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DEXMEDETOMIDINA DIMINUI A RESPOSTA INFLAMATÓRIA APÓS CIRURGIA MIOCÁRDICA SOB MINI-CIRCULAÇÃO EXTRACORPÓREA

TESE DE DOUTORADO

Neusa Maria Heinzmann Bulow

Santa Maria, RS, Brasil

2013

DEXMEDETOMIDINA DIMINUI A RESPOSTA INFLAMATÓRIA APÓS CIRURGIA MIOCÁRDICA SOB MINI-CIRCULAÇÃO EXTRACORPÓREA

Neusa Maria Heinzmann Bulow

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Orientador: Prof. Dr. João Batista Teixeira da Rocha

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DEXMEDETOMIDINA DIMINUI A RESPOSTA INFLAMATÓRIA APÓS CIRÚRGIA MIOCÁRDICA SOB MINI-CIRCULAÇÃO EXTRACORPÓREA

Elaborada por
Neusa Maria Heinzmann Bulow

como requisito parcial para obtenção do grau de
Doutora em Bioquímica Toxicológica

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"Sabemos de quase nada adequadamente, de poucas coisas *a priori*, e da maioria por meio da experiência".

Gottfried Wilhelm Leibniz

RESUMO

Tese de Doutorado
Programa de Pós-Graduação em Ciências Biológicas: Bioquímica Toxicológica
Universidade Federal de Santa Maria, RS, Brasil

DEXMEDETOMIDINA DIMINUI A RESPOSTA INFLAMATÓRIA APÓS CIRURGIA MIOCÁRDICA SOB MINI-CIRCULAÇÃO EXTRACORPÓREA

AUTORA: Neusa Maria Heinzmann Bulow
ORIENTADOR: João Batista Teixeira da Rocha
LOCAL E DATA DA DEFESA: Santa Maria, 09 de Março de 2013

Apesar dos grandes avanços tecnológicos nas cirurgias de revascularização miocárdica (CRM), ocorre uma grande incidência de disfunção cardíaca e déficit neurocognitivo no período pós-operatório. As medidas preventivas são essenciais para a redução destas situações adversas, responsáveis pelo comprometimento da qualidade de vida dos pacientes. A cirurgia e a circulação extra-corpórea (CEC) produzem alterações importantes no sistema imunológico, diretamente envolvidas na incidência das complicações e acredita-se que a escolha anestésica possa modificá-las. Em estudo prospectivo e randomizado, pretendemos demonstrar a influência da dexmedetomidina (grupo AIVT-DEX), um anestésico (α)-2-agonista, associado à anestesia intravenosa total (AIVT) no comportamento da resposta inflamatória em pacientes submetidos à CRM, sob mini-circulação extracorpórea (mini-CEC). O grupo AIVT-DEX recebeu infusão contínua de dexmedetomidina associado à técnica de AIVT convencional e o outro grupo foi submetido à AIVT convencional (infusão contínua de propofol e sufentanil). Os grupos foram comparados pela dosagem plasmática trans-operatória de citocinas, como a interleucina-1(IL-1), a interleucina-6 (IL-6), a interleucina-10 (IL-10), o interferon gama (INF-γ) e o fator de necrose tumoral alfa (TNF-α), bem como a proteína C reativa (PCR), creatinofosfoquinase (CPK), creatinofosfoquinase miocárdio específica (CPK-MB), troponina I (cTnI), cortisol e glicose. A peroxidação lipídica foi avaliada pelo estudo das substâncias reativas ao ácido tiobarbitúrico (TBARS) e a presença de estresse oxidativo pela atividade da enzima delta-aminolevulinato desidratase (δ-ALA-D). O uso da dexmedetomidina induziu redução significativa de IL-1, IL-6, TNF-α e INF-γ se comparado ao grupo sem dexmedetomidina. Houve redução progressiva dos níveis de IL-10 ao longo do tempo, de forma semelhante entre os grupos. Não houve diferença entre os grupos para a atividade da enzima δ-ALA-D e os níveis de TBARS foram maiores no grupo AIVT-DEX. Concluímos que a dexmedetomidina associada à AIVT convencional foi capaz de reduzir os níveis plasmáticos das citocinas pró-inflamatórias IL-1, IL-6, TNF-α e INF-γ em pacientes submetidos à CRM sob mini-CEC, se comparados aos pacientes que receberam apenas a AIVT convencional. Estes resultados reforçam os dados da literatura quanto à potencialidade da dexmedetomidina como agente modulador da resposta inflamatória no período trans-operatório.

Palavras Chave: Dexmedetomidina. Inflamação. Estresse Oxidativo. Anestesia Intravenosa Total (AIVT). Circulação Extracorpórea (CEC).

ABSTRACT

Thesis of PhD's Degree
Graduate Course in Biological Sciences: Toxicological Biochemistry
Federal University of Santa Maria, RS, Brazil

DEXMEDETOMIDINE DECREASE THE INFLAMMATORY RESPONSE TO MYOCARDIAL SURGERY UNDER MINI CARDIOPULMONARY BYPASS

AUTHOR: NEUSA MARIA HEINZMANN BULOW
ADVISER: João Batista Teixeira da Rocha
PLACE AND DATE OF THE DEFENSE: Santa Maria, 09 March of 2013

Despite great technological advances in coronary artery bypass grafting (CABG) surgery, there is a high incidence of cardiac dysfunction and neurocognitive deficits in the postoperative period. Preventive measures are essential to reducing these adverse situations that are responsible for significant morbidity and impairment on life quality of these patients. Surgery and cardiopulmonary bypass (CPB) produces important changes in the immune system, directly involved in the incidence of these complications and is credible that anesthesia choice can it modified. We hypothezised that dexmedetomidine, an (α)-2-agonist, could the inflammatory response to CABG and CPB modified. In a prospective and randomized study, we intend to demonstrate the influence of dexmedetomidine (TIVA-DEX group), as a component of a conventional total intravenous anesthesia (TIVA-propofol+sufentanil) in patients undergoing CABG, with mini-CPB, on the behavior of this inflammatory response. The TIVA-DEX group received a continuous infusion of dexmedetomidine associated to a conventional venous anesthesia (continuous infusion of propofol+sufentanil). Intraoperative dosage of cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-10 (IL-10), gamma interferon (INF-γ) and tumor necrosis factor (TNF-α) were performed, and also C-reactive protein (CRP), creatine phosphokinase (CPK), creatine phosphokinase-MB (CPK-MB), I troponin (cTnI), cortisol and glucose. The occurrence of lipid peroxidation, by the study of thiobarbituric acid reactive substances (TBARS) and the activity of delta-aminolevulinate dehydratase (δ-ALA-D) to oxidative stress verify were also avaliated. Dexmedetomidine induce a significative reduction of IL-1, IL-6, TNF-α and INF-γ, as compared to group that not receive dexmedetomidine. The levels of IL-10 were decreased in both groups along the time, at a similar pattern. Differences between groups on δ-ALA-D activity do not occur and TBARS was higher in TIVA-DEX group. We concluded that dexmedetomidine associated to TIVA was able to reduce plasma levels of proinflammatory cytokines IL-1, IL-6, TNF-α and INF-γ in patients submitted to CABG surgery under mini-CPB, as compared to a conventional TIVA. These results reinforce literature data about dexmedetomidine potentiality as an anti inflammatory agent.

Keywords: Dexmedetomidine. Inflammation. Oxidative Stress. Total Intravenous Anesthesia (TIVA). Cardiopulmonary Bypass (CPB).

LISTA DE ILUSTRAÇÕES

INTRODUÇÃO

MANUSCRITO 1

MANUSCRITO 2

LISTA DE TABELAS

MANUSCRITO 2

LISTA DE ABREVIATURAS E SIGLAS

δ-ALA-D - δ-aminolevulinato desidratase

ADP - difosfato de adenosina

AIVT- anestesia intravenosa total

ATP - trifosfato de adenosina

AVC - acidente vascular cerebral

BIS - índice biespectral

CEC - circulação extracorpórea

CPK - creatino fosfoquinase

CPK-MB - creatino fosfoquinase miocárdio específica

CRM - cirurgia de revascularização miocárdica

cTnI - troponina

DNA - ácido desoxirribonucleico

EROs - espécies reativas de oxigênio

H2O2 - peróxido de hidrogênio

ICAM - intercellular adhesion molecule

IgE - imunoglobulina E

IL-1 - interleucina-1

IL-6 - interleucina-6

IL-8 - interleucina-8

IL-10 - interleucina-10

INF-γ - interferon gama

NOS - enzima óxido nítrico sintase

I/R - isquemia/reperfusão

MECC - mini extracorporeal circulation

MEEM - mini exame do estado mental

NADPH - nicotinamida adenina dinucleotideo fosfato

NADPH-oxidase - nicotinamida adenina dinucleotideo fosfato oxidase

NO - óxido nítrico

OONO - peroxinitrito

O2 - radical superóxido

$PaCO_2$ - pressão arterial de gás carbônico

PAF - fator de ativação plaquetária

PCR - proteina C reativa

PECAM - platelet/ intercellular adhesion molecule

ROS: reactive oxygen species

SECC- standard extracorporeal circulation

SNS - sistema nervoso simpático

SOD - superóxido dismutase

SIRS: systemic inflammatory response syndrome

SRIS - síndrome da resposta inflamatória sistêmica

TNF-α- fator de necrose tumoral alfa

TBARS - substâncias reativas ao ácido tiobarbitúrico

UFSM - Universidade Federal de Santa Maria

UTI- unidade de tratamento intensivo

SUMÁRIO

APRESENTAÇÃO

No item **INTRODUÇÃO**, está descrita uma breve apresentação sobre os temas trabalhados nesta tese.

Uma revisão sobre a resposta inflamatória induzida pela circulação extracorpórea e a discussão sobre as potencialidades do anestésico dexmedetomidina como agente modulador desta resposta é apresentada como **MANUSCRITO 1**.

Os resultados que fazem parte desta tese estão apresentados sob a forma de artigo, o qual se encontra no item **MANUSCRITO 2**. As seções Materiais e Métodos, Resultados, Discussão dos Resultados e Referências Bibliográficas, encontram-se nos próprios manuscritos e representam os resultados finais deste estudo.

Os itens, **DISCUSSÃO E CONCLUSÕES**, encontram-se no final desta tese, apresentam interpretações e comentários gerais sobre os artigos científicos contidos neste trabalho.

As **REFERÊNCIAS BIBLIOGRÁFICAS** referem-se somente às citações que aparecem nos itens **INTRODUÇÃO, DISCUSSÃO e CONCLUSÕES** desta tese.

1 INTRODUÇÃO

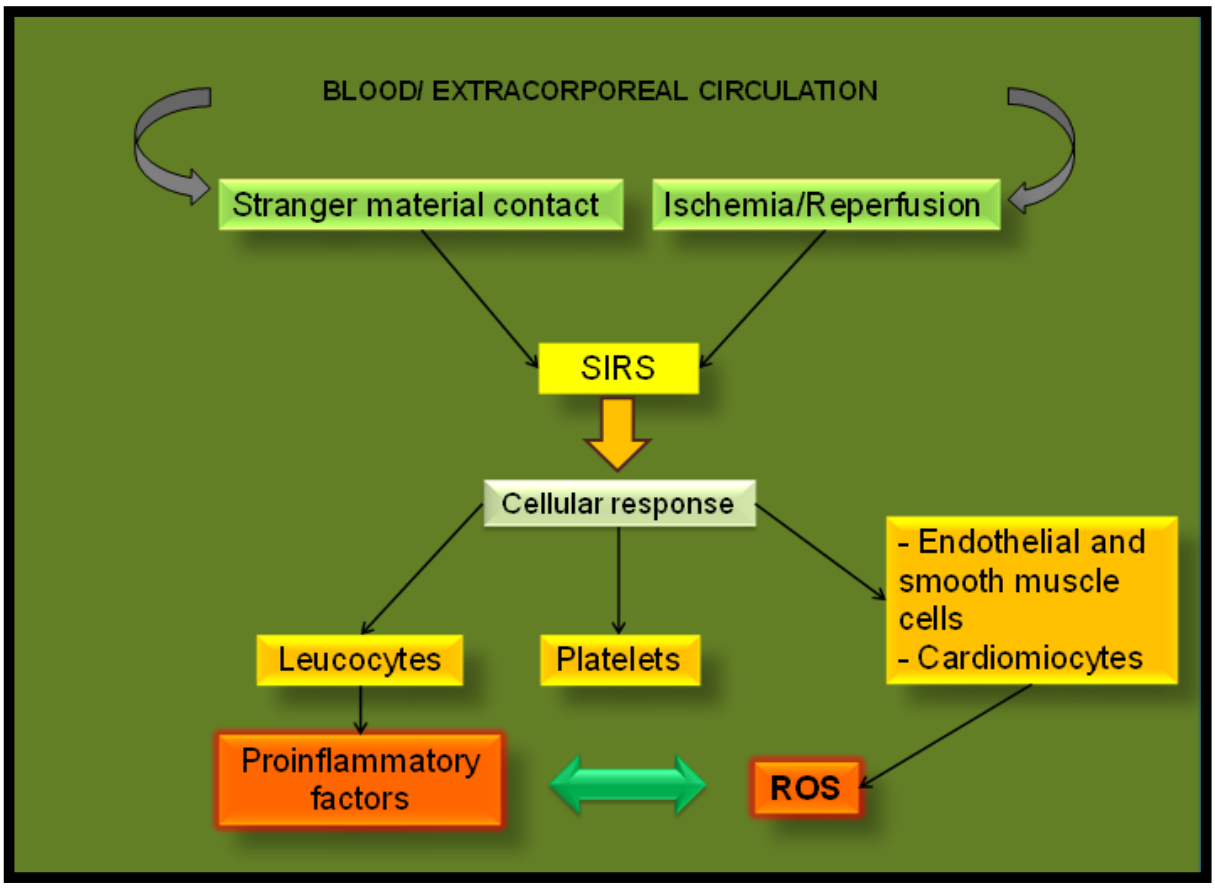
Durante os procedimentos cirúrgicos cardiológicos, devido à agressão tecidual, como uma resposta fisiológica, ocorre o aumento agudo de citocinas pró-inflamatórias, a redução dos níveis de citocinas anti-inflamatórias, o aumento de metabólitos do ácido araquidônico, de espécies reativas de oxigênio (EROs) e de outros mediadores (STEINBERG e cols., 1993; CASEY e cols., 1993; FRANGOGIANNIS e cols., 1998; SAVARIS e cols., 2001; SANDER e cols., 2006; WARREN e cols., 2009; PERRY e cols., 2010). Vários métodos são utilizados para minimizar esta resposta, com o intuito de melhorar as condições pós-operatórias dos pacientes e a técnica anestésica utilizada pode interferir nos mecanismos envolvidos (CROZIER e cols., 1994), sendo objeto interessante para estudo e pesquisa.

Na verdade, em pacientes submetidos à cirurgia de revascularização miocárdica (CRM) sob circulação extra-corpórea (CEC), pelo contato do sangue com superfícies não endoteliais e pela reperfusão de órgãos isquêmicos ocorrem alterações que se assemelham à síndrome da resposta inflamatória sistêmica (SRIS) (FRANGOGIANNIS e cols., 1998; de MOURA e cols., 2001; WARREN e cols., 2009) (Esquema 1). A SIRS caracteriza-se por temperatura corporal > 38°C ou < 36°C, freqüência cardíaca >90 batidas por minuto, freqüência respiratória > 20 inspirações por minuto ou pressão arterial de gás carbônico ($PaCO_2$) <32mmHg, contagem de glóbulos brancos >12.000 ou < 4000 ou >10% das formas imaturas (De MOURA e cols., 2001).

A liberação de citocinas pró-inflamatórias (interleucina-1(IL-1), interleucina-6 (IL-6), fator de necrose tumoral alfa (TNF-α) e interferon gama (INF-γ)), é responsável por induzir febre, neutrofilia e modular a produção de outras citocinas pelos monócitos e neutrófilos, correlacionando-se com maior mortalidade pós-operatória (SAVARIS e cols., 2001; SANDER e cols., 2006). As citocinas anti-inflamatórias, ao contrário, têm papel regulador importante na redução da liberação das interleucinas pró- inflamatórias. A interleucina-10 (IL-10) inibe a síntese do TNF-α, IL-1, IL-6 e IL-8 em monócitos e macrófagos (SABLOTZKI e cols. 1997). Sander e colaboradores (2006) confirmaram em seus estudos, achados anteriores de que a cirurgia cardíaca com CEC leva ao aumento pós-operatório da IL-10 (SABLOTZKI e cols., 1997; SANDER e cols., 2006) e relataram também aumentos significativos para IL-10 em pacientes que desenvolveram infecção no período pós-operatório. O aumento da IL-10 tem sido descrito como preditivo de evolução desfavorável

após a cirurgia (GALLEY e cols., 2003). Seu aumento parece estar correlacionado à infecção e sépsis após trauma ou cirurgia (LYONS e cols., 1997) e indica aumento da mortalidade (VANDISSEL e cols., 1998) sendo que um estado anti-inflamatório acentuado também parece ser prejudicial à evolução clínica do paciente (GOGOS e cols., 2000).

As espécies reativas de oxigênio (EROs) também possuem papel fundamental no aumento de complicações pós-operatórias que ocorrem em cirurgias de revascularização miocárdica sob CEC (BOLLI e cols., 1988; MAULIK e cols., 1998). Com um ou mais elétrons não pareados, tornam-se altamente reativas e exercem seus efeitos nocivos sobre as células, obtendo elétrons de outras moléculas que poderão ser de lipídios, de proteínas e mesmo do ácido desoxirribonucleico (DNA) (MARCZIN e cols., 2003; ELAHI e cols., 2008).



Esquema 1 - Resposta inflamatória gerada pela circulação extracorpórea que se assemelha à síndrome da resposta inflamatória systêmica (SRIS). O contato do sangue com os materiais estranhos do circuito de circulação extracorpórea, a isquemia/reperfusão e a indução pela hiperoxigenação, geram uma resposta semelhante à SRIS. Esta resposta está associada com a ativação patológica de leucócitos, plaquetas (que contribuem para o aumento da coagulação), células endoteliais e cardiomiócitos. A secreção de fatores pró-inflamatórios pelos leucócitos e o aumento da tensão sanguínea de oxigênio estimulam a produção anormal de espécies reativas de oxigênio (EROs), o que leva a um ciclo inflamatório vicioso. SIRS: systemic inflammatory response syndrome; ROS: reactive oxygen species.

1.1 Circulação Extra-Corpórea Convencional (CEC-SECC) e Mini-Circulação Extra-Corpórea (Mini-CEC-MECC)

A circulação extracorpórea (CEC) (Figura 1) é um procedimento que surgiu na década de cinquenta, com o objetivo de simular, mecanicamente, as funções do coração e manter a oxigenação do sangue, permitindo aos cirurgiões, examinar e corrigir as lesões cardíacas com maior especificidade. John e Mary Gibbon (GIBBON, 1970; GIBBON, 1971), depois de várias pesquisas e experiências, montaram um efetivo sistema de respiração e circulação artificiais. Com o passar dos anos, os aparelhos foram sendo modificados, com a utilização de materiais de maior biocompatibilidade e a introdução de outros mecanismos que possibilitaram uma dinâmica mais adequada do sistema circulatório (GALLETTI e BRECHER, 1962; GOMES e CONCEIÇÃO, 1985). Hoje, a CEC é de grande utilização, nas mais diversas cirurgias, permitindo intervenções em recém-nascidos, em crianças, em portadores de lesões múltiplas e/ou graves, em idosos com doenças sistêmicas associadas e em cirurgias para transplantes cardíacos.

Apesar de a CEC ter solucionado os obstáculos que impediam o acesso às cavidades do coração, apresenta um conjunto de complicações advindas da resposta do organismo às agressões impostas por seu mecanismo pouco fisiológico. Dentre os problemas, os principais são a importante resposta inflamatória apresentada pelos pacientes, a hemodiluição excessiva e/ou hemólise, a necessidade de uso de sangue homólogo para o preenchimento do circuito de CEC e a lesão da microcirculação, causada pelo tipo de fluxo induzido pelas bombas do aparelho. A hemodiluição apresenta efeitos indesejados, tais como a redução da pressão osmótica sangüínea e da capacidade de carrear oxigênio, causando acidose, hipóxia, edema e alterações na coagulação (GIBBON, 1954).

Durante a CEC, a circulação é totalmente modificada pela indução de um fluxo não pulsátil do lado arterial, passando o fluxo capilar a ser contínuo, o que aumenta a pressão do lado venoso. Este fluxo contínuo leva à adaptação celular que resulta no desenvolvimento de uma resposta inflamatória semelhante à síndrome da resposta inflamatória sistêmica (SRIS) (De SOUZA e ELIAS, 2006). Ocorrem formações de microbolhas, que causam obstrução dos capilares, promovendo isquemia, inflamação, ativação de complemento e da agregação plaquetária (BARAK e KATZ, 2005).

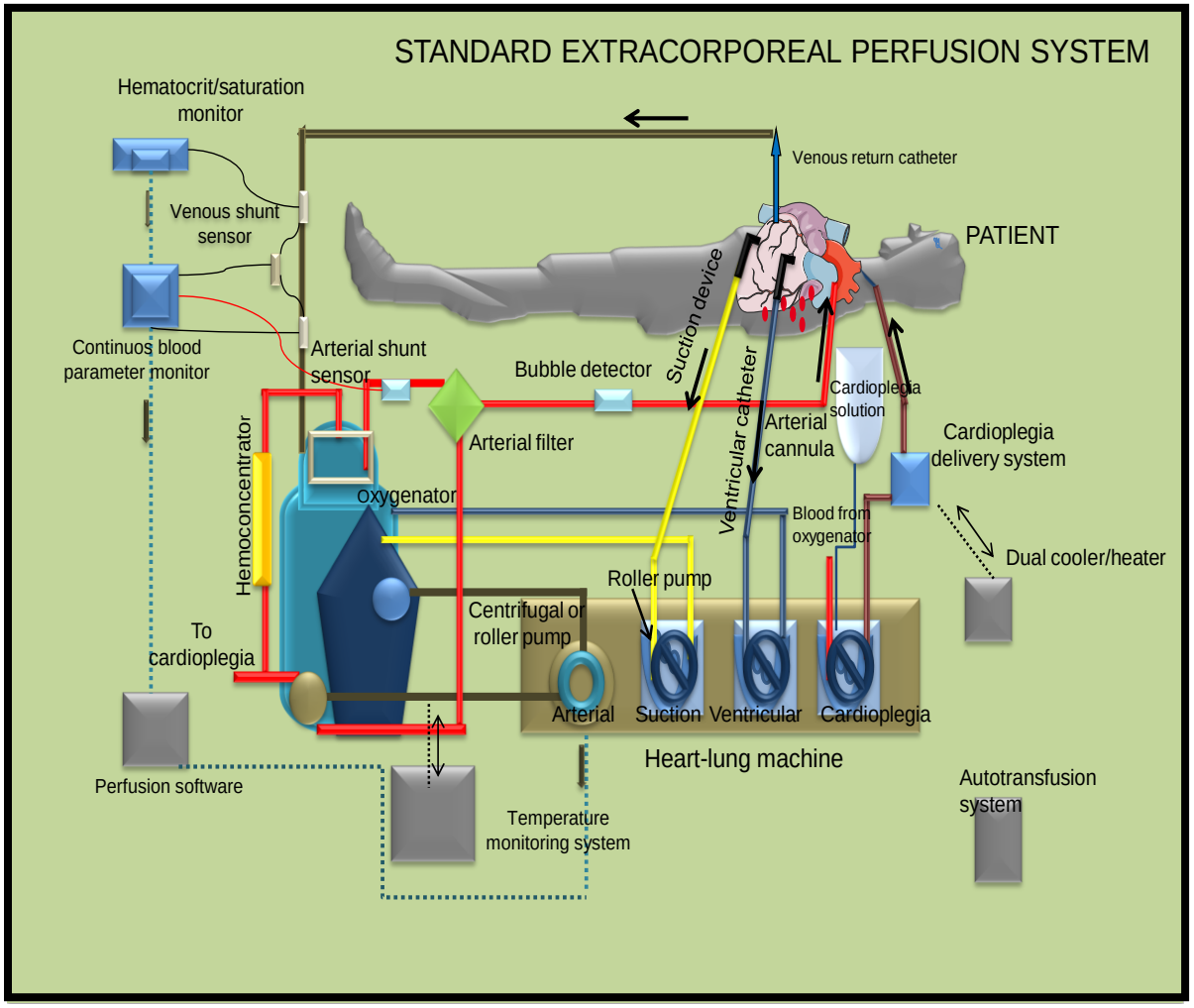


Figura 1 - Sistema Convencional de Circulação Extracorpórea. Em cirurgias com parada circulatória e uso de circulação extracorpórea, o sangue é desviado do coração e pulmões, passando por um oxigenador externo e por amplo sistema de tubulações e bombas que permitem a oxigenação dos tecidos, durante a cirurgia.

A SRIS não é complicação exclusiva da CEC em cirurgias cardíacas, mas a CEC continua sendo o maior fator envolvido em seu aparecimento (BUTLER e cols., 1993; NIEMAN e cols., 1999). Na tentativa de reduzir esta resposta, surgiram os circuitos menores, fechados, que parecem reduzir a hemodiluição e as superfícies de contato do sangue com material estranho. A evolução destes sistemas de CEC levou ao desenvolvimento do sistema de mini-CEC, ou sistema de MECC (Mini-Extracorporeal Circulation). Este circuito pode oferecer algumas vantagens, tais como uma menor exposição do sangue a componentes estranhos pela sua menor extensão, por ser fechado sem contato com o ar, o que também diminui as alterações celulares, por ter a necessidade de volume inicial menor para preencher

o sistema (*priming*), levando a menor hemodiluição e pelo uso de bombas centrífugas, o que diminui a lesão celular e a resposta inflamatória (Figura 2).

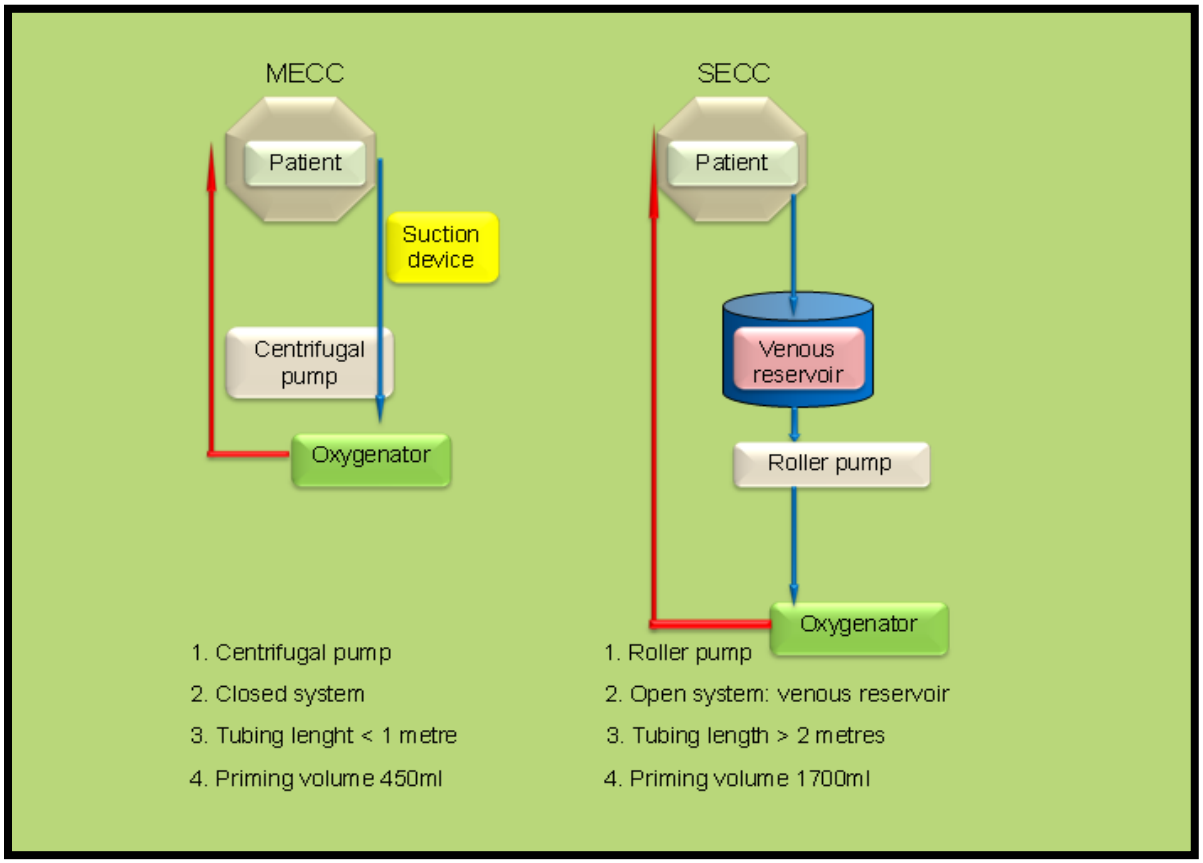


Figura 2 - Comparação entre os sistemas de MECC (Mini-Extracorporeal Circulation) e SECC (Standard Extracorporeal Circulation). No sistema de MECC, existem vantagens por ser um circuito com menor extensão, usar bomba centrífuga, usar um sistema fechado onde o sangue não entra em contato com o ar e ter uma necessidade de *priming* menor que o sistema convencional (SECC).

Demonstrou-se inicialmente que o sistema de mini-CEC pode reduzir a SRIS se comparado com os circuitos convencionais (FROMES e cols., 2002; REMADI e cols., 2006). Contudo, apesar de alguns resultados promissores, ainda não parece existir consenso sobre as vantagens destes circuitos miniaturizados sobre a resposta inflamatória. Em estudo de Bical e colaboradores (BICAL e cols., 2006), os níveis de proteína C reativa (PCR) e interleucina-6 (IL-6) aumentaram sem haver diferenças entre o grupo submetido aos circuitos convencionais de CEC e o grupo submetido à mini-CEC, contudo, ocorreu menor liberação de interleucina-10 (IL-10) com o uso de mini-CEC. Outros autores mostram inclusive não haver diferença para estes marcadores (PCR e IL-6) entre grupos de revascularização miocárdica com CEC se

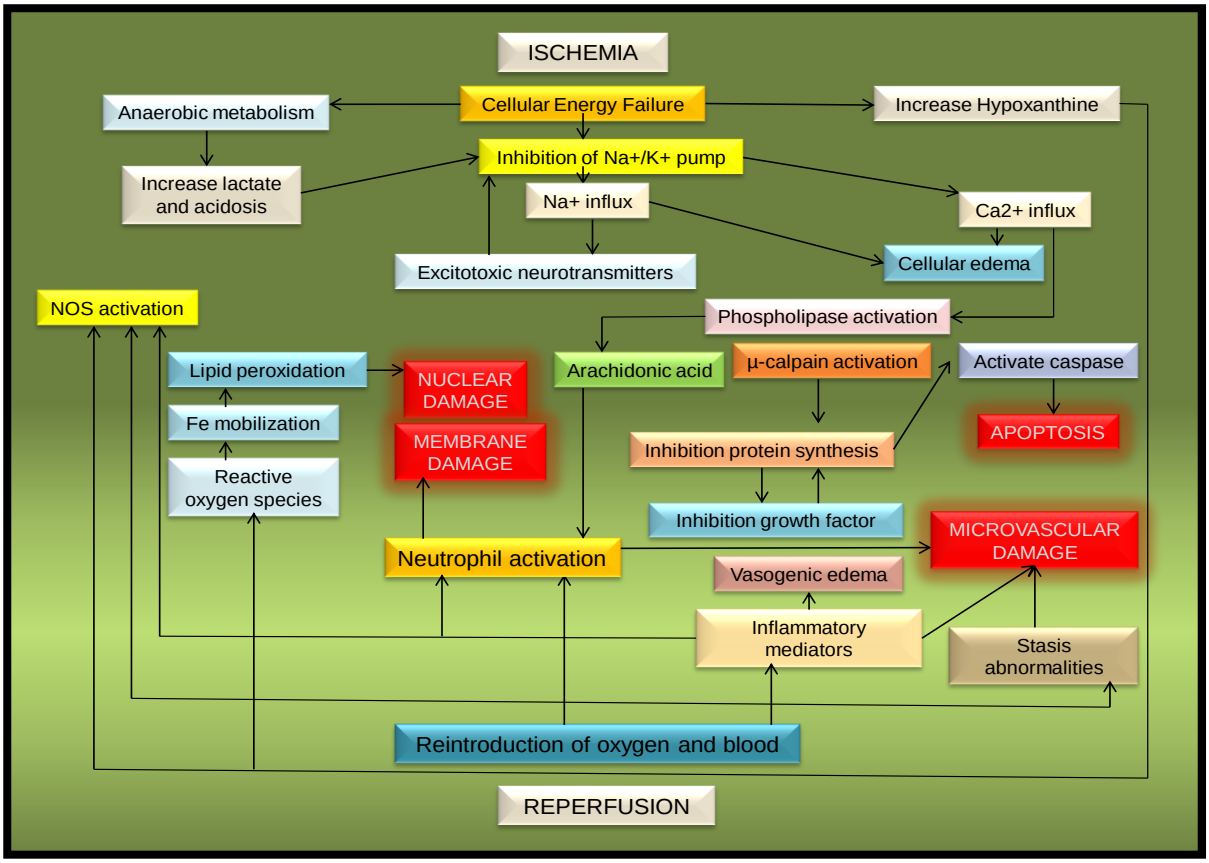
comparados ao grupo sem CEC (ASCIONE e cols., 2000; FRANKE e cols., 2005), sugerindo que a PCR e IL-6 possam ser, na verdade, marcadores ativados principalmente pelo trauma cirúrgico e não propriamente pela CEC. O fator de necrose tumoral-α (TNF-α) e a elastase parecem ser mais sensíveis em avaliar a SRIS pós-CEC (TORRE-AMIONE e cols., 1995; EPPINGER e cols., 1996; TANG e cols., 2004). Foi relatada uma menor liberação de TNF-α e elastase em pacientes submetidos ao sistema de mini-CEC se comparado a circuitos convencionais (FROMES e cols., 2002).

A disfunção orgânica após a CEC, tendo como base a SRIS, é um dos grandes problemas envolvendo a cirurgia cardiovascular (KAPOOR e cols., 2004) e a presença de endotoxemia piora a resposta clínica dos pacientes, principalmente pela indução de disfunção respiratória (LI e cols., 2005; MADDEN e cols., 2007). Como a SRIS tem fisiologia multifatorial, uma única intervenção não seria capaz de minimizá-la. O uso do mini- circuito de circulação extracorpórea é uma solução parcial para o problema em questão. Porém, como os resultados continuam contraditórios em demonstrar diferenças na evolução clínica de pacientes, se comparadas cirurgias sob CEC e mini-CEC (REMADI e cols., 2004; PERTHEL e cols., 2005) ou mesmo entre grupos sem uso de CEC (SHROYER e cols., 2009), há motivação para se buscar outros meios para redução da SRIS relacionada a cirurgias cardíacas.

1.2 Resposta Inflamatória em Cirurgia Cardíaca

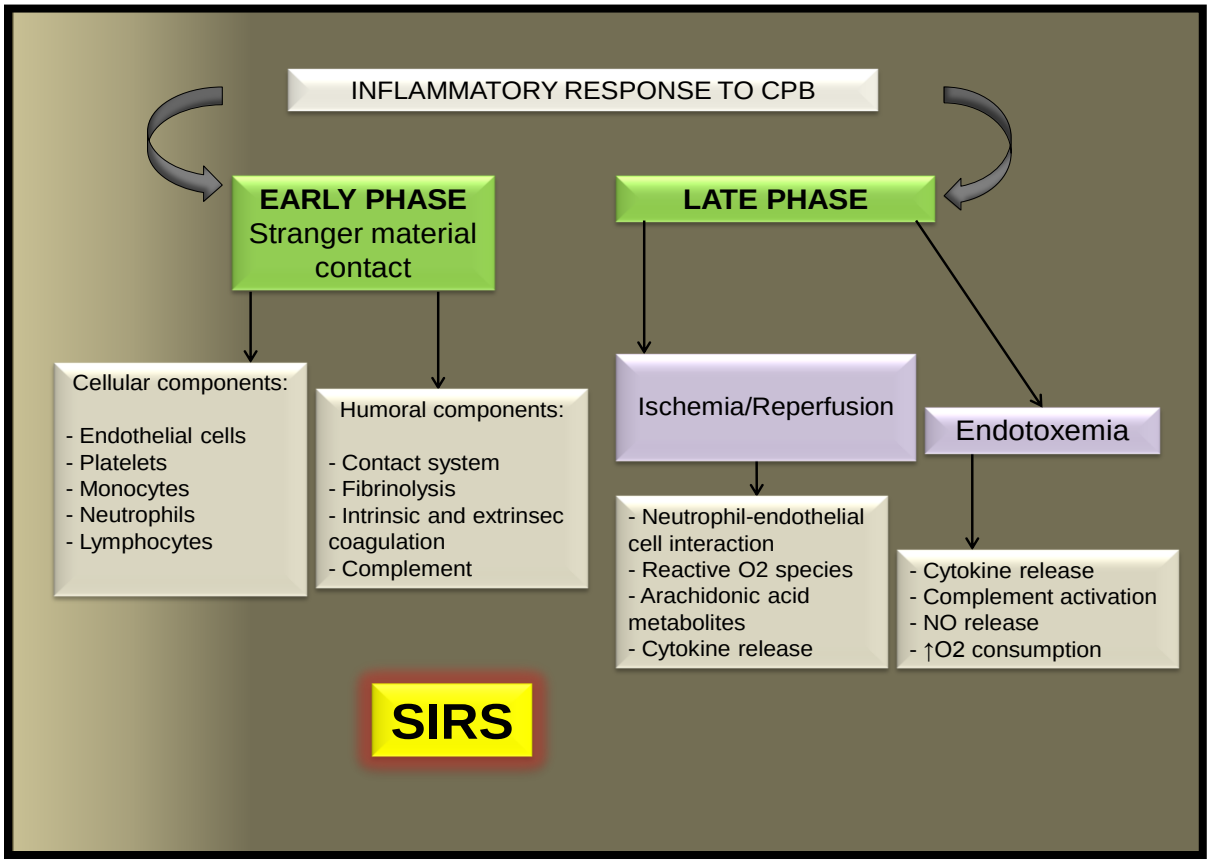
Maqsood e colaboradores (MAQSOOD e cols., 2008), fizeram ampla revisão sobre a resposta inflamatória relacionada à cirurgia cardíaca, com suas alterações humorais e celulares**,** e as possibilidades de interferência sobre as mesmas. Além da exposição do sangue a estruturas não fisiológicas do circuito externo de circulação, o trauma cirúrgico, a anestesia, a hipotermia com posterior reaquecimento, a liberação de endotoxinas intestinais e a lesão por isquemia/reperfusão (I/R) são importantes mediadores destas alterações (Elahi e cols., 2006) (Esquema 1). A isquemia/reperfusão, principalmente, leva a uma complexa reação imunológica, intermediada pelos leucócitos, com a liberação de EROs, metabólitos do ácido araquidônico, fatores plaquetários ativados, endotelinas, citocinas pró-inflamatórias e moléculas de adesão plaquetária e endotelial (MATATA e cols., 2000; MATATA e GALINANES, 2000) (Esquema 2).

Manifestações clínicas, tais como internações prolongadas, maior incidência de infecção na ferida operatória, falência respiratória, disfunção miocárdica, alterações metabólicas hepáticas, coagulopatias, insuficiência renal, distúrbios neurológicos e maior mortalidade podem decorrer de tais alterações (PLOMONDON e cols., 2001).



Esquema 2 - Complexa cascata inflamatória relacionada à isquemia/reperfusão. O metabolismo anaeróbico leva a um aumento do lactato e redução do pH com falência das bombas trans-membrana, levando a um acúmulo de Ca^{2+} e Na^{+}, gerando edema celular. O aumento intracelular de Ca^{2+} ativa a fosfolipase A2 e a calpaína, levando à degradação do ácido araquidônico e inibição da síntese proteica, com ativação dos neutrófilos e ativação das caspases, gerando apoptose celular. A ativação dos neutrófilos leva a lesões de membrana e liberação de mediadores inflamatórios, inclusine óxido nítrico pela ativação da oxidonítrico sintase (NOS), com alteração da microcirculação lesão endotelial, formando-se um círculo vicioso inflamatório.

Franke, Warren e colaboradores (FRANKE e cols., 2002; WARREN e cols., 2009) demonstraram que a resposta inflamatória pós-CEC ocorre em duas fases (Esquema 3).



Esquema 3 - A resposta inflamatória decorrente da circulação extra corpórea (CPB-Cardiopulmonary Bypass) está dividida em duas fases: fase precoce (early phase) e fase tardia (late phase). A primeira fase é induzida pelo contato com material estranho do circuito extracorpóreo, enquanto a fase tardia se deve mais à reperfusão de oxigênio após a isquemia e à endotoxemia. SIRS: systemic inflammatory response syndrome; CPB: cardiopulmonary bypass.

A fase precoce decorre da exposição do sangue a superfícies não endoteliais do circuito de CEC, favorecendo a formação de coágulos, pelo desequilíbrio entre substâncias pró-coagulantes e anti-coagulantes, normalmente produzidas pelo tecido endotelial. As proteínas plasmáticas aderidas no circuito sofrem alterações conformacionais, levando à ativação de outros grupos de proteínas plasmáticas e grupos celulares que, numa complexa interação, iniciam uma resposta inflamatória difusa. Conforme a CEC avança, diminui esta resposta humoral e celular inicial, possivelmente pela aderência das proteínas plasmáticas ao circuito interno, tornando-o mais biocompatível. Começa a ser verificada então, a segunda fase da resposta inflamatória, ou fase tardia, relacionada à isquemia/reperfusão dos órgãos e tecidos e à endotoxemia (Esquema 2, Esquema 3).

O clampeamento aórtico realizado durante a CEC retira o aporte de sangue ao coração e aos pulmões (estes recebendo ainda algum suprimento das artérias brônquicas). A liberação do clampeamento, reperfunde amplamente estas áreas anteriormente isquêmicas, gerando uma

resposta inflamatória com alteração da perfusão capilar, acúmulo de fluido intersticial, leucocitose e coagulopatia. A ativação dos neutrófilos leva a uma extensa lesão endotelial. Em reação independente da ativação leucocitária, ocorre também a produção de EROs. Estas levam à liberação de metabólitos do ácido araquidônico, liberação de TNF-α e citocinas pelas células isquêmicas e ativação do sistema do complemento e da coagulação. A endotoxemia que ocorre pela liberação de toxinas (lipopolissacarídeos da parede celular das bactérias gram-negativas intestinais) na corrente circulatória parece ser um dos maiores estímulos para o desenvolvimento da SRIS (OPAL e cols., 2007).

Em nível celular, o metabolismo anaeróbico durante a isquemia leva a um aumento do lactato e fosfato inorgânico e redução do pH, que por sua vez leva à falência das bombas transmembrana, com acúmulo de sódio e cálcio, gerando edema intracelular (Esquema 2). O cálcio intracelular ativa a fosfolipase A2 e a calpaína entre outras proteases, e a falência das bombas de hidrogênio lisossomais e a queda do pH ativam enzimas lisossômicas que lesam as organelas celulares (De MOURA e cols., 2001).

A fosfolipase A2 degrada o ácido araquidônico, originando mediadores da inflamação, como leucotrienos, prostaglandinas e tromboxanos, substâncias que levam à adesão e ativação neutrofílica, vasoconstrição, lesão tecidual, agregação plaquetária e quimiotaxia na área isquêmica (De MOURA e cols., 2001). As EROs e os produtos da reação inflamatória, em um círculo vicioso, atraem e ativam os leucócitos, os quais liberam várias enzimas proteolíticas, como elastases, hidrolases, mieloperoxidases e proteases, causando destruição tecidual e amplificando a resposta inflamatória e a quimiotaxia (JUNQUEIRA e CARNEIRO, 2004; FRANCISCHETTI e cols., 2010).

Além dos leucócitos, as células endoteliais também são ativadas pelas substâncias inflamatórias circulantes. Inicia-se, então, a fase de rolamento dos leucócitos (principalmente os neutrófilos) (Figura 3) que por meio da exposição das L-selectinas (seus receptores) e a interação destas com os receptores P-selectinas (glicoproteínas intracelulares) das células endoteliais ativadas, desenvolvem uma fase de adesão frouxa ao endotélio vascular (MITCHELL e BEVILACQUA, 2006). Essa ligação é normalmente induzida pelo TNF-α e IL-1.

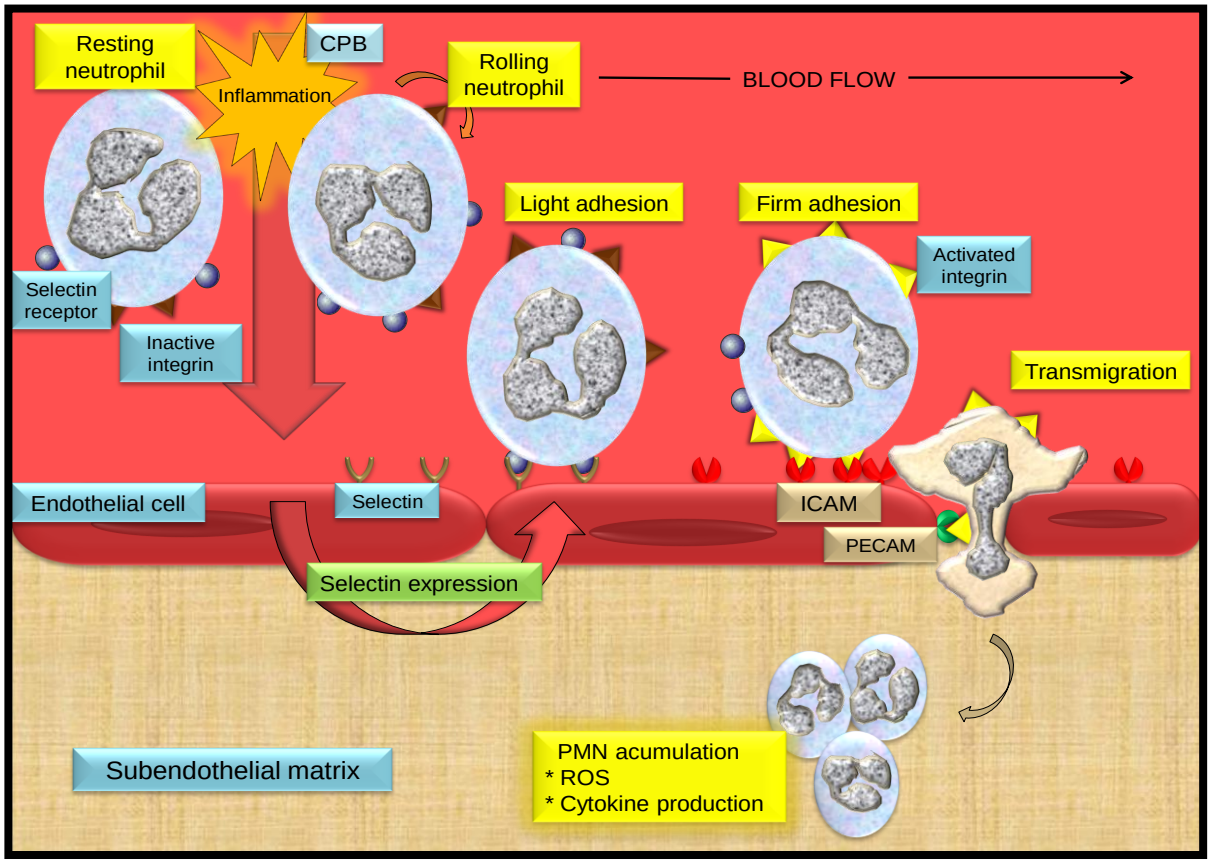


Figura 3 - Fase de estímulo dos neutrófilos e células endoteliais pelos fatores inflamatórios circulantes. Ocorre o rolamento dos neutrófilos, adesão ao endotélio e posterior transmigração aos sítios inflamatórios, gerando acúmulo de polimorfonucleares e lesão tecidual. CPB: Cardiopulmonary Bypass; PMN: polymorphonuclears; ROS: Reactive Oxygen Species; ICAM: Intercellular adhesion molecule PECAM: Platelet/endothelial cell adhesion molecule.

A adesão intensa ocorre logo a seguir, por meio do contato das integrinas leucocitárias (complexos CD11/CD18) com as imunoglobulinas endoteliais vasculares (intercellular adhesion molecule- ICAM) (MITCHELL e BEVILACQUA, 2006), com migração dos leucócitos por diapedese aos sítios de inflamação. Estes são guiados por vários fatores quimiotáticos (MITCHELL e BEVILACQUA, 2006) (as aminas vasoativas, como a histamina e a serotonina, os metabólitos do ácido araquidônico (prostaglandinas, leucotrienos), as proteínas plasmáticas (sistemas do complemento, das cininas e da coagulação), o fator de ativação plaquetária (PAF), as citocinas (TNF-α e IL-1), o óxido nítrico (NO), os componentes lisossômicos dos leucócitos e as EROs) (FRANCISCHETTI e cols., 2010). A IL-8 parece ter papel importante na indução da migração dos neutrófilos pela parede endotelial (HUBER e cols., 1991). Há evidências de que a aderência induzida pelo CD11/CD18 induz à degranulação dos neutrófilos (RICHTER e cols., 1990), gerando EROs e

enzimas proteolíticas, que resultam em lesão importante às células endoteliais e consequentemente aos tecidos (SHAPPELL e cols., 1990).

A histamina e a serotonina, encontrados nos mastócitos, nos basófilos e nas plaquetas, são os primeiros mediadores liberados durante a inflamação. A imunoglobulina E (IgE), fragmentos do complemento C3a e C5a, citocinas e fatores liberadores de histamina derivados de leucócitos participam da liberação nos mastócitos. A liberação de histamina das plaquetas é estimulada após contato com colágeno, trombina, difosfato de adenosina (ADP), complexos antígeno- anticorpo e o fator ativador plaquetário (PAF). Os fragmentos C3a e C5a são importantes iniciadores da ativação neutrofílica e da produção de IL-8 (De MOURA e cols., 2001) nas lesões de isquemia/reperfusão (WALSH e cols., 2005). Desde estudo inicial de Weisman e colegas (WEISMAN e cols., 1990), que demonstrou depósitos de complemento em miocárdio reperfundido, outros estudos também comprovaram sua participação nos mecanismos de isquemia/reperfusão em outros órgãos (PEMBERTON e cols., 1993; WADA e cols., 2001; ZHAO e cols., 2002). Uma vez ativado, o complemento libera potentes substâncias inflamatórias, incluindo anafilatoxinas e complexos citolíticos, interagindo com as EROs (STAHL e cols., 2003).

As citocinas pró-inflamatórias são produzidas por linfócitos e macrófagos, mas também por células endoteliais e as principais são o TNF-α e as interleucinas (IL-1, IL-6 e IL-8). As citocinas levam à exposição de cargas negativas na superfície das células endoteliais (fase de rolamento e adesão), ativando a pré-calicreína que, então, converte-se em calicreína e ativa o fator XII, o qual, ativado, ativa os neutrófilos, levando à destruição da arquitetura endotelial vascular por meio da liberação de enzimas proteolíticas (FRANCISCHETTI e cols., 2010). Ocorre aumento progressivo de elastase sérica, de IL-6, de IL-8 e de PCR (CHRISTEN e cols., 2005; ELAHI e MATATA, 2006), tornando-se um mecanismo mantenedor da liberação de substâncias inflamatórias.

O óxido nítrico (NO) é outro mediador da resposta inflamatória que modifica o tônus e a permeabilidade vascular além de ser um agente quimiotático. É produzido pela enzima indutora óxido nítrico sintetase (iNOS) do endotélio, ativada pelo aumento do cálcio intracelular ou pelos macrófagos após indução por determinadas citocinas, como o INF-γ. Pode-se combinar com as EROs levando à formação de metabólitos como o peroxinitrito (OONO-), altamente reativo (CERQUEIRA e YOSHIDA, 2002). Estudos envolvendo a reação inflamatória pós-CEC, sugeriram que a iNOS esteja relacionada à indução de citocinas pró-inflamatórias, tais como o TNF-α (MATATA e GALINANES, 2002; ELAHI e cols.,

2006) e o NO induzido na resposta inflamatória relaciona-se à disfunção miocárdica (SATO e cols., 1997; OYAMA e cols., 1998).

As EROs, além de mediadores químicos da resposta inflamatória, ativam diferentes vias, tanto de adaptação celular como de apoptose. Enquanto níveis baixos são controlados pelos mecanismos antioxidantes endógenos, níveis elevados podem lesar o DNA das células, assim como proteínas e lipídios, levando à apoptose (MITCHELL e BEVILACQUA, 2006). Nos tecidos pós-isquêmicos (na reperfusão), há o acúmulo da xantina oxidase que, em lugar da nicotinamida adenina dinucleotídeo fosfato (NADPH), utiliza o O_2 como aceptor final de elétrons. Na reação hipoxantina-xantina, os elétrons são transferidos para o O_2, gerando o radical superóxido (O2 •-), o qual sofre dismutação em peróxido de hidrogênio (H_2O_2). A auto-oxidação de catecolaminas e a enzima NADPH-oxidase dos neutrófilos ativados (JOHNSON e cols., 1994) são outras vias na produção de EROs.

1.3 Métodos para reduzir a SRIS pós-CEC

Desde a observação de que a liberação de substâncias inflamatórias e EROs durante a CEC e isquemia/reperfusão leva a eventos indesejáveis como dano microvascular e disfunção em diversos órgãos (ELAHI e MATATA, 2006; GONENC e cols., 2006), pesquisadores buscam a comprovação de estratégias para proteção celular com resultados discrepantes. Além do uso dos mini- circuitos já descritos (TAKAY e cols., 2005), o uso de antioxidantes exógenos foi um dos mais estudados. Porém, como estes possuem uma ação predominantemente extracelular, são limitados na sua capacidade para a proteção celular (PRYOR, 1984). Estudos não comprovaram o benefício de antioxidantes exógenos em pacientes submetidos à CEC (ELAHI e cols., 2005; ELAHI e MATATA, 2006; GONENC e cols., 2006) mesmo que estes possam reduzir de alguma maneira a formação de EROs (KAWAHITO e cols., 2000).

A administração de corticosteróides durante a CEC também foi extensamente investigada, pois podem reduzir a liberação de complemento (SANO e cols., 2003; LIAKOPOULOS e cols., 2007). Apesar dos resultados positivos, em pacientes submetidos à CEC (WAN e cols., 1999; CHANEY e cols., 2001; ASIMAKOPOULOS e cols., 2003; LEVY e TANAKA, 2003; RUBENS e cols., 2005), benefícios clínicos evidentes não foram confirmados e efeitos pouco desejáveis, como uma maior demora na extubação dos pacientes

(WAN e cols., 1999; CHANEY e cols., 2001; ASIMAKOPOULOS e cols., 2003; LEVY e TANAKA, 2003; RUBENS e cols., 2005) em doses expressivas.

A aprotinina, um polipeptídeo extraído de pulmão bovino, também pode limitar a fibrinólise associada à exposição sanguínea a superfícies estranhas, pois tem efeito anti-inflamatório pela redução da produção de NO (BRUDA e cols., 1998), podendo aumentar a liberação de IL-10 (HILL e cols., 1998). Clinicamente, a aprotinina reduziu a necessidade de uso de transfusão homóloga e o risco de Acidente Vascular Cerebral (AVC), se comparada ao placebo (SEDRAKYAN e cols., 2004; LEVI e cols., 1999), porém, estudos retrospectivos correlacionaram o seu uso a uma maior morbi-mortalidade no pós-operatório dos pacientes submetidos à cirurgia cardíaca (VAN DER LINDEN e cols., 2007).

O revestimento dos circuitos da CEC com heparina promove uma maior biocompatibilidade dos mesmos, por reduzir a ativação do complemento, pela inibição da ativação de granulócitos ou adesão plaquetária e por diminuir a liberação de TNF-α e IL-8 (KUTAY e cols., 2006; JESSEN, 2006), protegendo os pacientes de alterações cognitivas e disfunções renais durante a CEC (HEYER e cols., 2002; de VROEGE e cols., 2005). Em estudo prospectivo e randomizado, Goudeau e colaboradores (GOUDEAU e cols., 2007) demonstraram concentrações significativamente menores de PCR, IL-6, CPK-MB, troponina I, ácido lático e EROs em plasma de pacientes tratados com heparina, com redução de complicações pós-operatórias e menor tempo de permanência em unidade de tratamento intensivo (UTI). A heparina tem sido usada de rotina em procedimentos que envolvem a CEC.

Como são gerados vários mediadores inflamatórios durante a CEC, sugeriu-se que o uso de filtros para reter leucócitos e outros componentes celulares ativados também poderia reduzir a lesão pulmonar pós-operatória induzida pela CEC (WARREN e cols., 2007). Contudo, a remoção simultânea das plaquetas influencia negativamente a hemostasia trans-operatória (WARREN e cols., 2007). O uso de oxigenadores de membrana em lugar do oxigenador de borbulhas parece reduzir o trauma sanguíneo e a embolia gasosa (LAUTH e cols., 1990). As superfícies hidrofílicas, resistentes ao depósito de proteínas e células e o óxido de polietileno, pela sua configuração molecular favorável, têm sido estudados (TAN e cols., 2007) para uso na construção dos circuitos de CEC.

Como podemos observar, o mecanismo envolvido na resposta do sangue ao circuito de CEC é complexo e está longe de ser completamente elucidado. O estresse oxidativo e a inflamação, intimamente relacionados, correlacionam-se com uma pior evolução clínica dos pacientes submetidos à CRM o que leva à tentativa de adoção de estratégias para o equilíbrio destas respostas.

1.4 Imunomodulação trans-operatória pelos anestésicos

A imunomodulação trans-operatória pelos agentes anestésicos pode ser exemplificada por alguns estudos (CROZIER e cols., 1994; KEVIN e cols., 2005), a maioria deles sugerindo que os anestésicos possuem efeitos anti-inflamatórios, mas relacionados à imunossupressão e maior suscetibilidade dos pacientes a infecções (KRUMHOLZ e cols., 1994; HELLER e cols., 2008), exceção provavelmente feita aos agonistas (α)-2-adrenérgicos (Pandharipande e cols., 2007; PANDHARIPANDE e cols., 2008).

O uso do anestésico propofol (2-6 di-iso-propilfenol), cuja estrutura é semelhante aos anti- oxidantes fenólicos (KAHRAMAN e DEMIRYUREK, 1997), em modelos animais experimentais, é efetivo na proteção a vários órgãos (YOUNG e cols., 1997; NAVAPURKAR e cols., 1998). O propofol é bastante utilizado na indução e manutenção da anestesia geral, principalmente nas anestesias intravenosas totais (AIVT). Em concentração anestésica habitual, leva à redução da peroxidação lipídica (MURPHY e cols., 1992;) com efeito protetor miocárdico (CORCORAN e cols., 2006; XIA e cols., 2006). Porém, dados *in vivo* e *in vitro* (KRUMHOLZ e cols., 1994; HELLER e cols., 1998; KOTANI e cols., 1999) sugerem que os efeitos anti-inflamatórios do propofol podem, em caso de infecções associadas, levar a uma piora do quadro infeccioso.

Os opióides, outra classe de medicamentos que são importantes analgésicos utilizados em anestesia, tiveram seu efeito imunossupressor primeiramente demonstrado em 1898 (CANTACUZENE, 1898). A morfina foi a droga mais estudada, sendo que pouco se sabe sobre o efeito imunossupressor de outros opiódes. Foi demonstrado que a morfina tem efeito ainti-inflamatório *in vitro* e que aumenta a mortalidade em modelos de infecção em animais (WEINERT e cols., 2008). Interessante foi a observação de que a clonidina, um agonista (α)-2-adrenérgico, de maneira dose-dependente, em ratos, foi eficiente em modular a supressão imunológica causada pela morfina (WEST e cols., 1999). Para uma revisão dos efeitos imunomodulatórios dos sedativos/ anestésicos em geral, o trabalho de Sanders e colegas (SANDERS e cols., 2011) constitui-se ótima referência.

Os agonistas (α)-2-adrenérgicos podem exercer seus efeitos através de interações neuro-imunes, pela ação direta sobre o Sistema Nervoso Simpático (SNS), o que mostrou ter efeitos benéficos sobre o sistema imunológico (SMITH e cols., 1977; NANCE e SANDERS, 2007). De maneira controversa, o estímulo de receptores (α)-2-adrenérgicos parece provocar uma resposta pró- inflamatória *in vitro* (SPENGLER e cols., 1990) e *in vivo* (FLIERL e cols., 2007), porém, na maioria dos estudos em animais e humanos a sua administração induziu

resposta anti-inflamatória (NADER e cols., 2001; VENN e cols., 2001; Taniguchi e cols., 2004; MEMIS e cols., 2007; TANIGUCHI e cols., 2008). Esta dualidade parece ser decorrente dos diferentes efeitos, centrais e periféricos, destas drogas. Em nível periférico, os agonistas (α)-2-adrenérgicos parecem estimular a imunidade inata (MILES e cols., 1996; WEATHERBY e cols., 2003; GETS e MONROY, 2005) e a ação simpatolítica central induz a um aumento do tônus parassimpático que parece conseguir promover o controle do quadro infeccioso (STERNBERG, 2006; TRACEY, 2007). Em presença de inflamação, um agonista (α)-2-adrenérgico como a dexmedetomidina age de forma anti-inflamatória preferencialmente (SUD e cols., 2008).

A dexmedetomidina, um anestésico agonista (α)-2-adrenérgico, pode ser uma droga promissora como indutora de proteção celular, pela sua capacidade de ativação pré- sináptica de receptores (α)-2-adrenérgicos (Figura 4), atenuando a liberação excessiva de noradrenalina durante a isquemia (MATSUMOTO e cols., 1993) com diminuição do potencial para a formação de EROs (SCHOLZ e TONNER, 2000; ROCHA e cols., 2010).

A administração trans-operatória de dexmedetomidina tem demonstrado vantagens, como em reduzir as doses de outros anestésicos, em melhorar a estabilidade hemodinâmica e em manter a sedação dos pacientes no período de recuperação de cirurgias de grande porte (JALONEN e cols., 1997; HERR e cols., 2003; AANTAA e JALONEN, 2006) (Figura 5). Kang e colegas (KANG e cols., 2012), demonstraram que a dexmedetomidina (dose de 1 μg. kg^{-1} em bolus e infusão posterior de 0.6 μg. $kg^{-1}.h^{-1}$) reduziu a necessidade de propofol durante a anestesia venosa com o opióide remifentanil sem comprometer o padrão de recuperação, mantendo os pacientes hemodinamicamente mais estáveis. O efeito sedativo da dexmedetomidina é mediado no tronco cerebral, pelo *locus ceruleus,* onde a dexmedetomidina diminui o tônus simpático e aumenta o tônus parassimpático (ARCANGELI e cols., 2009) (Figura 5).

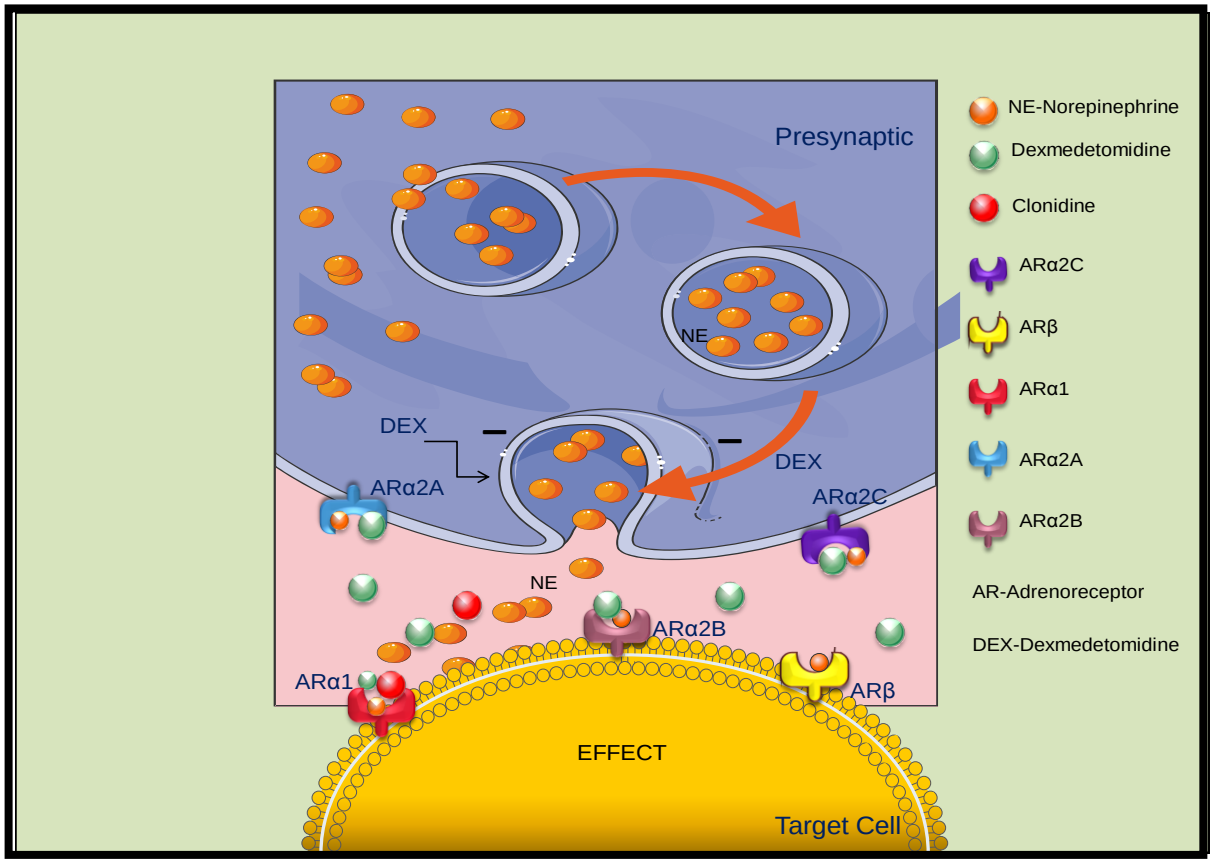


Figura 4 - Efeito da dexmedetomidina sobre os receptores (α)-2-adrenérgicos pré e pós-sinápticos. A dexmedetomidine pode exercer seus efeitos sobre três subtipos de (α)-2-adrenorreceptores. As subclasses pré-sinápticas de (α)-2-adrenorreceptores ((α)-2A e (α)-2C), estimulados pela dexmedetomidina, inibem a liberação de norepinefrina, por feed-back negativo. Localizados pós-sinapticamente estão a subclasse (α)-2B-adrenorreceptores e também (α)-1-adrenorreceptores, pois a dexmedetomidina não é (α)-2-adrenérgica específica. Os (α)-2-adrenorreceptores também existem extrasinapticamente.

Os mecanismos diferentes para produzir sedação entre a dexmedetomidina, o propofol e os opióides sugerem um sinergismo benéfico em sua combinação. O efeito poupador de propofol que a dexmedetomidina apresenta pode ser atraente, por reduzir as doses necessárias do propofol, evitando os seus principais efeitos adversos, tais como a acidose metabólica, a depressão miocárdica, a alteração da agregação plaquetária e a demorada recuperação, relacionados ao seu uso em grandes doses ou por período prolongado (BOLLI e cols., 1988; De LA CRUZ e cols., 1997; AOKI e cols., 1998; BUROW e cols., 2004; SALENGROS e cols., 2004; LIOLIOS e cols., 2005; MERZ e cols., 2006; KAM e CARDONI, 2007).

Autores relataram um efeito anti-inflamatório da dexmedetomidina superior aos dos outros anestésicos (NADER e cols., 2001; VENN e cols., 2001; MEMIS e cols., 2007), atividade anti-apoptótica (MaD e cols., 2004) e capacidade de melhor modulação da função dos macrófagos (MILES e cols., 1996; WEATHERBY e cols., 2003; GETS e cols., 2005;

YANG e cols., 2008). Hofer e colegas (HOFER e cols., 2009) em modelo animal válido para sépsis em humanos, demonstraram que a administração prévia de clonidina e dexmedetomidina aumentou significativamente a sobrevida. Observou-se uma redução dos mediadores pró-inflamatórios IL-1β, IL-6 e TNF-α, inibindo a reação inflamatória à sépsis. Estes resultados suportam a idéia de se considerar o uso de drogas simpatolíticas como adjuvantes importantes em pacientes que serão submetidos a cirurgias de grande porte e/ou em pacientes em unidade de tratamento intensivo (UTI) sujeitos a desenvolver um quadro séptico. Pandharipande e colegas (PANDHARIPANDE e cols., 2007) descreveram o aumento da sobrevida em pacientes críticos sedados em UTI, pelo efeito simpatolítico e vagomimético da dexmedetomidina. Spies e colegas (SPIES e cols., 1996) também demonstraram que pacientes tratados com clonidina para crises de abstinência ao álcool tiveram menor incidência de pneumonia se comparados àqueles tratados com agentes apenas simpatolíticos.

Apesar de que resultados de estudos em humanos continuem contraditórios (WIJEYSUNDERA e cols., 2003; SULEMANJI e cols., 2007; TASDOGAN e cols., 2009), em modelo animal, foi demonstrado também o efeito neuroprotetor da dexmedetomidina (MAIER e cols., 1993) após isquemia cerebral induzida e reperfusão. Estudos bem recentes sugerem que a dexmedetomidina possa ser o anestésico de eleição para pacientes sob o risco de desenvolver lesões neurológicas no período trans-operatório (CHEN e cols., 2013; PENG e cols., 2013).

Os fatores hematológicos também são sensíveis às mudanças metabólicas sendo que a capacidade de deformidade dos eritrócitos e a viscosidade plasmática podem afetar de maneira importante a perfusão dos órgãos e tecidos (SIMCHON e cols., 1987; ZINCHUK, 2001). A ocorrência de estresse oxidativo leva à peroxidação lipídica, com consequente comprometimento das funções e da integridade das membranas dos eritrócitos (KUYPERS, 1998; THEROND e cols., 2000; SIVILOTTI, 2004). Arslan e colegas (ARSLAN e cols., 2012) demonstraram a capacidade de proteção da deformidade dos eritrócitos pelo uso prévio de dexmedetomidina em ratos submetidos à isquemia/reperfusão hepática. O estudo mostrou que ocorre claramente uma alteração importante na capacidade para a deformidade dos eritrócitos no modelo experimental de isquemia/reperfusão hepática em ratos, relacionada à peroxidação lipídica, e que houve proteção pelo uso da dexmedetomidina.

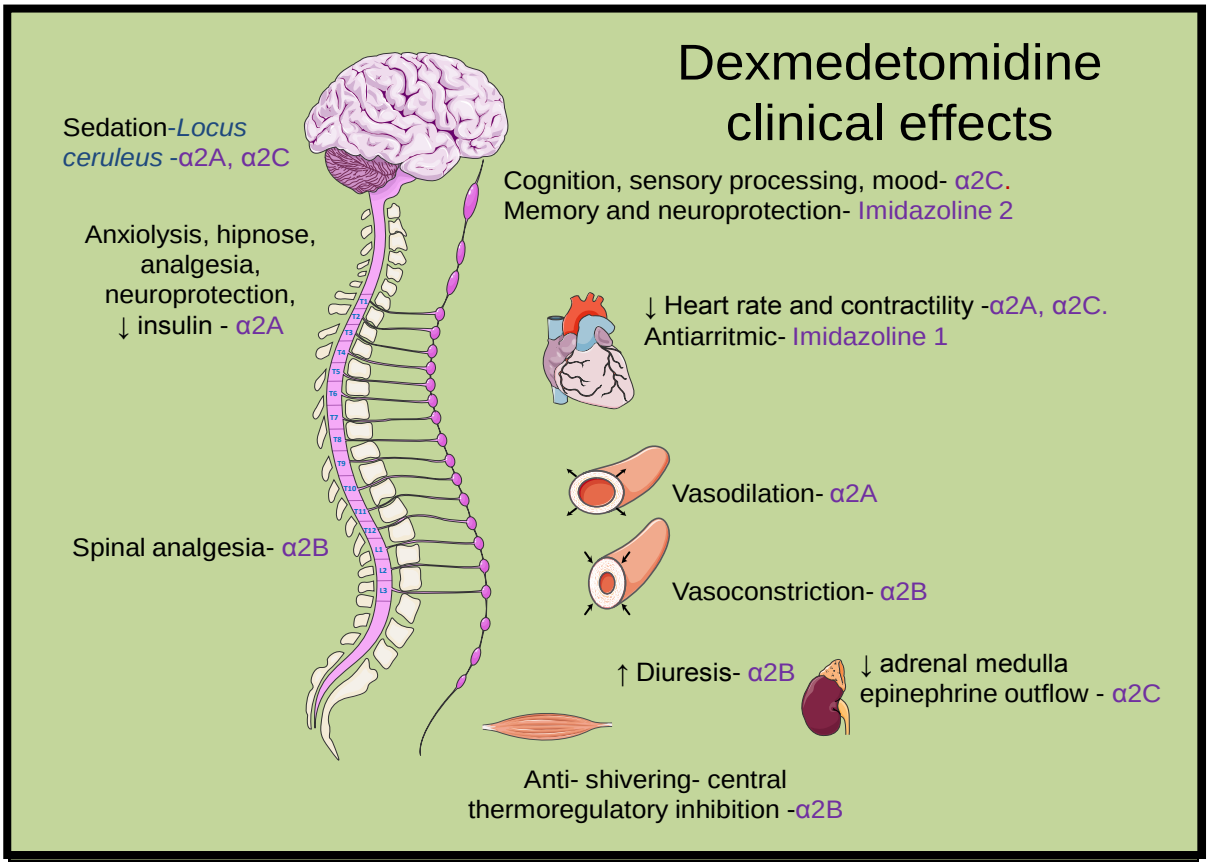


Figura 5 - Efeitos clínicos induzidos pelo uso da dexmedetomidina e os receptores específicos envolvidos. Através do agonismo a adrenorreceptores pré-sinápticos α-2A, a dexmedetomidina induz sedação, ansiólise, hipnose, analgesia, promove a neuroproteção, reduz a liberação de insulina, reduz a frequência cardíaca, reduz a contratilidade miocárdica e leva à vasodilatação. Pelo efeito pré-sináptico sobre os adrenorreceptores α-2C, induz sedação, modulação da cognição, memória e processamento sensório e reduz a liberação de epinefrina na medula adrenal. Pelo agonismo a adrenorreceptores α-2B pós-sinápticos, a dexmedetomidina leva à analgesia em nível espinhal, vasoconstrição (efeito pós-sináptico, com doses elevadas em *bolus*), aumento da diurese e inibição central dos tremores. A dexmedetomidina também atua sobre os receptores imidazolínicos, levando à neuroproteção (receptores imidazolínicos 2) e tendo efeito antiarrítmico (receptores imidazolínicos 1).

1.5 Justificativa

A taxa de mortalidade dos pacientes submetidos à cirurgia de revascularização miocárdica (CRM), no Brasil é bastante elevada (6,2%) (PIEGAS e cols., 2009) se comparada a outros países como os Estados Unidos (2.9%) (HANNAN e cols., 2003) e Canadá (1.7%) (CARTIER e cols., 2008). Diversos estudos têm demonstrado a ocorrência da síndrome da resposta inflamatória sistêmica (SRIS) associada à CRM com circulação extracorpórea (CEC) e suas implicações clínicas indesejadas. Em nosso estudo, propomos investigar o efeito da dexmedetomidina, um anestésico agonista (α)-2-adrenérgico, sobre esta resposta inflamatória. Considerando os resultados positivos obtidos em estudos anteriores quanto à potencialidade da dexmedetomidina, acreditamos que ela possa ser capaz de modificar a resposta inflamatória ao trauma e a evolução clínica dos pacientes. Assim, pretendemos avaliar os níveis plasmáticos de citocinas pró e anti- inflamatórias e outros biomarcadores inflamatórios, além de avaliar a peroxidação lipídica pela dosagem das substâncias reativas ao ácido tiobarbitúrico (TBARS) (PUNTEL e cols., 2007) e o estresse oxidativo pela atividade da enzima delta aminolevulinato desidratase (δ-ALA-D) (BERLIN e SCHALLER, 1974).

1.6 Objetivos

1.6.1 Objetivo Geral

O presente estudo teve como objetivo geral investigar o efeito do uso da dexmedetomidina, uma droga agonista (α)-2-adrenérgica sobre os biomarcadores de inflamação e estresse oxidativo em pacientes submetidos à cirurgia de revascularização miocárdica com mini-circulação extracorpórea.

1.6.2 Objetivos Específicos

Manuscrito 1

1. Determinar o novo estado da arte da dexmedetomidina e suas potencialidades;
2. Discutir a capacidade da dexmedetomidina na proteção celular e de órgãos, visando promover o seu uso, ainda muito incipiente durante os procedimentos cirúrgicos.

Manuscrito 2

1. Comparar dois grupos de pacientes submetidos à cirurgia de revascularização miocárdica com mini-circulação extracorpórea, usando técnicas diferentes de anestesias venosas totais, uma delas com o uso associado da dexmedetomidina;
2. Avaliar o efeito da dexmedetomidina nos níveis dos marcadores inflamatórios, como de IL-1, IL-6, TNF-α, INF-γ e PCR e no nível do marcador antiinflamatório IL-10;
3. Estudar o efeito do uso da dexmedetomidina sobre as respostas ao estresse oxidativo, através da avaliação de TBARS e da atividade da enzima δ-ALA-D;
4. Determinar os níveis dos marcadores de lesão celular miocárdica, como CPK, CPK-MB e cTnI;
5. Avaliar o efeito da dexmedetomidina nos níveis de outros biomarcadores bioquímicos.

2 MANUSCRITOS

Os resultados que fazem parte desta tese estão apresentados sob a forma de manuscritos científicos, os quais se encontram aqui organizados. Uma referência ao estado da arte em relação resposta inflamatória em pacientes submetidos à CRM e potencialidades da dexmedetomidina sobre estas alterações encontram-se no **Manuscrito 1**. Os itens Materiais e Métodos, Resultados e Discussão dos Resultados encontram-se no **Manuscrito 2**. Os **Manuscrito 1** e **Manuscrito 2** estão dispostos na forma em que normalmente se submete para publicação.

2.1 MANUSCRITO 1 – Resposta inflamatória em pacientes submetidos à cirurgia de revascularização miocárdica (CRM) e implicações clínicas: uma revisão da relevância do uso de dexmedetomidina.

Manuscrito 1

INFLAMMATORY RESPONSE IN PATIENTS UNDER CORONARY ARTERY BYPASS GRAFTING SURGERY (CABG) AND CLINICAL IMPLICATIONS: A REVIEW OF THE RELEVANCE OF DEXMEDETOMIDINE USE

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2.1.1 Summary

Despite coronary artery bypass grafting surgery (CABG) with cardiopulmonary bypass (CPB) prolongs life and reduces symptoms in patients with severe coronary artery diseases, these benefits are accompanied by increased risks. Morbidity associated with cardiopulmonary bypass can be attributed to the generalized inflammatory response induced by blood-xenosurfaces interactions during extracorporeal circulation and the ischemia/reperfusion implications, including exacerbated inflammatory response resembling the systemic inflammatory response syndrome (SIRS). The use of specific anesthetic drugs that could, as antiinflammatory agents, these inflammatory response modulate and promote a postoperative recovery may be advantageous. It is known that the stress response to surgery can be attenuated by sympatholytic effects caused by activation of central (α)-2-adrenergic receptor, leading to reductions in blood pressure and heart rate, and more recently, that they can have antiinflammatory properties. This review discusses the clinical significance of the dexmedetomidine use, a selective (α)-2-adrenergic agonist, as a coadjuvant in general anesthesia. Actually, dexmedetomidine use is not in anesthetic routine, but this drug can be considered a particularly promising agent in perioperative multiple organ protection.

Keywords: Dexmedetomidine; Inflammation; Oxidative Stress; Total Intravenous Anesthesia (TIVA); Cardiopulmonary Bypass (CPB).

2.1.2 Introduction

2.1.2.1 Inflammatory response and ischemia/reperfusion in CABG surgery

Surgery induces a variety of metabolic, endocrine, and immune changes known as the "stress response", which may lead to prolonged in-hospital stay. The clinical manifestation of this reaction include postoperative complications such as respiratory failure, wound infections (1) myocardial damage with contractile dysfunction, renal impairment, coagulopathy, neurologic dysfunction (2) and altered liver function with an increased mortality (3).

Inflammatory response in cardiac surgical patients is produced by complex interactions with numerous pathways including generation or activation of complement, cytokines, neutrophils, thrombin, mast cells, and others multiple inflammatory mediators. Cardiopulmonary bypass responses has often been compared with the pathophysiologic

changes occurring in systemic inflammatory response syndrome (SIRS) (4) and remain not fully understood. Several interlinked mechanisms could play a role in the pathological effects associated with cardiopulmonary bypass, for instance, the exposure of blood to nonphysiologic surfaces, surgical trauma, anesthesia, changes in body temperature, increased intestinal permeability to endotoxins, and ischemia-reperfusion injury (5). It results in a complex immunologic reaction with the release into circulation of arachidonic acid metabolites, proinflammatory cytokines, endothelins, platelet-activating factors, endothelial and leukocyte adhesion molecules that stimulate the overproduction of reactive oxygen species (6, 7) (Scheme 1).

SCHEME 1 ABOUT HERE

Although it has been shown that, compared with clinical management alone, conventional coronary artery bypass grafting surgery with cardiopulmonary bypass prolongs life and reduces symptoms in patients with severe coronary artery diseases, these benefits are accompanied by increased risks of transfusions (30–90%), mortality (2–6%), stroke (2%), atrial fibrillation (30%), and neurocognitive dysfunction (50–60%) (8, 9). The adverse clinical consequences, associated with conventional coronary artery bypass surgery, have been largely attributed to the extracorporeal blood circulation (ECC) on cardiopulmonary bypass circuit, general systemic effects (including exacerbated inflammatory response resembling the SIRS, Scheme 1), hypothermic cardiac arrest, aortic cannulation, and cross-clamping (10,11,12). Consequently, it may be of interest to study the potential benefit of specific anesthetic drugs exhibiting anti-inflammatory mechanism. By modulating inflammatory response, anesthetic drugs could reduce the postoperative complications and mortality associated with CABG.

One potential candidate that has been little explored is dexmedetomidine. Dexmedetomidine, an (α)-2-adrenergic receptor agonist, can provide anxiolysis and sedation without respiratory depression (13). It decreases central nervous system sympathetic outflow in a dose-dependent manner and has analgesic effects described as opioid-sparing effect. There is increasing evidence that dexmedetomidine has organ protective effects against ischemic and hypoxic injury, including cardioprotection, neuroprotection, and renoprotection (13). However, little is known about the cellular and molecular mechanism(s) involved in dexmedetomidine protective effects. Here we will discuss the potential systemic antioxidant and anti-inflammatory action of dexmedetomidine and its possible relationship with cadio- and neuroprotective effects after coronary artery bypass grafting surgery (CABG).

2.1.3 Cardiopulmonary bypass (CPB)

Cardiopulmonary bypass (CPB) replaces the functions of the heart and lungs during cardiac surgery, allowing the heart to be opened and operated (Figure 1). The first successful human intracardiac operation was performed by Gibbon in 1953, using a mechanical extracorporeal pump oxygenator (14). Despite the long time since the first CPB surgery and numerous studies about CPB pathophysiological side-effects, the complex mechanisms involved in the responses of blood and tissues to cardiopulmonary bypass are still far from clear.

Clinical points of evidence suggest that morbidity associated with cardiopulmonary bypass can in part be attributed to the generalized inflammatory response induced by blood-xenosurfaces (from catheters and filtration membranes) interactions during extracorporeal circulation (4) (Scheme 1, Figure 1). Although conflicting data exist, the prominent hypothesis is that a metabolic unbalance occurs during extracorporeal blood recirculation involving every line of the inflammatory response including complement activation. Total perioperative values of inflammatory markers are probably less important than the balance between the oxide inflammatory cascade and antiinflammatory feedback mechanisms. Oxidative stress and inflammation are related and perhaps inseparable and, a reduced cytokine response may be directly translated into changes in clinical outcomes (15, 16).

FIGURE 1 ABOUT HERE

The pump and the oxygenator used for cardiopulmonary bypass function in a nonphysiologic manner, with altered vascular pressure and gas composition. Inflammmation is the initial, nonspecific response of vascularized tissue to a variety of injuries, involving both the activation of humoral and cellular inflammatory pathways. Significant hemodilution also occur leading to a dilution and denaturation of plasma proteins. The blood exposition to nonendothelial surfaces activates the production of vasoactive mediators, altering capillary permeability and causing hemolysis (which increase the free concentration of the prooxidant heme and non-heme iron) and the coagulation system will be impaired (17). One important question that needs to be explored in details is whether or not the ECC induced hemolysis increases the concentration of iron in pathologically relevant tissues such as brain, heart and kidney. Increase in free hemoglobin, heme and iron can further feed the pro-oxidative-pro-inflammatory cycle in different tissues (18-24). The potential role of iron on “early and late phases” of inflammation associated with cardiopulmonary bypass (see below) should be

investigated in detail as well as the possibility of utilizing chelation therapy as co-adjuvant in patients at risk of developing SIRS-like response. Of particular significant, literature data have indicate a beneficial effect of desferoxamine in sepsis (25-27), which indicate that buffering of free iron can reduce the toxicity found in SIRS or SIRS-like situations (25-27).

The inflammatory response to cardiopulmonary bypass can be divided into 2 phases: “early” and “late” (Scheme 2). The early phase occurs as a result of the direct blood contact with nonendothelial surfaces, and the late phase is triggered by ischemia-reperfusion injury and endotoxemia (For a comprehensive review see the work of Warren and colleagues) (17).

SCHEME 2 ABOUT HERE

In the early phase, thrombosis becomes favorable, and it can be reduced or ameliorated with the administration of heparin before cardiopulmonary bypass initiation. When heparinized blood comes into cardiopulmonary bypass circuit, plasma proteins are adsorbed onto the circuit, leading to the activation of plasma protein systems and cell groups. These initiate a whole-body inflammatory response, associated with tissue edema, coagulopathy and organ dysfunction (28). With the course of cardiopulmonary bypass, the activation of the humoral and cellular components diminishes, but a second phase of inflammatory response initiates, which is related to ischemia-reperfusion injury and release of endotoxins from intestinal microflora (29). The ischemia-reperfusion injury is mediated by neutrophil-endotelial interactions (Fig. 2). High levels of endothelial injury occur during ischemic period, resulting in neuthrophil activation and sequestration on reperfusion. Independent of leukocytes, production of toxic reactive oxygen species also occur, leading to release of arachidonic acid metabolites, proinflammatory cytokines by ischemic cells (eg, plasma tumor necrosis factor-alpha and interleukins like IL-1, IL-6 and IL-8) and activation of the humoral protein systems (30). The reintroduction of oxygen during reperfusion promote a high concentration of damaging reactive oxygen species inpreviously ischemic cells, and can damage cell membranes, denature proteins and act as second messengers to stimulate an acute inflammatory response (4) (Scheme 2 and scheme 3).

SCHEME 3 ABOUT HERE

There are many possible sources of endotoxin, including lipopolysaccharides from cell wall of gram-negative bacteria, release during bypass, with gut translocation as the primary source (31). The increased level of endotoxin related to cardiopulmonary bypass stimulate the release of nitric oxide and proinflammatory cytokines and increase levels of oxygen consumption (32). These stimuli and the complexity of this disequilibrium, the balance between the processes of activation and inhibition of these systems, suggest that the implementation of effective antiinflammatory and antioxidant strategies (though to be desirable in theory) can be a difficult challenge. Of particular pharmacological significance, recent experimental data have indicated that dexmedetomidine can attenuate sepsis-induced lung and kidney damage, in part by decreasing tissue migration of inflammatory cells in rats (33). These results may indicate a potential role of dexmedetomidine as a negative modulator of SIRS-like response in cardiopulmonary bypass.

2.1.3.1 Mini-extracorporeal circulation (MECC)

Biocompatible circuits designed to prevent the early activation of inflammatory cascades have been shown to affect some aspects of blood activation but not all. There have been some progresses in cardiopulmonary bypass design that has shown promising clinical outcomes, particularly, those aiming to reduce the incidence of SIRS-like response and its complications. Recently, a new cardiopulmonary bypass system, the mini-extracorporeal circulation (MECC), has been developed and it use has been associated with a reduced inflammatory response, when compared with the conventional system (standard cardiopulmonary bypass or extracorporeal circulation). It has no venous reservoir, a reduced priming volume, and less blood-synthetic interface contact (Figure 3).

FIGURE 3 ABOUT HERE

In a review, Vohra and colleagues have consolidated the current literature on the mini-extracorporeal circulation system (34). They have paid particular attention to the role that cardiopulmonary bypass has in generating a systemic inflammatory response and have outlined ways in which MECC may be superior to standard cardiopulmonary bypass. The MECC system has shown promising results with regard to cardiac damage and end-organ dysfunction. Many studies cited by this author have also shown that changes in blood markers of inflammation (for instance, C-reactive protein, leucocytes, and cytokines) were lower when

MECC is used. Of clinical significance, utilization of MECC has been associated with a decrease in complications found more frequently in standard ECC, particularly arrhythmias and thromboembolic events.

2.1.3.2 Oxidative stress and inflammation associated with coronary artery bypass grafting surgery (CABG)

Reactive oxygen species are recognized as critical mediators of cardiac and neurologic injury during ischemia and reperfusion. Sources of these reactive oxygen species are the mitochondrial electron transport chain, the enzymes xanthine oxidase, NADPH oxidase, lipoxygenase/cyclooxygenase and nitric oxide synthase (NOS), and auto-oxidation of various substances, such as catecholamines. An unpaired electron usually makes the species highly reactive. There are endogenous antioxidant systems that counteract the potential for injury to cellular structures by regulating the balance of reactive oxygen species. These endogenous antioxidants are upregulated when exposure of the cell to the reactive oxygen species is increased. Under pathologic conditions, such as ischemia-reperfusion, their formation can rapidly overcome antioxidant defenses and cellular injury ensues. It is known that the cardiopulmonary bypass can be responsible for activating neutrophils that represents a prominent source of systemic primary reactive oxygen species production (Figure 2). The synergism of damages related to reactive oxygen species, activation and infiltration of neutrophils in reperfused tissues, has been well recognized for many years (4).

Some investigators suggested that strategies of neurological and myocardial protection must not be limited to interventions targeted at the heart or brain itself, but should take in account the systemic response of organism to cardiopulmonary bypass (35, 36). These concepts should be particularly relevant for high-risk patients, who are more prone to organ injuries. But, despite the improvement in the medical cardiac treatment, for instance, endovascular interventions and robotic surgery, cardiopulmonary bypass remains an essential part of many cardiovascular procedures. The multifactorial nature of inflammatory response suggests that no single pharmaceutical or technical intervention can in isolation inhibit the adverse clinical outcomes of such type of surgery. And more, theoretical and experimental data supporting that negative modulation of systemic inflammatory response (observed during and after cardiopulmonary bypass) might ameliorate brain injury found after cardiac surgery, are not clear. Accordingly, the association between cardiopulmonary bypass-induced inflammation with neurocognitive deficits is still a matter of controversy.

Clermont et al. (37) demonstrated with electron spin resonance spectroscopy measurements the time course and origin of reactive oxygen species release, derived from myocardial source or not, in patients undergoing coronary artery surgery involving cardiopulmonary bypass. Their results demonstrated that systemic oxidative stress occurs in patients undergoing open heart surgery, illustrated by the increased alkyl and alkoxyl radicals detected and quantified by electron spin resonance spectroscopy. Other studies have already taken an interest in classical indirect oxidative stress markers such as vitamins, antioxidant plasma status, or thiobarbituric acid reactive substances and the results were controversial. The concept that oxidative stress could influence post-operative outcome in patients subjected to coronary artery bypass surgery also remains a controversial and inconclusive issue (38, 39, 40).

Oxidative stress (measured by lipid peroxidation) also has been compared in patients undergoing coronary artery surgery with or without cardiopulmonary bypass (on-pump or off-pump) (41), and it has been shown to be lesser in the off-pump (without cardiopulmonary bypass) than in the on-pump (with cardiopulmonary bypass) group. These results are not surprising since it is clear that the ischemia and reperfusion involved in on-pump surgery are expected to induce oxidative stress. However, there are some results in the literature indicating that glutathione levels decreased and catalase activity increased to similar values between on-pump or off-pump groups with a little difference between them (41). These observations may support the assumptions of Milei and colleagues (42), that the induction of oxidative stress could be relatively benign. It is interesting to note that, the patients in this study were at low risk with good ventricular function; it is expected, therefore, that these patients could have minimal increases in oxidative stress. The study of Milei and colleagues (42) investigated markers of oxidative stress in a small number of low risk patients (24 in total) undergoing coronary artery bypass surgery. They measure myocardial release of glutathione, myocardial antioxidants (vitamin E and ubiquinol) and lipid peroxidation markers (TBARS) in blood, as well as ultrastructural assessment of tissue injury (from myocardial biopsies) and evaluation of post- ischemic hemodynamic function and clinical outcome. The results show that there was evidence of increased glutathione release in the initial 20 min of reperfusion, and a decrease in tissue antioxidant levels of ubiquinol (but not vitamin E), and minimal increase in tissue lipid peroxidation or any ultrastructural damage. The study indicates that, for the majority of low risk patients undergoing coronary artery bypass surgery, oxidative stress remains a constant underlying factor, unlikely to significantly influence clinical outcome as long as myocardial protection is provided and the ischemic

duration is kept as short as possible. However, in critically ill patients an intervention to attenuate oxidative stress might be considered beneficial, because reactive oxygen species may contribute to myocardial stunning, infarction and apoptosis and vascular disfunction (1, 2, 3).

2.1.3.3 Neuroinflammation associated with coronary artery bypass grafting surgery (CABG)

It is largely suggested that neurocognitive decline after cardiopulmonary bypass results from an inflammatory response that is initiated by extracorporeal circulation (43, 44, 45). However, a more comprehensive review of the literature does not consistently support this hypothesis. For example, in an animal model that included both elderly rats and diabetic rats, de Lange and colleagues (46) found no differences in short-term neurocognitive performance (8 –14 days after surgery) in rats undergoing surgery with cardiopulmonary bypass, compared with those undergoing a sham operation. They noted an increase in cytokine release (interleukin-6) after cardiopulmonary bypass in diabetic rats, but not in elderly rats. In humans, Westaby and colleagues (47) did not found an association between maximal levels of inflammatory markers (complement C4a and C5b-9) with early or late neurocognitive function after coronary artery bypass graft surgery with cardiopulmonary bypass. Furthermore, Parolari and colleagues (48) demonstrated that postoperative levels of inflammatory markers, including interleukin-6, plasma tumor necrosis factor-alpha, C-reactive protein, and fibrinogen, differed little in patients undergoing coronary artery bypass graft surgery with or without cardiopulmonary bypass.

Nevertheless, it is largely know that necrosis and apoptosis after an acute ischemic event are accompanied by other processes which lead to a posterior neurodegeneration. It was demonstrated that release of cytokines, such as tumor necrosis factor alpha and interleukins, as mediated by oxidative stress, and prolonged microglial activation by interleukin-1 induce to a neuronal degeneration that follow cerebral ischemia (49) and that excessive formation of reactive oxygen species, induce to direct tissue damage and stimulate inflammatory and proapoptotic cascades (50). Central norepinephrine release during brain ischemia also increases neuronal metabolism and carry to the formation of reactive oxygen species from auto-oxidation of neurotransmitters, induce damage caused by glutamate during ischemia and can exacerbate the underliyng disease of patients (49).

If the inflammatory response is or not the primary cause of neurocognitive injury after cardiopulmonary bypass, the question is whether or not neurocognitive decline in adult cardiac surgical patients could be related to the cardiopulmonary bypass pump. Van Harten and colleagues (51) discuss the evidence for cardiopulmonary bypass-related neuronal injuries in adult cardiac surgery patients, and review the evidence that immune priming is a key factor in the pathogenesis of cognitive dysfunction after cardiac surgery. They suggest further studies about pathophysiology of post-operative cognitive dysfunction (POCD) that may lead to strategies and therapies to prevent or attenuate POCD and also define the better choice of hypnotic, and dose of opioid, on the inflammatory response to surgery and on the incidence of POCD. These studies could determine the benefit, if any, of immune system modulation, by antiinflammatory agents and also by other drugs that may exert beneficial effects on the balance between pro and antiinflammatory mediators, such as interleukin-6 or tumor necrosis factor-alpha and interleukin-10, respectively.

A comparison of coronary artery bypass graft surgery with percutaneous coronary intervention failed to show difference in cognitive decline in patients undergoing cardiac revascularization (52). Age is considered to be the strongest predictive factor of post-operative cognitive dysfunction (POCD) and coronary artery bypass grafting without the use of cardiopulmonary bypass could be considered less harmful to the these patient group, especially in terms of neurological complications. Although an increasing number of patients with advanced age and other risk factors for neurocognitive injuries have been referred for coronary artery bypass grafting, Jensen and colleagues (53), in a randomized trial, investigated the effect of avoiding the heart-lung machine on cognitive function 1 year after surgery in aged patient population. They did not detect differences in cognitive outcomes in elderly high-risk patients 1 year after the operation between subjects which underwent coronary artery bypass grafting surgery without cardiopulmonary bypass with those subjected to extracorporeal circulation. The study of Jensen and colleagues (53) are in line with other randomized study about late cognitive outcome in younger patients with less advanced coronary artery disease and lower preoperative risk (54). In Jensen study (53), postoperative cognitive dysfunction, unexpectedly, tended to be less common in the on-pump group. This could be further suggestive that many other factors such as inflammatory processes including sternotomy, heparin administration and hemodynamic variations may be responsible for cognitive dysfunction observed after surgery (55). It seems that patient characteristics, such as the presence of atherosclerosis, are more relevant than the type of intervention as predictive factor of neurocognitive injury in patients with severe coronary artery disease (56). In

addition, late cognitive decline occurring 5 to 6 years after coronary artery bypass graft surgery did not differ in degree from longitudinal cognitive decline observed in patients of similar age either with coronary artery disease (57) or without coronary artery disease (46, 58). Perhaps, decline in neuropsychological tests with time is related to progression of underlying cardiovascular disease or simply to natural aging (59, 60, 61). In fact, neurocognitive impairment in many patients undergoing cardiac surgery may be preexisting, although subclinical (62).

2.1.3.4 S-100B as a marker and modulator of neuroinflammation

S100B protein might also participate in the brain inflammatory response. At the nanomolar concentrations found in the brain extracellular space, under normal conditions, S100B acts as neurotrophic factor, promoting neuronal survival under stress conditions and neurite outgrowth (63) and stimulating the uptake of the cytotoxic glutamate by astrocytes (64). The level of S100B in blood is considered a clinical marker of brain cell damage and/or increased permeability of the blood/brain/barrier. Moreover, S100B release by astrocytes can be augmented upon stimulation by the proinflammatory cytokines tumor necrosis factor-alpha, interleukin-1 (IL-1) and interleukin-6 (IL-6) (65, 66, 67, 68). As demonstrated before, cytokines contribute to a cascade of events typical of inflammation and especially proinflammatory cytokines, such as IL-6 and IL-8, are thought to contribute to the development of sickness behavior (69). Trophic effects of the S100B protein on neurons depend on interaction with the receptor for advanced glycation end products (RAGE) (70), a multiligand receptor belonging to the immunoglobulin family that has been implicated in both neuroprotection and neurodegeneration, and in the inflammatory response (71). Acute stimulation of RAGE with high doses of S100B causes neuronal apoptosis via overproduction of reactive oxygen species (72) and stimulates inducible nitric oxide synthase in astrocytes and microglia (73, 74, 75), which might contribute to astrocytic and neuronal apoptosis (75). Moreover, S100B also stimulates interleukin-1 (IL-1) release from microglia (76).

S100B protein increases 50 to 100 fold after cardiac surgery using standard cardiopulmonary bypass (77, 78), a finding that could support association between cardiopulmonary bypass and brain damage. The postoperative serum concentration of S-100B appear to increase with the duration of cardiopulmonary bypass and with the number of cerebral emboli detected by transcranial doppler imaging (79). Several studies have suggested

that, in the absence of clear neurologic signs, transient elevations in serum S100B protein can reflect subclinical cerebral damage (80, 81). But, early release of S100B after cardiopulmonary bypass has not been associated with adverse neurological outcome. In contrast, cerebral complications such confusion, delayed awakening and stroke have been correlated with late increase in S100B detected 5 to 48 hours after cardiopulmonary bypass (82). The increase in plasma S100B could also be linked with postoperative delirium incidence (83) and be a consequence of S100B release by astrocytes stimulated by circulating proinflammatory mediators (IL-6, Il-8, etc) (83, 84). Such complex and not fully well characterized relationship between S100B, inflammatory markers and neurobehavioral changes has been studied in more detail in elderly hip fracture patients (83).

Of particular clinical significance, many studies have demonstrated that the development of delirium in critically ill patients increases morbidity, mortality, and healthcare costs (85, 86). It has been hypothesized also a higher frequency of dementia in patients who presented with delirium at the end of the surgery (87). The neurocognitive impairments might reflect an irreversible brain damage triggered by surgery pathophysiological effects. Consequently, it could be supposed that the higher the level of S100B in a delirious patient, the higher the risk of dementia after delirium, and thus cerebral damage. This cerebral damage could be mediated via neuroinflammatory mechanisms because the level of S100B and the incidence of neurodegeration are higher in patients with an infectious disease (which normally is associated with inflammatory response) as compared to non infected subjects (88, 89).

2.1.4 Alpha (α)-2-adrenergic receptor agonists

Alpha (α)-2-adrenergic receptor agonists have been utilized in surgery because they have sedative, analgesic, hemodynamic-stabilizing properties and sympatholytic pharmacologic effects (90, 91) (Figure 4).

FIGURE 4 ABOUT HERE

The stress response to surgery can be attenuated by sympatholytic effects caused by postsynaptic activation of central (α)-2-adrenergic receptor, leading to reductions in blood pressure and heart rate (89). Of clinical significance, two adrenergic agonists have been used as coadjuvant in general anesthesia or even as anesthetic agents by themselves, i.e., clonidine and dexmedetomidine (Figure 5). Here we will briefly discuss the use of clonidine, because

clonidine has a smaller selectivity for (α)-2-adrenergic receptor than dexmedetomine, consequently, a low efficacy as an anesthetic agent.

FIGURE 5 ABOUT HERE

2.1.4.1 Clonidine

Clonidine was first used for postoperative pain relief and regional anesthesia (93.94, 95). In effect, clonidine has antinociceptive properties and reduces anesthetic requirements by attenuating sympathoadrenal responses during surgery and plasma concentrations of norepinephrine by stimulating presynaptic (α)-2-adrenergic receptors. While the use of clonidine during coronary artery bypass graft surgery did not appear to influence the perioperative stress response (96), its immunomodulatory effects remains to be characterized. Of clinical significance, perioperative use of clonidine was associated with reduction in the incidence of myocardial ischemia and death after non-cardiac surgery in patients at risk of coronary disease (97, 98, 99). Von Dossow and colleagues (100) investigated the influence of perioperative clonidine infusion on the early T-cell immune response, in patients undergoing elective coronary artery bypass graft surgery, and demonstrated early T-cell response ratios in the clonidine group 6 h after cardiac surgery. No differences were found with respect to plasma cytokine levels. In contrast to these findings, Ellis and Pedlow (101) reported no influence of clonidine on lymphocytes, but a significant decrease in plasma norepinephrine levels in patients undergoing major noncardiac surgery. The decreased norepinephrine plasma levels after clonidine administration have been previously reported (102), especially in patients undergoing cardiac surgery (103). It has been hypothesized that the major effect of (α)-2-adrenergic receptor agonists is on tonic activity, while sympathetic nervous system responsiveness to stressful stimuli appears to be unaffected.

Here it is important to emphasize that there are few studies about the modulation of inflammatory response after systemic use of clonidine in anesthesia. In a study with 7 patients, preoperative administration of clonidine was associated with a reduction in plasma and cerebrospinal fluid levels of TNF-alpha (104) Similarly, perioperative epidural clonidine administration caused a decrease in blood IL-6 and suggested that (α)-2-adrenergic receptor stimulation can modulate systemic inflammatory response in human (105).

2.1.4.2 Dexmedetomidine

Dexmedetomidine is a selective (α)-2-adrenergic receptor agonist with an increased ratio of (α)-2 to (α)-1 activity of 1.620:1, as compared to clonidine (220:1). In 1999, dexmedetomidine was approved by the United States of America (USA) Food and Drug Administration (FDA) only for sedation of patients. In 2008, based on two randomized, double-blind, placebo-controlled, multicenter trials (106), FDA approved the update labeling use for dexmedetomidine, including the indication for sedation in surgery or other procedures.

Dexmedetomidine is the dextro enantiomer of medetomidine, the methylated derivative of etomidine, and specific (α)-2 adrenergic receptor subtypes mediate its pharmacodynamic effects (Figure 4). Agonism at the (α)-2A adrenergic receptor appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection (107) and inhibition of insulin secretion (108). Agonism at the (α)-2B adrenergic receptor suppresses shivering centrally (109), induces analgesia at spinal cord and vasoconstriction in peripheral arteries. The (α)-2C adrenergic receptor is associated with cognition, sensory processing, mood and regulation of epinephrine outflow from the adrenal medulla (110). Inhibition of norepinephrine release appears to be equally affected by all three alpha-2 receptor subtypes (111) (Figure 6). Dexmedetomidine also binds to imidazoline receptors and this activity may explain some of the non-(α)-2 adrenergic receptor effects of this drug, and receptor subtypes have also been identified. Imidazoline-1 receptors are linked to G-proteins and modulate blood pressure and have anti-arrhythmic effects (90). Imidazoline-2 receptors have been implicated in neuroprotection in a cerebral ischemia model in animals and in acquisition and retention of memory. They are not G-protein coupled receptors and located on the mitochondrial outer membrane and probably exert their effects by decreasing tissue norepinephrine levels (90, 112).

FIGURE 6 ABOUT HERE

2.1.4.3 Dexmedetomidine pharmacokinetics

After intravenous injection, dexmedetomidine has an onset of action after 15 minutes and peak concentrations are achieved within 1 hour after continuous intravenous infusion. Rapid distribution occurs away from the central neurological system with an alpha half-life ($t_{½}$ α) of 6 minutes and a terminal elimination half-life ($t_{½}$ β) between 2.0 and 2.5 hours. The drug is highly protein-bound, with a 6% free fraction, and has a large steady state volume of

distribution (Vdss, 1.33 L. kg^{-1}). Total plasma clearance and protein binding is age independent (113).

Hepatic clearance may be decreased to 50% of normal with severe liver disease. Pharmacokinetics is not significantly altered in patients with severe renal impairment, but patients remained sedated for longer than normal controls, suggesting an enhanced pharmacodynamic effect (114). Thus, dosages should be decreased in the presence of either hepatic or renal diseases. There are no recognized active or toxic hepatic derivatives of dexmedetomidine after its metabolism via glucuronide conjugation and biotransformation by cytochrome P450 enzymes.

Intravascular doses of dexmedetomidine induced dose-dependent decreases in systolic and diastolic blood pressure and in heart rate with important decreases in plasma norepinephrine levels. However, at high-bolus intravascular doses (50-75 μg), a transient initial hypertensive response may be seen, because an activation of peripheral vascular (α)-2B adrenergic receptors before the central sympatholytic effect on the vasomotor center occur (115). Dexmedetomidine apparently does not induce alterations in plasma renin activity, atrial natriuretic peptide or arginine vasopressin levels (116).

Targeted plasma dexmedetomidine levels revealed desirable pharmacodynamic effects between 0.5 and 1.2 ng. mL^{-1}. Subsequent clinical studies designed to achieve these effects used a loading dose of 1 μg. kg^{-1} during a period of 10 minutes, followed by a continuous intravenous infusion rate of 0.2 to 0.7 μg. kg^{-1}. h^{-1}, the dosing regimen originally approved by the USA Food and Drug Administration in 1999. Studies examining very high dexmedetomidine plasma levels (up to 8.0 ng. mL^{-1}) demonstrate that the (α)-2B peripheral vasoconstrictor effects become predominant, with increasing systemic vascular resistance and decreasing cardiac index, associated with marked catecholamine suppression and deepening sedation. Even at these very high plasma levels of dexmedetomidine, there was no clinically significant respiratory depression (117) and it appears to be safe. Case reports of large accidental overdoses of dexmedetomidine describe oversedation as the only important effect, with resolution within an hour of discontinuation (118). There are reports of dexmedetomidine safely use as the sole agent at high rates of infusion (5-15 μg. kg^{-1}. h^{-1}) to anesthetize patients with tracheal stenosis while preserving spontaneous ventilation (119). In October 2008, the US Food and Drug Administration approved an increased dose of dexmedetomidine (up to 1.5 μg. kg^{-1}. h^{-1}) for surgical procedures.

2.1.4.4 Dexmedetomidine analgesic and sedative effects

Dexmedetomidine possesses analgesic properties and other advantageous pharmacological effects that make it a potential useful and safe adjunct in several clinical applications, as demonstrated Sleigh in a recent review (120). When used as an adjunct to general anesthesia, dexmedetomidine can reduce both the minimum alveolar concentration requirement of inhalation agents and provide opiate-sparing properties up to 90% (121).

The mechanism by which (α)-2-adrenergic receptor agonists produce analgesia and sedation is multi-factorial. Both, hypnotic and supra-spinal analgesic effects of dexmedetomidine are mediated by noradrenergic neurons. Dexmedetomidine causes inhibition of norepinephrine release and its neuron associated activity in the descending medullo-spinal noradrenergic pathway and suppresses neuronal activity in the *locus coeruleus* (122). Suppression of these inhibitory controls causes release of mediators and neurotransmitters that decrease the secretion of histamine and produce hypnosis, similar to normal sleep, without evidence of depression of ventilation (123). The suppression of activity along the descending noradrenergic pathway terminates propagation of pain signals, resulting in analgesia or decreased awareness at noxious stimuli. In neurons of the superficial dorsal horn of the spinal cord, dexmedetomidine suppresses and reduces pain transmission by inhibiting the release of glutamate and substance P (nociceptive transmitters) from primary afferent terminals and with G-protein-mediated activation of potassium channels causing hyperpolarization of inter-spinal neurons. Antinociception may also be provided by non-spinal mechanisms, as demonstrated in intra-articular administration of dexmedetomidine during knee surgery, which was associated with improved postoperative analgesia, with less sedation than the intravenous route (124). The suggested mechanisms are activation of alpha-2A adrenoreceptors (125) inhibition of the conduction of nerve signals through C and Aδ fibers, and the local release of encephalin. Figure 7 demonstrated the possible effector mechanisms of the (α)-2-adrenoreceptors, linked to G proteins.

FIGURE 7 ABOUT HERE

Dexmedetomidine provides dose-dependent increases in anxiolysis and sedation that appears to be unique in comparison with GABAergic agents such as midazolam or propofol. Arousability is maintained at deep levels of sedation (126) and once aroused, patients normally performed well the tests of vigilance (127), and they can cooperate with nursing, radiologic, and airway procedures (128). There appears to be particular value in a drug such

as dexmedetomidine that facilitates the arousal and rapid orientation of a sedated patient. The amnestic effects of dexmedetomidine are far less than the benzodiazepines, which provide profound anterograde amnesia that may contribute to confused states on emergence. In contrast, amnesia is achieved with dexmedetomidine only at high plasma levels (≥1.9 ng. mL^{-1}), without retrograde amnesia (117).

Unlike opioids, dexmedetomidine achieves its sedative, hypnotic, and analgesic effects without causing any clinically relevant respiratory depression, even when dosed to plasma levels up to 15 times those normally recommended for therapy (117). Sedation induced by dexmedetomidine has the respiratory pattern and electroencephalogram (EEG) changes comparable with natural sleep. Compared with remifentanil, hypercapnic arousal is preserved (129) and functional magnetic resonance imaging studies show that unlike GABAergic agents, dexmedetomidine preserves a cerebral blood flow pattern from natural sleep (130).

Administration of dexmedetomidine during sevoflurane or desflurane anesthesia with spontaneous ventilation has no effect on end-tidal carbon dioxide (131) and arterial saturation is better preserved with dexmedetomidine than propofol under magnetic resonance imaging procedures (132). In contrast to infusions of opioids, benzodiazepines, or propofol, dexmedetomidine can safely be infused through tracheal extubation and beyond. It has been used successfully to facilitate tracheal extubation in patients who had previously failed extubation because of excessive agitation (133).

2.1.4.5 Antiinflammatory effects of dexmedetomidine

Reactive oxygen species (ROS) are considered as key regulatory molecules vital for life, but they cause cellular and organ damage when produced in excess or when antioxidant defenses are overwhelmed such in cardiac and neurologic ischemic and reperfusion injury. ROS can contribute to myocardial stunning, infarction and apoptosis, to the genesis of arrhythmias and neurologic deficits. Several intravascular anesthetic drugs can act as reactive oxygen species scavengers. It was demonstrated in patients with impaired preoperative left ventricular function undergoing elective coronary artery bypass surgery with cardiopulmonary bypass, that the administration and maintenance of a clinically relevant dose of propofol from before aortic cross-clamp release, maintained until 4 hours after reperfusion, attenuate myocardial lipid peroxidation, associated with a decrease in IL-6 production and a late increase of IL-10 release (134).

Recently, Arslan and colleagues (2012) concluded that dexmedetomidine protected liver from lipid peroxidation, when given before induction of ischemia in an experimental model (135). Rocha and colleagues have also indicated the protective potential of dexmedetomidine in women which underwent pelvic videolaparoscopic surgery (136). In their study dexmedetomidine protected blood aminolevulinate dehydratase (ALA-D) from inactivation caused by hyperoxygenation in total intravenous anesthesia. The results of the investigation indicated that blood ALA-D from patients anesthetized with dexmedetomine was not modified by exposure to high concentrations of oxygen, whereas the activity of enzyme from those patients anesthetized with remifentanil exhibited a statistical significant decrease in activity. Regarding the dexmedetomidine group, it is possible that the anesthetic has protected the enzyme from oxidation by hyperoxygenation process.

Several investigators have published reports about the effects of dexmedetomidine and other (α)-2-adrenergic receptors agonists on cytokines (137) and on (α)-2-agonists modulated lipopolissacaride-induced tumor necrosis factor-α production by macrophages (138). Taniguchi and colleagues (139) demonstrated that dexmedetomidine has an inhibitory effect on cytokine responses to endotoxemia. These findings suggest that one of the mechanisms of antiinflammatory effects of dexmedetomidine may be *via* modulation of cytokine production by macrophages and monocytes. Hofer and colleagues demonstrated that dexmedetomidine infusion decreased cytokine production in sepsis (140), which is in accordance with a recent study showing reno and pulmonary protective effect of dexmedetomidine in an experimental model of sepsis in rats (33). They have shown that preventive administration of clonidine or dexmedetomidine improved survival in induced sepsis. This was accompanied by a reduction in the proinflammatory mediators IL-1β, IL- 6 and tumor necrosis factor-α. Furthermore, they suggested that, administration of a central acting (α)-2- adrenoreceptor agonist might be considered as a preventive therapeutic option in high-risk patients undergoing major surgery. In another animal study, dexmedetomidine treatment was equally effective to methylprednisolone in reducing TNF-α and IL-6 levels induced by spinal cord injury. Aparently, dexmedetomidine treatment reduced neutrophils' infiltration at the site of spinal cord injury (141). Dexmedetomidine inhibited cortisol synthesis at supratherapeutic concentrations but this has not been reported in short-term use in humans (142,143). Our study group, have the influence of dexmedetomidine on cortisol levels avaliated (144). At this study, we measured cortisol concentrations before anesthetic induction, 5 minutes after intubation, and 30 minutes after surgical incision in patients undergoing gynecologic videolaparoscopic surgery, receiving dexmedetomidine or remifentanil. After intubation, there

was a significant decrease in cortisol concentrations from baseline in both groups (–4.3 ± 1.4 μg. dL^{-1} and –4.6 ± 1.6 μg. dL^{-1}, respectively) but only in the remifentanil group at 30 minutes after incision (2.6 ± 1.8 μg. dL^{-1} and –7.1 ± 2.1 μg. dL^{-1}) and we could concluded that dexmedetomidine did not suppress steroidogenesis (144). In the MENDS trial (145), cortisol concentrations were determined at baseline and 2 days after stopping dexmedetomidine infusion, and there was no statistically significant difference in cortisol concentrations. At high doses as 1.5 μg. kg^{-1}. h^{-1} dexmedetomidine does not appear to cause clinically significant adrenal suppression (146).

Laringoscopy and endotracheal intubation also provoke marked sympathetic and sympathoadrenal response that increase the risk of perioperative myocardial ischemia and infarction. The perioperative use of dexmedetomidine may improve endocardial perfusion and decrease heart rate with attenuation of stress response (147). Dexmedetomidine increases the hemodynamic stability by altering the stress-induced sympatho-adrenal responses to intubation, during surgery and emergence from anesthesia (148) and this reflect a better outcome.

In a recent study, Sukegawa and colleagues (149) described the potent inhibitory effect of dexmedetomidine on inflammatory reactions, including edema, accumulation of inflammatory cells, and production of tumor necrosis factor-alpha and cyclooxygenase-2 (COX-2), induced by an injection of carrageenin into the paw of mice. They have also demonstrated a potent antiinflammatory effect of dexmedetomidine at a high dose on endotoxin-induced inflammation in murine macrophages (150).

Yagmundur and colleagues (151) have examined the effect of dexmedetomidine on ischemia-reperfusion injury due to tourniquet during upper-extremity surgery by determining blood malondialdeyde and hypoxanthine levels. Dexmedetomidine significantly attenuated plasma hypoxanthine production in the ischemia and plasma malondialdeyde production in the reperfusion periods. They suggest that dexmedetomidine can have advantages over other anesthetic agents (for instance, opiods and propofol) by inhibiting lipid peroxidation in the case of anticipated ischemia-reperfusion injury, such as would occur in upper-extremity surgery requiring tourniquet application. Bekker and colleagues (152) hypothesized that the intraoperative administration of dexmedetomidine could reduce the stress response and improve the quality of recovery in patients undergoing major spinal surgery. They compare a propofol/fentanil/dexmedetomidine anesthesia group with propofol/fentanil/placebo-saline anesthesia. In both groups, plasma cortisol levels were elevated in the postanesthesia care unit, whereas C-reactive protein levels were elevated only in the first postoperative day.

Dexmedetomidine significantly reduced the levels of cortisol, but not those of C-reactive protein. Levels of cytokines IL-6 and IL-8 were significantly higher immediately after surgery and at first postoperative day. Dexmedetomidine delayed postoperative rise of IL-10 but not of IL-6 or IL-8. Plasma levels of others cytokines were not affected by surgery. Clinically, dexmedetomidine infusion moderately improved the quality of recovery (106).

Gu and colleagues also conducted a study (153) to investigate dexmedetomidine antiinflammatory capacity. They utilized an animal model of renal ischemia-reperfusion that induced an acute lung injury and either pre-treated mice with dexmedetomidine (25μg. kg^{-1} before ischemia) or gave it after reperfusion. Renal ischemia/reperfusion induced an increase of inflammatory markers in lungs (mieloperoxidase (MPO) activity, intercellular adhesion molecule-1(ICAM-1) and TNF-α mRNA level). Both pre- and post-treatment with dexmedetomidine markedly reduced lung edema and inflammatory response and lowered MPO activity and ICAM-1 and TNF-α mRNA expression. Other study explored the antiinflammatory effects of dexmedetomidine in rats, using an intravenous infusion of dexmedetomidine at the rate of 5.0 μg. kg^{-1}. h^{-1} after bilateral blunt chest trauma-induced pulmonary contusion (154). Dexmedetomidine not only significantly modified hemodynamics and relieved the infiltration of inflammatory cells into alveolar spaces but also inhibited the injury-induced increase in plasma TNF-α and IL-1β production.

In humans, Kang and colleagues (155) demonstrated the antiinflammatory dexmedetomidine effects in patients subjected to laparoscopic cholecystectomy. Patients in the dexmedetomidine group received a loading dose of dexmedetomidine (1.0 μg. kg^{-1}), followed by infusion of dexmedetomidine at 0.5 μg. kg^{-1}. h^{-1}. Dexmedetomidine decreased the plasma level of IL-1β, TNF-α, and IL-10, when compared to saline group. The C-reactive protein (CRP) level and leukocyte count on post-operative day 1 were also lower in dexmedetomidine group. Tasdogan and colleagues (156) conducted other study to compare the effects of an intravenous infusion of propofol and dexmedetomidine, on inflammatory responses and intra-abdominal pressure in severe sepsis after abdominal surgery. Dexmedetomidine infusion decreases tumor necrosis factor-alpha, IL-1, and IL-6 levels and intra-abdominal pressure significantly more than a propofol infusion.

2.1.4.6 Neuroprotective effects of dexmedetomidine

The brain has a high requirement for oxygen and glucose, but is unable to store these substrates and rapid necrosis occurs to hypoxic–ischemic injury. It results in dysfunction of

adenosine triphosphate (ATP) dependent ion channels and pumps, leading to cellular depolarization and the release of extracellular excitatory neurotransmitters. The most important neurotransmitter is glutamate, which activates the N-methyl-D-aspartate receptor (NMDA), increasing intracellular calcium and sodium, contributing further to depolarization and neuronal activation. Excess of calcium promotes activation of pathways which disrupt ionic homeostasis, leading to membrane degeneration and excytotoxic cell death (157). Apoptotic mechanisms are also activated in response to ischemic brain injury, days to weeks after ischemic insult, especially in the region surrounding the necrotic area (158).

Neurological injury remains a major cause of morbidity in cardiac surgery patients and, in an extensive review, Hogue and colleagues (43) concluded that about 60% of patients have evidence of cognitive decline one month after cardiac surgery. Central nervous system deficits after cardiopulmonary bypass ranging from postoperative cognitive dysfunction (POCD), with incidence of 30- 60% (159, 160) to stroke, over 1-5% of patients (161). Adverse cerebral outcomes after cardiac surgery have been studied for a long time and literature data suggest that modalities modifying the systemic inflammatory response to cardiopulmonary bypass might protect brain against potential injury after cardiac surgery (44, 162, 45). But, the association between cardiopulmonary bypass-induced inflammation and neurocognitive deficits itself remains less than clear. A review of the literature did not support neurocognitive decline after cardiopulmonary bypass as a result of an exacerbated inflammatory response initiated by extracorporeal circulation. In recent issue, Jungwirth and colleagues (61) have published a well-controlled study in a rat model that fails to demonstrate a relationship between neurologic injury and the foreign surface area of cardiopulmonary bypass or donor blood used to prime the cardiopulmonary pump. They have suggested that other factors than cardiopulmonary bypass lead to adverse neurocognitive outcomes after cardiac surgery. Elsewhere, neurocognitive impairment in many patients undergoing cardiac surgery may be preexisting, although subclinical (62, 163, 164,165,166,167), and the cognitive outcomes for patients needing cardiac surgery with cardiopulmonary bypass appear to depend little on the perfusion technique, but rather on the underlying diseases (168). However, inflammatory response, oxidative stress and massive extracellular catecholamine release may lead to adictional neurodegeneration (168).

Nevertheless, Singh and colleagues (169) concluded that anesthetic choice in patients under cardiac surgery may have implications on S100B protein serum levels, a neuroinflammatory component, that could be a marker for brain injury on serum (170) and/or

damage to blood-brain barrier (76). In other trials (171, 145, 172), patients receiving dexmedetomidine developed significantly less delirium compared with patients receiving other drugs, such midazolam or propofol in intensive central unit. The pathogenesis of postoperative delirium is not completely clear but appears to be related, in part, to increased release of inflammatory mediators and the binding to the gama-aminobutyric acid (GABA) receptor (172). Dexmedetomidine does not bind to the GABA receptor and hence may minimize the development of delirium by decreasing release of norepinephrine. Because of conflicting results (173) more studies are needed to determine whether dexmedetomidine can really prevent or treat postoperative associated delirium. Many anesthetics act as gama-aminobutyric acid (GABA) receptor agonists, and in animal models, a GABA agonist can suppress neural cell proliferation, whereas GABA antagonist can enhance neurogenesis (174, 175). Dexmedetomidine acts by reducing noradrenergic output from the *locus coeruleus*, and decreasing brain norepinephrine levels, and in animals, manipulations that decrease brain norepinephrine also suppress cell proliferation (176, 177). Inhaled anesthetics such as isoflurane inhibit the cholinergic basal forebrain, and suppress hippocampal neurogenesis in animals (178). However, Tung and colleagues (179) found no effect of prolonged (8 hours) anesthesia with isoflurane, propofol, or dexmedetomidine on hippocampal cell proliferation in 3 or 12-months-old Sprague-Dawley rats. These results suggest that the sum of the many potential mechanisms linking cell proliferation to the anesthetized state (vigilance state, environmental stimuli, adrenal effects of anesthesia, direct pharmacologic effects), result in no overall effect and that suppression of adult hippocampal cell proliferation is unlikely to be an effect of brief or prolonged anesthesia, and thus unlikely to cause postoperative cognitive dysfunction in humans.

The neuroprotective effects of dexmedetomidine have been also demonstrated *in vivo* and *in vitro* in a variety of models of ischemia. These include models of incomplete ischemia in the rat (180, 181), transient focal ischemia in rabbits (182) and transient global ischemia in gerbils (183). *In vitro* studies of neuronal injury, using hippocampal slices (184) and neuronal and cortical cell cultures (185) also support dexmedetomidine as a neuroprotectant drug.

Originally, all dexmedetomidine neuroprotective activities were supposed to be caused by inactivation of presynaptic (α)-2-adrenergic receptors, inhibiting noradrenergic activity. However, dexmedetomidine concentrations well below 100 nM exert prominent effects on cultured astrocytes (185, 186) and the (α)-2-adrenoceptor is densely expressed in astrocytes freshly isolated from mouse brain by fluorescence-activated cell sorting (187). Thus, instead

of receiving a subtype-mixed noradrenergic signal from *locus coeruleus* the cells can be directly activated at their (α)-2-adrenoceptor sites by the drug.

The (α)-2-adrenergic signaling pathway has been studied in cultured astrocytes (186, 188). It connects activation of (α)-2-adrenoceptors with extracellular signal-regulated kinase (ERK) phosphorylation in two-stages, separated by trans-activation of the epidermal growth factor (EGF) receptor. This receptor is highly expressed in both neurons and astrocytes. In the first stage, the βγ subunits of the activated heterotrimeric Gi protein lead, *via* activation of cytosolic Src tyrosine kinases, to metalloproteinase-mediated 'shedding' of heparin-binding epidermal growth factor (HB-EGF) from its transmembrane-spanning HB-EGF precursor. In the second stage, released HB-EGF 'transactivates' EGF receptors in the same and adjacent cells (including neurons) by phosphorylating EGF receptors, leading to Ras- and Raf-dependent ERK phosphorylation (186, 188).The astrocytic effects may contribute also to dexmedetomidine's analgesic effects, at least in the spinal cord (189, 190).

FIGURE 8 ABOUT HERE

Despite dexmedetomidine has repeatedly been found to have neuroprotective effects against ischemia in experimental models (191) and could be able to protect against trauma in hippocampal organotypic cultures (192), these neuroprotection capacity have not been confirmed clinically.

More recently, Zhang and colleagues (193) described a possible mechanism through which dexmedetomidine induces neuroprotection. Based on knowledge that oxidative damage contributes greatly to post-traumatic brain injury (194) they induced oxidative neuronal injury with H_2O_2 in the glutamatergic cerebellar granule neurons. The hypothesis was tested that 'conditioned' medium from dexmedetomidine-treated astrocyte cultures would enhance neuronal viability due to release of an epidermal growth factor (EGF) receptor agonist, whereas direct administration of dexmedetomidine to neurons or treatment with non-conditioned medium would have no effect. Furthermore, it was examined if the protection found after addition of medium from dexmedetomidine treated astrocytes was abolished by treatment of the astrocytes with the specific (α)-2-adrenergic antagonist atipamezole. This was confirmed, but atipamezole addition directly to H_2O_2- exposed neurons treated with dexmedetomidine had no effect. They demonstrated, that dexmedetomidine at clinically relevant concentrations, was neuro-protective against oxidative damage by stimulating directly the astrocytic (α)-2-adrenoceptors, causing release of heparin-binding epidermal

growth factor (HB-EGF). HB-EGF in turn activates neuronal epidermal growth factor (EGF) receptors. At these concentrations however, dexmedetomidine has no direct neuronal effect (193).

The practice of neuroprotection is difficult because the process of neuronal damage and cell death is complex and not completly understood. The complexity of pathophysiologic mechanisms suggests that neuroprotection may have a multimodal approach and it is unlikely that a single pharmaceutical agent will be effective in improving neurological outcome. Recent evidence indicates, indeed that new neurons are produced in the adult hippocampus (195), and play a functional role in cognitive processes such as learning and memory (196, 197). Because anesthetics also affected these factors, it can be suspected that anesthetics or the anesthetized state also affected adult hippocampal cell proliferation. Anesthetic management may thus improve the quality of recovery in patients undergoing coronary artery bypass graft surgery, affecting the postoperative course, reduce the stress response and possible reduce neurological deficits onset.

2.1.4.7 Dexmedetomidine as protective agent against ischemia

Regarding the cerebral circulation in humans, during cardiopulmonary bypass, relatively little information was available until Henriksen and colleagues (198) reported evidence of cerebral hyperemia in 1983. In 1984, Govier and colleagues (199) incite controversy and debate with their observations of ischemic threshold levels of cerebral blood flow during cardiopulmonary bypass. Murkin and colleagues (200), subsequently, reported a decrease in cerebral blood flow and metabolic rate (oxygen consumption) during hypothermic cardiopulmonary bypass in humans. These low values were restored to control levels shortly after separation from cardiopulmonary bypass system. This study demonstrated a physiological basis for the embolic theory of central nervous system impairment after cardiac surgery. Ganushchak and colleagues (201) tested with a retrospective study the hypothesis that combinations of hemodynamic events from apparently normal cardiopulmonary bypass procedures are related to the development of postoperative neurological complications and affect the impact of patient common clinical risk factors on postoperative neurological complications. Patients who underwent cardiopulmonary bypass procedures with large fluctuations in hemodynamic parameters particularly showed an increased risk for the development of postoperative neurological complications (201).

There are increasing points of evidence both *in vitro* and *in vivo* which indicates that dexmedetomidine has a cell-protective effect on nervous tissue under ischemic conditions (202, 203, 204, 205). Considering that ischemia enhances the formation of reactive oxygen species in brain tissue and the activation of brain cells as microglia to synthetize cytokines, Eser and colleagues (206) investigated the neuroprotective effects of dexmedetomidine on an animal model of transient global cerebral ischemia-reperfusion injury. They showed a lower number of apoptotic neurons at hippocampus and decreased levels of citokynes on dexmedetomidine group as compared to the saline control group. These results indicated a clear neuroprotective effect of dexmedetomidine after transient global cerebral ischemia-reperfusion injury.

In a recent review, Afonso and Reis (207) observed that dexmedetomidine seems to have promising applications on neuro- and cardioprotection, and may confer this protection by targeting a number of different areas. The attenuation of ischemia-elicited increase in blood catecholamine levels and a limitation of excitotoxicity from glutamate might be involved in the protective underlying mechanism of dexmedetomidine. But, more evidence has been obtained suggesting that this effect can be mediated also by the stimulation of imidazoline-receptors (208). The signal transduction cascade linked to these receptors comprises extracellular signal-regulated protein kinase 1 and 2 and is known to be an important regulator for cell survival and mediator of neuroprotective effects of various agents (209). Dexmedetomidine was reported also to be effective in protecting against focal ischemia in rabbits, in cardiac ischemia-reperfusion injury in rats, in kidney ischemia-reperfusion injury in rats, and in incomplete forebrain ischemia in rats (210, 211, 202).

There is considerably more experimental evidence that dexmedetomidine has neuroprotective effects by sympatholysis, preconditioning, and attenuation of ischemia-reperfusion injury (112) and under decreases on cerebral blood flow (213, 214, 215) with its ratio with cerebral metabolic rate to be preserved (216).

Schoeler and colleagues (217) found that dexmedetomidine has a protective effect on hippocampal slice cultures subjected to a focal mechanical trauma, with the observed trauma reduction being significantly more pronounced than observed in slices treated with hypothermia. But other studies have indicated conflicting results (218). These authors investigated twenty-four patients, aged 50-70 years, undergoing coronary artery bypass graft surgery, randomized into two groups: those receiving dexmedetomidine (group D) and those which did not receive it (group C). As basal blood samples from arterial and jugular bulb catheters were drawn, dexmedetomidine (1 μg. kg^{-1} bolus and infusion at a rate of 0.7 μg. kg^{-}

^{1}. h^{-1}) was administered to patients in group D. Arterial and jugular venous blood gas analyses, serum S-100B protein (S-100B), neuron-specific enolase (NSE) and lactate measurements were performed after induction, 10 minute after the initiation of cardiopulmonary bypass, 1 minute after declamping, at the end of cardiopulmonary bypass, at the end of the surgery and at 24 hours after surgery. No significant differences between-groups were found regarding arterial and jugular venous pH, PO_2, PCO_2 and O_2 saturations. S-100B, NSE and lactate levels were also similar between groups D and C. During the postoperative period, there were no clinically overt neurological complications in any patient. Cerebral ischemia marker (S-100B, NSE and lactate) patterns were increased during cardiopulmonary bypass, as expected; however, there were no differences between the groups, which led to believe that during coronary artery bypass graft surgery dexmedetomidine has no neuroprotective effects (218).

At periferic level, in spinal cord, dexmedetomidine can preserve neurologic function in mice after aortic cross-clamping, as demonstrated by Bell and colleagues (219). It was also observated that mice exhibited almost complete reversal of the protective effect with the administration of the (α)-2A receptor antagonist atipamezole. Dexmedetomidine appears to attenuate spinal cord ischemia-reperfusion injury via (α)-2A receptor-mediated agonism (219).

At renal site, Gu and colleagues investigated whether the (α)-2-adrenoceptor agonist dexmedetomidine provides protection against ischemia-reperfusion induced kidney injury *in vitro* and *in vivo* (220). Pre- or post-treatment with dexmedetomidine provided cytoprotection, improved tubular architecture and function following renal ischemia. Associated with this cytoprotection, dexmedetomidine reduced plasma high-mobility group protein B1 (HMGB-1) elevation when given prior to or after kidney ischemia-reperfusion, and pre-treatment also decreased toll-like receptor 4 (TLR4) expression in tubular cells. Dexmedetomidine treatment promoted long-term functional renoprotection, and even increased survival following nephrectomy. However, prospective human studies establishing a benefit of dexmedetomidine against kidney damage are not yet available.

Despite its increased clinical use and potential benefits, the effect of dexmedetomidine on inflammation and neuroprotection remains limited and somewhat controversial. Future investigators may examine the clinical benefits of the use of dexmedetomidine, and the correlation of better neurological outcome with anesthesia choice.

2.1.4.8 Dexmedetomidine hemodynamic and myocardial protective effects

Dexmedetomidine has complex hemodynamic effects specific to its activation of pre- and postsynaptic (α)-2-adrenergic receptors. These effects are dose-dependent and biphasic: vasodilation at lower dosages, vasoconstriction at higher dosages and an initial short-term increase in blood pressure followed by a longer lasting reduction in blood pressure and heart rate. Several investigations have identified the cardiovascular effects of dexmedetomidine (221, 222, 117), however its effect on intraoperative hemodynamics during a propofol-supplemented remifentanil-based anesthesia regimen, which produces a strong vasodilatory effect, has not been well investigated.

There is a latent risk for excessive bradycardia and even sinus arrest when dexmedetomidine is administered in combination with sympatholytic or cholinergic agents (beta-blockers, fentanyl, neostigmine), especially with concomitant vagal stimulation (sternal separation) (223, 224, 225). Dexmedetomidine causes dose-dependent decreases in heart rate and blood pressure, concomitant with decreasing plasma catecholamines. This is of considerable benefit in tachycardic, hypertensive patients with improvement of hemodynamic stability in the perioperative period. These effects, however, may be unwanted in patients with congestive heart failure, whose cardiac output is rate dependent, or with conduction system disease. As mentioned, a high-dose bolus may result in a biphasic response, with bradycardia and hypertension consequent to initial stimulation of peripheral (α)-2B vascular receptors, followed by central sympatholysis and a decline in blood pressure (226). Unlike clonidine, cessation of dexmedetomidine administration does not appear to be associated with rebound hypertension or agitation.

The ability of (α)-2 receptor agonists to decrease tachycardia and hypertension suggests that they may play a role in cardioprotection by enhancing myocardial oxygen balance. There is little evidence that dexmedetomidine could enhance myocardial ischemic preconditioning or attenuates reperfusion injury, for example, when used after cardiac surgery, dexmedetomidine decreased the incidence of ventricular arrhythmias from 5% to zero, compared with propofol (117). Other authors have described the safe use of dexmedetomidine as an anesthetic adjunct in coronary artery bypass grafting, improving a stable hemodynamic status (227, 228).

Guo and colleagues (228) investigated the protective effects of dexmedetomidine on left ventricular contractile performance under myocardial hypoxia. They study indicates that hypoxia immediately impairs left ventricular function with a rapid increase in coronary flow

followed by a gradual decrease, with poor recovery of left ventricular function at reoxygenation. Dexmedetomidine administration only in prehypoxia, improve recovery of left ventricular function and coronary flow, and the protective effects are antagonized by yohimbine. The mechanisms are not clear, but there are several possibilities.

Dexmedetomidine might exert the protective effect on left ventricular dysfunction through inhibition of the release of norepinephrine as suggested also by Chen and colleagues (229) that showed the post-ischemic heart had a large amount of coronary norepinephrine overflow and that it reduction significantly improved the recovery of postischemic left ventricular function in an isolated working heart preparation. As demonstrated before, it is believed that high interstitial concentrations of norepinephrine result in myocyte calcium overload and cell death causing development of cardiac dysfunction (230). The high plasma concentrations of cathecolamines (norepinephrine and epinephrine) would lead to a calcium overload into the myocardial cells, increased cytosolic and intramitochondrial calcium, reactive oxygen species release, and adenosine triphosphate (ATP) depletion, with resulting electrocardiogram (ECG) changes, failing in myocardial contraction and possible cell death (231, 232). In patients under extreme sympathetic discharge caused by an acute stress a tissue lesion characterized by contraction of sarcomeric myofibrilles, and interstitial mononuclear infiltration was described (233). Ebert and colleagues (234) reported that dexmedetomidine diminished the hemodynamic and norepinephrine response to the activation of cardiac sympathetic nerves by the cold pressor test. Dexmedetomidine could also prevent a myocardial ischemia-induced norepinephrine release in anesthetized dogs (235).

Dexmedetomidine increase the cyclic adenosine monophosphate (cAMP) level in the coronary artery. Guo and colleagues (228) demonstrated that hypoxia caused an immediate increase in coronary flow followed by a gradual decrease, similarly to the results of Karmazyn and colleagues (236), and reoxygenation resulted in poor recovery. Pinsky and colleagues (237) reported that the graft vasculature with hypoxia impaired vascular function and decreased blood flow after transplantation, and it enhanced phosphodiesterase activity and caused a time dependent decline in cAMP levels in the vascular smooth muscle cells. Kitakaze and colleagues (238) reported that an increase in cAMP level by stimulation of adenosine receptors was amplified by the (α)-2-adrenergic stimulation in the coronary artery. Thus it is possible that dexmedetomidine could increase the cAMP level and attenuate coronary vascular damage of an adenosine-induced coronary vasodilative effect and preserve coronary flow. Kitakaze and colleagues (238**)** provided evidence that alpha-2-adrenergic stimulation increased coronary flow during ischemia as a result of enhancement of adenosine-

induced coronary vasodilation, although (α)-2-adrenergic stimulation exerted prominent vasoconstriction in nonischemic hearts. However, in Guo study, dexmedetomidine did not significantly improve the coronary flow during hypoxia, contesting this hypothesis.

A large European study demonstrated that perioperative infusion of mivazerol, another (α)-2-adrenergic agonist, significantly decreased cardiac death after vascular surgery in patients with known coronary artery disease (239). And, a meta-analysis of noncardiac vascular surgery patients receiving any (α)-2-adrenergic agonist agent demonstrated decreased risk of myocardial infarction and death (240), but dexmedetomidine alone on cardiovascular outcomes after noncardiac surgery did not show statistical significance (241). Therefore, larger studies are required to clearly ascertain the cardioprotective effect of dexmedetomidine and they whether or not should be included in patients at high cardiac risk.

2.1.4.9 Dexmedetomidine other potential effects

The effects of dexmedetomidine on renal function are complex. Alpha-2 agonists exert a diuretic effect with decreased salt and water reabsorption (242). There are experimental evidence that dexmedetomidine attenuates murine radiocontrast nephropathy by preserving cortical blood flow (243). This mechanism is supported by the observation that dexmedetomidine decreases the renal cortical release of norepinephrine (211). There are also evidence that dexmedetomidine attenuates murine ischemia-reperfusion injury (171). However, prospective human studies cannot establish renal benefits of dexmedetomidine.

Based on preliminary studies, the USA Food and Drug Administration approved duration of infusion of dexmedetomidine remains 24 hours. However, there are several studies that have demonstrated safe use for a week or longer in mechanically ventilated critically ill patients (244). With prolonged administration, tolerance to dexmedetomidine´s hypnotic effects has been demonstrated in animals (245), but it does not appear to be clinically significant.

Dexmedetomidine also suppress shivering, possibly by their activity at (α)-2B receptors in the hypothalamic thermoregulatory center of the brain (246). Low-dose dexmedetomidine has an additive effect with meperidine on lowering the shivering threshold, when these drugs are combined (247). Dexmedetomidine may be beneficial in decreasing patient discomfort and oxygen consumption that occur on postoperative shivering (248).

Alpha-2 adrenergic agonists, such as clonidine, have also an established role in the treatment of central hyperadrenergic states induced by withdrawal of drugs, including cocaine, alcohol, or opioids. Numerous case reports of successful treatment of withdrawal using dexmedetomidine have been publish (226, 249, 250, 251, 252), but to date, no randomized trials have been performed.

2.1.5 Conclusions

Until December 2007, when results of the MENDS (Maximizing Efficacy of Targeted Sedation and Reducing Neurologic Dysfunction) trial were published, most of the data published on dexmedetomidine were from its use in surgical patients unique as a coadjuvant anesthetic (106). Administered intravenously, dexmedetomidine has been used for sedation and anxiolysis in the intensive care unit and as others additional perioperative uses: premedication, to reduce emergence delirium and postoperative pain, and to attenuate the stress responses associated with surgery and anesthesia. But, it will be necessary to explore the pharmacological mechanisms for the actions of these (α)-2-adrenergic receptor agonist in more detail. The incipient clinical use of dexmedetomidine can be ascribed to its recent introduction as anesthetic in human and veterinary practices. Since inflammation is normally a component of surgery-associated injuries, it would be valuable to have a safe and effective means of preventing inflammatory response to major surgery, especially to coronary artery bypass grafting, and its complications, with the beneficial actions of anesthetic drugs. We believe that dexmedetomidine can be considered a particularly promising agent. Other anesthetic approaches will be required to test the efficacy of dexmedetomidine as an anti-inflammatory agent and to further clarify both safety and efficacy to dexmedetomidine use in patients undergoing extremely invasive surgeries, such as cardiopulmonary bypass.

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Legends of Figures

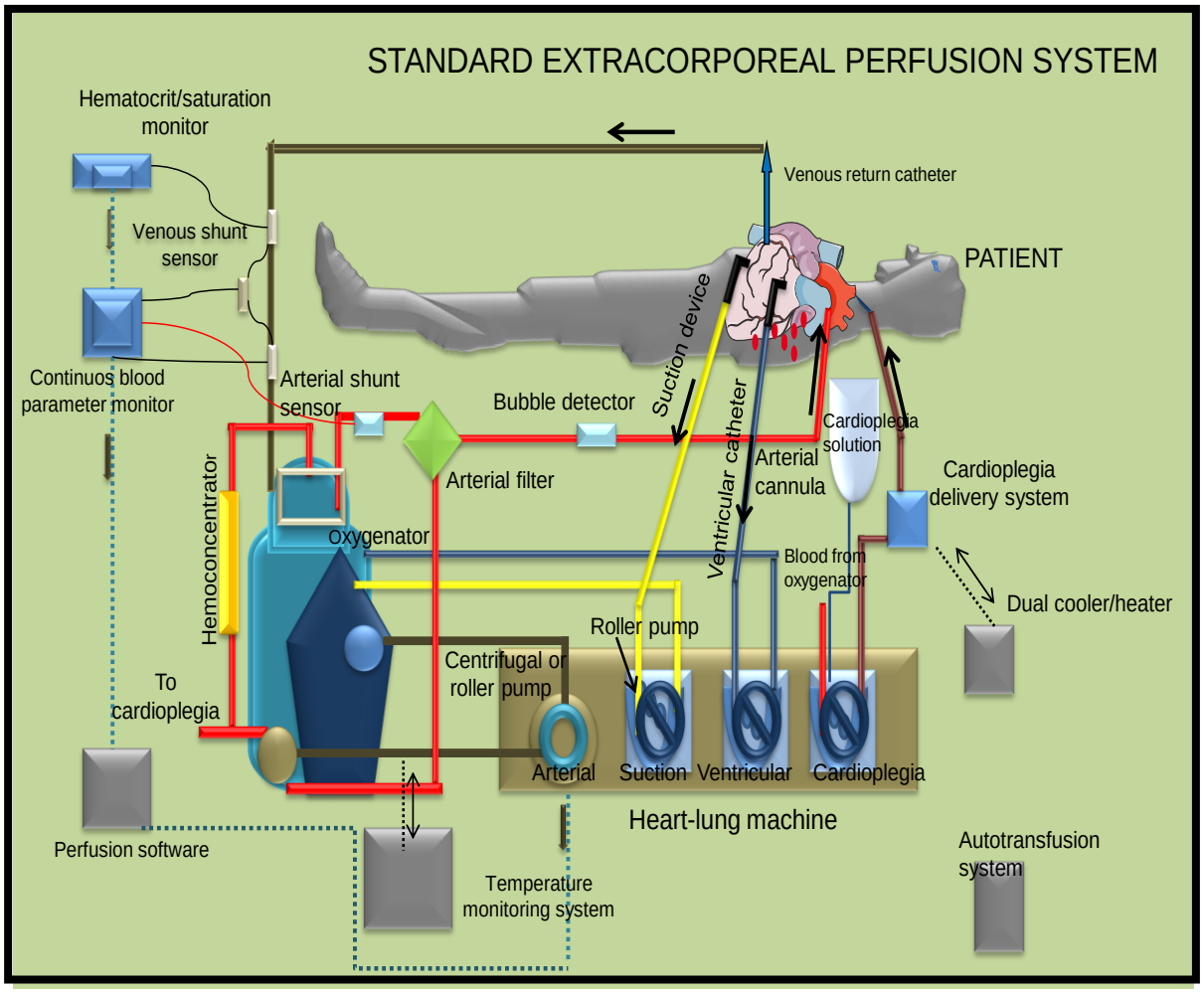

Figure 1. Standard Extracorporeal Circulation System. At coronary artery bypass grafting surgery, blood is deviated by pumps of heart and lungs, through an oxygenator, and circulating at an extensive tubulation device to permit the oxygenation of tissue during the ischemia period.

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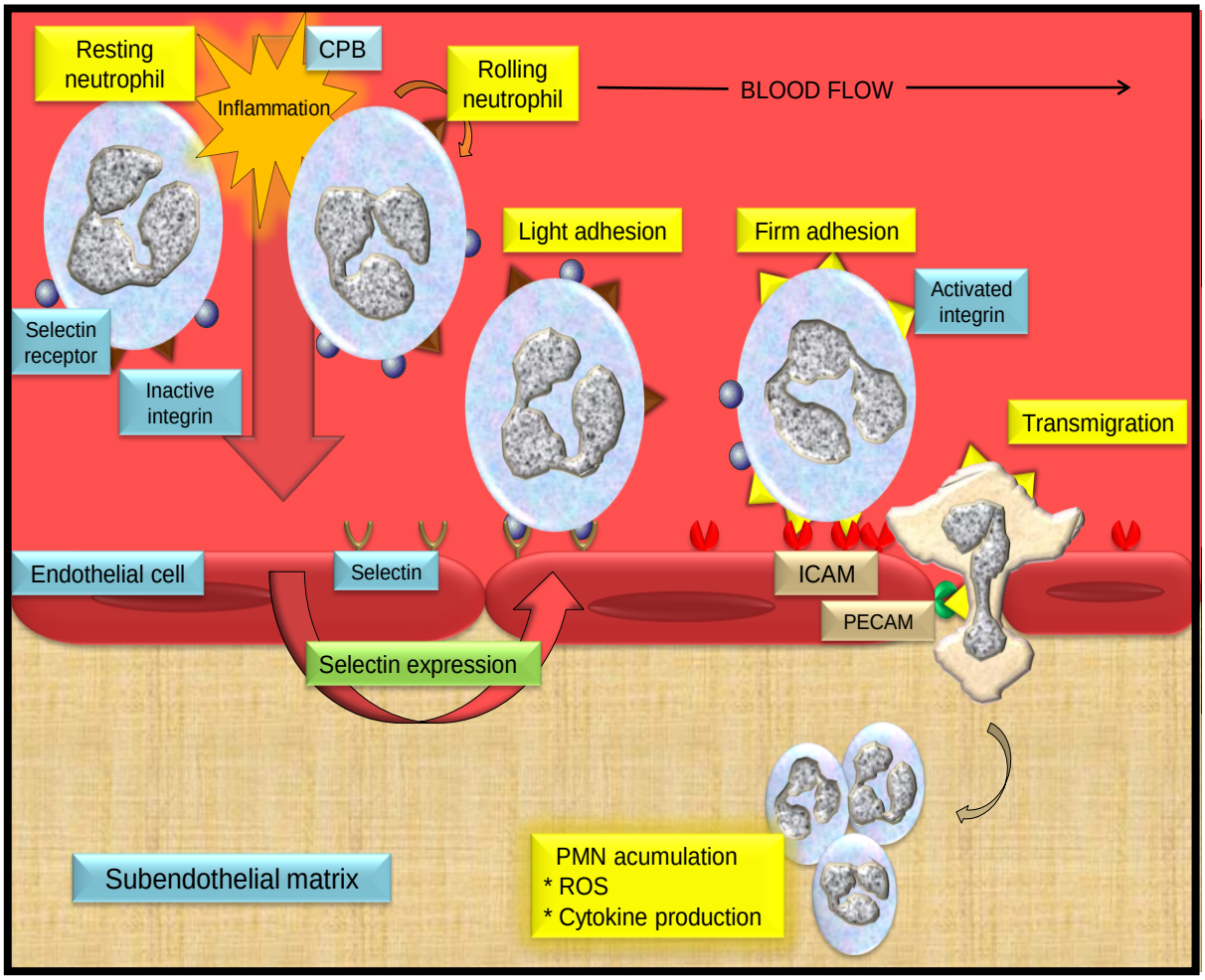

Figure 2. Cardiopulmonary Bypass neutrophil activation. At neutrophil activation by inflammatory mediators a neutrophil rolling phase occur, with posterior endothelial adesivity, initially light, thus firm and culmining with the neutrophil endothelial transmigration. It leads to neutrophil accumulation, reactive oxygen species (ROS) production and cytokine release, maintaining the vicious circles. CPB: Cardiopulmonary Bypass; PMN: polymorphonuclears; ROS: Reactive Oxygen Species; ICAM: Intercellular adhesion molecule PECAM: Platelet/endothelial cell adhesion molecule.

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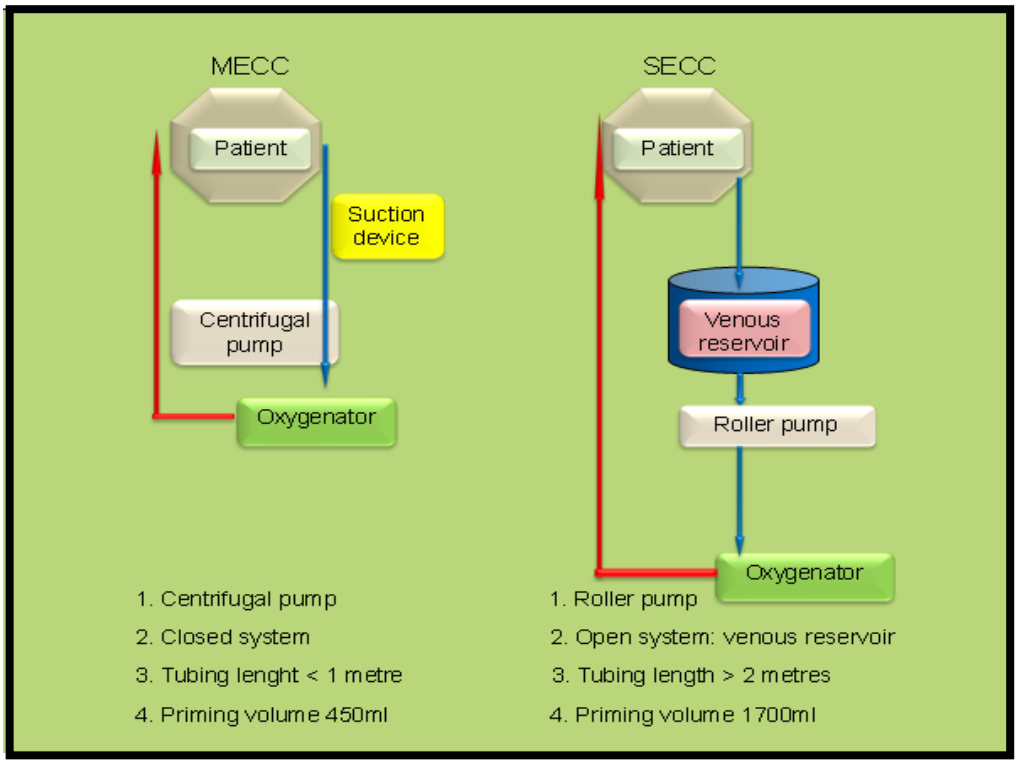

Figure 3. Mini-Extracorporeal Circulation System compared to Standard Extracorporeal Circulation System. In MECC system they exist various advantageous, such a shorter tubular circuit, only a centrifugal pump use, a closed system when blood no contact air and a smaller priming volume resulting in lesser hemodilution as compared to SECC. MECC: mini-extracorporeal circulation; SECC: standard extracorporeal circulation.

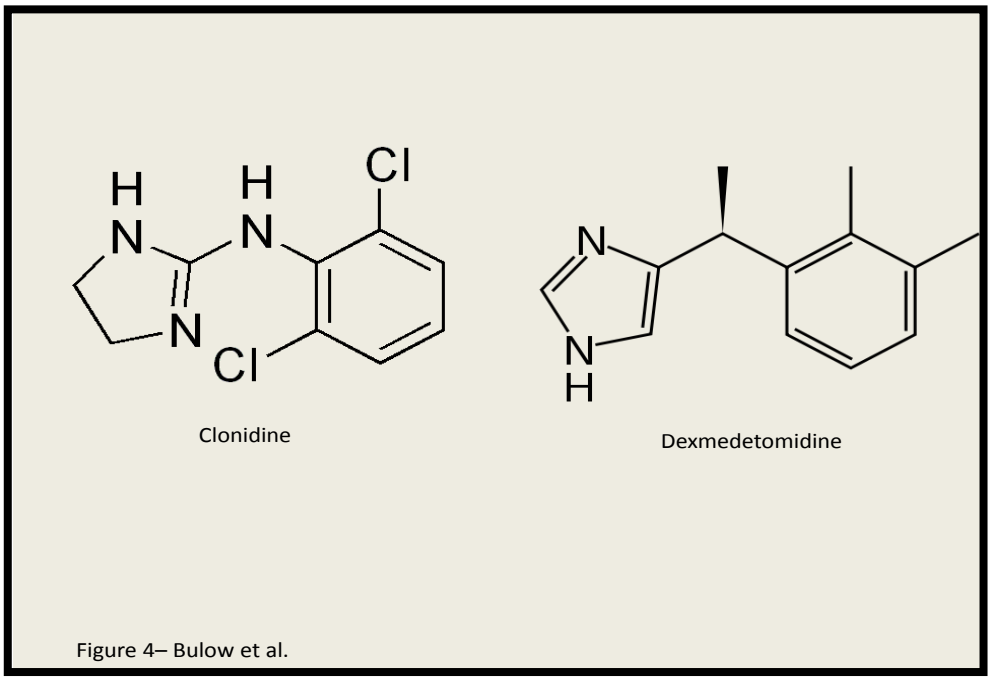

Figura 4. Dexmedetomidine and Clonidine structural formulae.

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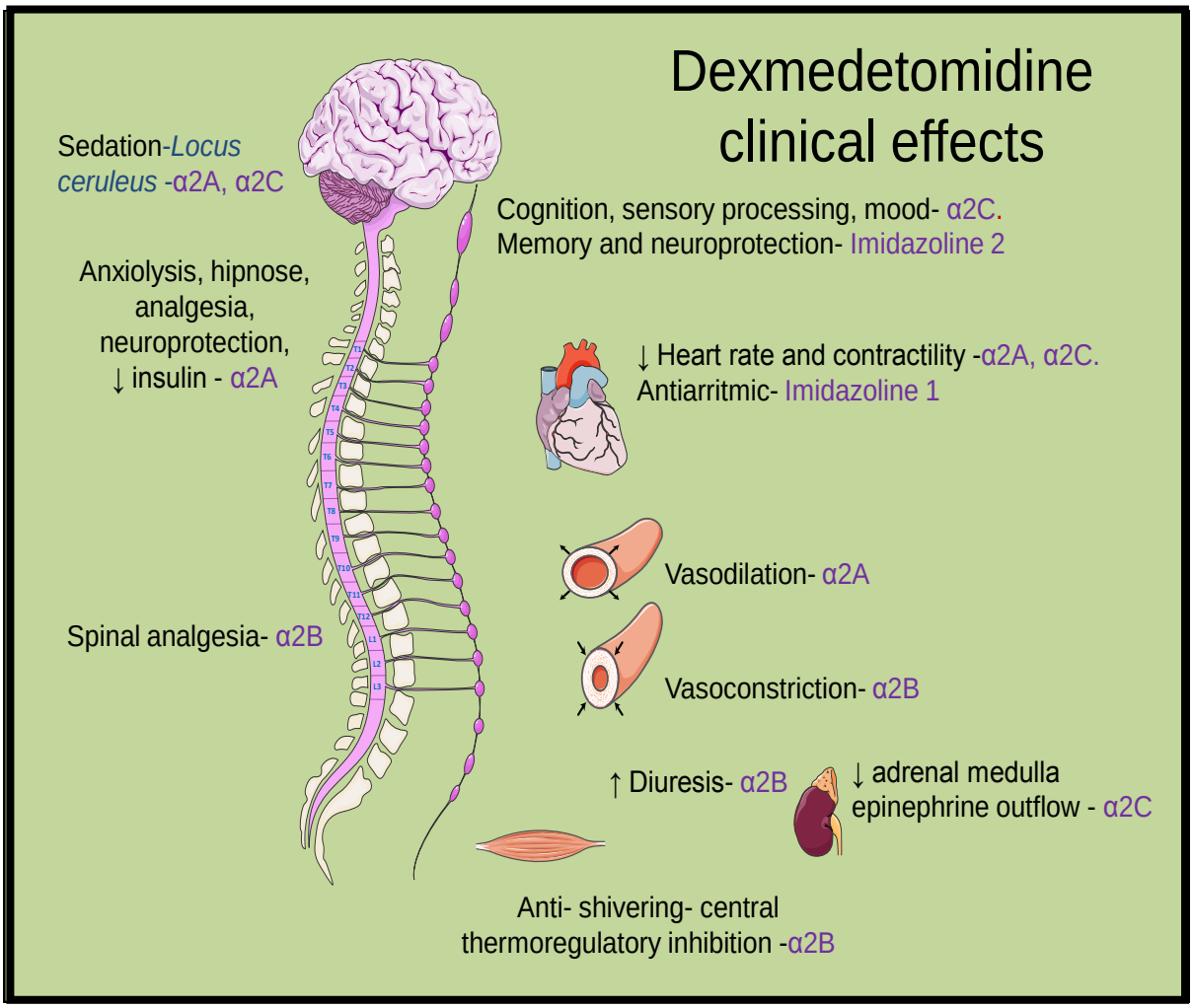

Figure 5. Dexmedetomidine clinical effects mediated via activation of (α)-2-adrenergic and imidazoline receptors. Through the presynaptic α-2A-adrenoreceptors agonism, dexmedetomidine induce sedation, anxiolysis, hipnose, analgesia, neuroprotection, reduce insulin release, reduce heart rate and myocardic contractility and lead to vasodilation. Also by presynaptic agonistic effect on α-2C-adrenoreceptors induce sedation, mood and cognition modulation, sensorial processing and reduction of adrenal medulla epinephrine. By the postsynaptic α-2B-adrenoreceptors agonism, dexmedetomidine cause analgesia at spinal level, vasoconstriction (with high bolus doses), improve of diuresis and central inhibition of shivering. Dexmedetomidine act also at imidazoline receptors, with a neuroprotection mechanism (imidazoline-2) and with antiarritmic effect (imidazoline-1).

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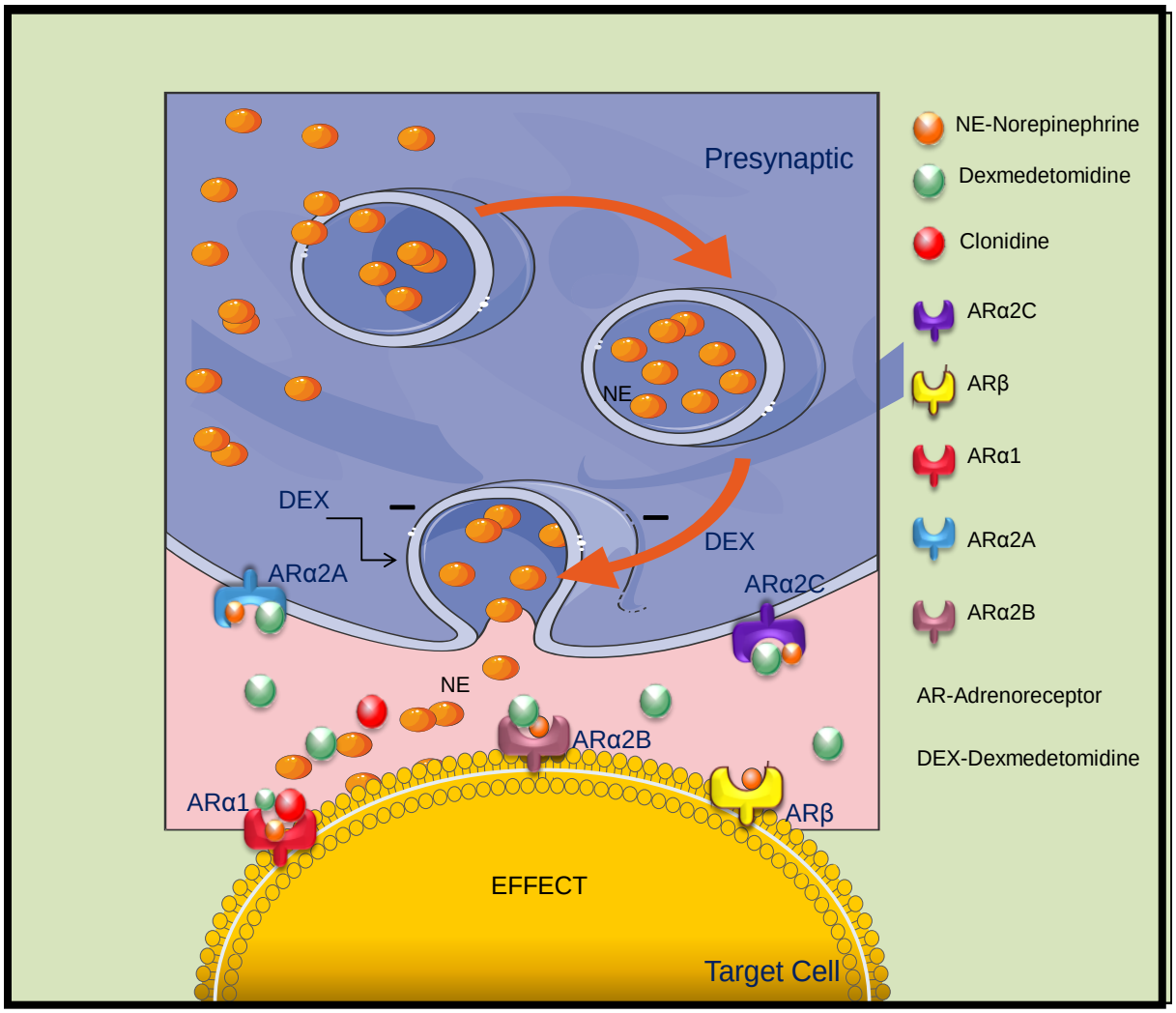

Figure 6. Dexmedetomidine can exert its effects via activation of three (α)-2-adrenoreceptor subtypes. A subclass of (α)-2-adrenoreceptor located presynaptically ((α)-2A and (α)-2C) regulated the release of neurotransmitter (norepinephrine). Located postsynaptically, a subclass of (α)-2B-adrenoreceptor, and also the (α)-1-adrenoceptor, while dexmedetomidine is not (α)-2-adrenoceptor selective. The (α)-2-adrenoceptors could exist also extrasynaptically.

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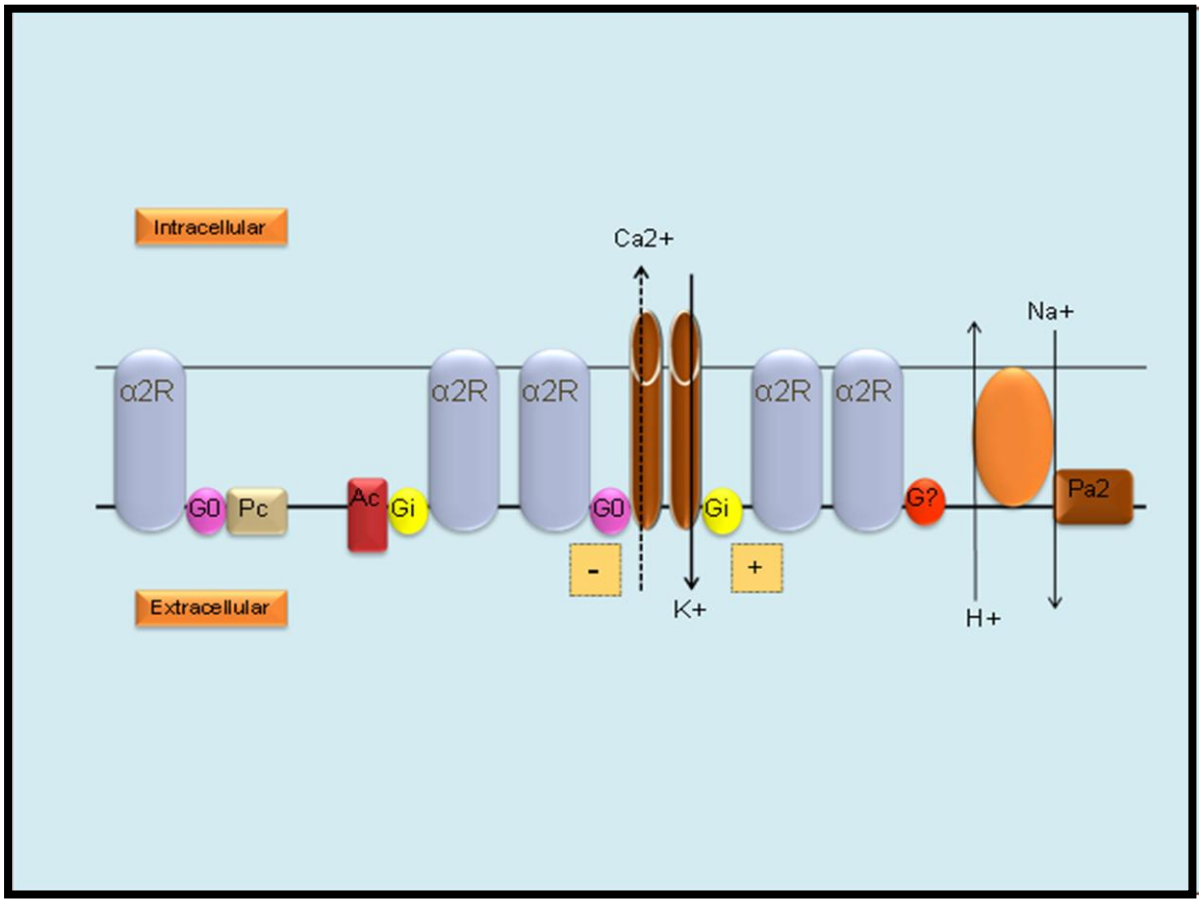

Figure 7. Putative Intracellular Mechanisms Involved in the (α)-2-adrenoreceptors Activation. The (α)-2-adrenoreceptor subtypes are transmembrane receptors that can be coupled to different classes of G-protein. The activation of (α)-2-adrenoreceptor (α2R) inhibits adenyl cyclase (Ac) via activation of receptor-coupled Gi protein. This causes outward opening of the K^+ channel via Gi protein, which results in cell hyperpolarization. The coupling of adrenoreceptors to G0 can either inhibit Ca^{2+} translocation or modulate phospholipase C (Pc). The coupling with an undertermined class of G protein (G?) stimulates an exchange of H^+ and Na^+ (Modified from Ma D, Rajakumaraswamy N, Maze M: 2-Adrenoreceptor agonists: shedding light on neuroprotection? Br Med Bull 71:77-92, 2005[107]).

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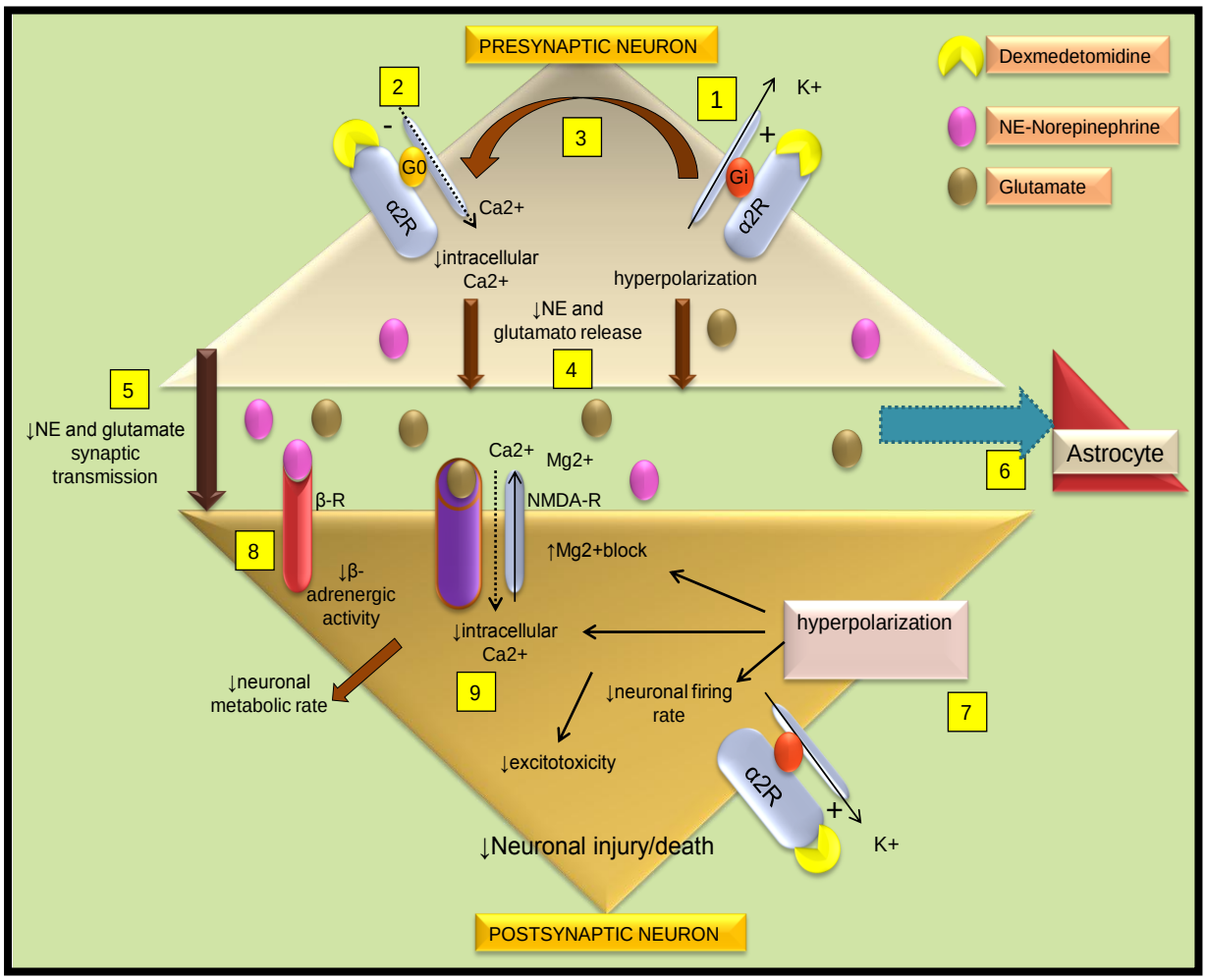
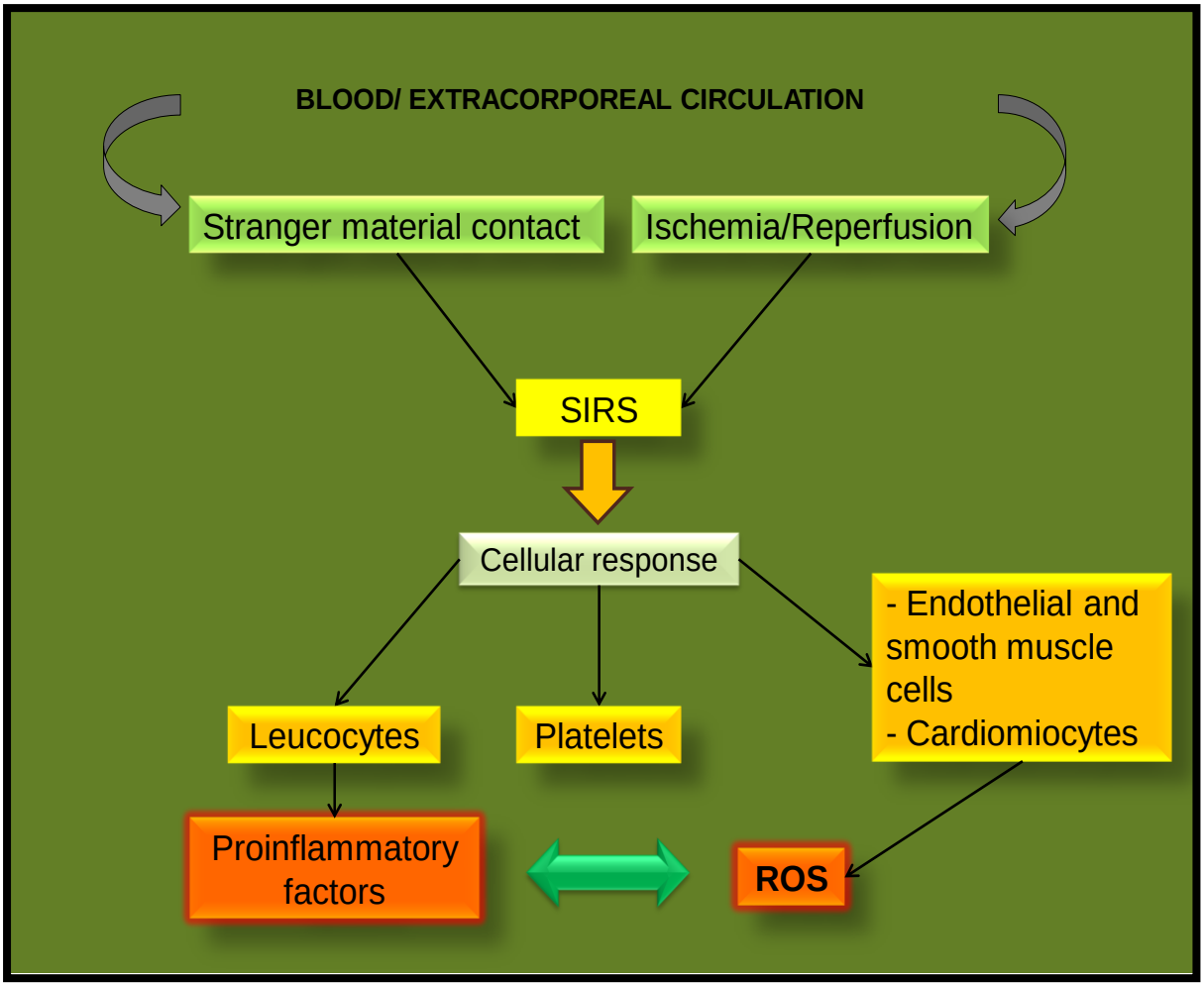


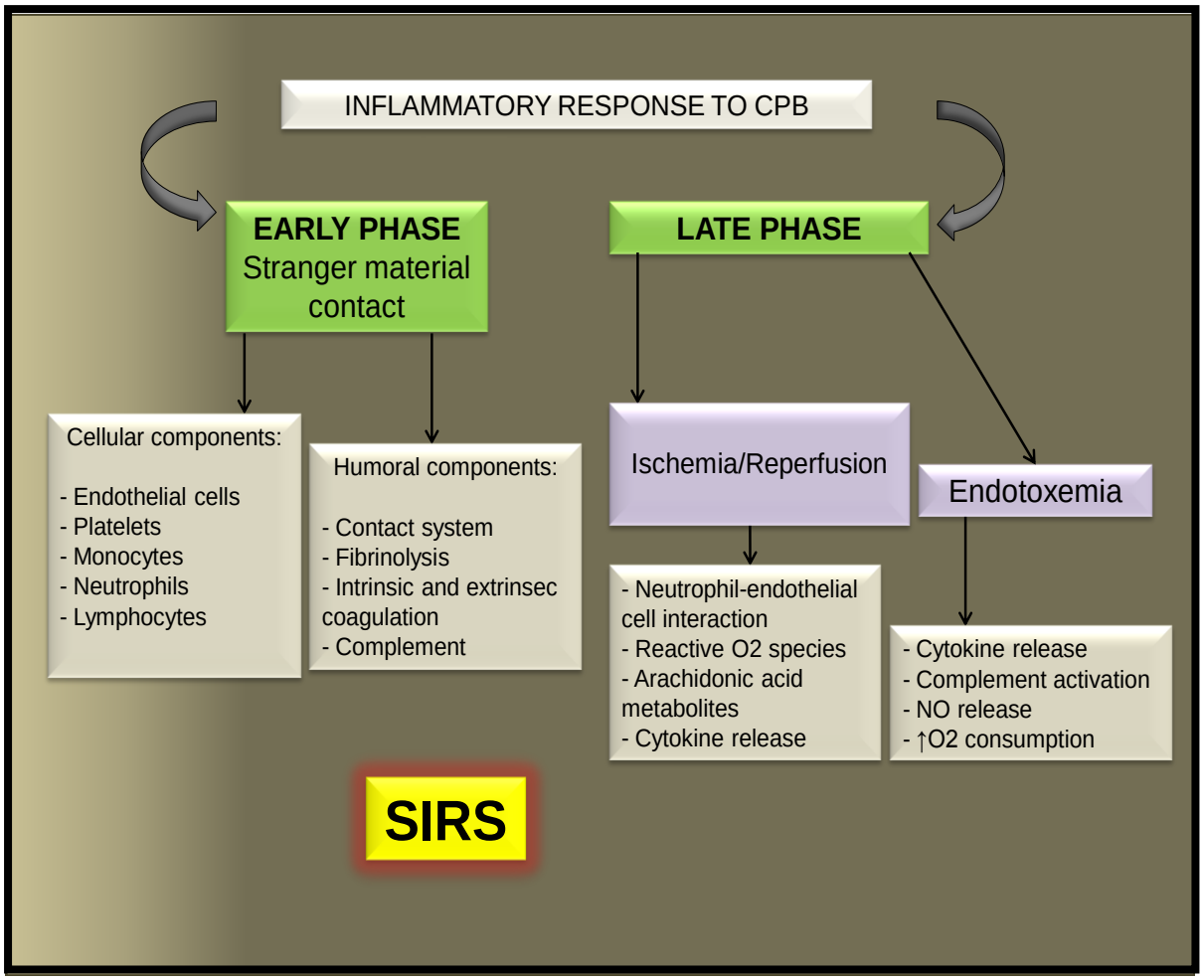
Figure 8. Neuroprotective mechanism(s) triggered by (α)-2-adrenoreceptors agonists. **Pre-synaptically**:1- Activation of outward rectifying K^+ channels causing hyperpolarization; 2- Inhibition of inward translocation of Ca^{2+} ions; 3- Hyperpolarization resulting from action-1 causes reduced Ca^{2+} entry; 4- Reduced intracellular Ca^{2+} (as a result of actions 2 and 3) causes diminished neurotransmitter release. **Synaptically**: 5- Due to action-4 as well as reduced receptor sensitivity; 6- Extrasynaptic scavenging of glutamate by astrocytes. **Post-synaptically**: 7- Hyperpolarization reduces the activation of NMDA receptors by enhancing Mg^{2+} block, and also causes reduced neuronal firing and reduced intracellular Ca^{2+} release; 8- Due to action 5 and 9. The reduced excytotoxic neuronal death due to combination of all actions but the main pathway is via a reduction in the free intracellular Ca^{2+}. (Ma D, Rajakumaraswamy N, Maze M: α2-Adrenoreceptor agonists: shedding light on neuroprotection? Br Med Bull 2005; 71:77- 92 [107]) (Modified of Dexmedetomidine and neuroprotection Janke, EL, Samra, S. Seminars in Anesthesia, Perioperative Medicine and Pain 2006 25: 71–76 [158]).

Legends of schemes



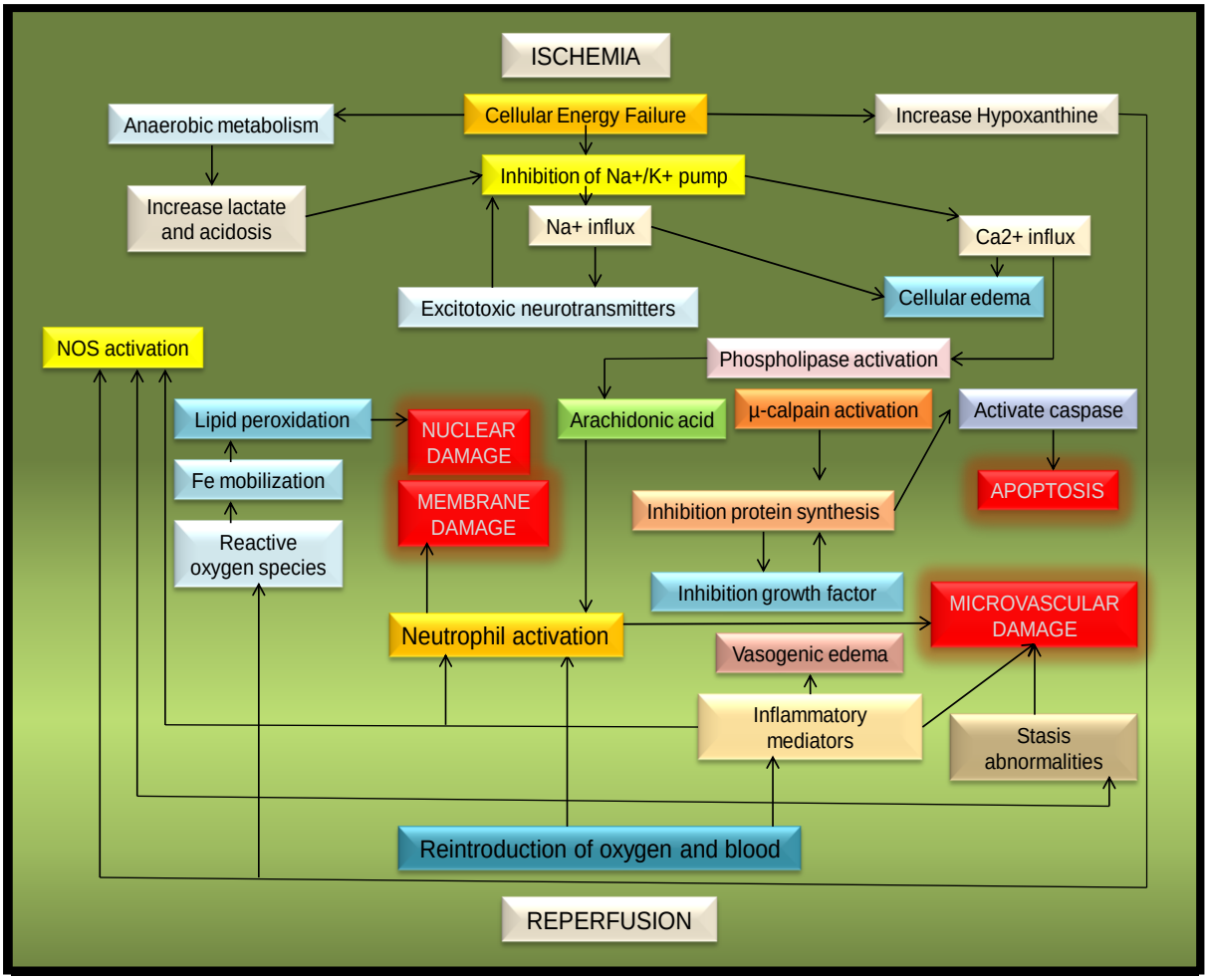
Scheme 1. Cardiopulmonary bypass and the extracorporeal circulation responses with the pathophysiologic changes resembling the systemic inflammatory response syndrome (SIRS). The contact of blood with xenosurfaces of the extracorporeal machine device, the ischemia/reperfusion and the hyperbaric oxygen triggered SIRS-like pathophysiological responses. The SIRS-like response is associated with overactivation of leukocytes, platelets (which can contribute to an increased coagulopathy), endothelial and cardiac cell. The secretion of pro-inflammatory factors by leucocytes and the increase tension and blood oxygenation stimulate the overproduction of reactive oxygen species (ROS), which feeds a vicious cycle of inflammation ← → ROS production.

Legends of schemes



Scheme 2 - The inflammatory response to cardiopulmonary bypass is divided into 2 phases: “early” and “late” phases. The first phase is induced by the contact with xenosurfaces and the late phase is more related to oxygen reperfusion after ischemia and endotoxemia.

Legends of schemes



Scheme 3. Complex cascade of pathophysiologic phenomena associated with ischemia/reperfusion in CABG. Anaerobic metabolism carry to an increase on lactate and reduced pH with transmembrane pump impairment, wich lead to a intracellular Ca^{2+} and Na^{+} increases, and consequently cellular edema. Increase on intracellular Ca^{2+} activated phospholipase A2 and calpain, with arachidonic acid degranulate and protein synthesis inhibition. Thus, caspase and neutrophil activation occur with cellular apoptosis. The neutrophils activation induce membrane lesions and more proinflammatory mediators liberation, including nitric oxid, through oxidonitrico sintase (NOS) activation and that lead to microvascular damage and endothelial impairment, in a vicious circle.

2.2 MANUSCRITO 2 - Dexmedetomidina reduz a resposta inflamatória após cirurgia miocárdica sob mini-circulação extracorpórea

Manuscrito 2

DEXMEDETOMIDINE DECREASE THE INFLAMMATORY RESPONSE TO MYOCARDIAL SURGERY UNDER MINI CARDIOPULMONARY BYPASS

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Dexmedetomidine decrease the inflammatory response to myocardial surgery under mini cardiopulmonary bypass

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2.2.1 Abstract

Despite great technological advances in cardiac surgery, there is a high incidence of myocardial dysfunction and neurocognitive deficit or severe strokes in the postoperative period. Preventive measures are essential to reducing these adverse situations that are responsible for significant impairment on life quality. Surgery and cardiopulmonary bypass (CPB) with extracorporeal circulation produces important changes in the immune system, directly involved in the incidence of these complications. During this period occurs the release of proinflammatory cytokines and reduction of antiinflammatory cytokines, and an increase of reactive oxygen species (ROS). We hypothetize that the anesthetic choice could modified these inflammatory responses in patients undergoing coronary artery bypass grafting (CABG) surgery with mini-CPB. Methods: In a prospective, randomized and blinded study, we intended to demonstrate the influence of dexmedetomidine (TIVA-DEX group), an alpha-2-agonist anesthetic drug, as a component of a conventional total intravenous anesthesia (TIVA), on the behavior of this inflammatory response. Intraoperative dosage of cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-10 (IL-10), gamma interferon (INF-γ), tumor necrosis factor (TNF-α), C-reactive protein (CRP), creatine phosphokinase (CPK), creatine phosphokinase-MB (CPK-MB), I troponin (cTnI), cortisol and glucose were performed. Lipid peroxidation was avaliated by the study of thiobarbituric acid reactive substances (TBARS) and the activity of delta-aminolevulinate dehydratase (d-ALA-D) was avaliated as an indicator of the production of reactive oxygen species. The blood collect samples times were before anesthesia (Time 1), at 90 minute after beginning of CPB (Time 2), 5 hours after beginning of CPB (Time 3) and at 24 hours after the end of surgery (Time 4). Results: Dexmedetomidine induce to a statistical significative reduction of IL-1, IL-6, TNF-α and INF-γ as compared to did not received dexmedetomidine group.The levels of IL-10 decreasing in both groups along the time, in a similar pattern. Do not ocur difference between groups on δ-ALA-D activity and TBARS were higher in dexmedetomidine group. Conclusion: Dexmedetomidine associated to TIVA was able to reduce plasma levels of IL-1, IL-6, TNF-α and INF-γ in patients under coronary artery bypass grafting surgery with mini-cardiopulmonary bypass, as compared to conventional TIVA patient group.

Keywords: Cytokines; Systemic Inflammatory Response Syndrome (SIRS); Total Intravenous Anesthesia (TIVA); Dexmedetomidine, Coronary Artery Bypass Grafting Surgery (CABG), Mini-Cardiopulmonary Bypass (Mini-CPB).

2.2.2 Introduction

Cardiac surgery induces a variety of metabolic, endocrine, and immune changes known as the "stress response", which may lead to prolonged in-hospital stay. Clinical manifestation include postoperative complications such as respiratory failure, wound infections (1), myocardial damage with contractile dysfunction, renal impairment, coagulopathy and neurologic dysfunction (2) with an increased mortality (3). Responses to cardiopulmonary bypass have been compared with the changes occurring in systemic inflammatory response syndrome (SIRS) (4). Mechanisms such the exposure of blood to nonphysiologic surfaces, surgical trauma, anesthesia, changes in body temperature, increased intestinal permeability by endotoxins, and ischemia/reperfusion injury (5) can be responsible to release into circulation of reactive oxygen species (ROS), proinflammatory cytokines, endothelins, platelet-activating factors, and endothelial and leukocyte adhesion molecules (6, 7).

Reactive oxygen species are recognized as critical mediators of cardiac and neurologic injury during ischemia/reperfusion. It is known that the cardiopulmonary bypass is potentially responsible for an activation of neutrophils, an important source of systemic primary reactive oxygen species, and damages related to activation and infiltration of neutrophils in reperfused tissues (4).

Although it has been shown that, compared with clinical management alone, conventional coronary artery bypass surgery with cardiopulmonary bypass prolongs life and reduces symptoms of pacient, these benefits are accompanied by risks such as necessity of transfusions (30–90%), mortality (2–5%), stroke (2%), atrial fibrillation (30%), and neurocognitive dysfunction (50–60%) (8,9). These adverse clinical consequences have been attributed to the inflammatory responses to the cardiopulmonary bypass circuit, hypothermic cardiac arrest, aortic cannulation and cross-clamping (10, 11, 12). Nevertheless, there are considerable evidence that multiple pathways exist by which anesthetic agents have the potential to exert clinically important benefits (13, 14, 15, 16, 17, 18, 19, 20) and may be of interest to study potential benefit of specific anesthetic drugs, through its potential antiinflammatory mechanisms, that could reduce these postoperative complications and mortality.

Alpha(α)-2-adrenergic receptor agonists, such clonidine and dexmedetomidine, have been utilized in anesthesia to the sedative, analgesic, hemodynamic-stabilizing properties, and sympatholytic pharmacologic effects (21, 22). The stress response to surgery

can be attenuated by sympatholytic effects caused by postsynaptic activation of central (α)-2-adrenergic receptor, leading to reductions in blood pressure and heart rate (23). Recently, a few numbers of studies have investigated whether or not dexmedetomidine have antiinflammatory properties (24, 25, 26, 27, 28).

As corollary, it would be of great interest to have a safe and effective anesthetic drug with antiinflammatory properties to be used in a major surgery, especially in coronary artery bypass grafting surgery. In this regard, dexmedetomidine can be considered a promising candidate, because (α)-2-adrenergic agonists can modulate inflammatory response (29, 30, 31, 19). Here, we have hypothesized that dexmedetomidine in association with a conventional total intravenous anesthesia (infusion of propofol and sufentanil), could decrease the inflammatory response and oxidative stress associated with coronary artery bypass grafting surgery.

2.2.3 Materials and Methods

After institutional ethics review board approval and written informed patient consent, 30 clinical ASA II to III class patients, aged 42-72 yr, presenting for scheduled coronary artery bypass surgery under mini-cardiopulmonary bypass were assigned, according randomization, to the conventional total intravenous anesthesia (propofol/sufentanil) (TIVA; group 1-15 patients) or to TIVA with dexmedetomidine (propofol/sufentanil/dexmedetomidine) (TIVA-DEX; group 2- 15 patients) group. The surgery team, surgeon and perfusionist, was the same for all the patients that were recruited during two years (period of data collection).

Patient exclusion criteria included: severe ventricular dysfunction (left ventricle ejection fraction < 40%), reintervention surgery, need of blood products on the enter of cardiopulmonary bypass, preoperative history of liver or kidney dysfunction, immunological disease, preoperative intake of corticosteroids or anti-inflammatory drugs (except salicylic-acetil acid) and history of a recent myocardial infarction (last two weeks).

Group 1 patients (TIVA): patients anesthetized with total intravenous anesthesia in target-controlled infusions (TCI infusion system, Diprifusor®; AstraZeneca, Wedwel, Germany) of propofol as hypnotic (an initial target blood concentration of 4 μg. ml^{-1}) in induction and maintenance of anesthesia, based on bispectral (BIS) index evaluation (BIS values between 45 and 55). Associated with propofol, an infusion of sufentanil at a dose of 0.5 to 1 μg. kg^{-1} at induction and posterior maintenance of 0.5 to 1 μg. kg^{-1}. h^{-1} during surgery

time. The muscle relaxation for tracheal intubation was obtained with pancuronium (0.1 mg. kg^{-1}) at induction and additional 1/3 dose if necessary.

Group 2 patients (TIVA-DEX): patients anesthetized with total intravenous anesthesia in target-controlled infusions (TCI infusion system, Diprifusor®; AstraZeneca, Wedwel, Germany) of propofol as hypnotic (an initial target blood concentration of 4 μg. ml^{-1}) in induction and maintenance of anesthesia, based on bispectral (BIS) index evaluation (BIS values between 45 and 55). Associated with propofol, an infusion of sufentanil at a dose of 0.5 to 1 μg. kg^{-1} at induction and posterior maintenance of 0.5 to 1 μg. kg^{-1}. h^{-1} during surgery time. All patients receive at anesthesia induction and during surgery, a continuos dexmedetomidine infusion, at 0.3 μg. kg^{-1}. h^{-1} rate. The muscle relaxation for tracheal intubation was obtained with pancuronium (0.1 mg. kg^{-1}) at induction and additional 1/3 dose if necessary. Surgeons working in the operation room and the medical team on intensive care unit (ICU) were blinded to treatments protocols.

Systemic arterial blood pressure was measured via a radial artery catheterization. A Swan-Ganz catheter was inserted for central venous pressure (CVP), pulmonary capillary pressure (PCP) and cardiac index (CI) determinations. Hemodynamic parameters are intermitently monitored 24 hours after surgery, to intend maintenance of arterial blood pressure and cardiac index range at 20% basal levels. Cardioscopy, pulse oximetry, CO_2 expirated levels, nasopharinx temperature and bispectral index were monitored. The surgery was conducted under mini-cardiopulmonary bypass and mild hypothermia (34-35 ^{o}C). Serials blood samples were collected to verify arterial gasometry, hemodilution and electrolytes.

For biomarkers determination, arterial blood was sampled at the radial performed catheterization before anesthesia induction (Time 1 or basal), 90 minutes after mini-cardiopulmonary bypass beginning (Time 2, during surgery), five hours after mini-CPB beginning (Time 3, within 2 to 3 hours after the end of surgery) and 24 hours after surgery end (Time 4).

FIGURE 1 ABOUT HERE

Citokynes (interleukin-1, interleukin-6, interleukin-10, TNF-α and INF-γ), were measured by chemical analysis (commercial kits: eBIOSCIENCE®, San Diego, USA). The plasma levels of C-reactive protein was measured by immunoassay (Dimension®, Siemens, Healthcare Diagnostics Inc., Newark, DE, USA), for cTnI determination was used a chemiluminescent method (IMMULITE®, Siemens, Healthcare Diagnostics Inc., Newark,

DE, USA), CPK and CPK-MB were avaliated by an enzymatic method (Dimension®, Siemens, Healthcare Diagnostics Inc., Newark, DE, USA), cortisol was determined using a chemiluminescent enzyme immunoassay (IMMULITE®, Siemens, Healthcare Diagnostics Inc., Newark, DE, USA) and glucose was determined by biochromatic method (Dimension®, Siemens, Healthcare Diagnostics Inc., Newark, DE, USA). TBARS (nmolMDA.ml^{-1} erithrocytes) were determinate based on a colorimetric method previously described (32) and δ-ALA-D activity were also performed at a colorimetric method (33).

Plasma samples were coded, and the investigators were blinded regarding treatment regimen. Similarly, all hemodynamic data were collected by trained observers who were not authors of this study and who were blinded to the anesthetic regimen used. They also recorded surgery duration, duration of mini-cardiopulmonary bypass, time for extubation, time in ICU and time for in-hospital stay. Possibly postoperative complications and necessity of inotropic support were investigated (considered the necessity of two or more inotropic drugs for hemodynamic stability) and the mini mental state examination (MMSE) was performed before and five days after surgery, considering the scholarity of patients.

All continuous data were expressed as mean± SD. Statistical analysis were performed by two-way ANOVA (2 anaesthetic procedures x 4 sampling time) with time factor treated as repeated measures. Values were considered to be statistical significant when *P* was < 0.05.

2.2.4 Results

The characteristics of the two groups were similar in age, wheight, height, comorbydities, mini-cardiopulmonary bypass time, total surgery time, time for extubation, time in intensive care unit (ICU), in-hospital stay time and mini mental state examination (Table 1).

TABLE 1 ABOUT HERE

Two-way ANOVA of mean arterial pressure (MAP), heart rate (HR) and arterial O_2 pressure (PO_2), indicated only a significant main effect of time of sampling ($P< 0.001$ for all cases), indicating that the anesthetic procedure for the groups were not significantly different (Table 2). Comparison in each group revealed a progressive statistical significant decrease in mean arterial pressure, as compared the basal time and anothers colected times (Figure 2) however, none patient necessited special postoperative inotropic drug support.

Intravascular doses of dexmedetomidine induced dose-dependent decreases in systolic and diastolic blood pressure and in heart rate with important decreases in plasma norepinephrine levels (34). However, at high-bolus intravascular doses (50–75 μg), a transient initial hypertensive response may be seen, because an activation of peripheral vascular (α)-2-adrenergic receptors before the central sympatholytic effect on the vasomotor center occur (34). Here, we do not use a bolus dose of dexmedetomidine, and these patients were hemodynamic stable. Statistical analysis of the mean arterial pressure of both patient groups indicated only a significant main effect of sampling time ($p<0.0001$) (Figure 2 and Table 2).

TABLE 2 AND FIGURE 2 ABOUT HERE

Statistical analysis of heart rate (HR) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two different anesthesia (TIVA and TIVA-DEX) indicated only a significant main effect of sampling time ($p<0.0001$) (Figure 3).

FIGURE 3 ABOUT HERE

The hemodilution observed was important and similar between groups, with a significant diference intragroup with de time, as considered the basal time (Table 3). Statistical analysis of hematocrit (HT) of patients using two different anesthesia (TIVA and TIVA-DEX) indicated only a significant main effect of sampling time ($p<0.0001$) (Figure 4). Statistical analysis of hemoglobin (HB) of patients also indicated only a significant main effect of sampling time ($p<0.0001$) (Figure 5).

TABLE 3 ABOUT HERE
FIGURE 4 ABOUT HERE
FIGURE 5 ABOUT HERE

Plasma interleukin-1 (IL-1) statistical analysis of patients indicated a significant type of anesthesia versus sampling time ($p<0.0001$), and that the increase in IL-1, as a function of sample was lower in the patients anesthesized with TIVA-DEX than that with TIVA (Figure 6). A significant type of anesthesia versus sampling time ($p<0.0001$), indicating that the increase in interleukin-6 (IL-6), as a function of sample was also lower in the patients anesthesized with TIVA-DEX than that with TIVA (Figure 7).

FIGURE 6 ABOUT HERE
FIGURE 7 ABOUT HERE

Plasma interleukin-10 (IL-10) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two different anesthesia (TIVA and TIVA-DEX) indicated only a significant main effect of sampling time ($p<0.0001$) (Figure 8) with a progressive reduction of IL-10 along time in both groups.

FIGURE 8 ABOUT HERE

Statistical analysis of plasma gamma interferon (INF-γ) of patients indicated a significant type of anesthesia versus sampling time ($p<0.0001$) and also indicating that the increase in INF-γ, as a function of sample was lower in the patients anesthesized with TIVA-DEX than that with TIVA (Figura 9). The same was observed with plasma tumor necrosis factor alpha (TNF-α) ($p<0.0001$) (Figure 10).

FIGURE 9 ABOUT HERE
FIGURE 10 ABOUT HERE

Erithrocytic thiobarbituric acid reactive substances (TBARS) of patients using two different anesthesia (TIVA and TIVA-DEX) indicated a significant interaction effect of type of anesthesia vs sampling time ($p<0.0001$) and revealed that the increase in TBARS after surgery was higher in TIVA-DEX than in TIVA patient group (Figure 11).

FIGURE 11 ABOUT HERE

Delta-amino levulinate dehidratase (δ-ALA-D) activity statistical analysis of patients using two different anesthesia (TIVA and TIVA-DEX) revealed no significant main or interaction effects (table 4).

TABLE 4 ABOUT HERE

Plasma C-reactive protein (CRP) of patients under coronary arterial bypass graft (CABG) surgery using two different anesthesia (TIVA and TIVA-DEX) indicated only a significant main effect of sampling time ($p<0.0001$) (Figure 12) with a great increase in levels at 24 hour after surgery in both patient groups.

FIGURE 12 ABOUT HERE

Statistical analysis of plasma creatine phosphokinase (CPK) (Figure 13) and MB-creatine phosphokinase (MB-CPK) (Figure 14) of patients using two different anesthesia (TIVA and TIVA-DEX) presented only a significant main effect of sampling time ($p<0.0001$). Plasma I troponin (cTn-I) statistical analysis of patients indicated only a significant main effect of sampling time ($p<0.0001$) (Figure 15).

FIGURE 13 ABOUT HERE
FIGURE 14 ABOUT HERE
FIGURE 15 ABOUT HERE

Statistical analysis of cortisol (Figure 16) and glucose (Figure 17) of patients using two different anesthesia (TIVA and TIVA-DEX) indicated only a significant main effect of sampling time ($p<0.0001$).

FIGURE 16 ABOUT HERE
FIGURE 17 ABOUT HERE

Mini mental state examination (MMSE) statistical analysis of patients under coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two different anesthesia (TIVA and TIVA-DEX) indicated no significant main or interaction effects (all p values > 0.10) (Figure 18).

FIGURE 18 ABOUT HERE

2.2.5 Discussion

The main finding of the present study was that dexmedetomidine (as a component of total intravenous anesthesia-TIVA) modified the inflammatory response in coronary artery bypass grafting surgery under mini-cardiopulmonary bypass. Dexmedetomidine use was associated with less statistical significant increase in plasma IL-1, IL-6, TNF-α and INF-γ levels as compared to conventional TIVA patients group. In both groups of patient occured a similar delayed postoperative decrease in IL-10.

Dexmedetomidine is a selective (α)-2-adrenergic receptor agonist with a great ratio of (α)-2 to (α)-1 activity, of 1.620:1. Specific (α)-2-adrenergic receptor subtypes mediate dexmedetomidine pharmacodynamic effects. Agonism at the (α)-2A-adrenergic receptor

appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection (35) and inhibition of insulin secretion (36). Agonism at the (α)-2B-adrenergic receptor suppresses shivering centrally (37) induces analgesia at spinal cord and promote vasoconstriction in peripheral arteries. The (α)-2C-adrenergic receptor is associated with cognition, sensory processing, mood and regulation of epinephrine outflow from the adrenal medulla (38). Inhibition of norepinephrine release appears to be equally affected by all three (α)-2-adrenoreceptor subtypes (39). Dexmedetomidine also binds to imidazoline receptors and this activity may explain some of the non (α)-2-adrenergic receptor effects of this drug. Imidazoline-1 receptors are linked to G-proteins, modulate blood pressure regulation and have anti-arrhythmic effects (21). Imidazoline-2 receptors have been implicated in neuroprotection in a cerebral ischemia model in animals and in generation of memory (40.

Limited literature data have investigated the effects of dexmedetomidine and others (α)-2-adrenergic receptors agonists on cytokines (41) and TNF-α production by macrophages (30). Taniguchi et al. (19, 20) demonstrated that dexmedetomidine has an inhibitory effect on cytokine responses to endotoxemia. These findings suggest that one of the mechanisms of antiinflammatory effects of dexmedetomidine may be via modulation of cytokine production by macrophages and monocytes. Hofer et al. (2009) demonstrated that the dexmedetomidine infusion decreased proinflammatory cytokine production in sepsis (42). They have shown that preventive administration of clonidine or dexmedetomidine significantly improved survival after sepsis induction. This was accompanied by a reduction in the plasma proinflammatory mediators IL-1β, IL- 6 and tumoral necrosis factor-α. Furthermore, Hofer et al. (2009) suggested that administration of a central acting (α)-2-adrenergic receptor agonist might be considered as a preventive therapeutic option in high-risk patients undergoing major surgery. In our study, patients were not in sepsis, but coronary artery bypass grafting surgery demanded a high immunological stress response, which resembles SIRS. Of particular therapeutic significance, here dexmedetomidine promoted IL-1, IL-6, INF-γ and TNF-α lesser increase, when compared to conventional TIVA group.

Tasdogan et al. (43) conducted a study to compare the effects of an intravenous infusion of propofol and dexmedetomidine, on inflammatory response and intra abdominal pressure in severe sepsis after abdominal surgery. Dexmedetomidine infusion decreased tumor necrosis factor-alpha, IL-1, and IL-6 levels and intra abdominal pressure more than did propofol infusion. In vitro studies with murine macrophages have also indicated an antiinflammatory effect of dexmedetomidine in experimental endotoxemia (44).

Bekker et al. (45) hypothesized that the intraoperative administration of dexmedetomidine would reduce the stress response and improve the quality of recovery in patients undergoing major spinal surgery. They compared a propofol/ fentanyl/ dexmedetomidine anesthesia group with propofol/ fentanyl/ placebo-saline anesthesia. Plasma cortisol levels increased in the post-anesthesia care unit in both groups; however, the increase was less accentuated in the dexmedetomidine group than in non-dexmedetomidine group (45). In contrast, C-reactive protein levels were similarly elevated in both groups after surgery, which is similar to our findings.

Erythrocyte TBARS levels were increased after CAGB surgery, which indicates an increase in oxidative stress after cardiopulmonary bypass. However, TBARS levels were higher in dexmedetomidine-TIVA than in TIVA group. Literature has indicated that dexmedetomine can decrease TBARS production in rodents after experimental surgery (46). Yagmurdur et al. (47), in human, related that dexmedetomidine significantly attenuated plasma hypoxanthine production in the ischemia and plasma malondialdehyde production in the reperfusion periods, after upper-extremity surgery requiring tourniquet application. Blood creatine phosphokinase and uric acid levels were significantly lower in the dexmedetomidine group as compared with those in the control group after reperfusion (47). Previously, in another investigation (48), our laboratory demonstrated that dexmedetomidine did not blunt blood TBARS increase, but protected δ-aminolevulinate dehydratase from inactivation caused by hyperoxygenation in total intravenous anesthesia, whereas the activity of enzyme decreased in patients anesthesized with remifentanil (48). Here δ-ala-D activity was not modified by anesthesia after CABG surgey in both groups.

In animal studies, dexmedetomidine inhibited cortisol synthesis at supratherapeutic concentrations but this has not been reported in short-term use in humans (49, 50). We have, before, in a human study, dexmedetomidine influence on cortisol levels of anesthetized patients also investigated (51). We measured cortisol concentrations before anesthetic induction, 5 minutes after intubation, and 30 minutes after surgical incision in patients undergoing gynecologic videolaparoscopic surgery, receiving dexmedetomidine or remifentanil. After intubation, there was a significant decrease in cortisol concentrations from baseline in both groups (–4.3 ± 1.4 μg. dL^{-1} and –4.6 ± 1.6 μg. dL^{-1}, respectively) but only in the remifentanil group at 30 minutes after incision (2.6 ± 1.8 μg. dL^{-1} and –7.1 ± 2.1 μg. dL^{-1}) (51) and dexmedetomidine did not suppress steroidogenesis. Here, at present study, we concluded the same. In the MENDS trial (52) cortisol concentrations were determined at baseline and two days after stopping dexmedetomidine infusion, and there was no statistically

significant difference in concentrations. At doses up to 1.5 μg. kg^{-1}. h^{-1}, it does not appear that dexmedetomidine causes any clinically significant adrenal suppression (53).

Recently, Peng et al. (54) suggest that dexmedetomidine is a potent suppressor of lipopolysaccharide-induced inflammation in activated microglia and may be a potential therapeutic agent for the treatment of intensive care unit delirium. They investigated the effects of dexmedetomidine on the production of proinflammatory mediators in lipopolysaccharide-stimulated microglia. The concentrations of dexmedetomidine were chosen to correspond to 1, 10, and 100 times of clinically relevant concentration (i.e., 1, 10, and 100 ng. mL^{-1}). They measured the levels of proinflammatory mediators, such as inducible nitric oxide synthase or nitric oxide, prostaglandin E2, interleukin 1β, and tumor necrosis factor alpha. Dexmedetomidine at 1 ng. mL^{-1} did not affect the production of proinflammatory mediators, but at 10 and 100 ng. mL^{-1}, dexmedetomidine significantly inhibited the release of nitric oxide, prostaglandin E2, interleukin 1β, and tumor necrosis factor alpha. The dosage that we used here can be considered low to moderate, nevertheless affected significantly IL-1, IL-6, TNF-α and INF-γ levels.

Chen et al. (55) in a human model, demonstrated that cognitive deficit of patients, undergone laparoscopic cholecystectomy, assessed using the mini mental state examination (MMSE), for the dexmedetomidine and control groups one week after surgery (dexmedetomidine group, 27.6±1.2; control group, 25.7±1.5) were significantly different (P=0.005), with better scores on dexmedetomidine group. It suggested a dexmedetomidine neuroprotective effect in human patients. Here, we cannot significative differences on mini mental state examination scores between groups demonstrate at five days after surgery evaluation.

Intravascular doses of dexmedetomidine induced dose-dependent decrease in systolic and diastolic blood pressure and in heart rate with important decrease in plasma norepinephrine levels. However, at high-bolus intravascular doses (50–75 μg), a transient initial hypertensive response may be seen, because an activation of peripheral vascular (α)-2B-adrenergic receptors before the central sympatholytic effect on the vasomotor center ocur (34). Because that, we do not use a bolus dose of dexmedetomidine at anesthesia induction.

Laringoscopy and endotracheal intubation also provoke marked sympathetic and sympathoadrenal response that increase the risk of perioperative myocardial ischemia and infarction. The perioperative use of dexmedetomidine may improve endocardial perfusion and decrasing heart rate with attenuation of stress response (56). Dexmedetomidine appear to increase the hemodynamic stability by altering the stress-induced sympathoadrenal responses

to intubation, during surgery and emergence from anesthesia (57) and this reflect on a better outcome. There are increasing evidence that the decrease in central nervous system sympathetic outflow by dexmedetomidine, in a dose-dependent manner, has organ protective effects against ischemic and hypoxic injury, including cardio-, neuro-, and reno-protection (58).

Dexmedetomidine possesses analgesic properties and many other advantageous influences that may make it a useful and safe adjunct in several clinical applications. When used as an adjunct to general anesthesia, dexmedetomidine can reduce both the minimum alveolar concentration requirement of inhalation agents and provide opiate-sparing properties up to 90% (59). We based our anesthesia on BIS index control. It was not the aim of the study to verify the total consume of propofol or sufentanil, although it was apparently a reduction in these drugs consumptions when dexmedetomidine was used simultaneously. However, the tritation use of propofol did not induce an augmented release of stress hormones in response to cardiopulmonary bypass in the presence of potent narcotic, as previous demonstrated (60).

Althoug there were significant intergroup differences in plasma IL-1, IL-6, TNF-α and INF-γ levels, clinical outcome and in-hospital stay did not differ among groups at this study. Further larger studies are merited to determine the long-term relevance of the changes in biochemical markers observed in the related studies. One of the limitations of the present study was the small number of patients enrolled, however, the similarity on comorbidyties, smoky habits, time of cardiopulmonary bypass and the same surgical team, established to confirm these results. The dose of dexmedetomidine utilized was considered a low dose, and other results about the antiinflammatory response could be obtained with higher doses.

2.2.6 Conclusions

It would be valuable to have a safe and effective means of preventing inflammatory response to a major surgery, like coronary artery bypass grafting surgery, and its complications, with the beneficial actions of anesthetic drugs. We believe that dexmedetomidine can be considered particularly promising. In this study we demonstrated the effect of dexmedetomidine on promote a lesser increase in IL-1, IL-6, TNF-α and INF-γ levels in patients under coronary artery bypass grafting surgery with mini cardiopulmonary bypass, as compared to patients group that not received dexmedetomidine. Others approach will require and additional research to further clarify both safety and efficacy to

dexmedetomidine use on these patients group. This can reflect on a reduction of postoperative complications, with a better clinical outcome.

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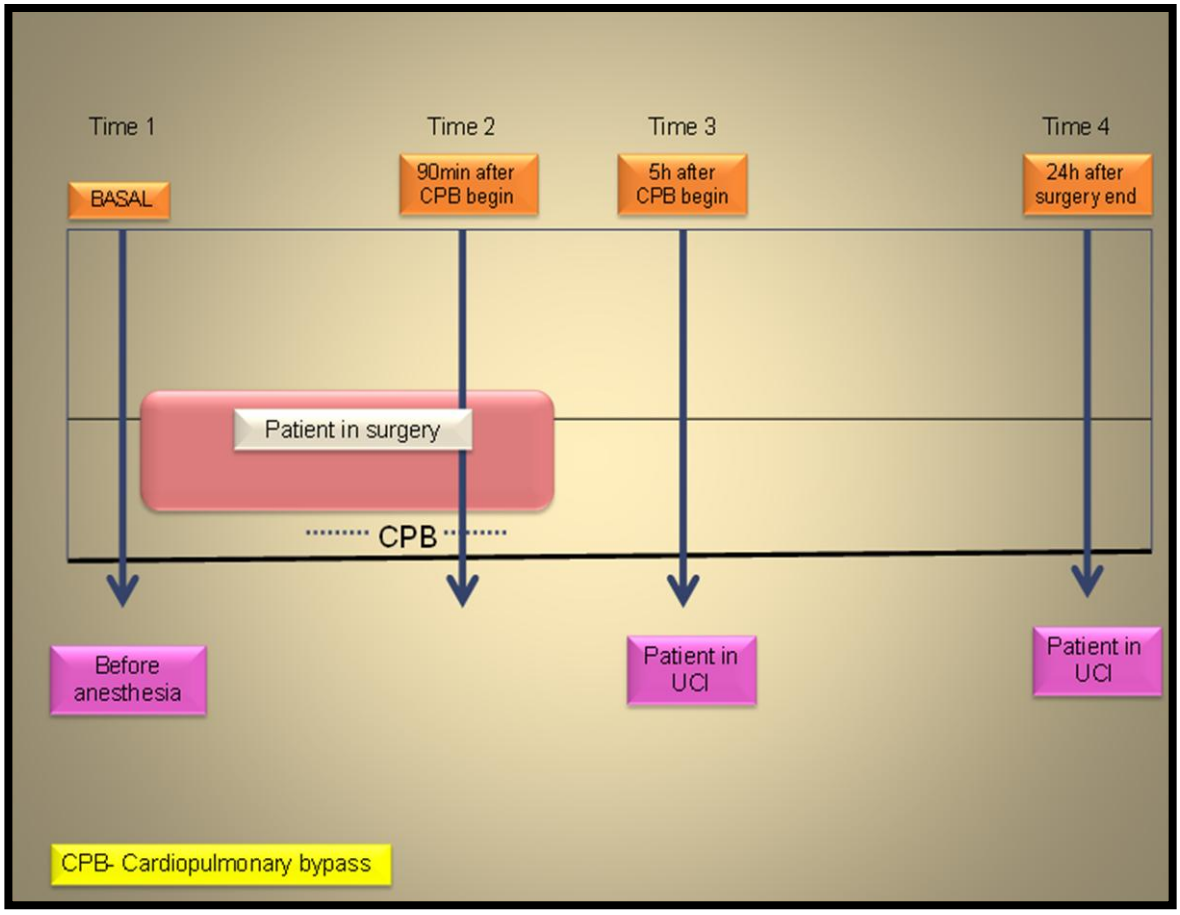

Figure 1. Sampling Protocol. Arterial blood at radial access was collected at four times. The first sample was before the anesthesia induction, considered the basal time (Time 1). Second sample was performed at 90 minute after cardiopulmonary bypass (CPB) beginning (Time 2). The third sample was at 5 hours after CPB beginning (Time 3) and the fourth sample was performed at 24 hours after surgery end (Time 4).

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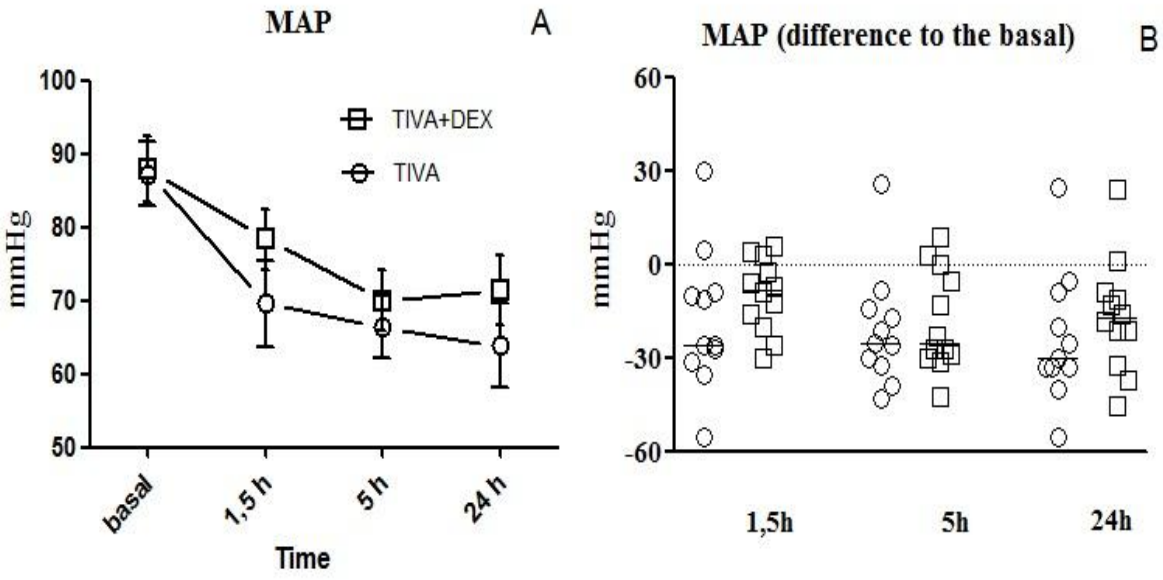

Figure 2. Mean arterial pressure (MAP) of patients submitted to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated only a significant main effect of sampling time ($p<0.0001$) (two-way) .

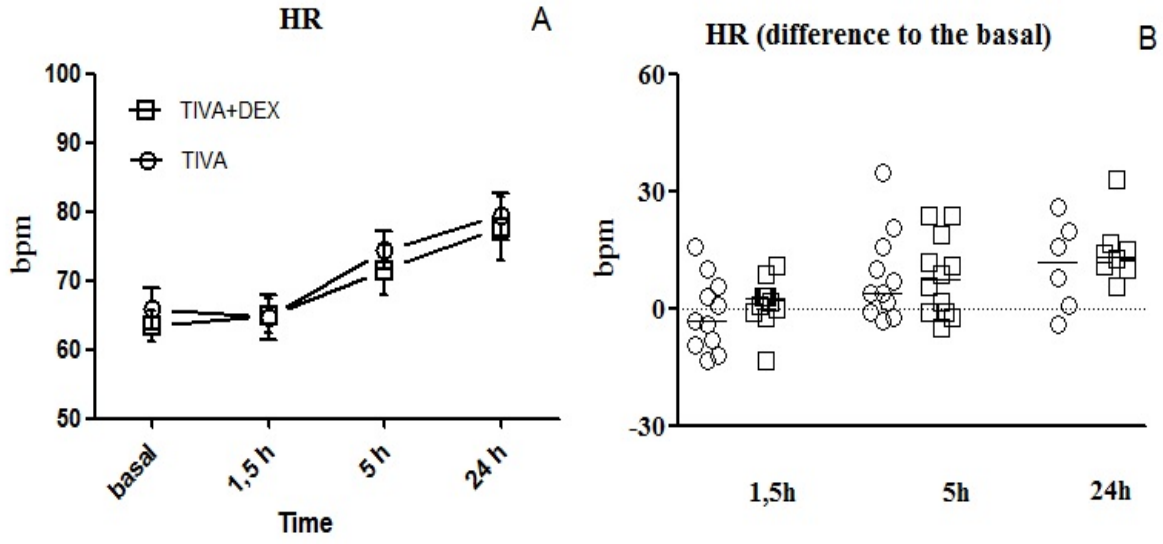

Figure 3. Statistical analysis of heart rate (HR) in patients submitted to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX) indicated only a significant main effect of sampling time ($p<0.0001$).

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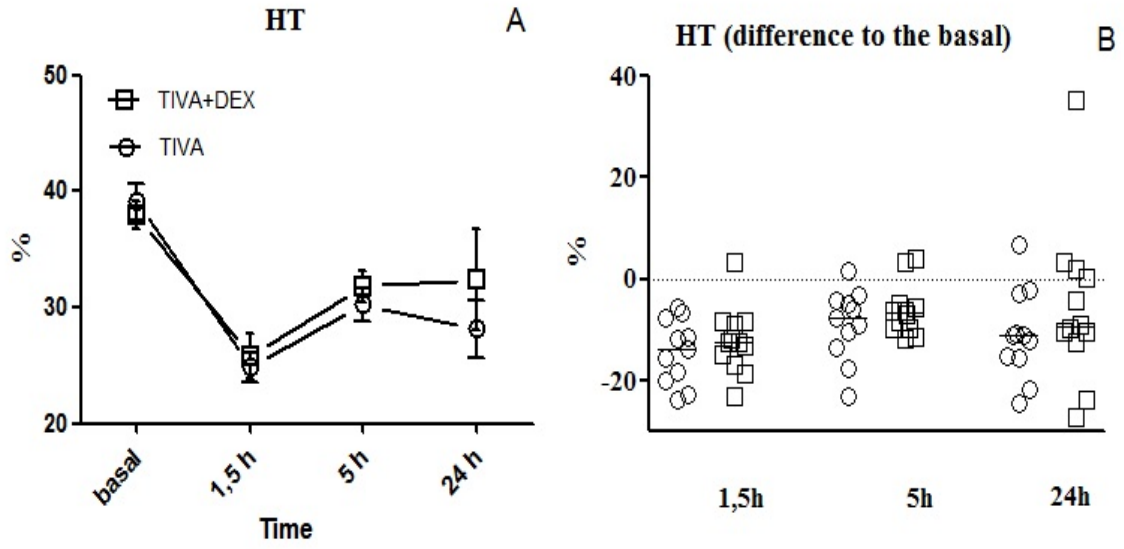

Figure 4. Hematocrit (HT) of patients submitted to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated only a significant main effect of sampling time ($p<0.0001$).

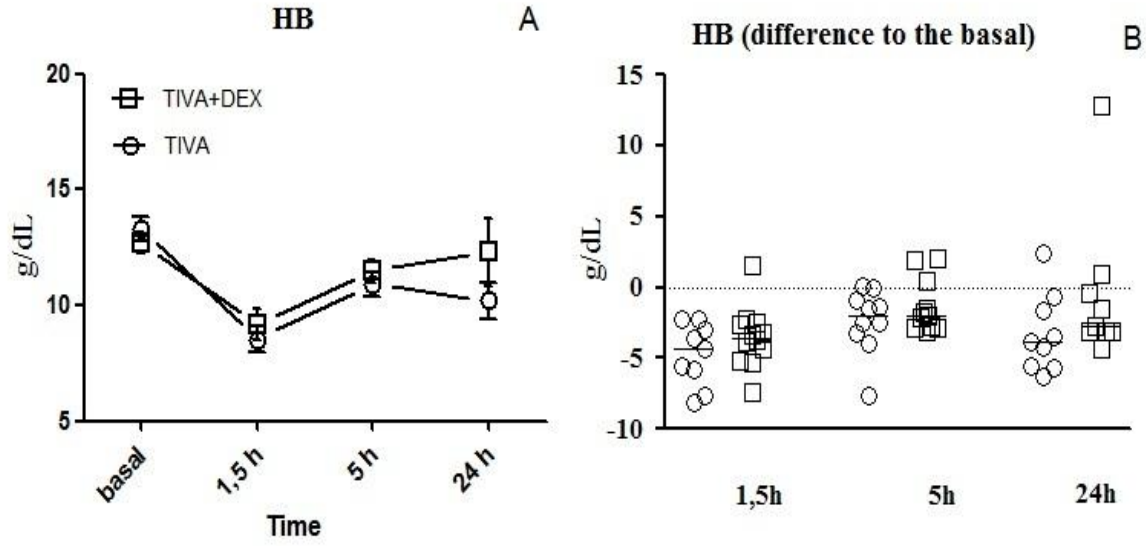

Figure 5. Hemoglobin (HB) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated only a significant main effect of sampling time ($p<0.0001$).

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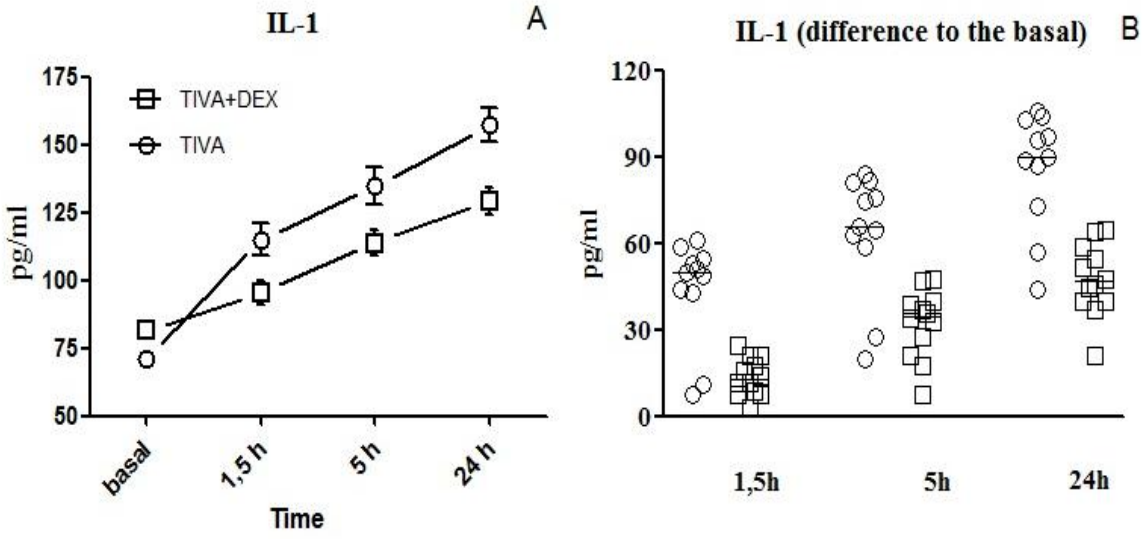

Figure 6. Plasma interleukin-1 (IL-1) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated a significant type of anesthesia versus sampling time ($p<0.0001$) and indicating that the increase in IL-1, as a function of sample was lower in the patients anesthesized with TIVA-DEX than that with TIVA.

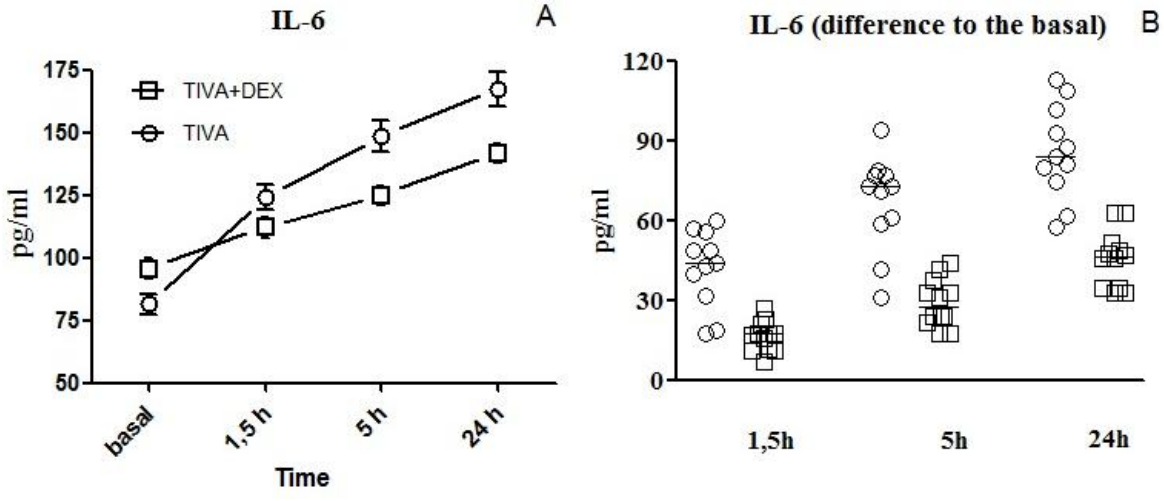

Figure 7. Plasma interleukin-6 (IL-6) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated a significant type of anesthesia versus sampling time ($p<0.0001$) and indicating also that the increase in IL-6, as a function of sample was lower in the patients anesthesized with TIVA-DEX than that with TIVA.

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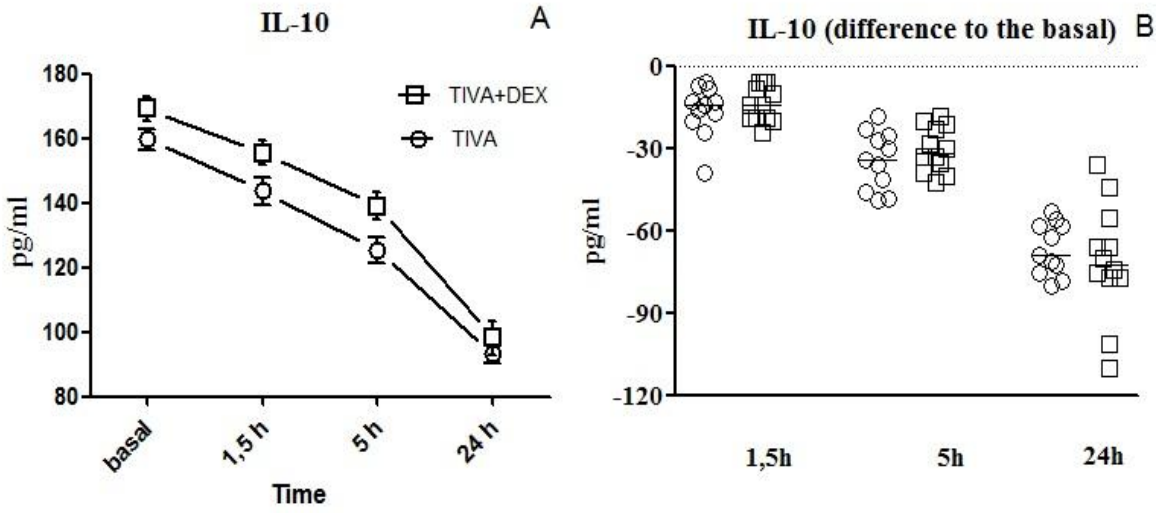

Figure 8. Plasma interleukin-10 (IL-10) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated only a significant main effect of sampling time ($p<0.0001$) with a progressive decrease of IL-10 in both groups along time.

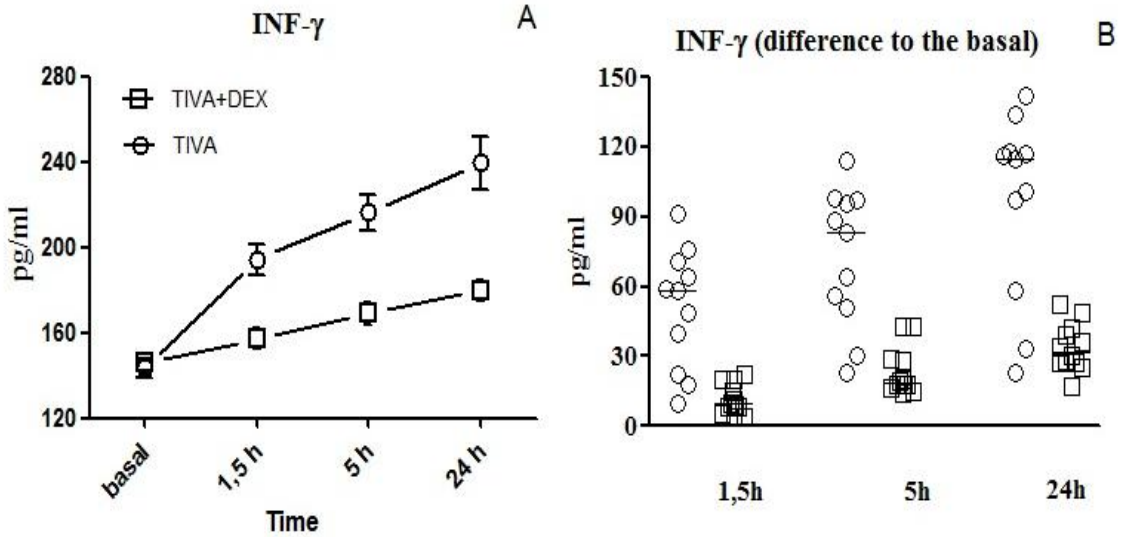

Figure 9. Plasma gamma interferon (INF-γ) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated a significant type of anesthesia versus sampling time ($p<0.0001$) and indicating that the increase in INF-γ, as a function of sample was lower in the patients anesthesized with TIVA-DEX than that with TIVA.

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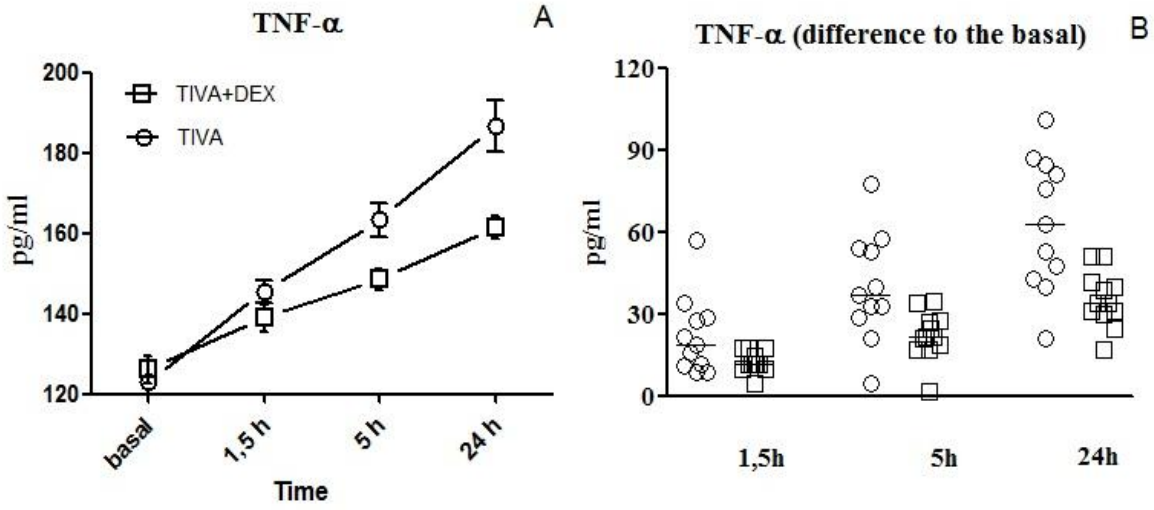

Figure 10. Plasma tumoral necrosis factor-alpha (TNF-α) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated a significant type of anesthesia versus sampling time ($p<0.0001$), indicating that the increase in TNF-α, as a function of sample was lower in the patients anesthesized with TIVA-DEX than that with TIVA.

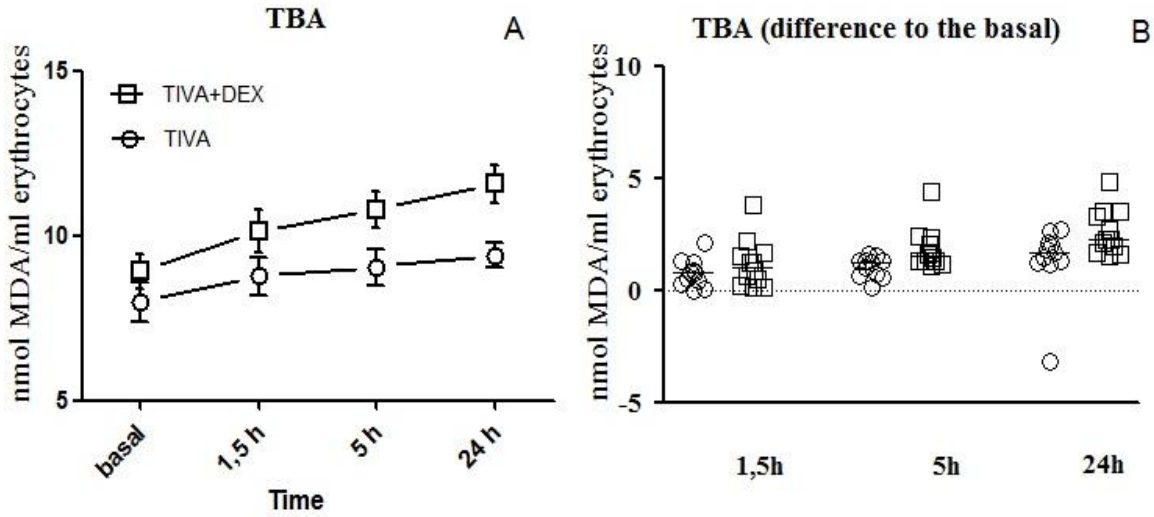

Figure 11. Erithrocytic thiobarbyturic acid reactive substances (TBARS) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated a significant interaction effect of type of anesthesia vs sampling time ($p<0.0001$), indicating that the increase in TBARS after surgery was higher in TIVA-DEX than in TIVA patient group.

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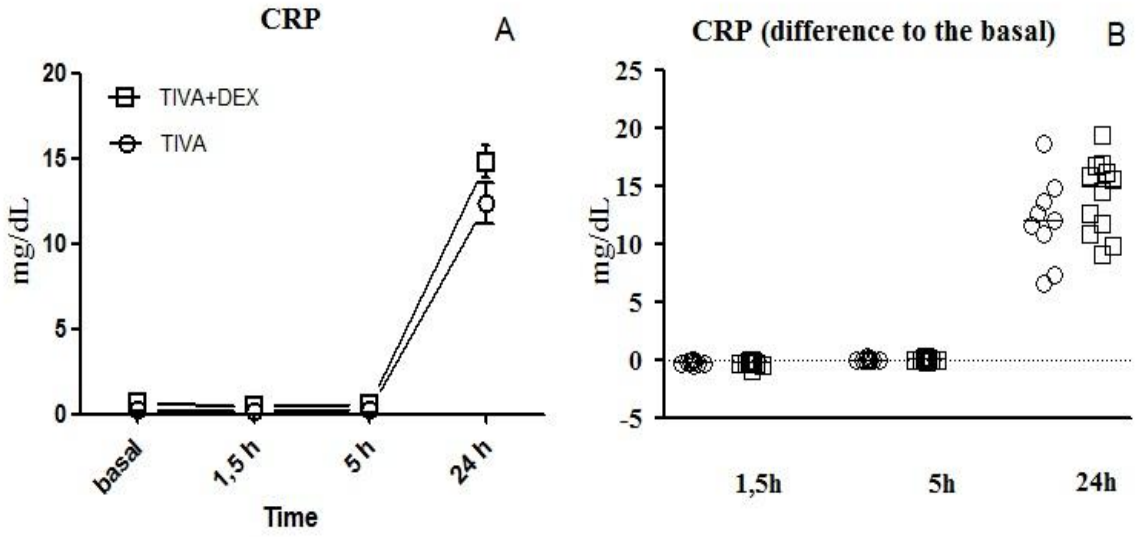

Figure 12. Plasma C-reactive protein (CRP) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated only a significant main effect of sampling time ($p<0.0001$) with a significative increase in CRP at 24 hours after end of surgery in both patients groups.

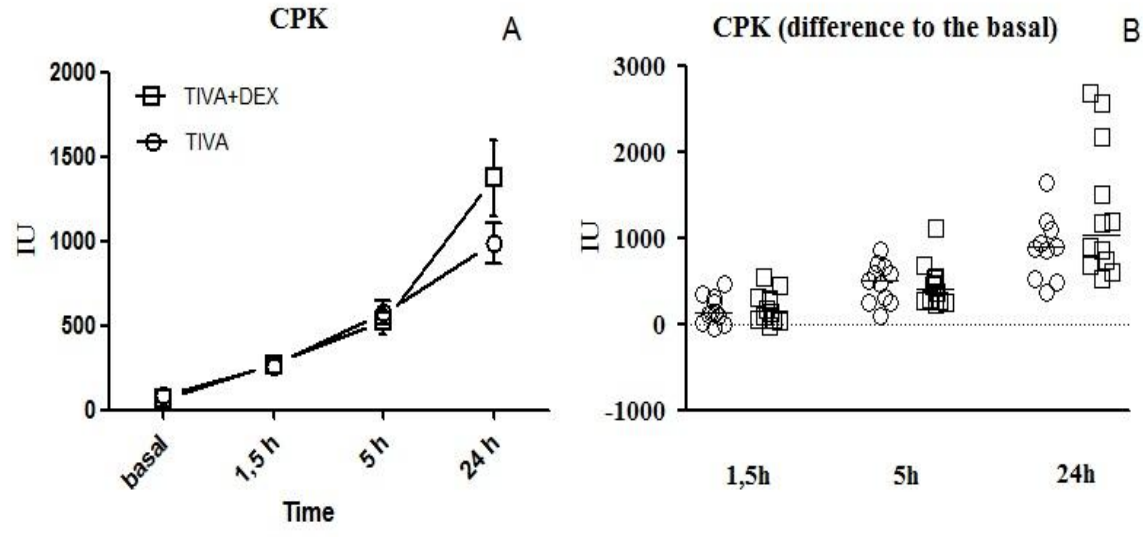

Figure 13. Plasma creatine phosphokinase (CPK) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated only a significant main effect of sampling time ($p<0.0001$) with a similarly increase of CPK levels along time in both groups.

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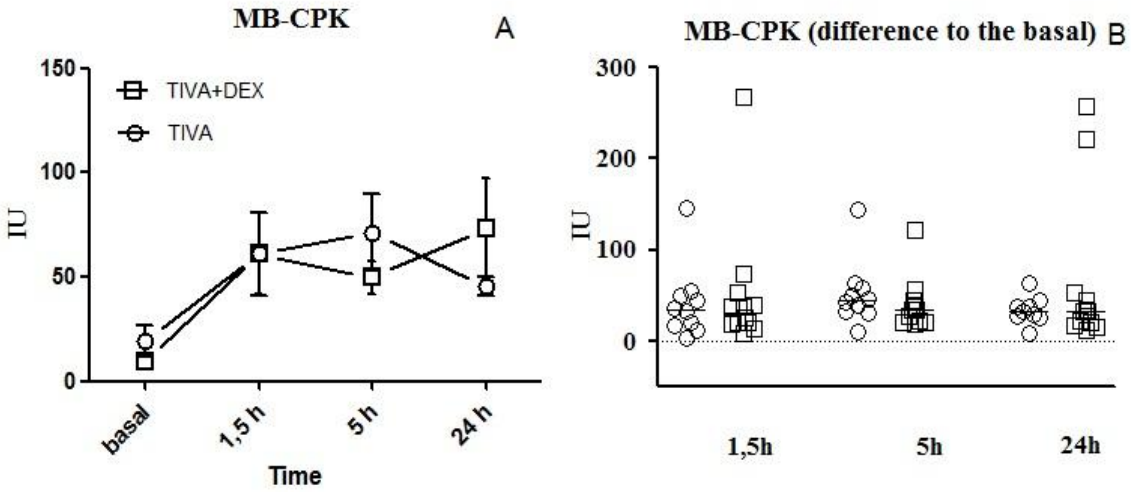

Figure 14. Plasma MB-creatine phosphokinase (MB-CPK) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated only a significant main effect of sampling time ($p<0.0001$).

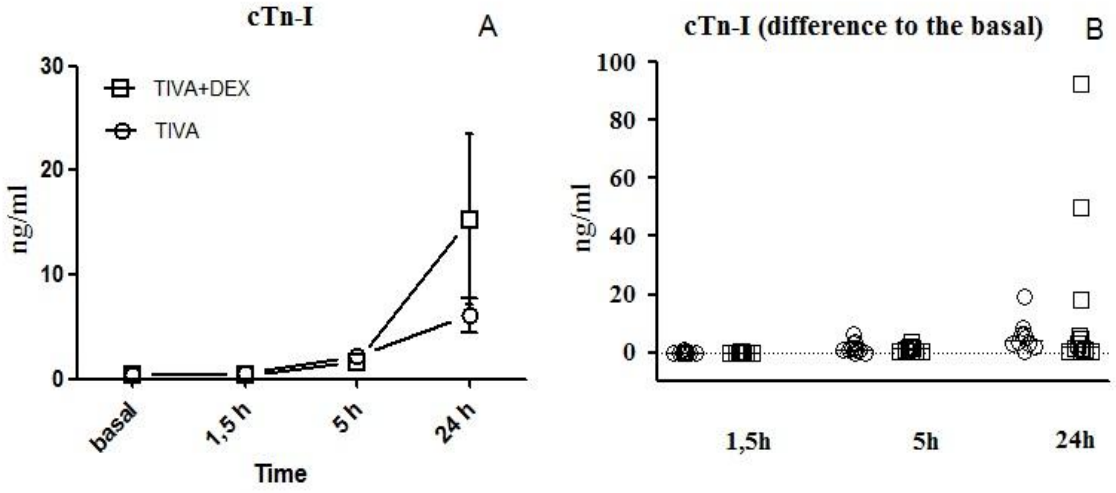

Figure 15. Plasma I troponin (cTn-I) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated only a significant main effect of sampling time ($p<0.0001$), with a significative increase in cTn-I at 24 hours after end of surgery in both patient groups.

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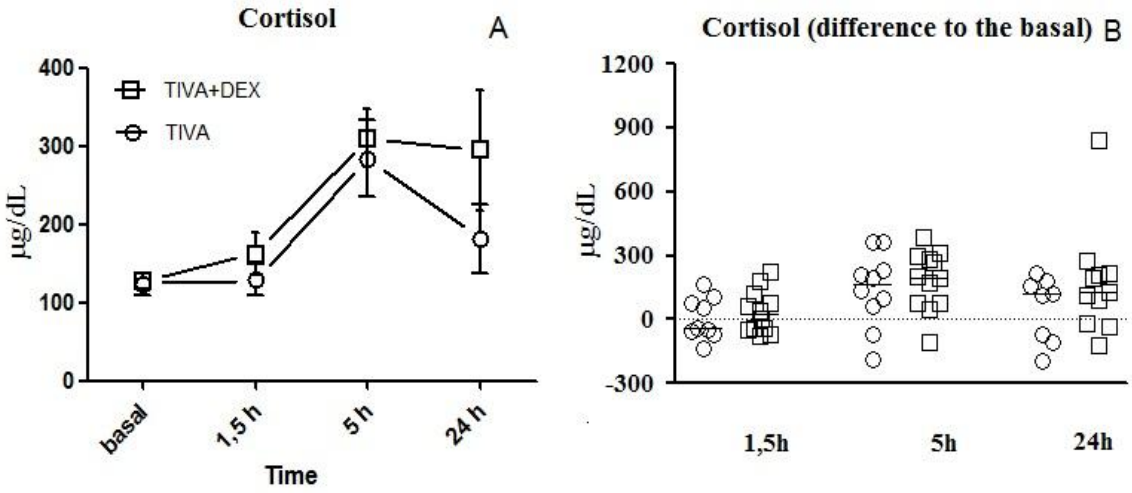

Figure 16. Plasmatic cortisol of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated only a significant main effect of sampling time ($p<0.0001$). Similarly, in both groups cortisol increase at 5 hours after CPB beginning and 24 hours after end of surgery.

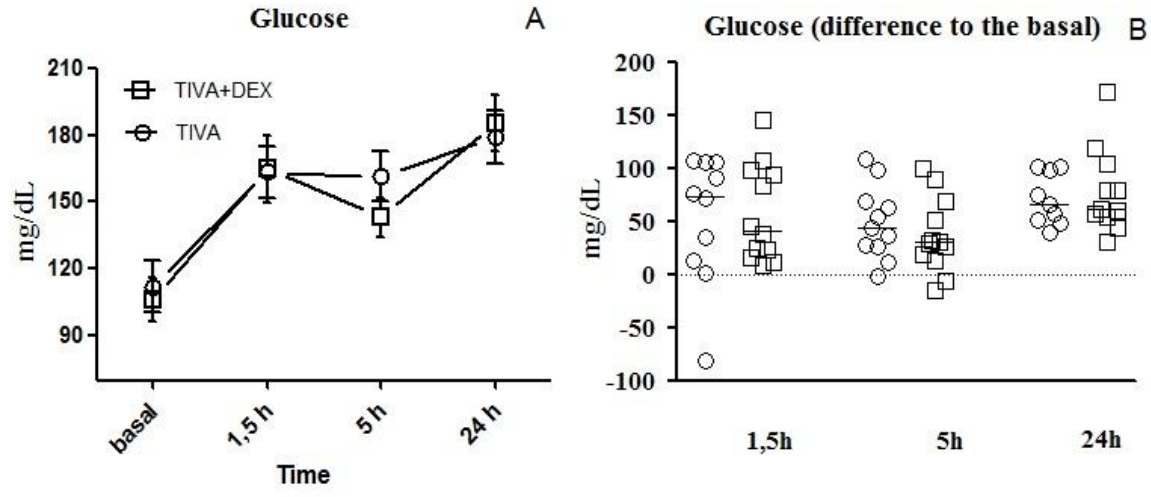

Figure 17. Plasmatic glucose of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated only a significant main effect of sampling time ($p<0.0001$) with increasing levels of glucose in both groups.

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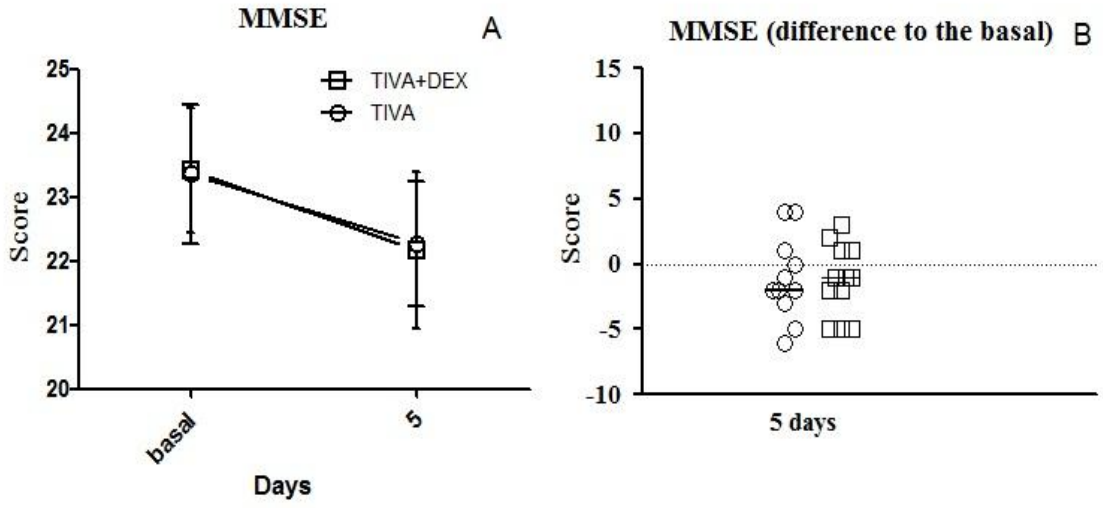

Figure 18. Mini mental state examination (MMSE) of patients submmited to coronary arterial bypass graft (CABG) surgery under mini-cardiopulmonary bypass, using two differents anesthesia (TIVA and TIVA-DEX). Statistical analysis indicated no significant main or interaction effects (all p values > 0.10).

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Table 1. Patients anthropometric characteristics and surgery related parameters. (CPB: cardiopulmonary bypass)

	TIVA group (n: 11)	TIVA-DEX group (n: 12)
Age (years)	65 ± 8	60 ± 6
Body weight (kg)	74 ± 13	77 ± 15
Height (cm)	164 ± 8	165 ± 10
Gender (female-male)	4- 7	4- 8
Diabetes mellytus	4	6
Tabaco	4	9
Hypertensive disease	10	12
CPB time (min)	94 ± 22	89 ± 25
Surgery time (min)	299 ± 34	324 ± 35
Time for extubation (hour)	14 ± 3	14 ± 4
Intensive care unit time (days)	4 ± 1	4 ± 1
In-hospital stay (days)	7 ± 1	8 ± 2
Mini mental state examination scores (before surgery)	23 ± 3	23 ± 3
Mini mental state examination scores (5 days after surgery)	22 ±3	22 ± 4

Legend of tables

Table 2. Perioperative haemodynamics parameters. HR: heart rate; MAP: mean arterial pressure; CI: cardiac index; CVP: central venous pressure; PO_2: arterial oxygen pressure; PCP: pulmonary capillary pressure.

GROUPS	TIVA group(n: 11)				TIVA-DEX group (n: 12)			
Time	Time 1	Time 2	Time 3	Time 4	Time 1	Time 2	Time 3	Time 4
HR (bpm)	65± 9	64±10	74±9	79±8	63±7	64±8	71±12	77±13
MAP (mmHg)	87±14	69±19	66±13	63±19	87±15	78±14	70±14	71±16
CI ($L.min^{-1}$)	-	6.0±3.0	4.1±1.4	5.3±1.4	-	5.5±2.5	5.0±1.4	5.6±1.1
CVP (mmHg)	9.0±0.0	8.5±3.3	8.6±4.0	10.3±2.7	10.0±0.0	10.2±2.6	8.2±3.9	10.8±3.3
PO_2 (mmHg)	164±42	213±54	146±39	81±32	164±32	166±55	124±38	85±16
PCP (mmHg)	-	16.5±6.6	14.4±7.5	16.2±5.6	-	16.2±6.2	14.1±4.3	19.1±6.3

Table 3. Hemodilution of patients in collected times. HT: hematocrit; Hb: hemoglobin.

	TIVA group (n: 11)				TIVA-DEX group (n: 12)			
Time	Time 1	Time 2	Time 3	Time 4	Time 1	Time 2	Time 3	Time 4
HT(%)	39.1±5.1	24.8±4.2	30.2±3.6	28.1±8.2	37.9±4.1	25.7±6.6	31.7±9.1	32.3±1.5
Hb(g/dL)	13.3±1.8	8.5±1.6	10.9±1.6	10.1±2.3	12.6±1.5	9.1±2.2	11.4±1.6	12.3±4.4

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Table 4. TBARS and δ-ALA-D activity in collected times. TIVA: total intravenous anesthesia; DTT: dithiothreitol reagent.

		After CBP		
	Baseline	1,5 h	5 h	24 h
δ-ALA-D activity (nmol PBG/h/mg protein)				
TIVA	429.5 ± 341.9	294.5 ± 234.9	367.0 ± 263.1	308.2 ± 249.7
TIVA-DEX	322.7 ± 274.7	278.0 ± 177.7	373.5 ± 237.8	349.0 ± 453. 6
δ-ALA-D activity with DTT (nmol PBG/h/mg protein)				
TIVA	425.0 ± 378.7	299.0 ± 211.5	439.9 ± 342.8	291.6 ± 265.1
TIVA-DEX	349.1 ± 203.0	327.2 ± 167.9	391.9 ± 227.9	370.2 ± 401.8
TBARS levels (nmolMDA/ml erythrocytes)				
TIVA	8.0 ± 2.0	8.8 ± 1.9	9.1 ± 1.8	9.4 ± 1.2
TIVA-DEX	8.9 ± 1.8	10.1 ± 2.2	10.7 ± 2.0	11.6 ± 2.1

3 DISCUSSÃO

O uso da dexmedetomidina como coadjuvante em anestesia ainda tem sido tímido e incipiente. Sua administração pode ter efeitos benéficos importantes em relação à proteção cerebral peri-operatória (MA e cols., 2005) e na atenuação da resposta inflamatória ao estresse induzido pela cirurgia (NADER e cols., 2001; VENN e cols., 2001; TANIGUCHI e cols., 2004; MEMIS e cols., 2007; TANIGUCHI e cols., 2008), sendo interessante explorar melhor os seus efeitos farmacológicos. A dexmedetomidina é um agonista (α)-2-adrenérgico, com grande seletividade para os receptores (α)-2/ (α)-1, na proporção de 1.620:1 e diferentes receptores (α)-2-adrenérgicos são responsáveis por seus efeitos clínicos específicos (TAKADA e cols., 2002; MA e cols., 2004; MOURA e cols., 2006; FAGERHOLM e cols., 2008; FAGERHOLM e cols., 2008). Também se liga a receptores imidazolínicos que modulam a pressão arterial sistêmica, possuem efeitos anti-arrítmicos (KHAN e cols., 1999) e têm sido implicados na sua capacidade de neuroproteção e geração de memória em modelos de isquemia cerebral em animais (TAKAMATSU e cols., 2008).

O principal resultado deste estudo clínico foi o de que a dexmedetomidina como componente da anestesia intravenosa total (AIVT) foi capaz de modular a resposta inflamatória em cirurgias de revascularização miocárdica (CRM) sob mini-circulação extracorpórea (mini-CEC). Os pacientes apresentaram menores níveis plasmáticos das citocinas pró-inflamatórias (IL-1, IL-6, TNF-α e INF-γ), se comparados ao grupo de pacientes que receberam AIVT convencional. Em ambos os grupos estudados, de maneira semelhante, houve diminuição progressiva pós-operatória da citocina anti-inflamatória IL-10.

Vários autores publicaram resultados sobre o efeito da dexmedetomidina e outros agonistas (α)-2-adrenérgicos sobre as citocinas (STRAUB e cols., 1997; Taniguchi e cols., 2004; HOFER e cols., 2009) e sobre a produção de TNF-α pelos macrófagos (SZELENYI e cols., 2000; TANIGUCHI e cols., 2004). Taniguchi e colaboradores (TANIGUCHI e cols., 2004) demonstraram que a dexmedetomidina possui efeito inibidor sobre a liberação de citocinas na endotoxemia em ratos, provavelmente através da modulação da produção de citocinas pelos macrófagos e monócitos. Hofer e colaboradores (HOFER e cols., 2009) demonstraram que a administração prévia de clonidina ou dexmedetomidina em sépsis induzida foi capaz de promover significativamente a sobrevida, sendo acompanhada pela redução de IL-1β, IL- 6 e TNF-α. Em nosso estudo, os pacientes não se apresentavam

sépticos, mas a cirurgia de revascularização miocárdica com circulação extracorpórea demanda uma grande resposta inflamatória, semelhante à SRIS. A dexmedetomidina não conseguiu anular o aumento das citocinas pró-inflamatórias, porém demonstrou grande capacidade em sua diminuição, se comparada à AIVT convencional.

Resultados semelhantes foram obtidos por Tasdogan e colaboradores (TASDOGAN e cols., 2009) que compararam os efeitos de uma infusão de propofol e de dexmedetomidina na resposta inflamatória e pressão abdominal em pacientes com quadro séptico após cirurgia abdominal. A dexmedetomidina foi capaz de reduzir significativamente os níveis de TNF-α, IL-1 e IL-6 e a pressão intra-abdominal se comparado ao grupo que recebeu infusão de propofol. Bekker e colaboradores (BEKKER e cols., 2012), investigaram se a administração intra-operatória de dexmedetomidina poderia reduzir a resposta ao estresse e promover a qualidade na recuperação dos pacientes após cirurgia espinhal de grande porte. Eles compararam um grupo de pacientes anestesiados com propofol/fentanil/dexmedetomidina com outro recebendo propofol/fentanil/placebo-salina. A dexmedetomidina reduziu os níveis de cortisol e IL-10 se comparada ao grupo controle, mas não afetou IL-6 e IL-8. Clinicamente, os pacientes que receberam dexmedetomidina mostraram uma maior qualidade de recuperação.

Sukegawa e colaboradores (SUKEGAWA e cols., 2011) descreveram o efeito inibitório da dexmedetomidina sobre as reações inflamatórias, como o edema, o acúmulo de células inflamatórias, a produção de TNF-α e ciclooxigenase-2 (COX-2) induzidos pela injeção de carragenina em pata de camundongo. Outro estudo em modelo animal, também demonstrou a capacidade anti-inflamatória da dexmedetomidina em altas doses na inibição da resposta inflamatória por macrófagos induzidos por endotoxinas (LAI e cols., 2009). Peng e colegas (PENG e cols., 2013) relataram que a dexmedetomidina mostrou-se um potente inibidor da inflamação induzida por lipopolissacarídeos em micróglia ativada, podendo ser um agente terapêutico potencial no tratamento de *delirium* em unidades de terapia intensiva. As concentrações de dexmedetomidina utilizadas foram 1, 10 e 100 vezes as concentrações clinicamente relevantes (i.e., 1, 10, e 100 ng. mL^{-1}). Foram medidos a óxido nítrico sintase (iNOS), o óxido nítrico (NO), a prostaglandina E2, a IL-1β e o TNF-α. A dexmedetomidina na dosagem de 1 ng. mL^{-1} não afetou a produção de mediadores pró- inflamatórios, mas a 10 e 100 ng. mL^{-1}, a dexmedetomidina inibiu significativamente a liberação de óxido nítrico, prostaglandina E2, IL-1β e TNF-α. A dose de infusão de dexmedetomidina que utilizamos em nosso estudo pode ser considerada de baixa a moderada, e mesmo assim foi capaz de reduzir

os níveis plasmáticos de IL-1, IL-6, TNF-α e INF-γ nos pacientes, se comparados ao grupo que não recebeu dexmedetomidina.

Arslan e colaboradores (2012), em modelo animal de isquemia hepática, demonstraram que a dexmedetomidina, administrada antes da indução da isquemia, protegeu contra a peroxidação lipídica (ARSLAN e cols., 2012). Yagmundur e colaboradores (YAGMURDUR e cols., 2008) avaliaram o efeito da dexmedetomidina em lesões por isquemia/reperfusão devido ao uso de torniquete durante cirurgia em membro superior pela determinação dos níveis sanguíneos de malondialdeído e hipoxantina. A dexmedetomidina atenuou significativamente os níveis plasmáticos de hipoxantina na isquemia e a produção de malondialdeído no período de reperfusão. Eles sugerem que a dexmedetomidina pode ter a vantagem de inibir a peroxidação lipídica em caso de uso antecipado ao período de isquemia/reperfusão, como no caso descrito. Em cirurgia de revascularização miocárdica sob CEC, ocorre aumento progressivo dos níveis plasmáticos de proteína C reativa (PCR) e de TBARS (MELEK e cols., 2012) que denota claramente a ocorrência de inflamação e estresse oxidativo. Esta resposta inflamatória relacionada à CEC tem o potencial para produzir manifestações clínicas, bioquímicas e radiológicas de disfunções orgânicas (DHALLA e cols., 2000; MAULIK e YOSHIDA, 2000; RAJAS e BERG, 2007) que são o resultado do desequilíbrio entre a formação de espécies reativas de oxigênio e a capacidade antioxidante endógena. O uso da dexmedetomidina em cirurgia de revascularização miocárdica em nosso estudo, não conseguiu modificar os níveis de TBARS e da atividade da δ-ALA-D dos pacientes. Anteriormente, porém, em estudo de nosso grupo de pesquisa, observamos em pacientes submetidas à videolaparoscopia pélvica cirúrgica, o potencial efeito da dexmedetomidina (ROCHA e cols., 2010) na proteção da enzima delta-aminolevulinato dehidratase (δ-ALA-D) do sangue de ser inativada pela hiperoxigenação em anestesia intravenosa total.

A profundidade anestésica em nosso estudo foi monitorizada pelo uso do índice biespectral (BIS) e não foi o nosso objetivo verificar o consumo total de propofol e sufentanil, embora, aparentemente, houvesse uma redução nas doses necessárias dos mesmos quando associados ao uso da dexmedetomidina, para manter os níveis do BIS entre 45-55. A titulação do uso de concentrações menores do propofol através da monitorização pelo BIS, em estudos anteriores, associado a narcóticos potentes não alterou por si só os níveis de mediadores de estresse oxidativo nos pacientes estudados (BAUER e cols., 2004), o que poderia se supor, uma vez que o propofol tem efeito antioxidante.

Em ambos os grupos estudados, de maneira similar, ocorreu aumento importante da PCR 24 horas após o término da cirurgia. Não houve diferenças entre os grupos quanto aos níveis de CPK-MB, cTnI e cortisol plasmático. Em estudos em animais, a dexmedetomidina inibiu a síntese de cortisol se usada em concentrações supraterapêuticas, mas este efeito supressor não tem sido relatado em usos de curta duração em humanos (MAZE e cols., 1991; VENN e cols., 2001; BULOW e cols., 2007), com doses de até 1.5 μg. kg^{-1}. h^{-1} (GERLACH e cols., 2009) e por até dois dias (PANDHARIPANDE e cols., 2007). No presente estudo, reforçamos estas conclusões prévias de que a dexmedetomidina não leva à supressão da esteroidogênese.

Embora houvesse significativa diferença nas concentrações plasmáticas de citocinas pró-inflamatórias entre os grupos estudados, não houve correlação das mesmas com diferenças na evolução clínica dos pacientes. Chen e colaboradores (CHEN e cols., 2013), usando o mini- exame do estado mental (MEEM), demonstraram em pacientes submetidos à videocolecistectomia, que os déficits cognitivos para o grupo recebendo dexmedetomidina se comparado ao grupo controle uma semana após a cirurgia foram significativemante diferentes (P=0.005), com melhores escores no grupo da dexmedetomidina, sugerindo um efeito neuroprotetor em humanos. Não conseguimos demonstrar diferenças clínicas significativas entre os grupos estudados pela avaliação do MEEM, sendo os escores para os pacientes de ambos os grupos semelhantes se comparados os valores antes da cirurgia e cinco dias após a mesma. Há aumento de evidências de que a dexmedetomidina possui efeito protetor sobre os órgãos expostos à isquemia, promovendo cardio, neuro e renoproteção (HALL e cols., 2000). Além disso, a dexmedetomidina possui propriedades analgésicas que a tornam uma droga vantajosa em várias situações clínicas. Quando usada associada a outros anestésicos, pode reduzir tanto a concentração alveolar mínima dos anestésics inalatórios, bem como de opióides, em até 90% das suas doses habituais (AHO e cols., 1992).

As doses intravasculares de dexmedetomidina induzem a redução dose-dependente da pressão arterial sistólica e diastólica e da frequência cardíaca, com importante diminuição nos níveis plasmáticos de norepinefrina. Contudo, doses elevadas, em *bolus* (50–75 μg), podem levar a uma hipertensão transitória inicial, devido à ativação dos receptores (α)-2-adrenergicos periféricos antes que ocorram os efeitos simpatolíticos centrais sobre o centro vasomotor (TALKE e cols., 1997). Evitamos o uso da dose inicial em *bolus*, justamente por este motivo, e o grupo de pacientes manteve-se hemodinamicamente estável, semelhante ao grupo sem dexmedetomidina, observando-se apenas uma redução da frequência cardíaca e pressão arterial média com o passar do tempo, como já era esperado. A laringoscopia e intubação oro-

traqueal provocam resposta simpática marcante que aumenta o risco de isquemia miocárdica perioperatória e infarto do miocárdio. O uso da dexmedetomidina melhora a perfusão endocárdica e diminui a frequência cardíaca com atenuação da resposta clínica ao estresse ao qual o paciente é submetido (SULAIMAN e cols., 2012). A dexmedetomidina promove a estabilidade hemodinâmica pela modulação da resposta simpático-adrenal ao estresse da intubação e extubação oro-traqueal (SCHEININ e cols., 1992) o que se reflete em melhor evolução clínica. Estudos futuros, com maior número de pacientes, são desejáveis para melhor avaliar a influência da dexmedetomidina e a relevância da redução dos biomarcadores inflamatórios, induzida por ela, sobre a evolução clínica dos pacientes.

4 CONCLUSÕES

Buscam-se meios efetivos para alterar a resposta inflamatória em cirurgias de grande porte, especialmente as cirurgias de revascularização miocárdica usando circulação extracorpórea, objetivando reduzir as complicações peri-operatórias. Acreditamos que o uso da dexmedetomidina possa ser especialmente promissor. Neste estudo demonstramos a capacidade da dexmedetomidina de reduzir significativamente os níveis plasmáticos de citocinas pró-inflamatórias, como IL-1, IL-6, TNF-α, INF-γ, em pacientes submetidos a cirurgia de revascularização miocárdica sob mini-circulação extracorpórea, se comparados aos pacientes que não a receberam.

MANUSCRITO 1

A busca por resultados de um novo estado da arte no uso da dexmedetomidina em anestesia na literatura reforça a idéia de sua potencialidade ainda pouco explorada, na proteção dos órgãos durante períodos de agressão tecidual, como acontece no perioperatório. O seu uso ainda não se tornou rotineiro. Acreditamos ser a dexmedetomidina uma droga de múltiplas possibilidades, cada vez mais confirmadas através de estudos em animais e humanos, podendo promover evolução clínica mais adequada àqueles pacientes submetidos à cirurgia.

MANUSCRITO 2

Neste estudo demonstramos a capacidade da dexmedetomidina em reduzir os níveis plasmáticos de citocinas pró-inflamatórias, como IL-1, IL-6, TNF-α, INF-γ, em pacientes submetidos à cirurgia de revascularização miocárdica sob mini-circulação extracorpórea, se comparados aos pacientes que não receberam dexmedetomidina. Reforçamos o potencial benéfico da dexmedetomidina como anestésico com efeitos moduladores sobre a resposta inflamatória.

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