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GLOBAL JOURNAL OF Anesthesiology

ISSN: 2455-3476 DOI: https://dx.doi.org/10.17352/gja

Review Article

# Volatile agents and renal transplantation

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**Received:** 08 January, 2020
**Accepted:** 11 May, 2020
**Published:** 12 May, 2020

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**Keywords:** Renal transplantation; Volatile agent; Anesthesia

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## Abstract

Living donor and cadaveric donor renal transplantation have received a significant interest. During the procedure, both volatile agents and total intravenous anesthesia are used. However, the effects of volatile agents used during anesthesia on primary graft dysfunction is controversial. Besides evidence-based scientific data is not enough to conclude the ideal inhalation agent in renal transplantation. This review aimed to determine the effects of volatile agents preventing or improving the Ischemia Reperfusion (IR) injury during general anesthesia in patients undergoing renal transplantation. The possible mechanisms that affect the outcome of the patients after transplantation will be discussed.

## History

The first flammable halogenated volatile anesthetic gas was methoxyflurane which was used in Manhattan Project in 1948 during the 2nd World War. It has been *withdrawn* for *use* as an anesthetic agent due to the high rate of vasopressin resistant renal failure. Afterwards the attempts to find a new agent continued with the discovery of another fluoride agent. This agent was Sevoflurane and its conversion to haloalkenes by dehydrofluorination when it encountered $CO_2$ absorber to produce Compound A: trifluoro methyl vinyl ether, has shown a new concern in rats [1]. Although nephrotoxicity has not been established in clinical studies; according to the FDA recommendations, sevoflurane can only be used up to 1 h with a fresh gas flow of 1L/min. Moreover sevoflurane can be considered more than 1h with a flow of >2 L/min. As a result, desflurane gained popularity because of its structure being a fluorinated methyl ether and highly stable with sodalime. Desflurane has almost no metabolism even administered at 7 MAC values, and it has the least solubility among volatile agents. By this way the recovery time is almost 50% of isoflurane [2]. Like isoflurane, causes a dose-dependent increase in heart rate and blood pressure and a decrease in systemic vascular resistance with myocardial depression and peripheral vasodilation. On the other side, coronary vasodilatation also leads to a decrease in cardiac workload. The metabolism in liver is about 0.02%. The most unfavorable property is the stimulation of airway reflexes with irritant odor leading to cough and bronchospasm.

### Volatile agents and immune response

The inflammatory response to surgery and changes in cell-mediated immunity may lead different results. Based on the current literature, changes in the immune system response were found to be more pronounced after a balanced volatile anesthesia compared to total intravenous anesthesia. It is clear that volatile agents can increase inflammation and cellular adhesion due to their high doses resulting with hypotension and transient hypoxia. They decrease Th1 phenotype, increase cell-mediated immunity and directly affect immune system by manipulating glucose control. For instance, isoflurane has been shown to inhibit normal insulin production and produce a hyperglycemic response.

The NK cell activity is suppressed by volatile agents [3]. Besides they enhance angiogenesis through hypoxia inducible factor-1α activity. Moreover, volatile anesthetics suppress cell-mediated immunity and promote cancer cell proliferation [4,5]. In addition volatile agents induce T-lymphocyte



**Citation:** Saracoglu KT, Bilgili B, Saracoglu A (2020) Volatile agents and renal transplantation. Glob J Anesth 7(1): 005-008.
DOI: https://dx.doi.org/10.17352/2455-3476.000050

apoptosis. Sevoflurane inhibits the intracellular signaling cascade, and activates the NF-κB, involves in inflammation as a transcription factor [6].

## Volatile agents-induced renal protection

The first successful renal transplantation was performed between twins in 1954 by Joseph Murray under subarachnoid block with limited monitoring of blood pressure and Electrocardiogram (ECG). The first successful live renal tx was performed by Johny and Mohan Rao in 1971 in India [7].

The graft care requires professionalism during the transplantation. A number of pathological processes play a role in the failure of graft [8]. Ischemia Reperfusion Injury (IRI) can lead to early renal dysfunction which causes acute rejection episodes and graft failure. However, the most obvious cascade is the loss of renal function caused by the immune response and the resulting deepening of hemodynamic instability, which in turn leads to more immune activation with a vicious cycle. The release of vasoactive hormones during hemodynamic instability causes intrarenal vasoconstriction and aggregates intrarenal hypoxia. This may lead to potentialization of acute tubular necrosis and tubular damage in the transplanted kidney. Finally renal ischemia causes depletion of ATP stores, bleb formation and a loss of renal tubular polarity. Cytokines and chemokines released from renal tubular epithelial cells increase renal tubular and endothelial damage. The destruction of the endothelial basement membrane causes vascular leakage and neutrophil migration into the interstitial area.

Since years, ischemia-reperfusion injury during kidney transplantation continues to be an important challenge in maintaining organ function and graft viability. IRI is a process that involves a reperfusion injury in live ischemic tissue and its etiology involves biochemical, cellular, vascular endothelial and tissue-specific factors with inflammation. Renal parenchymal destruction leads to increased graft loss resulting in increased vascular damage and fibrosis. ICAM1 secondary to ischemia, macrophage inflammatory protein, monocyte chemotactic protein, interferon inducible protein are effective in renal damage. The mechanism of apoptosis occurs with the reduction of granzyme, Fas / Fas ligand, cytotoxic T lymphocyte antigen 4, IL-2. The interaction of cytotoxic T lymphocyte antigen 4 with CD 80/86 and T regulatory activity with MHC II cells disrupts T cell activation. Here, apoptosis triggers this contact-dependent pathway. In addition, cytokine production (IL35, TGF beta, IL 10, IL 8) is also associated with T cell activation. IRI results in tubular damage by inducing inflammatory cells, which causes the accumulation of T cells in the area of the danger zone or in the reperfusion area. These areas are fields of hypovascularization and hypoperfusion where IRI occurs. Upregulation of all these substances causes innate immune response in renal tubular cells and endothelium. Endothelial vasoconstriction and necrosis are the products of prolonged ischemia. Reactive Oxygen Species (ROS) production secondary to reperfusion and dysfunction of the antioxidant system exacerbate tubular cell damage and lead to death. Ongoing hypoxia leads to disruption of mitochondrial function, and apoptosis is triggered, afterwards fibrosis begins. On the other hand, activation of procoagulant pathways in peritubular and glomerular capillaries as a response during reperfusion causes fibrin deposits and plt aggregation. This is accompanied by a decrease in Glomerular Filtration Rate (GFR) due to the reduction of renal perfusion. Again, adhesion of erythrocytes and leukocytes to the vascular endothelium contributes to the obstruction of the renal microvasculature. And ultimately, all these events cause thrombosis in renal vasculature and graft loss.

Activation of toll-like receptors by expression of adhesion molecules, polymorphonuclear cells and neutrophil infiltration as a result of micvovascular plug and local tissue destruction is also exacerbated. Activation of complement by an alternative pathway also contributes to this situation. Acute tubular necrosis is responsible for 75% of acute renal injury. These necrotic tissues cause more inflammation and a vicious cycle with danger signals [9]. Therefore, the inhibition of IRI is responsible for the development of all these processes by maintaining nephron support with reduced graft immunogenicity and renal microvasculature. Despite advances in immunosuppression, long-term graft survival rates remain ideal. There are studies showing that immune rejection and chronic graft failure are not only responsible reasons, but also the severity of IRI can affect graft function. There is a relationship between prolonged ischemia duration and delayed graft failure, and even the severity of IRI and the frequency of acute rejection episodes. So even short-term hypoxia episodes damage the kidneys. Almost half of donor kidneys are exposed to short-term hypoxia in renal transplantation and lead to a failure rate of 10% in transplanted primary grafts. Restoring perfusion can lead to recovery of injured tissues from the ischemic phase, but may also cause more damage paradoxically. A kidney graft should carry the workload of two previously existing kidneys. However, this workload should be performed in spite of an inflamed graft as well as a rapidly decreasing nephron pool due to ischemia-reperfusion injury. Workload is becoming more complicated in cadaveric donors. An autonomic response develops with the donor cytokine storm. Thus, the amount of circulatory catecholamine increases and this rises the level of the microvascular and parenchymal damage. Continuous process reduces circulating catecholamines and develops vasodilation bradycardia and tissue hypoxia.

## Ischemic preconditioning

In fact, the whole story was decribed in 1986 by Murry et al. and is based on the definition of ischemic preconditioning. The sublethal doses of ischemia periods become injury-resistant against the following episodes of lethal ischemia. Many studies have shown that the use of volatile anesthetics before ischemic injury increases the tolerance of cell against IR damage in brain and heart. Moreover the effects of isoflurane in favor of renal protection are also reported.

To date, the choice of anesthetic agent in renal tx was only performed according to the personal preference of the anesthesiologist. However, the renoprotective effect of isoflurane by preconditioning has been shown after 24-72 hours and this protective effect of volatile agents has been mentioned. This effect is known to occur by signaling molecules



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such as hypoxia-inducible factor-1a (HIF-1a) and hypoxia inducible factor. Adenosine-producing, ecto-50-nucleotidase (CD73), sphingosine-1-phosphate (S1P) via Sphingosine Kinase (SK) and IL-11 molecules such as transforming growth factor-b1 (TGF-b1) have been identified. The relation between sevoflurane and heat shock proteins including ERK, AKT and TGF-b1 has been revealed. The protection mechanism formed by volatiles in the kidney is formed by different paths from the heart, liver and brain. Volatile agents affect on calcium haemostasis in heart, activate myocardial protection pathways with their immunomodulatory effects. The depletion of ATP stores causes an increase in intracellular free calcium, and it has been shown that volatiles inhibit the IR in the heart by inhibiting the Na-Ca exchanger. Renal protection of volatile anesthetics is based on the inhibition of renal tubular, endothelial and interstitial inflammation by secretion of cytoprotective and anti-inflammatory molecules.

Volatile agents interact with the plasma lipid membrane in renal tubular cells and induce TGF-β1 production by exogenous phosphoditylserin. Volatiles have antinecrotic, antiinflammatory and antipytotic effects in renal tubule cells with SK and S1P signaling and TGF-β1-induced CD73 increase. In addition, Toll-like receptor-mediated T-cell immune response occurs. They increase megakaryocyte maturation by inducing IL-11 release and inhibiting endothelial cell death. The regulatory T (T reg) cells protect the kidney from IR damage by suppressing inflammation damage. Preventing the opening of pores with changes in mitochondrial permeability after ischemia, which causes the release of proapoptotic factors and necrotic cell death, is another advocated mechanism [10]. Volatile agents also suppress natural immunity, by the effects on NK, monocyte, neutrophil and macrophages. They also suppress T lymphocytes of CD4, CD 8 with B lymphocytes. Clinically effective concentrations of volatile agents also reduce the activation of mitogen-activated protein kinases with a reduction in inflammation and apoptosis [11].

## Ideal volatile agent

The inorganic fluoride amount formed by isoflurane and halothane biodegradation was found to be 3 - 5 and 1 - 2 µmol/L, respectively. These levels are below the renal toxic threshold however desflurane is not even metabolised. And compared to intravenous anesthetic agents, volatils decrease plasma creatinine, neutrophil and macrophage migration in kidney, decrease expression of proinflammatory and adhesion molecules, decrease necrotic and apoptotic damage [12]. Ham, et al. [13], conducted a study in human kidney cells. A 16 h of 1.25-2.5% isoflurane exposure followed 30 min renal ischemia and 4 h period of reperfusion. In contrast with pentobarbital, there was an increase in the synthesis of IL 11 in 1.2% isoflurane post-conditioning. This proves the cytoprotective effects of isoflurane. In a retrospective study, the records of 200 renal transplant patients were examined [14]. Postoperative creatinine levels of patients treated with Isoflurane (n= 103) and sevoflurane (n= 97) were evaluated at the 1st, 3rd and 6th months. There was no statistically significant difference between the isoflurane and sevoflurane groups in terms of postoperative serum creatinine, urea nitrogen and creatine clearance. The incidence of rejection was 4.9% in the isoflurane group and 9.3% in the sevoflurane group (P= 0.22), although not statistically significant. Postoperative dialysis requirement was also found to be higher in sevoflurane than isoflurane group (8.7% vs 13.4%, respectively). However, in a meta-analysis, the studies between 1995 and 2016 were evaluated and the main outcome was a change in plasma creatinine, urine protein and glucose excretion at 24th and 72nd h [15]. Sevoflurane and isoflurane were compared in terms of nephrotoxic potentials and no statistically significant difference was found in 6 studies.

Researchers have begun to study whether an almost non-metabolized inhalation agent, such as desflurane, would be more useful in the IRI. In an exprimental study, in the first 15th minutes of reperfusion, post-conditioning was performed using desflurane and found protective on both renal function and tissue perfusion [16]. Guye, et al. [17], investigated tubular cell damage in rabbits, with desflurane preconditioning. Three hours of reperfusion phase was observed following a 45 min bilateral renal ischemia period. The histopathological damage score was found to be the lowest in desflurane and sham groups. Karadeniz, et al. [18], divided renal transplant donors into two groups: sevoflurane (n= 35 pairs) and desflurane (n= 30 pairs). Preoperatively and on postoperative 1st and 7th days, GFR, creatine, NGAL, IL-18 levels were analysed. No difference was found between the two groups. In another retrospective study, the effects of sevoflurane (n= 73) and desflurane (n= 71) were compared at postoperative 1st year [19]. Creatinine, BUN levels and glomerular filtration rate didnot differ between groups.

However, in several studies, the opposite results were obtained. The effects of desflurane and sevoflurane (n= 37 in each group) on hepatic and renal functions were evaluated in live donors undergoing right hepatectomy [20]. In sevoflurane group, there was an increase in BUN and creatine levels at 30th day with a reduction in GFR [20]. In a study comparing IV and inhalation anesthetics, it was shown that mRNA coding for chemokines with ICAM 1 and proinflammatory cytokine in the renal cortex was less in the volatile group and renal necrosis was rarely detected after 24 - 72h [21]. Another study included renal transplant patients from live donors and desflurane has been shown to provide better preconditioning of renal IR injury than sevoflurane and isoflurane [22]. In another study comparing the effects of volatile agents on neutrophil migration in reperfused organ, it has been shown that Sevoflurane and Desflurane reduce the neutrophil transmigration induced by IL-8 expression of CXR1 and CXCR2, which are ELR + receptors [23]. In addition, inhibition of CD11b (17% for sevoflurane and 27% for desflurane) has been shown to reduce the adherence of neutrophils to the endothelium.

Volatile Anaesthetic Protection of Renal Transplants-1 study aimed to compare the biochemical and clinical effects of propofol vs sevoflurane-based anaesthesiology. Sixty pairs of patients were divided in 3 groups: PROP (donor and recipient received propofol), SEVO (donor and recipient received sevoflurane), and PROSE (propofol for donor and sevoflurane for recipient) [24]. No difference was found between the groups in terms of the amount of first-line renal injury molecule-1



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(KIM-1), N-acetyl-b-D-Glucosaminidase (NAG), and heart-type fatty acid binding protein (H-FABP). On the second day KIM-1 was higher in SEVO than PROP. However, the acute rejection rate in the second year was 35% in the PROP group and 5% in the PROSE group.

In a murine model, desflurane was found to be related with higher creatinine levels in comparison with halothane, isoflurane and sevoflurane [25]. This was consistent with renal tubular edema, dilatation, and necrosis in histopathological sampling. According to the results of this study, desflurane was found to be weaker in renal preservation than other anesthetic agents, however this was an experimental study and it was also stated that clinical trials are needed [25]

## Conclusion

As a result, according to the information obtained from the literature, isoflurane has the most severe effects on hemodynamic variables. It has been shown that sevoflurane has less effect on renal blood flow, GFR and urinary output with less stable hemodynamics, including a reduction in mean arterial blood pressure. Moreover the nephrotoxic side-effect of inorganic fluoride and compound A, which is associated with the defloration of sevoflurane, is still under discussion and there is no clinical evidence. In renal transplantation the main goal should focus on preserving the kidney and maintain the optimal postoperative renal functions.

## References


1. Stollings LM, Jia LJ, Tang P, Dou H, Lu B, et al. (2016) Immune Modulation by Volatile Anesthetics. Anesthesiology 125: 399-411. Link: https://bit.ly/2ztl3Gv
2. Baxi V, Jain A, Dasgupta D (2009) Anaesthesia for Renal Transplantation:An Update. Indian J Anaesth 53: 139-147. Link: https://bit.ly/3cuHf1y
3. Kim R (2018) Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. J Transl Med 16: 8. Link: https://bit.ly/3bhdgZU
4. Gottschalk A, Sharma S, Ford J, Durieux ME, Tiouririne M (2010) The role of the perioperative period in recurrence after cancer surgery. Anesth Analg 110: 1636-1643. Link: https://bit.ly/2yxgTxy
5. Neeman E, Ben-Eliyahu S (2013) Surgery and stress promote cancer metastasis: new outlooks on perioperative mediating mechanisms and immune involvement. Brain Behav Immun 30: 32-40. Link: https://bit.ly/2YOJJ7i
6. Sedghi S, Kutscher HL, Davidson BA, Knight PR (2017) Volatile Anesthetics and Immunity. Immunol Invest 46: 793-804.
7. Kar SK, Khurna HS, Ganguly T (2018) Anesthesia management of renal transplantation: an update. Anaesth Pain & Intensive Care 22: 383-390. Link: https://bit.ly/2yxqG6L
8. Wojciuk B, Salabura A, Grygorcewicz B, Kędzierska K, Ciechanowski K, et al. (2019) Urobiome: In Sickness and in Health. Microorganisms 548. Link: https://bit.ly/3cliFQP
9. Motayagheni N, Phan S, Eshraghi C, Nozari A, Atala A (2017) A Review of Anesthetic Effects on Renal Function: Potential Organ Protection. Am J Nephrol 46: 380-389. Link: https://bit.ly/3bhb3gZ
10. Zhao H, Alam A, Soo AP, George AJT, Ma D (2018) Ischemia-Reperfusion Injury Reduces Long Term Renal Graft Survival: Mechanism and Beyond. EBiomedicine 28: 31-42. Link: https://bit.ly/2YO3knO
11. Khajuria A, Tay C, Shi J, Zhao H, Ma D (2014) Anesthetics attenuate ischemia–reperfusion induced renal injury: Effects and mechanisms. Acta Anaesthesiologica Taiwanica 52: 176-184. Link: https://bit.ly/2Lg3TyY
12. Fukazawa K, Lee HT (2014) Volatile Anesthetics and AKI: Risks, Mechanisms, and a Potential Therapeutic Window. J Am Soc Nephrol 25: 884-892. Link: https://bit.ly/35KNj3t
13. Ham A, Kim M, Kim JY, Brown KM, Yeh J, et al. (2013) Critical Role of Interleukin-11 in Isoflurane-mediated Protection against Ischemic Acute Kidney Injury in Mice. Anesthesiology 119: 1389-1401. Link: https://bit.ly/3biZtSD
14. Teixeira S, Costa G, Costa F, da Silva Viana J, Mota A (2007) Sevoflurane Versus Isoflurane: Does It Matter in Renal Transplantation? Transplant Proc 39: 2486-2488. Link: https://bit.ly/2zsstK4
15. Ong Sio LCL, dela Cruz RGC, Bautista AF (2017) Sevoflurane and renal function: a meta-analysis of randomized trials. Med Gas Res 7: 186-193. Link: https://bit.ly/2yGEI5Y
16. Obal D, Rascher K, Favoccia C, Dettwiler S, Schlack W (2006) Post-conditioning by a short administration of desflurane reduced renal reperfusion injury after differing of ischaemia times in rats. Br J Anaesth 78: 3-91. Link: https://bit.ly/35R9LrR
17. Guye ML, Mc Gregor B, Weil G, Arnal F, Piriou V (2010) Ischaemic and pharmacologic preconditioning: desflurane reduces renal reperfusion injury in rabbits. Ann Fr Anesth Reanim 29: 518–523. Link: https://bit.ly/3ckhaSS
18. Karadeniz MS, Ciftci HS, Tefik T, Mammadov O, Yazıcı H, et al. (2017) Comparison of Two Different Inhalation Anesthetics on Grafted Kidney Function in Patients Undergoing Renal Transplantation Surgery: Desflurane or Sevoflurane? Transplant Proc 49: 448-453. Link: https://bit.ly/3dBoxpv
19. Park JH, Lee JH, Joo DJ, Song KJ, Kim YS, et al. (2012) Effect of sevoflurane on grafted kidney function in renal transplantation. Korean J Anesthesiol 62: 529-535. Link: https://bit.ly/2SRIFLV
20. Ko JS, Kim G, Shin YH, Gwak MS, Kim GS, et al. (2010) The effects of desflurane and sevoflurane on hepatic and renal functions after right hepatectomy in living donors. Transpl Int 23: 736-744. Link: https://bit.ly/2A5f6jp
21. Lee HT, Ota-Setlik A, Fu Y, Nasr SH, Emala CW (2004) Differential Protective Effects of Volatile Anesthetics against Renal Ischemia–Reperfusion Injury In Vivo. Anesthesiology 101: 1313-1324. Link: https://bit.ly/35I3b74
22. Lee JH, Joo DJ, Kim JM, Park JH, Kim YS, et al. (2013) Preconditioning effects of the anesthetic administered to the donor on grafted kidney function in living donor kidney transplantation recipients. Minerva Anestesiol 79: 504-514. Link: https://bit.ly/3cic0Hf
23. Müller-Edenborn B, Frick R, Piegeler T, Schläpfer M, Roth-Z'graggen B, et al. (2015) Volatile anaesthetics reduce neutrophil inflammatory response by interfering with CXC receptor-2 signalling. Br J Anaesth 114: 143-149. Link: https://bit.ly/3dyTiLJ
24. Nieuwenhuijs-Moeke GJ, Nieuwenhuijs VB, Seelen MAJ, Berger SP, van den Heuvel MC, et al. (2017) Propo fol-based anaesthesia versus sevoflurane-based anaesthesia for living donor kidney transplantation: results of the VAPOR-1 randomized controlled trial. Br J Anaesth 118: 720-732. Link: https://bit.ly/2T5SgPB
25. Lee HT, Ota-Setlik A, Fu Y, Nasr SH, Emala CW (2004) Differential protective effects of volatile anesthetics against renal ischemia-reperfusion injury in vivo. Anesthesiology 101: 1313-1324. Link: https://bit.ly/35I3b74


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