Genetic Variation of beta-blockers in Perioperative Myocardial Infarction

An Essay
Submitted for Partial Fulfillment of Master Degree
In Anesthesia

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2013

Acknowledgment

First of all, I wish to express my sincere thanks to **God** *for his care and generosity throughout my whole life.*

I would like to express my sincere appreciation and my deep gratitude to **Prof. Dr. GehanFouadKamel,** *Professor of Anesthesiology and Intensive Care, Faculty of Medicine, Ain Shams University who assigned the work, kindly supplied me with all necessary facilities for its success and helped me to complete this work.*

I am deeply gratefulto **Dr. Dalia Abdelhamed Mohammed,** *Assistant Professor of Anesthesiology and Intensive Care,Faculty of Medicine, Ain Shams University for her continuous help, support and direct supervision of the work and for her fruitful thinking which was behind the progress of the work.*

I am also deeply indebted to **Dr. Ahmed Salah Omran**, *Lecturer of Anesthesiology and Intensive Care, Faculty of Medicine, Ain Shams University for his supervision, help and cooperation.*

I would like to thank my beloved fiancée, my parents, my brothers, my sisters and all my family, sacrifice and for being there for me.

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Introduction

Perioperative myocardial infarction is a common and potentiallyfatal complication after noncardiac surgery, particularamong patients with cardiovascular risk factors.Beta-blockershave been considered a mainstay in prevention and treatmentof perioperative myocardial infarction, yet recent evidencesuggests that beta-blockers may have an unfavorable risk profilein this setting, and the use has become controversial. The most important issue is how much interindividual genetic variationinfluences the clinical response to beta-blocker therapy.Genetic variation in the adrenergic signaling pathway is common,and has a major impact on adrenergic receptor functionand beta-blocker efficacy in other cardiovascular diseases, suchas heart failure and hypertension. Genetic variation in thecytochrome P450 2D6, or CYP2D6, enzyme, which is responsiblefor the metabolism of most beta-blockers, is also importantand can lead to poor metabolizing ofbeta-blockers(potential toxicity) or their ultra-rapid degradation (decreased efficacy).The molecular, cellular, andphysiologic consequences of polymorphisms in the adrenergicsignaling pathway and CYP2D6 gene are likely relevant factors influencing efficacy, safety,and toxicity of beta-blocker therapy in prevention and treatmentof perioperative myocardial infarction ***(Peter and Stephen, 2011).***

Most beta-blockers, such as metoprolol and propranolol, areextensively metabolized in the liver by cytochrome P4502D6, or CYP2D6, a hepatic enzyme of the cytochrome P450family***(Gardiner and Begg, 2006).***

CYP2D6 is responsible for the phase- I metabolismof approximately 25% of all commonly used drugs and isthus one of the most important drug-metabolizing enzymes***(Owen et al., 2009)***.

The CYP2D6 (cytochrome P450 2D6) gene is very polymorphic, with close to100known variants**.** These CYP2D6 gene variants have amajor impact on the CYP2D6 enzyme activity, with somevariants resulting in a complete loss-of-function phenotypewhereas others lead to a gain-of-function***(Zanger et al., 2004).***

Aim of the Work

Here we provide a concise overview of the genetic variability within those pathways relevant to beta-blocker responses. Furthermore, we discuss potential links between genetic factors and the risk for the adverse outcomes during beta-blocker treatment, such as hypotension and stroke, observed in recent clinical trials in the perioperative period.

Myocardial Infarction

Definition:

Myocardial infarction (MI) is the rapid development of myocardial necrosis caused by a critical imbalance between oxygen supply and demand of the myocardium. This usually results from plaque rupture with thrombus formation in a coronary vessel, resulting in an acute reduction of blood supply to a portion of the myocardium ***(Thygessen et al.,2007).***

Any necrosis in the setting ofmyocardial ischemia should be labelled as MI ***(The Joint European Society of Cardiology/American College of CardiologyCommittee, 2000).***

The three major determinants of myocardial oxygen consumption are myocardial wall tension, contractility, and heart rate.

Myocardial wall tension is estimated by the following:

- The Laplace equation states that the wall tension (T) is analogous to the diameter of the ventricle (R) and the intracavitary pressure (P) and inversely proportional to the myocardial thickness wall (Th): $T = P \times R \div 2Th$.
- Preload- left ventricular end diastolic volume (LVEDV), LVEDP.

- Afterload- systolic ventricular pressure or systolic blood pressure if there is no aortic stenosis.

Contractility is measured by the following:

- Invasive technique. Maximal velocity of contraction(Vmax), diastolic pressure(dp)/diastolic time(dt) [pressure time indices of ventricle: how fast (dt) the intraventricular pressure (dp) develops].
- Noninvasive technique. Preejection period/left ventricular ejection time, and global and regional ventricular wall motion by echocardiography.

Myocardial oxygen supply = coronary blood flow X arterial oxygen content.

The coronary blood flow depends on the following:

- Aortic diastolic pressure (DAP).
- LVEDP.
- Patency of coronary arteries.
- Coronary vascular tone.

And it can be determined by the formula:

Coronary blood flow = coronary perfusion pressure ÷ myocardial vascular resistance, or

(DAP – LVEDP) ÷ myocardial vascular resistance

Arterial O2 content is determined by the following equation:

$Cao_2 = 1.34 \times O_2 \text{ saturation} + (0.0031 \times Pao_2)$

(O'Brien and Nathan, 2011)

Pathophysiology of myocardial infarction:

Transmural acute MI results from a dynamic interaction among several orall of the following coronary atherosclerosis, acute atheromatous plaquechange (such as rupture), superimposed platelet activation, thrombosis,and vasospasm resulting in an occlusive intracoronary thrombusoverlying a disrupted plaque. In addition, either increased myocardialdemand (as with hypertrophy or tachycardia) or hemodynamiccompromise (as with a drop in blood pressure) can worsen the situation. Also collateral circulation may provide perfusion to ischemiczones from a relatively unobstructed branch of the coronary tree,bypassing the point of obstruction and protecting against the effects of anacute coronary occlusion***(Schoen et al., 2005).***

The most common cause of MI is narrowing of the epicardial blood vessels due to atheromatous plaques. Plaque rupture with subsequent exposure of the basement membrane results in platelet aggregation, thrombus formation, fibrin accumulation, hemorrhage into the plaque, and varying degrees of vasospasm. This can result in partial or complete occlusion of the vessel and subsequent myocardial ischemia. Total occlusion of the vessel for more than 4-6 hours results in irreversible myocardial necrosis, but reperfusion within this period can salvage the myocardium and reduce morbidity and mortality ***(Corti et al.,2003)***.

The pathophysiology of early perioperative MI seems to be related to a prolonged imbalance between myocardial oxygen supply and demand in the setting of coronary artery disease (CAD)***(Morrow et al., 2001).***

After major non-cardiac surgery, an early increase in plasma concentrations of both pro- and anti-inflammatory cytokines was also reported***(Sarbinowski et al., 2005).***

Proinflammatory cytokines affect vascular function and endothelium-derived factors involved in blood pressure regulation. Tumour necrosis factor-(TNF) alpha and interleukin-6 (IL-6) were both shown to induce structural as well as functional alterations in endothelial cells***(Armstrong et al., 2006).***

These cytokines enhance the formation of a number of endothelial cell substances, such as endothelin; reduce acetylcholine-induced vasodilatation; and destabilise the mRNA of endothelial nitric oxide synthase ***(Giardina et al., 2002)***.

The combination of increased prothrombotic and reduced fibrinolyticactivity could initiate propagation and total occlusion of thecoronary artery by a mural thrombus overlying a small plaqueerosion that might otherwise have been harmless. The perioperativeperiod is characterized by comparable adrenergic stimulation,and increased prothrombotic and reduced fibrinolytic activity. Inflammatory activation of the endothelium can turnits physiological vasodilatory and antithrombotic propertiesinto pathological vasoconstrictor and prothrombotic properties.In addition, the inflammatory response of the circulating bloodmay activate coagulation***(Sambola et al., 2003).***

Several important differences exist between perioperative MIand acute MI in a nonoperative setting. Perioperative myocardialischemia and infarction are often silent, with minimalclassic clinical symptoms of an acute MI, such as chestpain or dyspnea ***(Landesberg et al., 2005).***

The risk of perioperative MI peaks within the first three postoperative days, a period of time when patients begin to mobilize fluids administered in the operating room, and a time when the thrombotic risk may be most pronounced. Surgery is accompanied by a catecholamine surge that is exacerbated by postoperative pain. Subsequent increases in heart rate and blood pressure can lead to a diffuse myocardial oxygen supply/demand mismatch in the postoperative patient***(Kumar et al., 2001).***

It was found that PMI occurred earlier than previously thought, with most events occurring on the day of surgery or the day after surgery, the mechanism is not as well understood but is thought to be similar to nonoperative MI***(Steven et al., 2003).***

There are two mechanisms involved in the causation of perioperativeMI:

(i) Coronary artery occlusion: Plaque erosion or rupture leadingto thrombogenesis and consequent occlusion or thromboembolicocclusion of an already narrowed coronary lumen.

(ii)Prolonged ischemia (usually silent) secondary to an imbalancebetween myocardial oxygen demand and supply.

(Landesberg, 2003)

The first type of infarction occurringin the postoperative period is not preceded by ischaemic myocardialdamage, is associated with a sudden increase in the serum troponinconcentration to a level diagnostic of MI (cTnI >1.5 ng ml^{-1} and cTnT >0.1 ng ml^{-1} for certain assays), and is probably becauseof coronary occlusion secondary to plaque hemorrhage, ruptureor thrombus formation. The later or delayed type of perioperativeMI is preceded by a long period, >24 h, of ischaemic myocardialdamage observed as a moderate increase in the troponin level,not initially in the range diagnostic of MI but above the upperreference limit of normal. Pathological studies examiningthe coronary vessels at autopsy of patients who have sufferedfatal perioperative MI shows that the incidence of these twotypes of MI is roughly equal***(Howard-Alpe et al., 2006).***

The frequent combination ofincreases in heart rate preceding the ischaemic episodes, ST-segmentdepression rather than elevation during all ischaemic episodes;non-Q-wave rather than Q-wave MIs in almost all cases; the lackof angiographically visible thrombus or ruptured plaques insome patients who underwent coronary angiography following PMI;and complete reversal of ECG changes to baseline in all of the patients with ischemia (including those with infarction),are highly suggestive that prolonged stress-induced myocardialischemia is the likely primary cause of PMI. Repeated briefischemic episodes may well have a cumulative effect and ultimatelycause myocardial necrosis***(Landesberg, 2003)***.

Ischemia begins in most patients at the end of surgery and during emergence from anesthesia. It usually manifests as ST-segment depression on continuous ECG monitoring. The ST-segment depression is preceded by an increase in heart rate, which may not exceed 90 to 100 beats/min and may resolve even if untreated***(Landesberg et al., 2004).***

This period is characterizedby increase in heart rate, arterial pressure, sympathetic tone,and procoagulant activity. Increased sympathetic tone canresult in increases in arterial pressure, heart rate, contractility,coronary vasomotor tone, and coronary vascular shear stress.This, in turn, may trigger coronary vasospasm, plaque disruption,and coronary thrombosis. Increases in arterial pressure, heartrate, and cardiac contractility lead to subendocardial ischemiaby increasing myocardial oxygen demands in the presence of limitedor absent coronary vasodilator reserve as a result of underlyingCAD. Surgery-induced simultaneous procoagulant and anti-fibrinolyticactivity may trigger coronary artery thrombosis during low-flowconditions in the presence of underlying stable CAD even inthe absence of acute plaque disruption***(White, 2003).***

The ultimate fate of the thrombus and, thus, the extent of jeopardizedmyocardium will depend on the duration and degree of coronaryocclusion. If the plaque disruption is major with extensiveexposure of thrombogenic core material to the blood stream,acute total coronary occlusion with subsequent MI, or suddendeath may develop. If the disruption is minor, the forming thrombuscan be non-occlusive and the patient may stay asymptomatic ordevelop unstable angina or a non-Q-wave infarction ***(Kereiakes, 2003).***

A concomitantincrease in coagulability and coronary vasoconstriction (asis common in the perioperative setting) may, however, transforma non-occlusive thrombus to an occlusive thrombus.Ultimately,the balance between thrombosis and thrombolysis, and the flowconditions (affected by coronary vasomotor tone, perfusion pressure,and rheological properties) are the decisive factors in determiningwhether the clinical outcome will be myocardial ischemia oran MI***(Feldman and Stone, 2000).***

Management:

Incidence

In patients with or at risk of coronary artery disease, the reported incidence of perioperative myocardial ischemia varies considerably, i.e. between 20 and 63% ***(Landesberg et al., 2002).***

Risk Factors

Risk factors for atherosclerotic plaque formation include the following:

- Old age.
- Male gender.
- Smoking.
- Hypercholesterolemia and hypertriglyceridemia, including inherited lipoprotein disorders.
- Diabetes mellitus.
- Poorly controlled hypertension.
- Type A personality(nervous person).
- Family history.
- Sedentary lifestyle.

(Sambola et al., 2003)