**Supplemental Table 1.** Baseline characteristics of patients with HFrEF and controls.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **HFrEF**  **(N=148)** | **Control**  **(N=36)** | **p-value** |
| **Clinical characteristics** | | | |
| Age, years | 54 ± 12 | 54 ± 10 | 0.923 |
| Male, n (%) | 127 (84) | 22 (61) | 0.004 |
| Body mass index, kg/m2 | 27.4 ± 4.5 | 28.3 ± 4.8 | 0.282 |
| NYHA class, n (%): I-II; III-IV | 34 (23); 114 (77) | NA | NA |
| Ischemic HF aetiology, n (%) | 65 (44) | NA | NA |
| Diabetes mellitus, n (%) | 50 (33) | 3 (8) | 0.002 |
| Ischemic heart disease, n (%) | 69 (46) | 4 (11) | 0.002 |
| Haemoglobin, mg/L | 137.0 ± 18.3 | 139.1 ± 17.3 | 0.525 |
| BNP, ng/L | 1019 [509; 1824] | 29 [9; 46] | <0.001 |
| **Echocardiography\*** | | | |
| LV end-diastolic diameter, mm | 69.7 ± 8.5 | 46.7 ± 4.1 | <0.001 |
| LV mass index, gr/m2 | 128.5 ± 31.7 | 75.9 ± 14.2 | <0.001 |
| LV ejection fraction, % | 22.0 ± 6.7 | 60.0 ± 5.0 | <0.001 |
| Mitral regurgitation, n (%): 0-2 grade; 3-4 grade | 72 (48); 78 (52) | 36 (100); 0 (0) | <0.001 |
| Tricuspid regurgitation, n (%): 0-2 grade; 3-4 grade | 98 (65); 52 (35) | 34 (97); 1 (3) | <0.001 |
| Right ventricular basal dimensions, mm | 45.0 ± 3.4 | 36.0 ± 4.2 | <0.001 |
| Tricuspid annular plane systolic excursion, mm | 15.2 ± 4.2 | 23.8 ± 4.8 | <0.001 |
| **Electrocardiography** | | | |
| Heart rate, bpm | 80 ± 16 | 68 ± 12 | <0.001 |
| Atrial rhythm, n (%): Sinus; Paced; AFib or AFlu | 128 (85); 3 (2); 19 (13) | 36 (0); 0 (0); 0 (0) | <0.001 |
| QRS morphology, n (%): LBBB; RBBB; normal; other alterations\* | 31 (21); 13 (9); 36 (24); 68 (45) | 1 (3); 2 (5); 30 (83); 3 (8) | <0.001 |
| QRS duration, ms | 120.4 ± 24.8 | 93.2 ± 18.3 | <0.001 |
| **Therapy** | | | |
| Furosemide, n (%) | 143 (97) | 4 (12) | <0.001 |
| ACE, ARB or ARNI, n (%) | 103 (70) | 13 (36) | <0.001 |
| MRA, n (%) | 128 (86) | 4 (11) | <0.001 |
| Betablocker, n (%) | 124 (84) | 9 (25) | <0.001 |
| Devices, n (%): ICD; CRT; none | 111 (75); 12 (8); 25 (17) | NA | NA |

\*Mitral and tricuspid regurgitation were assessed semiquantitatively and reported using a 4-stage grading (i.e., 0) none-trace; 1) mild; 2) moderate; 3) severe).

**Abbreviations:** ACE – Angiotensin Converting Enzyme Inhibitor; AFlu – Atrial Flutter; AFib – Atrial Fibrillation; ARB – Angiotensin Receptor Blocker; ARNI – Angiotensin Receptor Neprilysin Inhibitor; BNP – Brain Natriuretic Peptide; CRT – Cardiac Resynchronization Therapy; HFrEF – Heart Failure with Reduced Ejection Fraction; ICD – Implantable Cardioverter-Defibrillator; LBBB – Left Bundle Branch Block; MRA – Mineralocorticoid Receptor Antagonist; NA – Not Applicable; NYHA – New York Heart Association; RBBB – Right Bundle Branch Block. **\***Other alterations include: left anterior fascicular block, left posterior fascicular block, incomplete LBBB and nonspecific intraventricular conduction delay.

**Supplemental Table 2.** Imaging and hemodynamic datain patients with HFrEF and controls

|  |  |  |  |
| --- | --- | --- | --- |
|  | **HF patients**  **(N=148)** | **Controls**  **(N=36)** | **p-value** |
| **GSPECT** | | | |
| RV phase SD, % | 11.2 ± 4.9 | 7.6 ± 2.5 | <0.001 |
| RV end-diastolic volume – mL | 256.4 ± 97.9 | 204.4 ± 61.1 | <0.001 |
| RV end-diastolic volume index – mL/m2 | 138.0 ± 47.9 | 103.1 ± 24.3 | <0.001 |
| RV end-systolic volume – mL | 165.5 ± 82.1 | 96.5 ± 32.1 | <0.001 |
| RV end-systolic volume index – mL/m2 | 85.8 ± 41.9 | 48.1 ± 14.0 | <0.001 |
| RV ejection fraction - % | 37.7 ± 14.9 | 53.1 ± 5.4 | <0.001 |
| **Right heart catheterization** | | | |
| RA mean pressure - mmHg | 9.6 ± 5.8 | 5.0 ± 2.9 | <0.001 |
| RV systolic elastance (Ees) - mmHg/mL | 0.32 [0.23; 0.49] | 0.32 [0.23; 0.47] | 0.177 |
| RV diastolic compliance - mL/mmHg | 0.03 [0.02; 0.05] | 0.04 [0.03; 0.06] | 0.003 |
| Cardiac output, L/m | 3.8 ± 0.9 | 5.6 ± 1.4 | <0.001 |
| Stroke volume, mL | 48.8 ± 14.7 | 76.9 ± 23.8 | <0.001 |
| PA mean pressure - mmHg | 34.3 ± 10.8 | 16.3 ± 6.5 | <0.001 |
| PA compliance - mL/mmHg | 1.8 [2.3; 2.6] | 4.8 [3.5; 6.5] | <0.001 |
| PA elastance (EaPA) - mmHg/mL | 1.00 [0.73; 1.53] | 0.36 [0.26; 0.44] | <0.001 |
| PA wedge pressure - mmHg | 22.8 ± 8.5 | 8.2 ± 4.2 | <0.001 |
| PVR - WU | 2.9 [1.9; 4.2] | 1.4 [1.0; 2.1] | <0.001 |
| RV ventricular-arterial coupling ratio | 0.29 [0.21; 0.51] | 0.92 [0.61; 1.37] | <0.001 |
| Systolic blood pressure - mmHg | 109.4 ± 16.2 | 128.5 ± 20.9 | <0.001 |
| Diastolic blood pressure - mmHg | 75.0 ± 10.0 | 77.1 ± 9.9 | 0.258 |

**Abbreviations:** GSPECT - Gated Single-Photon Emission Computed Tomography; HFrEF – Heart Failure with Reduced Ejection Fraction; PA – Pulmonary Artery;PVR – Pulmonary Vascular Resistance;RA – Right Atrial; RV – Right Ventricular; SD – Standard deviation; SVR – Systemic Vascular Resistance; WU - Wood Units

**Supplemental Table 3** Effect of afterload reduction (sildenafil) and preload increase (leg rise) on right ventricular dyssynchrony, hemodynamics and cardiac volumes derived from SPECT

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Baseline** | **Afterload reduction (N=15)** | **p-value** | **Baseline** | **Preload modulation**  **(N=135)** | **p-value** |
| RV dyssynchrony, degrees | 44.9 ± 19.2 | 29.6 ± 13.9 | 0.004 | 40.5 ± 17.6 | 37.7 ± 16.4 | 0.080 |
| ***Right heart catheterization*** | | | | | | |
| RA mean pressure, mmHg | 7.9 ± 3.5 | 4.3 ± 2.5 | <0.001 | 9.3 ± 5.7 | 11.7 ± 6.4 | <0.001 |
| RV end-diastolic pressure, mmHg | 12.0 ± 4.3 | 6.3 ± 3.7 | <0.001 | 11.5 ± 6.1 | 14.4 ± 6.0 | <0.001 |
| PA mean pressure, mmHg | 44.0 ± 8.6 | 31.2 ± 9.9 | <0.001 | 33.6 ± 10.4 | 38.5 ± 9.7 | <0.001 |
| PA wedge pressure mean, mmHg | 25.3 ± 5.9 | 19.6 ± 8.7 | 0.005 | 22.3 ± 8.1 | 26.3 ± 7.8 | <0.001 |
| PA elastance, mmHg/mL | 1.7 [1.1; 1.9] | 0.9 [0.6; 1.1] | <0.001 | 1.0 [0.7; 1.5] | 1.2 [0.8; 1.6] | <0.001 |
| RV systolic elastance (Ees) - mmHg/mL | 0.48 [0.29; 0.79] | 0.50 [0.25; 0.90] | 0.889 | 0.31 [0.22; 0.49] | 0.31 [0.22; 0.49] | 0.489 |
| RV ventricular-arterial coupling ratio | 0.43 [0.15; 0.54] | 0.57 [0.34; 0.90] | 0.002 | 0.29 [0.20; 0.51] | 0.28 [0.17; 0.47] | 0.001 |
| Pulmonary vascular resistance - WU | 4.9 [4.3; 6.6] | 2.7 [1.8; 3.8] | <0.001 | 2.8 [1.8; 3.9] | 3.1 [2.1; 4.4] | 0.031 |
| Cardiac output, L/min | 3.7 ± 0.8 | 4.4 ± 0.8 | 0.003 | 3.8 ± 0.9 | 3.7 ± 0.9 | 0.411 |
| ***SPECT-derived data*** | | | | | | |
| RV end-diastolic volume, mL | 256.1 ± 77.7 | 214.3 ± 75.4 | 0.002 | 278.2 ± 98.4 | 289.8 ± 94.1 | 0.001 |
| RV end-systolic volume, mL | 152.7 ± 75.5 | 107.1 ± 66.1 | <0.001 | 173.1 ± 86.9 | 178.9 ± 84.0 | 0.023 |
| RV ejection fraction, % | 43.1 ± 12.6 | 54.1 ± 14.1 | <0.001 | 40.8 ± 14.9 | 41.0 ± 14.0 | 0.867 |

**Abbreviations:** PA – Pulmonary Artery; PVR – Pulmonary Vascular Resistance;RA – Right Atrial; RV – Right Ventricular; WU - Wood Units.

Immagine che contiene schermata, lastra dei raggi X, arte

Descrizione generata automaticamente**Supplemental Figure 1**

**Supplemental Figure 2**

Immagine che contiene diagramma, linea, Disegno tecnico

Descrizione generata automaticamente

**Supplemental Figure 3**

**Immagine che contiene diagramma, schizzo, disegno

Descrizione generata automaticamente**

**Supplemental Figure 4**

Immagine che contiene testo, albero di Natale, diagramma

Descrizione generata automaticamente

**Supplemental Figure 5**

**Immagine che contiene linea, diagramma, Diagramma, schermata

Descrizione generata automaticamente**