

## METFORMIN EFFECT ON CHEST TUBE DRAINAGE AFTER CORONARY ARTERY BYPASS GRAFT SURGERY

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**Key words:** heart surgery, bleeding, chest tube drainage, metformin, hemostasis, thromboelastometry.

### Summary

Increasing numbers of patients with diabetes mellitus are referred to cardiac surgery. Biguanides are still first-line treatment for type 2 diabetes in all over the world. According preoperative guidelines, oral diabetes medications should be held on the day of surgery because of increased risk of lactic acidosis, induced by Metformin in patients after heart surgery. However, not well described in medical literature mechanism of biguanides is its influence to coagulation. We observed patients, who were scheduled for an elective coronary artery bypass graft surgery (CABG). Eighteen were diabetics, fourteen were Metformin users, where medication was stopped 72 to 24 hours before surgery. Prothrombin time, activated partial thromboplastin time, platelet count, fibrinogen measurement were performed at the baseline, 2 hours and 6 hours after weaning from CPB. Chest tube drainage was checked at 2, 6 and 24 hours after weaning from CPB at the ICU. Presence of fibrinolysis was checked with rotational thromboelastometry testing (Rotem, Tem Innovation, Germany). Statistical analysis showed weak negative correlation between chest tube output in 24 hours and Metformin use ( $r=-0.255$ ,  $p=0.03$ ). Patients with Metformin preoperatively had less chest tube drainage ( $457.1 \pm 143.9$ ml) compared to patients without Metformin ( $622.2 \pm 269.9$ ml). Here was no significant fibrinolysis in ROTEM tests registered (ML  $3.5 \pm 2.5\%$ ) and apTEM didn't show improved maximal cloth firmness (MCF) nor shorter clotting time (CF).

### Introduction

Many of patients who undergo coronary artery bypass

graft surgery are diabetics. Metformin is still recommended as the first-line treatment for people with type 2 diabetes. With increasing numbers of patients diagnosed with diabetes, the number of such patients referred to cardiac surgery is increasing [1]. Patients have significant risk of bleeding after cardiac surgery with cardiopulmonary bypass (CPB) and bleeding still is a big problem in cardiac surgery, because it is associated with increased usage of blood components and worse outcome. Problems, related to extended blood loss, can cause higher frequency of complications postoperatively, longer intensive care unit (ICU) time, extended hospital stay and even lethal outcomes [2, 3].

Coagulopathy after CPB is caused by many perturbations in cellular and humoral elements of coagulation [4]. Existing studies showed a wide range of risk factors: advanced age, emergency surgery, low body surface area, prolonged CPB time (more than 150 minutes), combined valve and coronary artery bypass graft surgery, number of bypass grafts, re-exploration, hypothermia, preoperative use of antiplatelet agents.

**Aims:** to study perioperative blood loss after isolated on pump coronary artery bypass grafting and to evaluate the relationship between preoperative Metformin treatment and postoperative bleeding (chest tube drainage) after on pump coronary artery bypass grafting.

### Methods

Seventy-four patients, scheduled for elective CABG surgery using CPB, were included. Eighteen were diabetics. Fourteen were treated with Metformin preoperatively, Metformin hold time was from 72 to 24 hours before surgery (table 1).

Anesthetic induction consisted of intravenous thiopental sodium and fentanyl. Anesthesia was performed with inhaled sevoflurane, intravenous fentanyl and rocuronium bromide. In all patients 400 U/kg porcine heparin was given before instituting CPB. The circuit of CPB was primed with crystalloid solution (1300 to 1500 ml) with additional

**Table 1.** Baseline patient demographic data

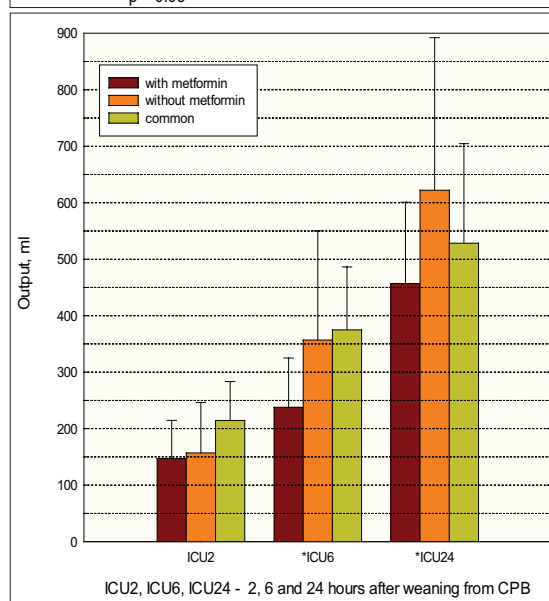
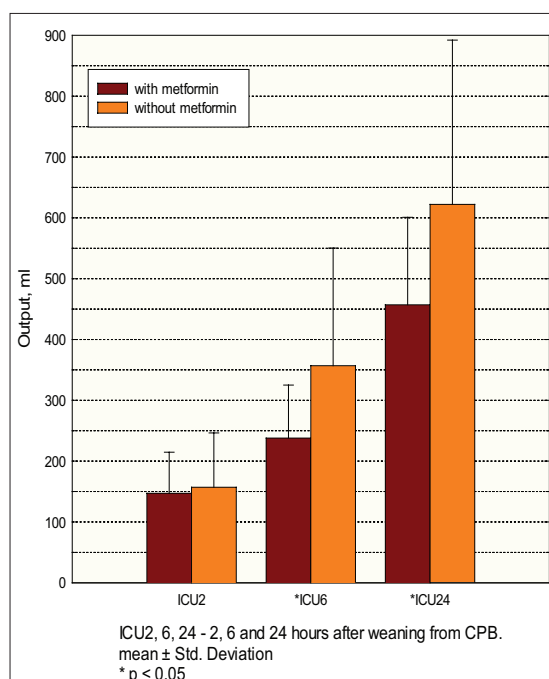
BMI - body mass index, EF - left ventricle ejection fraction, CPB - cardiopulmonary bypass, \*mean  $\pm$  standard deviation

Patient demographics	
age (years)*	64.0 $\pm$ 9.2
weight (kg)*	88.9 $\pm$ 15.1
height(cm)*	175.5 $\pm$ 6.3
BMI (kg/m <sup>2</sup> )*	28.8 $\pm$ 4.6
EF (%)*	48.5 $\pm$ 7.3
Diabetes mellitus type 1 patients	1
Diabetes mellitus type 2 patients	17
Aortic cross-clamp time (min)	49 $\pm$ 16
CPB time (min)	96 $\pm$ 26
Metformin therapy before surgery	14 (18.9%)
Aspirin monotherapy before surgery	22 (30%)
Clopidogrel monotherapy before surgery	3 (4.1%)
Aspirin + klopidoqrel before surgery	31 (41.9%)
Use of tranexamic acid intraoperatively	61 (82.4%)

10000 U of heparin. During CPB, activated clotting time was maintained above 400 seconds. Heparin anticoagulation was reversed after CPB with 200 to 250 mg of protamine sulfate. Rotational thromboelastometry analysis (ROTEM) was performed at baseline and at the end of CPB. Prothrombin time (PT), activated partial thromboplastin time (APTT), platelet count (PLT), fibrinogen measurement were performed at the baseline, 2 hours and 6 hours after weaning from CPB. Chest tube drainage was checked at 2, 6 and 24 hours after weaning from CPB at the ICU.

## Results

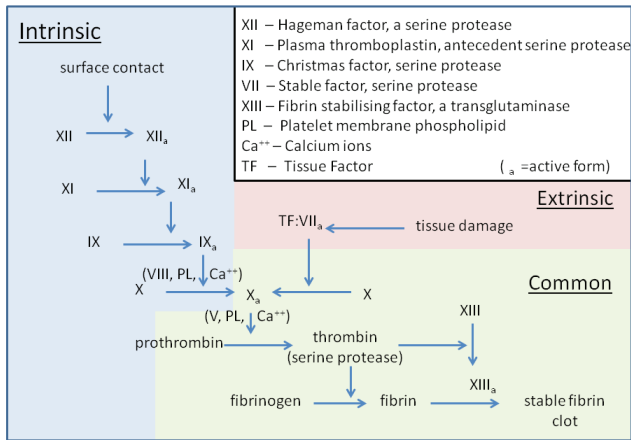
Statistical analysis showed weak negative correlation between chest tube output in 24 hours and Metformin use ( $r=-0.255$ ,  $p=0.03$ ). Patients with Metformin use preoperatively had less chest tube drainage (457.1  $\pm$  143.9 ml) compared to patients without Metformin (622.2  $\pm$  269.9 ml) (fig. 1). ROTEM analysis did not show increased fibrinolysis at the end of CPB in any of performed tests (maximal lysis, ML, 3.5  $\pm$  2.5%) and here was no significant correlation between ML and chest tube drainage after 24 hours after weaning from CPB.



**Figure 1.** Chest tube drainage in patients with and without Metformin

## Discussion

According preoperative guidelines, oral diabetes medications should be held on the day of surgery. However, Metformin administration is controversial. Based on recommendations, many anesthesiologists stop Metformin 48 hours before surgery. No evidence exists to support this recommendation in patients with normal renal function [1,



**Figure 2.** The classical blood coagulation pathway [10]

16] and the main problem is an increased risk of lactic acidosis, induced by Metformin in patients after heart surgery.

Metformin reduces cardiovascular risk in patients with type 2 diabetes of lowering blood glucose concentration [5, 6], beneficial effects of preoperative Metformin use have been found in a randomized trial of non diabetic patients with established cardiovascular disease (the CAMERA study) [7], although the mechanism involved are still unclear. It inhibits glycosylation-related protein cross-linking, a process similar to fibrin cross-linking catalyzed by activated factor XIII. Standeven K F et al have researched effects of dimethylbiguanide on thrombin activity, factor XIII activation, fibrin polymerization, and fibrin clot formation and the results suggest that Metformin interferes with factor XIII activation and fibrin polymerization, but not only by binding to thrombin on a different location than the active site. In patients on Metformin therapy, factor XIII antigen and activity levels in vivo were reduced over a 12-week period [8] and may be reason of alterations in fibrin structure/function. Factor XIII is terminal enzyme in the coagulation cascade, fibrin-stabilizing factor, that catalyses covalent cross-linking chains of fibrinogen to a stable structure that is resistant to physical and chemical influence, makes cloth stabilization [10] (fig. 2).

Studies showed, that use of Metformin in type 2 diabetics is associated with increased fibrinolysis where the main mechanism is lowering of plasminogen activator inhibitor-1 (PAI-1) concentrations in plasma and fall tissue plasminogen activator (tPA) [11]. Fibrinolysis is one of fundamental processes in coagulation. It eliminates fibrin clots during the healing process, removes intravascular clots to prevent thrombosis. Plasmin causes fibrin cleavage into degrading products. Plasmin is synthesized from plasminogen by two activating agents

of plasminogen: the tissue activator (tPA) and the urokinase type activator (uPA). Regulation of these activators depends on the activity of inhibitor agents (PAI) [12].

Inhibiting PAI-1 expression is done possibly through the activation of adenosine monophosphate kinase (AMPK) and via inhibition of mitochondrial respiration [14]. However in medical literature we found some reports that while depressing PAI-1 expression, Metformin had no influence to plasma fibrinogen concentrations and platelet function [15].

Increased fibrinolysis can lead to increased chest tube drainage after operation. However in our study, ROTEM didn't show us significant increase of fibrinolysis at the end of CPB. Maximal lysis (ML) was not increased in exTEM and inTEM tests and apTEM didn't show improved cloth firmness (MCF) nor shorter clothing time (CF). Absence of fibrinolysis we explain with antifibrinolytic effect of tranexamic acid, 1 to 3g which was perioperatively used in study patients.

## Conclusions

Preoperatively used Metformin, according in literature explained mechanism of action to fibrin polymerization, may increase bleeding after heart surgery in patients, treated with Metformin last 12 weeks before scheduled heart surgery. However our results indicated, that blood coagulation was enhanced: patients with Metformin preoperatively had reduced chest tube drainage after coronary artery bypass graft surgery, compared to patients without Metformin preoperatively. Also our results showed, that tranexamic acid had sufficient antifibrinolytic effect in patients with Metformin to prevent excessive fibrinolysis and bleeding after CABG.

We acknowledge, that our study had not randomised, but selective character, but it could be good start for further research to validate or negate our results, because effect on reduced chest tube output was noticed as a component of other study and was not main focus of our investigation.

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## METFORMINO ĮTAKA KRAUJO NETEKIMUI PO AORTOVAINIKINIO NUOSRUVIO SUFORMAVIMO OPERACIJŲ

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Raktažodžiai: širdies chirurgija, kraujavimas, metforminas, hemostazė, tromboelastometrija.

### Santrauka

Pasaulyje daugėja pacientų, gydomų biguanidais, kuriems atliekamos aortovainikinio nuosruvio suformavimo operacijos. Metforminas išlieka pirmo pasirinkimo vaistu gydant antro tipo cukrinį diabetą ir jo teigiamas efektas sergantiems dismetaboliniu sindromu yra plačiai ištyrinėtas ir aprašytas medicininėje literatūroje. Taip pat literatūroje nurodomos rekomendacijos nutraukti metformino skyrimą 2 dienas prieš numatomą širdies operaciją dėl jo sukeltos laktacidozės rizikos. Tačiau biguanidai ne tik didina laktacidozės tikimybę, taip pat turi poveikį fibrino polimerizacijai, XIII faktoriaus aktyvacijai ir tai siejama su padidėjusia fibrinolize ir sumažėjusiu krešulio stabilumu. Tyrėme 74 pacientus, kuriems atliekama aortovainikinio nuosruvio operacija. Iš jų aštuoniolika sirgo cukriniu diabetu, keturiolika buvo gydomi metforminu, kurio nutraukimo laikas svyravo nuo 72 iki 24 valandų iki operacijos. Pacientams buvo atliekami rutininiai kraujo krešėjimo tyrimai prieš operaciją, po 2, 6 ir 24 valandų nuo operacijos pabaigos. Taip pat tirta kraujo krešėjimo sistemos būklė rotaciniu tromboelastografu ROTEM (Tem Innovation, Vokietija) prieš operaciją bei užbaigus dirbtinę kraujo apytaką po heparino inaktyvacijos protamino sulfatu. Rezultatai. Pacientams, kurie prieš operaciją buvo gydyti metforminu, sekrecija per drenus pirmas 24 valandas buvo mažesnė ( $457,1 \pm 143,9$  ml), nei pacientams, kurie metforminu gydyti nebuvo ( $622,2 \pm 269,9$  ml),  $r = -0,255$ ,  $p = 0,03$ . Tromboelastografinis tyrimas neparodė kliniškai reikšmingos fibrinolizės, maksimali krešulio lizė (ML) buvo  $3,5 \pm 2,5\%$ , o apTEM testas taip pat neparodė maksimalaus krešulio storio (MCF) pagerėjimo ar krešėjimo laiko (CT) sutrumpėjimo, kas rodytų fibrinolizę kraujo mėginyje.

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