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CLINICAL RESEARCH ARTICLE

Assessment of trimethylamine N-oxide (TMAO) as a potential biomarker of severe stress in patients vulnerable to posttraumatic stress disorder (PTSD) after acute myocardial infarction

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ABSTRACT

Background: Posttraumatic stress disorder (PTSD) is a frequently observed stress-related disorder after acute myocardial infarction (AMI) and it is characterized by numerous symptoms, such as flashbacks, intrusions and anxiety, as well as uncontrollable thoughts and feelings related to the trauma. Biological correlates of severe stress might contribute to identifying PTSD-vulnerable patients at an early stage.

Objective: Aims of the study were (1) to determine whether blood levels of trimethylamine N-oxide (TMAO) vary immediately after AMI in patients with/without AMI-induced PTSD symptomatology, (2) to investigate whether TMAO is a potential biomarker that might be useful in the prediction of PTSD and the PTSD symptom subclusters re-experiencing, avoidance and hyperarousal, and (3) to investigate whether TMAO varies immediately after AMI in patients with/without depression 6 months after AMI.

Method: A total of 114 AMI patients were assessed with the Hamilton-Depression Scale after admission to the hospital and 6 months later. The Clinician Administered PTSD Scale for DSM-5 was used to explore PTSD-symptoms at the time of AMI and 6 months after AMI. To assess patients' TMAO status, serum samples were collected at hospitalization and 6 months after AMI.

Results: Participants with PTSD-symptomatology had significantly higher TMAO levels immediately after AMI than patients without PTSD-symptoms (ANCOVA: TMAO(PTSD x time), F = 4.544, df = 1, $p = 0.035$). With the inclusion of additional clinical predictors in a hierarchical logistic regression model, TMAO became a significant predictor of PTSD-symptomatology. No significant differences in TMAO levels immediately after AMI were detected between individuals with/without depression 6 months after AMI.

Conclusions: An elevated TMAO level immediately after AMI might reflect severe stress in PTSD-vulnerable patients, which might also lead to a short-term increase in gut permeability to trimethylamine, the precursor of TMAO. Thus, an elevated TMAO level might be a biological correlate for severe stress that is associated with vulnerability to PTSD.

Evaluación del N-óxido de trimetilamina (TMAO) como posible biomarcador de estrés severo en pacientes vulnerables al trastorno de estrés postraumático (TEPT) después de un infarto agudo de miocardio

Antecedentes: El trastorno de estrés postraumático (TEPT) es un trastorno relacionado con el estrés que se observa con frecuencia después de un infarto agudo de miocardio (IAM) y se caracteriza por numerosos síntomas, como flashbacks, intrusiones y ansiedad, así como pensamientos y sentimientos incontrolables relacionados con el trauma. Los correlatos biológicos del estrés severo podrían contribuir a identificar a los pacientes vulnerables al TEPT en una etapa temprana.

Objetivo: Los objetivos del estudio fueron (1) determinar si los niveles sanguíneos de N-óxido de trimetilamina (TMAO, por sus siglas en ingles) varían inmediatamente después del IAM en pacientes con o sin sintomatología de TEPT inducida por IAM, (2) investigar si el TMAO es un biomarcador potencial que podría ser útil en la predicción de TEPT y los subgrupos de síntomas

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de TEPT que experimentan, evitación e hiperactivación, y (3) para investigar si el TMAO varía inmediatamente después del IAM en pacientes con o sin depresión 6 meses después del IAM.

Método: Un total de 114 pacientes con IAM fueron evaluados con la Escala de Depresión de Hamilton tras su ingreso al hospital y 6 meses después. La Escala de TEPT para el DSM-5 administrada por el médico se utilizó para explorar los síntomas de TEPT en el momento del IAM y 6 meses después del IAM. Para evaluar el estado de TMAO de los pacientes, se recolectaron muestras de suero en la hospitalización y 6 meses después del IAM.

Resultados: Los participantes con sintomatología de TEPT tenían niveles de TMAO significativamente más altos inmediatamente después del IAM que los pacientes sin síntomas de TEPT (ANCOVA: TMAO (TEPT x tiempo), F = 4.544, df = 1, p = 0.035). Con la inclusión de predictores clínicos adicionales en un modelo de regresión logística jerárquica, TMAO se convirtió en un predictor significativo de la sintomatología del TEPT. No se detectaron diferencias significativas en los niveles de TMAO inmediatamente después del IAM entre individuos con o sin depresión 6 meses después del IAM.

Conclusiones: Un nivel elevado de TMAO inmediatamente después del IAM podría reflejar un estrés severo en pacientes vulnerables al TEPT, lo que también podría conducir a un aumento a corto plazo de la permeabilidad intestinal a la trimetilamina, el precursor de TMAO. Por lo tanto, un nivel elevado de TMAO podría ser un correlato biológico del estrés severo asociado con la vulnerabilidad al TEPT.

对氧化三甲胺 (TMAO) 作为急性心肌梗死后创伤后应激障碍 (PTSD) 易感患者的严重应激潜在生物标志物的评估

背景: 创伤后应激障碍 (PTSD) 是急性心肌梗塞 (AMI) 后常被观测的应激相关疾病, 其特点是出现例如闪回, 闯入和焦虑, 以及无法控制的创伤相关想法和感觉的多种症状。 严重应激的生物学相关因素可能有助于在早期识别PTSD易感患者。

目的: 本研究旨在 (1) 确定有/无AMI诱发PTSD症状的患者在AMI后氧化三甲胺 (TMAO) 的血液水平是否立即不同, (2) 考查TMAO是否是一种可能有助于预测PTSD和PTSD再体验, 回避和高唤起症状亚簇的潜在生物标志物, 并且 (3) 考查AMI后6个月有无抑郁的患者在AMI后TMAO是否立即不同。

方法: 在入院后及6个月后共使用汉密尔顿抑郁量表评估了114例AMI患者。使用 DSM-5的临床用PTSD量表探究AMI期间及AMI后6个月的PTSD症状。为评估患者的TMAO状态, 在住院时和AMI后6个月收集了血清样本。

结果: 有PTSD症状的参与者在AMI后的TMAO水平立即显著高于无PTSD症状患者的 (ANCOVA: TMAO (PTSD x时间), F= 4.544, df = 1, p= 0.035) 。在分层逻辑回归模型中纳入其他临床预测因素后, TMAO成为PTSD症状的一个显著预测因素。在AMI后6个月有或无抑郁的个体之间未发现AMI后即刻TMAO水平的显著差异。

结论: AMI后立即升高的TMAO水平可能反映了PTSD易感患者的严重应激, 这也可能导致肠道对TMAO前体三甲胺的通透性的短期提升。因此, 升高的TMAO水平可能是与PTSD易感性相关的严重应激的生物学相关因素。

1. Introduction

1.1. Acute myocardial infarction (AMI) and psychiatric comorbidities

Acute myocardial infarction (AMI) is a major biopsychosocial health care issue and often occurs unexpectedly (Andersson, Pesonen, & Ohlin, 2007). Because of prolonged stress and impairments in health-related quality of life, many AMI patients suffer from clinically significant depression. In a recent meta-analysis, the pooled prevalence of depression among patients with AMI was 28.7% (Feng et al., 2019). In comparison, the point prevalence of major depression in the Danish general population has been reported as 3.3% (Olsen, Mortensen, & Bech, 2004). Another frequent stress-related secondary psychiatric disease following AMI is post-traumatic stress disorder (PTSD) (Jbilou et al., 2019). In scientific studies the prevalence of full PTSD after AMI has ranged from 4 to 32%, depending on the methods used to assess PTSD (Edmondson et al., 2012).

In comparison, the U.S. National Comorbidity Survey Replication estimated the lifetime prevalence of PTSD in the general population of adult Americans to be 6.8% (Kessler et al., 2005).

1.2. AMI-induced post-traumatic stress disorder (PTSD)

PTSD is a common psychiatric stress disorder that is triggered by a severe traumatic event, such as AMI (Rothenhäusler, Stepan, Kreiner, Baranyi, & Kapfhammer, 2008). It is characterized by numerous symptoms, such as flashbacks, intrusions, nightmares and severe anxiety, as well as uncontrollable, intense and disturbing thoughts and feelings related to the trauma (Baranyi, Krauseneck, & Rothenhäusler, 2013). The DSM-5 lists the following criteria for the diagnosis of PTSD: Criterion A: severe or life-threatening traumatic event (defined as AMI in the present study); Criterion B: re-experiencing symptoms; intrusions and

flashbacks; Criterion C: avoidance symptoms; Criterion D: negative alterations in cognition and mood; Criterion E: hyperarousal; Criterion F: significant disturbance lasting at least one month; and Criterion G: disturbance causing significant impairment (American Psychiatric Association, 2013).

The precondition for the development of PTSD is exposure to extreme stress caused by an often-life-threatening traumatic event that alters the internal balance. However, with regard to the development of PTSD, individual stress perception might also be crucial because, not every serious traumatic event leads to PTSD in every affected person. Studies indicate that a higher level of perceived threat increases PTSD symptoms (Lancaster, Cobb, Lee, & Telch, 2016). This means that the individual experience of the severity of stress during trauma might also vary substantially. To date, only a few biological correlates (e.g. cortisol, metanephrine) of such an individual perception of stress that can affect the development of PTSD in the long term have been identified (Duke, 1971; LoPilato et al., 2020). One potential biomarker that could be useful in the assessment of individual stress is trimethylamine-N-oxide (TMAO). This gut bacteria-derived metabolite is an important cardiovascular risk marker that appears to interfere with many important physiological regulatory pathways (Aliev et al., 2020; Giannoni-Pastor, Eiroa-Orosa, Fidel Kinori, Arguello, & Casas, 2016).

1.3. Trimethylamine N-oxide (TMAO)

The small organic molecule TMAO is an amine oxide generated via gut microbial metabolism from dietary phospholipids, such as choline, betaine, and L-carnitine. For example, eggs, red meat, cheese and ocean fish contain large amounts of choline, betaine, and L-carnitine. In detail, the gut microbiota transforms L-carnitine, choline and betaine into the TMAO precursor trimethylamine (TMA). After subsequent absorption into the bloodstream, TMA is further oxidized to TMAO by the hepatic flavin-containing monooxygenase (FMO) family members FMO-1 and FMO-3 (Bennett et al., 2013; Querio, Antoniotti, Levi, & Gallo, 2019; Tang et al., 2013). TMAO acts as an important protein stabilizer, preserving protein folding. In addition, TMAO is an electron acceptor that enhances vascular inflammation and oxidative stress (Li, Chen, Gua, & Li, 2017; Ufnal, Zadlo, & Ostaszewski, 2015). TMAO also expedites endothelial cell senescence, platelet hyper-reactivity and thrombosis (Zhu et al., 2016). Thus, high circulating concentrations of TMAO may lead to the progression of atherosclerosis and other severe cardiovascular diseases, such as acute coronary syndrome (Querio et al., 2019).

A previous experiment with rats suggested that heart failure might be associated with functional and structural alterations in intestinal integrity, leading to increased gut-to-blood penetration of TMA and a subsequent elevation in serum TMAO levels (Drapala et al., 2020). In contrast to heart failure, acute coronary syndrome, which includes AMI, is an acute cardiological disease and a severe medical emergency associated with a sudden reduction in blood flow to the heart. In a recent study by Alhmoud et al., human patients with acute coronary syndrome had increased intestinal tight junctional permeability (leaky gut) but no immediate increase in TMAO concentrations (Alhmoud et al., 2019). This finding of a non-immediate TMAO increase after acute coronary syndrome corresponds with the hypothesis that while TMAO has less clinical significance in acute cardiological events, high TMAO levels might enhance the risk of severe cardiac events in the future (Alhmoud et al., 2019).

1.4. Gut permeability and gut microbial metabolism

1.4.1. Impacts of acute and chronic stress and gut microbial metabolism on gut permeability and TMAO

In the last decade, the gut-brain axis theory, which involves interactions between the gut microbiome and the brain, has gained substantial attention. This complex bidirectional interaction and communication pattern leads to a plethora of physiological consequences, such as (1) alterations in intestinal motility, (2) modifications in the production of local neurotransmitters and bacterial metabolites, and (3) a significant modulation of gut-blood barrier (GBB) permeability, causing leaky gut syndrome (Carabotti, Scirocco, Maselli, & Severi, 2015; Meinitzer et al., 2020). Correspondingly, numerous previous studies have shown that severe psychological stress may cause alterations in gut permeability, causing leaky gut syndrome (Hiki et al., 2001; Rezzi et al., 2009).

eaky gut syndrome might also have an impact on the release of the TMAO precursor TMA into the bloodstream (Jaworska et al., 2020). In confirmation of this, previous animal models of surgical stress with subsequently increased TMAO levels showed a strong relationship between acute stress and elevated blood TMAO concentrations (Kinross et al., 2011).

1.4.2. Impact of acute myocardial infarction on gut microbial metabolism

Another potential cause, in addition to the stress-related increase in intestinal permeability, might be direct microbial alterations after AMI. In addition, there is a bidirectional relationship between stress and gut microbial metabolism and many stressors impact gut microbial metabolism (Karl et al., 2018).

In a study by Wu et al. (2017), it was shown that the gut microbiota was altered in rats 7 days after AMI. The gut microbiota is essential for the formation of TMA, the precursor of TMAO. Thus, alterations in gut microbial community structures might also have an impact on TMAO production (Wu et al., 2017).

In summary, changes in TMAO levels in patients after AMI might be caused by stress-related changes in intestinal permeability (leaky gut) or alterations in the intestinal microbiome.

1.4.3. Impact of depression on gut microbial metabolism

In addition to PTSD, many AMI patients suffer from depression due to prolonged impairments in health-related quality of life in the period after myocardial infarction (Kala et al., 2016). Regarding TMAO, a previous study indicated that individuals with depression also have alterations in gut microbial metabolites, such as TMAO, dimethylamine and dimethylglycine (Zheng et al., 2013).

1.5. Theoretical background for TMAO analyses in AMI patients with PTSD

Exposure to severe mental stress due to a potential traumatic event, such as AMI, might affect the intestinal microbiome and gut-blood barrier permeability, thereby inducing leaky gut syndrome (Hiki et al., 2001; Rezzi et al., 2009; Wu et al., 2017). Such alterations might increase TMAO concentrations in the blood (Hiki et al., 2001; Jaworska et al., 2020).

The precondition for subsequent development of PTSD after an AMI is severe stress at the time of the AMI (Burg & Soufer, 2016). TMAO might indicate stress and a stress-induced increase in gut permeability. Thus, in PTSD vulnerable AMI patients TMAO might be a potential biomarker of severe stress and a stress-induced increase in gut permeability. Biological correlates of severe stress might contribute to identifying PTSD-vulnerable patients at an early stage.

2. Objectives

The first aim of the study was to determine whether blood levels of TMAO vary immediately after acute myocardial infarction (AMI) in patients with/without AMI-induced PTSD symptomatology (subsyndromal and full PTSD).

The second aim was to investigate whether TMAO is a potential biomarker that could be useful in the prediction of AMI-induced PTSD symptomatology and the PTSD symptom subclusters re-experiencing, avoidance and hyperarousal.

The third aim was to investigate whether TMAO varies immediately after AMI in patients with/without subsequent depression 6 months after AMI.

3. Methods

3.1. Participants and procedures

All 116 study participants were drawn from AMI inpatients hospitalized at the Division of Cardiology of the Department of Internal Medicine, Medical University of Graz, Austria. Of the 116 study participants, two patients died due to AMI shortly after hospital admission; therefore, the overall sample consisted of 114 patients (96 males, 84.2%; 18 females, 15.8%). All participants were Caucasian and the mean age was 59.9 (± 11.5) years. Exclusion criteria for enrolment in this study were pre-existing PTSD prior to AMI, delirium and dementia, as well as additional acute and severe somatic illnesses other than AMI.

After admission to the hospital and then again 6 months after AMI, patients were assessed by an experienced consulting psychiatrist (A.B.) with a standardized clinical psychiatric interview based on the Hamilton Depression Scale (HAMD-17; Hamilton, 1967). None of the participants had clinically significant depression at the time of AMI.

Baseline CAPS-5 (Clinician Administered PTSD Scale for DSM-5; Weathers et al., 2018) screenings for potential trauma A criteria prior to AMI and pre-existing PTSD symptoms were conducted to exclude pre-existing PTSD symptomatology prior to AMI. None of the participants had PTSD prior to acute myocardial infarction.

In addition, substance abuse and previous psychiatric morbidities other than PTSD and depression were recorded shortly after AMI in a baseline clinical psychiatric standard interview, based on the ICD-10 classification.

Six months after AMI the CAPS-5 was used to explore AMI-induced PTSD symptoms. These CAPS-5 assessments 6 months after AMI were conducted by investigating symptoms related to only the index trauma, that is, AMI. No symptoms related to any other trauma types were assessed.

For the assessment of TMAO, serum samples were collected at hospitalization and 6 months after AMI.

3.1.1. Ethics statement

This research project was approved by the Institutional Review Board of the Medical University of Graz (Approval number: 28–126 ex 15/16). Data protection measures met the standards by Austrian law. The methods were carried out in accordance with the approved guidelines. All participants in this

study had to provide signed informed consent, and subjects could decide to withdraw from this research project at any time. Research participants were not compensated for their time.

3.2. Psychiatric interviews

The widely used observer rating scale for depression HAMD-17, which was designed by Hamilton (1967), was used immediately after AMI and 6 months later to ascertain the severity of AMI-induced depressive symptoms. As recommended by Zimmerman et al., the severity of depression was classified as no depression (total score of 0–7 on the HAMD-17); mild depression (total score of 8–16); moderate depression (total score of 17–23); and severe depression (total score of ≥24 on the HAMD-17) (Zimmerman, Martinez, Young, Chelminski, & Dalrymple, 2013).

After admission to the hospital and then again 6 months after AMI, the 30-item structured Clinician Administered PTSD Scale for DSM-5 (CAPS-5, National Center of PTSD, 2020; Weathers et al., 2018) was administered to assess pre-existing PTSD prior to AMI and AMI-induced PTSD symptoms (subsyndromal PTSD and full PTSD) 6 months after AMI. The 30 items on the CAPS-5 cover the following main DSM-5 PTSD criteria: A: severe or life-threatening traumatic event (defined as AMI in the present study); B: re-experiencing symptoms, intrusions and flashbacks; C: avoidance symptoms; D: negative alterations in cognition and mood; E: hyperarousal; F: significant disturbance lasting at least one month; and G: disturbance causing significant impairment. For the diagnosis of full PTSD, a patient must fulfil criteria A, F, and G and at least one criterion B symptom, at least one criterion C symptom, at least two criterion D symptoms, and at least two criterion E symptoms (American Psychiatric Association, 2013). Subsyndromal PTSD symptomatology was diagnosed when one or two of the criteria from B-E were missing (Baranyi et al., 2010).

Substance abuse and previous psychiatric morbidities other than PTSD and depression were recorded shortly after AMI in a baseline clinical psychiatric standard interview, based on the ICD-10 classification that was performed by an experienced consultation-liaison psychiatrist (A.B.).

3.3. Sociodemographic characteristics

To obtain the participants' sociodemographic characteristics, an author-compiled sociodemographic questionnaire was used to assess age, sex, years of education and/or vocational training, and employment status at the time of psychiatric assessment. The patient's employment status was categorized as paid work (full- or part-time) or no paid work (disability, retired, or unemployed). Marital status was categorized as married, single, divorced, or widowed.

3.4. Anthropometry, renal function, cardiac status at the time of admission to the hospital, percutaneous coronary intervention (PCI)-related parameters, in-hospital outcome and cardiac risk factors of AMI patients

The following clinical data were obtained for this study to characterize the study sample and to investigate the predictive value of TMAO, in addition to AMI-related clinical factors, for the diagnosis of PTSD symptoms 6 months after AMI:

- Anthropometry: Height (cm), weight (kg).
- Cardiac status at the time of inpatient admission due to AMI: Type of myocardial infarction, Killip class (=post-AMI mortality risk stratification), cardiogenic shock, abnormal level of troponin T, and AMI-related reanimation.
- Percutaneous coronary intervention (PCI): coronary artery disease (number of affected vessels); thrombolysis in myocardial infarction flow (TIMI) before PCI, TIMI flow after PCI, and multivessel PCI.
- Outcome: Death, stroke, major bleeding, reinfarction, and left ventricular rejection fraction (%).
- Cardiac risk factors: nicotine abuse, peripheral arterial occlusive disease, insulin-dependent diabetes mellitus (IDDM), non-insulin-dependent diabetes mellitus (NIDDM), hypertension, hyperlipidaemia, relevant family history, previous myocardial infarction, and severe liver disease.
- Renal function: Glomerular filtration rate (GFR), representing renal function, is well known to have an impact on TMAO levels.
- Substance abuse at the time of the AMI.
- Previous psychiatric morbidity other than PTSD: e.g. depression, adjustment disorder, burn-out.

3.5. Laboratory analyses

TMAO was measured using a stable-isotope dilution assay and high-performance liquid chromatography (HPLC) with electrospray ionization tandem mass spectrometry on a SCIEX QTRAP 4500 triple quadrupole instrument (Applied Biosystems, Framingham, MA, USA) equipped with an Agilent 1260 Infinity HPLC system (Agilent Technologies, Santa Clara, CA, USA). The intra- and inter-day coefficients of variation (CVs) ranged between 2.2 and 3.4% and 6.9 and 9.9%, respectively (Enko, Zelzer, et al., 2020a).

The estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)-GFR equation (Levey et al., 2009).

4. Statistical analyses

Descriptive statistics were conducted based on socio-demographic and treatment-related data. Data are presented as the means and standard deviations (SDs). To analyse continuous variables, t-tests and Pearson's correlation coefficients were used. For categorical variables, χ^2 tests were performed. In the case of multiple comparisons, an alpha adjustment (Bonferroni) was performed. TMAO levels in patients with/without PTSD symptomatology were analysed with analysis of covariance (ANCOVA), in which age, sex, body mass index (BMI), renal function (glomerular filtration rate), previous psychiatric morbidity other than PTSD and substance abuse at the time of AMI were included as covariates. The same statistical procedures were performed for the patients with/without depression 6 months after AMI. Logistic and linear regression models were used (1) to examine the impact of TMAO as a predictor of AMI-related PTSD symptomatology (subsyndromal and full PTSD) and (2) as a predictor of the PTSD-symptom subclusters of re-experiencing, avoidance and hyperarousal. Interaction analyses were performed to consider the relationship among the variables. In the first step of the logistic regression analyses we regressed TMAO at the time of hospital admission against AMI-induced PTSD-symptomatology (PTSD-symptoms present: yes/no) (Model 1). In the second step, the hierarchical logistic regression model control variables age, sex, body mass index (BMI), renal function (GFR), previous psychiatric morbidity other than PTSD and substance abuse at the time of AMI (Model 2) were introduced. In the third step, the hierarchical logistic regression model clinical predictors coronary artery disease (number of affected vessels) and anxiety at the time of AMI (HAMD-17 item psychic anxiety) (Model 3) were added to the model.

All statistical analyses were performed with SPSS 25.0 for Windows (SPSS; Chicago, IL).

5. Results

5.1. AMI-induced PTSD symptomatology (full and subsyndromal PTSD)

Six months after AMI, 49/114 (43%) patients had acute myocardial infarction-induced PTSD symptomatology [full PTSD: 14/114 (12.3%), subsyndromal PTSD (one CAPS-V criterion from B-E missing): 21/114 (18.4%), subsyndromal PTSD (two CAPS-V criteria B-E missing): 14/114 (12.3%)].

Table 1 shows the sociodemographic characteristics and pre-existing psychiatric morbidities other than PTSD in the overall sample and in the patients with or without AMI-induced PTSD-symptomatology.

Table 2 presents the anthropometry, renal function, cardiac status at the time of admission to the hospital, percutaneous coronary intervention (PCI)-related parameters, in-hospital outcome and cardiac risk factors in the overall sample and in the patients with or without AMI-induced PTSD-symptomatology.

5.2. Trimethylamine N-oxide (TMAO)

5.2.1. Overall sample

In the overall sample (regardless of secondary psychiatric diseases), there was a slight trend for an increase in TMAO 6 months after acute myocardial infarction [t-test for paired samples; mean TMAO concentration at time of hospital admission: 3.63 μmol/l (SD = ±3.38); mean TMAO concentration after 6 months: 4.23 μmol/l (SD = ±2.39), t = −1.68, df = 113, p = 0.09].

Baseline TMAO levels immediately after myocardial infarction were not significantly correlated with cardiological parameters of the acute cardiac event (Killip class – post-AMI mortality risk stratification: Pearson's r = −0.77, p = 0.438; LVEF: Pearson's r = 0.109, p = 0.332).

5.2.2. TMAO in patients with AMI-induced PTSD symptomatology (full and subsyndromal PTSD) six months after AMI

Patients with AMI-induced full or subsyndromal PTSD symptomatology 6 months after AMI had significantly higher TMAO values immediately after AMI than patients without PTSD symptoms. Six months after AMI, TMAO levels remained high in patients with full or subsyndromal AMI induced PTSD symptomatology. In comparison to the levels at the time of AMI, patients without PTSD symptoms had higher TMAO levels 6 months after AMI [ANCOVA: TMAO (time) F = 4.824, df = 1, p = 0.03; TMAO (PTSD) F = 0.243, df = 1, p = 0.122; TMAO (PTSD × time) F = 4.544, df = 1, p = 0.035; covariate age: F = 0.021, df = 1, p = 0.886; covariate sex: F = 13.936, df = 1, p < 0.01; covariate BMI: F = 2.129, df = 1, p = 0.148; covariate renal function (GFR): F = 0.053, df = 1, p = 0.819; covariate previous psychiatric morbidity: F = 3.914, df = 1, p = 0.051; substance abuse: F = 0.102, df = 1, p = 0.750]. Figure 1 shows the levels of TMAO in patients with and without PTSD symptomatology.

5.2.3. Multivariate analyses: TMAO as a predictor of AMI-related PTSD-symptoms (full and subsyndromal PTSD)

A three-step hierarchical logistic regression model was used to examine potential correlates of AMI-induced

Table 1. Sociodemographic characteristics and pre-existing psychiatric morbidities other than PTSD in the patients with and without AMI-induced PTSD symptomatology.

Category		Total Sample ($n = 114$)	p	PTSD-Symptomatology ($n = 49/114$, 43%)	No PTSD ($n = 65/114$, 57%)	p
Sex						
Male	n (%)	96 (84.2%)	$\chi^2 = 53.368$, df = 1	39 (79,6%)	57 (87.7%)	$\chi^2 = 1.38$, df = 1
Female	n (%)	18 (15.8%)	$p < .001^a$	10 (20.4%)	8 (12.3)	$p = 0.24^a$
Age	mean (SD)	59.9 (±11.48)	-	59.2 (±11.52)	60.6 (±11.51)	t = 0.650, df = 112 $p = 0.52^b$
Marital Status						
Single	n (%)	14 (12.3%)	$\chi^2 = 117.643$, df = 3	8 (17%)	6 (78.5%)	$\chi^2 = 7.17$, df = 3
Married	n (%)	77 (67.5%)	$p < .001^a$	26 (55.3%)	51 (9.2%)	$p = 0.07^a$
Widowed	n (%)	4 (3.5%)		2 (4.3%)	2 (3.1%)	
Divorced	n (%)	17 (14.9%)		11 (23.4%)	6 (9.2%)	
Maximum Educational Level						
Secondary School without Graduation	n (%)	7 (6.1%)	$\chi^2 = 116.642$, df = 7	4 (8.7%)	3 (5%)	$\chi^2 = 6.49$, df = 7
Secondary School with Graduation	n (%)	49 (43.0%)	$p < .001^a$	23 (50%)	26 (43.3%)	$p = 0.48^a$
Business School without Diploma	n (%)	6 (5.3%)		2 (4.3%)	4 (6.7%)	
Business School with Diploma	n (%)	11 (9.6%)		5 (10.9%)	6 (10%)	
Grammar School without Graduation	n (%)	7 (6.1%)		2 (4.3%)	5 (8.3%)	
Grammar School with Graduation	n (%)	11 (9.6%)		5 (10.9%)	6 (10%)	
A-level without University degree	n (%)	2 (1.8%)		2 (4.3%)	0 (0%)	
A-level with University Degree	n (%)	13 (11.4%)		3 (6.5%)	10 (16.7%)	
Employment Status						
Paid Work (full- or part-time)	n (%)	53 (46.5%)	$\chi^2 = 87.754$, df = 3	21 (42.9%)	32 (49.2%)	$\chi^2 = 7.85$, df = 3
Homemaker	n (%)	3 (2.6%)	$p < .001^a$	0 (0%)	3 (4.6%)	$p = 0.05^a$
Retired	n (%)	54 (47.4%)		24 (49%)	30 (46.2%)	
Unemployed	n (%)	4 (3.5%)		4 (8.1%)	0 (0%)5	
Previous Mental Illness other than PTSD (Depression, Adjustment Disorder, Burn-out)	n (%)	14 (12.3%)	-	8 (16.3%)	6 (9.2%)	$\chi^2 = 1.306$, df = 1 $p = 0.25^a$
Previous Psychopharma-cological Medication	n (%)	11 (9.6%)	-	5 (10.2%)	6 (9.2%)	$\chi^2 = 0.03$, df = 1 $p = 0.86^a$
Substance Abuse						
Alcohol	n (%)	1 (0.87%)	-	1 (2.0%)	0 (0%)	$p = 0.429^c$
Illicit Drugs	n (%)	0 (0%)	-	0 (0%)	0 (0%)	-

Legend: [a] χ^2 – test; [b] t-test; [c] Fisher exact

PTSD symptomatology. In the first step, we regressed TMAO at the time of hospital admission against AMI-induced PTSD-symptomatology (PTSD-symptoms present: yes/no) (Model 1). In the second step, we introduced the hierarchical logistic regression model control variables age, sex, body mass index (BMI), renal function (glomerular filtration rate), previous psychiatric morbidity other than PTSD and substance abuse at the time of AMI (Model 2). In the third step, we introduced the hierarchical logistic regression model clinical predictors coronary artery disease (number of affected vessels) and anxiety at the time of AMI (HAMD-17 item psychic anxiety) (Model 3).

Regarding Model 1, baseline TMAO alone tended to be predictive of AMI-induced PTSD symptomatology (TMAO: $p = 0.079$). When the control variables (Model 2) and the clinical predictors (Model 3) were included in the hierarchical logistic regression analysis, TMAO became a significant predictor of AMI-induced PTSD symptomatology (TMAO: $p = 0.048$).

Table 3 shows the three-step hierarchical logistic regression model of AMI-induced PTSD symptomatology.

5.2.4. TMAO as a predictor of the AMI-induced PTSD symptom subcluster re-experiencing

In a linear regression model, we regressed TMAO at the time of hospital admission against the PTSD symptom subcluster re-experiencing. In this linear regression analysis, TMAO showed a minor trend ($p = 0.079$) for the prediction of the PTSD symptom subcluster re-experiencing.

Table 4 shows the linear regression model for the PTSD symptom subcluster re-experiencing.

5.2.5. TMAO as a predictor of the AMI-induced PTSD symptom subcluster avoidance

In a linear regression model, we regressed TMAO at the time of hospital admission against the PTSD symptom subcluster avoidance. In this linear regression analysis, TMAO was not a predictor ($p = 0.594$) of the PTSD-symptom subcluster avoidance.

5.2.6. TMAO as a predictor of the AMI-induced PTSD symptom subcluster hyperarousal

In a linear regression model, we regressed TMAO at time of hospital admission against the PTSD symptom

Table 2. Anthropometry, renal function, cardiac status at the time of admission to the hospital, percutaneous coronary intervention (pci)-related parameters, in-hospital outcome and cardiac risk factors in the patients with and without ami-induced ptsd symptomatology.

Category		Total Sample (n = 114)	p	PTSD-Symptomatology (n = 49/114; 43%)	No PTSD (n = 65/114; 57%)	
Anthropometry						
Height (cm)	Mean (SD)	174.79 (±8.15)	-	173.5 (±8.27)	176.0 (±7.97)	t = 1.435, df = 109 p = 0.154[a]
Weight (kg)	Mean (SD)	86.64 (±13.89)	-	87.7 (±16.82)	85.81 (±11.20)	t = −0.710, df = 108 p = 0.479[a]
BMI	Mean (SD)	28.31 (±-4.0)	-	29.01 (±4.89)	27.76 (±3.07)	t = −1.643, df = 108 p = 0.103[a]
Renal Function						
Glomerular Filtration Rate	Mean (SD)	84.69 (±17.87)	-	83.6 (±18.89)	85.53 (±17.17)	t = 0.578, df = 112 p = 0.56[a]
Cardiac Situation at the Time of Admission to the Hospital						
NSTEMI	n (%)	43 (37.7%)	-	20 (40.8%)	23 (35.4%)	χ^2 = 0.351, df = 1
STEMI	n (%)	71 (62.3%)		29 (59.2%)	42 (64.6%)	p = 0.55[b]
Killip Mortality Risk Stratification:						
Killip Class I	n (%)	88 (77.2%)	χ^2 = 197.62, df = 3	40 (85.1%)	48 (84.2%)	χ^2 = 0.807, df = 3
Killip Class II	n (%)	8 (7%)	p < .001[a]	3 (6.4%)	5 (8.8%)	p = 0.85[b]
Killip Class III	n (%)	5 (4.4%)		2 (4.3%)	3 (5.3%)	
Killip Class IV	n (%)	3 (2.6)		2 (4.3%)	1 (1.8%)	
Abnormal Level of Troponin T	n (%)	114 (100%)	-	49 (100%)	65 (100%)	-
Cardiogenic Shock	n (%)	0 (%)	-	0 (0%)	0 (0%)	-
AMI-related Reanimation	n (%)	3 (2.6%)	-	2 (4.1%)	1 (1.5%)	p = 0.576[c]
PCI-related Parameters						
TIMI Flow before PCI:						
0-I	n (%)	85 (74.6%)	χ^2 = 108.571.62,	35 (76.1%)	50 (84.7%)	χ^2 = 1.325, df = 2
II	n (%)	15 (13.2%)	df = 2	8 (17.4%)	7 (11.9%)	p = 0.52[b]
III	n (%)	5 (4.4%)	p < .001[a]	3 (6.5%)	2 (3.4%	
TIMI flow after PCI:						
0-I	n (%)	4 (3.5%)	χ^2 = 156.054.62,	0 (0%)	4 (6.3%)	χ^2 = 4.269, df = 2
II	n (%)	8 (7%)	df = 2	5 (10.6%)	3 (4.7%)	p = 0.12[b]
III	n (%)	99 (86.8%)	p < .001[a]	42 (89.4%)	57 (89.0%)	
Multivessel PCI	n (%)	23 (20.2%)	-	13 (27.7%)	10 (16.7%)	χ^2 = 1.887, df = 1 p = 0.17[b]
Coronary Artery Disease (number of affected vessels)	Mean (SD)	1.82 (±0.79)		1.84 (±0.83)	1.82 (±0.76)	t-test = −0.074, df = 112 p = 0.89[a]
In-hospital Outcome						
Major Bleeding	n (%)	0 (0%)	-	0 (0%)	0 (0%)	-
Reinfarction	n (%)	2 (1.8%)	-	1 (2.0%)	1 (1.5%)	χ^2 = 0.042, df = 1 p = 0.84[b]
Left-Ventricular Ejection Fraction (%)	Mean (SD)	53.15 (±10.559)	-	53.24 (±11.73)	53.07 (±9.60)	t-test = −0.074, df = 79 p = 0.94[a]
Cardiac Risk Factors						
Nicotine Abuse	n (%)	39 (34.2%)	-	23 (46.9%)	30 (46.2%)	χ^2 = 0.007, df = 1 p = 0.93[b]
Peripheral Arterial Occlusive Disease	n (%)	3 (2.6%)	-	2 (4.1%)	1 (1.5%)	χ^2 = 0.681, df = 1 p = 0.41[b]
IDDM	n (%)	2 (1.8%)	-	1 (2.0%)	1 (1.5%)	χ^2 = 0.041, df = 1 p = 0.84[b]
NIDDM	n (%)	17 (14.9%)	-	11 (22.4%)	6 (9.2%)	χ^2 = 3.847, df = 1 p = 0.05[b]
Hypertension	n (%)	102 (89.5%)	-	42 (85.7%)	60 (92.3%)	χ^2 = 1.290, df = 1 p = 0.26[b]
Hyperlipidaemia	n (%)	59 (51.8%)	-	28 (56.0%)	31 (47.7)	χ^2 = 1.077, df = 1 p = 0.30[b]
Relevant Family History	n (%)	23 (20.2%)	-	10 (23.3%)	13 (25.5%)	χ^2 = 0.063, df = 1 p = 0.80[b]
Previous Myocardial Infarction	n (%)	12 (10.5%)	-	8 (16.3%)	4 (6.5%)	χ^2 = 2.768, df = 1 p = 0.096
Severe Liver Disease	n (%)	2 (1.8%)	-	0 (0%)	2 (3.0%)	χ^2 = 1.54, df = 1 p = 0.22[b]

Legend: [a] t-test; [b] χ^2 – test, [c] Fisher exact; Abbreviations: AMI = Acute Myocardial Infarction; IDDM = Insulin-dependent Diabetes Mellitus; NIDDM = Non-Insulin-dependent Diabetes Mellitus; PCI = Percutaneous Coronary Intervention; TIMI flow = Thrombolysis in Myocardial Infarction Flow.
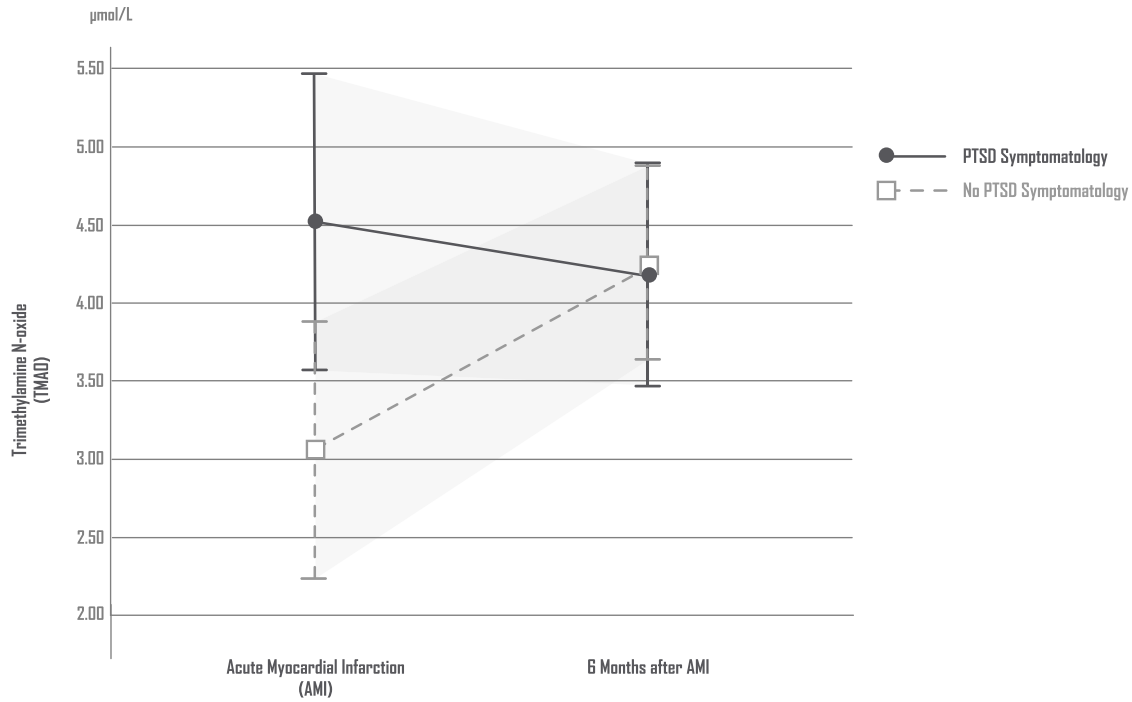
Figure 1. TMAO in patients with and without PTSD symptomatology.

Table 3. Three-step hierarchical logistic regression model of AMI-induced PTSD symptomatology.

	B	S.E.	WALD	df	Exp (B)	p
Step 1						
(Model 1)						
DV = PTSD Symptomatology (Yes/No)						
Constant	−0.741	0.320	5.357	1	0.477	0.021
TMAO at time of hospital admission	0.128	0.073	3.080	1	1.136	0.079

$R^2_{COX\ \&\ Snell}$: 0.036
(Omnibus: χ^2 = 4.046, df = 1, p = 0.044; Hosmer-Lemeshow-Test: χ^2 = 7.151, df = 8, p = 0.520)

	B	S.E.	WALD	df	Exp (B)	p
Step 2						
(Model 2)						
DV = PTSD Symptomatology (Yes/No)						
Constant	19.673	40,193.16	0.00	1	349,734,226.1	1.00
TMAO at time of hospital admission	0.163	0.082	3.929	1	1.177	0.047
Sex	0.434	0.638	0.463	1	1.544	0.496
Age	−0.023	0.21	1.210	1	0.978	0.271
BMI	0.106	0.055	3.681	1	1.111	0.055
GFR	−0.007	0.013	0.247	1	0.993	0.619
Previous psychiatric morbidity other than PTSD	−0.492	0.690	0.508	1	0.611	0.476
Substance abuse at the time of AMI	−21.284	40,193.16	0.00	1	0.000	1.00

$R^2_{COX\ \&\ Snell}$: 0.116
(Omnibus: χ^2 = 13.381, df = 7, p = 0.063; Hosmer-Lemeshow-Test: χ^2 = 8.872, df = 8, p = 0.353)

	B	S.E.	WALD	df	Exp (B)	p
Step 3						
(Model 3)						
DV = PTSD Symptomatology (Yes/No)						
Constant	18.441	40,192.93	.000	1	102,068,407.1	1.00
TMAO at time of hospital admission	0.167	0.085	3.908	1	1.182	0.048
Sex	0.332	0.689	0.232	1	1.394	0.630
Age	−0.016	0.022	0.568	1	0.984	0.451
BMI	0.111	0.058	3.669	1	1.118	0.055
GFR	−0.006	0.014	0.209	1	0.994	0.647
Previous psychiatric morbidity other than PTSD	−0.437	0.718	0.370	1	0.646	0.543
Substance abuse at the time of AMI	−21.312	40,192.936	0.000	1	0.000	1.00
PCI – coronary artery disease (number of affected vessels)	0.100	0.291	0.119	1	0.625	0.730
Anxiety at the time of AMI (HAMD-17 item psychic anxiety).	0.428	0.178	5.775	1	1.082	0.016

$R^2_{COX\ \&\ Snell}$: 0.165
(Omnibus: χ^2 = 19.716, df = 9, p = 0.020; Hosmer-Lemeshow-Test: χ^2 = 5.573, df = 8, p = 0.695)

Table 4. Linear regression model – PTSD-symptom subcluster re-experiencing.

DV = PTSD Subcluster Re-Experiencing	B	Beta	S.E.	p
Constant	2.572		0.441	0.000
TMAO at time of hospital admission	0.154	0.161	0.089	0.087

subcluster arousal. In this linear regression analysis, TMAO was not a predictor ($p = 0.910$) of the PTSD symptom subcluster hyperarousal.

5.3. TMAO in patients with depression 6 months after acute myocardial infarction

Six months after AMI, 60/114 (52.6%) patients had depressive symptomatology. In the group of depressed patients, the HAMD-17 score increased significantly after 6 months [mean HAMD-17 score at the time of hospital admission: 5.30 (SD = ±2.52); mean HAMD-17 score after 6 months: 13.73 (SD = ±4.79)]. In the group of non-depressed patients, the HAMD-17 score decreased after 6 months [mean HAMD-17 score at admission: 3.98 (SD = ±2.0); mean HAMD-17 score at 6 months: 1.77 (SD = ±1.87); ANOVA (depression × time): F = 201,483; df = 1, $p < .001$].

In comparison with the non-depressed patients, patients with depression 6 months after AMI did not have significantly different TMAO levels [ANCOVA: TMAO (time) F = 4.511, df = 1, $p = 0.036$; TMAO (Depression) F = 3.184, df = 1, $p = 0.569$; TMAO (Depression × time) F = 0.083, df = 1, $p = 0.774$; covariate age: F = 0.0, df = 1, $p = 0.987$; covariate sex: F = 14.712, df = 1, $p < 0.01$; covariate BMI: F = 1.246, df = 1, $p = 0.267$; covariate renal function (GFR): F = 0.021, df = 1, $p = 0.885$; covariate previous psychiatric morbidity: F = 3.459, df = 1, $p = 0.066$;

substance abuse: F = 0.019, df = 1, $p = 0.892$]. Figure 2 shows the levels of TMAO in patients with and without depression.

6. Discussion

6.1. TMAO levels after AMI

In the overall group, regardless of psychiatric symptoms, we found a trend for a slight increase in serum TMAO levels 6 months after AMI. This observed TMAO increase might be caused by AMI-induced changes in microbial community structures (Wu et al., 2017) and by chronic long-term stress after myocardial infarction. The results of our study are also partly consistent with the results of the study by Alhmoud et al. In this study, there was no immediate increase observed in TMAO after acute coronary syndrome (Alhmoud et al., 2019).

However, when secondary psychiatric diseases were included in our data analysis, a more differentiated pattern emerged. Thus, we found no significant difference in TMAO levels immediately after AMI between individuals with or without depression 6 months after AMI. In contrast, our study participants with AMI-induced PTSD symptoms had significantly higher TMAO levels immediately after AMI than patients without PTSD symptoms. This might be explained by the fact that the emergence of PTSD requires an individual perception of severe acute stress at the time of myocardial infarction. Several studies have demonstrated that such severe mental stress has a distinct impact on the microbiota-gut-brain axis, which becomes obvious based on the consequences of increased gut permeability (Obrenovich, Siddiqui, McCloskey, & Reddy, 2020; Rezzi et al., 2009).
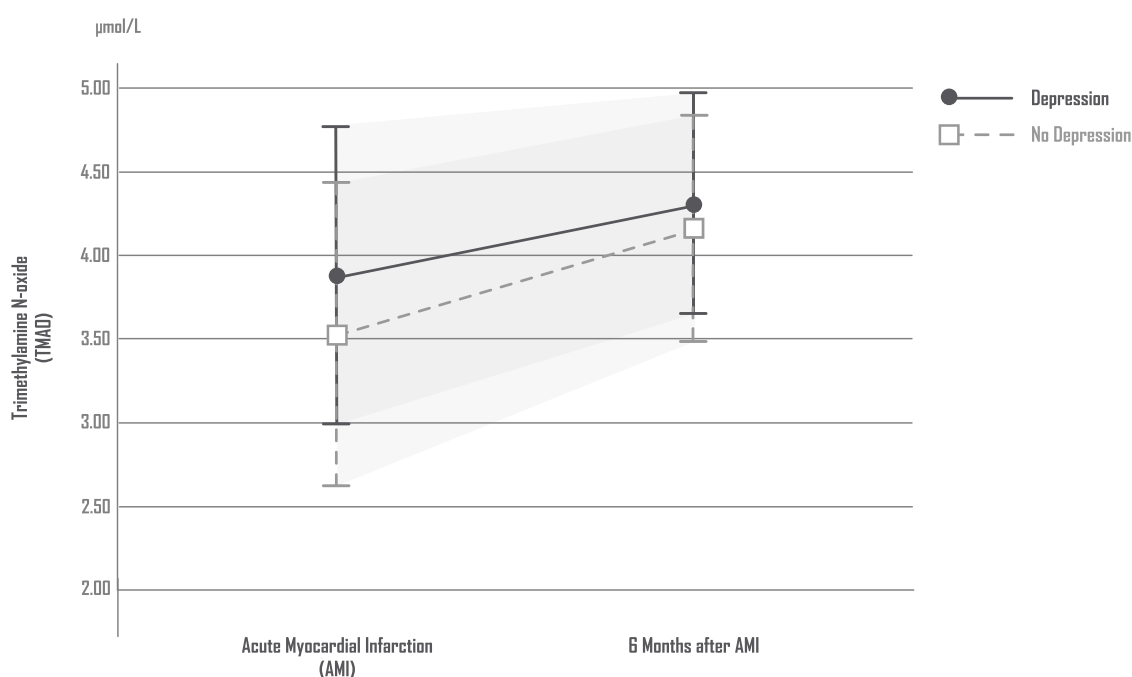
Figure 2. TMAO in patients with and without depression.

A leaky gut-brain axis is a serious consideration given the potential for the transmission of bacteria and gut bacteria-derived metabolites, which may also have impacts on the pathophysiology of cardiovascular and psychiatric diseases (Carabotti et al., 2015; Meinitzer et al., 2020). Therefore, in our study, the observed increased TMAO levels immediately after AMI may reflect such an increase in gut permeability with regard to the TMAO precursor TMA. These considerations are also in line with the findings of a previous study by Kinross et al. (2011), which described elevated TMAO levels after stressful surgical interventions in Wistar rats (Kinross et al., 2011). In a recent study, we further demonstrated that the small molecule TMAO can also cross the blood-CSF barrier via passive diffusion (Enko, Zelzer, et al., 2020b). Considering this fact, TMAO could also play a direct role in the central nervous system. However, the impact of TMAO on the pathophysiology of the central nervous system requires further studies (Del Rio et al., 2017).

While increased TMAO levels immediately after AMI may reflect an increase in gut permeability to the TMAO precursor TMA due to an acute overwhelming stress perception in PTSD-vulnerable patients, the observed high TMAO levels 6 months after AMI in the entire group might more likely be explained by AMI-induced prolonged alterations of gut microbial community structures. These long-term changes in gut microbial community structures are likely to emerge independent of PTSD symptoms due to acute myocardial infarction itself (Wu et al., 2017) and chronic long-term stress after myocardial infarction (familial, employment, health problems and other stressors), which do not reach a sufficiently high enough levels to trigger PTSD. Exposure to severe psychological stressors can modify microbial community structures, turning a normally stable microenvironment into a volatile dysbiotic profile (Galley, Mackos, Varaljay, & Bailey, 2017; Knowles, Nelson, & Palombo, 2008). These alterations in gut microbial community structures are also expected to be present in our study group of patients without PTSD. This might explain why in our study, even patients without PTSD had elevated TMAO levels 6 months after myocardial infarction.

With the exception of sex, none of the covariates (age, body mass index (BMI), renal function (glomerular filtration rate), previous psychiatric morbidity other than PTSD and substance abuse at the time of AMI significantly impacted the study results.

In our study, TMAO immediately after myocardial infarction was not correlated with cardiological markers, such as Killip class (=post-AMI mortality risk stratification) and LVE. This means that while TMAO is thought to have less clinical significance in acute

cardiological events, it might enhance the risk of severe cardiac events in the future (Alhmoud et al., 2019; Querio et al., 2019).

In addition, our study results (see Tables 1 and 2) showed that the differences in TMAO concentrations found between patients with and without new-onset AMI-induced PTSD were unlikely to be explained by anthropometry, renal function, cardiac status at the time of admission to the hospital, percutaneous coronary intervention (PCI)-related parameters, in-hospital outcomes or cardiac risk factors.

6.2. TMAO as a predictor of AMI-related PTSD-symptoms (full and subsyndromal PTSD)

Baseline TMAO at the time of AMI alone tended to be predictive of PTSD symptomatology. When the control variables and the clinical predictors were included in the hierarchical logistic regression model, TMAO became a significant predictor of PTSD symptomatology. In addition, TMAO showed a minor trend for the prediction of the PTSD symptom subcluster re-experiencing. The observation that the re-experiencing subcluster is particularly strongly reflected in biomarkers is also supported by two studies: Lima et al. (2020) investigated the association of AMI-related PTSD with mental stress-induced myocardial ischaemia among patients who survived AMI. In the study by Lima et al. (2020), the PTSD symptom-subcluster re-experiencing was most strongly associated with ischaemia during mental stress after AMI (Lima et al., 2020). Lima et al. further suggested that AMI survivors with comorbid PTSD might also have a more pronounced inflammatory response to subsequent acute psychological stress situations than AMI survivors without comorbid PTSD. In a recent study, they showed, that acute severe mental stress is associated with an increase in the inflammatory marker IL-6 in AMI survivors with comorbid PTSD. Re-Experiencing was again the PTSD-symptom-subcluster most strongly associated with an enhanced inflammatory response to subsequent acute severe mental stress (Lima et al., 2019).

6.3. Limitations

Follow-up studies should investigate the correlations of TMAO with well-known biomarkers of stress (e.g. cortisol, metanephrine). In addition, serum TMA level measurements would be of interest. Further studies should also assess stress perception with additional psychometric questionnaires. It should also be mentioned that a heart attack no longer constitutes a Criterion A trauma, according to the DSM-5 (American Psychiatric Association, 2013).

7. Conclusions

In summary, TMAO elevations immediately after AMI might reflect severe stress in PTSD-vulnerable patients, which might also lead to a short-term increase in gut permeability to TMA, the precursor of TMAO. Thus, an elevated TMAO level might be a biological correlate of AMI-related severe stress, which affects vulnerability to the development of PTSD.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data available Statement

To protect the confidentiality of patient information, the Medical University of Graz IRB will not allow the authors to make data publicly available. Data are available upon request from Andreas Baranyi at the Department of Psychiatry and Psychotherapeutic Medicine, Medical University of Graz, Graz, Austria, for researchers who meet the criteria for access to confidential data.

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