|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **SR**  **(n = 67)** | **pAF**  **(n = 38)** | **cAF**  **(n = 60)** | **p-value** |
| Age, years | 70.2 ± 1.1 | 69.3 ± 1.5 | 71.2 ± 1.2 | 0.416 |
| Male gender, n (%) | 49 (73%) | 23 (61%) | 50 (83%) | 0.504 |
| Body mass index, kg/m2 | 27.5 ± 1.2 | 27.3 ± 0.7 | 26.5 ± 0.8 | 0.746 |
| Arterial hypertension, n (%) | 35 (52%) | 14 (37%) | 42 (70%) | 0.083 |
| Diabetes, n (%) | 15 (22%) | 16 (42%) | 19 (32%) | 0.125 |
| Hyperlipidaemia, n (%) | 48 (72%) | **16 (42%)** | 43 (70%) | **0.008** |
| LVEF, % | 58.7 ± 1.4 | 55.2 ± 1.7 | 55.1 ± 1.2 | 0.098 |
| **Indication for surgery** |  |  |  |  |
| CABG, n (%) | 22 (33%) | 13 (34%) | 15 (25%) | 0.493 |
| AVD, n (%) | 8 (12%) | 4 (11%) | 16 (27%) | 0.077 |
| MVD, n (%) | 7 (11%) | 11 (29%) | 13 (22%) | 0.053 |
| CABG+ MVD/AVD, n (%) | 29 (43%) | 10 (26%) | 15 (25%) | 0.074 |
| Others, n (%) | 1 (2%) | 0 (0%) | 1 (1%) | 0.739 |
| **Medication** |  |  |  |  |
| Digitalis, n (%) | 1 (2%) | 2 (5%) | **10 (16%)** | **0.008** |
| Beta-blockers, n (%) | 34 (51%) | **29 (76%)** | **46 (77%)** | **0.010** |
| ACE inhibitors, n (%) | 36 (54%) | 22 (58%) | 28 (47%) | 0.418 |
| AT1 blockers, n (%) | 10 (15%) | 1 (3%) | 6 (10%) | 0.149 |
| Diuretics, n (%) | 10 (15%) | **15 (40%)** | **25 (42%)** | **0.006** |
| Nitrates, n (%) | 6 (9%) | 0 (0%) | 5 (8%) | 0.172 |
| Amiodarone, n (%) | 0 (0%) | 3 (8%) | **7 (12%)** | **0.021** |
| Statins, n (%) | 19 (28%) | 14 (37%) | 19 (31%) | 0.759 |

**Table S1: Clinical characteristics of all the patients included in the study**

Data presented as numbers (%) or as mean ± SEM; Ctl: control-sinus rhythm, pAF: paroxysmal atrial fibrillation, cAF: persistent (chronic) atrial fibrillation, MVD/AVD, mitral/aortic valve disease, LVEF - left ventricular ejection fraction, CABG: coronary artery bypass graft surgery, ACE - angiotensin-converting enzyme; AT – angiotensin.

**Table S2: Clinical characteristics of the patients employed for RT-qPCR experiments**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **SR**  **(n = 16)** | **pAF**  **(n = 8)** | **cAF**  **(n = 8)** | **p-value** |
| Age, years | 69.7 ± 2.1 | 76 ± 4.0 | 76.6 ± 1.8 | 0.053 |
| Male gender, n (%) | 11 (69%) | 6 (75%) | 7 (87%) | 0.378 |
| Body mass index, kg/m2 | 27.6 ± 1 | 29.9 ± 0.7 | 26.4 ± 0.7 | 0.097 |
| Arterial hypertension, n (%) | 2 (12%) | 4 (50%) | 4 (50%) | 0.079 |
| Diabetes, n (%) | 1 (6%) | 0 (0%) | 0 (0%) | 0.607 |
| Hyperlipidaemia, n (%) | 0 (0%) | **8 (100%)** | 2 (25%) | **0.0001** |
| LVEF, % | 62.1 ± 1.3 | 58.1 ± 2.3 | 59.1 ± 2.7 | 0.246 |
| **Indication for surgery** |  |  |  |  |
| CABG, n (%) | 4 (25%) | **6 (75%)** | 1 (12%) | **0.019** |
| AVD, n (%) | 1 (6%) | 0 (0%) | 2 (25%) | 0.201 |
| MVD, n (%) | 0 (0%) | 0 (0%) | 1 (12%) | 0.223 |
| CABG+ MVD/AVD, n (%) | 11 (69%) | 2 (25%) | 4 (50%) | 0.135 |
| **Medication** |  |  |  |  |
| Digitalis, n (%) | 0 (0%) | 1 (12%) | 0 (0%) | 0.223 |
| Beta-blockers, n (%) | 7 (44%) | 4 (50%) | 6 (75%) | 0.356 |
| ACE inhibitors, n (%) | 9 (56%) | 3 (37%) | 2 (25%) | 0.331 |
| AT1 blockers, n (%) | 0 (0%) | 0 (0%) | **2 (25%)** | **0.045** |
| Diuretics, n (%) | 2 (12%) | 3 (37%) | **5 (62%)** | **0.045** |
| Nitrates, n (%) | 0 (0%) | 0 (0%) | 0 (0%) | 0.172 |
| Amiodarone, n (%) | 0 (0%) | 0 (0%) | **2 (25%)** | **0.045** |
| Statins, n (%) | 4 (25%) | 3 (37%) | 2 (25%) | 0.799 |

Data presented as numbers (%) or as mean ± SEM; Ctl: control-sinus rhythm, pAF: paroxysmal atrial fibrillation, cAF: persistent (chronic) atrial fibrillation, MVD/AVD, mitral/aortic valve disease, LVEF - left ventricular ejection fraction, CABG: coronary artery bypass graft surgery, ACE - angiotensin-converting enzyme; AT – angiotensin.

**Table S3: Clinical characteristics of the patients employed to compare control and heart failure in RT-qPCR experiments**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Ctl**  **(n = 8)** | **HF**  **(n = 8)** | **p-value** |
| Age, years | 44 ± 4.7 | 43.6 ± 6.3 | 0.939 |
| Male gender, n (%) | 5 (62%) | 5 (62%) | 0.999 |
| Body mass index, kg/m2 | n.a. | 28.1 ± 1.5 | - |
| Arterial hypertension, n (%) | n.a. | 6 (75%) | - |
| Diabetes, n (%) | n.a. | 2 (25%) | - |
| Hyperlipidaemia, n (%) | n.a. | 3 (37%) | - |
| LVEF, % | n.a. | 27.6 ± 4.3 | - |
| **Indication for surgery** |  |  |  |
| Transplant, n (%) | 0 (0%) | 8 (100%) | - |
| **Medication** |  |  |  |
| Digitalis, n (%) | n.a. | 0 (0%) | - |
| Beta-blockers, n (%) | n.a. | 6 (75%) | - |
| ACE inhibitors, n (%) | n.a. | 3 (37%) | - |
| AT1 blockers, n (%) | n.a. | 1 (12%) | **-** |
| Diuretics, n (%) | n.a. | 7 (87%) | **-** |
| Nitrates, n (%) | n.a. | 0 (0%) | - |
| Amiodarone, n (%) | n.a. | 0 (0%) | **-** |
| Statins, n (%) | n.a. | 1 (12%) | - |

Data presented as numbers (%) or as mean ± SEM; Ctl: control-sinus rhythm, HF: heart failure, MVD/AVD, mitral/aortic valve disease, LVEF - left ventricular ejection fraction, CABG: coronary artery bypass graft surgery, ACE - angiotensin-converting enzyme; AT – angiotensin; n.a. – not available.

**Table S4: Clinical characteristics of the patients employed for western-blotting and co-immunoprecipitation experiments**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **SR**  **(n = 28)** | **pAF**  **(n = 14)** | **cAF**  **(n = 27)** | **p-value** |
| Age, years | 70.6 ± 1.5 | 69 ± 1.6 | 69.8 ± 1.6 | 0.832 |
| Male gender, n (%) | 24 (86%) | 10 (71%) | 18 (67%) | 0.248 |
| Body mass index, kg/m2 | 27.1 ± 1.7 | 27.9 ± 1 | 26.8 ± 1.4 | 0.906 |
| Arterial hypertension, n (%) | 20 (71%) | 7 (50%) | 21 (75%) | 0.184 |
| Diabetes, n (%) | 7 (28%) | 9 (64%) | 9 (33%) | 0.066 |
| Hyperlipidaemia, n (%) | 9 (32%) | 5 (36%) | 6 (22%) | 0.598 |
| LVEF, % | 57.1 ± 2.5 | 52.2 ± 3.8 | 51.5 ± 1.7 | 0.376 |
| **Indication for surgery** |  |  |  |  |
| CABG, n (%) | 11 (39%) | 4 (29%) | 8 (30%) | 0.689 |
| AVD, n (%) | 3 (10%) | 1 (7%) | 6 (22%) | 0.333 |
| MVD, n (%) | 4 (14%) | 4 (29%) | 7 (26%) | 0.459 |
| CABG+ MVD/AVD, n (%) | 9 (32%) | 5 (36%) | 6 (22%) | 0.598 |
| Others, n (%) | 1 (3%) | 0 (0%) | 0 (0%) | 0.331 |
| **Medication** |  |  |  |  |
| Digitalis, n (%) | 1 (3%) | 1 (7%) | 4 (15%) | 0.336 |
| Beta-blockers, n (%) | 16 (57%) | 11 (78%) | 21 (78%) | 0.184 |
| ACE inhibitors, n (%) | 17 (61%) | 9 (64%) | 17 (63%) | 0.972 |
| AT1 blockers, n (%) | 3 (10%) | 1 (7%) | 1 (4%) | 0.609 |
| Diuretics, n (%) | 4 (14%) | 5 (36%) | 6 (22%) | 0.288 |
| Nitrates, n (%) | 4 (14%) | 0 (0%) | 5 (18%) | 0.245 |
| Amiodarone, n (%) | 0 (0%) | 1 (7%) | 2 (7%) | 0.348 |
| Statins, n (%) | 5 (18%) | 6 (43%) | 5 (18%) | 0.152 |

Data presented as numbers (%) or as mean ± SEM; Ctl: control-sinus rhythm, pAF: paroxysmal atrial fibrillation, cAF: persistent (chronic) atrial fibrillation, MVD/AVD, mitral/aortic valve disease, LVEF - left ventricular ejection fraction, CABG: coronary artery bypass graft surgery, ACE - angiotensin-converting enzyme; AT – angiotensin.

**Table S5: Clinical characteristics of the patients employed for immunostaining experiments**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **SR**  **(n = 7)** | **pAF**  **(n = 5)** | **cAF**  **(n = 7)** | **p-value** |
| Age, years | 72.1 ± 6.2 | 72.4 ± 4.9 | 68.9 ± 6.9 | 0.574 |
| Male gender, n (%) | 4 (57%) | 5 (100%) | 7 (100%) | 0.083 |
| Body mass index, kg/m2 | 27.7 ± 1.1 | 27.5 ± 0.9 | 27.3 ± 0.8 | 0.954 |
| Arterial hypertension, n (%) | 2 (29%) | 1 (20%) | 4 (57%) | 0.499 |
| Diabetes, n (%) | 2 (29%) | 3 (60%) | 4 (57%) | 0.602 |
| Hyperlipidaemia, n (%) | 1 (14%) | 1 (20%) | 3 (43%) | 0.558 |
| LVEF, % | 59.7 ± 2.7 | 57.5 ± 2.5 | 62.6 ± 4.4 | 0.891 |
| **Indication for surgery** |  |  |  |  |
| CABG, n (%) | 0 (0%) | 1 (20%) | 0 (0%) | 0.263 |
| AVD, n (%) | 2 (29%) | 0 (0%) | 2 (29%) | 0.494 |
| MVD, n (%) | 2 (29%) | 2 (40%) | 3 (43%) | 0.999 |
| CABG+ MVD/AVD, n (%) | 3 (43%) | 2 (40%) | 2 (29%) | 0.999 |
| **Medication** |  |  |  |  |
| Digitalis, n (%) | 0 (0%) | 0 (0%) | 2 (29%) | 0.304 |
| Beta-blockers, n (%) | 3 (43%) | 5 (100%) | 4 (57%) | 0.206 |
| ACE inhibitors, n (%) | 0 (0%) | **4 (80%)** | 4 (57%) | **0.022** |
| AT1 blockers, n (%) | 2 (29%) | 0 (0%) | 1 (14%) | 0.747 |
| Diuretics, n (%) | 2 (29%) | 3 (60%) | **7 (100%)** | **0.021** |
| Nitrates, n (%) | 0 (0%) | 0 (0%) | 0 (0%) | - |
| Amiodarone, n (%) | 0 (0%) | 0 (0%) | 0 (0%) | - |
| Statins, n (%) | 3 (43%) | 2 (40%) | 5 (71%) | 0.602 |

Data presented as numbers (%) or as mean ± SEM; Ctl: control-sinus rhythm, pAF: paroxysmal atrial fibrillation, cAF: persistent (chronic) atrial fibrillation, MVD/AVD, mitral/aortic valve disease, LVEF - left ventricular ejection fraction, CABG: coronary artery bypass graft surgery, ACE - angiotensin-converting enzyme; AT – angiotensin.

**Table S6: Clinical characteristics of the patients employed for FRET experiments to measure cAMP in living myocytes**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **SR**  **(n = 6)** | **pAF**  **(n = 6)** | **cAF**  **(n = 6)** | **p-value** |
| Age, years | 65.7 ± 2.5 | 63.5 ± 2.6 | 71.3 ± 3.9 | 0.504 |
| Male gender, n (%) | 3 (50%) | 6 (100%) | 6 (100%) | 0.074 |
| Body mass index, kg/m2 | 27.4 ± 0.9 | 27.3 ± 0.7 | 26.8 ± 0.7 | 0.843 |
| Arterial hypertension, n (%) | 5 (83%) | 1 (16%) | 5 (83%) | 0.999 |
| Diabetes, n (%) | 0 (0%) | 2 (33%) | 2 (33%) | 0.735 |
| Hyperlipidaemia, n (%) | 1 (16%) | 1 (16%) | 3 (50%) | 0.473 |
| LVEF, % | 55.3 ± 3.2 | 55.3 ± 2.1 | 54.2 ± 2.9 | 0.554 |
| **Indication for surgery** |  |  |  |  |
| CABG, n (%) | 4 (66%) | 2 (33%) | 2 (33%) | 0.349 |
| AVD, n (%) | 1 (16%) | 2 (33%) | 2 (33%) | 0.999 |
| MVD, n (%) | 0 (0%) | 2 (33%) | 0 (0%) | 0.294 |
| CABG+ MVD/AVD, n (%) | 1 (16%) | 1 (16%) | 1 (16%) | 0.999 |
| Others, n (%) | 0 (0%) | 0 (0%) | 1 (16%) | 0.999 |
| **Medication** |  |  |  |  |
| Digitalis, n (%) | 0 (0%) | 0 (0%) | 1 (16%) | 0.999 |
| Beta-blockers, n (%) | 4 (66%) | 5 (83%) | 5 (83%) | 0.999 |
| ACE inhibitors, n (%) | 5 (83%) | 3 (50%) | 3 (50%) | 0.818 |
| AT1 blockers, n (%) | 0 (0%) | 0 (0%) | 1 (16%) | 0.999 |
| Diuretics, n (%) | 2 (33%) | 2 (33%) | 2 (33%) | 0.999 |
| Nitrates, n (%) | 0 (0%) | 0 (0%) | 0 (0%) | - |
| Amiodarone, n (%) | 0 (0%) | 1 (16%) | 1 (16%) | 0.999 |
| Statins, n (%) | 3 (50%) | 1 (16%) | 2 (33%) | 0.818 |

Data presented as numbers (%) or as mean ± SEM; Ctl: control-sinus rhythm, pAF: paroxysmal atrial fibrillation, cAF: persistent (chronic) atrial fibrillation, MVD/AVD, mitral/aortic valve disease, LVEF - left ventricular ejection fraction, CABG: coronary artery bypass graft surgery, ACE - angiotensin-converting enzyme; AT – angiotensin.

**Table S7: Clinical characteristics of the patients employed for patch-clamp experiments to measure ICa,L**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **SR**  **(n = 5)** | **cAF**  **(n = 5)** | **p-value** |
| Age, years | 68.8 ± 3.7 | 71.8 ± 2.3 | 0.444 |
| Male gender, n (%) | 4 (80%) | 5 (100%) | 0.999 |
| Body mass index, kg/m2 | 26.8 ± 0.9 | 26.2 ± 0.7 | 0.821 |
| Arterial hypertension, n (%) | 5 (100%) | 4 (80%) | 0.999 |
| Diabetes, n (%) | 2 (40%) | 0 (0%) | 0.444 |
| Hyperlipidaemia, n (%) | 4 (80%) | 1 (20%) | 0.999 |
| LVEF, % | 60.2 ± 1.7 | 56.4 ± 2.7 | 0.429 |
| **Indication for surgery** |  |  |  |
| CABG, n (%) | 3 (60%) | 1 (20%) | 0.524 |
| AVD, n (%) | 0 (0%) | 2 (40%) | 0.444 |
| MVD, n (%) | 0 (0%) | 1 (20%) | 0.999 |
| CABG+ MVD/AVD, n (%) | 2 (40%) | 1 (20%) | 0.999 |
| **Medication** |  |  |  |
| Digitalis, n (%) | 0 (0%) | 0 (0%) |  |
| Beta-blockers, n (%) | 2 (40%) | 5 (100%) | 0.444 |
| ACE inhibitors, n (%) | 2 (40%) | 0 (0%) | 0.444 |
| AT1 blockers, n (%) | 3 (60%) | 0 (0%) | 0.167 |
| Diuretics, n (%) | 0 (0%) | 2 (40%) | 0.141 |
| Nitrates, n (%) | 1 (20%) | 0 (0%) | 0.999 |
| Amiodarone, n (%) | 0 (0%) | 2 (40%) | 0.444 |
| Statins, n (%) | 3 (60%) | 2 (40%) | 0.999 |

Data presented as numbers (%) or as mean ± SEM; Ctl: control-sinus rhythm, pAF: paroxysmal atrial fibrillation, cAF: persistent (chronic) atrial fibrillation, MVD/AVD, mitral/aortic valve disease, LVEF - left ventricular ejection fraction, CABG: coronary artery bypass graft surgery, ACE - angiotensin-converting enzyme; AT – angiotensin.

**Table S8: Clinical characteristics of the patients employed for sharp electrode experiments to measure actions potentials in atrial tissue**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **SR**  **(n = 5)** | **pAF**  **(n = 5)** | **cAF**  **(n = 7)** | **p-value** |
| Age, years | 74.2 ± 4.3 | **63.4 ± 3.7** | 72 ± 2.2 | **0.033** |
| Male gender, n (%) | 3 (60%) | 3 (60%) | 6 (85%) | 0.519 |
| Body mass index, kg/m2 | 27.5 ± 1.2 | 27.3 ± 0.7 | 26.5 ± 0.8 | 0.955 |
| Arterial hypertension, n (%) | 1 (20%) | 1 (20%) | 4 (57%) | 0.378 |
| Diabetes, n (%) | 3 (60%) | 2 (40%) | 4 (57%) | 0.999 |
| Hyperlipidaemia, n (%) | 1 (20%) | 1 (20%) | 4 (57%) | 0.378 |
| LVEF, % | 64.8 ± 2.5 | 55.3 ± 2.1 | 61.3 ± 3.7 | 0.778 |
| **Indication for surgery** |  |  |  |  |
| CABG, n (%) | 0 (0%) | 0 (0%) | 3 (43%) | 0.081 |
| AVD, n (%) | 1 (20%) | 1 (20%) | 2 (29%) | 0.999 |
| MVD, n (%) | 1 (20%) | 3 (60%) | 1 (14%) | 0.293 |
| CABG+ MVD/AVD, n (%) | 3 (60%) | 1 (20%) | 1 (14%) | 0.293 |
| **Medication** |  |  |  |  |
| Digitalis, n (%) | 0 (0%) | 0 (0%) | 3 (43%) | 0.081 |
| Beta-blockers, n (%) | 2 (40%) | 4 (80%) | 6 (85%) | 0.293 |
| ACE inhibitors, n (%) | 3 (60%) | 3 (60%) | 2 (29%) | 0.568 |
| AT1 blockers, n (%) | 2 (40%) | 0 (0%) | 1 (14%) | 0.434 |
| Diuretics, n (%) | 2 (40%) | 2 (40%) | 3 (43%) | 0.999 |
| Nitrates, n (%) | 1 (20%) | 0 (0%) | 0 (0%) | 0.588 |
| Amiodarone, n (%) | 0 (0%) | 1 (20%) | 0 (0%) | 0.588 |
| Statins, n (%) | 1 (20%) | 2 (40%) | 3 (43%) | 0.830 |

Data presented as numbers (%) or as mean ± SEM; Ctl: control-sinus rhythm, pAF: paroxysmal atrial fibrillation, cAF: persistent (chronic) atrial fibrillation, MVD/AVD, mitral/aortic valve disease, LVEF - left ventricular ejection fraction, CABG: coronary artery bypass graft surgery, ACE - angiotensin-converting enzyme; AT – angiotensin.