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• BASIC RESEARCH •

The effects of anisodamine and dobutamine on gut mucosal blood flow during gut ischemia/reperfusion

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Abstract

AIM: **To determine if anisodamine is able to augment mucosal perfusion during gut I/R ischemia-reperfusion.**

METHODS: **A jejunal sac was formed in Sprague Dawley rat. A Laser Doppler probe and a tonometer were inserted into the sac which was filled with saline. The superior mesenteric artery was occluded (SMAO)for 60 minutes followed by 90 minutes of reperfusion. At the end of 60 minutes of SMAO, either 0.2mg/kg of anisodmine or dobutamine was injected into the jejunal sac. Laser Doppler mucosal blood flow and regional PCO_2 ($PrCO_2$)measurements were made.**

RESULTS: **Mucosal blood flow was significantly increased at 30,60 and 90 minutes of reperfusion (R_{30},R_{60},R_{90}) when intraluminal anisodamine or dobutamine was present compared to intraluminal saline only(44±3.3% or 48±4.1% *vs* 37±2.6% at R_{30}, 57±5.0% or 56±4.7% *vs* 45±2.7% at R_{60}, 64±3.3% or 56±4.2% *vs* 48±3.4% at R_{90},respectively $P<0.05$). Blood flow changes were also reflected by lowering of jejunal $PrCO_2$ measurements after intraluminal anisodamine or dobutamine compared with that of the saline controls (41±3.1mmHg or 44±3.0mmHg *vs* 49±3.7mmHg at R_{30},38±3.7mmHg or 40±2.1mmHg *vs* 47±3.8mmHg at R_{60},34±2.1mmHg or 39±3.0mmHg *vs* 46±3.4mmHg at R_{90}, respectively, $P<0.05$). Most interesting finding was that there were significantly higher mucosal blood flow and lower jejunal $PrCO_2$ in anisodamine group than those in dobutamine group at 90 minutes of reperfusion(64±3.3% vs 56±4.2% for blood flow or 34±2.1mmHg *vs* 39±3.0mmHg for $PrCO_2$,respectively,$P<0.05$),suggesting that anisodamine had a more lasting effect on mucosal perfusion than dobutamine.**

CONCLUSION: **Intraluminal anisodamine and dobutamine can augment mucosal blood flow during gut I/R and alleviate mucosal acidosis. The results provided benificial effects on the treatment of splanchnic hypoperfusion following traumatic or burn shock.**

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INTRODUCTION

With remarkable advancement in our understanding of shock and greater ability to resuscitate patients from shock, few people today died of hypovolemic shock. However there still exists an inadequate splanchnic perfusion, especially gut ischemia, despite apparent normalization of global hemodynamic parameters. Clinical and experimental studies have implicated gut hypoperfusion as an important inciting event which contributes to gut origin sepsis and multiple organ dysfunction[1-10]. To improve gut perfusion, thus averting compensated shock, is still an important goal of resusucitation of shook[11,12].Anisodamine and dobutamine are commonly used as antishock drugs,as they can improve the microcirculation flow and splanchnic perfusion[13-16].Anisodamine,an anticholinergic drug extract from a Chinese herb Anisodus tanguticus, also processes many other beneficial effects such as inhibition of thromboxane synthesis and protection of cell from reperfusion injury[17-20].Some researches indicated that anisodamine and dobutamine augmented gut perfusion during the shock[21,22],but there was no report concerning their intraluminal effects on mucosal blood flow and metabolism in the gut. The purpose of this study is to investigate the effects of local administration of anisodamine and dobutamine on mucosal blood flow and $PrCO_2$ in a gut ischemia-reperfusion (I/R) rat model.

MATERIALS AND METHODS

Animal model

Male Sprague-Dawley rats weighing 350-450 grams were employed after acclimatization to the experimental environment. Rats were fasted overnight but allowed free access to water.Anesthesia was induced and maintained with 2% isoflurane and body temperature maintained at 37℃ by the use of a warming blanket. Through an upper midline laparotomy, a segment of jejunum measuring 16cm in length was isolated 5cm distal to the ligament of Treitz with preservation of its mesentery. The isolated loop was closed at both ends with 3-0 silk ligatures[23,24]. The superior mesenteric artery (SMA) was isolated at its origin and clamped for 60 minutes, followed by release of the clamp and restoration of blood to the intestine for 90 minutes to produce gut ischemia and reperfusion injury (I/R injury). At the time of release of the clamp, either 0.2mg/kg of anisodamine or dobutamine was injected into the jejunal sac. At the conclusion of the experiment, cardiac puncture and exsanguination were used to achieve euthanasia.

Animals were divided into three groups: Group one (n=15): I/R + anisodamine + saline; group two (n=15): I/R + dobatamine + saline and group three (n=10): I/R + saline as control.

Measurement of mucosal blood flow

A Teflon-coated laser optic flow probe (Peri flux PF409, flexible probe with 0.25mm fiber separation) was inserted through a small enterotomy at the proximal end of the jejunal sac and it was positioned along the antimesenteric border of the jejunum to the center of the sac. Mucosal blood flow was continuously recorded with a laser Doppler flow monitor (Peri Flux 4001 Master; Perimed, Jaarnfalla, Sweden). Blood flow measurements using Laser Doppler flow meters are not absolute but rather indicate flow in arbitrary perfusion units. Measurements were taken as the average flow over a five-minute period following an initial 30 minute period of stabilization. The quality of the signal was monitored by visualization on the computer screen so that motion artifact and noise were excluded from measurement[25,26].

Measurement of PCO_2 ($PrCO_2$)

In the same animal, a 5F saline tonometer was inserted through a small enterotomy at the distal end of the sac and positioned to the center of the sac. The system was allowed to equilibrate for 30 minutes at which time a baseline $PrCO_2$ measurement was obtained by discarding the first 0.3ml saline from the tonometer balloon and using the remaining 0.7ml for analysis (model 1610 pH/blood gas analyzer, Milano,Italy), Regional PCO_2($PrCO_2$) was calculated using the following formula: $PrCO_2$=measure PCO_2×EF. EF=equlibration factor, and based on the equilibration period for saline which gained from the handbook[27-29].

Doppler measurements and $PrCO_2$ determinations were made every 30 minutes throughout the experimental period.

Statistics

Data were reported as mean ±SEM and were analyzed by one-way analysis of variance (ANOVA)or student *t* test, significance was set at $P<0.05$.

RESULTS

Laser doppler flow

Table 1 showed the effects of anisodamine and dobutamine on gut mucosal blood flow. Laser Doppler baseline flow(arbitrary units)was not different among groups. Flow dropped significantly during ischemia, with a reduction to 12% of baseline level,but notably not down to zero.With reperfusion,flow increased over time in all groups ($P<0.05$)but did not reach baseline by 90 minutes. When compared to saline group, mucosal blood flow were higher in the anisodamine and dobutamine groups ($P<0.05$) throughout the reperfusion period. Blood flow was also significantly higher at 90 minutes after reperfusion in anisodamine group compared with dobutamine animals($P<0.05$).

Table 1 Effects of anisodamine and dobutamine on gut mucosal blood flow (%)

Goups	B	I_{60}	R_{30}	R_{60}	R_{90}
Anisodamine	98±3.8	14±3.9	$44±3.3^{ab}$	$57±5.0^{ab}$	$64±3.3^{abc}$
Dobutamine	100±5.2	18±2.1	$48±4.1^{ab}$	$56±4.7^{ab}$	$56±4.2^{ab}$
Saline	103±6.9	16±3.4	$37±2.6^{a}$	$45±2.7^{a}$	$48±3.4^{a}$

Mean ± SEM; $^aP<0.05$, *vs* I_{60}; $^bP<0.05$, *vs* saline; $^cP<0.05$, *vs* Dobutamine;B, baseline;I_{60},ischemia 60 minutes;R_{30},reperfusion 30minutes;R_{60},reperfusion 60 minutes;R_{90}, reperfusion 90 minutes.

Tonometry $PrCO_2$

Table 2 depicts jejunal $PrCO_2$ during I/R. Jejunal $PrCO_2$ did not differ in baseline among the groups, but it was significantly increased at 60 minutes of ischemia in all groups, amounting to 204% of baseline level. With reperfusion, $PrCO_2$ dropped over time in all groups($P<0.05$), but did not reach the baseline. When compared with saline group, $PrCO_2$ values were lower in the anisodamine and dobutamine groups ($P<0.05$) throughout reperfusion period. There were no significant differences between anisodamine group and dobutamine animals at 30 and 60 minutes of reperfusion,but by 90 minutes of reperfusion anisodamine administration resulted in a significantly lower $PrCO_2$ than dobutamine($P<0.05$).

Table 2 Effects of anisodamine and dobutamine on $PrCO_2$ (mm Hg)

Goups	B	I_{60}	R_{30}	R_{60}	R_{90}
Anisodamine	28±2.2	55±3.9	$41±3.1^{ab}$	$38±3.7^{ab}$	$34±2.1^{abc}$
Dobutamine	31±3.8	61±7.8	$44±3.0^{a}$	$40±2.1^{ab}$	$39±3.0^{ab}$
Saline	26±2.5	57±5.4	49±3.7	$47±3.8^{a}$	$46±3.4^{a}$

Mean ± SEM;$^aP<0.05$, *vs* I_{60};$^bP<0.05$, *vs* saline;$^cP<0.05$, *vs* Dobutamine;B, baseline;I_{60},ischemia 60 minutes;R_{30},reperfusion 30minuts;R_{60},reperfusion 60 minutes;R_{90}, reperfusion 90 minutes

DISCUSSION

Both laboratory and clinical studies have demonstrated that splanchnic perfusion remains significantly impaired following resuscitation in traumatic, hemorrhagic and septic shock[30-33]. Intravital video microscopic studies by F1ynn *et al*[34,35] have shown that although inflow and premucosal arterioles return to normal after resuscitation from hemorrhagic shock, there is a progressive arteriolar constriction resulting in a decrease in blood flow. There have been few reports about effects of intraluminal vasoactive agents on gut mucosal blood flow during both ischemia and reperfusion. It has been demonstrated that dobutamine could augment gut microcirculatory blood flow in septic shock[36,37].Observation in extensively burned patients by Sheng, *et al*[22] have shown that intravenous administration of anisodamine 12 hours postburn resulted in a significant elevation in gastric pHi and decrease in plasma level of TNF. In a porcine model of 30% TBSA full-thickness burn, anisodamine (0.4mg/kg)infused intravenously for one hour could increase portal blood flow, and it showed a positive correlation with intestinal pHi[38]. The use of Laser Doppler-measured tissue perfusion is a reliable technique that has been validated in the assessment of gastrointestinal mucosal blood flow, and the results were shown to correlate with other techniques of measurement of local blood flow[33,38]. Recently, its use as a clinical tool for assessing jejunal mucosal perfusion had also been demonstrated[39]. In this study with advanced Laser Doppler technique, we further demonstrated the beneficial effect of anisodamine on gut mucosal perfusion during I/R injury in comparision with dobutamine. The results showed that intraluminal anisodamine or dobutamine did increase mucosal blood flow throughout reperfusion as compared to intraluminal saline only. Blood flow augmentation was reflected by lower jejunal $PrCO_2$ measurements with intraluminal anisodamine or dobutamine. The most interesting finding was that there were significantly lower jejunal $PrCO_2$ and higher mucosal blood flow in anisodamine group than those in dobutamine at 90 minutes of reperfusion, suggesting that anisodamine had a more lasting effect on mucosal perfusion than dobutamine.

Tissue CO_2 gas tonomery provides an indirect measurement of perfusion and /or mucosal metabolic stress. Gastric tonometry, in particular, has been suggested as a tool to monitor splanchnic perfusion in experimental animals and critically ill patients[40-43]. Though studies have demonstrated low gastric intramucosal pH (pHi) is a good predictor of poor outcome in critically ill patients, no improvement in outcome has been ascertained when patients are resuscitated based on the results of gastric tonometry[44-46]. In this study we used 5F gut tonometry, in which the air pocket can be matched with rat small bowel sac, and the results are more accurate than gastric tonometry in detecting gut perfusion and metabolism[47-50]. In our study significant increases in gut $PrCO_2$ following gut I/R were found, which could be markly reduced by intraluminal anisodamine or dobutamine. These results might suggest that anisodamine or dobutamine is capable of augmenting mucosal blood flow, thus improving gut mucosal metabolism.

In conclusion, we have demonstrated in this laboratory model of gut ischemia and reperfusion that intraluminal anisodamine or dobutamine could augment mucosal blood flow, alleviate mucosal acidosis, improve metabolism in mucosal cell. These results provided reliable evidence to clinicians to adopt anisodamine or dobutamine in the treatment of splachnic hypoperfusion, espcially gut mucosal blood flow reduction following traumatic or burn shock.

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