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Sufentanil–medetomidine anaesthesia compared with fentanyl/fluanisone–midazolam is associated with fewer ventricular arrhythmias and death during experimental myocardial infarction in rats and limits infarct size following reperfusion

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Abstract

To improve infarct healing following myocardial infarction in humans, therapeutic interventions can be applied during the inflammatory response. Animal models are widely used to study this process. However, induction of MI in rodents is associated with high mortality due to ventricular fibrillation (VF) during coronary artery ligation. The anaesthetic agent used during the procedure appears to influence the frequency of this complication. In this retrospective study, the effect on ventricular arrhythmia incidence during ligation and infarct size following in vivo reperfusion of two anaesthetic regimens, sufentanil–medetomidine (SM) and fentanyl/fluanisone–midazolam (FFM) was evaluated in rats. Anaesthetics were administered subcutaneously using fentanyl/fluanisone (0.5 mL/kg) with midazolam (5 mg/kg) (FFM group, $n = 48$) or sufentanil (0.05 mg/kg) with medetomidine (0.15 mg/kg) (SM group, $n = 47$). The coronary artery was ligated for 40 min to induce MI. Heart rate and ventricular arrhythmias were recorded during ligation, and infarct size was measured via histochemistry after three days of reperfusion. In the SM group, heart rate and VF incidence were lower throughout the experiment compared with the FFM group (6% versus 30%) ($P < 0.01$). Fatal VF did not occur in the SM group whereas this occurred in 25% of the animals in the FFM group. Additionally, after three days of reperfusion, the infarcted area following SM anaesthesia was less than half as large as that following FFM anaesthesia ($8.5 \pm 6.4\%$ versus $20.7 \pm 5.6\%$) ($P < 0.01$). Therefore, to minimize the possibility of complications related to VF and acute death arising during ligation, SM anaesthesia is recommended for experimental MI in rats.

Keywords

ischaemia, anaesthesia, arrhythmias, sufentanil, medetomidine

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Ischaemic heart disease is currently the leading cause of death worldwide.[1] There is increasing evidence that targeting the inflammatory response that occurs following cardiac ischaemia/reperfusion (I/R) injury associated with myocardial infarction (MI), contributes to improved cardiac healing.[2–8] Animal models are particularly useful for studying the inflammatory response and putative therapeutic interventions following I/R injury.

The acute inflammatory response triggered by cardiac I/R injury in rats mimics the human response. Therefore, rats are a common choice for use as an MI research model, where myocardial ischaemia is induced via temporary coronary artery ligation.[9] Induction of cardiac I/R requires a relative long period of surgical anaesthesia. Although this animal model has been used in numerous studies, induction of myocardial ischaemia is frequently associated with sudden death due to the development of ventricular tachycardia (VT) and eventually ventricular fibrillation (VF).[10,11] To avoid unnecessary use of animals, the model requires refinement to minimize fatal loss of animals when ischaemic damage is induced. In general, the anaesthetic effect on heart rate (HR), incidence of ventricular arrhythmias during ischaemia and infarct size can vary widely,[11] emphasizing the importance for the selection of anaesthetic regimen. Generally, different agents are combined to provide all of the components of general anaesthesia such as loss of consciousness, analgesia, reflex activity suppression and muscle relaxation.[12] Additionally, using a mixture of agents lowers the required dose per drug thereby diminishing dose-dependent side-effects which can result in a reduction of the total volume of anaesthetic required for injection.[12]

In this study, the response of the anaesthetic mixtures of sufentanil–medetomidine (SM) and fentanyl/fluanisone–midazolam (FFM) in rats during cardiac I/R surgery was evaluated retrospectively. Fentanyl or the more potent opioid sufentanil, in combination with the alpha-2 agonist medetomidine, have both been reported to be effective anaesthetic combinations in rats, providing excellent analgesia together with a prolonged sedation time.[13,14] Moreover, the effect of SM can be reversed rapidly using butorphanol and atipamezole, which greatly speeds recovery.[12] Fentanyl/fluanisone is a veterinary anaesthetic combination of the μ-opioid agonist fentanyl which abolishes pain perception, and the neuroleptic fluanisone which reduces undesirable side-effects of fentanyl and provides additional sedative effects.[12] Addition of midazolam to fentanyl/fluanisone provides muscle relaxation, and this combination results in a surgical plane of anaesthesia.[15] Both SM and FFM induce a longer analgesia and sedation time after a single injection compared with those anaesthetics such as pentobarbital or ketamine–xylazine that are most widely used in cardiac I/R studies.[13,14] To select the best agent for use in cardiac I/R rat models, the effect on HR and ventricular arrhythmias during 40 min of coronary artery ligation together with the infarct size after three days of reperfusion was evaluated in this study.

Animals, materials and methods

Male Wistar rats ($n = 95$, aged 6–8 weeks; Harlan Laboratories, Horst, The Netherlands) weighing between 350 and 420 g were used. Male rats were used in this study because observations in our laboratory showed a higher lethality in female rats following cardiac I/R (unpublished data). The animals were allowed to acclimatize for at least one week before surgery and were group-housed (3–4) in conventional type IV cages (Tecnilab-BMI, Someren, The Netherlands) placed in one room. Following surgery, the rats were placed individually in conventional type III cages for 48 h to allow proper healing of the scar. Cages were bedded with Lignocel (J Rettenmaier and Söhne, Zutphen, The Netherlands) enriched with Enviro-dri® paper fibers (Tecnilab-BMI). A 12 h:12 h light–dark cycle was maintained and room temperature was kept between 20 and 22°C and humidity at $50 \pm 5\%$. Water and a commercially pelleted diet (2016 Teklad Global 16% protein rodent diet; Harlan Laboratories) were provided ad libitum. Animals were tested and shown to be negative for all major rodent pathogens as described in the Federation of European Laboratory Animal Science Associations (FELASA) guidelines.[16,17]

Ethical permissions

The studies were approved in 2012 and 2014 by the VU University Amsterdam animal ethics and welfare committee. VU University Amsterdam is licensed according to the 2010/63/EU guidelines. The rats involved in this study were accommodated and cared for in conformity with the guidelines described in Appendix A of the European Treaty Series No. 123 of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes.

Anaesthesia and analgesia

The rats were anaesthetized with either SM ($n = 48$) or FFM ($n = 47$). The rats were not randomized and observers were not blinded since this study assessed ventricular arrhythmia data retrospectively from two separate studies using either SM or FFM anaesthesia. Medetomidine (1.0 mg/mL, Sedastart; AST Farma, Oudewater, The Netherlands) was diluted 1:6⅔ with water for injection (Frensenius Kabi Nederland BV,

Den Bosch, The Netherlands) and mixed with sufentanil (0.05 mg/mL; Hameln Pharmaceuticals GmbH, Hameln, Germany). The SM mixture was administered subcutaneously (SC) in a volume of 1.5 mL/kg containing 0.05 mg/kg sufentanil and 0.15 mg/kg medetomidine. Fentanyl/fluanisone (0.5 mL/kg of Hypnorm® containing 0.315 mg/mL fentanyl and 10 mg/mL fluanisone; Janssen Pharmaceuticals, Tilburg, The Netherlands) and 5 mg/kg midazolam (5 mg/mL, Dormicum®; Roche, Almere, The Netherlands) were administered SC using two separate syringes. The rats were weighed prior to the anaesthetic injections. To minimize stress, they were injected next to their cages to which the rats were returned until the anaesthesia had taken effect. Immediately following the surgical procedure, the rats were injected SC with 1 mL 0.9% NaCl to compensate for surgery-related fluid loss. In addition, after completion of the surgical procedure, the rats anaesthetized with SM received 0.2 mg/kg butorphanol (Torbugesic-Vet; Zoetis BV, Capelle aan de IJssel, The Netherlands) freshly mixed with 0.5 mg/kg atipamezole (Atipamezole-HCl; Eurovet Animal Health, Bladel, The Netherlands) SC to rapidly antagonize the sufentanil and medetomidine, respectively. One hour after the administered antagonists, buprenorphine (0.03–0.05 mg/kg, Temgesic® diluted 1:9 in 0.9% NaCl; Reckitt Benckiser BV, Hoofddorp, The Netherlands) was administered SC to provide a longer period of analgesia than butorphanol.[18] Although buprenorphine also reverses the effects of sufentanil, its onset of action is relatively slower. Hence, butorphanol was administered primarily as the reversal agent. Rats anaesthetized with FFM received buprenorphine immediately after completion of the procedure. Buprenorphine administration was continued in both groups every 8–12 h for 48 h following surgery to prolong analgesia. The rats were kept on a heating pad, and their HR and respiratory frequency were closely monitored until recovery from the anaesthesia.

Surgical procedure

After the loss of their pedal withdrawal reflex, the rats were intubated with a 16 gauge tube (B Braun Introcan; Oss, The Netherlands) for ventilation. They were placed on a heating pad to maintain body temperature at 37°C. Following intubation, the rats were ventilated using 40% oxygen (UNO micro ventilator-03; UNO, Zevenaar, The Netherlands), their fur was removed locally and their skin was disinfected with 70% v/v ethanol. All operations were performed by the same surgeon during daytime using freshly autoclaved instruments. Cardiac I/R was induced as described previously.[2] In brief, a left thoracotomy was performed between the third and fourth ribs. To prevent the lungs from collapsing, positive end expiratory pressure (PEEP) of 2 mbar was maintained using a microventilator. During surgery, the effects of anaesthesia were assessed by closely monitoring the HR, heart rhythm and signs of hypercapnia such as changes in respiratory rate and depth caused by carbon dioxide accumulation. To induce MI, the left anterior descending artery was ligated using a 6-0 prolene suture. After 40 min of ischaemia, the suture was removed to allow reperfusion and the thorax was closed using two sutures and maximal lung pressure. On average, total surgery time was 65 min. Welfare of the animals was assessed daily until termination.

Ventricular arrhythmia assessment

During the entire ligation period, HR as well as sinus rhythm (SR) of the rats were monitored using an electrocardiogram set according to Einthoven I ECG (ADInstruments, Oxford, UK). HR measurements were noted at three time-points, namely (1) at start of the surgery, (2) 10 min after ligation, and (3) after 10 min of reperfusion. These time-points were representative of HR during the baseline, ischaemia and reperfusion periods, respectively. The ventricular arrhythmias induced by ischaemia were denoted in accordance with the Lambeth conventions, namely[19]

- VT: defined as a sequence of four or more ventricular complexes with a rate faster than the resting sinus rate and with an autonomous return to SR;
- VF: defined as a rate where QRS complexes could not be distinguished individually and return to SR did not occur autonomously; and
- fatal VF: defined when rats died during ligation as a cause of VF and did not respond to mechanical defibrillation performed manually on the heart.

Infarct size measurements

Following three days of reperfusion, a subgroup of the rats were killed humanely by excision of the heart under deep anaesthesia using 5% isoflurane (SM anaesthesia $n = 9$, FFM anaesthesia $n = 6$). The hearts of the other rats were assessed at various times after reperfusion, depending on the design of other studies, and the data obtained from these hearts are not included in this study. The heart was excised and cut into five equal slices. Three of these slices were fixed in 4% formalin and embedded in paraffin, and the other two were snap-frozen in liquid nitrogen. To discriminate viable myocardium from diseased myocardium, histochemical staining with phosphotungstic acid haematoxylin was performed on all five slices as described

previously.[2] The stained slides were scanned and the infarcted area and total heart area were marked manually using the Pannoramic viewer programme (version 1.15.4; 3D Histech Ltd, Budapest, Hungary). The average infarct size of all five slices was calculated as a percentage of the complete transverse heart section.

Statistical analysis

The incidence of ventricular arrhythmias during the monitoring period was noted as categorical data, presented as a percentage (%), and treatment comparisons were made using a chi-squared test. Post hoc analyses were performed to test for associations between two groups using a Fisher's exact test. HR and infarct size data were distributed normally and differences between the two groups were analysed using a Student's *t*-test. HR data are presented with the mean and the standard error of mean (SEM) and infarct size data are presented as box plots with median, 25th–75th percentiles (boxes) and 5th–95th percentiles (whiskers). HR data at different time-points within groups were compared using a paired Student's *t*-test. Differences between results were considered to be statistically significant if the two-sided P value was < 0.05. The statistical analysis was performed using Statistical Packages for Social Sciences software (IBM SPSS 22.0.0.0 for Windows; IBM Corp, Armonk, NY, USA).

Results

Heart rate

Rats anaesthetized with SM had a significantly lower HR compared with FFM anaesthesia at baseline (246 ± 26 versus 323 ± 37 bpm, $P < 0.001$), during ischaemia (261 ± 31 versus 301 ± 25 bpm, $P < 0.01$) and following reperfusion (264 ± 12 versus 317 ± 36 bpm, $P < 0.01$), as shown in Figure 1. Comparison of HR in rats within the same group at different time-points did not show any significant differences.

Incidence of ventricular arrhythmias during 40 min of ischaemia

Figure 2 shows the incidence of ventricular arrhythmias during 40 min of ligation in rats anaesthetized with SM or FFM. In the SM group, 38% (18/48) of the rats maintained SR during ligation, which was significantly higher than the 2% (1/47) in the FFM group rats ($P < 0.001$). The remainder of the rats all experienced either VT or VF during ligation. The occurrence of VT during ischaemia did not differ between the two anaesthesia groups. However, the percentage of rats receiving SM that experienced VF during ligation was significantly lower compared with the FFM rats (6% [3/48] and 30% [14/47], $P < 0.01$). Moreover, no rats died during ligation when SM anaesthesia was used, whereas 25% (12/47) of the rats anaesthetized with FFM developed fatal VF ($P < 0.001$).

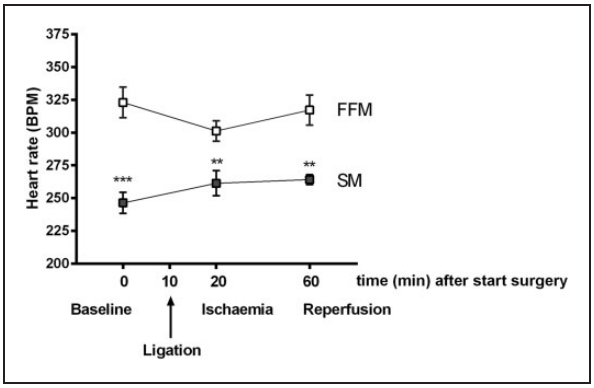

Figure 1. Heart rate (HR) in rats during experimental myocardial infarction using SM or FFM anaesthesia. HR in rats following anaesthesia administration of either SM or FFM at the start of surgery (Baseline), 20 min after surgery initiation (Ischaemia) and 60 min after surgery initiation (Reperfusion). These time-points are representative for HR during that period. Coronary artery ligation was initiated at 10 min following surgery initiation. HR data are presented with the mean and the standard error of mean (SEM). $***P < 0.001$, $**P < 0.01$ measured between SM and FFM groups using a Student's *t*-test. BPM: beats per minute, SM: sufentanil–medetomidine, FFM: fentanyl/fluanisone–midazolam.

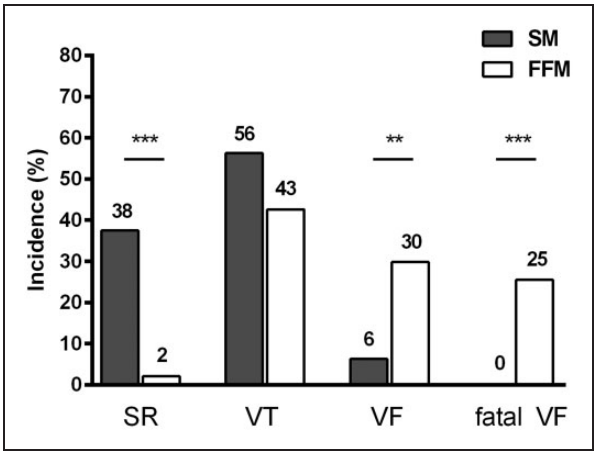

Figure 2. Incidence of ventricular arrhythmia during 40 min of coronary artery ligation. Incidence of VT, VF or death (in percentage) in rats during 40 min of coronary artery ligation using SM or FFM anaesthesia. $***P < 0.001$, $**P < 0.01$ as compared between groups. VT: ventricular tachycardia, VF: ventricular fibrillation, fatal VF: death during ischaemia, SM: sufentanil–medetomidine, FFM: fentanyl/fluanisone–midazolam.

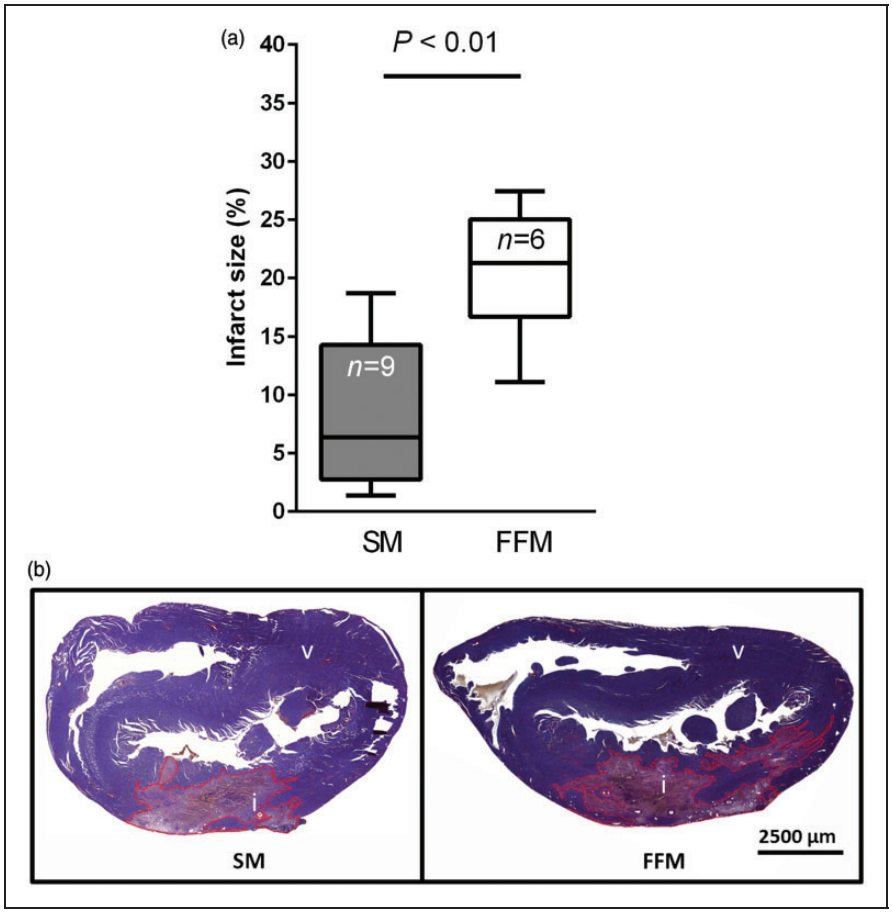

Figure 3. Infarct size in rats following three days of reperfusion. (a) Infarct size (in percentage) following 40 min of ischaemia and three days of reperfusion in rats using SM or FFM anaesthesia. Infarct size data are presented as box plots with median, 25th–75th percentiles (boxes) and 5th–95th percentiles (whiskers). (b) PTAH stain of paraffin embedded hearts showing the pink infarcted area (i) marked with a red line and the viable myocardium (v) in purple.
PTAH: phosphotungstic acid haematoxylin, SM: sufentanil–medetomidine, FFM: fentanyl/fluanisone–midazolam.

Infarct size after three days of reperfusion

Figure 3(a) shows the percentages of the infarcted area of the heart measured on day 3 following cardiac I/R surgery in a subgroup of rats using SM and FFM. The infarcted area of SM anaesthetized rats ($8.5 \pm 6.4\%$) was significantly smaller compared with the infarcted area of the rats using FFM anaesthesia ($20.7 \pm 5.6\%$) ($P < 0.01$). Figure 3(b) shows a representative photograph of a smaller infarcted area after cardiac I/R in rats using SM compared with FFM.

Discussion

To study putative therapeutic interventions during infarct healing following cardiac I/R injury, animal models are of considerable importance. However induction of MI in rodents can be associated with a high mortality rate, due mostly to the development of VF during coronary artery ligation, resulting in the use of a larger number of animals per study. In this study it has been shown for the first time that the use of SM anaesthesia in rats is associated with a lower HR and a reduced incidence of ventricular arrhythmias and deaths during 40 min of ligation compared with FFM anaesthesia, and is not associated with death during VF. In addition, the infarct size was significantly smaller after three days of reperfusion in the SM group compared with the FFM group. Thus VF occurs less, and the survival rate is higher, when rats undergo cardiac I/R surgery under SM anaesthesia compared with FFM anaesthesia.

As this was a retrospective study, the experimental design was not randomized or blinded, and this presents a limitation of the study. Rats in the FFM group underwent surgery 1.5 years before the rats in the SM group. However all other variables were kept similar, such as the surgeon performing the procedure, the rat strain, age and sex, as well as the entire surgical methodology, including the instruments used and the

operating room. Moreover, the analyses of the ventricular arrhythmias and the infarct size were carried out in an identical manner. Notwithstanding this, the possibility that the lack of randomization could have affected the outcome of the results cannot be completely excluded.

The reduction of ventricular arrhythmias observed using SM anaesthesia could be the result of a smaller infarct size following coronary occlusion. Activated opioid receptors are suggested to provide cardioprotection as they are also described to be involved in ischaemic pre- and postconditioning.[20–23] Ischaemic preconditioning, first reported in 1986, demonstrates how brief periods of hypoxia prior to prolonged coronary occlusion protect against infarction.[24] In ischaemic postconditioning, brief periods of ischaemia are applied at the start of reperfusion, and this has been shown to be as effective in preventing myocardial injury as preconditioning.[25] In rats, it has been demonstrated that non-selective blocking of the opioid receptor abolishes both ischaemic preconditioning[20] and postconditioning[22] protective effects. These results increased the interest in unravelling the mechanism of opioid receptor activation during the pre- or postconditioning of an ischaemic period. It remains debatable which particular opioid receptor is involved. Several studies have shown that κ- and δ-opioids are involved in cardioprotection whereas μ-opioids, the receptors of sufentanil and fentanyl, have been suggested to be less involved.[26–28] However, it has been demonstrated in rats that pharmacological postconditioning by sufentanil administration early during reperfusion contributes to infarct size reduction after 2 h of reperfusion.[29] Moreover, pre- and postconditioning with sufentanil prevent hypoxia-induced myocardial damage in cultured contracting human arterial trabeculae, a cell culture which mimics the beating human myocardium.[30] These results appear to be in line with the reduced infarct size as observed following SM anaesthesia in this study, since SM was present during both ligation and early reperfusion, as SM anaesthesia was antagonized after early reperfusion. Nevertheless, only the rats anaesthetized with SM received butorphanol following the surgical procedure, which reverses μ-opioid but simultaneously provides analgesia via agonist activity at the κ-opioid receptor.[14] Activation of κ-opioids in particular are suggested to be involved in attenuating cardiac I/R injury related to pre- or postconditioning.[28,31,32] Conversely, another study has shown that activated κ-opioid receptors do not mediate the beneficial ischaemic preconditioning effect.[33] Notwithstanding this, we cannot rule out the possibility that administration of butorphanol could have influenced the infarct size in the SM group. Since blood oxygen saturation levels were not monitored in this study, the possibility that hypoxia could have been a confounding factor on VF incidences during ligation cannot be excluded.

In addition, the presence of the alpha-2 agonist medetomidine in the SM mixture could have suppressed ventricular arrhythmias during ligation. A meta-analysis pointed out that the use of alpha-2 agonists in patients who undergo cardiac surgery can reduce perioperative mortality as a consequence of ventricular arrhythmias, and also reduces MI.[34] Stimulation of the alpha-2 adrenoceptors in the central nervous system results in a reduction of norepinephrine outflow and thereby directly dampens the sympathetic tone.[35] This can contribute to the development of bradycardia,[35,36] which is a common side-effect of medetomidine, especially when combined with opioids.[36,37] Moreover, bradycardia has been correlated with the suppression of VT and VF.[38]

Dampening of the sympathetic tone to reduce cardiac arrhythmias and mortality following cardiac surgery is widely used in clinical settings by administration of beta blockers, which antagonize beta adrenoceptors.[39,40] Recently, it was demonstrated that suppression of the sympathetic tone early after MI via administration of beta-blockers before reperfusion, reduced infarct size and resulted in an improved cardiac recovery following MI.[41] This suggests that administration of beta-blockers during ischaemia is beneficial to cardiac outcomes. However, even though both stimulation of alpha-adrenoceptors and inhibition of beta-adrenoceptors results in suppression of the sympathetic tone, it is still debatable whether this in turn results in an equal response to ventricular arrhythmia and infarct size following ischaemia.[42]

Whether the production of a smaller infarcted area as observed in this study when using SM anaesthesia would offer a better infarct model is dependent upon the goals of the specific study. For example where therapeutic interventions aiming to reduce the infarcted area are to be evaluated, a larger infarcted area might produce larger treatment effects. However, the considerable decrease in mortality rate when using SM anaesthesia enables the use of fewer animals. An alternative approach would be to consider altering the coronary artery ligation method, in order to increase the infarcted area, if this was necessary.

Based upon the results in this study it is recommended that SM anaesthesia should be used for experimental cardiac I/R surgery in rats. Our results show that a change of anaesthetics can consistently influence the infarct size following cardiac I/R, and that SM anaesthesia avoids loss of animals by preventing complications related to VF and acute death during coronary artery ligation. This results in a reduction in the number of animals needed for cardiac I/R studies. To unravel the mechanism of VF suppression by SM

anaesthesia is of considerable interest, not only for laboratory use, but also for clinical use in patients with coronary artery diseases.

Declaration of Conflicting Interests

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Résumé

Les interventions thérapeutiques au cours de la réponse inflammatoire après un infarctus du myocarde (IM) visent à améliorer la guérison des patients. Les modèles animaux sont largement utilisés pour étudier ce processus. Cependant, l'induction d'IM chez les rongeurs est associée à une mortalité élevée due à la fibrillation ventriculaire (FV) au cours de la ligature de l'artère coronaire. L'agent anesthésique utilisé pendant la procédure semble influer sur la fréquence de cette complication. L'étude rétrospective actuelle évalue l'effet sur l'incidence des arythmies ventriculaires au cours de la ligature et l'étendue de l'infarctus après reperfusion in vivo de deux régimes d'anesthésie, le sufentanil-médétomidine (SM) et le fentanyl/fluanisone-midazolam (FFM) chez le rat. Les anesthésiques ont été administrés par voie sous-cutanée en associant du fentanyl/fluanisone (0.5 ml/kg) au midazolam (5 mg/kg) (Group FFM, $n = 48$) ou du sufentanil (0.05 mg/kg) à de la médétomidine (0.15 mg/kg), (groupe SM $n = 47$). L'artère coronaire a été ligaturée pendant 40 minutes pour induire l'IM. La fréquence cardiaque et les arythmies ventriculaires ont été enregistrées au cours de la ligature et l'étendue de l'infarctus a été mesurée via une histochimie après trois jours de reperfusion. Dans le groupe SM, la fréquence cardiaque et l'incidence de FV étaient plus faibles tout au long de l'expérience par rapport au groupe FFM (6% contre 30%) ($P < 0{,}01$). Aucune FV mortelle ne s'est produite dans le groupe SM alors qu'elle s'est produite chez 25% des animaux du groupe FFM. En outre, après trois jours de reperfusion, la zone de l'infarctus suivant une anesthésie SM était au moins à moitié plus petite qu'après une anesthésie FFM (8.5 ± 6.4 % et 20.7 ± 5.6 %) ($P < 0.01$). Par conséquent, afin de minimiser le risque de complications liées à la FV et les décès aigus survenant au cours de la ligature, l'anesthésie SM est recommandée pour étudier l'IM chez le rat.

Abstract

Therapeutische Eingriffe während der entzündlichen Reaktion auf Myokardinfarkt (MI) beim Menschen bezwecken eine bessere Infarktheilung. Tiermodelle werden zur Untersuchung dieses Prozesses häufig verwendet. Allerdings ist die Induzierung von MI bei Nagern mit einer hohen Sterblichkeit aufgrund von Kammernflimmern (VF) während der Ligatur der Koronararterie verbunden. Das für den Eingriff verwendete Narkosemittel scheint Einfluss auf die Häufigkeit dieser Komplikation zu haben. In der vorliegenden retrospektiven Studie wurde die Auswirkung von in-Vivo-Reperfusion zweier Anästhetikagaben, Sufentanil-Medetomidin (SM) und Fentanyl/Fluanison-Midazolam (FFM), auf das Auftreten ventrikulärer Arrhythmie während der Ligatur und auf die Infarktgröße bei Ratten untersucht. Es erfolgte subkutane Anästhesie-Verabreichung von Fentanyl/Fluanison (0.5 ml/kg) mit Midazolam (5 mg/kg) (FFM-Gruppe, $n = 48$) oder Sufentanil (0.05 mg/kg) mit Medetomidin (0.15 mg/kg) (SM-Gruppe, $n = 47$). Die Koronararterie wurde 40 Minuten lang zwecks Induzierung von MI ligiert. Herzfrequenz und ventrikuläre Arrhythmien wurden während der Ligatur erfasst, und die Infarktgröße wurde mittels Gewebechemie nach drei Tagen Reperfusion gemessen. Bei der SM-Gruppe waren Herzfrequenz und Auftreten von VF während des gesamten Versuchs geringer als bei der FFM-Gruppe (6% versus 30%) ($P < 0.01$). Tödliche VF trat in der SM-Gruppe nicht auf, während dies bei 25 % der Tiere in der FFM-Gruppe der Fall war. Zudem war drei Tage nach Reperfusion der infarzierte Bereich nach SM-Narkose weniger als halb so groß als nach FFM-Narkose (8.5 ± 6.4 % versus 20.7 ± 5.6 %) ($P < 0.01$). Beim experimentellen MI bei Ratten empfiehlt sich daher der Einsatz von SM-Anästhesie, um die Möglichkeit von Komplikationen im Zusammenhang mit VF und plötzlichem Tod während der Ligatur zu minimieren.

Resumen

Las intervenciones terapéuticas durante la respuesta inflamatoria tras un infarto miocardio (IM) en personas trata de mejorar la recuperación del infarto. Para estudiar este proceso se utilizan muchos modelos de animales. No obstante, la inducción de IM en roedores se asocia a un alto número de mortalidad debido a una fibrilación ventricular (FV) durante la ligadura de la arteria coronaria. El agente anestésico utilizado durante el procedimiento parece influir en la frecuencia de esta complicación. En el actual estudio retrospectivo, se evaluó utilizando ratas el efecto en la incidencia de arritmias ventriculares durante la ligadura y el tamaño del infarto después de una reperfusión en vivo de dos regímenes anestésicos, sufentanil-medetomidina (SM) y fentanil/fluanisona-midazolam (FFM). Se administraron anestésicos de forma subcutánea utilizando fentanil/fluanisona (0.5 ml/kg) con midazolam (5 mg/kg) (grupo FFM, $n = 48$) o sufentanil (0.05 mg/kg) con medetomidina (0.15 mg/kg) (grupo SM, $n = 47$). La arteria coronaria fue ligada durante 40 minutos para inducir la IM. Se registraron el ritmo cardíaco y arritmias ventriculares durante la ligadura y el tamaño de infarto fue medido mediante histoquímica después de tres días de reperfusión. En el grupo SM, el ritmo cardíaco y la incidencia FV fue inferior durante todo el experimento en comparación al grupo FFM (6% frente a 30%) ($P < 0.01$). En el grupo SM no hubo ninguna fatalidad de FV mientras que sí que la hubo en el 25% de los animales del grupo FFM. Asimismo, después de tres días de reperfusión, el área del infarto después de la anestesia SM era menos de la mitad de grande que con la anestesia FFM (8.5 ± 6.4% frente a 20.7 ± 5.6%) ($P < 0.01$). Por tanto, para minimizar la posibilidad de complicaciones relacionadas con FV y muerte aguda durante la ligadura, se recomienda la anestesia SM para IM experimental en ratas.