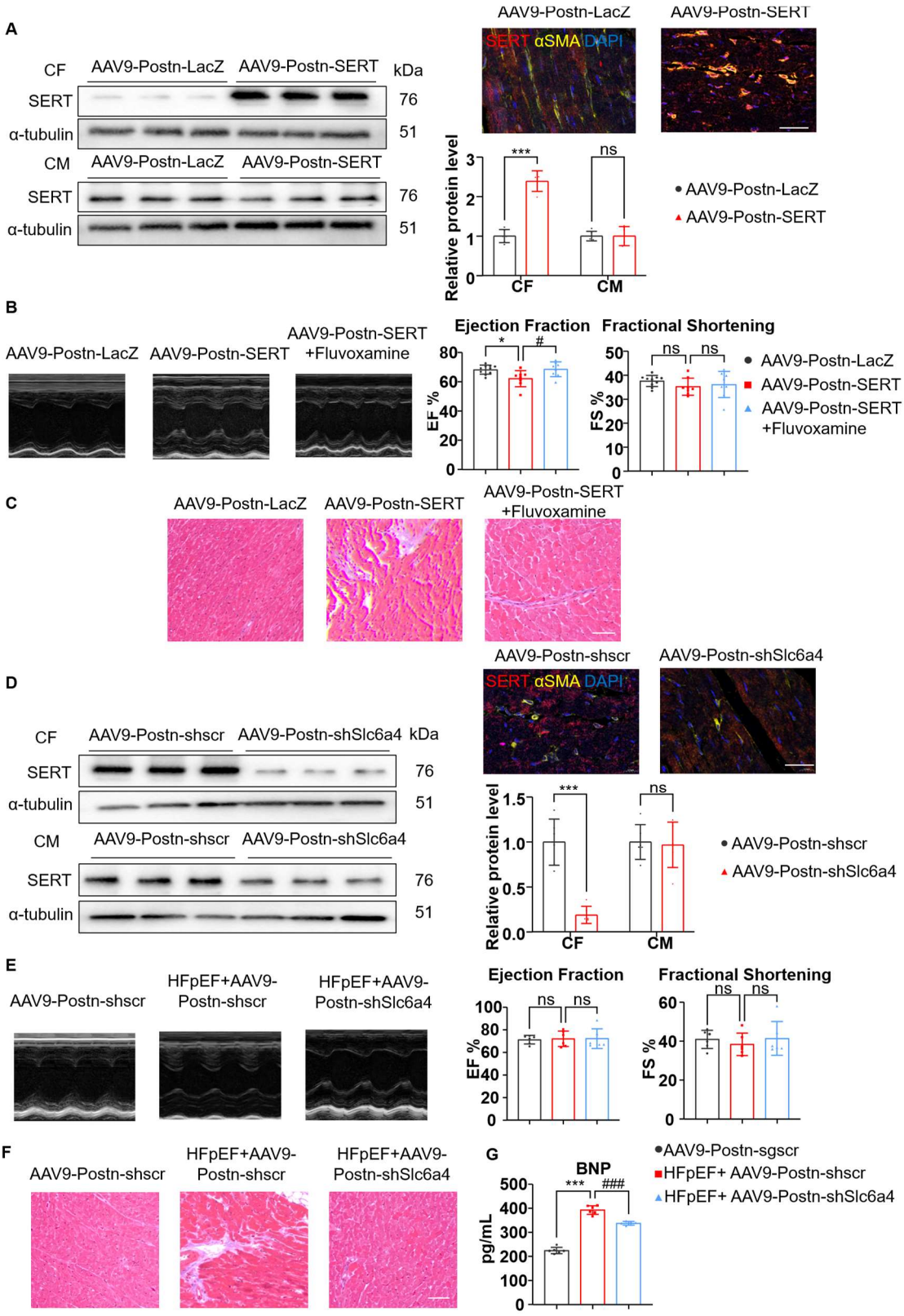



**Figure S4 A**, Representative Western blot and average data showing protein levels of SERT in hearts transfected with AAV9-Postn-SERT or AAV9-Postn-LacZ. n = 6

independent experiments. Statistical significance was assessed by unpaired 2-tailed Student *t* test. Immunofluorescence staining showing SERT in corresponding groups. Scale bar = 25 μm. **B**, Representative M-mode echocardiography images (showing end-systolic and end-diastolic volumes) and quantitative analysis of ejection fraction (EF) and fractional shortening (FS) in mouse hearts using AAV9 driven by the Postn promoter (AAV9-Postn-SERT) or AAV9-Postn-LacZ as control groups. Fluvoxamine is administered intraperitoneally 5mg/kg/d. n = 8-10 mice per group. Statistical significance was assessed by unpaired 2-tailed Student *t* test. **C**, Representative images of Masson's trichrome staining of heart tissues. Scale bar = 100μm. **D**, Representative Western blot and average data showing protein levels of SERT in hearts transfected with AAV9-Postn-shSlc6a4 or AAV9-Postn-scRNA. n = 6 independent experiments. Statistical significance was assessed by unpaired 2-tailed Student *t* test. Immunofluorescence staining showing SERT in corresponding groups. Scale bar = 25 μm. **E**, Representative M-mode echocardiography images (showing end-systolic and end-diastolic volumes) and quantitative analysis of ejection fraction (EF) and fractional shortening (FS) in mouse hearts using AAV9-Postn-shSlc6a4 or AAV9-Postn- scramble shRNA as control groups. n = 6 mice per group. Statistical significance was assessed by unpaired 2-tailed Student *t* test. **F**, Representative images of Masson's trichrome staining of heart tissues. Scale bar = 100μm. **G**, Serum BNP levels in mice using AAV9-Postn-shSlc6a4 or AAV9-Postn-LacZ as control groups. n = 6 mice per group. Statistical significance was assessed by unpaired 2-tailed Student *t* test.

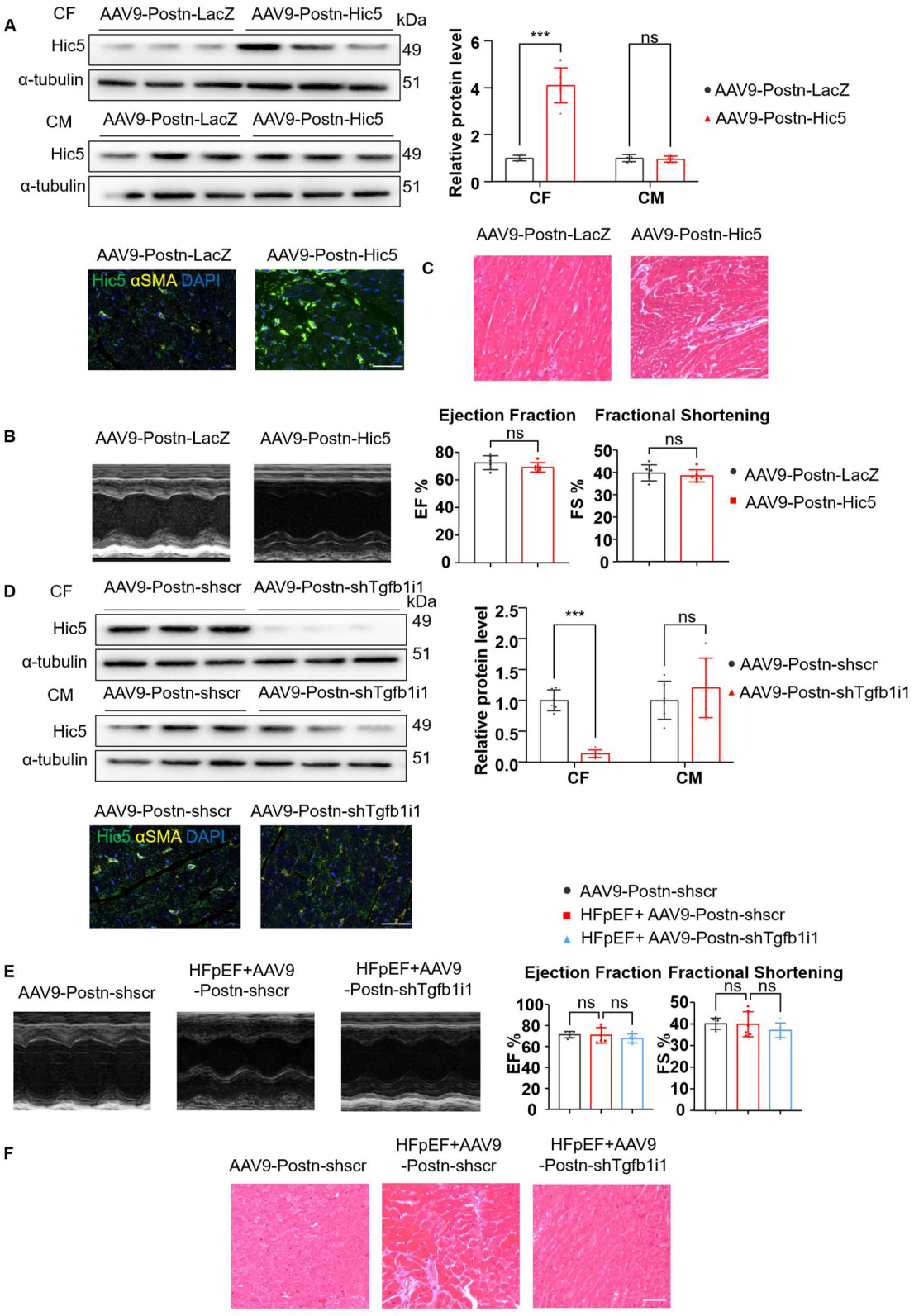



**Figure S5 A**, Representative Western blot and average data showing protein levels of Hic5 in hearts transfected with AAV9-Postn-Hic5 or AAV9-Postn-LacZ. n = 6 independent experiments. Statistical significance was assessed by unpaired 2-tailed Student *t* test. Immunofluorescence staining showing Hic5 in corresponding groups.

Scale bar = 25 μm. **B**, Representative M-mode echocardiography images (showing end-systolic and end-diastolic volumes) and quantitative analysis of ejection fraction (EF) and fractional shortening (FS) in mouse hearts using AAV9 driven by the Postn promoter (AAV9-Postn-Hic5) or AAV9-Postn-LacZ as control groups. Fluvoxamine is administered intraperitoneally 5mg/kg/d. n = 6 independent experiments. Statistical significance was assessed by unpaired 2-tailed Student *t* test. **C**, Representative images of Masson's trichrome staining of heart tissues. Scale bar = 100μm. **D**, Representative Western blot and average data showing protein levels of Hic5 and in hearts transfected with AAV9-Postn-shTgfb1i1 or AAV9-Postn-scRNA. n = 6 independent experiments. Statistical significance was assessed by unpaired 2-tailed Student *t* test. Immunofluorescence staining showing Hic5 in corresponding groups. Scale bar = 25 μm. **E**, Representative M-mode echocardiography images (showing end-systolic and end-diastolic volumes) and quantitative analysis of ejection fraction (EF) and fractional shortening (FS) in mouse hearts using AAV9-Postn-shTgfb1i1 or AAV9-Postn-scramble shRNA as control groups. n = 6 mice per group. Statistical significance was assessed by unpaired 2-tailed Student *t* test. **F**, Representative images of Masson's trichrome staining of heart tissues. Scale bar = 100μm.

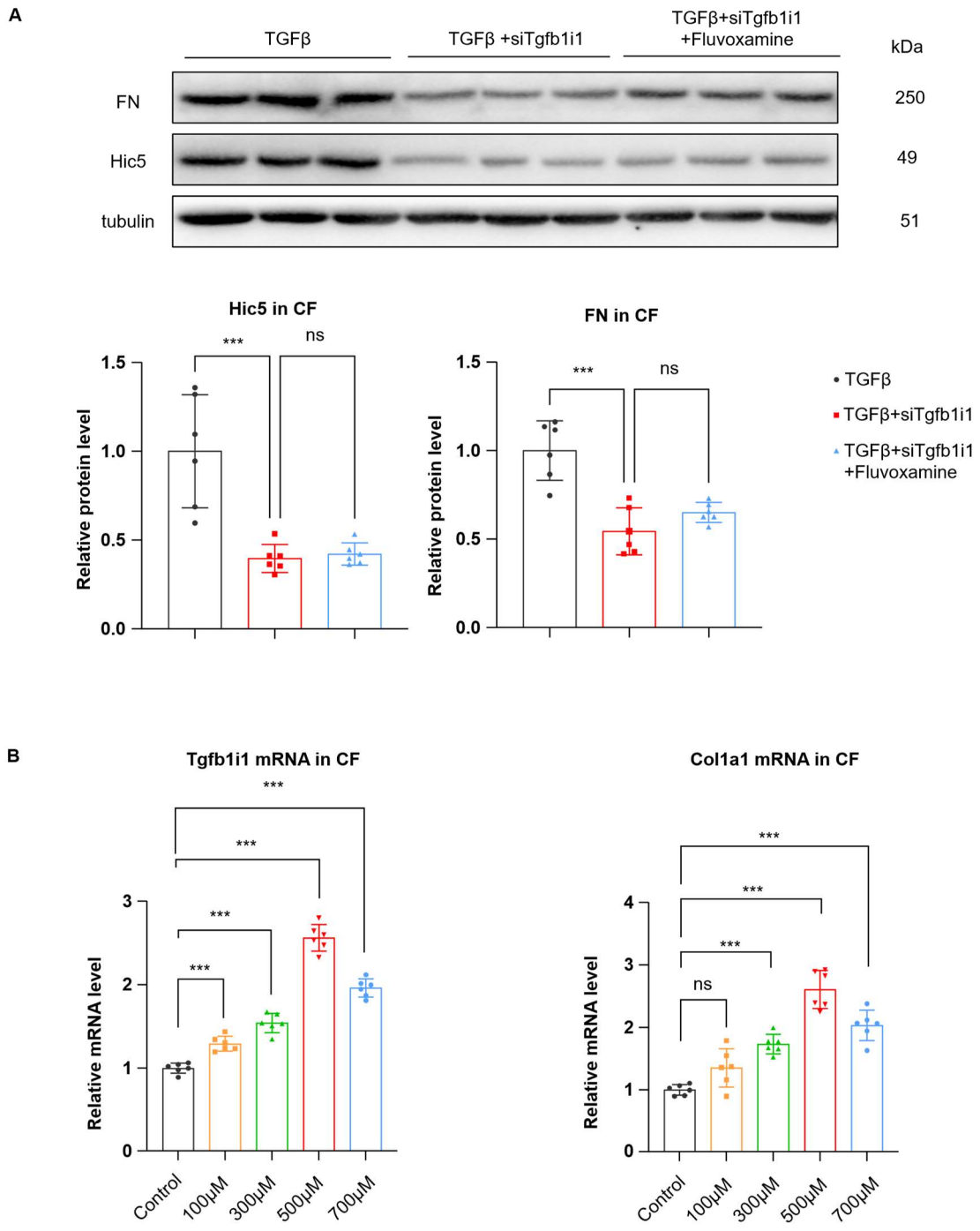



**Figure S6 A**, Representative Western blot and average data showing protein levels of FN and Hic5 in CF treated with TGFβ, siTgfb1i1 or fluvoxamine. n = 6 mice per group.

Statistical significance was assessed by One way ANOVA analysis followed by Bonferroni's post hoc test. **B**, Quantitative real-time PCR analysis of TGFB1I1 and COL1A1 mRNA levels in cardiac fibroblasts treated with hydrogen peroxide. n = 6 independent experiments. Statistical significance was assessed by One way ANOVA analysis followed by Bonferroni's post hoc test.

Table S1. Information of all clinical samples

| **Case Number** | **group Number** | **gender** | **Age/ year** | **diagnose** | **LV EF /%** | **E/A** | **E/e'** | **area%** | **SERT mRNA( qPCR)** | **HIC5 mRNA( qPCR)** |
|---|---|---|---|---|---|---|---|---|---|---|
| **823986** | control1 | M | 69 | Arrhythmia, hepatic steatosis, arteriosclerosis | 60 | 1 | 10 | 15.122 | 1.818228 | 1.413369 |
| **788487** | control2 | F | 53 | grade 3 hypertension | 66 | 0.73 | 9.8 | 11.11 | 0.780534 | 0.894490 |
| **822534** | control3 | M | 62 | Coronary artery disease, hypertrophic cardiomyopathy, grade 3 hypertension, type 2 diabetes mellitus | 60 | 0.44 | 6.67 | 8.59 | 0.401239 | 0.692141 |
| **830744** | HFpEF1 | M | 55 | acute exacerbation of chronic heart failure, type 2 diabetes mellitus, dyslipidemia | 63 | 0.87 | 18.18 | 24.21 | 4.007228 | 2.008063 |
| **829579** | HFpEF2 | F | 85 | Cardiomyopathy, pericardial effusion, coronary artery disease | 60 | 0.8 | 13.33 | 16.755 | 1.776699 | 0.645790 |
| **695566** | HFpEF3 | M | 77 | Unstable angina, coronary artery disease, hyperlipidemia, diabetes mellitus | 63 | 0.625 | 12.5 | 21.334 | 3.050825 | 2.132390 |
| **644668** | HFpEF4 | M | 52 | Hypertrophic obstructive cardiomyopathy, atrial flutter, grade 3 hypertension | 62 | 1 | 28 | 26.56 | 4.415365 | 2.489411 |
| **658394** | HFrEF1 | F | 59 | Hypertrophic cardiomyopathy, coronary artery disease, grade 3 hypertension, dyslipidemia | 33 | 0.5 | 18.52 | 41.97 | 1.604955 | 0.374353 |
| **851978** | HFrEF2 | M | 41 | Hypertrophic cardiomyopathy, dyslipidemia, grade 2 hypertension | 40 | 2 | 14.29 | 36.13 | 1.740135 | 0.671661 |
| **680007** | HFrEF3 | M | 52 | Chronic heart failure with reduced ejection fraction (HFrEF) | 49 | 1.39 | 15.44 | 31.93 | 0.113902 | 0.273410 |
| **840494** | HFrEF4 | F | 72 | Chronic heart failure, coronary artery disease, arrhythmia, orthostatic hypotension | 40 | 2.5 | 28.95 | 47.61 | 3.210652 | 1.084282 |