The additional use of methylene blue has a decatecholamination effect on the cardiac vasoplegia syndrome after cardiac surgery

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Abstract

Background: Postoperative vasoplegia syndrome with minimal responsiveness to vasopressors is common after cardiac surgery. This syndrome is called cardiac vasoplegia syndrome (CVS). The CVS is caused by multiple factors. The basic therapy of CVS consists of high dose fluids and catecholamines. High dosage of catecholamines and fluids are associated with serious side effects. There is evidence that new therapeutic strategies can reduce the high dose of norepinephrine and mortality in CVS. In particular, the use of non-adrenergic vasopressors such as methylene blue can be beneficial.

Methods: We retrospectivly analysed electronic records of 8716 adult cardiac surgery patients (November 2008 and December 2016). Data of medication, hemodynamic and outcome parameter were analysed for CVS until discharge. CVS was defined by postoperative onset ≤ 24 hours, reduced mean arterial pressure (MAP) < 60 mmHg, a dose of norepinephrine ≥ 0.8 $mg*h^{-1}$ and increasing catecholamine, none ventricular dysfunction.

Results: We identify 513 patients with CVS. Perioperative risk factors were higher in patients treated with MB. Before methylene blue administration patients had a significant higher dose of norepinephrine. After administration of MB, the MAP increased. Norepinephrine could be reduced after administration of methylene blue. The MAP remained stable at the same level even after the norepinephrine reduction.

Conclusions: CVS patients has a severe systemic disease accompanied with remarkable operative stress and a high catecholamine requirement. Additive administration of methylene blue to standard therapy in the first 24 hours was accompanied by an increase of MAP followed by a decrease of vasopressor requirement. Early MB administration can be beneficial.

Background

Postoperative hypotension is common in patients after cardiac surgery. The three major hemodynamic disorders after cardiac surgery are hypovolemia, vascular failure and heart failure. These three disorders are responsible for hypotension episodes which are associated with a worse of out come. Especially, vascular failure with minimal responsiveness to vasopressors for example (e.g.) norepinephrine, so called cardiac vasoplegia syndrome (CVS) is associated with an increased mortality.(1–3) Observational studies report a 5% − 50% incidence of vasoplegic syndrome in cardiac surgery with cardiopulmonary bypass .(1, 2, 4) The basic therapy of CVS is to administrate fluids and catecholamines (e.g. norephinephrine).(2) Catecholamines are associated with serious side effects such as an increased myocardial oxygen consumption, the development of arrhythmias or decrease of renal and visceral blood flow.(5) Also excessive administration of fluids is associated with side effects.(6) To reduce side effects therapy options with low levels of noreadrenalin would be needed.(7) Observational studies report methylene blue (MB) as a therapeutic alternative or adjuvant to the classic therapy of vasoplegia syndrome.(1) MB a non-catecholaminergic agent caused a statistically significant increase of the mean arterial pressure (MAP). This effect has no serious adverse events based on a meta-analysis on 5

randomized controlled trials.(8) MB reduce catecholamine stress in critical ill patients. This effect is called decatecholaminisation and may improve survival in CVS.(9, 10) Currently MB does not have any approved indications for the therapy of vasoplegia syndrome. The purpose of this study is to determine the incidence of CPB induced vasoplegia syndrome and describe practice of MB use at our cardiac surgery center. We hypothesized that administration of MB at ICU would reduce the risk of mortality in patients with CVS.

Methods

This study was approved by the ethics committee of the University of Regensburg (AZ 15 101-0046). For this study hemodynamic records of the intensive care unit (ICU) data management system (PDMS, Metavision®, Tel Aviv, Israel) were used. We screened all adult patients between December 2008 and November 2016 for CVS after cardiac surgery. The cardiac vasoplegia syndrome was defined by criteria shown in table 1. Vasopressor medication (e.g. catecholamines, hydrocortisone and vasopressin), and outcome parameters were analysed until discharge.

Patients with multiple MB administrations, MB administration on ICU > 24 hours (h), pregnant patients, patients with sepsis or patients with insufficient or missing data were exclude for the study. Perioperative data were obtained from sources including anaesthesia records (Medlinq®, Hamburg, Germany), data from ICU (PDMS), as well as records, medical reports and quality management (QM) data from the hospital information system (SAP®, Walldorf, Germany). The period of observation ended with the discharge of the patient from the hospital. The data were collected in a standardized and anonymised format.

MB administration was set as time point 0 in the MB-group. Haemodynamic parameter and medications were documented at -3, -2, -1 hour (h) before MB administration and at 1, 2, 3, 4, 8, 12, 24, 48 and 72 h afterwards. For the non-MB-group, time point 0 is defined as 6 h after arrival on the ICU, corresponding to the mean time of MB administration after patient's admission on the ICU in the MB-group.

The data were analysed with SPSS (IBM Corp., Armonk. USA, version 23) by applying Pearson's chi-squared test or t-tests. A p-value of < 0.05 was considered to be statistically significant. All data in the text, tables and figures are specified as percent (%), mean and standard deviation (SD) or standard error of mean (SEM).

Results

From December 2008 to November 2016, we performed 8716 cardiopulmonary bypasses (CPB) in our department. Using the definition of vasoplegia syndrome in table 1 a total of 710 patients had a vasoplegia syndrome (figure 1). Based on our study population 8.15% of the patients developed a vasoplegia syndrome. 113 patients with insufficient or missing data were excluded from further analysis. Of the remaining 597 patients with vasoplegia syndrome we identified 84 as sepsic vasoplegia

syndrome. These 84 patients with septic vasoplegia syndrome were excluded from further analysis. After excluding the 84 patients with septic vasoplegia syndrome, 513 patients with complete data sets fulfilled our criteria for cardiac vasoplegic syndrome. This corresponds to 5.86 % of all patients after cardiac surgery. Of these 513 patients 311 (60.23 %) had received MB in the first 24 hours after admission on ICU (MB-group). The remaining 202 patients had no administration of MB (non-MB-group). Demographic and intraoperative data of the MB-group and the Non-MB-group are provided in table 3 and table 4. Compared to non-MB groupn patients in the MB group had significantly more comorbidities and perioperative complications, e.g. kidney failure, acute myocardial infarction, emergency surgery, previous cardiac surgery events, prolonged CBP time, etc. In the MB-group patients had a mean continuous infusion rate of 1.2 ± 0.61 $mg*h^{-1}$ (mean ± SD) norepinephrine before administration of MB. In the non-MB-group mean continuous infusion rate of norepinephrine was 0.64 ± 0.51 $mg*h^{-1}$ (mean ± SD). The continuous infusion rate of norepinephrine was significantly higher in the MB group compared to the non-MB group at time 0 ($p < 0.05$) (figure 2). Mean arterial pressure (MAP) was significantly lower in the MB-group before MB administration compared to the non-MB-group ($p < 0.05$) (figure 3). Additional vasopressors such as epinephrine, vasopressin and hydrocortison were administered significantly more in the MB group ($p < 0.001$) table 5. Extended hemodynamic monitoring was used significantly more frequently in the MB group than in the non-MB group. Transesophageal echocardiography was performed significantly more frequently in the MB group (160 patients, 53 %) compared to the non-MB group (51 patients, 25 %) ($p <0.001$). Swan-Ganz-catheter (PAC) were performed 182 times (61 %) in the MB-group and in 38 times (19 %) in the non-MB-group ($p < 0.001$). Pulse contour cardiac output (PICCO) was only performed in the MB-group 5 (2 %). Mean central venous saturation ($ScvO_2$) in the MB-group 66 ± 24% was not significat (n.s.) differenent compared to non-MB 65 ± 70 %. Cardiac index (CI) was n.s. different MB (3.3 ± 1.0 $L/min/m^2$) vs. non-MB (3.4 ± 1.0 $L/min/m^2$) (mean ± SD). MB was administered 6.4 ± 5.2 (mean ± SD) hours after admission on ICU, with a dose of 174 ± 56 mg (milligram) (mean ± SD). This refers to approximately 2.0 $mg*kg^{-1}$ body weight. In 11% of all cases MB was given as a bolus. In 89 % MB was continuously adminitraed with an infusion pump over 51 ± 28 min (mean ± SD). The MAP increased significantly after the additional administration of methylene blue to standard therapy from 65 + 0.5 (mean ± SEM) at time point -1 to 71 + 0.5 (mean ± SEM) at time point 2 ($p < 0.05$). Compared to time point -3, -2, -1 and 0 the MAP increase in the MB-group at time point 1 significant ($p < 0.05$) (figure 3). The MAP level of the MB and non-MB groups no longer differed significantly from time 1 to the end of the observation period. The continuous norepinephrine infusion rate declined from time point 1 with constant hemodynamics and MAP values. The continuous norepinephrine infusion rate of the non-MB group was significantly lower at all times compared to the MB group. The 30-day mortality was significantly higher in the MB group compared to the non-MB group ($p < 0.001$) . The rate of organ failure ($p < 0.001$) and ventilation days were also significantly higher ($p < 0.001$) in the MB group.

Discussion

To our knowledge, this retrospective study is the study with the highest number of patients treated with MB in cardiac vasoplegia syndrome (CVS). The vasoplegia syndrome after cardiac surgery is an

independent mortality factor in cardiac surgery patients.(3) The cardiac vasoplegia syndrome is caused by multiple factors.(2, 11) There are currently no generally valid definition criteria for the cardiac vasoplegia syndrome.(12) For this reason, the incidence for CVS variates in a range from 5% to 50% in literature. (2, 4) Van Vessem et al. observed an incidence of 29% of vasoplegia syndrome in their study. (4) With our vasoplegic criteria we identified an all over incidence of 8,15 % (710 of 8716) for general vasoplegia syndrome. Excluding septic causes of vasoplegia syndrome and incomplete data sets the incidence of CVS in our study population is 5,88% (513 of 8716). This is incidence is comparable to some other studies investigating CVS. (13, 11) Typical risk factors for vasoplegia syndrome CBP can also be found in our study. (2, 4, 11)

The first mention of positive haemodynamic effect caused by MB in cardiac surgery was from the colleagues of Andrade using 1.5 $mg*kg^{-1}$ in 6 patients with an increase of SVRI from 868 to 1693 $dyn*s*cm^{-5}*m^{-2}$. (14) Further studies showed for MB different haemodynamic effects, which may be attributable to differences in the time point of administration at various levels of norepinephrine or other vasoconstrictors in different situations.(2, 5, 15, 16) the administartion of MB is a posibility to reduce catecholaminergic stress in critical ill patients. This typ of therapy is not new and called as decatecholaminisation.(8)

Some side effect are described for MB administration. This side effects can be divided in small (dizziness) and severe side effects such as a constriction of the mesenteric bed and resulting mesenteral ischemina. Severe MB side effects can have an influence on mortality in CVS.(3, 17) The mean dose of MB in our study was 2.0 $mg*kg^{-1}$. This dosage corresponds to those in others studies and is described as a save standard dosage.(18) In our study, a small group of twelve patients received an unintentional higher dosage of methylene blue (4.5 $mg*kg^{-1}$ - 5.5 $mg*kg^{-1}$). Neither the standard dose group (< 2.0 $mg*kg^{-1}$) nor the maximum dose group (4.5 $mg*kg^{-1}$ - 5.5 $mg*kg^{-1}$) experienced any small or serious side effects. Simple side effects like dizziness might be underestimated as all patients were intubated and sedated at MB administration.

In our study a significant increase of 5 mmHg MAP after MB administration can be detected (figure 3). MB administration was followed by a decrease of vasopressor requirement (figure 2). This findings are compareable to other studies discribing the catecholamine reducing effect of additional MB therapy in cardiac vasoplegia syndrome. Surprisingly, the by Mehaffey reported reduction of mortality after MB in cardiac vasoplegia syndrome was not identified in this study.(13) The mortality rate in the MB-group was twice as high as in the Non-MB-group (18 % vs. 5 %, $p < 0.001$). This differend findings are explanable by the typ of our study design. The purpose of this study was to determine the incidence of CVS and to describe practice MB use in our cardiac surgery center. Because because of that we performed the study as a retrospective analysis. Because MB administration is an established therapy at our center for severe CVS, the two CVS groups we have formed retrospectivly (MB and non MB) are not completely comparable. Comparing MB and non MB groups in noradrenaline dosage course and the MAP course (figure 2 and figure 3) a lower vasopressor requirement and higher MAP in the non MB group can be

detected. Also classical risk factors for vasoplegia syndrome like comorbidities and cardiac surgery typical risk factors like long CBP durations were significantly more frequent in the MB-group (table 3-4). This indicating that the patients in the MB group were more at risk and in worse conditions as well. Primarily it can now be said that the non MB group in our study had no vasoplegia. The very broad incidence rate of 5-50% in the literature and the lack of a general definition of the vasoplegic syndrome indicate that there are several degrees of vasoplegia. (19, 1, 20) If this knowledge is taken as the basis, the patients in the MB group would have a more severe course of the vasoplegia syndrome. The worse outcome of these patients who were treated with MB can therefore be explained by their serious illness compared to the control group non MB.

Not only the severity but also the duration of a vasoplegia influence the outcome. For example, Gomes et al. showed that a high mortality of 25 % is associated with a vasoplegic syndrome lasting > 36-48 h.(15) In our study with a mortality of 18%, MB was administered early after admission on ICU. After that norepinephrine decreases during the first 24 hours to a level below 0.8 $mg*h^{-1}$ (figure 2). Within the first hour after MB administration, MAP increased in treated patients while vasopressor requirement decreased (figure 3).

Some other studies demonstrate that MB approach to the treatment of severe vasoplegic syndrome resulted in an operative mortality rate of 21.2% compared to 44% previously reported. (19, 21) The reduction of mortality of CVS to around 20% is comparable to mortality of the severe CVS in the MB-group in our study. Mehaffey et al demonstrate that not only the administration but even the timing of the MB administration is important to produce a beneficial effect on mortality. In these study Mehaffey show that MB administration during operation reduced incidence of postoperative renal failure and operative mortality compared to administration at ICU (10.4 vs 28.6%) (13) Other studies show that a preoperative MB administration in patients with a high risk for vasoplegic syndrome during cardiac surgery was associated with no vasoplegic syndrome in the MB-treated group, whereas in the control-group the incidence was 26 %, and only in the control-group patients deceased.(18) It could be assumed that the therapeutic regime with MB as “on-top”-medication in high-risk patients is reasonable, and may account to some degree to a reduced total mortality. The therapy of vasoplegia syndrome is like therapy the sepis hit hard hit early. Therefore, early administration of MB is beneficial. (13, 19)

This study has a couple of limitations. First of all, there is no standard definition of the vasoplegia syndrome and therefore it differs between studies. For example, Ozal et al. defined it mainly through surrogate parameters as MAP < 50 mmHg, cardiac index > 2.5 $L*min^{-1}*m^{-2}$, right atrial pressure < 5 mmHg, left atrial pressure < 10 mmHg and reduced SVR < 800 $dyn*s^{-1}*cm^{-5}$ throughout i.v. infusion of norepinephrine (≥ 0.5 $\mu g*kg^{-1}*min^{-1}$).[15] In contrast, Weiner et al., defined it through a high dependency of catecholamines, here norepinephrine > 0.2 $\mu g*kg^{-1}min^{-1}$ and vasopressin > 2 $I.E.*h^{-1}$. (22) Therefore, a comparison of the results of each study has to be done carefully. In our study, we have a mixture of both: at the time of MB administration vasoplegic patients showed a MAP > 60 mmHg, norepinephrine of 1.2 +/- 0.6 $mg*h^{-1}$, and a SVR > 800 $dyn*s^{-1}*cm^{-5}$. While our norepinephrine dosing correlates with those

defined in the other studies, the MAPs and SVRs in the study at hand were higher than in other studies. (23) This may be due to a fast and close therapeutic response to a blood pressure drop. (14) Apparently, in our study there is a markedly ramping of norepinephrine in the first hours after admission (exaltation of 0.1 $mg*h^{-1}$ in at least 3 consecutive steps), which – in our view – characterises very unique the clinical catecholamine refractory vasoplegia situation leading to the MB administration. An additional dosage recalculation into common $\mu g*kg^{-1}*min^{-1}$ didn't not effect proposition from our clinically practiced dosage in $mg*h^{-1}$.

Second, one primary intention was to find a comparable non-MB-group (without MB administration) serving as control group. However, the retrospective analysis clarified that the non-MB-group is not a real control. Tables 1 and 2 show that the patients in the MB-group had a higher ASA-Class, had more urgent operations, showed more cardiac insufficiency, had a higher norepinephrine dose before and after the operation, had a longer CPB and ischemia time, and had an elevated need for mechanical cardiac support. Furthermore, as we pointed out, it seems that the Non-MB-group was probably not vasoplegic. Therefore, it is not surprising that morbidity and mortality in the MB-group was higher than in the Non-MB-group.

Conclusions

Vasoplegic patients had a significant severe systemic disease accompanied with marked operative stress and a high requirement of catecholamines. Additive administration of MB to standard therapy during the first hours after admission on the ICU was accompanied by an increase in blood pressure followed by a decrease vasopressor requirement. An early administration of MB (during operation) in vasoplegia syndrome may be more effective. Further prospective and randomized studies are necessary.

Declarations

Ethics Approval and consent to participate

The study "Additional use of methylene blue has a positive effect on vasoplegic syndrome after cardiac surgery was approved" by the ethics committee of the University of Regensburg before the start of data collection. The study "Additional use of methylene blue has a positive effect on vasoplegic syndrome after cardiac surgery was approved" is carried out under the ethics committee reference number "AZ 15 101-0046".

Consent for Publication

Not applicable.

Availability of supporting data.

Not applicable.

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Authors' contributions.

Walter Petermichl, York A. Zausig and Bernhard M. Graf conceived of the presented idea. Walter Petermichl, Michael Gruber, Ina Schoeller and Kwahle Allouch developed the theory and performed the computations. Walter Petermichl wrote the manuscript with support from York A. Zausig and Michael Gruber. York A. Zausig supervised the project. All authors discussed the results and contributed to the final manuscript.

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Competing interest statement:

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Submission declaration:

The authors declare that they agree with and are responsible for the data presented in this study. This manuscript has not been published and is not under consideration for publication elsewhere.

Abbreviations

CI	cardiac index
CPB	cardiopulmonary bypass
CVS	cardiac vasoplegia syndrome
e.g.	“exempli gratia” means for example
ICU	intensive care unit
h	hour
L/min/m2	liter per minute per square meter
MAP	mean arterial pressure
MB	methylene blue
mmHg	millimeter quicksilver
mg	milligram
mg*h-1	milligram per hour
mg*kg-1	milligram per kilogram
PICCO	pulse contour cardiac output
PAC	Swan-Ganz-catheter
QM	quality management
ScvO2	central venous saturation
SD	standard deviation
SEM	standard error of mean
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index

References

1. Hosseinian L, Weiner M, Levin MA, Fischer GW. Methylene Blue: Magic Bullet for Vasoplegia? Anesth Analg 2016; 122(1):194–201.
2. Omar S, Zedan A, Nugent K. Cardiac vasoplegia syndrome: pathophysiology, risk factors and treatment. Am J Med Sci 2015; 349(1):80–8.

3. Fischer GW, Levin MA. Vasoplegia during cardiac surgery: current concepts and management. Semin Thorac Cardiovasc Surg 2010; 22(2):140–4.
4. van Vessem ME, Palmen M, Couperus LE, Mertens B, Berendsen RR, Tops LF et al. Incidence and predictors of vasoplegia after heart failure surgery. Eur J Cardiothorac Surg 2017; 51(3):532–8.
5. Gamper G, Havel C, Arrich J, Losert H, Pace NL, Müllner M et al. Vasopressors for hypotensive shock. Cochrane Database Syst Rev 2016; 2:CD003709.
6. Hariyanto H, Yahya CQ, Widiastuti M, Wibowo P, Tampubolon OE. Fluids and sepsis: changing the paradigm of fluid therapy: a case report. J Med Case Rep 2017; 11(1):30.
7. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, Rhodes A, Landoni G, Osawa EA et al. Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery: The VANCS Randomized Controlled Trial. Anesthesiology 2017; 126(1):85–93.
8. Pasin L, Umbrello M, Greco T, Zambon M, Pappalardo F, Crivellari M et al. Methylene blue as a vasopressor: a meta-analysis of randomised trials. Crit Care Resusc 2013; 15(1):42–8.
9. Rudiger A, Singer M. Decatecholaminisation during sepsis. Crit Care 2016; 20(1):309.
10. Belletti A, Benedetto U, Biondi-Zoccai G, Leggieri C, Silvani P, Angelini GD et al. The effect of vasoactive drugs on mortality in patients with severe sepsis and septic shock. A network meta-analysis of randomized trials. J Crit Care 2017; 37:91–8.
11. Byrne JG, Leacche M, Paul S, Mihaljevic T, Rawn JD, Shernan SK et al. Risk factors and outcomes for 'vasoplegia syndrome' following cardiac transplantation. Eur J Cardiothorac Surg 2004; 25(3):327–32.
12. Evora PRB, Alves Junior L, Ferreira CA, Menardi AC, Bassetto S, Rodrigues AJ et al. Twenty years of vasoplegic syndrome treatment in heart surgery. Methylene blue revised. Rev Bras Cir Cardiovasc 2015; 30(1):84–92.
13. Mehaffey JH, Johnston LE, Hawkins RB, Charles EJ, Yarboro L, Kern JA et al. Methylene Blue for Vasoplegic Syndrome After Cardiac Operation: Early Administration Improves Survival. Ann Thorac Surg 2017; 104(1):36–41.
14. Andrade JCS. Methylene blue administration in the treatment of the vasoplegic syndrome after cardiac surgery Utilização do azul de metileno no tratamento da síndrome vasoplégica após cirurgia cardíaca. Rev Bras Cir Cardivasc:107–14.
15. Gomes WJ, Carvalho AC, Palma JH, Teles CA, Branco JN, Silas MG et al. Vasoplegic syndrome after open heart surgery. J Cardiovasc Surg (Torino) 1998; 39(5):619–23.
16. Manghelli J, Brown L, Tadros HB, Munfakh NA. A Reminder of Methylene Blue's Effectiveness in Treating Vasoplegic Syndrome after On-Pump Cardiac Surgery. Tex Heart Inst J 2015; 42(5):491–4.
17. Peter C, Hongwan D, Küpfer A, Lauterburg BH. Pharmacokinetics and organ distribution of intravenous and oral methylene blue. Eur J Clin Pharmacol 2000; 56(3):247–50.
18. Ozal E, Kuralay E, Yildirim V, Kilic S, Bolcal C, Kücükarslan N et al. Preoperative methylene blue administration in patients at high risk for vasoplegic syndrome during cardiac surgery. Ann Thorac

Surg 2005; 79(5):1615–9.
19. Levin MA, Lin H-M, Castillo JG, Adams DH, Reich DL, Fischer GW. Early on-cardiopulmonary bypass hypotension and other factors associated with vasoplegic syndrome. Circulation 2009; 120(17):1664–71.
20. Levin RL, Degrange MA, Bruno GF, Del Mazo CD, Taborda DJ, Griotti JJ et al. Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. Ann Thorac Surg 2004; 77(2):496–9.
21. Dagenais F, Mathieu P. Rescue therapy with methylene blue in systemic inflammatory response syndrome after cardiac surgery. Can J Cardiol 2003; 19(2):167–9.
22. Weiner MM, Lin H-M, Danforth D, Rao S, Hosseinian L, Fischer GW. Methylene blue is associated with poor outcomes in vasoplegic shock. J Cardiothorac Vasc Anesth 2013; 27(6):1233–8.
23. Leyh RG, Kofidis T, Strüber M, Fischer S, Knobloch K, Wachsmann B et al. Methylene blue: the drug of choice for catecholamine-refractory vasoplegia after cardiopulmonary bypass? J Thorac Cardiovasc Surg 2003; 125(6):1426–31.

Tables

Table 1: criteria of vasoplegic syndrome

Perioperative vasoplegic syndrome
· Vasoplegic syndrome ≤ 24 h after arrival on ICU
· Mean arterial pressure (MAP) ≤ 60 mmHg over 2 h or
· MAP 60 mmHg & concurrent increase of norepinephrine
· Non ventricular dysfunction
· Non Hypovolaemia
· Cardiac index > 2.5 L/min/m² (if available)

MAP: mean arterial pressure; ICU: Intensive care unit

Table 2: Determination criteria for methylene blue (MB) group and non-methylene blue (non-MB) group

MB-group	Non-MB-group
· Single MB administration on ICU	· No MB administration on ICU
· MB administration on ICU ≤ 24 h after arrival	· Norepinephrine at least once ≥ 0.8 mg/h on ICU ≤ 24 h

MB: Methylene blue; ICU: Intensive care unit

Table 3: Demographic data

		MB-group n = 311	Non-MB-group n =202	p-value
Age [yrs]		65.7 ± 12.0	65.8 ± 11.4	n.s.
Male gender		243 [78]	163 [81]	n.s.
BMI [kg/m²]		31.7 ± 57.8	27.7 ± 6.5	n.s.
ASA	1-2	5 [2]	8 [4]	0.001
	3	136 [46]	122 [60]	
	4	138 [47]	67 [33]	
	5	12 [4]	1 [1]	
Nicotine abuses		94 [32]	71 [35]	n.s.
Coronary heart disease		191 [65]	144 [71]	n.s.
with stent		22 [7]	11 [5]	n.s.
Angina pectoris		67 [23]	79 [39]	0.001
Former myocardial infarction		81 [27]	35 [17]	0.009
NYHA	1	1 [0.3]	0	0.014
	2	15 [5]	7 [4]	
	3	162 [56]	143 [71]	
	4	106 [36]	47 [23]	
Left ventricular ejectionsfraction [%]		47.5 ± 18.8	45.8 ± 17.	n.s.
Pacemaker		23 [8]	13 [6]	n.s.
Hypertension		203 [69]	147 [75]	n.s.
peripheral arterial disease		47 [16]	36 [18]	n.s.
with stent		25 [8]	17 [8]	n.s.
Pulmonary hypertension		30 [10]	16 [8]	n.s.
Renal failure	GFR >89 ml/min	35 [11]	42 [21]	0.004
	GFR 60-89	64 [21]	58 [29]	
	GFR 30-59	59 [19]	38 [19]	
	GFR <30	29 [9]	9 [5]	
	Dialysis	1 [0.3]	0	
Cerebrovascular events		20 [7]	6 [3]	n.s.

Allergy	54 [18]	39 [19]	n.s.

BM: Body Mass Index; ASA: American Society of Anesthesiologists;NYHA: New York Heart Association GFR: glomerular filtrationrate; All data ar presented as number [%] or mean +/- SD. n.s.: not significant.

Table 4: Intraoperative Data

		MB-group n = 311	Non-MB-group n= 202	p Value
Emergency operation		137 [44]	60 [30]	0.002
Surgery type	CABG	135 [46]	111 [55]	n.s.
	Valve	54 [18]	29 [14]	
	CABG+VALVE	47 [17]	19 [9]	
	Aorta	5 [2]	1 [1]	
	VAD	10 [3]	1 [1]	n.s.
	Others	53 [18]	42 [21]	
with CBP		273 [88]	172 [85]	n.s.
Former non-cardiac & cardiac surgery		98 [32]	32[16]	0.001
CBP time [min]		119 ± 68	102 ± 62	0.006
Cross-clamp time [min]		77 ± 49	64 ± 43	0.003
Hypothermia		24 [8]	8 [4]	n.s.
CPR		51 [17]	26 [13]	n.s.
ECMO		20 [7]	3 [2]	0.022
ECMO [min]		39 ± 51	0	n.s.
IABP		30 [10]	7 [4]	0.035
MAP [mmHg]	Pre induction	87 ± 18	90 ± 15	n.s.
	After induction	78 ± 13	80 ± 11	n.s.
	Postoperative in OR	68 ± 15	69 ± 16	n.s.
Heart rate [1/min]	Pre induction	79 ± 21	78 ± 17	n.s.
	After induction Postoperative in OR	74 ± 21	71 ± 17	n.s.
		98 ± 20	96 ± 19	n.s.
Diuresis [ml]		812 ± 608	881 ± 627	n.s.
Norepinephrine [mg/h]	after CBP	0.49 ± 0.8	0.33 ± 0.4	0.004
	before CPB	0.57 ± 0.5	0.72 ± 0.9	0.032
Dobutamine [mg/h]	after CBP	4.8 ± 7.5	3.6 ± 6.3	n.s.
	before CPB	6.9 ± 9.3	8.3 ± 9.1	n.s.

Epinephrine [mg/h]	after CBP	0.11 ± 0.5	0.03 ± 0.2	0.007
	before CPB	0.31 ± 0.3	0.21 ± 0.3	0.001
Vasopressin [I.E./h]	after CBP	0.03 ± 0.5	0.01 ± 0.1	n.s.
	before CPB	0.31 ± 2.1	0.07 ± 0.4	n.s.
Hydrocortison	Bolus [mg]	73 ± 44	96 ± 15	n.s.
	Continues [mg/h]	13 ± 21	65 ± 60	n.s.
Blood products	Erythrocytes	2.2 ± 2.6	1.4 ± 2.1	0.001
	Fresh frozen plasma	2.1 ± 3.9	1.0 ± 2.5	0.001
	Thrombocytes Cellsaver-blood [ml]	1.0 ± 1.4	0.7 ± 1.0	0.002
	PPSB [I.E.]	389 ± 742	289 ± 443	n.s.
	Minirin [µg]	1088 ± 1867	873 ± 1547	n.s.
		9.7 ± 36.6	5.9 ± 11.3	n.s.
Fluids [ml]	Crystalloids	1286 ± 959	1886 ± 1955	0.001
	Colloids	449 ± 458	386 ± 445	n.s.

CAPG: coronary artery bypass grafting; VAD: Ventric ular assist device; CPB: cardiopulmonary bypass; CPR: Cardiopulmonal resuscitation; ECMO: extracorporal membran oxygenation; CPB: cardiopulmonary bypass; IABP: intra aortic balloon pump; MAP: mean arterial pressure;OR: operation room; All data are presented as number [%] or mean +/- SD. n.s.: not significant.

Table 5: Additional vasopressor administation

	MB-group n =	Non-MB-group n =	p Value
Epinephrine	254	115	0.001
Vassopressin	40	6	0.001
Hydrocortisone	244	34	0.001

Additional vasopressor administration in MB and non-MB-group at time point 0.

Table 6: Outcome data

	MB-group n = 311	Non-MB-group n = 202	p Value
30-day-Mortality	57 [18]	10 [5]	0.001
Stay on			
ICU [d]	26 ± 29	16 ± 16	0.001
IMC [d]	15 ± 18	6 ± 8	0.001
GW [d]	6 ± 19	4 ± 7	n.s.
Renal failure	130 [42]	30 [15]	0.001
Renal replacement therapy	149 [48]	34 [17]	0.001
Respiratory failure	81 [27]	6 [3]	0.001
Liver failure	22 [7]	4 [2]	0.007
First defecation [d]	3.6 ± 2.2	2.3 ± 1.8	0.001
Cerebrovascular events	44 [15]	10 [5]	0.001
Multi organ failure	40 [13]	8 [4]	0.001
Sepsis	26 [9]	9 [45]	n.s.
TISS10	172	163	
ADM	23.2 ± 8.7	20.1 ± 6.9	0.001
MAXIMUM	30.2 ± 6.8	24.2 ± 6.6	0.001
SAPSII	140	163	
ADM	24.19 ± 13.62	21.91 ± 12.13	n.s.
MAXIMUM	35.52 ± 17.85	46.18 ± 252.34	n.s.
Ventilation time [h]	246 ± 900	60 ± 101	0.001
Vasopressor-free days on ICU [d]	12.3 ± 26.8	11.0 ± 12.4	n.s.

ICU: intensive care unit; IMC: intermediate care unit; GW: general ward; TISS:Therapeutic intervention scoring system; SAPSII: Simplified acute physiology score. All data are presented as number [%] or mean +/- SD. n.s.: not significant.

Figures

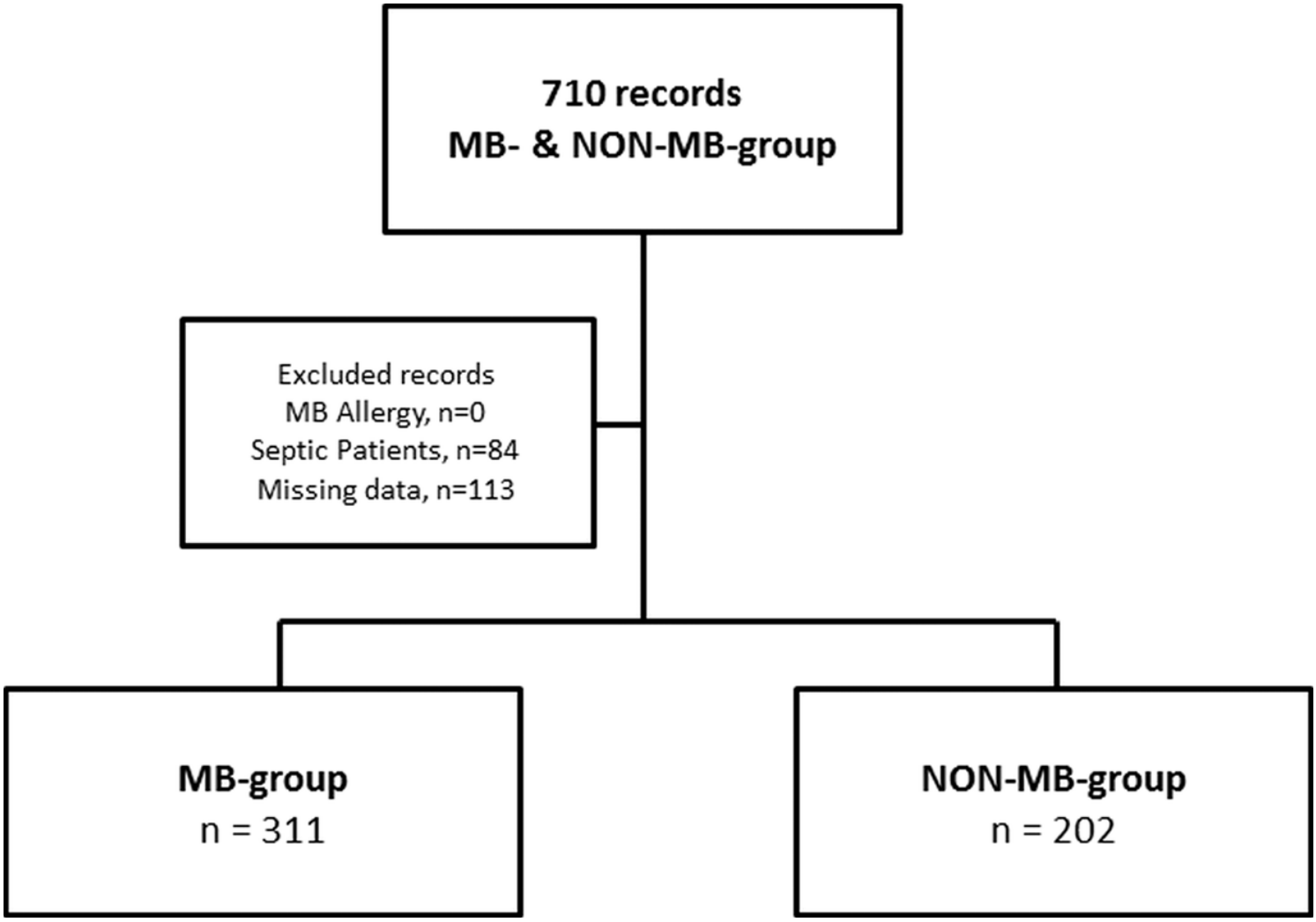

Figure 1

Trail profile of the study. Trial profile of the study showing both groups at the end: MB-group and Non-MB-group.

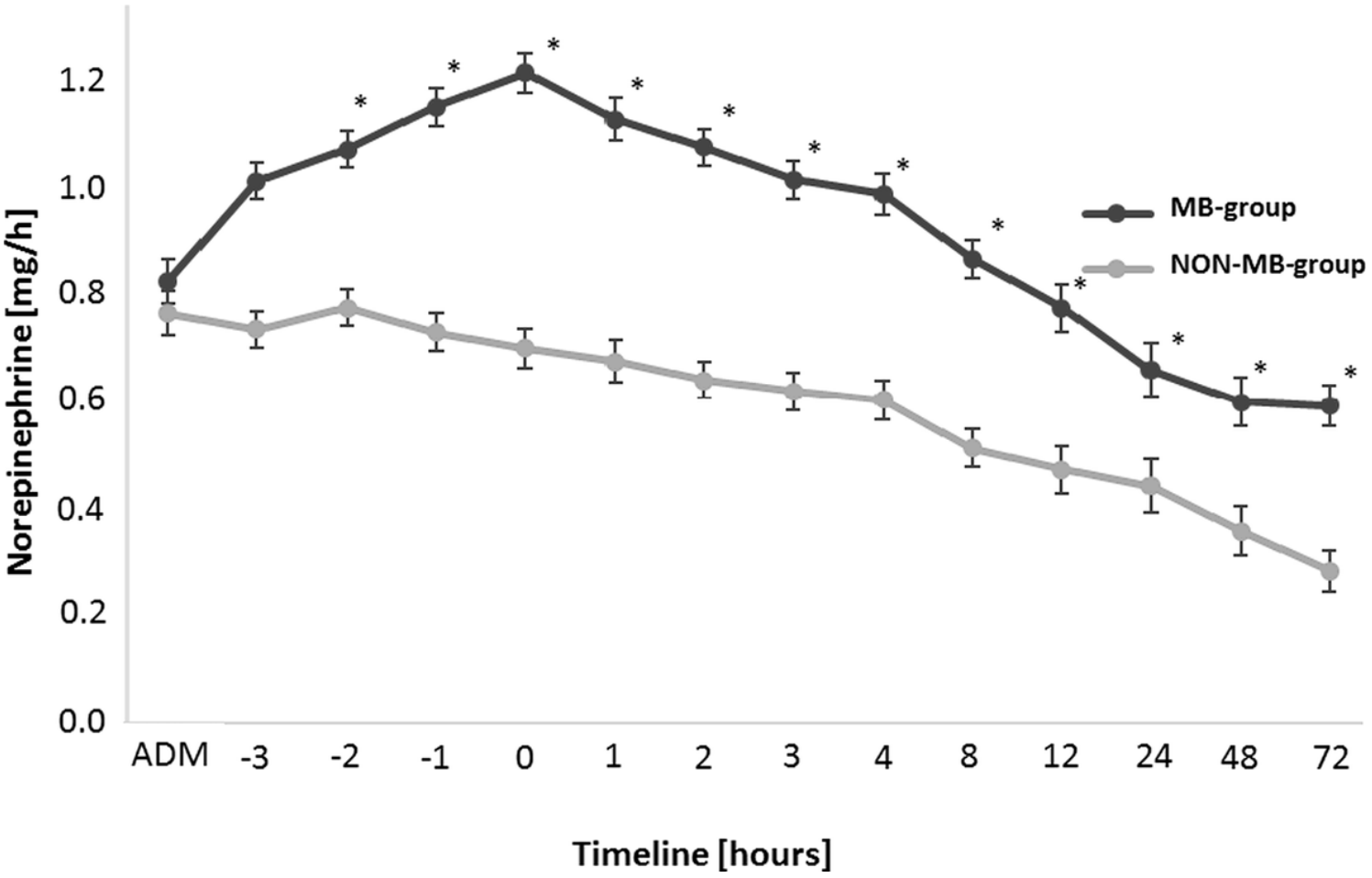

Figure 2

Timeline of norepinepgrin dose in MB and non-MB-group. Norepinephrine dose throughout the anaylsis time for MB-group and Non-MB-group. ADM: Admission on ICU; 0: administration of MB. All data are expressed as mean +/- SEM. *p < 0.05

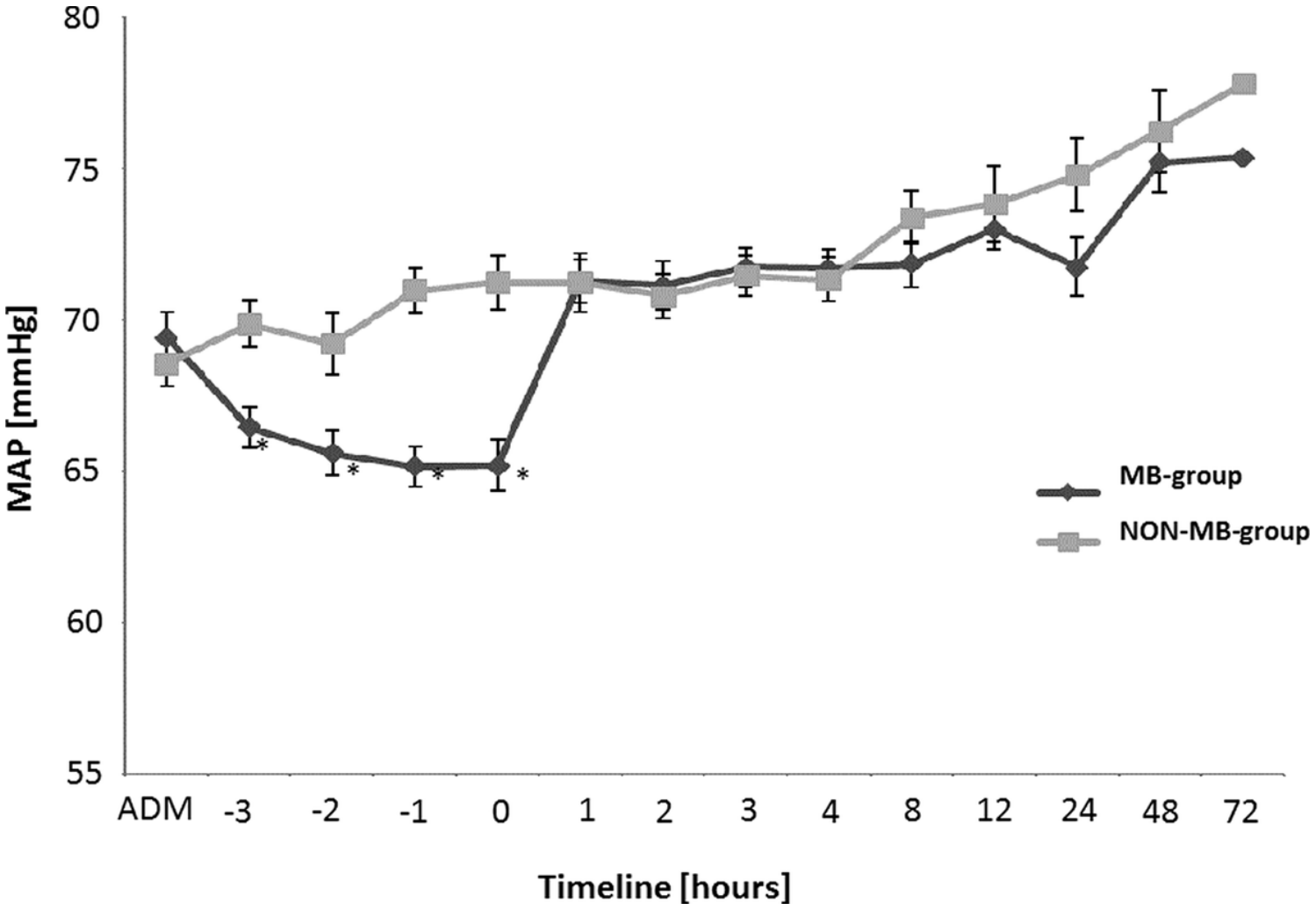

Figure 3

Timeline of mean arterial pressure in MB and non-MB-group. Mean arterial blood pressure (MAP) throughout the anaylsis for MB-group and Non-MB-group. ADM: Admission on ICU; 0: administration of MB. All data are expressed as mean +/- SEM. *p < 0.05