

# Central command and the cutaneous vascular response to isometric exercise in heated humans

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Cutaneous vascular conductance (CVC) decreases during isometric handgrip exercise in heat stressed individuals, and we hypothesized that central command is involved in this response. Seven subjects performed 2 min of isometric handgrip exercise (35% of maximal voluntary contraction) followed by postexercise ischaemia in normothermia and during heat stress (increase in internal temperature  $\sim 1^\circ\text{C}$ ). To augment the contribution of central command independent of force generation, on a separate day the protocol was repeated following partial neuromuscular blockade (PNB; i.v. cisatracurium). Forearm skin blood flow was measured by laser-Doppler flowmetry, and CVC was the ratio of skin blood flow to mean arterial pressure. The PNB attenuated force production despite encouragement to attain the same workload. During the heat stress trials, isometric exercise decreased CVC by  $\sim 12\%$  for both conditions, but did not change CVC in either of the normothermic trials. During isometric exercise in the heat, the increase in mean arterial pressure (MAP) was greater during the control trial relative to the PNB trial ( $31.0 \pm 9.8$  versus  $18.6 \pm 6.4$  mmHg,  $P < 0.01$ ), while the elevation of heart rate tended to be lower ( $19.4 \pm 10.4$  versus  $27.4 \pm 8.1$  b.p.m.,  $P = 0.15$ ). During postexercise ischaemia, CVC and MAP returned to pre-exercise levels in the PNB trial but remained reduced in the control trial. These findings suggest that central command, as well as muscle metabo-sensitive afferent stimulation, contributes to forearm cutaneous vascular responses in heat stressed humans.

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Isometric exercise increases heart rate, mean arterial pressure, and muscle and skin sympathetic nerve activities (Goodwin *et al.* 1972; Mitchell *et al.* 1983; Mark *et al.* 1985; Saito *et al.* 1990; Vissing *et al.* 1991), and two neural control mechanisms, central command and the exercise pressor reflex, contribute to these autonomic adjustments (Mitchell *et al.* 1983). Also, sweat rate can be modulated by both central command and muscle metabo-sensitive receptors during isometric handgrip exercise under both normothermic and hyperthermic conditions (Shibasaki *et al.* 2001, 2003). Similarly, the cutaneous circulation may be modulated by the aforementioned non-thermal factors (Johnson, 1986).

Partial neuromuscular blockade, using curare derivatives, augments central command during exercise at a given workload. Friedman *et al.* (1991) evaluated the contribution of central command in mediating cutaneous vasoconstrictor responses at the beginning of dynamic exercise in normothermic subjects. Counter to their

hypothesis, augmented central command due to partial neuromuscular blockade did not alter the reduction in cutaneous vascular conductance (CVC). However, given that the cutaneous circulation is controlled by both an active vasoconstrictor and an active vasodilator system (Johnson & Proppe, 1996), the effect of central command in modulating cutaneous vascular tone in heat stressed subjects, when skin blood flow is primarily controlled by the active vasodilator system, remains unknown.

Under normothermic conditions isometric handgrip exercise does not change CVC in non-glabrous skin, whereas during heat stress it causes vasoconstriction due to withdrawal of the active vasodilator activity (Crandall *et al.* 1995, 1998). Observations from those studies are consistent with the participation of muscle afferent stimulation in the reflex response to isometric exercise, although the contribution of central command to this response is unknown. The purpose of this study therefore was to test the hypothesis that central command

modulates cutaneous vascular responses to isometric handgrip exercise in heat stressed individuals.

## Methods

Seven healthy subjects aged 21–39 years participated in this study. All subjects were of normal weight ( $74 \pm 4$  kg; mean  $\pm$  s.d.) and height ( $182 \pm 9$  cm), and each subject was informed of the purpose and risks of this study before providing their written consent (an informed consent document, approved by the Ethical Committee of Copenhagen, KF01-080100, was reviewed and signed by each subject). All experiments were performed in accordance with the Declaration of Helsinki.

Upon entering the laboratory (room temperature:  $22$ – $23^\circ\text{C}$ ), each subject swallowed a telemetry pill for measurement of internal (intestinal) temperature. The utility and validity of this method has previously been confirmed in human studies (O'Brien *et al.* 1998). Subjects were instrumented for the measurement of mean skin temperature, from the weighted electrical average of six thermocouples (Taylor *et al.* 1989), and an electrocardiogram. Each subject was then dressed in a tube-lined suit that permitted the control of skin temperature by covering the entire body surface except for the head, the feet, and the forearms.

Each subject rested in the supine position while recording devices were attached. Mean arterial pressure (MAP) was recorded from the integrated signal obtained from a finger (Finapres, Amsterdam, the Netherlands) of the hand not performing exercise. Heart rate (HR) was obtained from the electrocardiogram, and respiratory frequency was monitored via piezoelectric pneumography to confirm the absence of Valsalva's manoeuvre during isometric exercise. Skin blood flow was measured by laser-Doppler flowmetry (LDF) from the non-exercising forearm and CVC was calculated as the ratio of LDF to MAP and expressed in arbitrary units (AU) or as a percentage reduction from the pre-exercise level.

Subjects performed two maximum voluntary handgrip contractions (MVC), and the highest value was used to calculate the workload to be performed during the ensuing isometric exercise bouts. Following a brief rest period, subjects performed isometric handgrip exercise at 35% MVC for 2 min. During the final 5 s of the bout, a cuff around the upper exercising arm was inflated to 350 mmHg and remained inflated for 2 min. The subjects were then heated via the water-perfused suit until the internal temperature increased  $\sim 1.0^\circ\text{C}$ , at which time subjects repeated the isometric exercise protocol.

Using a randomized crossover design, on a different day within a week of the first study, the aforementioned protocol was repeated. However, prior to each bout of exercise the non-depolarizing neuromuscular blocking agent cisatracurium besylate (Nimbex, GlaxoSmithKline) was administered intravenously. The onset of action of

this agent is within 2–3 min following administration, while the duration of action is 30–40 min. After this period of time the effects of the drug gradually diminish over a 15–20 min period. A  $2 \text{ mg ml}^{-1}$  bolus dose of cisatracurium was first administered, followed by a brief MVC. Supplemental doses were administered until MVC was reduced to less than 50%. Five minutes after the appropriate dose was administered, each subject performed the protocol. In the heat stressed condition, administration of the drug and the subsequent confirmation of reduced strength were repeated prior to each isometric exercise bout. Evidence of spontaneous recovery after each exercise bout was manifested by the requirement to administer supplemental doses of the drug sufficient to reduce MVC by less than 50% prior to each exercise trial. At all times an Ambu-E (Copenhagen, Denmark) resuscitator apparatus, neostigmine, and atropine were available; however, it was not necessary to use these interventions.

For both trials, the subjects were given verbal feedback as to the force necessary to maintain 35% MVC and the target force was not different between control and PNB trials. If during the PNB trials the subject was unable to maintain the prescribed force, the subjects were encouraged to maintain whatever force they could generate.

## Data analyses

Data were recorded at 200 Hz via a 16-bit A/D converter (Biopac, Santa Barbara, CA, USA) and stored as 20-s averages. Analysed data reported in Tables 1 and 2 and Fig. 3 are the average of the final 20 s from the period prior to exercise, at the end of exercise, and at the end of postexercise ischaemia.

Data obtained within each isometric exercise bout, and from subsequent postexercise ischaemia periods, were compared by one-way repeated measures ANOVA, followed by a Student-Newman-Keuls test when a significant main factor (time) was identified. Differences in resting values between control and PNB trials were compared using Student's paired *t* test. Data are expressed as means  $\pm$  s.d. and the level of statistical significance was set at  $P < 0.05$ .

## Results

The doses of cisatracurium administered prior to isometric exercise were  $1.37 \pm 0.17$  mg (normothermia) and  $0.79 \pm 0.16$  mg (during passive heating). These doses were sufficient to cause at least a 50% reduction in MVC and significantly reduced force during the isometric exercise bouts.

## Normothermia

Figure 1 shows typical responses from one subject in normothermia. Similar to this subject, force production

**Table 1. Thermal and haemodynamic responses during isometric handgrip exercise and subsequent postexercise ischaemia for control and partial neuromuscular blockade (PNB) trials**

		Normothermia			Hyperthermia		
		Rest	Isometric exercise	Post-exercise ischaemia	Rest	Isometric exercise	Post-exercise ischaemia
Internal temperature (°C)	Control	36.6 ± 0.2	36.6 ± 0.2	36.6 ± 0.3	37.5 ± 0.2	37.6 ± 0.2*	37.6 ± 0.2*
	PNB	36.6 ± 0.3	36.6 ± 0.3	36.6 ± 0.3	37.7 ± 0.3	37.7 ± 0.4	37.8 ± 0.4*
Mean skin temperature (°C)	Control	34.4 ± 0.5	34.4 ± 0.5	34.5 ± 0.5	38.0 ± 0.6	38.0 ± 0.7	38.0 ± 0.6
	PNB	34.5 ± 0.5	34.6 ± 0.5	34.6 ± 0.5*	38.6 ± 0.5	38.5 ± 0.5	38.6 ± 0.5
Heart rate (b.p.m.)	Control	64.9 ± 9.4	74.9 ± 6.8*†	61.6 ± 9.4	84.6 ± 12.0	103.9 ± 16.9*	90.8 ± 14.9
	PNB	64.4 ± 10.9	83.7 ± 8.2*	63.5 ± 10.8	90.0 ± 16.1	117.4 ± 20.6*	93.5 ± 16.2
Mean arterial pressure (mmHg)	Control	77.6 ± 6.4	100.6 ± 9.3*	89.7 ± 7.8*†	74.7 ± 4.0	105.7 ± 8.3*†	87.8 ± 7.5*†
	PNB	77.4 ± 9.2	100.7 ± 14.9*	77.1 ± 9.1	74.1 ± 9.1	92.7 ± 11.3*	77.0 ± 8.1

Rest: prior to isometric exercise. \*Different relative to the preceding resting period,  $P < 0.05$ ; †different relative to the PNB trial,  $P < 0.05$ .

**Table 2. Cutaneous vascular conductance (CVC) responses in arbitrary unit (AU) or as a percentage reduction of CVC from pre-exercise levels, during isometric handgrip exercise and subsequent postexercise ischaemia during control and partial neuromuscular blockade (PNB) in both thermal conditions**

		Normothermia			Hyperthermia		
		Rest	Isometric exercise	Post-exercise ischaemia	Rest	Isometric exercise	Post-exercise ischaemia
CVC (AU)	Control	0.69 ± 0.42	0.65 ± 0.38	0.67 ± 0.41	2.53 ± 1.23	2.22 ± 1.14*	2.41 ± 1.18†
	PNB	0.54 ± 0.25	0.60 ± 0.31	0.56 ± 0.22	2.89 ± 0.84	2.58 ± 0.87*	2.94 ± 0.88
CVC (%)	Control	100.0	97.1 ± 12.7	95.2 ± 9.0	100.0	88.3 ± 12.0*	95.8 ± 7.2†
	PNB	100.0	107.8 ± 9.8	106.6 ± 10.1	100.0	88.0 ± 4.9*	101.5 ± 2.8

Rest: prior to isometric exercise. \*Different relative to the preceding resting period,  $P < 0.05$ ; †different relative to the preceding resting period when excluding the subject showing no change in CVC during perturbation (see Discussion),  $P < 0.05$ .

for the entire group during the PNB trial gradually reduced throughout isometric exercise (onset:  $132 \pm 34$  N; end of exercise:  $16 \pm 24$  N), although the time course of decreasing force varied among subjects. On the other hand, all subjects maintained the prescribed force throughout the control trial ( $143 \pm 24$  to  $134 \pm 23$  N). Internal and skin temperatures and CVC did not change significantly during isometric exercise or during postexercise ischaemia (Table 1). Isometric exercise resulted in similar increases in MAP between trials (Control:  $23.0 \pm 9.4$  mmHg and PNB:  $23.2 \pm 8.2$  mmHg) and MAP remained elevated during postexercise ischaemia for the control trial, but returned to pre-exercise level during the PNB trial. The increase in HR during isometric exercise tended to be greater during the PNB trial relative to the control trial ( $19.3 \pm 9.4$  versus  $10.0 \pm 7.6$  b.p.m.,  $P = 0.07$ ); HR returned to the pre-exercise level during postexercise ischaemia for both trials.

### Heat stress

Passive heat stress increased internal and mean skin temperatures (Table 1) and the elevation of internal temperature was not different between control and

PNB trials ( $0.98 \pm 0.31$  versus  $1.12 \pm 0.22$ °C, respectively,  $P = 0.27$ ). Passive heating did not change MAP, while it elevated HR for both trials.

Figure 2 shows typical responses from the subject depicted in Fig. 1. As in normothermia, during passive heat stress isometric force initially reached the prescribed force, but then decreased throughout the exercise bout during the PNB trial. The peak force early during the bout of exercise was  $139 \pm 21$  N, and then decreased to  $10 \pm 14$  N at the end of exercise, whereas this force was maintained throughout the control trial ( $142 \pm 26$  to  $141 \pm 28$  N).

During isometric exercise, increases in MAP were greater in the control relative to the PNB trial ( $31.0 \pm 9.8$  versus  $18.6 \pm 6.4$  mmHg,  $P < 0.05$ ) and MAP remained elevated during postexercise ischaemia in the control trial. In contrast, MAP returned to pre-exercise levels during postexercise ischaemia during the PNB trial. In both trials HR increased during isometric exercise, but this elevation tended to be less during the control trial relative to the PNB trial ( $\Delta$ HR:  $19.4 \pm 10.4$  versus  $27.4 \pm 8.1$  b.p.m.,  $P = 0.15$ ). For both trials HR returned to pre-exercise levels during postexercise ischaemia.

The CVC decreased during isometric exercise in both trials (Fig. 3 and Table 2) and it returned to the pre-exercise

level during postexercise ischaemia in the PNB trial. For the control trial, CVC remained reduced during postexercise ischaemia for most subjects.

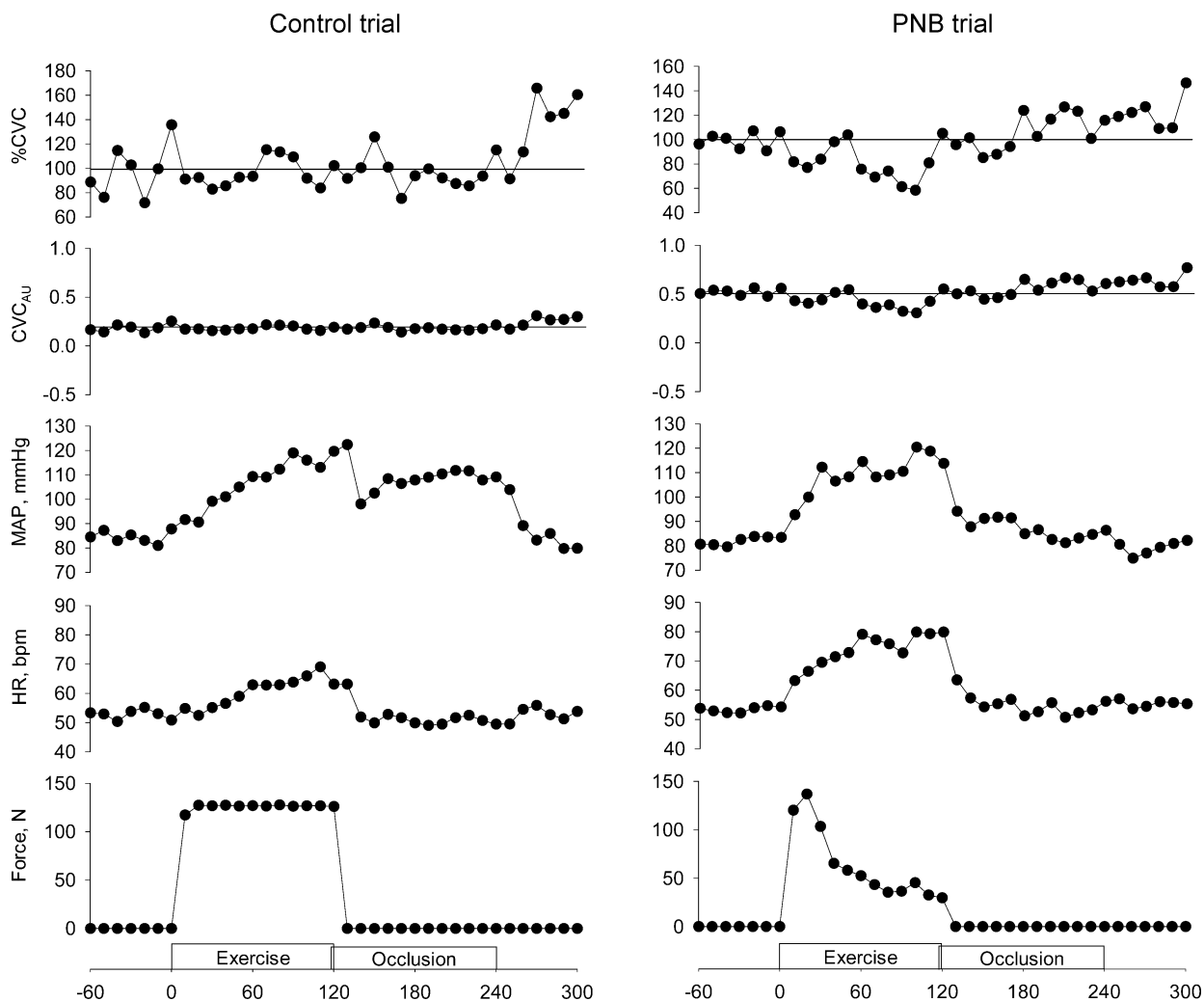
## Discussion

The primary finding of this study is that central command is capable of modulating cutaneous vascular responses in heat stressed subjects. This contention is supported by the observation that despite decreased force production, CVC was reduced when central command was augmented during exercise with PNB. The CVC remained decreased in the control trial during postexercise ischaemia, as previously described (Crandall *et al.* 1998), but it returned to the pre-exercise level during the PNB trial. Given the greatly attenuated force at the end of exercise for the PNB

trial, the reduction in CVC during this bout of exercise was not mediated secondarily to an exercise pressor reflex (e.g. metaboreflex and mechanoreflex stimulation).

Under both thermal conditions, administration of the neuromuscular blocking agent gradually reduced strength despite encouragement to maintain the workload. Yet, HR tended to be greater during the PNB trials regardless of the thermal condition, which is consistent with prior studies using neuromuscular blockade (Mitchell *et al.* 1989; Victor *et al.* 1989; Vissing & Hjortso, 1996) thereby providing evidence that central command was augmented.

In normothermia, CVC did not change during isometric handgrip exercise, which is consistent with previous observations (Taylor *et al.* 1989, 1990; Crandall *et al.* 1995, 1998; Saad *et al.* 2001). Conversely, during the heat stress trials CVC was reduced during



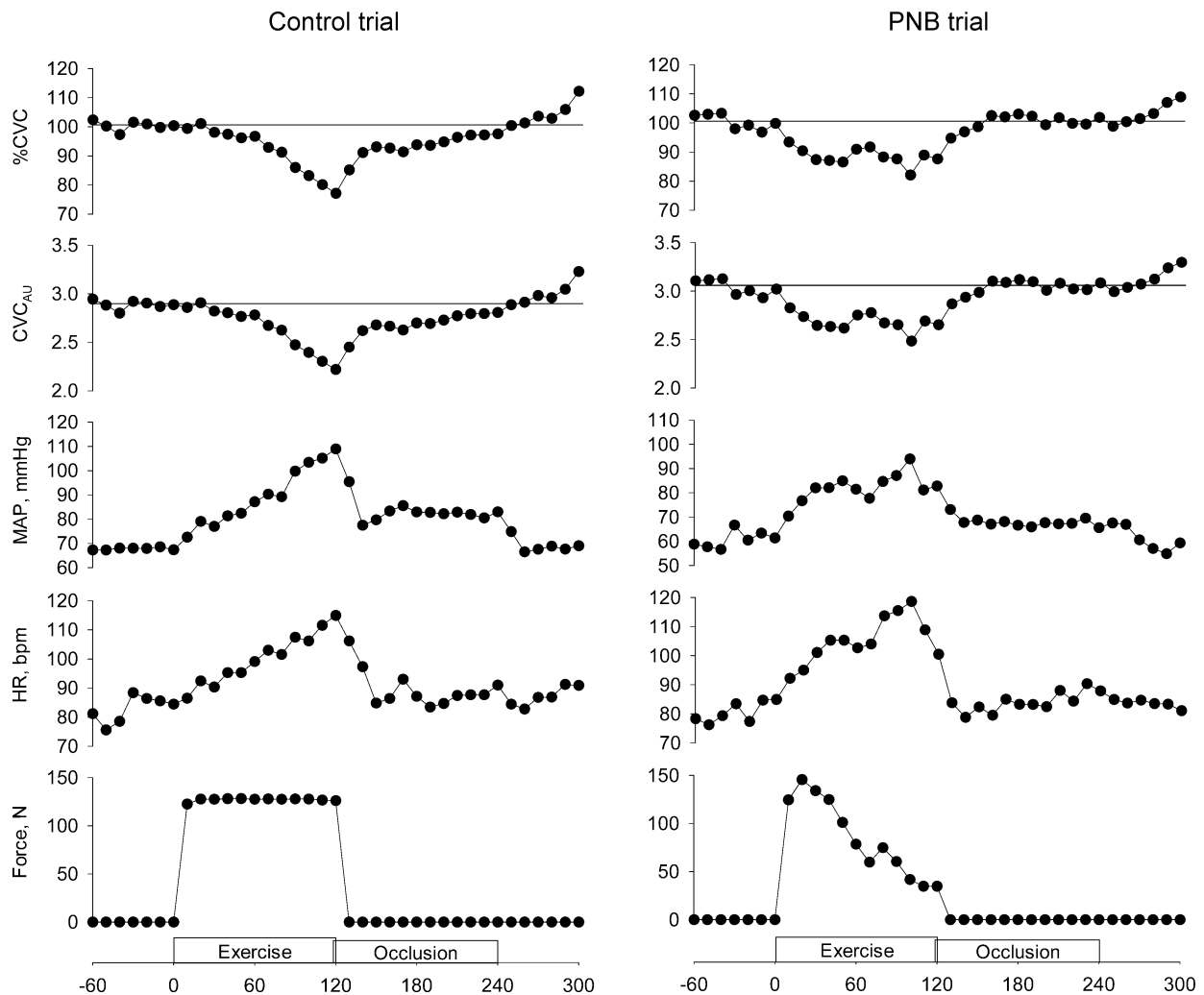
**Figure 1. Typical responses from one subject during 2 min of isometric handgrip exercise and subsequent postexercise ischaemia in normothermia**

Cutaneous vascular conductance (CVC), expressed as percentage change from the pre-exercise level (%CVC) and in arbitrary units (CVC<sub>AU</sub>), did not change during isometric exercise or during postexercise ischaemia (occlusion) in the control or partial neuromuscular blockade (PNB) trials. MAP: mean arterial blood pressure; HR: heart rate; Force: force generated during isometric exercise.

isometric exercise. In prior studies, selective blockade of the cutaneous vasoconstrictor system showed the cutaneous active vasodilator system to be a target of these reflexes (Crandall *et al.* 1995, 1998). Importantly, in the control trial, CVC remained reduced for most subjects while MAP remained elevated relative to the pre-exercise level, suggesting a contribution of the metaboreflex in mediating a component of the reduction in CVC. However, in the PNB trial MAP and CVC returned to the pre-exercise level during postexercise ischaemia, reflecting the lower absolute force generated in the PNB trial and a lack of engagement of the metaboreflex at the end of the preceding exercise bout. This result therefore suggests that the reduction in CVC during the attempted exercise portion of the PNB trial was independent of

metaboreflex mechanisms. This observation, coupled with greatly reduced force production and thus minimal mechanoreflex stimulation, strongly suggests the observed reduction in CVC occurred due to central command during this trial. This is in contrast to the control trial in which reductions in CVC during exercise were likely to have occurred via a combination of central command and muscle metabo/mechanoreceptor stimulation.

In normothermia, internal and skin temperatures did not change during isometric exercise or postexercise ischaemia. However, while heat stressed internal temperature was slightly elevated during both of these periods. Depending on the elevation in temperature for individual subjects, such a response provides a driving force for CVC to increase that will oppose central



**Figure 2. Typical responses from the subject depicted in Fig. 1, but during heat stress**

In the control trial, cutaneous vascular conductance (CVC), expressed as percentage change from the pre-exercise levels (%CVC) and as arbitrary units (CVC<sub>AU</sub>), decreased during isometric exercise and remained reduced during postexercise ischaemia. During partial neuromuscular blockade (PNB), CVC decreased similarly during isometric exercise but returned pre-exercise level during postexercise ischaemia. MAP: mean arterial blood pressure; HR: heart rate; Force: force generated during isometric exercise.

command and metaboreflex-mediated reductions in CVC. However, the increase in internal temperature during isometric exercise and postexercise ischaemia was not different between control and PNB heat stress trials, but CVC remained reduced during postexercise ischaemia for the control trial whereas it returned to the pre-exercise level during the PNB trial. Therefore the reduction in CVC during isometric exercise was independent of thermal factors, and observed differences in CVC responses during postexercise ischaemia were due primarily to stimulation of metaboreceptors during the control trial that was not present during the PNB trial.

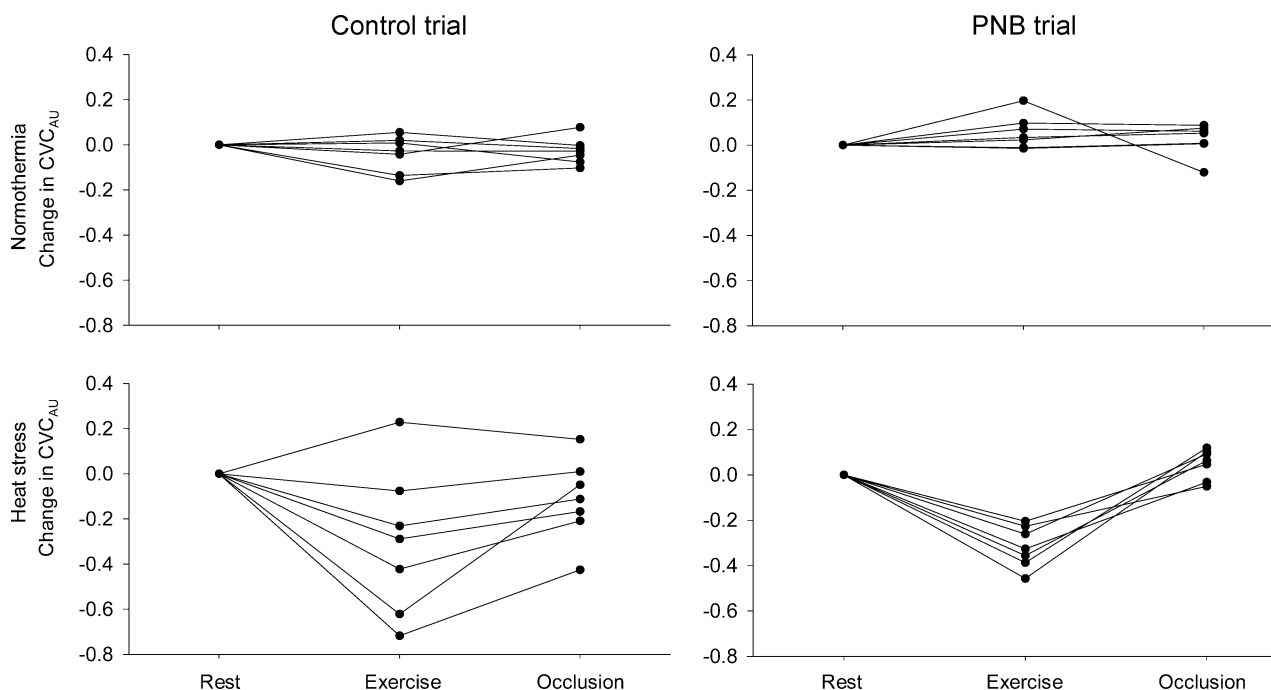
### Limitation of the study

In the control heat stress trial, one subject did not decrease CVC during isometric exercise and postexercise ischaemia (Fig. 3). Kondo *et al.* (2003) reported that during mild heat stress (internal temperature of  $\sim 37^{\circ}\text{C}$  or lower), CVC does not decrease, but rather increases slightly during isometric exercise. In the subject who did not reduce CVC during isometric exercise, the increase in internal temperature ( $0.6^{\circ}\text{C}$ ) prior to isometric exercise was well below the mean of the group. Thus, for this subject the absence of a reduction in CVC during isometric exercise may relate to the modest level of heating. When data from this subject

are excluded from the analysis for the control heat stress trial, a significant reduction in CVC during postexercise ischaemia is identified. Regardless, the potential limitation of the aberrant response for this subject does not discount the key observation of a reduction in CVC during isometric exercise when central command is augmented (PNB trial) without significant metaboreceptor stimulation.

Internal temperature was slightly but significantly elevated throughout the IHG + PEI test during passive heat stress, although this value did not change during normothermic exercise. Nevertheless, no significant differences in the elevation of internal temperature between the control and the PNB trials were observed during IHG ( $0.05 \pm 0.03$  versus  $0.05 \pm 0.04^{\circ}\text{C}$ ) and PEI ( $0.12 \pm 0.07$  versus  $0.13 \pm 0.06^{\circ}\text{C}$ ) while heat stressed. Thus, it is unlikely that this slight elevation in internal temperature confounded the interpretation of the results.

The elevation in MAP during isometric exercise might lead to an autoregulatory-mediated reduction in CVC, as recently suggested by McCord & Minson (2005), potentially confounding the interpretation of the data that central command is capable of modulating CVC. However, our results do not support this hypothesis because the elevation in MAP was greater during the control heat stress trial relative to the PNB trial. Given this observation, if autoregulatory mechanisms contributed to the reduction



**Figure 3. Individual responses of cutaneous vascular conductance during isometric exercise and post-exercise ischaemia in normothermic and heat stressed conditions**

In normothermia, cutaneous vascular conductance, expressed as arbitrary units ( $\text{CVC}_{\text{AU}}$ ), during isometric exercise and postexercise ischaemia did not change in either the control or partial neuromuscular blockade (PNB) trials. On the other hand, except for one subject,  $\text{CVC}_{\text{AU}}$  decreased during isometric exercise and remained reduced during postexercise ischaemia during the control trial. During the PNB heat stress trial,  $\text{CVC}_{\text{AU}}$  decreased for all subjects during isometric exercise but returned to pre-exercise level during postexercise ischaemia.

in CVC during isometric exercise, then greater reductions in CVC should occur during the isometric exercise bouts when the elevation in blood pressure was greater. This was not the case, as despite differences in MAP responses with isometric exercise between control and PNB trials, similar reductions in CVC were observed between these trials in the heat stressed condition. This observation argues against the hypothesis that reductions in CVC during isometric exercise were solely mediated by autoregulatory mechanisms.

In conclusion, administration of a neuromuscular blocking agent reduced force production during isometric exercise while HR remained elevated during the exercise bouts in both thermal conditions, demonstrating that central command was augmented. Under these conditions CVC was reduced during isometric exercise when subjects were heat stressed but not when they were normothermic. In the PNB trials, the contribution of muscle metaboreflex stimulation in mediating the CVC response was minimal given the observation that blood pressure returned to pre-exercise levels during ischaemia. These findings support the hypothesis that central command is capable of modulating CVC in heat stressed subjects, but not when subjects are normothermic.

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