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### ACTIVATION OF THE ATP-SENSITIVE $K^+$ CURRENT

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**INTRODUCTION:** Perioperatively, patients with ischemic heart disease are at risk for lethal arrhythmias secondary to myocardial ischemia. Within 30 seconds of the onset of hypoxia or ischemia in intact heart muscle, cellular $K^+$ efflux increases and is accompanied by progressive action potential duration (APD) shortening[1], which may predispose the myocardium to arrhythmias by altering conduction and refractoriness. An attractive explanation for these phenomena was provided by the discovery of the ATP-sensitive $K^+$ (K.ATP) channel, which is opened as $[ATP]_i$ falls.[2] However, in excised membrane patches K.ATP channels are half-maximally suppressed by $[ATP]_i$ about 100-fold lower than occur during early ischemia and hypoxia in intact tissue. Our goal was to determine how early and at what tissue ATP levels $I_{K.ATP}$ is activated during hypoxia by correlating changes in tissue ATP content with activation of $I_{K.ATP}$ in intact voltage-clamped rabbit papillary muscles.

**METHODS:** Adult rabbit right ventricular papillary muscles were mounted onto a 3 compartment, single sucrose gap voltage clamp apparatus (as previously described).[3] APD and current-voltage relations were recorded under control oxygenated conditions, after 10 min of hypoxia, and following 5-10 min of reoxygenation. Voltage clamp pulses (0.5 sec duration) were performed from a holding potential of -50 mV to various test potentials. In a parallel set of experiments, papillary muscles were freeze-clamped and assayed for tissue ATP by HPLC, as previously described.[1] Data are expressed as mean ± SE. Paired and unpaired two-tailed Student's *t* test with the appropriate Bonferroni correction were used for statistical analysis.

**RESULTS:** During 10 minutes of hypoxia, the outward $K^+$ current measured in response to a voltage clamp pulse step from -50 mV to 0 mV increased from 8.57 ± 0.27 to 15.67 ± 1.41 μA ($p < 0.05$, N = 6), and APD decreased from 452 ± 54 to 292 ± 56 ms ($p < 0.05$, N = 6). Both outward current and APD returned to control following reoxygenation. Pre-treatment of the muscles with 10 μM glyburide (N = 6), a specific $I_{K.ATP}$ blocker,[4] prevented both APD shortening and increase in outward current. In muscles assayed for tissue ATP, 10 min of hypoxia resulted in a comparable degree of APD shortening (441 ± 24 to 297 ± 18 ms, $p < 0.05$, N = 12), while tissue ATP levels fell from 13.2 ± 1.3 μmoles/gram dry weight to 9.7 ± 0.7 ($p < 0.05$, N = 12).

**CONCLUSIONS:** These results demonstrate that $I_{K.ATP}$ is activated and causes APD shortening during hypoxia in intact cardiac muscle despite only a modest decline in tissue ATP content. The mechanism by which $I_{K.ATP}$ is activated in the face of mM cytosolic [ATP] needs further investigation.

**REFERENCES:** 1. *Am J Physiol* 1989;256:H1165-1175. 2. *Nature* 1983;305: 147-148. 3.*Pediatr Res* 1988;23:428-432. 4. *Pflugers Arch* 414:669-675, 1989.

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### TITLE: DISCREPANCY BETWEEN TOTAL AND SPLANCHNIC $O_2$ DELIVERIES DURING DOBUTAMINE, DOPAMINE AND NOREPINEPHRINE

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**INTRODUCTION.** Various catecholamines are being used to increase total $O_2$ delivery ($DO_2TOT$). Knowledge of their concomitant effects on splanchnic $O_2$ deliveries becomes especially important in situations like post hepatic transplantation. Accordingly, this study was done to compare the effects of the commonly employed catecholamines dobutamine (DOBU), dopamine (DOPA), and norepinephrine (NE) on splanchnic oxygenation.

**METHODS.** Nine anesthetized (ketamine/flunitrazepam) pigs (28-32 kg) were studied. Following laparotomy for instrumentation (placement of EMF probes around hepatic artery [HA], portal vein [PV] and superior mesenteric artery [SMA], and of $PO_2$ surface electrodes onto liver and small intestine [SI], cannulation of portal and hepatic veins) baseline measurements were obtained. Subsequently, DOBU, DOPA and NE were administered randomly at doses that either increased mean arterial pressure (MAP) by approx. 20% (DOPA, NE), or that increased cardiac output (CO) and/or heart rate (HR) by approx. 50% (DOBU). Measurements were made 10 minutes after stable hemodynamics had been obtained. Data were analyzed by Friedman's statistic and Wilcoxon-signed rank test (significance level $p<0.05$).

**RESULTS** (Table). With comparable increases in $DO_2TOT$, total hepatic $O_2$ delivery ($DO_2TH$) remained unchanged during DOBU, decreased during NE, and increased during DOPA only. Similarly, small intestinal $DO_2$ ($DO_2SI$) increased, and $O_2$ extraction ($EO_2$) decreased during DOPA only. In contrast, neither $O_2$ uptakes ($VO_2$) nor tissue surface $O_2$ tensions ($P_sO_2$) were affected by either drug.

**DISCUSSION.** Our results suggest that increases in $DO_2$-TOT may not necessarily be associated with an increase (DOPA), but also with no change (DOBU) or even a decrease (NE) in $DO_2TH$. However, the different effects on $O_2$ delivery were not reflected in respective changes in surface $O_2$ tensions. This may change entirely in situations where $DO_2TH$ is reduced prior to any therapeutic intervention. In such case, a further reduction in $DO_2TH$ (as during NE) may adversely affect hepatic oxygenation, whereas an increase in $DO_2TH$ (as during DOPA) may improve it.

| VARIABLE | C | DOBU | DOPA | NE |
|---|---|---|---|---|
| HR ($min^{-1}$) | 104 ± 5 | 157 ± 9* | 142 ± 6* | 117 ± 8* |
| MAP (mmHg) | 110 ± 2 | 97 ± 6* | 130 ± 4* | 136 ± 3* |
| CO (l/min) | 4.3 ± 0.3 | 7.1 ± 0.5* | 5.9 ± 0.5* | 5.6 ± 0.4* |
| THBF (ml/min) | 777 ± 59 | 837 ± 40 | 898 ± 72* | 619 ± 41* |
| PVBF (ml/min) | 555 ± 49 | 635 ± 56 | 781 ± 69* | 490 ± 40* |
| HABF (ml/min) | 195 ± 37 | 202 ± 32 | 117 ± 18* | 128 ± 22* |
| SMABF (ml/min) | 363 ± 33 | 383 ± 34 | 477 ± 36* | 321 ± 32 |
| $DO_2TOT$(ml/min) | 481 ± 37 | 841 ± 67* | 787 ± 74* | 700 ± 57* |
| $DO_2TH$ (ml/min) | 70 ± 9 | 77 ± 6 | 98 ± 10* | 58 ± 5* |
| $DO_2SI$ (ml/min) | 41 ± 5 | 46 ± 5 | 65 ± 7* | 40 ± 5 |
| $VO_2TH$ (ml/min) | 24 ± 4 | 27 ± 3 | 24 ± 3 | 24 ± 3 |
| $VO_2SI$ (ml/min) | 13 ± 2 | 13 ± 2 | 16 ± 2 | 13 ± 2 |
| $EO_2TH$ (%) | 35 ± 3 | 35 ± 3 | 25 ± 2* | 40 ± 5 |
| $EO_2SI$ (%) | 32 ± 1 | 29 ± 3 | 23 ± 3* | 31 ± 2 |
| $P_sO_2HEP$ (mmHg) | 62 ± 3 | 58 ± 4 | 63 ± 5 | 64 ± 3 |
| $P_sO_2SI$ (mmHg) | 64 ± 3 | 57 ± 2 | 58 ± 2 | 56 ± 3 |
| $P_aO_2$ (mmHg) | 113 ± 3 | 100 ± 1* | 106 ± 3* | 105 ± 3* |

Means ± SEM. * = $p < 0.05$ compared to control (C). BF = blood flow. TH = total hepatic. $P_sO_2$ = surface $PO_2$. HEP = hepatic.