Non-invasive diagnostic method to monitor gastrointestinal microcirculatory disturbances (K116861)
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As an initial step we elaborated five animal models, which were accompanied by disturbance of microcirculation in gastrointestinal tract in order to map the connection between changes in exhaled methane level and hemodynamic parameters.

As a first step it was proved that reperfusion deteriorates macro- and microcirculation in rodent mesenteric ischemia-reperfusion model. This damage is accompanied by significant increase in epithelial permeability and structural destruction. In the background of these changes, increased production of pro-inflammatory mediators was detected (Mészáros A. et al. Inhalation of methane preserves the epithelial barrier during ischemia and reperfusion in the rat small intestine. *Surgery,* 2017, 161.6: 1696-1709.).

Two different gastrointestinal inflammatory processes were investigated in rodent models; colitis and acetyl salicylic acid (ASA) induced gastritis. The microcirculatory disturbance was recognized as a consequence of inflammation in both cases. Clearly, the ASA significantly reduced the Complex IV-linked respiration of liver mitochondria throughout decreased the ATP production. In case of 2-,4-,6-trinitrobenzene-sulfonic acid (TNBS)-induced colitis elevated inflammatory enzyme activities, NO production, TNF-alpha concentration, and induced morphological damage were detected. The decreased energetic level and the changes in biochemical parameters lead to the disturbance of microcirculation. Both models considered to be suitable to investigate the measurement of exhaled methane as a tool to identify the altered microcirculation, caused by gastrointestinal inflammation.
(Varga G. et al. Acetylsalicylic acid-tris-hydroxymethyl-aminomethane reduces colon mucosal damage without causing gastric side effects in a rat model of colitis. Inflammopharmacology, 2018, 26.1: 261-271.).

Hemodynamic consequences and inflammatory changes of nonocclusive mesenteric ischemia (NOMI) were studied with acute experimental pericardial tamponade (PT) model on minipigs, and partial aorta occlusion (PAO) on rats in clinically relevant time frames. After the relief of PT, elevated levels of oxidative stress markers and inflammatory mediators were detected in association with the signs of diminished splanchnic microcirculation. 24 hours after PAO the macrocirculatory parameters improved significantly, while the intramural microcirculation was significantly impaired and accompanied by increased leukocyte infiltration. The in vivo histology confirmed the structural and microvascular damage of the mucosa
(Nógrády M. Influencing the macro- and microcirculatory complications of nonocclusive mesenteric ischemia by complement C5a inhibitor treatments PhD tézis, 2016. Nógrády M. et al. Komplement C5a-antagonista-terápia hatása nem okklúzív mesenterialis ischaemia állatmodelljeiben. *Magyar Sebészet (Hungarian Journal of Surgery)*, 2017, 70.3: 221-231.).

To investigate which hemodynamic parameter can influence the exhaled methane levels We used two different pig model to investigate the correlation between exhaled methane and the macro- and microhemodynamic parameters. The first model was a graded mesenteric occlusion (GSO) model. The purpose of this model was to examine the changes in exhaled methane caused by different level of mesenteric occlusion caused by mesenteric causes and to identify possible correlations to the macrohemodynamic data. In anaesthetized minipigs (n=6) the superior mesenteric artery (SMA) flow was set at first to 30% of the baseline for 30 min

and that was followed by 30 min reperfusion. The occlusion was increased by 10% in each subsequent phase of occlusion and complete mesenteric ischemia was achieved in 4 cycles. Mean arterial pressure (MAP), heart rate (HR), cardiac output (CO) were monitored invasively for 240 min and exhaled methane level of the exhaled air was measured continuously. The exhaled methane was decreased by the occlusions and increased under reperfusion (16±8 ppm vs 64±14 ppm). Significant positive correlation was found between the exhaled methane concentrations and SMA flow ($r=0.83$; $p<0.05$). Correlation between the exhaled methane level and MAP, HR and CO could not be verified in this model.
(Szűcs Sz. et al. Detection of intestinal tissue perfusion by real-time breath methane analysis in rat and pig models of mesenteric circulatory distress. *Critical Care Medicine*, 2019, 47.5: e403-e411.)

The second series of experiments was executed in the PT model in order to investigate the connection between exhaled methane levels and the changes in SMA flow and in the microhemodynamics of the ileum, caused by mesenteric hypoperfusion of extramesenteric origin. In anaesthetized, ventilated and thoracotomized minipigs (n=7) PT was induced for 60 min by intrapericardial administration of colloid solution, meanwhile the mean arterial pressure (MAP) was kept between 40-45 mmHg. SMA flow was monitored and the red blood cell velocity (RBCV) of the ileal mucosa was recorded with orthogonal polarization spectral (OPS) imaging technique. In this model PT caused the deterioration of both, the SMA flow and the small intestinal microcirculation. During the PT, decrease of the exhaled methane could be observed, and significant correlation could be shown between exhaled methane levels and both, the SMA flow ($r=0.66$; $p<0.05$) and the microcirculation of the ileum ($r=0.58$; $p<0.05$). (Szűcs Sz. et al. Detection of intestinal tissue perfusion by real-time breath methane analysis in rat and pig models of mesenteric circulatory distress. *Critical Care Medicine*, 2019, 47.5: e403-e411.)

To examine, if exhaled methane, originating from endogenous source is adequate to monitor the GI microcirculatory changes in case of known baseline values of exhaled methane We found that the distribution of methane producer (P) and non-producer (NP) rats is approximately the same as in the human population. First we used a simple and well-known rodent mesenteric ischemia (by occluding the superior mesenteric artery for 45 min) and reperfusion (IR) (120 min) model on five groups (control, NP-IR, P-IR, NP-Met+IR; NP-IR+Met, n=8, each) of rat to assess the correlation between hemodynamic parameters and exhaled methane concentration. MAP, SMA flow and RBCV; observed by OPS imaging system) were measured at predetermined points of the experiment while the methane concentration data was obtained continuously. In case of endogenously methane producer rats; correlations were found between the methane levels and the SMA flow and RBCV. Exogenous methane source was needed in non-producers; therefore 4 ml of 2.18% methane containing normoxic gas mixture was applied intraluminaly into the jejunum. No correlations were found in the control and IR between the same parameters. The last two groups received methane before the ischemia (Met+IR) and during ischemia, 5 min prior to the reperfusion (IR+MET). Thus correlation was found between the SMA flow and methane level; however only the RBCV correlated only in the IR+Met group.

In conclusion, in this study it was proved that the changes of exhaled methane level show significant correlation to SMA flow and microcirculation in non-producer and producer rodents, as well. We have demonstrated that the exogenous methane per se is enough to follow up the changes in local circulation of small intestine

(Varga et al., A splanchnikus mikrokeringés nem-invazív monitorozása mesenterialis ischaemia-reperfúziós állatmodellben. *MÉT*, 2016.;
Szűcs Sz. et al. Detection of intestinal tissue perfusion by real-time breath methane analysis in rat and pig models of mesenteric circulatory distress. *Critical Care Medicine*, 2019, 47.5: e403-e411.)

To develop a methane-enriched liquid medium that is capable to deliver methane into the GI tract in sufficient amount for monitoring purposes. The use of exhaled methane level as a diagnostic tool in the early recognition of mesenteric circulatory disturbances is limited to naturally methane producers. However, larger portion of the population is considered to be non-producer according to the present definition (exhaled methane concentration exceeds 1 ppm). Moreover, in several clinical situations the measurement of baseline methane level in the exhaled air is not possible. Therefore, the development of a methane carrying medium is attempted. We tested the level of possible saturation of water, saline and starch containing colloid solution with pressurized methane. To achieve increased saturation of the investigated fluid with methane, 500 ml of fluid was filled in a 1000 cm3 pressurizing chamber and pure methane was introduced under pressure of 250 kPa on room temperature (21°C). To measure the methane content of the fluid, 10 ml of the saturated solution was filled in a 20 ml cuvette and gas concentration measurement was performed from the gas space above (10 ml). Measurements were completed immediately after the fluid was loaded into the cuvette, and thereafter at 60 minutes and at 24 hours. Methane content of all investigated fluid was significantly increased. Elevated methane concentration was still detectable at 24 hour. The idea of starch solution was rejected because of the risk of unexpected effects in the presence of damaged gastrointestinal mucosa. For further investigations and in vivo experiments the saline solution was selected, as it is considered to be safely administered even in case of critically ill with possible injury of the small intestinal epithelium.

In pilot rat studies we tested the necessary amount of fluid that provides sufficient methane levels in the small intestine, and appears in the exhaled air in methane non-producer rats. Further examinations were used to identify the required administration process. Bolus and continuous enteric administration were investigated. According to the final results, the most efficient method was the administration of methane enriched fluid with a rate of 10 ml/kg/h. The application of methane enriched fluid provided the possibility of intravenous administration as well. We hypothesized that the simultaneous enteric and intravenous administration of methane enriched fluid can be used to differentiate between mesenteric and pulmonary circulatory disturbances.

To test the idea, we carried out two series of experiments. Artificially ventilated, hemodynamically monitored rats (n=48) were used. Methane enriched saline solution was administered to the animals per os or intravenously (10 ml/kg/h).

Study I: In 2 groups (n=6 each) mesenteric ischemia (MI) was induced for 30 min, while in the other 2 groups (n=6 each) pulmonary arterial occlusion (PI) was established on the left side for 5-minute. During the first series we started to infuse methane enriched saline to the animals 10 minutes before the circulatory condition.

Study II: Animals were allotted in four groups (n=6 each) as in Study I. In Study II the animals received methane enriched fluid infusion after vascular obstruction was induced, which better illustrated the clinical practice.

In both studies the changes in the level of the exhaled methane was monitored continuously with photoacoustic spectroscopy. During the experiments the microcirculation of the small intestinal serosa and the lungs was recorded with CYTOCAM IDF camera.

In Sudy I, exhaled methane level was increased with *iv* or *per os* methane enriched fluid, administered before the occlusion of the mesenteric artery or the left pulmonary artery. In the case of per os administered methane enriched fluid, during mesenteric ischemic period, the breath methane output decreased to the baseline level. In contrast the first finding, iv methane enriched fluid administration did not cause detectable reduction in methane level in exhaled air during mesenteric ischemia. In case of left pulmonary artery occlusion, both iv and per os extra methane enriched fluid administration did cause significant decrease in methane level of the exhaled air.

During Study II, in case of methane enriched fluid administration after mesenteric artery occlusion, the *iv* administered exogenous methane appeared in exhaled air. During occlusion of the pulmonary artery, neither *iv, nor per os* administration of methane enriched fluid caused an increase in breath methane levels.

The new method is potentially suitable to identify and separate gastrointestinal or pulmonary circulatory disturbances. According to our findings, methane, supplemented exogenously – via *iv* - or *per os* administered methane enriched fluid – is suitable to track and monitor microcirculatory changes non-invasively in methane producer and non-producer population as well.

(Érces D. et al. Differentiation of pulmonary and mesenteric perfusion disorders from exhaled methane concentrations. *WISE3, JOINT MEETING of the Ludwig Boltzmann Institute for Experimental and Clinical Traumatology and AUVA Research Center, Vienna, Austria Oroboros Instruments and MitoFit Laboratory, Innsbruck, Austria Institute of Surgical Research, University of Szeged, Hungary;* 2018. március 26-27, Szeged

Érces D. et al. Non-invasive, photoacoustic spectroscopy-based method to differentiate between mesenteric and pulmonary circulatory disturbances. *53rd Congress of the European Society for Surgical Research*, 2018. május 30-június 2, Madrid)

In a further large animal model of cardiopulmonary bypass (CPB) we investigated the influence of membrane oxygenator. Open cardiac surgery requires the application of CPB and in intensive care units extra-corporeal membrane oxygenation can be a life-saving treatment. Nevertheless, we did not have any information if methane can pass through the membrane capillaries of the oxygenator.

The experiments were performed on two groups of anaesthetized, ventilated Vietnamese minipigs (n=11). The animals underwent a standard central CPB cannulation. The CPB was maintained for 120 minutes and afterwards the animals were monitored for further 180 minutes. Hemodynamics were registered and the exhaled methane was monitored continuously at the exhaust line of the ventilator. In group 1 (n=5) exogenous methane was supplemented through the membrane oxygenator. Methane-air mixture (2.25% normoxic methane-air; 200 ml/kg/min; Linde Gas, Hungary) was added to the oxygen flow during CPB. In group 2 (n=6) synthetic air was mixed to the oxygen flow during 120 min of CPB (200 ml/kg/min).
In group 1 after the CPB an increased exhaled methane level could be detected as methane was capable to pass the capillary tubes of the oxygenator. In group 2 with the measurement of exhaled methane from endogenous source the changes in the pulmonary circulation could be followed.

According to the results of the CPB model, methane can pass the membrane oxygenator and can be applied as a diagnostic tool in those situations as well, when extra-corporeal membrane oxygenation is needed. Moreover, if mesenteric circulation is properly maintained during cardiac surgery, it is also useful to identify failure in the restoration of lung circulation. The exact way to apply the photoacoustic methane monitoring in such cases still needs to be

established and the necessary investigations will be carried out later in the further execution phases.
(Szűcs Sz. et al. A tüdőkeringés nem invazív monitorozási lehetősége kísérletes ECC alatt. *Cardiologia Hungarica* 47; F13, 2017;
Bari G. et al. Metán kezelés hatása az extrakorporális keringést követő gyulladásos válaszra kísérletes nagyállat modellen. *Cardiologia Hungarica* 47; F2, 2017.
Bari G. et al. Methane inhalation reduces the systemic inflammatory response in a large animal model of extracorporeal circulation. *European Journal of Cardio-Thoracic Surgery*, 2019, 56.1: 135-142.)

In 2019 we have investigated the potential of exhaled methane measurement as a monitoring tool in a large animal model of experimental hemorrhage. Especially in case of non-visible, postoperative or traumatic internal beedings can be difficult to recognize. Under such conditions, the reactive changes of the mesenteric circulation may be part of the earliest hemodynamic responses. A successful bleeding control and resuscitation however may still accompanied by persisting defects of the splanchnic microvascular flow despite the improved macrohemodynamics. With the study, we wanted to compare our method with the examination of sublingual microcirculation, which may refer to the perfusion of more distal gastrointestinal regions. However, the latter requires sophisticated endomicroscopes and a time-consuming off-line evaluation of the records that makes real-time monitoring impossible.

We performed our experiments on anesthetized, ventilated Vietnamese minipigs. The animals were gradually bled by 5-5% of the calculated blood volume 7 times consecutively, that was followed by fluid resuscitation with colloid (hydroxyethyl starch; 5% of estimated blood volume/doses) until 80 mmHg mean arterial pressure was reached. During the experiments, we monitored the exhaled methane level continuously with photoacoustic laser-spectroscopy. The microcirculation of the sublingual area, the ileal serosa and the mucosa was examined with intravital videomicroscopy (Cytocam-IDF, Braedius). According to our most important results, the mesenteric perfusion was significantly reduced after 5% of blood loss, while the microperfusion in the oral cavity deteriorated later, only after 25% loss. We also found a statistically significant correlation between breath methane levels and the superior mesenteric artery flow ($r=0.93$) or the microcirculatory changes of the ileal serosa ($\rho=0.78$) and the mucosa ($r=0.77$) and those in the sublingual area ($r=0.53$). After resuscitation the mucosal microcirculation increased rapidly (De Backer score (DBS): 2.36 ± 0.42 vs. 8.6 ± 2.1 mm^{-1}), while the serosal perfusion changed gradually and with lower amplitude (DBS: 2.51 ± 0.48 vs. 5.73 ± 0.75 mm^{-1}). According to our results, the dynamic detection of breath methane output indicates the acute blood loss earlier than the sublingual microcirculatory changes. Moreover, the exhaled methane values are changing in association with the mucosal perfusion of the ileum in the early phase of fluid resuscitation.
(Bársony A. et al. Methane exhalation can monitor the microcirculatory changes of the intestinal mucosa in a large animal model of hemorrhage and fluid resuscitation. *Frontiers in Medicine*, 2020, 7: 669.)

Another progress in the project in 2019 was that we managed to test breath methane measurement first time in human clinical investigation. We measured exhaled methane levels of 12 patients, underwent intubated (n=6) or non-intubated lung surgery (NITS; n=6). According to our first, preliminary results, the exhaled methane levels normalized significantly faster in the NITS group than in the intubated group (2.3 ± 0.9 vs 11.8 ± 2.1 min), which may refer to the faster recovery of the alveolar perfusion and ventilation.

In late 2019 we started the investigations in the rat 2-,4-,6-trinitrobenzene-sulfonic acid (TNBS)-induced colitis model which was continued in 2020. In this study we examined the possible connection between the severity of the inflammatory process and the exhaled methane levels. We found significantly increased microcirculatory parameters (De Backer score: 19.7±3 vs 27.6±3.3 and microvascular flow index: 2.2±0.3 vs 3.2±0.4) 3 days after the induction of colitis which was accompanied by increased methane levels (814±168 vs 1387±358 photoacoustic unit (PAU)) in parallel with the increase of inflammatory enzymes (myeloperoxidase: 1029±308 vs 2122±297 mU/(mg protein) and xanthine-oxidoreductase: 24.2±3.38 vs 42.6±16.4 pmol/min/(mg protein)) and markers of the oxidative stress (malondialdehyde: 0.09±0.04 vs 0.5±0.16 mmol/ml)

Moreover, we have also shown the importance of dietary factors that can alter the concentration of volatile markers of inflammation. This aspect has to be considered for the diagnostic process of inflammatory bowel diseases. The high methane content of local tap water was capable to increase the whole body methane emission in control rats which was reduced when drinking water was switched to methane free mineral water. Therefore, to achieve valuable data we used methane free mineral water in the above mentioned study, as well as the drinking water of rats involved in the control and colitis group.

The preliminary data of the colitis study were demonstrated on the 55th Conference of the European Society of Surgical Research the data of the pig hemorrhagic model was presented under the title "*Relationship between methane output and the development of inflammation in experimental colitis*". The publication of the results is under preparation.

Also in 2020 on the 55th Conference of the European Society of Surgical Research the data of the pig hemorrhagic model was presented in the under the title "*Microcirculatory changes of the ileal serosa and mucosa during early fluid resuscitation in a large animal model of hemorrhage – monitoring significance of exhaled methane*". The presentation was selected by the scientific committe in the "*Best Abstract Award Session of the Austrian Society for Surgical Research*".

Unfortunately the completion of the clinical studies, involving patients with lung operations which was planned for 2020 had to be postponed until an unspecified date because of the pandemic situation caused by the SARS-CoV II virus. The lockdown and the lack of clinical personnel prevented us to continue this work. After consultation with our clinical coworkers the study was postponed on their suggestion. Furthermore, because of the pandemic situation, several ELISA kit were unavailable which significantly delayed the work.

Nonetheless, we started to coordinate the development of a second, more advanced prototype of the photoacoustic device based on our experiences, gained under the earlier 3 years of research. Our industrial partner (Hilase Ltd., Székesfehérvár, Hungary) supported the idea and undertook the design of the new prototype. The dimensions are going to be significantly more compact and a more advanced, LabChart based data acquisition software is going to be applied. Partly because of the difficulties in obtaining key components of the device caused by the COVID 19 pandemic and partly because of other tasks they undertook the completion of the device by the second half of 2021.

In the second half of 2020 we started to investigate the effects of methane treatment in a large animal model of 24-hour venovenous extracorporeal membrane oxygenation (vvECMO). The vvECMO treatment can be lifesaving in severe respiratory distress which makes it especially important in the treatment of the most severe COVID-19 patients. Nonetheless, it still has severe complications, most importantly, the development of acute kidney injury has a high incidence, which may result in chronic renal failure or can cause the death of the patient. Methane gas was administered through the oxygenator, similarly as in case of the earlier CPB model and we used the opportunity to further test the possibilities in our photoacoustic method. We demonstrated the methane level in the blood samples collected from

the femoral vein (pre-oxygenator), the jugular vein (post-oxygenator) and from the femoral artery (arterial). We found that, 2% methane-air mixture at 1 l/min flow rate was capable to increase methane levels in all three blood samples, which again proved the capability of methane to pass through the oxygenator and enter the blood stream. Methane treatment could reduce the histological signs of kidney injury and plasma level of kidney injury marker neutrophil gelatinase associated lipocalin.

Publications 2016-2020 (K116861):

Scientific articles:

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4. Varga G, Ugocsai M, Hartmann P, Lajkó N, Molnár R, Szűcs S, Jász DK, Érces D, Ghyczy M, Tóth G, Boros M.: Acetylsalicylic acid-tris-hydroxymethyl-aminomethane reduces colon mucosal damage without causing gastric side effects in a rat model of colitis., Inflammopharmacology. 2017 Apr 27., 2017
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9. Bársony A, Vida N, Gajda Á, Rutai A, Mohácsi Á, Szabó A, Boros M, Varga G, Érces D. Methane exhalation can monitor the microcirculatory changes of the intestinal mucosa in a large animal model of hemorrhage and fluid resuscitation. Frontiers in Medicine 7; 669, 2020.

Abstracts:

1. Bari G, Szűcs Sz, Érces D, Rutai A, Balogh B, Bogáts G, Boros M,Varga G: Metán kezelés hatása az extrakorporális keringést követő gyulladásos válaszra kísérletes nagyállat modellen, Cardiologia Hungarica 47; F2, 2017., 2017

2. Érces D, Varga G, Szűcs Sz, Balogh D, Bozsó N, Boros M: Artesunatkezelés hatása a nem okklúzív mesenterialis ischaemia során kialakuló keringési elégtelenségre, Magyar Sebészet 2017; 70(3): p. 260, 2017
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