Pakistan J. Zool., pp 1-7, 2023. **DOI**: https://dx.doi.org/10.17582/journal.pjz/20230813075411

Effects of Desflurane on Inflammatory Response and Cardiac Function During Cardiopulmonary Bypass in Cardiac Surgery

Jingjing Guo, Ruitong Niu, Shanshan Mu* and Anshi Wu

Department of Anesthesiology, Beijing Chaoyang Hospital of Capital Medical University, Beijing 100020, China

ABSTRACT

The objective of this study was to investigate the effect of desflurane on inflammatory response and cardiac function during cardiopulmonary bypass in cardiac surgery. Thirty adult male Sprague-Dawley rats (body weight, 250-300g) were purchased from the Provincial Academy of Agricultural Sciences, and the rats were housed in a specific pathogen-free facility and maintained under controlled conditions. The rats were divided into control group (CG), surgical model group (SMG) and desflurane group (DG). The level of circulating mtDNA and the mRNA expressions of interleukin 6 (IL-6), Tumor necrosis factor α (TNF-α) and IL-1β were detected by RT-PCR. Organ damage during extra corporeal circulation (ECC) was compared by histopathological analysis. Compared with the CG, the mtDNA level in the SMG was higher ($P<0.05$), and the mtDNA level in the DG was lower than that in the SMG ($P<0.05$). The mRNA expressions of IL-6, TNF-α and IL-1β in the SMG were higher than those in the CG ($P<0.05$). The mRNA expressions of IL-6, TNF-α and IL-1β in the DG were lower than those in the SMG ($P<0.05$). It was found that the use of the volatile anesthetic desflurane in the rat cardiac surgery model can significantly reduce the levels of inflammatory factors in cardiopulmonary bypass, inhibit myocardial cell apoptosis and oxidative stress, and improve cardiac function.

Article Information
Received 13 August 2023
Revised 28 August 2023
Accepted 15 September 2023
Available online 29 December 2023 (early access)

Authors' Contribution
JG and RN conducted the experiments in this study. SM and AW contributed to the design and interpretation of the current study and wrote the article. All authors read, revised, and approved the final manuscript.

Key words
Desflurane, cardiac surgery, cardiopulmonary bypass, inflammatory response, cardiac function

Online First Article

INTRODUCTION

Extracorporeal circulation (ECC) is very important for routine cardiac surgery and life support (Bang *et al*., 2021; Bartoszko and Karkouti, 2021). Although ECC has brought profound benefits to patients all over the world, it often triggers severe systemic inflammatory response, which significantly reduces the quality of clinical results (Bavare *et al*., 2021; Belhadjer *et al*., 2020; Benke *et al*., 2021). Cardiac surgery using ECC is related to systemic inflammatory response, which may lead to significant morbidity and mortality (Bielecka-Dabrowa *et al*., 2020; Bojkova *et al*., 2020; Bughrara *et al*., 2020). This kind of reaction is multifactorial, including extracorporeal circuit of circulating blood exposed to artificial surface, non-physiological shear stress of ECC roller pump, hypothermia and possibly inevitable ischemia-reperfusion injury. The subsequent activation of a series of inflammatory cascades may be further aggravated by the tissue damage during ECC, which is quite different from the normal vascular endothelium (Busch *et al*., 2021; Chetrit *et al*., 2020). During this inflammatory reaction, white blood cells, especially neutrophils, are activated and adhere to vascular endothelial cells, and then migrate to the stroma, where they may release proteases, oxygen free radicals and pro-inflammatory factors, thus damaging tissues (Deng *et al*., 2021; Floh *et al*., 2020; Glasenapp *et al*., 2020). The clinical sequelae of this pro-inflammatory state will lead to high dynamic circulation, increased cardiac output and decreased systemic vascular resistance, thus requiring positive muscle strength and vasoconstriction support. Therefore, the clinical results after improving ECC depend on suppressing this systemic inflammatory response. Although ECC loop has some significant improvements, such as heparin coated loop, complications secondary to tissue injury and inflammatory reaction still exist, and may have a profound impact on postoperative results (Heijman *et al*., 2020; Hinterdobler *et al*., 2021). Recent studies have shown that volatile anesthetics have neuroprotective effects on ischemia-reperfusion injury.

* Corresponding author: mushanshan2022@163.com
0030-9923/2023/0001-0001 $ 9.00/0

Copyright 2023 by the authors. Licensee Zoological Society of Pakistan.
This article is an open access ∂ article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

Halothane, isoflurane, sevoflurane and desflurane play a protective role during focal and global cerebral ischemia. Desflurane is also a vasodilator, which can uniformly promote the cooling of ECC. Recently, desflurane has a neuroprotective effect on piglets during deep hypothermic circulatory arrest. The present study evaluated the effects of desflurane on inflammatory response and cardiac function during cardiopulmonary bypass (CPB) in cardiac surgery.

MATERIALS AND METHODS

Experimental rats

Thirty adult male Sprague-Dawley rats (body weight, 250-300g) were purchased from the Provincial Academy of Agricultural Sciences. They were kept in a facility free of specific pathogens and kept under controlled conditions (22±3°C, 55% humidity and 12-h day-night circulation). Rats can get food and water at will. All animals had accepted the principles of experimental animal care and had been approved by the local animal welfare and ethics review committee. The study has been approved by the hospital's animal ethics committee, and observe the experiment process ARRIVE guidelines (https://arriveguidelines.org) for the reporting of animal experiments.

ECC rat model and grouping

Rats were given pentobarbital (50 mg/kg body weight), ketamine (50 mg/kg body weight) or volatile anesthetic (about 1 minimum alveolar concentration [MAC] or 6.7% desflurane). Rats anesthetized with pentobarbital and ketamine were allowed to spontaneously breathe indoor air on an electric heating pad in warm light, while rats treated with volatile anesthetics spontaneously breathed when they received about 1 MAC of volatile drugs in indoor air. Their body temperature was monitored by rectal probe and kept at 37 °C. To initially anesthetize rats with volatile anesthetic (desflurane), the rats were placed in a 10-L closed room on a warm blanket, with inflow and outflow hoses at the top and bottom of the room, respectively. Volatile anesthetics were transported in the indoor air at a rate of 5 l/min using a drug-specific evaporator. The evaporator was set to maintain the volatile anesthetic concentration in the chamber at 1 MAC, which was monitored by the sampling gas of the infrared analyzer at the outflow hose. According to the research scheme, rats were divided into the following three groups: control group (CG) (this group of rats did not receive midline laparotomy and ECC intubation, n=10), operation model group (SMG) (rats received median sternotomy to simulate heart surgery after anesthesia, and then ECC was performed by Stöckert multi-flow roller pump (GMBH, Munich, Germany) using the same bypass loop system as humans, n= 10), desflurane group (DG) (rats were anesthetized with volatile anesthetic for 1 h, and after volatile anesthetic treatment for 1 h, pentobarbital was anesthetized in abdominal cavity immediately after waking up, and midline laparotomy and ECC intubation were performed, n=10).

Detection of total mtDNA

According to the manufacturer's agreement, QIAamp DNA Blood Mini Kit (Qiagen®) was used to purify DNA from blood or body fluids. DNA was extracted from 200 µl plasma and concentrated by double elution with 50 µl AE buffer. Real-time polymerase chain reaction (RT-qPCR) was used to detect the primer of cytochrome C oxidase subunit III of rat mitochondrial gene, and the level of mtDNA was measured. In each test well, 1 µl DNA, 12.5 µl SYBR Green PCR Master Mix (Applied Biosystems of Thermo Fisher Scientific), 0.5 µlmtDNA primer and 10.5 µl water were used to prepare the reaction. For each research probe, the same RT-qPCR reaction was also carried out using sterile water negative control and HUVECmtDNA positive control.

RNA isolation and quantitative real-time PCR

In order to measure the plasma markers of ECC-induced systemic inflammation in our model, blood samples were taken at the end of the experiment, and plasma was separated by centrifuging the total sample at 1000 ×g and 4 ℃ for 15 min. Remove the plasma supernatant and store it at-70 ℃ until analysis. Total RNA was extracted with Trizol (invitrogen, Carlsbad, California) reagent. RNA concentration was determined by spectrophotometry reading at 260 nm, and it was run on agarose gel to verify the equal RNA input and RNA quality. Reverse transcriptase polymerase chain reaction (RT-PCR) was performed to analyze the expression of pro-inflammatory genes. The primers were designed according to the published sequence of rat gene bank (Bethesda, MD). All PCR reactions were completed after incubation at 68°C for 7 min to allow enzymatic completion of incomplete complementary DNA. Optimize the number of PCR cycles of each primer pair, so that the optical density measurement of the obtained band can increase linearly with the increase of the number of PCR cycles (15-30 cycles). The initial amount of RNA was also optimized to produce a linear increase in the measured optical density of the obtained band at a certain number of polymerase chain reaction cycles. The product was separated in 6% polyacrylamide gel and stained with Syber Green (Roche, Indianapolis), and the band strength was quantified by Fluor-S Multi Imager (BioRad Laboratory).

Online First Article

Evaluation of organ function and tissue damage

After the operation, the left lung and kidney of rats were harvested and fixed in 4% paraformaldehyde at 4 ℃ overnight, and the organ damage was evaluated by histopathology. The paraffin-embedded sections (3 μm thick) were stained with hematoxylin and eosin, and examined by a pathologist who was unaware of the experimental group under an optical microscope. The severity of lung injury was scored on a 5-point scale (0 = normal histology, 5 = the most serious injury), taking into account alveolar congestion, hemorrhage, neutrophil accumulation in air cavity or blood vessel wall, alveolar wall thickness and transparent membrane formation. Renal tubular injury was defined as epithelial swelling, absence of brush edge at the top and vacuolation in cytoplasm. The degree of acute renal tubular necrosis was graded by four grades, and the percentage of affected renal tubules in four high-power fields of light microscope was: 0, no renal tubules were affected; 1, < 25% renal tubular involvement; 2, 25–50%; 3 points, 50–75%; 4 points, > 75%. Calculate the average score of each part for each animal.

Echocardiography

A series of M-mode echocardiography images of rats anesthetized with desflurane were injected by Vevo 2100 imaging platform (VisualSonics ultra-high resolution small animal ultrasound imaging system). Using rectal temperature probe, the body temperature was carefully kept between 36.7°C and 37.3°C during the whole study. Observe the heart on the short axis between the two papillary muscles. By averaging the results of 3 consecutive heartbeats, each measurement was obtained in M mode. The LV internal dimension (LVID) was measured during diastole and systole (LVIDd and LVIDs). The LV EF was calculated by the following formula: EF (%) = 100 × ([LVIDd3 – LVIDs3]/LVIDd3). Digital images were analyzed offline by blind observers using Vevo 2100 workstation software.

TUNEL staining

At the end of the experiment, the heart was retrograde perfused with heparinized ECC, and then 10% neutral buffered formalin solution was added for 15 min. Then, the heart was cut into 3 pieces from the top to the bottom, fixed in formalin for 24 h, then tissue treatment, paraffin embedding and heart sectioning were performed. Paraffin-embedded 4μm thick heart slices were dewaxed in xylene, rehydrated gradually with 100%, 95% and 70% ethanol, and then antigen repaired. After pre-incubation with serum blocking solution, primary antibody was used to identify the expression of different markers, including anti-α-actin (sarcomere) antibody of myocardial cells. According to the manufacturer's protocol (GeneCopoeia, VB-4005G), TUNEL staining was performed to detect apoptotic nuclei by using terminal deoxynucleotidyl transferase-mediated in situ fluorescein-conjugated dUTPnick end labeling technique. Re-staining with nuclear DAPI. The fluorescence staining was observed by Zeiss 780 confocal laser scanning microscope. The number of apoptotic cells with TUNEL positive nuclei was expressed as the percentage of total cells.

Western blot analysis

The frozen heart tissue was treated in radioimmunoassay (RIPA) lysis buffer (10 mM Tris-HCl, pH 7.2, 150 mM NaCl, 1% NP-40, 0.5% SDS and 0.5% deoxy-acid salt), supplemented by protease inhibitor and phosphatase inhibitor (Thermo Fisher Scientific Shile Technology Co., Ltd., used for western blot analysis in protein). The crude extracts of experimental animal hearts were washed twice with ice-cold PBS, and lysed in RIPA buffer and the same inhibitor. The cardiac lysate was passed through 10% SDS-PAGE and transferred to polyvinylidene fluoride (PVDF) membrane. The blots were washed with Tris buffered saline containing Tween 20 (TBST) and blocked with TBST of 5% milk for 1 h. The western blot was observed by ECL Plus kit (Pierce).

Statistical analysis

Graphpad prism version 8.1.2 was used for statistical analysis. The result was expressed as the average SE of each time point in each group, and the P-value < 0.05 was considered statistically significant. Due to the nature of experiments with few animals, nonparametric comparative analysis was used. Wilcoxon symbol rank test was used for matching pairs, and in relevant cases, Bonferroni correction method was used to adjust P value for multiple comparison. For more than two groups of comparisons, Friedman test was used, and Dunn method was used to correct multiple comparisons.

RESULTS

The level of circulating mtDNA was detected by RT-PCR. The mtDNA results in Figure 1 shows that the level of mtDNAin the SMG was higher than that in the CG ($P<0.05$), while that in the DG was lower than that in the SMG ($P<0.05$). According to the results of detection of inflammatory factors during cardiopulmonary bypass, the mRNA expression of IL-6, TNF-α and IL-1β was detected by RT-PCR. The mRNA expression of IL-6, TNF-α and IL-1β in the SMG was higher than that in the CG ($P<0.05$), while the mRNA expression of IL-6, TNF-α and IL-1β in the DG was lower than that in the SMG ($P<0.05$) (Fig. 2).

Online First Article

Table I. Effect of desflurane on inflammatory response and cardiac function during cardiopulmonary bypass cardio.

Indexes	Groups			Variance ratio	P value
	CG	SMG	DG		
Lung injury	0.34±0.05	4.25±1.26	2.16±0.52	11.426	0.025
Renal tubular injury	0.24±0.03	1.94±0.16	1.21±0.08	9.187	0.014
LVEF	86.35±10.26	42.53±5.73	68.26±8.41	9.364	0.004
LVFS	52.38±8.44	27.42±5.13	38.56±6.57	12.517	0.011
Apoptosis	5.35±2.47	37.56±8.56	19.14±5.88	12.853	0.027
Catalase	1.87±0.15	1.14±0.10	1.82±0.14	11.683	0.028
GPX1	1.94±0.17	1.06±0.05	1.90±0.15	13.425	0.015
NOX4	1.02±0.01	1.95±0.14	1.13±0.06	9.374	0.007

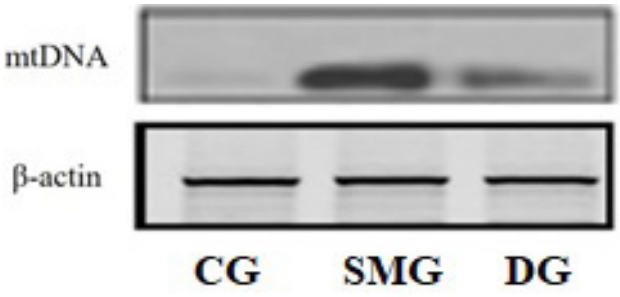

Fig. 1. mtDNA results among the study groups.

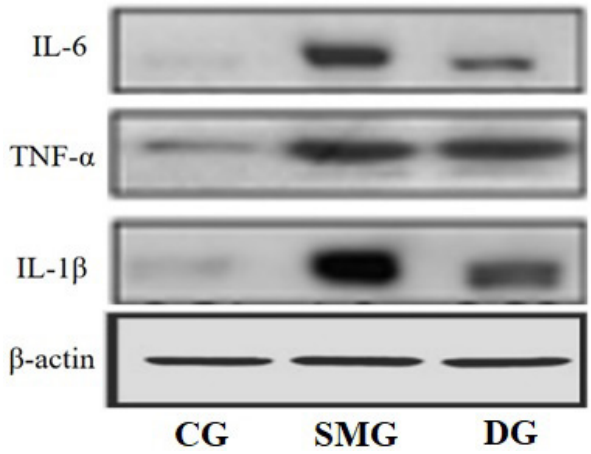

Fig. 2. mRNA expression of inflammatory factors was detected by rt-PCR.

The desflurane results for organ damage, cardiac function, cardiomyocyte apoptosis and oxidative stress during ECC have shown in Table I. Compared with the CG, the lung injury and renal tubular injury in the SMG increased (P<0.05), and the lung injury and renal tubular injury in the DG decreased (P<0.05). Desflurane can reduce the organ injury during ECC. The left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) during ECC were recorded by echocardiography. LVEF and LVFS in the SMG were lower than those in the CG (P<0.05), while LVEF and LVFS in the DG were higher than those in the SMG (P<0.05). The apoptosis of myocardial cells was detected by TUNEL staining. The results showed that the apoptosis of the SMG was higher than that of the CG (P<0.05), and that of the DG was lower than that of the SMG (P<0.05). It indicated that desflurane reduced the apoptosis of cardiomyocytes during ECC. The desflurane results also showed that The expression of Catalase, glutathione peroxidase (GPX1) and NADPH oxidase 4 (NOX4) in the heart was detected by western blot analysis. Compared with the CG, the expression of Catalase and GPX1 in the SMG decreased (P<0.05), while that of DG increased (P<0.05), and that of NOX4 in the SMG increased (P<0.05).

First Article

DISCUSSION

Heart disease is the main cause of death and often requires surgery. However, patients undergoing cardiac surgery often suffer from heart failure, which is the main cause of morbidity and mortality in this environment (Jahnukainen *et al*., 2021; Jian *et al*., 2020). Ischemia induced by ECC can lead to heart failure, in which cardioplegia is injected to cause diastolic cardiac arrest. This complication is related to the duration of ECC and the baseline cardiac status of patients. In the field of anesthesiology and postoperative intensive care, more and more attention has been paid to the cardioprotective effects of halogenated anesthetic desflurane and intravenous hypnotic (propofol)-induced myocardial preconditioning (and postconditioning). The concept that the choice of narcotic drugs may provide additional cardioprotection during open heart surgery is relatively new. ECC open heart surgery is related to acute inflammatory reaction,

which has an impact on postoperative recovery and myocardial function (Karunakaran *et al*., 2021; Lee *et al*., 2021). Despite major changes and improvements in surgical techniques, inflammation is still a major problem. Therefore, the development of strategies to control inflammatory response is still the focus of extensive experimental and clinical research. Besides ECC, reperfusion injury of myocardium and lung and surgical trauma are also important triggers of inflammatory response.

Desflurane is favored as an anesthetic in cardiac surgery, and it may be advantageous because it has better myocardial protection against ischemia-reperfusion injury than isoflurane in animal experiments. A large number of experimental animal studies have attempted to evaluate the vasomotor effect of this intoxicating agent on coronary artery. It has been shown that volatile anesthetics of different degrees can reduce myocardial contractility and myocardial oxygen demand, and this characteristic has been suggested to explain the cardioprotective effect on ischemia and reperfusion. It is also found that these anesthetics induce cardioprotection through a mechanism similar to that involved in ischemic preconditioning. Mitochondrial damage-related proteins have been shown to be inflammation regulators, which can cause tissue damage in various pathological conditions, including systemic inflammatory response syndrome, connective tissue diseases, myocardial infarction, vascular dysfunction, and individuals undergoing chemotherapy and hemodialysis (Lesouhaitier *et al*., 2022). Relevant studies have proved that mtDNA activates neutrophils through TLR9/p38 MAPK, and the increase of circulating mtDNA can be used as a means to predict inflammatory response. In this study, firstly, the accumulation of mitochondrial DNA in circulation was confirmed by cardiac surgery/ cardiopulmonary bypass model. In addition, it was shown that pretreatment with desflurane, a volatile anesthetic, can significantly reduce the expression of inflammatory factors IL-6, TNF-α and IL-1β during cardiopulmonary bypass, and improve the cardiac function of model rats. After cardiac surgery, inflammation was thought to be related to stimulation including cardiopulmonary bypass, surgical trauma and ischemia-reperfusion. Our results showed that cardiac surgery/ECC leaded to the increase of mtDNA and pro-inflammatory cytokines. For myocardial cell apoptosis, the death of necrotic cells will further activate the inflammatory cascade reaction, leading to more serious secondary tissue damage. TUNEL analysis showed that desflurane reduced the apoptosis of cardiomyocytes during ECC. In addition, the cascade reaction of inflammatory and cytotoxic injury activated during reperfusion can amplify the sublethal injury. In this study, organ damage during ECC was compared by histopathological analysis. The results showed that desflurane pretreatment could significantly improve organ damage caused by cardiac surgery/ECC. Oxidative stress can cause myocardial damage during open heart surgery. The main source of ROS during ECC open heart surgery is considered to be neutrophils, which also release several proteolytic enzymes. Neutrophils are activated by agents from systemic circulation, coronary vascular system and muscle cells. Cytokines stimulate the up-regulation of adhesion molecules on cardiomyocytes, and make neutrophils adhere and release ROS and proteolytic enzymes, which will lead to cardiac function inhibition and apoptosis. A previous study showed that overexpression of Catalase in mouse model can significantly improve the phenotype of heart aging. Our results showed that heart surgery /ECC could reduce the expression of antioxidant proteins (Catalase and GPX1) and increase the level of protein of NOX4 in the heart of model rats, and desflurane treatment could restore the expression of catalase and GPX1 and reduce the expression of NOX4. These findings suggested that desflurane can reduce oxidative stress in cardiac surgery /ECC. Inflammation consists of the expression of cytokines, chemokines and adhesion molecules. The regulation of volatile anesthetics on inflammatory cascade and ischemia-reperfusion injury has been described in heart and liver. In the heart, volatile anesthetics can prevent ischemia-reperfusion injury by reducing the adhesion of neutrophils in the coronary artery system after ischemia. Studies have shown that desflurane weakens the activation of adhesion molecules involved in neutrophil activation. Another study showed that desflurane significantly reduced the inflammatory response associated with multiple organ dysfunction syndrome. Lesouhaitier et al. (2022) was described that volatile anesthetic exposure of human monocytes significantly reduced the release of pro-inflammatory cytokines, IL-1β and TNF-α. Therefore, these previous studies and our current research supported our hypothesis that volatile anesthetics can protect ECC injury by reducing necrosis and inflammatory cardiomyocyte death.

Online First Article

CONCLUSION

The research proves that the volatile anesthetic desflurane can significantly reduce the level of inflammatory factors during cardiopulmonary bypass, inhibit myocardial apoptosis and oxidative stress, and improve the state of cardiac function, which has a cardioprotective effect during cardiopulmonary bypass.

ACKNOWLEDGEMENT

The authors would like to express their gratatitute

the support from Beijing Chaoyang Hospital of Capital Medical University.

Funding

The study received no external funding.

IRB approval

This study was approved by the Advanced Studies Research Board of Beijing Chaoyang Hospital of Capital Medical University, Beijing, China.

Ethical approval

The study was carried out in compliance with guidelines issued by ethical review board committee of Beijing Chaoyang Hospital of Capital Medical University, China. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

REFERENCES

Bang, V., Ganatra, S., Shah, S.P., Dani, S.S., Neilan, T.G., Thavendiranathan, P., Resnic, F.S., Piemonte, T.C., Barac, A., Patel, R. and Sharma, A., 2021. Management of patients with giant cell myocarditis: JACC review topic of the week. *J. Am. Coll. Cardiol.*, **77**: 1122-1134. https://doi.org/10.1016/j.jacc.2020.11.074

Bartoszko, J. and Karkouti, K., 2021. Managing the coagulopathy associated with cardiopulmonary bypass. *J. Thromb. Haemost.*, **19**: 617-632. https://doi.org/10.1111/jth.15195

Bavare, A., Rissmiller, B., Devaraj, S., Guffey, D., Rajapakshe, D., Weiner, H., Caldarone, C. and Shekerdemian, L., 2021. Perioperative procalcitonin in predicting infection in children undergoing surgical procedures. *J. Surg. Res.*, **258**: 332-338. https://doi.org/10.1016/j.jss.2020.09.028

Belhadjer, Z., Méot, M., Bajolle, F., Khraiche, D., Legendre, A., Abakka, S., Auriau, J., Grimaud, M., Oualha, M., Beghetti, M. and Wacker, J., 2020. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation*, **142**: 429-436. https://doi.org/10.1161/CIRCULATIONAHA.120.048360

Benke, K., Jász, D.K., Szilágyi, Á.L., Baráth, B., Tuboly, E., Márton, A.R., Varga, P., Mohácsi, Á., Szabó, A., Széll, Z. and Ruppert, M., 2021. Methane supplementation improves graft function in experimental heart transplantation. *J. Heart Lung Transplant.*, **40**: 183-192. https://doi.org/10.1016/j.healun.2020.11.003

Bielecka-Dabrowa, A., Ebner, N., Dos Santos, M.R., Ishida, J., Hasenfuss, G. and Von Haehling, S., 2020. Cachexia, muscle wasting, and frailty in cardiovascular disease. *Eur. J. Heart Fail.*, **22**: 2314-2326. https://doi.org/10.1002/ejhf.2011

Bojkova, D., Wagner, J.U., Shumliakivska, M., Aslan, G.S., Saleem, U., Hansen, A., Luxán, G., Günther, S., Pham, M.D., Krishnan, J. and Harter, P.N., 2020. SARS-CoV-2 infects and induces cytotoxic effects in human cardiomyocytes. *Cardiovasc. Res.*, **116**: 2207-2215. https://doi.org/10.1093/cvr/cvaa267

Bughrara, N., Diaz-Gomez, J.L. and Pustavoitau, A., 2020. Perioperative management of patients with sepsis and septic shock, Part II: Ultrasound support for resuscitation. *Anesthesiol. Clin.*, **38**: 123-134. https://doi.org/10.1016/j.anclin.2019.11.001

Busch, K., Kny, M., Huang, N., Klassert, T.E., Stock, M., Hahn, A., Graeger, S., Todiras, M., Schmidt, S., Chamling, B. and Willenbrock, M., 2021. Inhibition of the NLRP3/IL-1β axis protects against sepsis-induced cardiomyopathy. *J. Cachexia Sarcopenia Muscle*, **12**: 1653-1668. https://doi.org/10.1002/jcsm.12763

Chetrit, M., Xu, B., Kwon, D.H., Ramchand, J., Rodriguez, R.E., Tan, C.D., Jellis, C.L., Johnston, D.R., Renapurkar, R.D., Cremer, P.C. and Klein, A.L., 2020. Imaging-guided therapies for pericardial diseases. *Cardiovasc. Imaging*, **13**: 1422-1437. https://doi.org/10.1016/j.jcmg.2019.08.027

Deng, Y., Xie, M., Li, Q., Xu, X., Ou, W., Zhang, Y., Xiao, H., Yu, H., Zheng, Y., Liang, Y. and Jiang, C., 2021. Targeting mitochondria-inflammation circuit by β-hydroxybutyrate mitigates HFpEF. *Circ. Res.*, **128**: 232-245. https://doi.org/10.1161/CIRCRESAHA.120.317933

Floh, A.A., McCrindle, B.W., Manlhiot, C., Nakada, M., La Rotta, G., Van Arsdell, G. and Schwartz, S.M., 2020. Feeding may modulate the relationship between systemic inflammation, insulin resistance, and poor outcome following cardiopulmonary bypass for pediatric cardiac surgery. *J. Parenter. Enteral Nutr.*, **44**: 308-317. https://doi.org/10.1002/jpen.1529

Glasenapp, A., Derlin, K., Wang, Y., Bankstahl, M., Meier, M., Wollert, K.C., Bengel, F.M. and Thackeray, J.T., 2020. Multimodality imaging of inflammation and ventricular remodeling in pressure-overload heart failure. *J. Nucl. Med.*, **61**: 590-596. https://doi.org/10.2967/jnumed.119.232488

Heijman, J., Muna, A.P., Veleva, T., Molina, C.E.,

Online First Article

Sutanto, H., Tekook, M., Wang, Q., Abu-Taha, I.H., Gorka, M., Künzel, S. and El-Armouche, A., 2020. Atrial myocyte NLRP3/CaMKII nexus forms a substrate for postoperative atrial fibrillation. *Circ. Res.*, **127**: 1036-1055. https://doi.org/10.1161/CIRCRESAHA.120.316710

Hinterdobler, J., Schott, S., Jin, H., Meesmann, A., Steinsiek, A.L., Zimmermann, A.S., Wobst, J., Müller, P., Mauersberger, C., Vilne, B. and Baecklund, A., 2021. Acute mental stress drives vascular inflammation and promotes plaque destabilization in mouse atherosclerosis. *Eur. Heart J.*, **42**: 4077-4088. https://doi.org/10.1093/eurheartj/ehab371

Jahnukainen, T., Rautiainen, P., Tainio, J., Pätilä, T., Salminen, J.T. and Keski-Nisula, J., 2021. Renal function and inflammatory response in neonates undergoing cardiac surgery with or without antegrade cerebral perfusion. A post hoc analysis. *Ann. Card. Anaesth.*, **24**: 434-440. https://doi.org/10.4103/aca.ACA_183_20

Jian, D., Wang, Y., Jian, L., Tang, H., Rao, L., Chen, K., Jia, Z., Zhang, W., Liu, Y., Chen, X. and Shen, X., 2020. METTL14 aggravates endothelial inflammation and atherosclerosis by increasing FOXO1 N6-methyladeosine modifications. *Theranostics*, **10**: 8939-8956. https://doi.org/10.7150/thno.45178

Karunakaran, D., Nguyen, M.A., Geoffrion, M., Vreeken, D., Lister, Z., Cheng, H.S., Otte, N., Essebier, P., Wyatt, H., Kandiah, J.W. and Jung, R., 2021. RIPK1 expression associates with inflammation in early atherosclerosis in humans and can be therapeutically silenced to reduce NF-κB activation and atherogenesis in mice. *Circulation*, **143**: 163-177. https://doi.org/10.1161/CIRCULATIONAHA.118.038379

Lee, M.J., Tannenbaum, C., Mao, G., Jia, Y., Leung, S., Yilmaz, H.O., Ince, I., Soltesz, E. and Duncan, A.E., 2021. Effect of 6% hydroxyethyl starch 130/0.4 on inflammatory response and pulmonary function in patients having cardiac surgery: A randomized clinical trial. *Anesth. Analg.*, **133**: 906-914. https://doi.org/10.1213/ANE.0000000000005664

Lesouhaitier, M., Gregoire, M., Gacouin, A., Coirier, V., Frerou, A., Piau, C., Cattoir, V., Dumontet, E., Revest, M., Tattevin, P. and Roisne, A., 2022. Neutrophil function and bactericidal activity against *Staphylococcus aureus* after cardiac surgery with cardiopulmonary bypass. *J. Leukoc. Biol.*, **111**: 867-876. https://doi.org/10.1002/JLB.5AB1219-737RR

Online First Article