stimuli was not significantly different between TRN and SED hearts ($P > 0.05$ unpaired t-test n = 9-10).
We suggest that despite the occurrence of both cardiac hypertrophy and electrical remodelling in response to voluntary exercise, these changes do not pre-dispose the exercise trained heart to arrhythmias. Our findings are consistent with the overall beneficial effect of mild exercise on the heart.

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Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

PC25

Carbon monoxide inhibits human cardiac L-type Ca^{2+} channels

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Conditions of stress such as myocardial infarction stimulate up-regulation of heme oxygenase-1 (HO-1) to provide cardioprotection, but its mechanism of action is unknown (Clarke et al., 2003). One of the products of HO-1 catabolism is carbon monoxide (CO). We have investigated the ability of CO to act as a modulator of L-type Ca^{2+} channels, using whole-cell patch clamp recordings from HEK 293 cells stably expressing the human α_{1C} Ca^{2+} channel subunit as previously described (Scragg et al., 2005).
CO, applied via the CO donor molecule CORM-2 (1-70μM; Williams et al., 2004), caused reversible, voltage-independent Ca^{2+} channel inhibition of up to ca. 40%, whereas its inactive form (iCORM) was without significant effect. CO-mediated inhibition was independent of protein kinase G activation since effects were unaltered in cells pretreated with PET-cGMPS (100nM). Two distinct NO donors, SIN-1 (10μM) and GSNO (2mM) failed to mimic the inhibitory actions of CO and did not significantly alter Ca^{2+} currents. The actions of CO were prevented by the antioxidant MnTMPyP (100μM). Inhibition of NADPH oxidase (apocyanin; 30μM, or diphenyleneiodonium; 3μM), or xanthine oxidase (allopurinol, 1μM) did not affect the inhibitory actions of CO. Instead, inhibitors of complex III (but not complex I) of the mitochondrial electron transport chain, namely antimycin A (3μM) and stigmatellin (1μM) and a mitochondrially-targeted antioxidant (Mito Q; 250nM), fully prevented the effects of CO.
Our data indicate that the cardioprotective effects of HO-1 activity may be attributable to an inhibitory action of CO on cardiac L-type Ca^{2+} channels. Inhibition arises from the ability of CO to promote generation of reactive oxygen species from complex III of mitochondria.

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PC26

SAPHIR: a Guyton-based extensible, modular 'core model' of blood pressure regulation for the Physiome

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We present current progress on the SAPHIR project, an open-source, modular modeling environment of cardiovascular and respiratory physiology using state-of-the-art multi-scale simulation methods. Our model initially targets blood pressure and body fluid homeostasis. We present re-implementations of two legacy models that treated overall regulation of blood pressure (Guyton et al. 1972), and fluid regulation (Ikeda et al. 1979).
The basic "core model" includes lumped-parameter input-output descriptions of relevant organs as modules, i.e., heart, vasculature, intra- and extracellular spaces, lungs, kidneys, and muscles. This core model can be modified/extended by customizing existing modules or by replacing one or several of the core modules by more detailed, mechanistic models at finer resolution. As modeling/simulation environments, Berkeley-Madonna was used for Ikeda's model (JF, PB); Fortran (SRT), Matlab/Simulink (PH, FG) and the M2SL C++ software library (Rennes laboratory, AH & VL), were used for implementation of the original Guyton models. M2SL will be the basic solver package for the multi-module modeling environment.
The resulting modular modeling environment is compact enough to run on a personal computer and yet accomodate detailed mechanistic submodules.
This open-source, modular approach allows for (i) selected extensions/refinements of the model (e.g. addition of a pancreas module and regulation of blood glucose) and (ii) assessment of system-level consequences of local perturbations (e.g. models of functional consequences of genetic polymorphisms). One important goal is to keep the model compact enough to ensure fast execution time (in view of eventual use in clinical settings), yet to allow detailed sub-modules (to maintain system-integrated feedback loops).
This approach will eventually provide a platform for patient-specific exploration of therapeutic scenarios in the context of the IUPS Physiome.

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PC29

The time course of muscle deoxygenation is dependent on the rate of increase of workload during incremental exercise

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The kinetic response of microvascular oxygen extraction in the exercising muscle, as estimated via the deoxyhaemoglobin (Hb) signal of near infrared spectroscopy (NIRS) to constant workload exercise has been well characterised (DeLorey et al, 2003; Grassi et al, 2003; Ferreira et al, 2005). In contrast the typical response to incremental exercise is less well-defined despite a number of authors utilising the "inflection" point of Hb as a marker of anaerobic threshold (Bhambani, 2004). However recent data suggest that the rate of increase of workload during exercise may have some bearing on the nature of Hb kinetics during this type of exercise (Wang et al, 2006). The purpose of the present study was therefore to investigate the response of Hb to ramp exercise during a slow (SR) and fast (FR) rate of increase of workload. Following approval from London South Bank University Research Ethics Committee, 7 young healthy male (recreational athletes) subjects completed a ramp test (40 W / min, FR) to exhaustion and an incremental exercise test (SR) consisting of 2 min stages at 30, 40, 50, 60, 70 & 80 % VO2max (mean incremental rate ~16 W / min), on a cycle ergometer. During each test the oxygenation status of the vastus lateralis was determined via NIRS. The inflection point of the Hb data was evaluated by iteratively fitting combinations of 2 regression lines to yield the lowest sum of squared residuals. The regression line gradient prior to the inflection point (S1) was greater than the regression line gradient after the inflection point (S2) during FR for all subjects. In contrast during SR, the gradient for the S1 regression line was less than S2 for 5 out of 7 subjects. There was a significant correlation between the power output at the inflection point during SR and FR ($r=0.84$, $p<0.01$), however the average power output at the inflection point was significantly higher in the FR (219 ± 11 W) compared to the SR (125 ± 11 W), $p<0.01$. The present data demonstrate that the rate of increase of workload during exercise impacts upon the time-course of muscle deoxygenation as measured via NIRS. Furthermore, the use of the inflection point of Hb as a proxy for the anaerobic threshold should be treated with caution.

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Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

PC30

Astroglia as a potential cellular substrate of action of angiotensin 1-7 in the ventrolateral medulla of the rat

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Angiotensin(1-7) (Ang1-7) has recently emerged as an important player in both peripheral and central renin-angiotensin systems. Ang(1-7) is generated by angiotensin converting enzyme-2 from angiotensin I or angiotensin II and that some of its effects are mediated by the Mas receptor (Kostenis et al. 2005). The Mas receptor in the brain including the ventrolateral medulla has been shown to be both abundant and functionally important for cardio-vascular homeostasis (Becker et al. 2007). However, the cellular mechanisms of Ang(1-7) action in the brain remain elusive. We hypothesised that glia could be involved in Ang(1-7) signalling in the ventrolateral medulla. Ca^{2+} signalling in astrocytes of ventro-lateral medulla was studied using the novel high fidelity genetically engineered Ca^{2+} sensor Case12 (Souslova et al. 2007) targeted specifically to astroglia using adenoviral vectors (ADV). The expression was controlled with a truncated version of GFAP promoter enhanced using previously described two-step transcriptional amplification strategy (Liu et al. 2006). Organotypic slices were prepared from brainstem of P7-8 rats and transduced as per (Teschemacher et al. 2005) with ADV-sGFAP-Case12. 7-10 days later slice cultures were transferred into a recording chamber, perfused with bicarbonate-buffered artificial cerebro-spinal fluid at 34°C and astroglia were imaged using a Leica confocal microscope. Ang(1-7) at 200 nM slightly but significantly increased $[Ca^{2+}]_i$ in 12/15 astrocytes by 13±1% while 2 μM resulted in an increase of 41 ± 9%. Blockers of glutamatergic transmission CNQX (10 μM) and dAP5 (50 μM) had no obvious effect on resting $[Ca^{2+}]_i$ levels. However, both the ionotropic glutamate receptor antagonists strongly potentiated the effect of Ang(1-7). Thus, 200 nM Ang(1-7) & 10 uM CNQX increased $[Ca^{2+}]_i$ by +177 ± 4% (n=13) while 200 nM Ang(1-7) & 50 μM dAP5 raised levels by +155±25% (n=15). Thus, a direct excitatory effect of Ang(1-7) on astroglia is masked by the presence of glutamate-mediated transmission perhaps via release of an inhibitory transmitter from adjacent neurones. Consistent with this idea, the sodium channel blocker - TTX (1 μM) triggered increases in $[Ca^{2+}]_i$ in ventrolateral medullary astroglia (83±17%). We suggest that

Further to these findings, potential responses of these cells to injury were investigated in rats using a mild dorsal root ganglion injury caused by injection of neuronal tracer CTb. In this case, preliminary data indicates a redistribution of the CSFcNs around the central canal and in some circumstances what appears to be migration of the cells in response to injury. Investigation into potential changes in neurochemistry in response to injury is currently underway. Given the immature status of CSFcNs, and their potential response to injury, this is an interesting avenue to explore in the context of aiding endogenous repair in spinal trauma.

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Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

PC46

The post-exercise recovery period affects dynamic baroreceptor-related cortical activation patterns in humans

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The higher brain centres involved with the processing of afferent baroreceptor information are poorly understood in humans. We have recently documented cortical neural activity patterns associated with the larger muscle sympathetic and heart rate responses elicited by moderate steady-state lower body negative pressure (LBNP) after exercise (1). The present study tested the hypotheses that: 1) the post-exercise recovery period modifies cortical activity patterns during the onset (baroreceptor unloading) and offset (baroreceptor reloading) phases of moderate LBNP, and 2) that this cortical network is associated with the functional integration of baroreceptor afferent information. Cortical activity was assessed using functional magnetic resonance imaging (fMRI) with blood oxygen level-dependent (BOLD) contrast in young healthy volunteers (n=11, 2♀/9♂). Continuous measures of cardiac stroke volume (SV) were collected separately (Doppler ultrasound). Repeated fMRI and laboratory tests were performed under control (no exercise) and following 1 hour of cycle ergometry exercise at ~60% of heart rate reserve. Cardiovascular and BOLD data were collected at baseline and during 4 repeated 45-s bouts of moderate (-35 mm Hg) LBNP separated by 30-s rest periods. A mild (-5 mm Hg) level of LBNP served as a control task. Significant changes ($P < 0.005$, uncorrected) in cortical BOLD signal were determined by a mixed effects ANOVA using the Statistical Parametric Mapping software package (SPM2). Compared to -5 mm Hg LBNP, moderate LBNP elicited larger ($P < 0.05$, 2-way ANOVA) reductions in SV after exercise (-26 ± 10 mL vs. -41 ± 8 mL, Mean ± S.D.). In both conditions, LBNP onset produced an increase in BOLD signal within the caudate body, pulvinar thalamic nucleus and Precuneus. However, BOLD signal increases during LBNP onset were greater in the caudate body, pulvinar thalamic nucleus, anterior cingulate, Precentral and Postcentral gyri after exercise. Common sites of cortical activation during LBNP offset were observed in the right insular cortex, cingulate and medial frontal gyri. Furthermore, the post-exercise recovery period elicited larger BOLD signal changes in the ventral lateral thalamic nucleus, caudate tail and inferior frontal gyrus during this period of baroreceptor reloading. We have highlighted the involvement of a discrete cortical network associated with post-exercise differences in baroreceptor loading/unloading stimulus profiles. These findings may facilitate our current understanding of the higher brain regions involved with the integration of baroreceptor afferent sensory signals versus those associated with the generation of baroreflex-mediated efferent autonomic and cardiovascular responses.

Kimmerly DS et al. (2007) Am J Physiol Heart Circ Physiol 293, 299-306.

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PC47

Effects of a specialised massage sequence on oxygenation of spastic muscle in cerebral palsy

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Regular application of a specialised massage sequence to leg muscles has been shown to promote motor skills in cerebral palsy (MacGregor et al., 2007) when assessed with the Gross Motor Function Measure–66 (Russell et al., 2000). It is proposed that the sequence acts by resolving localised imbalances of forces in the muscles at the level of sarcomeres, and that this resets sensory feedback from muscle receptors, permitting adaptive changes in motor control function. Since work against frictional forces would also liberate heat within muscles, possibly causing vasodilatation, this was investigated by monitoring surface temperatures and by near infra red spectroscopy (NIRS).

7 adolescents (3 males and 4 females) with cerebral palsy (CP) and a matching group of controls participated in the study. The adolescents gave their informed consent; permission for the study was obtained from their parents, doctors, and the local Ethics Committee. Skin temperatures over the medial gastrocnemius muscles were taken immediately before and after the massage sequence. The NIRS optodes were positioned over the upper part of these muscles. The optical path length determines the depth of recording from the skin surface. Since subcutaneous fat thickness varies, path lengths were chosen for

each individual for which there was a maximal reduction in oxygenated haemoglobin during standardised isometric contractions of the calf muscles. The massage was applied to the lower part of the calf not covered by the optodes. Oxygenated, deoxygenated and total haemoglobin were continuously monitored during, and for at least 2 minutes before and after the sequence.

Before massage mean skin temperatures over the gastrocnemius muscles were significantly lower in the group with cerebral palsy (26.8 ± 0.2°C compared with 28.7 ± 0.2°C; $P < 0.05$; n=35). After massage there was no difference in mean temperatures (30.0°C). In 14 trials, in the control group there was a significant increase in total haemoglobin during the massage in 7 cases, a reduction in 4, and no effect in 3 cases. Increases in total haemoglobin were maintained after massage, and in 3 of the 4 cases in which it was reduced during massage there was a later increase. In participants with CP the total haemoglobin increased during massage in 11 cases, and the increase was maintained in 8 of them after massage. In one case total haemoglobin fell during massage, and there was no effect in two cases. Clearly the massage sequence can indeed increase muscle oxygenation in CP. However since motor performance improved in all adolescents with CP who received regular massage, the lack of consistency of local effects on oxygenation suggests that they cannot be held solely responsible.

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PC48

Expression of connexins 30.2 and 36 in spinal cord and medulla oblongata of transgenic reporter mice

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Cx30.2 and Cx36 are neuronal gap junction proteins, contributing to electrical coupling between neurones. Such coupling is important for generation of network activity in the nervous system. To understand the mechanisms and results of this coupling knowledge of the expression of gap junction proteins in central neurones is of prime importance. Our aim here is to examine the expression pattern of Cx30.2 and Cx36 in neurones of spinal cord and medulla oblongata with particular reference to neurones associated with autonomic function.

The study employed transgenic mice that expressed LacZ or cyan fluorescent protein (CFP) reporter genes under control of the Cx30.2 (Kreuzberg et al., 2008) or Cx36 (Wellershaus et al., 2008) gene promoters, respectively. Homozygous Cx30.2Lac/LacZ (n=5) and Cx36CFP/CFP (n=5) mice were anaesthetised with sodium pentobarbital (60mg/kg IP) and perfused transcardially with 4% paraformaldehyde. Brainstems and spinal cords were sectioned on a vibratome and sections analysed by standard immunohistochemical and immunofluorescence protocols. Three mice in each group were injected intraperitoneally with 0.1ml of 1% hydroxystilbamidine (Sigma) 3 days prior to perfusion, to label preganglionic and motor neurones. Cx30.2/LacZ-IR was detected with rabbit anti-b-galactosidase (Sigma), Cx36/CFP-IR – with rabbit anti-green fluorescent protein (Abcam). Sections treated for Cx30.2 or Cx36 were double immunostained with mouse antibodies against tyrosine hydroxylase (TH, ABCAM) and/or goat antibodies against choline acetyl transferase (ChAT, CHemicon).

Cx30.2 expression, represented by B-galactosidase, was detected throughout the spinal cord and brainstem. Numerous labelled cells were present throughout the NTS, some of which were confirmed as TH positive. No motor or preganglionic neurones contained BGal (identified by the presence of hydroxystilbamidine and/or ChAT) but rather it was detected in cells surrounding these nuclei. TH positive neurones in the A1/C1 regions were also B-Gal positive. Cx36 expression was not detected in cranial nerve nuclei, but was present in sympathetic preganglionic neurones. In the medulla oblongata CFP was detected in the NTS and in TH neurones in the NTS and ventrolateral medulla. Current analysis is quantifying the extent of co-localisation.

These experiments show that both Cx30.2 and Cx36 are expressed in neurones that could influence autonomic control. Of the autonomic output neurones only sympathetic preganglionic neurones express one of these gap junctions, Cx36. However, other neurones in a position to influence autonomic function express these proteins, including neurones in the NTS and ventrolateral medulla. Future experiments will characterise the neurochemistry of these neurones and investigate functional properties.

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PC49

Programmed hypertension is associated with changes in both the cardiac and sympathetic components of the baroreceptor and peripheral chemoreceptor reflexes

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The developmental origins of hypertension have been increasingly investigated in recent years. In the rat, administration of high levels of glucocorticoid during late pregnancy produces