**Supplementary Table 3**

**Studies utilizing exercise and postural changes to alter cardiac output**

*AF, atrial fibrillation; CBF, cerebral blood flow;* *CCA, common carotid artery; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; ECA, external carotid artery; ETCO2, end-tidal carbon dioxide; HF, heart failure; ICA, internal carotid artery; MAP, mean arterial pressure; PWA, pulse wave analysis; TCD, transcranial Doppler; VA, vertebral artery;* *Vmca, middle cerebral artery flow velocity*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author (Year) [Reference #]** | **N** | **Subjects** | **Method of CBF measurement** | **Method of CO measurement** | **Intervention** | **Change in CO/CI** | **Change in MAP** | **Change in pCO2 (measure)** | **Change in CBF** |
| Sato (2011) [50] | 10 | 10 healthy volunteers | TCD ICA, CCA, VA, MCA and ECA velocity and flow | PWA | Exercise (recumbent bike) | CO increased linearly with increasing exercise stress. | MAP increased linearly with increasing exercise stress. | ETCO2 increased linearly with increasing exercise stress until submaximal threshold, where it then decreased | VA flow increased linearly with increasing exercise stress.  ICA flow increased with moderate exercise, but decreased with maximal. |
| Seifert (2009) [35] | 8 | 8 healthy volunteers | TCD Vmca  Transcranial cerebral oximetry | PWA | Exercise (cycling) with and without propranolol | CO increased linearly with increasing exercise (from a baseline of ~6L/min to a maximum of ~20L/min) (data approximated from histogram). Propranolol decreased CO, but only to a significant degree at maximal exercise. | MAP increased linearly with increasing exercise (from a baseline of ~85L/min to a maximum of ~120L/min) (data approximated from histogram). Propranolol appeared only to decrease MAP at maximal exercise | pCO2 decreased only with submaximal and maximal exercise.  Rest = 5.5±0.3 kPa  120W = 5.5±0.3  180W = 5.0±0.6  Exhaustion = 3.9±0.3  Propranolol increased pCO2 only at exhaustion | Mean Vmca tended to increase with increasing exercise (from a baseline of ~47cm/s to a maximum of ~60cm/s (data approximated from graph). Propranolol appeared to blunt this increase. |
| Van Lieshout (2001) [36] | 10 | 10 healthy adults | TCD Vmca  Transcranial cerebral oximetry | PWA | Standing form sitting then leg tensing while standing | CO decreased with standing by 1.9±0.4 L/min (from approximately 6 L/min) and CVP decreased by 4.3±2.5 mmHg (from approx. 3mmHg).  With muscle tensing, CVP increased by 1.4±2.7mmHg and CO increased by 1.8±0.4 L/min | With standing, MAP decreased by 9±4mm̱̱Hg. MAP did not alter with muscle tensing. | PaCO2 decreased significantly from baseline (5.34±0.18 kPa) with standing (4.64±0.17). Leg tensing increased PaCO2 slightly (4.9±0.13) | With standing, Vmca decreased by 16±5% (67±4 to 56±3 cm/s).  With tensing, Vmca increased, almost returning to baseline (supine) levels (63±3 cm/s) |
| Ide 1999 [37] | 14 | 9 patients with AF and 5 healthy controls | TCD Vmca | PWA | Rest, sustained handgrip and cycling | During rhythmic handgrip in AF patients CO increased by 111(105-135)%  During cycling CO increased by 156(130-169)% | During rhythmic handgrip in AF patients MAP increased from 85(71-95) mmHg to 101(96-104) mmHg.  During cycling MAP increased from 94 (79±102) to 107 (100±139) mmHg | During rhythmic handgrip in AF patients ETCO2 remained stable: 4.7 (4.1±5.3) to 4.5 (4.3±5.5) kPa.  During cycling ETCO2 increased from 4.4 (4.0±5.3) to 4.7 (4.1±5.5) kPa | During rhythmic handgrip in AF patients mean Vmca increased by 12% (1%±24%; during contralateral rhythmic handgrip and by 9% (4±26%) during ipsilateral rhythmic handgrip  During cycling mean Vmca increased by 10% to 49 (42±69) cm/s. |
| Ide (1998) [40] | 9 | 9 healthy volunteers | TCD Vmca | PWA | Large and small muscle group exercise (cycling vs hand grip) before and after Metoprolol | CO increased with handgrip (+16%) and maximal cycling (+193%) (p<0.05).  Metoprolol decreased CO compared to control with handgrip and maximal cycling, but was still significantly increased compared to rest. | MAP increased with handgrip (94±4 to 106±5) and maximal cycling (94±4 to 122±3) (p<0.05).  Metoprolol decreased MAP compared to control with handgrip and maximal cycling, but was still significantly increased compared to rest | PaCO2 remained constant during handgrip and was not effected by metoprolol.  PaCO2 decreased with maximal exercise 5.1±0.1kPa to 4.4±0.3, although NS) and was not effected by metoprolol. | Mean Vmca increased with handgrip (59±3 to 67±3 cm/s) and was not effected by metoprolol (p<0.05).  Mean Vmca increased with mild cycling, but returned to rest levels with maximal cycling. It was not effected by Metoprolol |
| Fraser (2015) [52] | 22 | 22 patients with heart failure (NYHA I-III) and 22 age and sex matched controls | TCD ICA flow | PWA | Moving form lying to sitting | CI was less in HF patients than controls (3.2±1.5 vs. 5.2±1.3 L/min/m2)  CI decreased by 12% with standing in HF patients compared to 0.4% in controls | MAP was similar between HF patients and controls (89.9±11.0 vs 93.7±9.1mmHg) and did not change significantly with standing | ETCO2 was similar between HF patients and controls (36.2±5.5 vs 36.7±4.5mmHg).  Both groups had small decreases in ETCO2 with standing. | CBF was less in HF patients than controls (258±54 vs. 301±69 ml/min).  With standing, CBF decreased significantly in HF patients, but not in controls. |
| Bronzwaer  (2017) [30] | 40 | 40 adults stratified by age and gender. (Young = 19-27y, middle-aged = 51-61y, elderly = 70-79y) | TCD Vmca | PWA  and inert  gas rebreathing. | CO was decreased by LBNP. This was followed by a dynamic handgrip exercise session  to increase CO. | With handgrip, CO increased by 11±6%, 9±6%, and 10±3% in young, middle and old aged groups respectively (all P<0.05) | With handgrip, MAP increased by 8±3%, 10±6%, and 13±5% in young, middle and old aged groups respectively (all P<0.05) | With handgrip, ETOC2 decreased by 1±3% in the young group, and increased by 2±5%, and 5±5% in middle and old aged groups respectively (only old group P<0.05) | With handgrip, mean Vmca increased by 6±6%, 14±14%, and 14±6% in young, middle and old aged groups respectively (all P<0.05) |
| Bogert (2005) [28] | 6 | 6 patients with compete heart block | TCD of Vmca | PWA | Two different pacemaker settings (default and optimized) | CO increased with exercise in both the default and optimized groups 201% (158–227) and 195% (176–208) of rest values respectively. | MAP did not significantly change with exercise in either the optimized (93 (75-100) to 100 (79-115 mmHg) or default (89 (73-105) to 94(71-105)) setting groups | ETCO2 was increased with exercise compared to control in the optimized group (33 (29-37) to 37(32-45)) but not the default group (33(29-37) to 36(32-42) compared to rest | Mean Vmca did not change with exercise in either the optimized (46(35-56) to 45 (42-51) or default group (46(37-62) to 44(41-49), but systolic velocity increased and diastolic velocity decreased |