Impact of Low Dose Maltodextrin/Citrulline Loading on the Severity and Duration of Stress Induced Hyperglycemia in Cardiac Surgery

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Abstract

INTRODUCTION: Postoperative stress induced insulin resistance, and the resulting glycemic variability, is clearly associated with complication rates in cardiac surgery. Despite this, there is a paucity of data regarding the duration of stress induced hyperglycemia in cardiac surgery as well as the impact of specific strategies for carbohydrate loading in cardiac surgery patients. Prior work in colorectal and bariatric surgery has shown a significant reduction in glycemic events with the use of a low dose maltodextrin and citrulline loading strategy, but there is no data that the commonly recommended 50 gram supplements provides any impact on stress induced postoperative hyperglycemia. The aim of this study was to compare standard of care (SOC group) versus a three dose, 25 gram dose carbohydrate loading strategy (CL group) on the duration and severity of postoperative glycemic variability in both diabetic and non-diabetic cardiac surgery patients.

METHODS: We compared CABG/AVR/MVR retrospective patients who received standard of care (SOC) to a prospective set of patients who were carbohydrate loaded (CL) with 3 preoperative doses of 25g maltodextrin/3g citrulline (G.E.D.™, SOF Health, LLC).

RESULTS: 152 patients total were included (SOC n=80, CL n= 72). 66 patients were diabetic. In both non-diabetic and diabetic patient populations, there was a statistically significant reduction in glycemic variability in G.E.D. groups for non- diabetics (27% reduction) and diabetics (40% reduction). The glycemic variability on POD 2 was not statistically different between treatment groups in non-diabetics (G.E.D. 25.2% vs SOC 24.7%) but approached significance in diabetics (G.E.D. 24.7% vs SOC 32.9%e).

CONCLUSION: These are the first data demonstrating the reduction in post operative stress induced glycemic variability in cardiac surgery using a low dose carbohydrate loading regimen which includes the amino acid citrulline. The impact of surgical stress on glycemic variability appears to resolve by POD#2 in non-diabetics but may persist longer in diabetic patients. These data represent the first information regarding the benefits of a specific strategy for carbohydrate loading to reduces the stress induced component of post operative hyperglycemia in cardiac surgery.

Introduction

Enhanced Recovery Protocols (ERPs) have only recently been actively investigated and their adoption in cardiothoracic surgery (CTS) has been relatively slow.[1–4] The negative impact of post-operative stress induced post-operative hyperglycemic events is well-documented. [5–6]. A recent meta-analysis highlighted the challenges of assessing the role of carbohydrate loading in cardiac surgery, primarily due to the lack of standardized supplement composition and dosing, as well as inconsistent assessment of hyperglycemia event rates.[7] There is a clear need for improved assessment on the optimal carbohydrate loading strategy in cardiac surgery. The first assessment of an implemented ERP in cardiac surgery utilized a single preoperative dose of a carbohydrate drink and failed to demonstrate any improvement in perioperative hyperglycemia rates, indicating that further studies into preoperative carbohydrate loading are needed.[8]

Although carbohydrate (CHO) loading in the pre-operative setting has been shown to increase post-operative insulin sensitivity, the effectiveness on reducing postoperative hyperglycemia to reduce complications has been poorly assessed.[9,10] Several large population studies have demonstrated higher incidence of complications associated with post-operative insulin resistance and increased episodes of hyperglycemia in both diabetic and non-diabetic patients, including infection, mortality, and overall morbidity.[11,12] Rather than a single value, maximal glucose or mean glucose level, these data suggest a threshold effect based on spikes in glucose > 140 mg/dl in non-diabetics, as well as increased risk with increasing frequency of these events. [7] Previously described protocols have implemented formulations which provide 50 grams of maltodextrin per drink with varying intervals and total amounts, however there has been a lack of consistent reporting on the incidence and magnitude of hyperglycemic events. Without established protocols for administering and monitoring glucose levels in the perioperative period, there is no agreement regarding the optimal supplement, treatment regimen, and efficacy of carbohydrate loading in cardiac surgery. This inconsistency is not limited to cardiac surgery, as similar confusion exists in non-cardiac studies of carbohydrate loading. Gianotti et al assessed ad lib consumption of a supplement containing 100 grams of maltodextrin and a modest amount of fructose over approximately 18 hours preoperatively.[13] The study did not report the frequency of hyperglycemic events between groups and this omission made it impossible to understand if there was a difference in glycemic variability between groups.[13]. Conversely, experience with a 3 dose regimen of a 25 gram maltodextrin, fructose-free, 3 gram citrulline supplement in bariatric and colorectal surgery has demonstrated significant reductions in hyperglycemic event rates.[14,15]. No similar data analysis exists for any of the 50 gram maltodextrin supplements.

The purpose of this study was to perform the first pilot/historical control study assessment of a strategy of reduced dose maltodextrin/citrulline administration on the rate of post-operative hyperglycemia in both diabetic and non-diabetic CABG patients versus the standard of care without a specific carbohydrate loading process.

Methods

This cardiac surgery quality improvement pilot project was performed for diabetic and non-diabetic patients undergoing coronary artery bypass graft (CABG), aortic valve repair (AVR), or mitral valve repair (MVR). Patients older than 18 years of age undergoing CABG, AVR, or MVR at a single institution were included in the study. The retrospective cohort serving as the historical control group received the standard of care (SOC) from January 2019 to May 2019 which did not include a standard carbohydrate loading supplement. The experimental carbohydrate-loading group (GED) were patients undergoing CABG, AVR, or MVR from June 2019 to September 2019. The conduct of the ERP care plan during preoperative preparation, intraoperative management and post-operative care plans were at the discretion of the treating surgical team however the care plans were similar for both groups other than the carbohydrate loading process in the study group. Importantly, both groups had the same glycemic management protocol for both testing frequency and insulin administration.

The historical SOC group was made nil per os (NPO) at midnight prior to the surgical procedure. The experimental group (GED) received 3 pre-operative doses of a proprietary blend – Glycemic Endothelial Drink (G.E.D.™, SOF Health, LLC) consisting of 25g maltodextrin/3g citrulline in 10oz of water for each dose. The GED group consumed 10oz of G.E.D. at 7pm and 10pm the evening before surgery and a final dose 2–4 hours prior to surgery. They did not consume any other carbohydrates during this interval but were allowed non-carbohydrate clear liquids ad libitum.

Data collected included surgical procedure type, diabetes status, most recent Hemoglobin A1c (A1c), pre-operative point-of-care glucose, glucose levels for each hospital day, and length of stay. Demographic information, diabetes status, A1c, and glucose measurements were obtained through electronic medical record review. The surgical procedure performed was obtained from the surgeon's dictated operative report. Post-operative days were defined as each subsequent day of inpatient hospital stay after the index day of surgery. The primary outcome of interest was the rate of glycemic variability. High glucose events were defined by incidence of serum glucose > 140 mg/dl for non-diabetic patients or > 180 mg/dl for diabetic patients. Glycemic variability was defined by the ratio of the number of hyperglycemic episodes to the number of post-operative glucose measurements. All descriptive analyses are presented as mean ± standard deviation as appropriate. Statistical analysis consisted of Fisher's Exact test. All tests were two sided and $p < 0.05$ was considered statistically significant.

Results

A total of 152 patients were included in the study. The SOC group included 80 patients and the GED group included 72. 86 patients were non-diabetic (SOC 49; GED 37); 66 patients were diabetic (SOC 31; GED 35). There was no significant difference in age, gender, chronic obstructive pulmonary disease (COPD) diagnosis, pre-operative albumin measurement, tobacco use, or distribution of procedure type (CABG/AVR/MVR) between the groups. For diabetic patients, the A1C was significantly higher in the GED group compared to the SOC group (Table 1).

Table 1
Patient Demographic Data

	SOC	**GED**	***p***
Total Patients	n = 80	n = 72	
Age – mean(SD)	64.11(9.13)	68.56(8.73)	0.635
Male Gender – n(%)	62(77.5%)	52(72.85%)	0.195
Comorbidities			
HgbA1c – mean(SD)	6.28(0.96)	6.74(1.89)	0.001
COPD – n(%)	16(18.75%)	17(24.28%)	0.479
Pre-Op Albumin – mean	3.99(0.36)	4.02(0.38)	0.484
Tobacco – n(%)	52(65.82%)	42(58.57%)	0.069

There was a statistically significant reduction in glycemic event rates for GED treated patients on POD 1 in both non-diabetic and diabetic patient populations (27% reduction in non-diabetics; 40% reduction in diabetics) (Table 2). On POD 1, diabetic patients experienced significantly fewer glycemic events in both treatment groups, primarily due to the differences in glucose level definitions (140 mg/dl in non-diabetic vs 180 mg/dl in diabetic patients) and the fact that protocol driven interventions used 180 mg/dl as the threshold for intervention. (See Table 2).

Table 2
POD#1 Glycemic Event Rates for Nondiabetic and Diabetic Patients

	Treatment	Hyperglycemic Events	Glucose Measurements	% Event Rate	*p value*	*P value*
Non-Diabetic (N-DM)						
	SOC	153	453	33.7%	N-DM SOC v N-DM GED 0.0131	N-DM SOC v DM SOC 0.0001
	GED	104	441	24.5%		
Diabetic (DM)						
	SOC	48	444	10.8%	SOC v GED 0.02	N-DM GED v DM GED 0.0001
	GED	34	513	6.6%		

During the 2-day assessment of hyperglycemic event rates, non-diabetic GED patients had no significant differences in glycemic event rates (POD 1–24.5% vs POD 2–24.7%), whereas diabetic GED patients demonstrated a numerical decrease in hyperglycemic events from POD 1 to POD 2 which approached statistical significance. (SOC – 33.7% vs GED – 25.2%; $p < 0.075$; Fisher's Exact Test).(See Table 3) On POD 2 diabetic patients in both groups experienced significantly higher glycemic event rates compared to POD 1 (SOC – 10.8% vs 32.9%; GED – 6.6% vs 24.7%; $p < 0.0001$; Fisher's Exact Test).

Table 3
POD2 Glycemic Event Rates for Nondiabetic and Diabetic Patients

	Treatment	Hyperglycemic Events	Glucose Measurements	% Event Rate	*p value*
Non-diabetic (N-DM)					
	SOC	60	238	25.2%	N-DM SOC v N-DM GED NS
	GED	45	182	24.7%	N-DM SOC v DM SOC P = .0002
Diabetic (DM)					
	SOC	56	170	32.9%	DM SOC v DM GED p = 0.074
	GED	59	239	24.7%	N-DM GED v DM GED NS

Discussion

We performed a novel quality improvement study assessing a structured, lower dose maltodextrin, citrulline preoperative carbohydrate loading regimen in cardiac surgery. We found that stress induced insulin resistance leading to postoperative hyperglycemia to be impacted by the type of carbohydrate loading performed. The regimen implemented significantly reduced hyperglycemia on POD 1 for both non-diabetic (27%) and Type 2 diabetic patients 40%, suggesting that both populations are as risk for stress induced hyperglycemia. For non-diabetics we found that GED inhibits the risk for stress induced hyperglycemia as event rates remained similar on POD 1 and POD 2.

The trajectory of hyperglycemic event rates was different for the diabetic patients, as both GED and SOC groups experienced an approximately 3-fold increase in glycemic event rates from POD 1 to POD 2. GED did produce a numerical decrease in event rate approaching significance, suggesting an impact on glycemic variability from surgical stress. The data suggest that although hyperglycemia remains a concern for non-diabetic patients, it stabilizes by POD 2, suggesting that the duration of stress induced insulin resistance is < 48 hours in non-diabetics.

It is well-established that postoperative hyperglycemia increases risk of complications in cardiac surgery. 30–40% of patients undergoing cardiac surgery are diabetic and at higher risk for glycemic variability and approximately 60% of patients without diabetes develop stress hyperglycemia in the postoperative period.[17,18] Perioperative hyperglycemia in diabetic and non-diabetic patients increases risk for wound infection, acute renal failure, duration of hospital stay, and perioperative mortality.[18] Hyperglycemia has been associated with impaired leukocyte function, decreased phagocytosis and chemotaxis, nuclear factor kB activation and production of inflammatory cytokines. It also suppresses formation of nitric oxide, impairs endothelium-dependent flow-mediated dilation, increases platelet activation, adhesion, and aggregation, and reduces plasma fibrinolytic activity.[19] Hyperglycemia in the initial phases of postoperative care is increased in both cardiac and non-cardiac surgical patients. Particularly concerning is that the rate of hyperglycemia appears similar in frequency and severity for both diabetic and nondiabetic patients.[17,20] In a non-cardiac surgery population of 40,000 patients, non-diabetic patients demonstrated a dose-response relationship between the level of hyperglycemia and risk of adverse effects, with higher rates at higher glucose levels.[16] The adverse effects found in this population include myocardial infarction, stroke, transient ischemic attack, atrial arrhythmia requiring treatment, readmission to ICU, infectious complications (surgical site infection, pneumonia, urinary tract infection, clostridium difficile), renal insufficiency.[16]

Maltodextrin is the recommended complex carbohydrate in enhanced recovery programs, however the dosing regimens and timing have been poorly controlled and studied, especially with respect to the incidence of postoperative hyperglycemia.[3,21] This study provides a unique and initial assessment of the combination of low dose maltodextrin coupled with citrulline using a multidose regimen. Use of this supplement has demonstrated significant reductions in glycemic variation in gastric bypass (versus grape juice) and in colorectal surgery (versus Gatorade®), which is why it was selected for this study.[14,15] Euglycemic clamp studies have demonstrated improved perioperative insulin sensitivity and reduced post-operative gluconeogenesis as a result of the administration of preoperative maltodextrin.[22] The delivery of 40 + grams of maltodextrin per dose can result in treatment related hyperglycemia, an effect is rarely assessed in clinical studies.[23] A limitation of non-maltodextrin containing products composed of simple sugars, especially fructose, (i.e. fruit juices or sports drinks) is the delivery of a potentially excessive glycemic index load, resulting in rapid and early glucose and insulin spikes followed by compensatory glucagon secretion. There is no data demonstrating improvd insulin sensitivity in these patients.[24] Therefore, there appears to be need for a structured assessment of the optimal dosing for carbohydrate loading and precise definitions for the impact on postoperative hyperglycemia.

The provision of 3 grams of L-Citrulline in each dose of the supplement used in this study directly inhibits hepatic gluconeogenesis, which may enhance the clinical benefits demonstrated with low dose maltodextrin/citrulline formation.[25] The surgical stress response also induces a decrease in arginine(Arg) bioavailability and an increase in asymmetric dimethyl arginine, a natural inhibitor of arginine associated nitric oxide function.[26] The net result is a lowering of the Arg/ADMA(asymmetric dimethylarginine) in the early post-operative period, associated with increased surgical site infection rates, cardiovascular complications, and acute kidney injury. A reduced Arg/ADMA ratio has been demonstrated to correlate with poor outcomes in a variety of settings with physiologic stress, including both cardiac and non-cardiac surgery, acute coronary syndrome, stroke, and sepsis.[27,28] L-Citrulline has recently and consistently been demonstrated to safely and effectively restore systemic arginine levels and reduce ADMA in a variety of clinical scenarios.[29] Enteral arginine administration and the surgical stress response both increase constitutively active hepatic arginase, resulting in the destruction of the majority of administered arginine. Conversely citrulline is nearly 100% absorbed within the GI tract and converted completely to arginine in the kidney for systemic circulation.[29–31]

Our pilot study has several limitations that warrant further investigation. First, the use of a historical control group risks the potential for unrecognized processes of care which were implemented over time and may have impacted glycemic outcomes. Secondly, we were not able to capture granular data on specific patient-level thresholds of glucose and the impact on intensity of insulin therapy administered for either group. The impact of the carbohydrate loading formulation on both the frequency and the intensity of insulin rescue is important information for the perioperative team and bears further study. The study was not powered to allow for either sub-group analyses or an assessment of the relative degrees of glycemic variability and postoperative outcomes.

Conclusion

This is the first cardiac surgery study assessing the role of a specific preoperative carbohydrate loading regimen on occurrences of postoperative hyperglycemia. The regimen used for the administration of 3 doses of a 25 gram maltodextrin/3 gram citrulline supplement is the first to demonstrate a significant reduction in glycemic variability in both diabetic and non-diabetic populations. The benefit was durable over the first two postoperative days in non-diabetic patients, while diabetic patients experienced a potential delay in the manifestation of stress induced hyperglycemia. Interestingly, both non-diabetic and diabetic patients regardless of treatment experienced approximately 25% hyperglycemia event rates on POD 2, suggesting additional mechanisms for postoperative hyperglycemia beyond carbohydrate loading sensitive factors. These data support the concept that a specific carbohydrate loading regimen can minimize hyperglycemic events in cardiac surgery, potentially reducing postoperative complication rates and reducing the intensity of hyperglycemia treatment.

Declarations

Ethics approval/consent to participate: Ethics approval was waived as this project was a quality improvement project. All participants did consent as part of the presurgical discussion and operative consent process.

Consent for publication: All authors do consent to publication of this manuscript

Availability of data and materials: The datasets generated and analyzed in this study are included in this published article. Any further information may be obtained from the corresponding author on request.

Competing interests: N/A

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Authors’ Contributions: JE, JB, JJ, and SK contributed to writing the manuscript and compiling sources. JE and JB composed tables. JP and AD were principle investigators and oversaw the project as well as approved the manuscript.

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References

1. Gregory AJ, Grant MC, Manning MW, et al. Enhanced Recovery After Cardiac Surgery (ERAS Cardiac) Recommendations: An Important First Step—But There Is Much Work to Be Done. *J Cardiothorac Vasc Anesth*. 2020;34(1):39-47. doi:10.1053/j.jvca.2019.09.002
2. Williams JB, McConnell G, Allender JE, et al. One-year results from the first US-based enhanced recovery after cardiac surgery (ERAS Cardiac) program. *J Thorac Cardiovasc Surg*. 2019;157(5):1881-1888. doi:10.1016/j.jtcvs.2018.10.164
3. Kotfis K, Jamioł-Milc D, Skonieczna-żydecka K, Folwarski M, Stachowska E. The effect of preoperative carbohydrate loading on clinical and biochemical outcomes after cardiac `2020;12(10):1-21. doi:10.3390/nu12103105
4. Li M, Zhang J, Gan TJ, et al. Enhanced recovery after surgery pathway for patients undergoing cardiac surgery: A randomized clinical trial. *Eur J Cardio-thoracic Surg*. 2018;54(3):491-497. doi:10.1093/ejcts/ezy100
5. Carr JM, Sellke FW, Fey M, Doyle MJ, Krempin JA, de la Torre R, et al. Implementing tight glucose control after coronary artery bypass surgery. Ann Thorac Surg. 2005;80(3):902–9.
6. Ouattara A, Lecomte P, Le Manach Y, Landi M, Jacqueminet S, Platonov I, et al. Poor intraoperative blood glucose control is associated with a worsened hospital outcome after cardiac surgery in diabetic patients. Anesthesiology. 2005;103(4):687–94.
7. Omar, A.S., Salama, A., Allam, M. *et al.* Association of time in blood glucose range with outcomes following cardiac surgery. *BMC Anesthesiol* **15,** 14 (2015).
8. Williams JB, McConnell G, Allender JE, Woltz P, Kane K, Smith PK, Engelman DT, Bradford WT. One-year results from the first US-based enhanced recovery after cardiac surgery (ERAS Cardiac) program. J Thorac Cardiovasc Surg. 2019 May;157(5):1881-1888.
9. Nygren J, Soop M, Thorell A, Efendic S, Nair KS, Ljungqvist O. Preoperative oral carbohydrate administration reduces postoperative insulin resistance. *Clin Nutr*. 1998;17(2):65-71. doi:10.1016/S0261-5614(98)80307-5

10. Wang ZG, Wang Q, Wang WJ, Qin HL. Randomized clinical trial to compare the effects of preoperative oral carbohydrate versus placebo on insulin resistance after colorectal surgery. Br J Surg. 2010 Mar;97(3):317-27.
11. Li X, Zhou X, Wei J, Mo H, Lou H, Gong N, Zhang M. Effects of Glucose Variability on Short-Term Outcomes in Non-Diabetic Patients After Coronary Artery Bypass Grafting: A Retrospective Observational Study. Heart Lung Circ. 2019 Oct;28(10):1580-1586. doi: 10.1016/j.hlc.2018.08.006.
12. Clement KC, Suarez-Pierre A, Sebestyen K, Alejo D, DiNatale J, Whitman GJR, Matthew TL, Lawton JS. Increased Glucose Variability Is Associated With Major Adverse Events After Coronary Artery Bypass. Ann Thorac Surg. 2019 Nov;108(5):1307-1313.
13. Gianotti L, Biffi R, Sandini M, et al. Preoperative Oral Carbohydrate Load Versus Placebo in Major Elective Abdominal Surgery (PROCY). In: *Annals of Surgery*. Vol 267. Lippincott Williams and Wilkins; 2018:623-630.
14. Kielhorn BA, Senagore AJ, Asgeirsson T. The benefits of a low dose complex carbohydrate/citrulline electrolyte solution for preoperative carbohydrate loading: Focus on glycemic variability. *Am J Surg*. 2018;
15. Knight P, Chou J, Dusseljee M, Verseman S, Elian A. Effective reduction in stress induced postoperative hyperglycemia in bariatric surgery by better carb loading. *Am J Surg*. 2020;219(3):396-398.
16. Kotagal M, Symons RG, Hirsch IB, Umpierrez GE, Dellinger EP, Farrokhi ET, Flum DR; SCOAP-CERTAIN Collaborative. Perioperative hyperglycemia and risk ofadverse events among patients with and without diabetes. Ann Surg. 2015 Jan;261(1):97-103.
17. Li X, Zhou X, Wei J, et al. Effects of Glucose Variability on Short-Term Outcomes in Non-Diabetic Patients After Coronary Artery Bypass Grafting: A Retrospective Observational Study. *Hear Lung Circ*. 2019;28(10):1580-1586. doi:10.1016/j.hlc.2018.08.006
18. Galindo RJ, Fayfman M, Umpierrez GE. Perioperative Management of Hyperglycemia and Diabetes in Cardiac Surgery Patients. *Endocrinol Metab Clin North Am*. 2018;47(1):203-222. doi:10.1016/j.ecl.2017.10.005
19. Pandolfi A, Giaccari A, Cilli C, et al. Acute hyperglycemia and acute hyperinsulinemia decrease plasma fibrinolytic activity and increase plasminogen activator inhibitor type 1 in the rat. *Acta Diabetol*. 2001;38(2):71-76. doi:10.1007/s005920170016
20. Clement KC, Suarez-Pierre A, Sebestyen K, et al. Increased Glucose Variability Is Associated With Major Adverse Events After Coronary Artery Bypass. *Ann Thorac Surg*. 2019;108(5):1307-1313. doi:10.1016/j.athoracsur.2019.06.046
21. Bilku DK, Dennison AR, Hall TC, Metcalfe MS, Garcea G. Role of preoperative carbohydrate loading: A systematic review. *Ann R Coll Surg Engl*. 2014;96(1):15-22.
22. Ljunggren S, Hahn RG, Nyström T. Insulin sensitivity and beta-cell function after carbohydrate oral loading in hip replacement surgery: A double-blind, randomised controlled clinical trial. *Clin Nutr*. 2014;33(3):392-398.

23. Singh BN, Dahiya D, Bagaria D, et al. Effects of preoperative carbohydrates drinks on immediate postoperative outcome after day care laparoscopic cholecystectomy. *Surg Endosc*. 2015;29(11):3267-3272.
24. Vlachos D, Malisova S, Lindberg FA, Karaniki G. Glycemic Index (GI) or Glycemic Load (GL) and Dietary Interventions for Optimizing Postprandial Hyperglycemia in Patients with T2 Diabetes: A Review. Nutrients. 2020 May 27;12(6):1561.
25. Yoshitomi H, Momoo M, Ma X, et al. L-Citrulline increases hepatic sensitivity to insulin by reducing the phosphorylation of serine 1101 in insulin receptor substrate-1. *BMC Complement Altern Med*. 2015;15(1). doi:10.1186/s12906-015-0706-4
26. Willeit P, Freitag DF, Laukkanen JA, et al. Asymmetric dimethylarginine and cardiovascular risk: Systematic review and meta-analysis of 22 prospective studies. *J Am Heart Assoc*. 2015;4(6). doi:10.1161/JAHA.115.001833
27. Betz B, Möller-Ehrlich K, Kress T, et al. Increased symmetrical dimethylarginine in ischemic acute kidney injury as a causative factor of renal L-arginine deficiency. *Transl Res*. 2013;162(2):67-76. doi:10.1016/j.trsl.2013.04.005
28. Maas R, Dentz L, Schwedhelm E, et al. Elevated plasma concentrations of the endogenous nitric oxide synthase inhibitor asymmetric dimethylarginine predict adverse events in patients undergoing noncardiac surgery. *Crit Care Med*. 2007;35(8):1876-1881. doi:10.1097/01.CCM.0000277038.11630.71
29. Ekeloef S, Larsen MHH, Schou-Pedersen AMV, Lykkesfeldt J, Rosenberg J, Gögenür I. Endothelial dysfunction in the early postoperative period after major colon cancer surgery. *Br J Anaesth*. 2017;118(2):200-206. doi:10.1093/bja/aew410
30. Schwedhelm E, Maas R, Freese R, et al. Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: Impact on nitric oxide metabolism. *Br J Clin Pharmacol*. 2008;65(1):51-59. doi:10.1111/j.1365-2125.2007.02990.x
31. Piton G, Manzon C, Monnet E, et al. Plasma citrulline kinetics and prognostic value in critically ill patients. *Intensive Care Med*. 2010;36(4):702-706. doi:10.1007/s00134-010-1751-6