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Resveratrol as antioxidant in cardiac surgery: is there potential for clinical application?

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Cardiopulmonary bypass (CPB) is an essential technique in cardiac surgery but is also associated with adverse effects, including the systemic inflammatory response syndrome that manifests itself as ischaemia-reperfusion injury and multi-organ dysfunction. The aim of this mini review is to take a look at the current knowledge of resveratrol, a stilbenoid and natural antioxidant believed to have many cardioprotective effects including vasodilation, lowering of blood pressure and reactive oxygen species levels, suppression of low-density lipoprotein peroxidation, and mitigation of ischaemia/-reperfusion injury. We mostly focus on its cardioprotective potential in patients undergoing cardiac surgery supported by CPB. Current findings, however, are still inconclusive and call for further research, including clinical trials.

KEY WORDS: cardioprotective effects; cardiopulmonary bypass; ischaemia/reperfusion injury; polyphenols

Cardiac surgery saw its boom with the development and clinical application of cardiopulmonary bypass technique (CPB), which allows bloodless surgery while it oxygenates the blood bypassing the heart and lungs (1). However, besides its pivotal place in modern cardiac surgery, CPB has also some deleterious effects on human physiology. The contact of blood with non-endothelial surfaces and surgical trauma may trigger inflammatory response, coagulation, and oxidative stress (2, 3). This, in turn, may lead to the development of systemic inflammatory response syndrome (SIRS), which manifests itself as ischaemia-reperfusion injury affecting multiple organs. It can damage the cells and tissues as soon as perfusion is restarted after heart standstill and may lead to relative or complete ischaemia. Clinical manifestations include myocardial injury, ventricular arrhythmia, and transient lung, liver, and kidney failure (4). These injuries are largely related to the generation of excess reactive oxygen species (ROS) and oxidative stress (5).

Considering that resveratrol has gained much scientific and popular attention thanks to the "French paradox" (6) and claimed cardioprotective effects, the aim of this mini review is to take a closer look at its beneficial effects and potential use as accompanying therapy in cardiac surgery supported by CPB.

RESVERATROL AND ITS BENEFICIAL EFFECTS

Resveratrol (3,5,4'-trihydroxy-*trans*-stilbene) is a stilbenoid and phytoalexin produced by several plants in response to injury. Food sources of resveratrol include grape skins, blueberries, raspberries, mulberries, and peanuts (7), but it is also extracted from the root of Japanese knotweed (*Polygonum cuspidatum*) as nutritional supplement (8).

Its popularity can be associated with the phenomenon called the "French paradox", observed in people who consume fatty diet with moderate amounts of red wine (30–50 g of alcohol per day) and yet run a lower risk of mortality from coronary heart disease (CHD) (6). This effect has been reported in France and Switzerland, where red wine is regularly consumed, but not in countries where other alcoholic drinks like beer are consumed more frequently (such as UK, Denmark, Austria, or Germany). This turned the scientific interest to resveratrol, although red wine also contains other polyphenolic compounds, tannins, and alcohol. In wine resveratrol takes the *trans*- and *cis*- form, whose isomers are distinguished by high-performance liquid chromatography (HPLC) thanks to different λ_{max} and retention times (9). However, the *cis*-resveratrol is unstable and measurements more often refer to its *trans*-form, which results in the underestimation of total resveratrol quantities in wine. In other words, humans are probably ingesting more of resveratrol than measurements show.

One toxicokinetic study of ^{14}C-resveratrol in humans (10) revealed its high absorption and very rapid metabolism, mostly to resveratrol-3-O-sulphate, which binds to albumin in blood. Resveratrol undergoes enterohepatic recirculation and is excreted via urine and faeces (9). No adverse effect has been reported, even with concentrations more than 1,000 times higher than in moderate red wine consumption (11).

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Literature suggests that resveratrol activates a class of proteins with deacylase activity called sirtuins, which render it a powerful antioxidant with neuroprotective, antidiabetic, anticancerogenic, and cardioprotective properties (12–20). Regarding its cardioprotective effects, resveratrol decreases low-density lipoproteins (LDL) and increases high-density lipoproteins (HDL), lowers oxidative stress, improves glucose homeostasis, prevents platelet aggregation, promotes coronary vasodilation, and reduces ventricular arrhythmias (13, 16, 20). Research in humans has shown that these cardioprotective effects occur when plasmatic resveratrol concentrations range from 0.1 to 1 μmol/L, which is the amount found in 450 mL of red wine (5, 14).

Cardioprotective effects of resveratrol evidenced in animal models include attenuated ischaemia-reperfusion injury, inhibition of apoptosis, vasodilation, endothelial protection and anti-atherogenic effects (13). All these effects are further enhanced by resveratrol preventing lipid peroxidation and platelet aggregation through stimulation of NO release from endothelial cells (15, 16). In adult male Wistar rats with induced chronic obstructive pulmonary disease (21) resveratrol treatment lowered neutrophil count and oxidative stress and inhibited cytokine (IL-6 and IL-8) expression. In another study with male Sprague-Dawley rats with induced hypercholesterolemia (22) it suppressed superoxide levels and promoted vasodilation by activating endothelial cells through stimulated expression of hemoxigenase-1, endothelial nitric oxide synthase, and vascular endothelial growth factor. In mice with induced hepatic steatosis (23) it protected the mitochondria and inhibited accumulation of lipid droplets in the liver cells.

As for *in vitro* research, resveratrol-induced platelet apoptosis (24) implies its therapeutic potential for patients suffering from thrombotic conditions.

Furthermore, resveratrol can alleviate the adverse effects of chronic inhibition of NO production and resulting medial hyperplasia of carotid arteries and hypertension (25–27). Treatments with resveratrol can also counter the adverse effects of high blood sugar resulting in endothelial dysfunction, impaired angiogenesis, and deficits in myocardial blood flow (16) and enhances endothelial NO production, significantly improves systolic blood pressure, and reduces aortic eNOS expression, as reported in obese Zucker rats (25).

Recent research has proposed a new paradigm – hormesis – as a phenomenon that can explain positive resveratrol effects (17). It opposes the common perception that they are mainly owed to its antioxidative properties or that it is a protein-specific ligand and suggests instead that cellular response to resveratrol is essentially based on oxidative triggering which induces cells to activate their own mechanisms against oxidative stress (18).

So far, clinical trials have not included cardiac patients undergoing open heart surgery. One meta-analysis of six randomised clinical trials in patients with type 2 diabetes has evidenced that resveratrol lowers systolic blood pressure and cholesterol and HbA1c levels (26). In contrast, two other meta-analyses of 17 (27) and 21 (28) studies have concluded that it neither lowers systolic or diastolic pressure nor LDL or HDL levels.

POTENTIAL APPLICATION OF RESVERATROL IN CARDIAC SURGERY PATIENTS

Some studies report that preoperative treatment with antioxidants/anti-inflammatory drugs such as acetylsalicylic acid, vitamins A and C, or curcumin can reduce SIRS and lower negative effects of CPB, but no significant effect was ever verified in in cardiac surgery patients (5, 8).

In adult male Sprague Dawley rats resveratrol (0.5, 2.5, and 10 mg/kg) combined with diltiazem (a benzodiazepine calcium channel blocker) significantly increased the bioavailability of diltiazem due to the inhibition of both the cytochrome P450 (CYP) 3A4-mediated metabolism and the efflux pump P-glycoprotein (P-gp) in the intestine and/or liver (29).

In 75 18–80 years old patients on statin treatment for more than three months and high cardiovascular risk factors, including diabetes mellitus, hypercholesterolemia, arterial hypertension, active tobacco smoking, and/or obesity resveratrol lowered high-sensitivity C-reactive protein (hsCRP), TNF-a, plasminogen activator inhibitor type 1 (PAI-1), and IL-6/IL-10 ratio and increased IL-10 (30) with no drug interactions or adverse effects on haematological, hepatic, thyroid, and renal function.

However, no study has so far evaluated the efficacy of resveratrol in lowering oxidative stress in patients undergoing heart surgery supported by CPB. Usta et al. (22) reported that resveratrol suppressed simulated cardioplegia and reperfusion injury of human cardiomyocytes in an *in vitro* microperfusion chamber by arresting the apoptosis cascade. Recent animal studies with endovascular balloons coated with resveratrol in combination with paclitaxel (31, 32) showed a variety of beneficial effects, including the inhibition of platelet aggregation and enhancement of nitric oxide production, both of which protect the endothelium. Another recent study by Xu et al. (18) demonstrated that pre-treatment with resveratrol protected rat lung in the early post-transplantation stages thanks to induced necroptosis. Cheng and al. (19), in turn, reported significant antioxidant and cardioprotective effects of resveratrol in a rat heart model following myocardial ischaemia, possibly through the activation of the Nrf2/ARE signalling pathway. Zhu et al. (32) showed promising beneficial effects of resveratrol in reducing rabbit endothelial cell injury after coronary artery bypass surgery using an autologous jugular vein, as, in combination with hawthorne, it reduced the levels of circulating endothelial cells and the expression of albumen and mRNA of the intercellular cell adhesion molecule-1 (ICAM-1).

In their reviews Penumathsa and et al. (20, 33) claim that resveratrol holds great promise in the treatment of myocardial ischaemia, hypercholesterolemia, and diabetes as it regulates several target molecules that protect the myocardium against ischaemic

injury and thrombotic restenosis by inducing neovascularisation. There are additional studies that promote the idea of resveratrol having an important role in endothelial function as well as antioxidant effects on human cardiovascular health (34, 35).

Furthermore, there is no evidence of possible interactions with anaesthetics used during cardiac surgery.

AVENUES OF FURTHER RESEARCH

Even with rather compelling evidence, mostly based on animal studies, resveratrol has never been clinically studied in cardiac surgery patients. We therefore believe that further research should involve controlled randomised trials in patients undergoing the same type of elective surgery such as aortic valve replacement. They could be receiving either resveratrol or placebo before and after surgery, and have their blood sampled before, during, immediately after, and 24 hours after the procedure to determine changes in inflammatory and oxidative stress parameters (such as MDA, GSH, SOD, and CAT). To exclude potential antioxidative effects of anaesthetics, no patient should receive propofol or volatile anaesthetics (such as isoflurane or sevoflurane) nor should they be taking any other antioxidants for at least one month prior to surgery. The statistical analysis of laboratory results and of records of postoperative complications should then help to establish possible benefits of resveratrol and provide new insights into its mechanisms of action, as research done in humans so far varies greatly in study design and is based on a small sample.

Conflicts of interest

None to declare.

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Resveratrol kao antioksidans u kardijalnoj kirurgiji – ima li potencijala u kliničkoj primjeni?

Kardijalna kirurgija je kirurška struka koja se vrlo brzo razvija, a u kojoj se pri radu koristi uređaj za izvantjelesni krvotok. Njegovo korištenje dovodi do sustavnog upalnog odgovora koji se prezentira kao ishemijsko-reperfuzijska ozljeda i multiorganska disfunkcija. Resveratrol, stilbenoid iz skupine fenola, prirodni je antioksidans koji se nalazi u grožđu, borovnicama, malinama, murvi i kikirikiju, a smatra se da ima neuroprotektivna, antidijabetička, antikarcinogena i kardioprotektivna svojstva. Prema dosadašnjim znanstvenim istraživanjima, resveratrol je moguće glavni čimbenik kardioprotektivnoga djelovanja vina, koje se očituje vazodilatacijom, smanjenjem količine reaktivnih radikala kisika i arterijskoga krvnog tlaka, zatim smanjenjem peroksidacije lipoproteina male gustoće i ublažavanjem ishemijsko-reperfuzijske ozljede. Cilj je ovoga pregleda sažeti trenutačno znanje o potencijalnim kardioprotektivnim svojstvima resveratrola u bolesnika koji se podvrgavaju kardiokirurškom zahvatu pri kojem se koristi uređaj za izvantjelesni krvotok. Resveratrol ima razne učinke na ljudsku kardiovaskularnu fiziologiju, od kojih mnogi još moraju biti istraženi.

KLJUČNE RIJEČI: kardioprotektivni učinak; polifenol; uređaj za izvantjelesni krvotok