The effect of medetomidine–ketamine anaesthesia on haemodynamic parameters during haemorrhagic shock in minipigs

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Summary

Haemorrhagic shock (HS) represents an acute event with high mortality. The optimal combination of anaesthetics that would prevent haemodynamic collapse and allow damage control surgery has not yet been determined. We tested the hypothesis that a combination of dissociative anaesthetic ketamine with alpha$_2$-agonist medetomidine (MK group, n=10) would provide superior haemodynamic control compared to propofol-remifentanil (PR group, n=10) during HS in minipigs. A modified Wiggers' model of HS with a target mean arterial pressure (MAP) of 40 mm Hg and 2 h duration was used. All minipigs survived. HS led to a ~ 50% decrease in cardiac output in both groups (P<0.001 for baseline vs. HS 120 min) with no differences between groups. Total volume of removed blood was larger in the MK group (1321±133 ml vs. 1111±246 ml in the PR group, respectively; P<0.05). MAP was higher during the initial phases of HS in the MK group vs. PR group (P<0.05 at HS 30–90 min). HR was lower in the MK group at the late phases of HS (P<0.05 at HS 60–120 min). In conclusion, medetomidine-ketamine provides a feasible and possibly a more favourable alternative to the propofol-remifentanil combination in our model of HS in minipigs.

Key words: Haemorrhagic shock; ketamine; alpha$_2$-agonists; remifentanil; propofol

Introduction

Haemorrhagic shock (HS) remains a leading cause of preventable death in both civilian and military settings (Alam and Rhee 2007). The acute hypovolaemia causes haemodynamic derangement that - if untreated - could lead to exsanguination cardiac arrest. While victims of HS require anaesthesia to allow for a damage control surgery, virtually all anaesthetics adversely affect haemodynamics even in intact patients. The optimal combination of drugs for pre-hospital analgesia and in-hospital anaesthesia for HS patients that would preserve haemodynamics has not yet been determined.

Ketamine is a dissociative anaesthetic frequently used for sedation, analgesia, or general anaesthesia because of its analgetic capacities and favorable haemodynamic effects even in disrupted circulation (Haskins and Patz 1990). Because of its psychomimetic effects, ketamine is often combined with benzodiazepines which, however, in the presence of hypovolaemia may lead to further decrease of blood pressure (Adams *et al.* 1985).

Medetomidine, a highly specific alpha$_2$-agonist, has a central sympatholytic effect resulting in a decrease in blood pressure and heart rate. In contrast, continuous intravenous infusion of medetomidine increased blood pressure in pigs (Vainio *et al.* 1992), and also reduced the incidence of psychomimetic effects following ketamine administration (Levanen *et al.* 1995).

A combination of ketamine and medetomidine in normovolaemic animals generally induces bradycardia and severe hypertension (Caulkett *et al.* 1999, Jalanka *et al.* 1989, Ko *et al.* 2000, Sladky *et al.* 2000, Stegmann and Jago 2006, Tomizawa *et al.* 1997).

Considering the above-mentioned drug characteristics, we considered the combination of medetomidine-ketamine to be a promising candidate to be tested for anaesthesia in compromised circulation. In our study we tested the hypothesis that the combination of

medetomidine with ketamine has beneficial effects on haemodynamic parameters during HS in minipigs. The control group was anaesthetized with commonly used anaesthetics propofol and remifentanil.

Methods

The experimental study was approved by the Institutional Animal Care and Use Committee, Institute for Clinical and Experimental Medicine, Prague, Czech Republic. The experiments were conducted in conformity with the European Convention on Animal Protection. The study was carried out on twenty Minnesota minipigs weighing 35–42 kg of either sex with randomization to study and control groups (n=10 per group).

The animals were obtained from a licensed vendor and housed in the facility for at least 72 h before the experiment. After intramuscular premedication with standard doses of azaperone (4 mg/kg) and fentanyl (2 μg/kg), an 18-gauge (G) intravenous cannula was placed in the ear vein, and a general anaesthesia was induced with intravenous administration of 5 mg/kg of metomidate. Neuromuscular blockade was not used. The minipigs were then intubated and ventilated with inspired oxygen fraction (FiO_2) 0.5, tidal volume of 10 ml/kg with a variable frequency to maintain normocapnia.

Anaesthesia before the induction of HS was maintained in both groups by a combination of propofol (10 mg/kg/hr) and remifentanil (1 μg/kg/min). Pulmonary artery catheter (model 831, Edwards Lifesciences, CA, USA; 7.5 French [F]) was advanced via the right internal jugular vein for continuous monitoring of haemodynamic parameters. An 8.5 F introducer placed in the internal jugular vein was used for blood withdrawal. A 20 G catheter was placed into the femoral artery for invasive blood pressure monitoring.

After instrumentation, the infusion of anaesthetics was discontinued for 15 minutes to allow for a washout of the anaesthetics used during the preparation phase. Animals were then randomized into two groups. In the control group, total intravenous anaesthesia (TIVA) was maintained by continuous infusion of propofol and remifentanil (PR group, the doses see above). In the study group, from the beginning of HS, TIVA was maintained by a combination of medetomidine (10 μg/kg/hr) with ketamine (5 mg/kg/hr) (MK group).

A modified Wiggers' model of HS was used (Wiggers *et al.* 1945). In brief, HS was induced by a rapid blood withdrawal to target mean arterial pressure (MAP) of 40 mm Hg, followed by repeated blood withdrawals every 30 minutes when necessary to reach MAP 40 mm Hg again. The total duration of HS was 2 hours. Surviving animals were then sacrificed with intravenous thiopental combined with a potassium chloride overdose.

Heart rate (HR), MAP, central venous pressure (CVP), mean pulmonary artery pressure (MPAP) and cardiac output (CO) were recorded at baseline and at 30 min intervals and considered independent variables. The values were used to calculate stroke volume (SV) and systemic vascular resistance (SVR), considered dependent variables. The total withdrawn blood volume was determined at the end of experiment.

The outcome parameters were statistically evaluated with one-way analysis of variance with Bonferroni's significance level correlation (SPSS v. 16.0, Chicago, IL, USA). A P value <0.05 was considered statistically significant.

Results

Baseline (BL) physiologic data were similar in both groups (Table 1). All animals survived in both groups.

HS led to a ~ 50 % decrease in CO (PR group: BL 3.4±0.6 l/min, HS 120 min 1.7±0.2 l/min; MK group: BL 3.9±0.7 l/min, HS 120 min 1.8±0.6 l/min; $P<0.001$ BL vs. HS 120 min in either group; Fig. 1). MAP decreased over time in both groups, but it was better preserved during the initial phases of HS in the MK group, reaching statistical significance in HS 30-90 min timepoints (Fig. 2). HR was lower in the MK group at the late phases of HS (HS 60-120 min timepoints; Fig. 3). SVR was higher in the MK groups only at HS 30 min timepoint (MK, 3464±1049 dyn.sec/cm^5, PR, 2414±355 dyn.sec/cm^5; $P<0.05$). There were no differences in SV, CVP or MPAP between groups at any timepoint (data not shown). The total amount of removed blood was larger in the MK group (1321±133 ml vs. 1111±246 ml in the PR group, respectively; $P<0.05$). Based on the formula to calculate blood volume of minipigs (Diehl *et al.* 2001), this represents 53% of removed blood volume in the MK group vs. 45% in the PR group, which is consistent with an impending shock state in transition to an irreversible shock state (Wiggers and Ingraham 1946).

Discussion

We demonstrated that the combination of alpha$_2$-agonist medetomidine with ketamine is characterized by haemodynamic stability during HS in minipigs. The MAP values were significantly higher in the MK group during the whole HS. This was caused by the sympathomimetic effects of ketamine and peripheral vasoconstriction exerted by medetomidine. SVR was constantly higher in the MK group vs. PR group during the entire experiment. HR in the MK group was lower in the late phases of HS (HS 90 and 120 min), resulting in an insignificant decrease in CO. This was probably caused by sympatholytic effects of medetomidine. Most importantly, the favourable haemodynamic profile was

achieved despite larger volume of removed blood during pressure-targeted HS in the MK group.

A standard treatment for HS victims includes analgesia and sedation. However, currently there is not available a single specific drug designed for analgesia, general anaesthesia or sedation during HS. It has been shown that nociceptive stimuli from traumatized area of the body together with pain and fear can augment sympathoadrenergic reactions, thus worsening shock conditions. On the other hand, they can contribute to positive haemodynamic compensatory changes. Unanaesthetized dogs subjected to HS showed better survival than their sympathectomized controls (Chien 1964). In contrast, norepinephrine infusion during HS decreased both survival time and rate (Close *et al.* 1957).

All anaesthetics virtually cause ablation of sympathetic activity by decreasing SVR, followed by a decrease in blood pressure. The effects of anaesthetics could be even more pronounced in an acutely hypovolaemic patient. The choice of an anaesthetic could have a significant impact on the outcome of the HS. Peng et al. showed a 87.5% survival after 30 or 40% blood loss in unanaesthetized rats vs. 0% survival in those anaesthetized with sodium pentobarbital (Peng *et al.* 2006). Longnecker at al. documented superior acute and long-term survival rates in a rat HS model with ketamine compared to halothane, fluroxene or pentobarbital (Longnecker and Sturgill 1976). This effect was accompanied by a relative absence of pathologic changes in the small intestine and liver, suggesting preferential shifting of perfusion to the gut.

Ketamine, an N-methyl-D-aspartate (NMDA)-antagonist, has unique characteristics in comparison with commonly used anaesthetics. It increases sympathoadrenal reactions, SVR and venous return. Spontaneous breathing and protective reflexes of upper airways are partially preserved. Ketamine has been successfully used from the 1970s in hypovolaemic patients or in patients in HS (Bond and Davies 1974, Chasapakis *et al.* 1973). In these reports,

a combination of ketamine with pancuronium, a neuromuscular blocking agent with vagolytic properties, has been used. However, further studies showed that the use of pancuronium in decompensated HS is deleterious (Christian *et al.* 1979). A favourable effect on survival from HS in rats was reported using a combination of ketamine and alpha$_2$-agonist clonidine (Kaukinen 1978).

Psychomimetic effects associated with ketamine are often unpleasant. The combination of ketamine with benzodiazepines to ameliorate this phenomenon is effective but not devoid of side-effects, namely further reduction in SVR and ensuing hypotension in hypovolaemic patients (Adams *et al.* 1985).

Alpha$_2$-agonists are used for their anti-hypertensive properties. They elicit a dual response: the first phase is characterized by a transient hypertension (caused by a peripheral vasoconstriction) followed by hypotension in the second phase (caused by a central vasodilation). The overall blood pressure response to alpha$_2$-agonists depend on several factors: dose, route of administration, selectivity for alpha$_2$-receptors, and concurrently given drugs (Sinclair 2003). With intravenous application of ketamine, continuous infusion of alpha$_2$-agonist antagonizes sympathomimetic effects of ketamine, and the net cardiovascular effects depend on the balance between the effects of both drugs.

Medetomidine is a highly specific alpha$_2$-agonist with short half-life of 2.5 hours (Scheinin and Schwinn 1992). In continuous infusion it was also shown to attenuate the psychomimetic effects to ketamine, although to a lesser degree than midazolam (Levanen *et al.* 1995). Vainio et al. published detailed haemodynamic data in minipigs using combination of medetomidine-ketamine anaesthesia. MAP increased from 116 mm Hg to 142 mm Hg and then slowly decreased to baseline values during 60 minutes. SVR increased three-fold. CO decreased from 1.8±0.7 l/min to 0.4±0.3 l/min. The plasma levels of norepinephrine and epinephrine significantly decreased (Vainio *et al.* 1992). In humans, clonidine significantly

reduced hypertension caused by ketamine during inhalational anaesthesia (Tanaka and Nishikawa 1994) or at the time of endotracheal intubation (Munro *et al.* 1993). Dexmedetomidine and ketamine combination has been successfully used in paediatric patients undergoing cardiac catheterization with little haemodynamic variations (Barton *et al.* 2008, Mester *et al.* 2008).

Medetomidine is a racemate designed for veterinary medicine. Dexmedetomidine is eight-times more selective for alpha$_2$-receptors compared to a partial alpha$_2$-agonist clonidine (Scheinin *et al.* 1989). The difference in selectivity for alpha$_2$-receptors between medetomidine and clinically used dexmedetomidine has not been studied.

Thus, we considered the use of medetomidine in minipigs for our study a logical and a reasonable choice that would adequately mirror a clinical scenario. Nevertheless, the differences in haemodynamic response to alpha$_2$-agonists among species should be taken into consideration while interpreting the results of our study.

The importance of maintaining pre-set levels of MAP vs. CO in HS patients has been a matter of ongoing debate and large controversy. In our study, CO decreased by ~ 50 % in both groups, while MAP was better preserved in the MK group, suggesting greater haemodynamic stability in the MK group. Also, the combination of medetomidine with ketamine – despite blunting the physiologic response of increase in HR due to hypovolemia – maintained CO with lower HR, i.e. by higher stroke volume due to better left ventricular filling despite higher blood loss compared with the combination of propofol-remifentanil.

Our study has several limitations. There were no deaths in either group suggesting that despite no fluid resuscitation, the severity of the insult was only moderate. We did not monitor biochemical markers of organ injury that would provide an additional information of the metabolic derangements of the animals. Selected metabolic parameters, e.g. lactate, base

deficit or pH, were shown to have better predictive value than classic haemodynamic parameters used traditionally as outcome parameters in HS studies (Rixen *et al.* 2001).

Also, our experiment was terminated at the end of HS. We did not assess the effect of the anaesthetic combinations on the long-term survival following resuscitation. It has been shown recently that a combination of an alpha$_2$-agonist dexmedetomidine with ketamine mitigates acute lung injury in rats subjected to HS (Yang *et al.* 2009). A protective dose-dependent effects of propofol that mitigated end-organ injury after HS have been described across species (Lee *et al.* 2008, Lee *et al.* 2009, Yao *et al.* 2009). Similar effect was found with fentanyl (Yao *et al.* 2009). Thus, all drugs used in our study could play a distinct role in ameliorating ischaemia-reperfusion injury during the resuscitation phase and ultimately affect long-term outcome from HS.

We also assumed that the doses of drugs and their respective combinations were equipotent but this was not verified in an independent study. The pharmacologic protocols allowed to perform the study in nonparalyzed animals, confirming an adequate anaesthesia depth in both groups. We did not adjust the doses of individual drugs during the HS. HS was shown to alter the pharmacokinetics of remifentanil, suggesting that less remifentanil would be required to maintain a target plasma concentration (Johnson *et al.* 2001). Both pharmacokinetics and pharmacodynamics of propofol were changed in the setting of HS (Johnson *et al.* 2003, Kurita *et al.* 2009). Of note, all afore-mentioned pharmacological studies used similar Wiggers‘ model of HS. In a separate study, hypnotic potency of propofol was shown to be increased even in an isovolaemic model of HS in humans with preserved CO (Takizawa *et al.* 2006).

We chose not to include a group that would be treated with a volatile anaesthetic. Instead, we focused on a combination of intravenous agents that could be used in the prehospital settings or in locations with limited resources. Other combinations of drugs, e.g.

ketamine-midazolam, represent another alternative. However, the deleterious effects of midazolam in compromised circulation (Adams *et al.* 1985) lessen the enthusiasm for its use in this setting. Further studies using novel drugs with enhanced profile, e.g. dexmedetomidine or S-ketamine, devoid of psychomimetic properties, are thus warranted.

In conclusion, a combination of medetomidine and ketamine during HS in minipigs resulted in a higher blood pressure and decreased HR compared to propofol-remifentanil combination. There were no differences in CO between the groups. Haemodynamic stability was maintained despite larger volume of removed blood in the MK group. Our results suggest that medetomidine-ketamine provides a feasible and possibly a more favourable alternative to the propofol-remifentanil combination in our model of HS in minipigs.

Acknowledgement

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Conflict of Interest

None of the authors declare any conflict of interest.

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Table 1. Baseline hemodynamic parameters of PR and MK minipig groups.

	PR	**MK**
HR (beats/min)	72 ± 6	71 ± 18
MAP (mm Hg)	92 ± 8	100 ± 16
CO (l/min)	3.4 ± 0.6	3.9 ± 0.7
CVP (mm Hg)	7 ± 2	7 ± 3
MPAP (mm Hg)	24 ± 3	21 ± 4
SVR (dyn.sec/cm^5)	2068 ± 373	1862 ± 525

PR, propofol-remifentanil; MK, medetomidine-ketamine; HR, heart rate; MAP, mean arterial pressure; CO, cardiac output; SVR, systemic vascular resistance; MPAP, mean pulmonary artery pressure; CVP, central venous pressure. Values are mean ± S.D. No differences between groups.

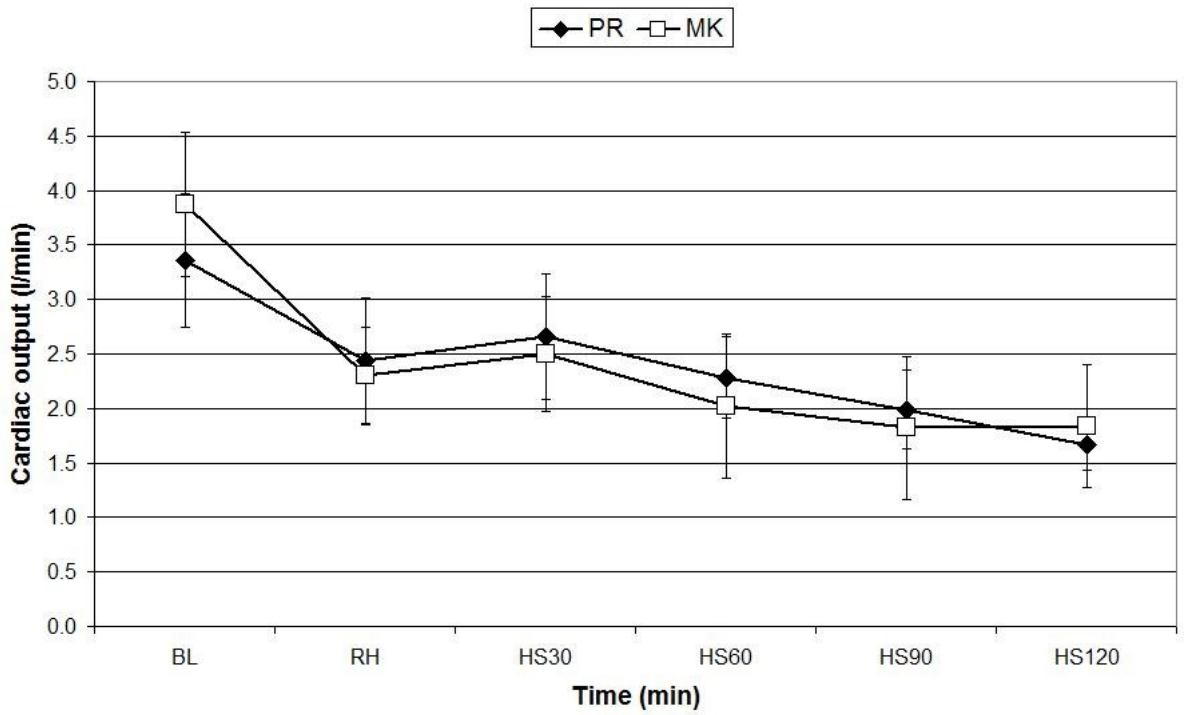

Fig. 1. Cardiac output during haemorrhagic shock.

PR, propofol-remifentanil; MK, medetomidine-ketamine; BL, baseline; RH, after initial rapid haemorrhage. $P<0.001$ BL vs. HS 120 min in either group. No differences between groups.

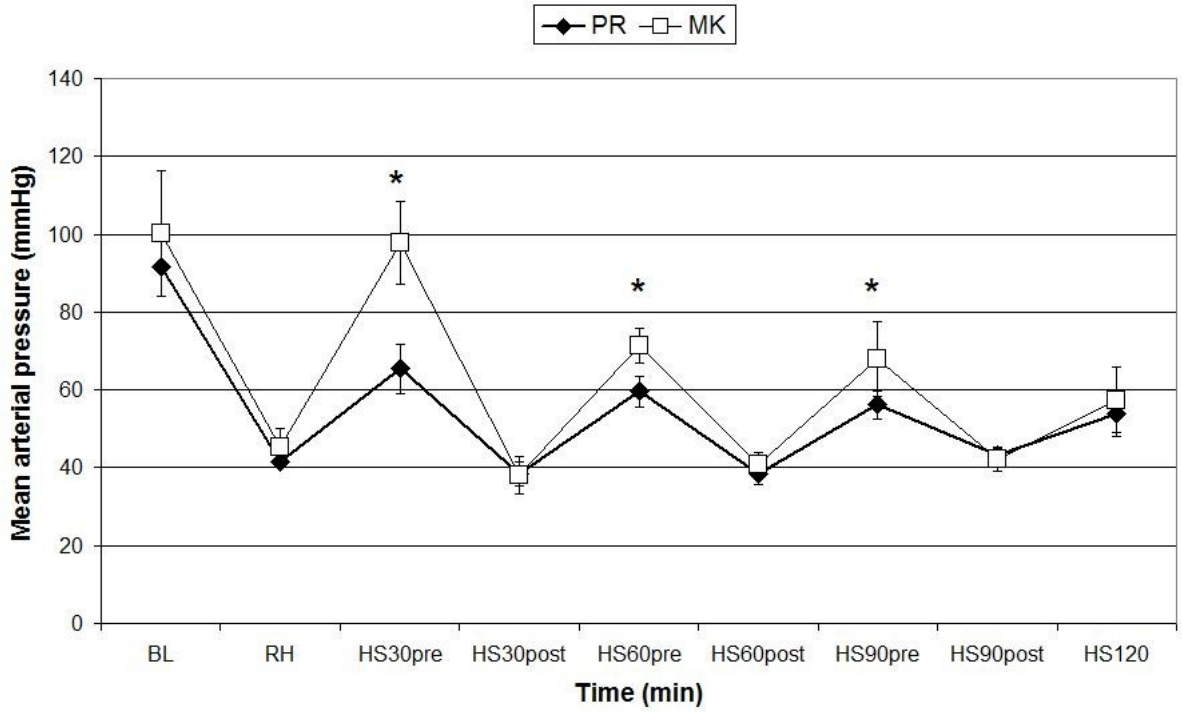

Fig. 2. Mean arterial pressure during haemorrhagic shock.

PR, propofol-remifentanil; MK, medetomidine-ketamine; BL, baseline; RH, after initial rapid haemorrhage. $P<0.001$ BL vs. HS 120 min in either group. * $P<0.05$ between groups.

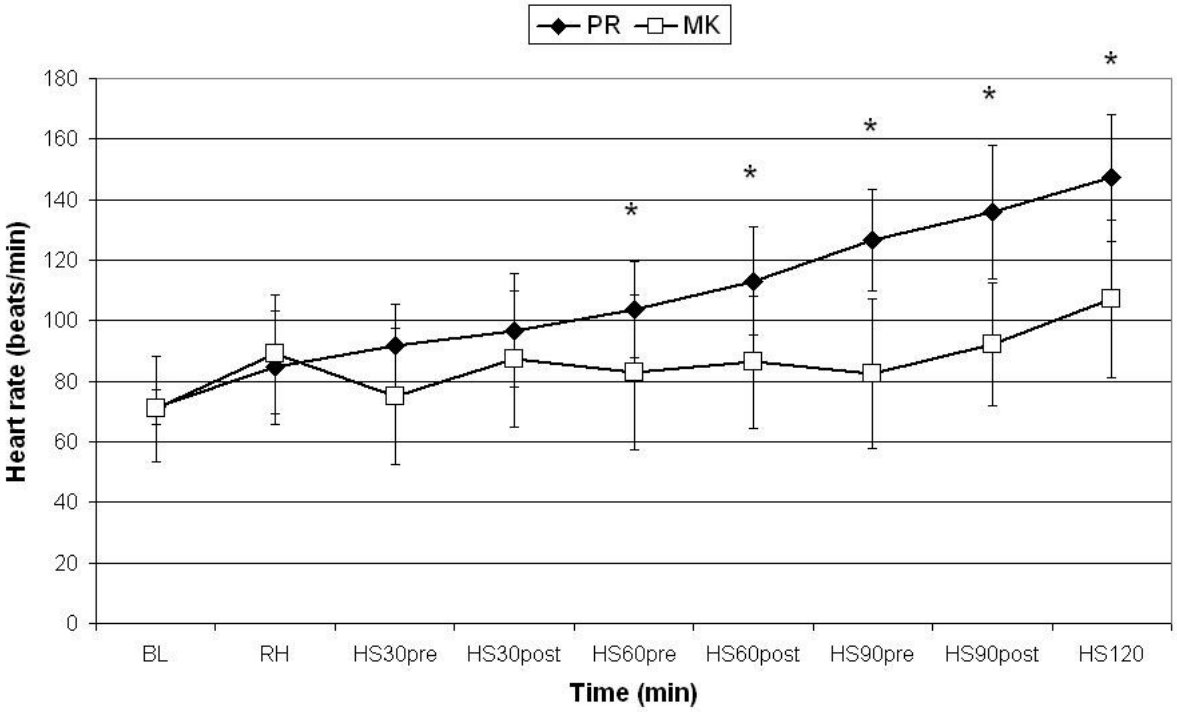

Fig. 3. Heart rate during haemorrhagic shock.

PR, propofol-remifentanil; MK, medetomidine-ketamine; BL, baseline; RH, after initial rapid haemorrhage. $P<0.001$ BL vs. HS 120 min in either group. * $P<0.05$ between groups.