Chapter 3

Preparation and Monitoring of Small Animals in Renal MRI

Tamas Kaucsar, Adam Hosszu, Erdmann Seeliger, Henning M. Reimann, and Andrea Fekete

Abstract

Renal diseases remain devastating illnesses with unacceptably high rates of mortality and morbidity worldwide. Animal models are essential tools to better understand the pathomechanism of kidney-related illnesses and to develop new, successful therapeutic strategies. Magnetic resonance imaging (MRI) has been actively explored in the last decades for assessing renal function, perfusion, tissue oxygenation as well as the degree of fibrosis and inflammation. This chapter aims to provide an overview of the preparation and monitoring of small animals before, during, and after surgical interventions or MR imaging. Standardization of experimental settings such as body temperature or hydration of animals and minimizing pain and distress are essential for diminishing nonexperimental variables as well as for conducting ethical research.

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Key words Magnetic resonance imaging (MRI), Kidney, Rodent surgery, Anesthesia

1 Introduction

Renal diseases are devastating illnesses with unacceptably high rates of mortality and morbidity worldwide. End-stage renal disease is the final stage of chronic kidney disease (CKD) characterized by complete loss of kidney function. Global prevalence is estimated to be 8–16% and the overall years of life lost due to premature death is third behind AIDS and diabetes mellitus [1]. Kidney diseases create a huge burden on healthcare systems; thus, the social and economic impact of prevention and early treatment would be enormous. Several publications have highlighted the need for new, effective therapies as well as superior diagnostic tools.

At present, diagnosis of kidney disease is difficult and often involves invasive procedures. Conventional markers of renal function such as serum creatinine and blood urea nitrogen are poorly sensitive and poorly selective, as they represent a delayed indication

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of functional change that lags behind structural deterioration during the early stage of acute kidney injury (AKI). Currently kidney biopsy is the single method to assess renal microstructure in humans, but it is an invasive procedure and sampling bias can alter results. Thus, noninvasive, in vivo imaging methods are crucial for the adequate assessment of kidney function, oxygenation, and structure in both preclinical and clinical setups. Importantly, state-of-the-art functional MRI techniques are available to determine tissue oxygenation, perfusion, fibrosis, inflammation, or tissue edema that can be used as biomarkers of renal disease [2]. MRI affords full kidney coverage, soft tissue contrast that helps to differentiate the renal layers, second-to-minute temporal resolution, support of longitudinal studies and high anatomical detail without the use of ionizing radiation [3, 4].

However, imaging rodents can be challenging because in contrast to human studies, imaging of animals requires anesthesia to physically restrain the animals and minimize their gross motion. Anesthetic agents can profoundly alter physiology of the experimental animal and may thus influence the image data acquired. It is therefore necessary to use the most appropriate anesthetic compound and to monitor the physiology of anesthetized animals during image acquisition [5–7].

It is essential that researchers use animals in scientifically, technically, and humanely appropriate ways. Effective and appropriate animal care before, during, and after experimentation not only is important for the enhancement of animal well-being but can also have a major effect on the quality of research. Hydration status, the type of anesthesia used, or body temperature of the animals during surgery or MRI measurements, as well as postoperative care are all factors that can affect results, and thus should be carefully planned prior to the intervention. Standard protocols can be modified, but should not compromise the well-being of the animals.

This chapter summarizes preoperative procedures, advantages and disadvantages of different anesthetic agents, monitoring of physiological functions during surgical or imaging procedures, and how these challenges can be successfully addressed.

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2 Hydration

Animals can experience considerable fluid loss during surgery mainly due to evaporation from open body cavities or blood loss. Rodents are particularly vulnerable to intraoperative fluid loss because of their small size and relatively small total body fluid content. Warm, sterile isotonic fluids should be administered at 3–5% of the body weight subcutaneously or intraperitoneally

prior to and at the end of surgery. Alternatively, isotonic fluid can be continuously administered via intravenous infusion or even via intra-arterial infusion in case a catheter has already been placed into an artery for monitoring of blood pressure and heart rate. The operative field should be irrigated with warm saline and drying out of tissues should be avoided [8, 9]. In any case, quantity of hydration has to be logged and/or standardized to eliminate non-experimental variable factors. For example, with proper hydration tubular reabsorption, an energy-dependent process can be spared. Hence, some procedures such as ischemia will have less effect on renal injury in well hydrated animals. Intraoperative fluid replacement is also important because during the recovery phase water intake is usually reduced, even though ad libitum water access is usually ensured after surgery.

An ophthalmic lubricating ointment should be applied to the eyes to protect the cornea from drying out.

3 Anesthesia

The use of anesthetics for surgical or in vivo imaging procedures comes with an inevitable autonomic nervous system depression, causing cardiovascular and respiratory depression, hypothermia, and altered metabolism [10]. Different anesthetics influence these physiological processes differently; thus, various anesthetic agents should be selected for different experimental models. For example, anesthesia used during renal ischemia–reperfusion injury (IRI) surgery has an important impact on the extent of injury. Numerous studies showed that anesthetics are renoprotective due to their anti-inflammatory, antiapoptotic, or antinecrotic effect, independently of the way of administration. Also different anesthetics impose different effects on vasomotion (dilation and constriction). Vasomotion, in turn, has a direct impact on local renal blood volume fraction, which affects the measure T_2*. Furthermore, it influences perfusion, which affects the blood oxygenation and ultimately T_2* as well. R_2*—the transverse relaxation rate—can vary by more than 100% depending on the anesthetic regimen [11]. In animal experiments inhalable and injectable anesthetics are both popular. Advantage of inhalable anesthetics (e.g., halothane or fluranes) are that they are rapidly eliminated through the lungs; therefore, incidence of fatal events is lower and fast recovery can be achieved. On the other hand, they are frequently irritant, and it is hard to set a precise dosage; hence, it is easier to cause hypoxia, and if apnea occurs loss of consciousness will last longer. Injectable anesthetics (barbiturates, ketamine, propofol, etc.) promote a quick loss of consciousness with better control of cardiopulmonary function and induce anesthesia at a lower dose. They frequently influence blood pressure, and hypothermia can also develop. Although barbiturates can be precisely dosed through intravenous administration, the

intraperitoneal, subcutaneous, or intramuscular injection of other injectable anesthetics may lead to variable levels of anesthesia. Because of the short time of action (with the exception of urethane) repeated dosing or constant infusion of injectable anesthetics is sometimes needed, prolonging recovery time [12]. During procedures respiratory rate and alertness of the animal should be followed. Anesthesia should be intensified at the first signs of alertness such as movement of whiskers or reflex triggered by pinching the toes outside the MR environment. It should be noted that deeper anesthesia is needed for surgical interventions than for MRI alone.

3.1 Injectable Anesthetics

Ketamine is one of the safest and most widely used injectable anesthetics in animal surgeries because it does not require intravenous access and cardiorespiratory depression occurs only at a much higher dose than what is needed for anesthesia [13]. Ketamine is frequently used in combination with other anesthetics like α2 agonists (xylazine) or benzodiazepines to prevent muscle rigidity and produce more stable anesthesia [7]. In these cases, the dose of ketamine can be reduced. However, ketamine may reduce IRI in rats in low doses, when its antioxidant capacity is the greatest [14]. On the other hand, ketamine may be harmful at higher doses due to its sympathomimetic effect [15]. Despite the low cardiovascular and respiratory influence of ketamine alone [16], cardiac influences, like hypotension with minimal respiratory depression must also be considered when using ketamine together with xylazine [17]. Substantial cardiovascular effects (bradycardia, hypotension) were observed when acepromazine, buprenorphine, or carprofen was also added to the ketamine–xylazine combination. Nevertheless, the addition of acepromazine led to stable hemodynamic parameters while sustaining adequate anesthesia for performing surgical procedures [18]. Cerebral hemodynamics are also affected by ketamine–xylazine combinations, which may cause reduction of cerebral blood flow thus affecting brain oxygenation and leading to interferences with several imaging procedures [19]. Metabolic changes could also occur during ketamine–xylazine anesthesia. Decreased insulin secretion by pancreatic β cells together with the blockade of ATP-dependent potassium channels may cause elevated levels of blood glucose and potassium [20].

Short and ultrashort acting barbiturates (pentobarbital and thiopental, respectively) are also frequently used in animal experiments. They are relatively inexpensive and have a rapid and smooth onset of action as well as recovery [21]. On the other hand, they have small therapeutic margin and even though they can be precisely dosed via intravenous administration, the risk of fatal events is much higher than for ketamine [22]. However, their use is limited in renal ischemia–reperfusion surgery, since they reduce blood pressure and thus blood flow to the kidney. Although by lowering pentobarbital dose there are less cardiovascular side effects, poor anesthetic depth, and serious respiratory depression with low

oxygen saturation can be expected during pentobarbital monoanesthesia [17]. Thiopental decreased malondialdehyde levels and reduced histopathologic damage to the kidneys after IRI in subanesthetic doses [15]. Moreover, clinically high doses of thiopental effectively protected against renal IRI [23]. What may lie behind this renoprotective effect is that thiopental is also an antioxidant [24] and inhibits neutrophil function [25]. Thiopental might also depress brain metabolism and thus elevate brain glucose content in the cortex [26]; however, pentobarbital has no effect on blood glucose levels [20].

Propofol is a rapid acting anesthetic, with short recovery duration, thus convenient for short procedures [10]. Propofol has a serious respiratory depressant effect and decrease in cerebral blood flow and intracranial pressure have also been reported [27]. The renoprotective effect of propofol via reduced production of proinflammatory cytokines, less neutrophil infiltration, and hence lower reactive oxygen species accumulation is well documented [15, 28, 29]. Due to its renoprotective effect, propofol is currently not used in experimental models of renal injury.

Urethane is extensively used alone or in combination with ketamine and xylazine in nonrecovery procedures. Advantages are its long-lasting (several hours) surgical plane of anesthesia [30, 31] and least effects on cardiovascular and respiratory control compared to other anesthetics [32, 33]. At least 8 h of fasting of the animals is recommended before urethane anesthesia.

3.2 Inhalable Anesthetics

Halogenated ethers are the preferred volatile anesthetics during animal experiments. Due to their rapid onset and short recovery time and low metabolism the side effects of inhalation anesthesia can be well controlled [10]. For example, isoflurane is preferred in cardiovascular studies, since it causes less hemodynamic depression than injectable anesthetics [17, 34]. It also reduces peripheral resistance thus hypotension might occur [35]. On the other hand, the rate of respiratory depression is higher than by injectable anesthetics; therefore, respiratory rate monitoring is indispensable when adjusting gas concentration. By maintaining high tidal volumes a stable oxygen saturation may be achieved during isoflurane anesthesia [17]. Yet isoflurane-induced respiratory depression results in hypercapnia, leading to substantial vasodilation in the brain and increased baseline cerebral blood flow [36]. To maintain physiological cerebral blood flow mechanical ventilation of the animal is recommended. In contrast, hypercapnia has only negligible effects on vasomotion in the kidney [37]. However, vasodilatory effects of isoflurane may be reflected in renal T_2* that has been found substantially higher compared to other anesthetics [11]. Metabolic changes have also been reported: isoflurane decreases insulin production, thus leads to higher blood glucose levels [20].

There is increasing evidence that halogenated ethers provide significant protection against renal IRI, which effect is differential: desflurane being less protective than isoflurane or sevoflurane [38]. Moreover, anesthesia with isoflurane has a preconditioning effect on renal IRI, with the involvement of JNK and ERK protein kinases [39]. When compared to propofol, isoflurane provided the same level of protection against ischemia reperfusion injury and therefore should be used with caution [40].

4 Physiological Monitoring

4.1 Body Temperature

Due to their large surface to body weight ratio rodents lose heat rapidly especially if the abdominal cavity is exposed. Hypothermia might further be exacerbated by the use of cold, dry gases, hair clipping, or the administration of cold fluids. Hairless strains and neonates which are considered exothermic in the early stages of life are especially susceptible to hypothermia because of their diminished insulation. Hypothermia poses multiple risks during anesthesia and recovery, including infection, bleeding complications and cardiac dysfunction. These factors may be the difference between life and death and if the animal survives, the difference between good and unreliable data; therefore, it is highly recommended that an external heat source be used during surgery. Adjustable heating pads or circulating warm water blankets usually allow a good maintenance of body temperature. Homogeneous warming of large surface areas of the animal's body—instead of using planar heating pads that provide comparably smaller contact areas—permits to reduce the heating temperature and allows for better maintenance of overall physiological body temperature [41]. For accurate control, a thermometer should be used to measure the temperature rectally and—if abdominal surgery is part of the procedure—also a second temperature probe placed close to the kidney should be used. Here it is important to consider the possible interactions of the temperature probe with the MRI. Conventional resistive probes with metallic cables may suffer from electrical currents induced by the time-varying magnetic field gradients used during imaging. This might disturb the temperature measurement and even heat up the cables. Use of fiber optical probes helps to avoid these issues but some optical probes experience a sizable offset in the measured temperature with a very strong magnetic field. For instance, a negative offset of 4.7 °C at a magnetic field strength of 9.4T was observed with GaAs-based probes. Some heating pads can automatically regulate the temperature with the help of a thermostat [42]. Too high temperatures can cause protein denaturation and tissue injury, which might result in death.

Kidney temperature during ischemia significantly influences IRI. Body temperature drops after anesthesia, which mitigates IRI

[9]. Therefore, close control and maintenance of body temperature is needed in order to perform reproducible AKI. Ischemia should only be initiated if the desired stable temperature is set and maintained.

4.2 Respiration

Respiratory monitoring can be achieved by observation of chest motion, depth and character of respiration during surgical interventions. Direct visualization of the animal is not feasible during imaging; therefore, respiratory motion detection systems that are compatible with and safe to use for most imaging modalities should be employed. These systems typically detect breathing motion by compressions of a respiratory sensor placed in contact with the chest.

During MRI, breathing often causes motion artefacts, which can severely compromise imaging acquisitions and hence measures to reduce or eliminate such artefacts should be taken. Gating techniques allow for the synchronization of data acquisition with the respiratory cycle. The largest movement of the abdomen occurs between inspiration and expiration; therefore, this period should be excluded from data acquisition.

4.3 Cardiovascular System

Heart rate can be monitored using an electrocardiograph system. Heart rate usually correlates with anesthetic depth. A pulse oximeter can be used to measure arterial O_2 saturation, pulse strength, breath rate and blood flow in real time, and can thus detect hypoventilation, airway obstruction, or other problems during anesthesia. Pulse oximeters are not remarkably accurate in rodents, but can detect trends and are nevertheless valuable tools. Whenever possible, cardiovascular monitoring should include continuous blood pressure measurement. For nonrecovery experiments, direct blood pressure (and heart rate) monitoring via a catheter in the femoral or carotid artery connected to a pressure transducer is preferred. Alternatively, an inflatable tail pressure cuff can be used noninvasively [10].

5 Recovery

Proper postoperative care is needed to minimize the loss of animals, to reduce intraexperimental variation and to offer humane conditions for recovery [8]. Body temperature should be maintained within physiological limits until the end of anesthesia, when the animal starts to be active.

5.1 Analgesia

If activity is resumed, analgesics may be given without the risk of further respiratory depression. Opioids are most commonly used for this purpose [9]; however, some of them can protect against IRI. For example, morphine and naloxone inhibited superoxide

anion production after renal IRI in rabbits [43] and naloxone alone can also improve warm renal IRI in dogs [44]. However, buprenorphine, a mixed partial μ-opioid receptor agonist and κ-and δ-opioid receptor antagonist improved animal health by reducing postsurgical stress response, without interfering with renal IRI [45].

Other analgesics, like α2-agonists are proven to have benefic effect on renal IRI [46, 47]. Nonsteroidal anti-inflammatory drugs also interfere with the renal IRI model [48, 49].

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5.2 Antibiotics

Although there is a risk for postoperative infections after surgery, there is no indication for empiric use of antibiotic prevention [50]. Focus has to be placed on aseptic surgical infrastructure, cautious animal handling, and well-managed animal facilities (SPF, etc.). If systemic antibiotic use is inevitable, then fluoroquinolones and the trimethoprim–sulfonamide combination are generally recommended, since they are not harmful to the symbiotic intestinal bacterial population of mice [51]. Gentamicin is reported to ameliorate IRI mostly during the reperfusion phase and should not be used in such experiments [52]. Antibiotic administration should be delayed until complete anesthetic recovery takes place because of hypotension and prolonged anesthesia due to their calcium blocking action [51].

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