Penson, PE, Ford, WR, Kidd, EJ and Broadley, KJ

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Journal: *Naunyn-Schmiedeberg Archives of Pharmacology*

Manuscript ID: Naunyn-00087-2008

Manuscript Type: Original

Keywords: beta-adrenoceptor, Cardioprotection, Heart, Ischaemia/reperfusion, Preconditioning, Rat
Activation of \(\beta\)-adrenoceptors mimics preconditioning of rat isolated atria and ventricles against ischaemic contractile dysfunction

\(\beta\)-adrenoceptor-mediated cardioprotection

Peter E. Penson, William R. Ford, Emma J. Kidd and Kenneth J. Broadley

Pharmacology Division, Welsh School of Pharmacy, Cardiff University

King Edward VII Avenue, Cathays Park, Cardiff, CF10 3NB, UK :

Correspondence should be addressed to Professor Kenneth J. Broadley

Tel: +44 29 20 875832

Fax: +44 29 20 874149

Email: BroadleyKJ@cf.ac.uk
Abstract

Effects of ischaemia and reoxygenation on cardiac contractile function can be abrogated by ischaemic preconditioning (IPC). We tested whether β-adrenoceptor agonists could mimic IPC and whether IPC was dependent on β-adrenoceptor activation in rat isolated cardiac tissues.

Paced left atria and right ventricular strips were set-up in Krebs’ solution and isometric developed tension recorded. Ischaemia was simulated by replacing with hypoxic glucose-free Krebs’ solution for 30 minutes. IPC and isoprenaline (10⁻⁷M) preconditioning for 10 minutes were examined. Developed tension post-reoxygenation was expressed as a percentage of the pre-ischaemic baseline.

Recovery at 15 minutes was significantly increased by IPC in atria (47±4.0 % v. 29.3±1.7 %, p<0.05) and ventricles (39.0±5.2 % v. 22.4±2.8%, p<0.05). At 60 minutes, isoprenaline treated atria recovery (75.8±16.6%) was significantly (p<0.05) greater than controls (47.9±2.3%). Propranolol (10⁻⁶M) abolished both effects.

Therefore, both IPC and β-adrenoceptor agonist-induced improvement of contractile recovery was propranolol-sensitive and β-adrenoceptor mediated.

Keywords: β-adrenoceptor; Cardioprotection; Heart; Ischaemia/reperfusion; Preconditioning; Rat.

Abbreviations: β-adrenoceptor-mediated preconditioning, βP; Ischaemic Preconditioning, IPC; Propranolol, Pro; Protein kinase A, PkA
Introduction

Ischaemic preconditioning is an extremely powerful cardioprotective phenomenon whereby transient periods of ischaemia protect the heart against later more severe ischaemic insult. The phenomenon, first discovered by Reimer’s group (Murry et al. 1986) protects the heart against arrhythmias (Ravingerová et al. 2002) and importantly prevents lethal cell injury and reduces infarct size (Jennings 1996). However, controversy exists as to whether preconditioning reduces stunning (contractile dysfunction of a reversible nature) (Jennings 1996). Whilst the salutatory effects of preconditioning are undoubted, induction of ischaemia is impractical for widespread use in the clinic, thus attempts have been made to understand the mechanisms behind this protective phenomenon in order that it can be replicated pharmacologically.

Several groups (Frances et al. 2003; Lange et al. 2006a; Lochner et al. 1999; Marais et al. 2001; Moolman et al. 2006a; Moolman et al. 2006b; Nasa et al. 1997; Robinet et al. 2005; Tong et al. 2005; Yabe et al. 1998). including ourselves (Yates et al. 2003) have demonstrated that a preconditioning-like adapted state can be induced by transient pre-treatment with an agonist of the β-adrenoceptor. However it is unclear whether or not ischaemic preconditioning is dependent on β-adrenoceptor activation (Frances et al. 2003; Iliodromitis et al. 2004; Spear et al. 2007; Tong et al. 2005).

Much of this work has been carried out using the Langendorff perfused heart, an excellent model for studying ischaemic damage and reperfusion injury, as both functional data and infarct-size data can be obtained. However, results obtained from isolated hearts and indeed in vivo procedures are complicated by the fact that activation of β2-adrenoceptors in the coronary vasculature, leads to coronary vasodilatation (Tune et al. 2004). Activation of β-adrenoceptors in the heart also results in a positive chronotropic
response (Ahlquist, 1948) which may be another confounding factor unless rate is held constant by electrically pacing the preparations.

We therefore utilised electrically paced isolated cardiac tissues which allowed us to study the direct effects of ischaemic preconditioning and drug treatment on contractile function in different regions of the heart. As this model does not involve coronary flow, then true ischaemia cannot be induced, however ischaemia was simulated by using a hypoxic buffer containing no glucose. Reperfusion was simulated by replacing normal buffer and reoxygenating the tissues.

It was therefore our aim to test the hypothesis that ischaemic preconditioning and β-adrenoceptor-mediated preconditioning could be demonstrated in isolated paced cardiac tissues which provide a coronary-vascular-independent model of myocardial ischaemia. One would expect β-adrenoceptor-mediated preconditioning to be susceptible to a β-adrenoceptor antagonist, however we also aimed to test the hypothesis that ischaemic preconditioning is dependent on β-adrenoceptor activation by endogenously released catecholamines in this model.

**Methods**

**Atrial preparations**

Male Sprague-Dawley rats (Harlan, Bicester, U.K.) were used throughout and weighed 250-350g at the time of killing. These studies complied with the guidelines for the care and use of laboratory animals according to the Animals (Scientific Procedures) Act 1986. Rats were killed by a blow to the head followed by cervical dislocation. The abdominal cavity was opened using curved scissors and lateral incisions were made on each side of
the rib cage to expose the heart. The pericardium was removed and the heart was clamped at the apex using a pair of Spencer-Wells forceps. The left atrial appendage was lifted using curved forceps and a 5-0 suture was inserted through the tip and tied off for attachment to an isometric transducer (Pioden dynamometer UF1 range ± 55 g). Another suture was inserted at the atrioventricular junction for securing the tissue to a bipolar platinum electrode. The atrial appendage was then cut free from the ventricle and immediately immersed in ice-cold Krebs’ solution (composition (in mM): NaCl 118.4; MgSO$_4$ 1.2; KCl 4.7; CaCl$_2$.6H$_2$O 2.5; KH$_2$PO$_4$ 1.2; NaHCO$_3$ 25.0 and glucose 11.7) gassed with 95% O$_2$ in CO$_2$. A suture was then inserted into the apical end of the right ventricular muscle and tied off for attachment to an isometric transducer. A strip approximately 4 mm wide and 20 mm long was then cut by dissecting up to the atrioventricular border where another suture was passed through the tissue for attaching the tissue to an electrode. Both tissues were submerged in ice-cold Krebs’ whilst they were being tied on to the electrodes before being transferred to a 20 ml organ bath containing Krebs solution at 37°C gassed with 5% CO$_2$ in O$_2$. Contractile tension was measured via transducers, the signal was amplified using a Grass model 79D EEG polygraph data recording system (Grass instrument Co. Quincy, Mass., U.S.A.), converted from analogue to digital data using a Powerlab 200 (ADInstruments), and passed to a computer. Data were recorded at a sampling frequency 200 Hz using Chart v.4.1.1 software (ADInstruments). The apparatus was adjusted so that there was an initial resting tension of 1±0.1 g on atrial preparations and 1.5±0.1 g on ventricles. Both tissues received punctuate electrical stimulation via a bipolar platinum electrode at 2 Hz and 150% of the threshold voltage required to cause contraction. All preparations were left for one hour to stabilise, during which time they were frequently washed.

After the stabilisation period, the tissues were randomised to one of the following treatment groups (Fig. 1). Control; tissues underwent a further thirty minutes normoxia, followed by 30 minutes simulated ischaemia, achieved by bathing the tissues in glucose-free Krebs’ and gassing with 5% CO$_2$ in N$_2$. Glucose-free Krebs’ contained choline
chloride 7mM in order to maintain osmolarity (Carr et al. 1997). Normoxic glucose-containing Krebs’ was then restored and the contractile function of the tissues was monitored for one hour, during which time the Krebs’ was replaced every fifteen minutes. *Ischaemic preconditioning* (IPC); tissues underwent ten minutes of simulated ischaemia and ten minutes normal oxygenation prior to the index ischaemia. *Ischaemic preconditioning in the presence of propranolol* (IPC + Pro). Ischaemic preconditioning was performed as described as above, in the presence of $10^{-6}$ M propranolol which was added twenty-five minutes prior to the preconditioning ischaemia and maintained throughout simulated ischaemia and throughout the experiment after reoxygenation and glucose replacement. *β-adrenoceptor-mediated preconditioning* (βP). Tissues were exposed to isoprenaline ($10^{-6}$ M) under normoxic conditions for 10 minutes, followed by washout. Simulated ischaemia began twenty minutes later. *β-adrenoceptor-mediated preconditioning in the presence of propranolol* (βP + Pro). Tissues were exposed to propranolol ($10^{-5}$ M) for fifteen minutes prior to isoprenaline treatment as described above. Propranolol was maintained throughout the experiment. The protocols for ischaemic and pharmacological preconditioning were chosen based on preliminary data to find the optimum protocols for protection in this model.

The tissues were washed by replacing the Krebs’ solution with fresh warmed oxygenated Krebs’ three times. Tissues were paced throughout the experiment using a Grass S48 stimulator (Grass instrument Co. Quincy, Mass., U.S.A.) with threshold voltage + 50% (typically 1-5 V) at 2 Hz.

**Materials**

All Krebs’ components and ascorbic acid were purchased from Fisher Scientific (Loughborough, UK). (−)-Isoprenaline (+)-bitartrate and (±)-propranolol were obtained from Sigma Aldrich (Poole, UK). Drugs were prepared daily as fresh solutions in distilled water.
Data analysis

Prism version 4.02 for windows (GraphPad Software, Inc) was used for production of graphs and statistical analyses. Tension was monitored continuously, enabling calculation of diastolic (baseline) and developed tension. The degree of ischaemic contracture was quantified by measuring the increase in diastolic tension during simulated ischaemia at its maximum point (Fig. 2). The time taken to reach maximal contracture was also recorded. Cardiac function was assessed at fifteen and sixty minutes post reoxyg enation. Developed tension at these time points was calculated as a percentage of developed tension at the end of the stabilization period for each preparation. Groups of data were compared by one-way ANOVA followed by Tukey’s post hoc test.

Results

Effect of simulated ischaemia on contractile function

In control preparations in both atria and ventricles, simulated ischaemia led to a rapid reduction in developed tension, which fell to near-zero levels after five minutes. Diastolic tension rose during simulated ischaemia reaching a maximum between 20 and 25 minutes and fell thereafter. Maximum contracture was $0.65 \pm 0.1g$ in atria and $1.94 \pm 0.18 g$ in ventricles. Upon reoxygenation, recovery of developed tension occurred rapidly during the first 15 minutes, and more slowly thereafter (Fig. 2). Therefore we chose to compare contractile function at 15 and 60 minutes post-reoxygenation.
Effects of ischaemic and β-adrenoceptor-mediated preconditioning on ischaemic contracture

Ischaemic preconditioning in ventricular tissues led to a significant (p<0.05) reduction in maximal ischaemic contracture from 1.95 ± 0.18g in controls to 0.92 ± 0.28g. A similar trend was evident in atrial tissues although this did not reach significance. β-Adrenoceptor-mediated preconditioning did not alter the maximal contracture compared with controls (Fig. 3).

Ischaemic preconditioning led to a significant (p<0.01) reduction in the time taken to achieve maximal contracture in ventricular tissue from 22.5 ± 3.5 minutes in controls to 16.3 ± 1.5 minutes. β-Adrenoceptor-mediated preconditioning did not alter the time taken to reach maximal contracture (Fig. 4).

Propranolol alone had no significant effect on either the magnitude of the maximal contracture, or the time taken to achieve this contracture. When ischaemic preconditioning was carried out in the presence of propranolol, the magnitude of ischaemic contracture was neither significantly different from control nor preconditioned ventricular tissues. In atria, however, the combination of ischaemic preconditioning and propranolol led to an ischaemic contracture of 1.58 ± 0.36g which was significantly (p<0.001) greater than either control atria or those which had undergone ischaemic preconditioning.

Effects of ischaemic preconditioning on contractile recovery

The timecourse of developed tension in atria and ventricles is shown in Figure 5.
Ischaemic preconditioning led to an improved recovery of developed tension in both atrial and ventricular preparations compared with controls (Fig. 5). The improvement in recovery was significant at fifteen minutes after reoxygenation (Fig. 6). By this time point, developed tension in control (untreated) atrial tissues had recovered to 29.3 ± 1.7 % of the preischaemic developed tension. Recovery of function was significantly (p<0.05) improved to 47.0 ± 4.0 % in tissues that had undergone ischaemic preconditioning. When ischaemic preconditioning was carried out in the presence of propranolol, the protective effect was lost. Tissues thus treated recovered to 26.4 ± 5.1 % which was not significantly different from control, but was significantly (p<0.01) smaller than after ischaemic preconditioning without propranolol. Propranolol alone had no significant effect on the recovery of tissues (Fig. 6a).

A similar picture was observed in ventricular tissues. Untreated tissues recovered to 22.4 ± 2.8 % of pre-ischaemic values in the first fifteen minutes of reoxygenation. Ischaemic preconditioning significantly (p<0.05) increased this value to 39.0 ± 5.2 %. Propranolol had no significant effect on recovery when given alone, however when combined with ischaemic preconditioning, recovery at this time point was significantly (p<0.01) less than ischaemic preconditioning alone, and not significantly different from control (Fig. 6b).

By 60 minutes after reoxygenation, however, the beneficial effect of ischaemic preconditioning upon recovery was lost (Fig. 7).

Effect of β-adrenoceptor-mediated preconditioning on contractile recovery
Recovery of developed tension in tissues which had received a preconditioning exposure of isoprenaline was not different from control in either tissue at 15 minutes after reoxygenation (Fig. 6). However, after 60 minutes reoxygenation in atria, the isoprenaline treated tissues had recovered to 75.8 ± 16.6% (Fig. 7a), significantly (p<0.05) greater than controls which recovered to 47.9 ± 2.3%. This increase was blocked in propranolol treated tissues to 44.0 ± 3.0 % which was significantly (p<0.05) smaller than isoprenaline preconditioned tissues, and not significantly different from controls. Propranolol alone had no significant effect on recovery at this time point (Fig. 7a). Isoprenaline treatment did not improve recovery of function in ventricular tissue at either 15 or 60 minutes (Figs. 6b and 7b).

**Discussion**

We have demonstrated cardioprotection by ischaemic preconditioning in both atria and ventricles. This was manifest by improved functional recovery at 15 minutes after reoxygenation in preconditioned tissues compared with control. Pretreatment of atrial tissues with the non-selective β-adrenoceptor agonist isoprenaline, also resulted in improved functional recovery, although this was manifest later, 60 minutes after reoxygenation. The failure of β-adrenoceptor-mediated preconditioning to protect ventricular tissue in this model is unlikely to reflect the fact that ventricular tissue cannot be preconditioned by β-adrenoceptor activation, because isolated whole-heart models have demonstrated that post ischaemic cardiac function can be improved by β-adrenoceptor preconditioning (Frances et al. 2003), a fact which would necessitate a protective effect on the left ventricle. Thus, the failure to demonstrate protection in this study either reveals a peculiarity of this model or of the right ventricle.

It has been suggested that ischaemia-induced release of catecholamines in the heart is a mechanism by which ischaemic preconditioning induces a protective state (Broadley and
Catecholamine release and subsequent activation of β-adrenoceptors has also been implicated in the mechanism of cardioprotection achieved by administration of opioids (β₂) (Huang et al. 2007) and anaesthetics (β₁) (Lange et al. 2006b). However, controversy remains as to whether activation of β-adrenoceptors is an essential part of ischaemic preconditioning, or whether there are redundancies in the pathway which leads to protection. – that is to say, that preconditioning could be activated by β-adrenoceptors, but equally well by unrelated receptors. In the isolated rat heart, depletion of endogenous catecholamines by reserpine does not affect the improved functional recovery or reduction in markers of cell death (creatine kinase and lactate dehydrogenase) in hearts that had undergone ischaemic preconditioning (Frances et al. 2003; Weselcouch et al. 1995). In rabbits in vivo, it has been demonstrated that blockade of β₁-adrenoceptors by esmolol had no effect on the infarct-size limitation afforded by ischaemic preconditioning (Iliodromitis et al. 2004). However, a study in Langendorff perfused rabbit hearts showed protection of ischaemic preconditioning against necrosis was blocked by the β₁-adrenoceptor antagonist CGP-20712A (Spear et al. 2007). In a mouse Langendorff model, preconditioning protection (improved functional recovery and reduced infarct size) was abolished in knockout animals lacking the β₂-adrenoceptor (Tong et al. 2005).

It would seem likely that the reliance of ischaemic preconditioning on β-adrenoceptor activation varies between species and indeed different models, and the varying conditions and endpoints used in studies account for the apparently contradictory results observed.

A number of other endogenous mediators have been demonstrated to mimic preconditioning, including adenosine (Carr et al. 1997), nitric oxide (Cohen et al. 2006), opioids (Schultz et al. 1995, 1996) and anaesthetics (Cason et al. 1997). Thus, preconditioning may be triggered by a number of independent mechanisms. This is an important question in the clinic, where β-adrenoceptor antagonists are administered for the treatment of angina, hypertension and heart failure (Mehta 2006). Ischaemic preconditioning can be used as a protective strategy prior to cardiac surgery. It is thought that angina attacks may also induce preconditioning that can be protective against the damage sustained during a later myocardial infarction (Kloner and Rezkalla 2006).
Therefore it is important to understand how these protective phenomena may be modified by commonly used β-blocking medication.

It is possible that positive inotropes such as isoprenaline could result in preconditioning by causing the energy demands of the tissue to exceed the capacity of diffusion to supply the substrates, and remove the waste products of metabolism. Indeed, it has been noted that rapid pacing of the heart can mimic preconditioning by inducing ischaemia (Vegh et al. 1991). Such an effect might be exaggerated in a model such as we used, in which there is no flow of buffer through blood vessels in the tissue, and the core of the preparation is entirely dependent on diffusion to receive oxygen and nutrients. However, there is a large body of evidence, from in vivo and Langendorff isolated heart experiments, in which the myocardium is inevitably better supplied with perfusate via the coronary vasculature and are therefore less dependent on diffusion, that activation of protein kinases cascades as a result of β-adrenoceptor activation results in the heart undergoing adaptive changes and becoming resistant to later ischaemic damage. Protein kinase A (PKA) has often been implicated in the preconditioning achieved by β-adrenoceptor agonists (Lochner et al. 1999; Robinet et al. 2005). This is to be expected, as cAMP is also an essential mediator in classic β-adrenoceptor signalling leading to positive inotropic and chronotropic effects of β-adrenoceptor agonists (May et al. 1985).

In this study, the beneficial effects of ischaemic preconditioning on post-ischaemic recovery were blocked by the non-selective β-adrenoceptor antagonist, propranolol, suggesting an important role for β-adrenoceptors in ischaemic preconditioning in this model. However, the timecourses of β-adrenoceptor-mediated and ischaemic preconditioning were different; ischaemic preconditioning led to improved contractile function early after reoxygenation (15 minutes) but not after 60 minutes. At this later time point, however, β-adrenoceptor agonist pretreatment led to improved function. Furthermore, tissues preconditioned by ischaemia and by β-adrenoceptor stimulation
behaved differently from one another during ischaemia. Ischaemic preconditioning led to a reduction in the magnitude of ischaemic contracture which is consistent with a protective effect. Ischaemic contracture is of the rigor type, and develops under conditions where ATP concentrations are insufficiently high to break actin-myosin cross-links (Piper et al. 2003). Rigor contracture can lead to cytoskeletal damage and thus any reduction in the magnitude of contracture is likely to be protective. In contrast, β-adrenoceptor stimulation by isoprenaline did not reduce the magnitude of contracture in either atria or ventricles even in tissues where there was improved recovery at 60 minutes. Thus, ischaemic preconditioning may involve wider ranging beneficial effects than those seen with β-adrenoceptor-mediated preconditioning.

In agreement with studies in whole hearts (Kolocassides et al. 1995), ischaemic preconditioning in ventricular preparations reduced the time taken to achieve maximum contracture. It is difficult to make predictions on the recovery of ischaemic tissues based on the profile of ischaemic contracture (Pantos et al. 2006). However, the difference seen in these experiments between ischaemic- and β-adrenoceptor-mediated preconditioning suggest that different mechanisms may be involved in each.

This study is limited by the fact that it was not possible to measure infarct size in this model. Thus, we were unable to distinguish between functional impairment as a result of cell death and reversible contractile dysfunction (stunning). Additionally, the model uses atrial appendage tissue and right ventricular strips rather than left ventricle which is of more functional importance. However, these tissues were chosen because of their thin walls, in order to minimise diffusional limitations into the tissue. We believe that these preparations provide a convenient model for studying the functional implications of interventions before, during and after simulated ischaemia. Additionally, our use of a non-selective β-adrenoceptor agonist and antagonist do not enable us to identify which...
receptor subtype is involved in the protection seen, which future studies will examine in more detail.

In conclusion, we have demonstrated that isolated left atria and right ventricles can be used as a convenient model of ischaemic and pharmacological preconditioning. Ischaemic- and β-adrenoceptor-mediated preconditioning both led to an improvement in post ischaemic contractile function. The protective effects in both cases were abrogated by propranolol. However, the timecourse of protection during ischaemia and reoxygenation was different in each case suggesting that ischaemic preconditioning involved more complex mechanisms than the simple release of catecholamines and subsequent signalling activation of β-adrenoceptors. We believe that simulated ischaemia in isolated cardiac tissues, as used in this model, represents an important and valid technique for exploring the effects of interventions upon ischaemic contracture and post-ischaemic contractile dysfunction. In terms of physiological relevance, this model falls between isolated whole hearts and cell culture, but is not subject to the problems of cell differentiation seen in culture and is not complicated by the effects upon coronary flow which would be expected when β-adrenoceptor agonists are administered in a Langendorff heart preparation. Indeed, the effects seen in this model must occur at the level of the myocardium. The most clinically relevant finding of this study was that the functional improvements of ischaemic preconditioning were blocked by propranolol. This finding mirrors the result of other studies (Spear et al. 2007; Tong et al. 2005) in which β-adrenoceptor activation has been shown necessary for the protection by ischaemic preconditioning. However, in our study, the protective effect must be at the level of the myocardium. This requires further investigation in vivo and in vitro of the β-adrenoceptor subtypes that are involved because many patients with cardiovascular diseases take β-adrenoceptor antagonists which may have the potential to abrogate the effects of ischaemic preconditioning induced prior to cardiac surgery (Laskey 2005) or as a result of angina attacks (Kloner and Rezkalla 2006).
Acknowledgement

This work was funded by a British Heart Foundation Studentship (FS-05-075-19397) awarded to P.E.P. for which the authors are grateful.

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Figures

Fig. 1 Experimental Protocols. Time (minutes) is shown along the abscissa with the point of reoxygenation designated 0. White regions correspond to normoxic conditions, black simulated simulated ischaemia and grey, drug treatment.
Fig. 2 A representative trace from a ventricular preparation exposed to simulated ischaemia and reoxygenation. S represents the final minutes of the stabilisation period. Time (minutes) from reoxygenation are shown along the abscissa. Note the rapid fall in developed tension during simulated ischaemia and the increased diastolic tension indicating ischaemic contracture. Diastolic and developed tension both recover rapidly over the first 15 minutes of reoxygenation and more slowly thereafter.
Fig. 3 Mean (+SEM) magnitude of ischaemic contracture (maximum increase in diastolic tension (g) during simulated ischaemia) in a) atria and b) ventricular strips. * indicates p<0.05; *** indicates p<0.001
Fig. 4 Mean (±SEM) time (minutes) into simulated ischaemia at which maximum contracture was reached in a) atria and b) ventricular strips. ** indicates p<0.01; *** indicates p<0.001.
Fig. 5 Timecourse of developed tension throughout ischaemia and reperfusion in control and ischaemic pre-conditioned (IPC) tissues in a) atria and b) ventricles. Mean developed tension (±SEM) is expressed as a percentage of the developed tension achieved at the end of the stabilisation period.
a) Atria

b) Ventricles

Developed tension (% post-stabilisation value)

Control  IPC  IPC + Pro  βP  βP + Pro  Pro

*  **

0  10  20  30  40  50  60
Fig. 6 Mean developed tension (+SEM) after 15 minutes reoxygenation in a) atria and b) ventricular strips. Developed tension is expressed as a percentage of the developed tension achieved at the end of the stabilisation period. * indicates p<0.05; ** indicates p<0.01.
Fig. 7 Mean developed tension (±SEM) after 60 minutes reoxygenation in a) atria and...
b) ventricular strips. Developed tension is expressed as a percentage of the developed tension achieved at the end of the stabilisation period. * indicates p<0.05.