

Participants

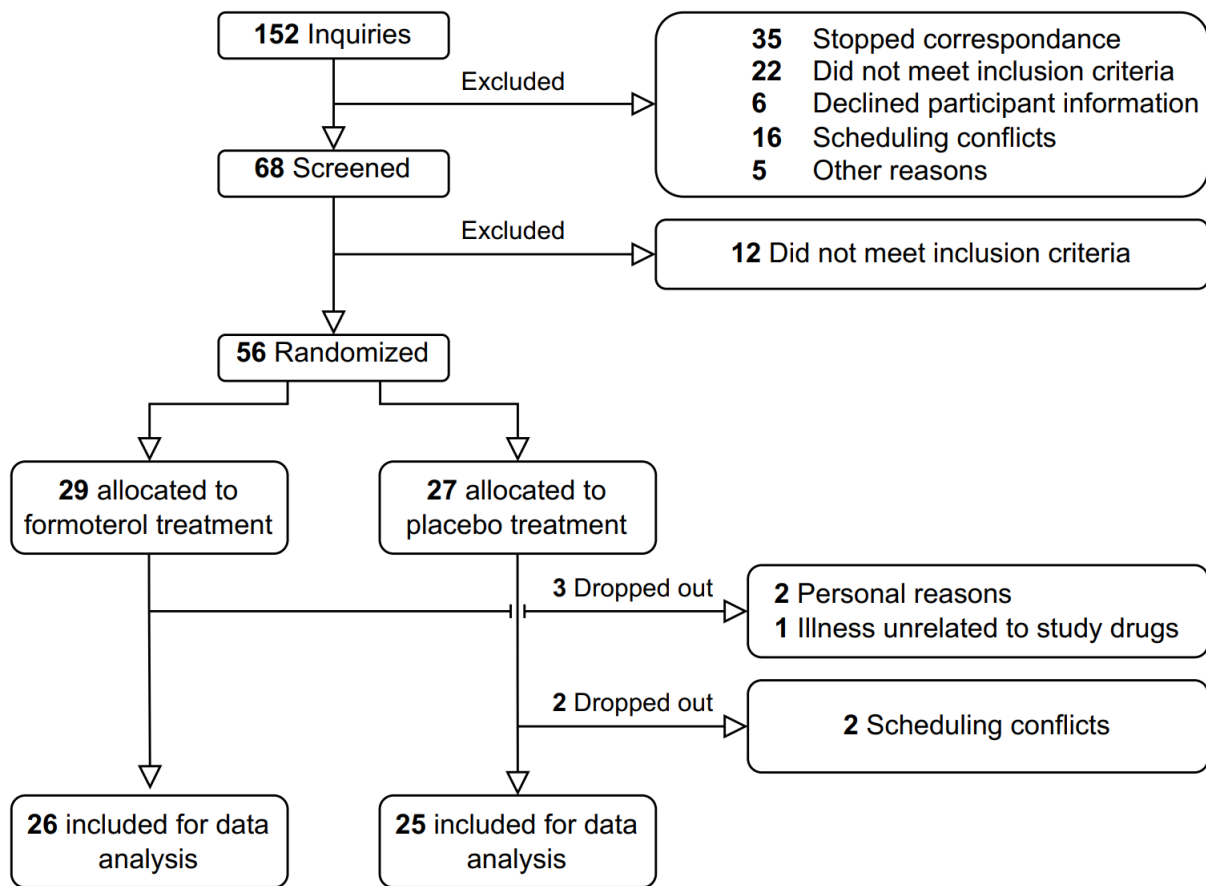


Figure 1. Participant flow diagram.

Cardiac and haematological parameters

Table 1: Cardiac structure and function and haematological parameters before (Pre) and after (Post) 6 weeks of twice-daily administration of formoterol (48 µg/day) or placebo in endurance-trained participants (19 male 1 female). LV: left ventricle; Mitral valve E: transmitral early/passive filling velocity; Mitral valve A: transmitral late/active filling velocity; E/A ratio: ratio of mitral valve E and mitral valve A; s': average of septal and lateral mitral annular systolic longitudinal velocity; e': average of septal and lateral mitral annular early/passive diastolic longitudinal velocity; E/e': ratio of mitral valve E and e'; LV end diastolic volume, ejection fraction, and stroke volume are measured using biplane method. Pre and post values are mean ± SD. Effect size is mean change (95% confidence interval). *different from pre within-group (p<0.05). #treatment×time interaction effect (p<0.05).

| | Formoterol (n = 8-10) | | Placebo (n = 8-10) | | | |
|--|-----------------------|-------------|--------------------|-------------|------------------------------------|---------------------|
| | Pre | Post | Pre | Post | Formoterol vs. placebo effect size | Interaction p-value |
| Left ventricle structure and volume | | | | | | |
| LV posterior wall thickness (cm) | 1.07 ± 0.17 | 1.11 ± 0.15 | 1.05 ± 0.15 | 1.07 ± 0.12 | 0.13 (-0.07 to 0.10) | 0.757 |
| Interventricular septal wall thickness (cm) | 1.11 ± 0.13 | 1.13 ± 0.14 | 1.12 ± 0.19 | 1.11 ± 0.13 | 0.03 (-0.05 to 0.11) | 0.389 |
| LV end diastolic volume (mL) | 159 ± 27 | 157 ± 22 | 151 ± 15 | 145 ± 16 | 4 (-15 to 22) | 0.670 |
| Stroke volume (mL) | 95 ± 16 | 92 ± 14 | 85 ± 11 | 80 ± 10 | 2 (-10 to 15) | 0.698 |
| Left ventricle systolic function | | | | | | |
| LV ejection fraction (%) | 58 ± 3 | 58 ± 3 | 57 ± 4 | 55 ± 3 | 1 (-3 to 5) | 0.636 |
| Global longitudinal strain (%) | -19.6 ± 1.9 | -19.2 ± 1.3 | -18.3 ± 1.6 | -17.7 ± 1.0 | -0.3 (-1.7 to 1.1) | 0.337 |
| s' (cm/s) | 11 ± 1 | 11 ± 1 | 11 ± 2 | 11 ± 2 | 1 (-1 to 2) | 0.225 |
| Left ventricle diastolic function | | | | | | |
| Mitral valve E (cm/sec) | 102 ± 18 | 101 ± 26* | 84 ± 18 | 78 ± 9 | 5 (-5 to 15) | 0.306 |
| Mitral valve A (cm/sec) # | 53 ± 14 | 41 ± 6 | 46 ± 0.13 | 47 ± 8 | -14 (-26 to -1) | 0.033 |
| E/A ratio # | 2.1 ± 0.9 | 2.5 ± 0.7* | 1.9 ± 0.5 | 1.8 ± 0.5 | 0.5 (0.8 to 0.9) | 0.024 |
| e' (cm/sec) | 19 ± 1 | 19 ± 4 | 17 ± 3 | 16 ± 3 | 1 (-2 to 3) | 0.440 |
| E/e' | 5.3 ± 0.8 | 5.3 ± 1.3 | 5.0 ± 0.8 | 5.1 ± 0.5 | 0 (-1 to 1) | 0.654 |
| Haematological parameters | | | | | | |
| | Pre | Post | Pre | Post | Formoterol vs. placebo effect size | Interaction p-value |
| Red blood cell count (10 ³ /µl) | 4.7 ± 0.4 | 4.7 ± 0.3 | 4.8 ± 0.5 | 4.8 ± 0.4 | 0.1 (-0.1 to 0.2) | 0.879 |
| White blood cell count (10 ³ /µl) | 6.3 ± 1.8 | 5.8 ± 1.6 | 5.7 ± 1.3 | 6.1 ± 1.1 | -0.9 (-2 to 0.4) | 0.168 |
| Platelet count (10 ³ /µl) | 196 ± 27 | 210 ± 37 | 217 ± 48 | 217 ± 49 | 13 (-8 to 34) | 0.216 |
| Neutrophil count (10 ³ /µl) | 4.1 ± 1.7 | 3.6 ± 1.5 | 3.3 ± 1.2 | 3.9 ± 1 | -1.1 (-2 to 0.2) | 0.098 |
| Haematocrit (%) | 41 ± 2 | 41 ± 2 | 42 ± 3 | 42 ± 2 | 0 (-2 to 2) | 0.778 |

Muscle mitochondrial respiration

Table 2: Muscle mass-specific and intrinsic mitochondrial respiration before (Pre) and after (Post) 6 weeks of twice-daily inhalation of either formoterol (48 µg/day; males n=5; females n=5) or placebo (males, n=5; females, n=5) in endurance-trained participants. Data are pooled for sexes. LN: leak respiration; FAOp: fatty acid oxidation; CIp: complex I coupled respiration; CI+CIIp: complex I+II coupled respiration; LOmy: oligomycin-induced leak respiration. Pre and post values are mean ± SD. Effect size is mean change (95% confidence interval). *different from pre within-group (p<0.05). #treatment×time interaction effect (p<0.05).

| | Formoterol (n = 10) | | | Placebo (n = 10) | | |
|-----------|--|-------------|--------------------------|------------------|-------------|-------------------------|
| | Muscle mass specific mitochondrial respiration (pmol O₂/s/mg w.w.) | | | | | |
| | Pre | Post | Change (95%CI) | Pre | Post | Change (95%CI) |
| LN | 11 ± 5 | 11 ± 3 | 0 (-3 to 2) | 9 ± 4 | 11 ± 3 | 2 (-1 to 4) |
| FAOp | 56 ± 15 | 52 ± 9 | -4 (-10 to 3) | 48 ± 11 | 52 ± 13 | 4 (-2 to 11) |
| CIp # | 85 ± 19 | 77 ± 18 | -8 (-17 to 0) | 73 ± 14 | 77 ± 17 | 4 (-4 to 13) |
| CI+CIIp # | 137 ± 28 | 123 ± 31 | -14* (-27 to -2) | 115 ± 19 | 123 ± 20 | 8 (-5 to 21) |
| LOmy # | 31 ± 8 | 29 ± 5 | -2 (-5 to 1) | 26 ± 6 | 30 ± 6 | 4* (1 to 7) |
| | Muscle intrinsic mitochondrial respiration (pmol O₂/s/mg w.w./citrate synthase activity) | | | | | |
| LN | 0.20 ± 0.09 | 0.25 ± 0.11 | 0.05 (-0.03 to 0.12) | 0.16 ± 0.11 | 0.19 ± 0.05 | 0.03 (-0.05 to 0.10) |
| FAOp | 1.04 ± 0.35 | 1.15 ± 0.25 | 0.11 (-0.07 to 0.292) | 0.85 ± 0.36 | 0.93 ± 0.32 | 0.08 (-0.10 to 0.27) |
| CIp | 1.60 ± 0.53 | 1.70 ± 0.39 | 0.10 (-0.13 to 0.32) | 1.30 ± 0.57 | 1.39 ± 0.48 | 0.09 (-0.14 to 0.31) |
| CI+CIIp | 2.55 ± 0.74 | 2.71 ± 0.70 | 0.17 (-0.15 to 0.49) | 2.02 ± 0.79 | 2.19 ± 0.64 | 0.18 (-0.14 to 0.50) |
| LOmy | 0.55 ± 0.11 | 0.64 ± 0.14 | 0.09* (0.14 to 0.17) | 0.44 ± 0.14 | 0.53 ± 0.16 | 0.09* (0.01 to 0.17) |