FULL PAPER

Neutrophil gelatinase associated lipocalin as biomarker in predicting acute renal tubular injury following general anesthesia with sevoflurane on low-flow anesthesia

Kohar Hari Santoso[a],* |Syamsuri Wahyu[b] |Maulydia Maulydia[a]

[a]Department of Anesthesiology and Reanimation, Faculty of Medicine, Airlangga University, Surabaya, Indonesia

[b]Master's Level Clinical Medicine Study Program, Faculty of Medicine, Airlangga University, Surabaya, Indonesia

The administration of general anesthesia through inhalation is a frequently employed method. The volatile anesthetic substance known as sevoflurane is believed to possess nephrotoxic properties due to its metabolites, including fluoroacetic acid and molecule A. The combination of low fresh gas flow and elevated concentrations of sevoflurane within the respiratory circuit, along with its passage via the CO_2 absorbent, results in heightened degradation of sevoflurane, hence increasing the risk of renal tubule injury. NGAL expression in healthy kidneys is mostly produced by proximal tubular epithelial cells and is primarily located in the loop of Henle and distal tubules of the kidney. NGAL is crucial in controlling cell proliferation, facilitating healing processes, and promoting tubular re-epithelialization following kidney injury. Increased NGAL levels are indicative of acute renal injury. Segrepsis, chronic obstructive pulmonary disease, and cardiac failure are conditions that can disrupt the performance, sensitivity, and specificity of NGAL as a biomarker for renal tubular injury. Age seems to have an impact on the performance of the NGAL biomarker. The NGAL examination can be conducted using either urine or plasma samples, yielding comparable outcomes. The receiver operating characteristic (ROC) curve for urine NGAL in predicting acute renal injury was 0.998, while for plasma NGAL it was 0.91. The NGAL examination is based on the utilization of monoclonal antibodies. The ELISA approach is commonly employed in the majority of NGAL testing conducted for research purposes. One of the benefits associated with NGAL is its non-invasive nature, rapidity, and sensitivity in facilitating early detection.

*Corresponding Author:
Kohar Hari Santoso
Email: kohar.hari@fk.unair.ac.id
Tel.: +628123216768

Introduction

Sevoflurane is a volatile anesthetic compound that is made from a combination of fluorine and isopropyl ether. It possesses the characteristic of being non-flammable and non-explosive. Sevoflurane has a poor solubility in blood and a blood gas partition coefficient of 0.09 for adults and 0.06 for newborns. This results in a short period of

J. Med. Pharm. Chem. Res. 6 (2024) 1567-1582

P a g e | **1567**

increased alveolar concentrations during induction and a short period of decreased concentrations once sevoflurane is stopped [1]. Currently, there are two suggested pathways for the nephrotoxic effects of sevoflurane. The metabolite of sevoflurane, known as fluoroacetic acid, has been observed to possess nephrotoxic and hepatotoxic properties. Another fluorinated molecule, known as compound A, is produced during an exothermic interaction between the absorbent sevoflurane and carbon dioxide. Animal investigations have revealed that this product can lead to reversible renal tubular damage. The exact method by which compound A causes kidney damage is still a subject of debate, particularly in relation to the renal cysteine -lyase conjugation pathway, which plays a role in the conversion of compound A. The potential for compound A to cause kidney damage in humans may vary depending on the amount of exposure [2].

The combination of a low flow rate of fresh gas and a high concentration of sevoflurane in the breathing circuit, when passing through a CO_2 absorbent made up of strong bases (sodium hydroxide and potassium hydroxide), can raise the temperature of the CO_2 absorbent tube and decrease the water content in the absorbent. These two circumstances enhance the degradation of sevoflurane into the vinyl ether product, fluoromethyl-2,2-difluoro-1-(trifluoromethyl (chemical A), which can lead to renal tubular damage and mortality in an animal research, with the severity of the condition varying with the dosage.

Sevoflurane has been found to induce nephrotoxicity in rats, particularly when administered in low fresh gas flow conditions. There are varying perspectives on the impact of sevoflurane in the low fresh gas flow approach on kidney injury. Hence, the objective of this study is to examine the impact of reduced fresh gas flow in conjunction with the anesthetic gas sevoflurane on renal tubular injury. This

investigation will utilize the NGAL biomarker, a highly sensitive and specific indicator of tubular epithelial damage.

Perioperative renal injury

The prevalence of perioperative acute kidney damage (AKI) exhibits significant variation, encompassing rates that span from 6% to 13% among patients undergoing elective general surgical procedures, and peaked at 42% following heart surgery. Perioperative acute kidney damage has a complex etiology [3]. The occurrence of acute kidney injury (AKI) is associated with the mortality of patients, with a reported mortality rate of approximately 50-70% among those with AKI who require renal replacement therapy (RRT). Within the confines of the operating room, patients frequently encounter dehydration as a consequence of preoperative fasting. In addition, they undergo substantial fluid depletion throughout the intraoperative and postoperative phases, primarily attributable to insensible water loss, the redistribution of fluid towards inflammatory organs, and blood loss incurred during surgical interventions. In addition to their effects on peripheral vasodilation, most anesthetic drugs have the potential to induce cardiac depression, hence exacerbating the impairment of overall renal perfusion. However, it is important to note that there are other renal disorders that can occur during the perioperative period. These disorders may include exposure to nephrotoxins, such as antibiotics and contrast agents used for diagnostic imaging. In addition, hyperglycemia, anemia, blood transfusions, and inflammatory mediators released as a result of surgical trauma, ischemia, and organ reperfusion may also be encountered [4].

The volatile anesthesia drug, sevoflurane, is subjected to catalytic breakdown within a carbon dioxide absorber, resulting in the formation of vinyl ether known as "Compound A". In low flow or closed circuit breathing

systems, as well as in warm or very dry CO_2 absorbents, the production of compound A exhibits an increase. The production of component A is higher in barium hydroxide lime compared to soda lime, which can be attributed to the slightly elevated temperature during CO2 extraction [5].

Acute tubular necrosis (ATN)

The main cause of AKI is acute tubular necrosis (ATN) and parenchymal damage. The pattern of ATN damage includes damage and death of renal parenchymal tubular cells. ATN is triggered by acute ischemia or toxins or sepsis which releases inflammatory mediators that damage the tubules. Prerenal azotemia and ATN ischemia have similar causative factors. Some of these include hypovolemia statuses such as diarrhoea, vomiting, bleeding, dehydration, burns, post diuretics use, and fluid sequestration into the third space. Edema states such as heart failure and cirrhosis decrease renal perfusion. Sepsis or anaphylaxis causes systemic vasodilation. Coagulopathies such as disseminated intravascular coagulation also can cause ATN.

Kidneys clear and metabolize several types of drugs. Some of these drugs are toxic and can directly cause ATN or induce crystallization in the renal tubules that trigger ATN. Aminoglycosides, amphotericin B, contrast agent, sulfa, acyclovir, cisplatin, calcineurin inhibitors (tacrolimus, cyclosporine), foscamet, isfosfamet, cidofovir, and intravenous immunoglobulin contain sucrose that may cause ATN. Heme-containing proteins such as hemoglobin and myoglobin are endotoxins because they can directly damage tubules, and cause intraluminal tubular obstruction and renal vasoconstriction.

The AKI incidence really depends on where the kidney injury occurs [6]. Several studies state that the breakdown of sevoflurane in vivo and in vitro produces inorganic fluoride and vinyl ether (compound A) which have the potential to harm kidney and liver function where compound A causes local corticomedullary tubular necrosis and intrinsic AKI [7].

The occurrence of acute tubular necrosis (ATN) is influenced by sepsis, which is characterized by renal hypotension and hypoperfusion, endotoxemia leading to intrarenal vasoconstriction, and the detrimental impact of mediators and free radicals on renal tubules.

Various diagnostic tests are employed to distinguish between intrarenal aetiology and prerenal and post-renal acute kidney injury (AKI). These tests encompass urinalysis, urine sodium concentration, sodium excretion fraction, urea excretion fraction, comparison of blood urea nitrogen (BUN) and serum creatinine levels, as well as numerous emerging biomarkers that are gaining prominence. Urinalysis microscopic findings in prerenal causes may exhibit normal results, or hyaline casts may be detected. In the context of ATN injury, microscopic examination reveals the existence of brown granular casts or tubular epithelial cell casts within the tubular lumen, which can be attributed to ischemia or toxic effects.

The objective of the sodium excretion fraction (FeNa) test is to distinguish between kidney injury caused by prerenal factors and harm to the acute tubular necrosis (ATN). A FeNa result below 1% signifies prerenal kidney failure, whereas a value beyond 2% suggests an anomaly in the renal parenchyma (ATN). Nevertheless, FeNa may not always be precise. For example, the concentration of FeNa is lower than 1% in individuals diagnosed with liver cirrhosis and heart failure. The urine sodium concentration is indicative of the kidney's endeavor to save sodium under prerenal circumstances, characterized by a urine sodium concentration below 10 meq/L and the inability to reabsorb salt due to renal tubule injury, resulting in a urine sodium concentration exceeding 40-50 meq/L.

Renal damage biomarkers

Biomarkers encompass alterations in structural, biochemical, physiological, or genetic parameters that serve as indicators of the significance, intensity, or advancement of a disease. The onset of kidney injury is initiated by biological stimuli and subsequent molecular alterations, leading to cellular destruction and subsequent renal injury. The initial stress response resulting from acute kidney injury can be identified at an early stage by the use of biomarkers [8].

The identification of acute kidney injury is contingent upon the measurement of serum creatinine indicators within a minimum timeframe of 48 hours following therapy. It is plausible that this occurrence has already resulted in irreversible harm to the renal glomerulus [9]. Serum creatinine levels are not easily detectable for acute kidney injury (AKI), and elevations in serum creatinine and oliguria may not manifest until several hours after the initiation of a sudden decline in glomerular filtration rate (GFR). Furthermore, individuals experiencing minor muscle mass or volume loss may exhibit a delayed increase in serum creatinine levels, accompanied by a decrease in estimated glomerular filtration rate (GFR). In contrast, patients with substantial muscle mass or volume loss may experience a more rapid increase in serum creatinine levels [10]. Urea is generated during the process of protein metabolism. The excretion of ammonia occurs by the transfer of amino acids from the liver to the kidneys, resulting in an average daily excretion of 30 grammes. The typical blood urea concentration ranges from 20 to 40 mg per 100 mL of blood, although this is influenced by the quantity of normal protein consumed and the liver's role in urea production. Creatinine is a byproduct resulting from the process of creatine phosphate repair within muscle tissue, which is subsequently eliminated via renal excretion [11].

Multiple biomarkers with high sensitivity and specificity exist for the early identification of AKI. AKI can be detected well in advance of an increase in blood creatinine levels, particularly in malnourished and elderly or geriatric individuals. Furthermore, these biomarkers can serve as a means to monitor drug toxicity, forecast therapy, evaluate outcomes, and monitor kidney recovery following acute kidney injury (AKI) [8,12]. These biomarkers are secreted by impaired glomeruli and kidney tubules based on their specific location and characteristics, as displayed in Figure 1. Examples of these biomarkers include interleukin 18, tubular enzyme, N-acetyl-B glucosamidase, alanine aminopeptidase, kidney injury molecule 1, and Neutrophil Gelatinase-Associated Lipocalin (NGAL) [12].

Over the past few decades, numerous biomarkers for kidney injury have been suggested (Table 1), among which NGAL has emerged as a well investigated and promising candidate for early detection. Despite some studies conducted on NGAL, its application in clinical practice has not been extensive [13].

TABLE 1 Biomarkers of acute kidney injury [12]

Site of kidney injury	Biomarkers
Glomerulus	Urine: TP (total Protein), alpha2-Microglobulin, Albumin, and alpha 1-Microglobulin. Blood: creatinine, cystatin C, NGAL.
Proximal Tubule	Kim-1, NAG, nephrin-1, IL-18, L-FABP, NET-3, HGF, IGBP7, and TIMP-2
Distal Tubule	NGAL, GST, cystatin C, Cyr61, and NET-3
Collecting Duct	Calbindin D28

NGAL: Neutrophil Gelatinase-Associated Lipocalin, Kim-1: kidney injury molecule 1, NAG: N-acetyl-β-D-glucosaminidase, IL-18: interleukin 18, L-FABP: liver fatty acid binding protein, NET-3: Neutrophil extracellular Traps-3, HGF: hepatocyte growth factor, IGBP7: insulin-like growth factor binding protein 7, and TIMP-2: tissue inhibitor of metalloproteinases-2, GST: glutathione S-transferase, Cyr61: cysteine-rich protein 61.
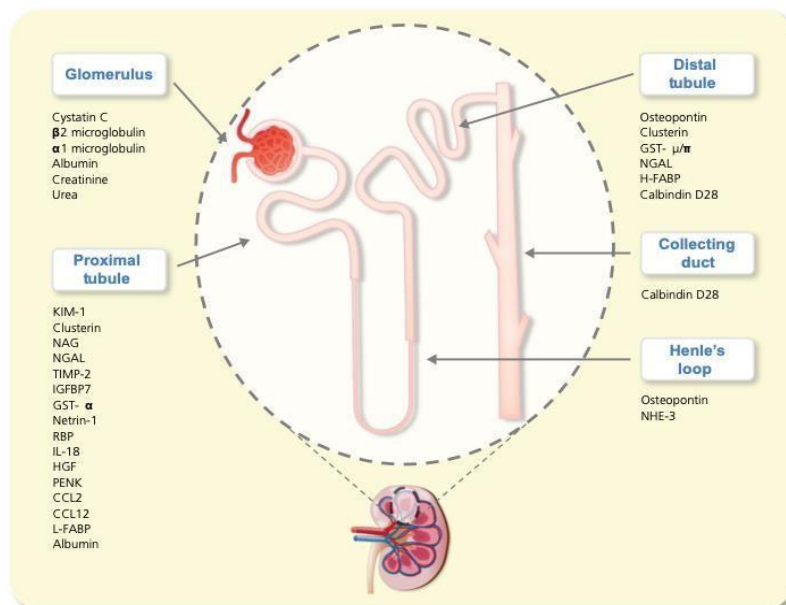

FIGURE 1 Location of renal injury biomarkers [12]

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL is a lipocalin protein that can bind and transport lipophilic molecules. NGAL can inhibit bacterial growth by binding to siderophores (proteins produced by bacteria). This siderophore will trap iron in the cell with a high affinity for the survival of the bacteria so that the cell becomes deficient in iron. The mechanism of NGAL is depicted in Figure 2. Apo-NGAL actively binds to siderophores and returns iron reserves trapped by siderophores back into the cell. In addition, Holo-NGAL efficiently transports iron into cells, where iron is produced and released into the blood through cellular reactions, to meet the iron levels in cells. Iron formation by NGAL involves the inhibition of bacterial growth and prevention of cell death, thereby increasing proliferation in the renal tubules, where NGAL indirectly provides a means of protection against acute kidney injury [15].

Renal NGAL

NGAL expression is mostly produced by proximal tubular epithelial cells in healthy kidneys, including the loop of Henle and distal tubules (Figure 3). NGAL has a significant function in controlling cell growth, repairing tissues, and regenerating the inner lining of kidney tubules following injury [16]. The NGAL production is associated with the iron transport system, leading to enhanced transcription of the hemeoxygenase enzyme. This enzyme exhibits proliferative and anti-apoptotic properties, hence safeguarding and preserving proximal tubule cells [16]. NGAL's presence in many regions of the kidney enables its utilization as a precise biomarker for kidney injury [13].

NGAL is present within epithelial cells, specifically on primary cilia that are often observed throughout the body, including the cilia of the kidney tubules. Primary cilia play a crucial role in preserving the structural integrity of the kidney tubules, ensuring organ

homeostasis, and facilitating the ongoing process of cell division. When there is injury to the cells of the kidney tubule, a cellular autonomous reaction takes place, leading to an increase in the expression of primary cilia. This, in turn, results in an elevation of NGAL levels within the body. During an elevation in NGAL, there is an augmentation in the expression of primary cilia, which play a crucial role in preserving the proper structure of renal tubule cells and regulating renal cell proliferation. Consequently, the number of primary cilia decreases. The occurrence of uncontrolled renal proliferation is attributed to the reduction or complete loss of primary cilia. Hence, the control of NGAL is crucial in safeguarding renal cells against acute kidney damage [17]. NGAL originates from damaged tubular parts of the kidney and extrarenal organs [18].
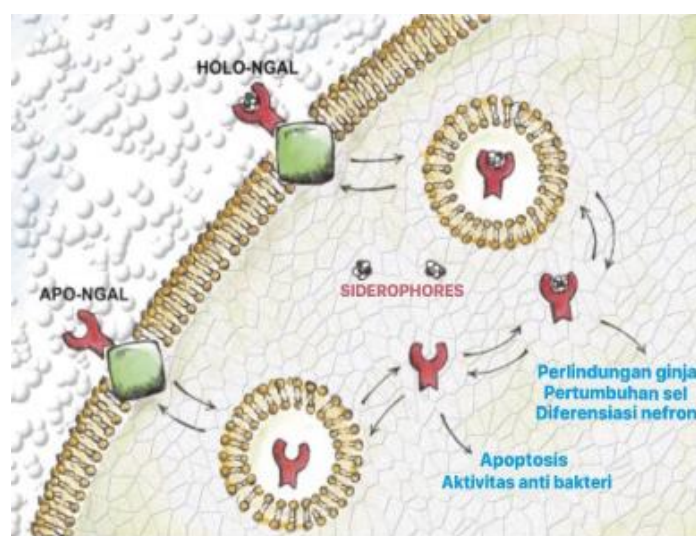

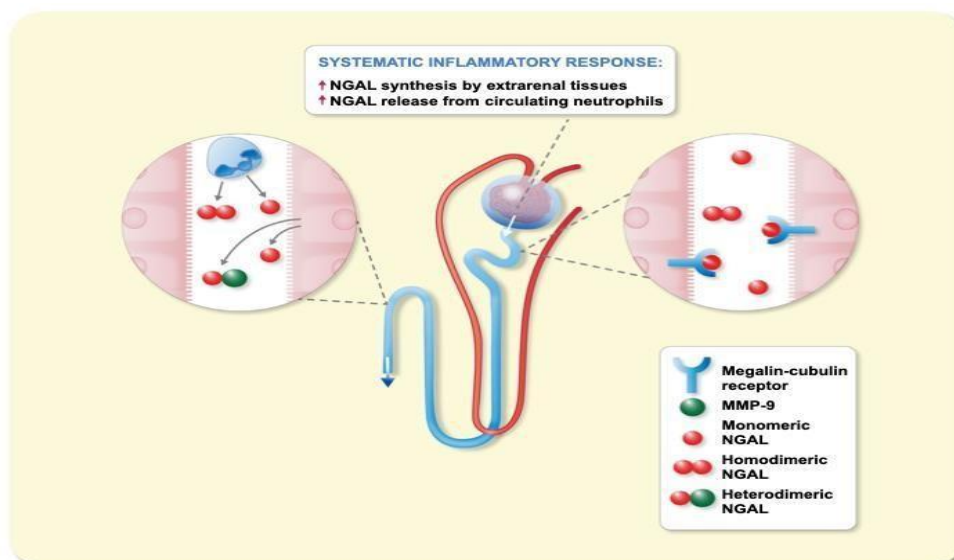**FIGURE 2** Schematic of the cellular mechanism of NGAL [13]

FIGURE 3 Renal tubular NGAL [13]

NGAL cut-off in AKI

Early in the progression of AKI, there is a known increase in NGAL levels. Numerous studies have assessed the efficacy of NGAL in the prevention of acute kidney injury (AKI) in diverse patient populations, including critically ill and septic patients in the intensive

care unit (ICU), as well as patients in the emergency room or undergoing kidney transplantation. Multiple investigations have shown that NGAL is capable of diagnosing AKI. Constantin et al conducted a study on plasma NGAL levels in 88 patients admitted to the ICU. The study indicated that plasma NGAL had a sensitivity of 82%, specificity of 97%, and an AUC of 0.92. The cut-off value for predicting AKI was set at 155 mmol/L. The study conducted by Nugroho at Dr. Soetomo Hospital Surabaya examined the effects of treatment for 48-72 hours on paediatric septic patients. The findings revealed that the cut-off value for this treatment was determined to be 1242 ng/mL, with a sensitivity of 76.5% and specificity of 61.5% [23].

The assessment of renal impairment using NGAL levels in postoperative individuals, is now restricted to cases involving significant surgical procedures, encompassing both pediatric and adult patients who have had cardiac surgery. According to a review research conducted in 2017, the utilization of NGAL in conjunction with other evaluations of renal function has the potential to be advantageous in the timely identification of acute kidney failure associated with cardiac surgery [24]. These findings are corroborated by a cohort study that included 1,371 high-risk patients who underwent cardiac surgery, a cohort study of 125 patients with impaired kidney function prior to cardiac surgery, and a cohort study of 408 pediatric patients who underwent cardiac surgery [24,26].

In 2016, De Geus HRH *et al.* mentioned that the CSA-NGAL score is employed to assess the presence of post-operative tubular damage (Figure 4). This is achieved by examining the absolute value of NGAL before surgery and the difference in NGAL values before and after surgery, thereby confirming the occurrence of tubular damage. Therefore, the initial NGAL value is necessary for interpretation and comparison with the value during or after surgery. The CSA-NGAL score assesses the likelihood of acute kidney injury (AKI) following surgery. Specifically, uNGAL levels ranging from 50 to 150 ng/mL or pNGAL levels ranging from 100 to 200 ng/mL are associated with an increased risk of kidney tubular damage. pNGAL levels exceeding 200 ng/mL (uNGAL levels exceeding 10 ng/mL) or an elevation in pNGAL or uNGAL levels over 100 ng/mL from pNGAL values exceeding 150 ng/mL (uNGAL levels exceeding 125 ng/mL) prior to surgery, serve as ATN indicators [27].

Figure 4 CSA–NGAL score

Measurement of NGAL

Sepsis, chronic obstructive pulmonary disease, and cardiac dysfunction are conditions that can disrupt the performance, sensitivity, and specificity of NGAL as a biomarker for renal tubular injury. Age seems to have an impact on the performance of the NGAL biomarker. Children exhibit a greater predictive value compared to older patients. Besides, gender also exerts an influence on the predictive value, specifically exhibiting a larger prevalence among female patients compared to male patients. Urinary tract infections and decreased kidney function are other factors that contribute to elevated predictive values. Patients with chronic renal disease are also encompassed within this category [21].

The measurement of urinary NGAL (uNGAL) is considered to be a more accurate indicator of localised kidney damage and offers a less invasive approach, resulting in a reduction in the need for frequent blood samples, particularly in critically sick patients and children. The findings indicated that there was an elevation in uNGAL levels prior to the manifestation of pathological proteinuria. The concentration of NGAL rises in both urine and serum within a span of 2 hours following kidney injury, whereas the expression of NGAL mRNA increases by a factor of 1000 within a period of 24 to 48 hours. NGAL is commonly regarded as an early, highly sensitive, and non-invasive biomarker for acute kidney injury (AKI) [11,28].

The NGAL measurement can be performed using either urine or plasma samples, although neither method is considered superior. The receiver operating characteristic (ROC) curve for urine NGAL in predicting acute kidney injury (AKI) was 0.998, whereas for plasma NGAL it was 0.91. Nevertheless, it has been observed that urinary tract infections have an impact on NGAL levels. At present, the measurement of NGAL can be conducted in an automated manner by the utilization of an auto-analyzer [12,28].

Devarajan (2020) conducted a study wherein they provided a summary of the benefits associated with NGAL as a diagnostic method for kidney injury, as presented in Table 2. One advantage of this method is its noninvasive nature, rapidity, and high sensitivity for early detection [18].

In a study by Devarajan in 2020, they summarized the advantages of NGAL as a modality for diagnosing kidney injury (Table 2). One of them is non-invasive, fast, and sensitive for early diagnosis [18].EDTA serum or plasma specimens can be used to measure NGAL. There should be no haemolysis or hyperlipemia in the specimens. No preparation is required before sampling and storage of specimens is recommended at -80 ºC [18].

Various techniques can be employed to quantify urine and/or plasma/serum NGAL levels, including Western blot analysis, enzyme-linked immunosorbent assay (ELISA), and the utilization of commercially available kits such as Triage® and Architect®. NGAL testing operates on the idea of employing monoclonal antibodies. The primary application of the ELISA method is in research. The NGAL testing involves the use of anti-NGAL monoclonal antibodies in the solid phase and enzyme-labeled anti-NGAL monoclonal antibody conjugates, following the sandwich ELISA principle. The least detectable amount of NGAL is 0.094 ng/mL, with a range of values spanning from 0.156 to 10 ng/mL [18]. A systematic review and meta-analysis conducted by Zhang *et al.* (2019) reported the diagnostic ability of plasma NGAL to predict AKI in septic patients, using a cut-off value of 150 ng/mL had an area under curve (AUC) of 0.94 (95% CI, 0.88-0, 97) and 0.92 (95% CI, 0.84-0.96) [27]. Meanwhile, using the same cut-off, another study reported a AUC of 0.81 (95% CI 0.74-0.87) [29].

TABLE 2 Characteristics of NGAL Biomarkers [18]

Biomarker Aspects	NGAL
Non-invasive, using urine or blood	Yes
Rapid and cheap to perform	Yes
Results are available with limited injury	Yes
Can be modified for clinical trial platforms	Yes
Sensitive for early diagnosis	Yes
High gradient to allow risk stratification	Yes
Specific to intrinsic (vs prerenal) AKI	Yes
Distinguish between acute and chronic kidney injury	No
Increases in proportion to the damage severity	Yes
Associated with understood mechanisms	Yes
Identify the primary location of injury within the kidney	Yes
Results predict clinical outcomes	Yes
Outcomes predict therapeutic efficacy	Yes
Results enhance drug development process	Yes

Inhalation anesthesia

In general anesthesia, inhalation anesthesia is a frequently employed technique. Inhalation anesthetics can induce drowsiness and, when present in high concentrations, can lead to relaxation of skeletal muscles. Inhalation anesthesia has been observed to have a direct impact on blood pressure reduction through the process of dilatation of blood vessels, as well as the inhibition of cardiac contractility. In contrast, the indirect consequence entails a reduction in the activity of the sympathetic nervous system. Central nervous system (CNS) variables serve as indicators for evaluating the extent of continuing anesthesia. Excessive use of inhalation anesthesia might result in low blood pressure, irregular heart rhythm, slow heart rate, and potentially even circulatory shock. In contrast to the solubility of other pharmaceutical substances, inhalation anesthetics undergo absorption and distribution within the bloodstream due to pressure gradients. This process occurs when the pressure of the inspired air is equivalent to the pressure of the inhaled air in the alveoli, blood, and surrounding tissues. Upon cessation of inhalation anesthesia, there is a reduction in alveolar pressure, leading to a restoration of equilibrium between the tissue, veins, and alveoli during the expiration process [1].

The location of action of inhalation anesthetic medicines is not confined to a single place at the macroscopic level. The reticular activating system, cerebral cortex, cuneate nucleus, olfactory cortex, and hippocampus are among the specific brain regions that are impacted by inhaled anesthetics. Anesthetic drugs that are inhaled have the ability to inhibit excitatory transmission in the spinal cord, particularly at the dorsal horn interneurons that play a crucial role in pain transmission. Inhalation anesthetics exhibit various associations with subcortical regions, such as the spinal cord or brainstem. A previous investigation conducted on mice indicated that the elimination of the

cerebral cortex did not have any impact on the efficacy of inhaled anesthetics [30].

Synaptic transmission is more susceptible to inhaled anesthetics at the microscopic level compared to axonal transmission. However, nerve axons with smaller diameters are more readily impacted. Inhalation anesthetics exert an effect on both presynaptic processes and postsynaptic mechanisms. The effects of general anesthetic medications might arise from alterations in many cellular systems, such as ligand-gated ion channels, second messenger activities, or neurotransmitter receptors. For instance, numerous anesthetic medications enhance the inhibition of β-aminobutyric acid (GABA) in the central nervous system (CNS). In addition, GABA receptor agonists have been found to augment anesthesia, while GABA antagonists have been observed to mitigate the effects of certain inhalation anesthetic medications. The potency of inhaled anesthetic medicines is strongly correlated with the potency of GABA receptor activity. The efficacy of inhaled anesthetic medicines is associated with the formation of hydrophobic interactions with channel proteins, specifically GABA receptors. The primary mechanism of action of many anesthetic medicines is the modulation of GABA function [30].

Sevoflurane

Sevoflurane is a volatile anesthetic substance that is generated from fluorine and isopropyl ether. It is non-flammable, non-explosive, and has a molecular weight of 200.05 [1]. The liquid form of sevoflurane is transparent and devoid of any chemical additions or stabilizers. When stored in a room storage, it remains non-irritative and stable. No degradation of sevoflurane was seen when exposed to strong acids or heat. Nevertheless, when the CO2 absorbent (sodalime/baralime) comes into direct contact with it, a degradation reaction occurs, resulting in the production of pentafluoroisopropenyl fluoromethyl ether (PIFE, C4H2F6O), a haloalken derivative known as Compound A, as well as some pentafluoromethoxyisopropyl fluoromethyl ether (PMFE, C5H6F6O) or Compound B. Compound A has been found to be nephrotoxic in mice, leading to kidney damage. However, there is currently no evidence to suggest that it is nephrotoxic in humans [1].

Sevoflurane, unlike other inhalation anesthetics, does not generate a significant amount of carbon monoxide when destroyed by sodalime. According to reference [1], sevoflurane does not cause corrosion on stainless steel, brass, or aluminum.

The lack of conversion into acylhalide in metabolism can be attributed to the chemical nature of sevoflurane. The metabolism of sevoflurane does not result in the production of liver protein that is trifluoroacetylated, hence it does not induce the production of antibodies targeting trifluoroacetylated proteins. In contrast to halothane, enflurane, isoflurane, and desflurane, all of these compounds undergo metabolism resulting in the formation of acetyl fluoride, a reactive intermediate product. This intermediate product has the potential to induce hepatotoxicity and cross-sensitivity between different treatments [1].

The quick increase in alveolar concentrations during induction and subsequent drop after cessation of sevoflurane administration can be attributed to the low solubility of sevoflurane in blood and its blood gas partition coefficient of 0.09 for adults and 0.06 for infants. The clinical investigation revealed that the inspiratory concentration (Fi) and end-tidal concentration (FA) recorded at 30 minutes were 0.85, as evaluated by the ratio of FA to Fi (Wash in). The FA/FAO (Wash out) value at the 5-minute mark is 0.15.

The process of rapid pulmonary clearance leads to a decrease in the metabolic activity of anesthetic drugs. The absorption and metabolism of sevoflurane in humans results

in the production of hexafluoroisopropanol, which is accompanied by the emission of inorganic fluoride and carbon dioxide (CO_2). After the formation of HFIP, it undergoes fast conjugation with glucuronic acid and subsequent elimination. Trifluoroacetic acid is not metabolized [1].

Sevoflurane has a modest decrease in renal blood flow, and its metabolites, which are produced in significant amounts, possess nephrotoxic properties [31].

Low fresh gas flow inhalational anesthesia

The field of anesthesia has had numerous modifications during its evolution, beginning with the advent of ether, open-drop, semi-close, and close systems. The utilization of anesthetic drugs in exhaled gases has garnered considerable interest. The utilization of anesthetic procedures with low fresh gas flow has been facilitated by advancements in current anesthesia machines, gas monitors, precision vaporizers, and the introduction of more volatile drugs with limited absorption. The utilization of this anesthesia approach is motivated by the significant pollution resulting from environmental contamination caused by anesthetic gases in routine clinical practice [32].

Anesthesia low FGF lacks a broadly acknowledged definition. Low gas flow anesthesia refers to techniques that utilize a gas flow that is lower than alveolar ventilation. The low flow technique is a type of inhalation anesthetic technique characterized by a minimum re-breathing fraction of 50%. This means that once the patient absorbs CO2, at least 50% of the exhaled gas mixture is returned to the patient for subsequent inspiration. To do this in contemporary anesthesia equipment, it is necessary to decrease the flow of FGF to a minimum of 2 L/min or lower [32].

The low fresh gas flow technique is based on the principle of minimizing the gas flow while effectively removing CO2 prior to its re-entry into the circulation. This approach

effectively reduces the emission of anesthetic chemicals into the surrounding environment [32].

The primary difficulties associated with employing the low fresh gas flow technique lie in effectively managing the equilibrium of the gas flow composition following reuptake and metabolism, as well as addressing the various elements that influence the consumption and production of gas components. The estimation of substance absorption, including oxygen, nitrous oxide, and inhalation anesthetic drugs, can be achieved through regular monitoring of gas flow control. The utilisation of an end-tidal usage gas analyzer for monitoring inspiration and concentration is a more precise approach in the implementation of a secure low fresh gas flow [32].

A manual bag will be utilized to collect exhaled gas, serving as a reservoir bag. During the following respiratory cycle, the exhaled air will be combined with a sudden inhalation of fresh gas. The air will traverse the CO_2 absorbent, where a chemical reaction will take place, resulting in the binding of CO_2 and the generation of heat. In all contemporary anesthesia circuits equipped with rebreathing systems, this chemical reaction is expected to take place [32].

The present approach to optimizing the re-breathing process involves enhancing the system's speed in order to facilitate the alteration of fresh gas composition. This objective can be accomplished through passive means, such as reducing the volume within the circuit, or through active means, such as managing the flow of mixed gas within the circular circuit. Furthermore, the utilization of a vaporizer with a high maximum dose will result in an augmentation of the system's velocity. The velocity holds significant importance in low FGF approaches. A low flow breathing system necessitates a longer duration to achieve the desired concentration due to the inverse relationship between gas flow and time [33].

Requirements for using low fresh gas flow technique [32]

a) Calibrate flow meters with low flows up to 50 mL/minute

b) Monitor for leaks in circle systems and endotracheal tube (ETT) airway devices; low FGF may also be performed on appropriately sized supraglottic airway devices.

c) Monitoring system of agent's inspiratory gas and end-tidal concentration.

d) Measurement of expiratory gas concentration more closely with Ypiece that reflects patient's alveolar concentration.

e) Vaporizer is able to provide high concentrations and calibrated accurately at low FGF.

f) Breathing system should have minimal internal volume to minimize reserve volume.

Contraindications of low fresh gas flow techniques

The face mask approach, when used for a brief period of anesthesia, may not effectively maintain the seal of the face mask and airways, particularly in bronchoscopy operations involving stiff bronchoscopy that necessitate a significant flow of new gas. Patients with ketoacidosis, such as diabetes, may have an elevation in the concentration of acetone in their blood during anesthesia. To prevent the creation of unwanted acetone, it is necessary to maintain a gas flow rate greater than 1 liter per minute [33].

Disadvantages of low fresh gas flow technique

The presence of a reduced and consistent gas flow rate will result in a prolonged induction period. It is not feasible to achieve rapid alterations in inspired concentration when the FGF is low. To prevent hypoxia and proper dosage of anesthetic drugs, it is crucial to be vigilant and make appropriate adjustments to the gas flow increased utilization of CO_2 absorbents and the potential for hypercarbia and CO_2 re-breathing due to absorbent saturation. The circuit system may experience an undesired accumulation of gaseous agents. The aforementioned substances encompass carbon monoxide, acetone, methane, hydrogen, ethanol, and compound A. According to the guidelines set forth by the United States Food and Drug Administration, it is advised to restrict the use of sevoflurane to alveolar minimum concentration (MAC) hour at gas flow rates ranging from 1 to 2 L/min. It is not recommended to administer sevoflurane at flow rates below 1 L/min.

In animal studies, it has been observed that Compound A, which is a byproduct of sevoflurane, can lead to AKI. Insufficient fibroblast growth factor (FGF) can trigger the creation of this chemical and build up in the respiratory system [30].

Compound A is formed through renal metabolism of sevoflurane, resulting in the formation of thionacyl fluoride, a reactive and poisonous compound. Cysteine conjugate beta lyase is required in the kidneys. The abundance of this enzyme in animals, particularly mice, is 20-30 times greater than in humans. This may elucidate the reason behind the non-toxicity of chemical A towards humans [34,35].

Conclusion

The anesthetic substance known as sevoflurane is believed to possess nephrotoxic properties due to the presence of its metabolites, specifically fluoroacetic acid and molecule A. The combination of low fresh gas flow and high concentrations of sevoflurane leads to increased degradation of sevoflurane, thereby increasing the risk of kidney tubular damage. NGAL has a significant function in controlling cell proliferation, facilitating healing processes, and promoting the regeneration of tubules following kidney injury. An increased level of NGAL is indicative of acute renal injury. NGAL testing can be conducted utilizing either urine or plasma specimens, yielding comparable outcomes.

The NGAL examination employs monoclonal antibodies as its underlying premise. NGAL offers the benefit of being non-invasive, quick, and highly sensitive for early detection.

Authors' Contributions

The authors fully accept responsibility for all the work's content and have given permission for it to be submitted.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Orcid:

Kohar Hari Santoso:
https://orcid.org/0009-0003-2742-2940
Syamsuri Wahyu:
https://orcid.org/0009-0005-4003-4656
Maulydia:
https://orcid.org/0000-0003-3248-1540

References

[1] A.L. Hayu, E. Hanindito, H. Hamzah H, A. Utariani, Effectiveness of high-flow inhalation anesthesia technique using isoflurane compared to low-flow inhalation anesthesia technique using sevoflurane and isoflurane in terms of cost and safety, *Bali Journal of Anesthesiology,* **2019**, *3*, 170–173. [Crossref], [Google Scholar], [Publisher]

[2] F. Ratsmita, M. Ilyas, Biomonitoring of sevoflurane exposure in anesthesiologist, *The Indonesian Journal of Public Health,* **2021**, *16*, 57–69. [Crossref], [Google Scholar], [Publisher]

[3] M.E. Grams, Y. Sang, J. Coresh, S. Ballew, K. Matsushita, M.Z. Molnar, Z. Szabo, K. Kalantar-Zadeh, CP. Kovesdy, Acute kidney injury after major surgery: A retrospective analysis of veterans health administration data, *American Journal of Kidney Diseases,* **2016**, *67*, 872–880. [Crossref], [Google Scholar], [Publisher]

[4] A. Zarbock, M.K. Nadim, P. Pickkers, H. Gomez, S. Bell, M. Joannidis, K. Kashani, J.L. Koyner, N. Pannu, M. Meersch, T. Reis, T. Rimmelé, S.M. Bagshaw, R. Bellomo, V. Cantaluppi, A. Deep, S. De Rosa, X. Perez-Fernandez, F. Husain-Syed, S.L. Kane-Gill, Y. Kelly, R.L. Mehta, P.T. Murray, M. Ostermann, J. Prowle, Z. Ricci, E.J. See, A. Schneider, D.E. Soranno, A. Tolwani, G. Villa, C. Ronco, L.G. Forni, Sepsis-associated acute kidney injury: consensus report of the 28th acute disease quality initiative workgroup, *Nature Reviews Nephrology*, **2023**, *19*, 401–417. [Crossref], [Google Scholar], [Publisher]

[5] K. Harimin, T. Bisri, Efek anestesia aliran rendah sevofluran terhadap respon inflamasi pada susunan saraf pusat, *Jurnal Neuroanestesi Indonesia,* **2014**, *3*, 121–31. [Crossref], [Google Scholar], [Publisher]

[6] S.A. Price, Patofisiologi: konsep klinis proses-proses penyakit, *Universitas Indonesia Library*, **2006**, *1*. [Crossref], [Google Scholar], [Publisher]

[7] R. Sivaci, S. Demir, T. Koken, Y. Sivaci, S. Yilmaz, Biochemical effects of low-flow anesthesia with inhalation agents in patients undergoing laparoscopic surgery, *Journal of Medical Biochemistry*, **2012**, *31*, 53-59. [Crossref], [Google Scholar], [Publisher]

[8] R. Ghatanatti, A. Teli, S.S. Tirkey, S. Bhattacharya, G. Sengupta, A. Mondal, Role of renal biomarkers as predictors of acute kidney injury in cardiac surgery, *Asian Cardiovascular and Thoracic Annals*, **2014**, *22*,

234–241. [Crossref], [Google Scholar], [Publisher]

[9] S.A. Rampengan, Cardiorenal syndrome type 1: a literature review, *Bali Medical Journal*, **2019**, *8*, 537-541. [Crossref], [Google Scholar], [Publisher]

[10] C. Thongprayoon, P. Hansrivijit, K. Kovvuru, S.R. Kanduri, A. Torres-Ortiz, P. Acharya, M.L. Gonzalez-Suarez, W. Kaewput, T. Bathini, W. Cheungpasitporn, Diagnostics, risk factors, treatment and outcomes of acute kidney injury in a new paradigm, *Journal of Clinical Medicine*, **2020**, *9*, 1104. [Crossref], [Google Scholar], [Publisher]

[11] MR. Kurniawan, E. Kusrini, Ureum and creatinine health study in patient diabetes mellitus, *Indonesian Journal of Medical Laboratory Science and Technology,* **2020**, *2*, 85-92. [Crossref], [Google Scholar], [Publisher]

[12] K. Wang, S. Xie, K. Xiao, P. Yan, W. He, L. Xie, Biomarkers of sepsis-induced acute kidney injury, *BioMed Research International*, **2018**, *2018*, 6937947. [Crossref], [Google Scholar], [Publisher]

[13] F.F. Luft, Biomarkers and predicting acute kidney injury, *Acta Physiologica (Oxford, England)*, **2021**, *231*, 13479. [Crossref], [Google Scholar], [Publisher]

[14] A. Syadiah, E. Febrina, L. Levita, Review neutrophil gelatinase-associated lipocalin (ngal): perannya sebagai biomarker pada kerusakan ginjal akut, *Jurnal Sains Farmasi & Klinis*, **2021**, *8*, 35-42. [Crossref], [Google Scholar], [Publisher]

[15] J. Mårtensson, R. Bellomo, The rise and fall of NGAL in acute kidney injury, *Blood Purification,* **2014**, *37,* 304–310. [Crossref], [Google Scholar], [Publisher]

[16] K. Mori, H.T. Lee, D. Rapoport, I.R. Drexler, K. Foster, J. Yang, K.M. Schmidt-Ott, X. Chen, J.Y. Li, S. Weiss, J. Mishra, Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury, *The Journal of Clinical Investigation,* **2005**, *115*, 610-621. [Crossref], [Google Scholar], [Publisher]

[17] H. Cassidy, J. Slyne, M. Higgins, R. Radford, P.J. Conlon, A.J. Watson, M.P. Ryan, T. McMorrow, C. Slattery, Neutrophil gelatinase-associated lipocalin (NGAL) is localised to the primary cilium in renal tubular epithelial cells-a novel source of urinary biomarkers of renal injury, *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, **2019**, *1865*, 165532. [Crossref], [Google Scholar], [Publisher]

[18] P. Devarajan, NGAL for the detection of acute kidney injury in the emergency room, *Biomarkers In Medicine*, **2014**, *8*, 217–219. [Crossref], [Google Scholar], [Publisher]

[19] A. Clerico, C. Galli, A. Fortunato, C. Ronco, Neutrophil gelatinase-associated lipocalin (NGAL) as biomarker of acute kidney injury: a review of the laboratory characteristics and clinical evidences, *Clinical Chemistry and Laboratory Medicine*, **2012**, *50*, 1505–1517. [Crossref], [Google Scholar], [Publisher]

[20] K. Makris, D. Stefani, E. Makri, I. Panagou, M. Lagiou, A. Sarli, M. Lelekis, C. Kroupis, Evaluation of a particle enhanced turbidimetric assay for the measurement of neutrophil gelatinase-associated lipocalin in plasma and urine on Architect-8000: Analytical performance and establishment of reference values, *Clinical Biochemistry*, **2015**, *48*, 1291-1297. [Crossref], [Google Scholar], [Publisher]

[21] V. Pennemans, J.M. Rigo, C. Faes, C. Reynders, J. Penders, Q. Swennen, Establishment of reference values for novel urinary biomarkers for renal damage in the healthy population: are age and gender an issue?, *Clinical Chemistry And Laboratory Medicine*, **2013**, *51*, 1795-1802. [Crossref], [Google Scholar], [Publisher]

[22] K. Helanova, J. Spinar, J. Parenica, Diagnostic and prognostic utility of neutrophil

gelatinase-associated lipocalin (NGAL) in patients with cardiovascular diseases—review, *Kidney Blood Press Res*, **2014**, *39*, 623–629. [Crossref], [Google Scholar], [Publisher]

[23] N.S. Budi, A. Arie Utariani, E. Hanindito, B.P. Semedi, N. Asmaningsih, The validity of urinary neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker of acute kidney injury in pediatric patients with sepsis, *Critical Care Shock*, **2021**, *24.* [Google Scholar], [Publisher]

[24] W. Vandenberghe, J. De Loor, E.A. Hoste, Diagnosis of cardiac surgery-associated acute kidney injury from functional to damage biomarkers, *Current Opinion in Anesthesiology*, **2017**, *30*, 66–75. [Crossref], [Google Scholar], [Publisher]

[25] N. Tidbury, N. Browning, M. Shaw, M. Morgan, I. Kemp, B. Matata, Neutrophil gelatinase-associated lipocalin as a marker of postoperative acute kidney injury following cardiac surgery in patients with preoperative kidney impairment, *Cardiovascular & Haematological Disorders-Drug Targets (Formerly Current Drug Targets-Cardiovascular & Hematological Disorders)*, **2019**, *19*, 239-248. [Crossref], [Google Scholar], [Publisher]

[26] J.H. Greenberg, M. Zappitelli, Y. Jia, H.R. Thiessen-Philbrook, C.A. De Fontnouvelle, F.P. Wilson, S. Coca, P. Devarajan, C.R. Parikh, Biomarkers of AKI progression after pediatric cardiac surgery, *Journal of the American Society of Nephrology*, **2018**, *29*, 1549-1556. [Crossref], [Google Scholar], [Publisher]

[27] K.M. Tecson, E. Erhardtsen, P.M. Eriksen, A.O. Gaber, M. Germain, L. Golestaneh, M. de los Angeles Lavoria, L.W. Moore, P.A. McCullough, Optimal cut points of plasma and urine neutrophil gelatinase-associated lipocalin for the prediction of acute kidney injury among critically ill adults: retrospective determination and clinical validation of a prospective multicentre study, *BMJ Open*, **2017**, *7*, 16028. [Crossref], [Google Scholar], [Publisher]

[28] T. Rubinstein, M. Pitashny, B. Levine, N. Schwartz, J. Schwartzman, E. Weinstein, J.M. Pego-Reigosa, T.Y.T. Lu, D. Isenberg, A. Rahman, C. Putterman, Urinary neutrophil gelatinase-associated lipocalin as a novel biomarker for disease activity in lupus nephritis, *Rheumatology*, **2010**, *49*, 960-971. [Crossref], [Google Scholar], [Publisher]

[29] A.N. Saputra, P.S. Airlangga, B.A. Rahman, E. Kusuma, P. Kriswidyatomo, C. Sumartomo, Role of neutrophil gelatinase-associated lipocalin (NGAL) as a acute prerenal kidney injury marker: Exploring factors associated with its postoperative levels in hypotension-controlled otorhinolaryngology surgery, *Bali Medical Journal*, **2022**, *11*, 1844-1848. [Crossref], [Google Scholar], [Publisher]

[30] J.F. Butterworth IV, D.C. Mackey, J.D. Wasnick, Inhalation anesthetics, *Morgan & Mikhail's Clinical Anesthesiology*, New York, NY: McGraw-Hill Education, **2013**. [Google Scholar], [Publisher]

[31] P.D.D. RehI, Comparison of cost-effectiveness analysis (CEA) between sevoflurane inhalation anesthetic and propofol total intravenous anesthesia (TIVA) in craniotomy surgery: A literature review, *Bali Medical Journal*, **2023**, *12*, 1790-1795. [Google Scholar], [Publisher]

[32] M. Upadya, P.J. Saneesh, Low-flow anaesthesia- underused mode towards 'sustainable anaesthesia', *Indian Journal of Anaesthesia*, **2018**, *62*, 166–172. [Crossref], [Google Scholar], [Publisher]

[33] C. Hönemann, B. Mierke, Low-flow, minimal-flow and metabolic-flow anaesthesia. Clinical techniques for use with rebreathing systems, Drägerwerk AG&Co. Lübeck, Germany, **2014**. [Google Scholar], [Publisher]

[34] B.A. Gentz, T.P. Malan, Renal toxicity with sevoflurane: a storm in a teacup?, *Drugs,*

Journal of Medicinal and Pharmaceutical Chemistry Research

2001, *61*, 2155–2162. [Crossref], [Google Scholar], [Publisher]

[35] A.N.M. Ansori, M.H. Widyananda, Y. Antonius, A.A.A. Murtadlo, V.D. Kharisma, P.A. Wiradana, S. Sahadewa, F.D. Durry, N. Maksimiuk, M. Rebezov, R. Zainul, A review of cancer-related hypercalcemia: Pathophysiology, current treatments, and future directions, *Journal of Medicinal and Pharmaceutical Chemistry Research*, **2024**, *6*, 944-952. [Crossref], [Pdf], [Publisher]