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TESE DE DOUTORADO

AVALIAÇÃO DO VALOR PROGNÓSTICO DOS BIOMARCADORES CARDÍACOS PERIOPERATÓRIOS EM PACIENTES DE MODERADO A ALTO RISCO CARDIOVASCULAR SUBMETIDOS À CIRURGIA NÃO-CARDÍACA

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SUMÁRIO

INTRODUÇÃO

Nas últimas décadas, houve avanços significativos na cirurgia não-cardíaca para o tratamento de doenças e para a melhoria da qualidade de vida dos pacientes. Um estudo recente, utilizando dados de cirurgias de 56 países, estima que, pelo menos, 200 milhões de adultos sejam submetidos a cirurgias maiores não-cardíacas anualmente[1]. A maioria das cirurgias é realizada em países desenvolvidos, e dados de países em desenvolvimento são escassos. Estima-se que, no Brasil, em torno de 3 milhões de cirurgias não-cardíacas sejam realizadas anualmente[2].

Apesar de seus benefícios, a cirurgia não-cardíaca de grande porte está associada a eventos vasculares maiores no perioperatório: morte de causa vascular, infarto do miocárdio não-fatal, parada cardíaca não-fatal e acidente vascular cerebral não-fatal[3,4].

Mesmo representando um importante problema de saúde pública, existem poucos estudos, adequadamente delineados e de larga escala, que forneçam informações relevantes e atualizadas sobre questões envolvendo eventos cardiovasculares maiores no período perioperatório.

O estabelecimento de um método para facilitar a avaliação do risco cardiovascular acurada pré-operatória de cada indivíduo é extremamente relevante, uma vez que permite guiar a equipe assistente para um manejo perioperatório adequado como técnica anestésica e ambiente de recuperação pós-operatória. Da mesma forma, permite aos médicos, pacientes e seus familiares decidirem sobre a adequação do procedimento, considerando seus riscos e benefícios.

1 INCIDÊNCIA DE EVENTOS VASCULARES MAIORES EM PACIENTES SUBMETIDOS À CIRURGIA NÃO-CARDÍACA

Estudos que avaliaram pacientes portadores de alto risco para doença arterial coronariana, submetidos à cirurgia não-cardíaca, encaminhados a uma consulta médica no pré-operatório, demonstraram taxas de eventos que variaram de 0,7 a 2,4% para morte de causa vascular; 0,7 a 5,6% para infarto agudo do miocárdio (IAM); 0 a 1,5% para parada cardíaca (PCR); 0,1 a 1,6% para acidente vascular cerebral (AVC); e 2,2 a 7,4% para evento vascular maior[5-13].

Estudo realizado por Lee e colaboradores fornece a melhor estimativa da incidência de eventos vasculares maiores em pacientes adultos não-selecionados submetidos à cirurgia não-cardíaca[13]. A taxa de eventos vasculares maiores, no período perioperatório, foi de 1,4%, intervalo de confiança (IC) de 95%, entre 1,0 a 1,8%, nos adultos com mais de 50 anos de idade submetidos à cirurgia não-cardíaca eletiva, com permanência esperada de mais de dois dias. Entretanto, essas taxas podem ser subestimadas, pois os autores não incluíram o AVC como um desfecho e excluíram pacientes submetidos à cirurgia de emergência. Além disso, utilizaram a elevação da creatinoquinase fração MB (CK-MB) como um dos critérios diagnósticos para infarto do miocárdio, porque era o marcador disponível na época. Sabe-se, atualmente, que tal marcador apresenta sensibilidade e especificidade limitadas, o que predispõe a resultados falso-positivos e falso-negativos na detecção de infarto do miocárdio perioperatório[14].

Outras questões relevantes devem ser consideradas com relação à incidência de eventos cardiovasculares maiores perioperatórios. Os pacientes com doença arterial coronariana (DAC) estão vivendo mais como resultado dos avanços médicos[15]. Portanto, pacientes com DAC severa estão, agora, sobrevivendo para desenvolver outras afecções que requerem cirurgia, incluindo neoplasias e doenças degenerativas. Além disso, houve uma mudança, na prática clínica, direcionada a cuidados médicos mais avançados em idosos, e algumas intervenções cirúrgicas tornaram-se menos invasivas. Essas recentes tendências temporais limitam a generalização dos estudos conduzidos na década de 1980 e início de 1990,

deixando consideráveis incertezas quanto à atual incidência de eventos vasculares maiores em pacientes submetidos à cirurgia não-cardíaca.

2 ESTRATÉGIAS PARA PROGNOSTICAR OS EVENTOS VASCULARES MAIORES EM PACIENTES SUBMETIDOS À CIRURGIA NÃO-CARDÍACA

O estabelecimento de um método para facilitar uma avaliação pré-operatória precisa do risco de evento vascular maior atende a várias finalidades importantes. Estimativas do risco propiciam orientação aos médicos, no controle perioperatório, incluindo a escolha das técnicas anestésicas e a intensidade do cuidado pós-operatório. Ademais, a maior parte das cirurgias não-cardíacas é realizada de forma eletiva, e uma estimativa precisa do risco facilita a tomada de decisão pelo paciente e pelo médico.

2.1 Índices de risco

Diversos pesquisadores se propuseram a construir índices de risco, estabelecendo, a partir de inúmeras variáveis, escores capazes de calcular a taxa de eventos cardiovasculares prevista para cada paciente, de acordo com o risco do procedimento a ser realizado e características clínicas do indivíduo, como idade, comorbidades e exames pré-operatórios.

Os estudos de Goldman[16], Lee[13], Detsky[5] e Kumar[10] desenvolveram modelos clínicos para prognosticar desfechos cardíacos. Uma das limitações desses estudos é não considerar o AVC como desfecho vascular. Estudos sugerem que esse seja um evento, relativamente, frequente e, por certo, extremamente relevante por sua morbimortalidade. Um estudo que avaliou a incidência de acidentes vasculares cerebrais perioperatórios com 61 eventos demonstrou que, desses eventos, 18% causaram óbito e 31% dos pacientes necessitaram de cuidados após a alta[17].

Dentre os modelos clínicos existentes para prognosticar os eventos vasculares maiores em pacientes submetidos à cirurgia não-cardíaca, o Índice de Risco Cardíaco Revisado é o mais simples e fornece melhor prognóstico do que o Índice de Risco Cardíaco Original[13,16].

Entretanto, a atual precisão prognóstica do Índice de Risco Cardíaco Revisado é incerta, uma vez que não existe um estudo de alta qualidade que tenha estabelecido taxas de complicação atuais para cirurgias individuais ou grupos de

cirurgias comparáveis e não se sabe se as taxas de complicações atuais de uma instituição se aplicam a outra instituição.

2.2 Testes diagnósticos

Como muitos pacientes são assintomáticos, do ponto de vista cardiovascular, muitas vezes, por patologias que conferem limitação para avaliação de sua capacidade funcional, os índices de risco cardiovascular apresentam um poder preditivo limitado nesse contexto[4]. Com o intuito de aumentar essa predição de risco, técnicas não invasivas, como ecocardiografia de estresse com dobutamina e cintilografia miocárdica com dipiridamol, são, muitas vezes, utilizadas[18,19].

Os testes diagnósticos pré-operatórios, disponíveis na prática clínica, não são acurados o suficiente para predizer esses eventos. Uma metanálise, avaliando seis exames − eletrocardiograma, teste ergométrico, ventriculografia com radionuclídeo, cintilografia miocárdica perfusional, ecocardiografia de estresse com dipiridamol e ecocardiografia de estresse com dobutamina − para avaliação cardiovascular, no período pré-operatório, demonstrou claras limitações clínicas dos exames, atualmente, disponíveis[20].

Apesar da limitação das informações, tais testes parecem acrescentar valor preditivo às variáveis clínicas em algumas situações, porém são de alto custo e disponibilidade limitada[18,19].

Dessa forma, há uma busca contínua para a identificação de outros métodos mais rápidos, disponíveis e custo-efetivos com boa capacidade para predição de eventos cardiovasculares em pacientes submetidos a cirurgias não-cardíacas.

Nesse contexto, marcadores de lesão e de estresse miocárdico, como as troponinas e os peptídeos natriuréticos, vêm sendo estudados.

2.2.1 Troponinas

A dosagem de troponina sérica vem sendo estudada tanto para detecção de infartos silenciosos, no período perioperatório, como para predição de risco de eventos cardiovasculares com resultados promissores.

Há dados sugerindo que uma proporção substancial dos infartos do miocárdio perioperatórios não é detectada sem uma monitoração de enzimas cardíacas após a cirurgia. A maioria dos infartos do miocárdio ocorre durante os três primeiros dias de pós-operatório, um período durante o qual a maioria dos pacientes recebe medicação analgésica que pode diminuir ou mesmo mascarar a percepção da dor cardíaca[11,21]. Da mesma forma, um subgrupo de pacientes de alto risco cirúrgico permanecerá intubado e sedado, durante o período de risco mais alto, limitando sua capacidade de comunicar os sintomas. Por fim, a manifestação de sinais e sintomas pós-operatórios inespecíficos, muitas vezes, atribuídos a outras etiologias, pode ser uma apresentação atípica de infarto do miocárdio[22].

Estudos de coorte demonstram que apenas 16% (IC 95% 6 a 31) dos pacientes que sofreram um infarto do miocárdio perioperatório apresentaram desconforto torácico. Aproximadamente metade não apresentou dor torácica, nem outros sintomas ou sinais sugestivos de infarto do miocárdio[7,8,11].

Embora esses estudos ofereçam evidência encorajadora de que a monitoração das enzimas ou biomarcadores cardíacos, após cirurgia, pode ajudar a detectar uma proporção substancial de infartos do miocárdio silenciosos, eles são limitados pela baixa ocorrência desses eventos, os quais ficaram restritos aos pacientes sabidamente coronariopatas ou de alto risco para doença arterial coronariana. Esses estudos também são limitados pelo uso da CK-MB entre seus critérios diagnósticos para infarto do miocárdio e pelas variações no que se refere à monitoração das enzimas.

Atualmente, no diagnóstico de infarto agudo do miocárdio, o marcador de escolha é a troponina[22-24]. No contexto pós-operatório, vários outros fatores tornam-se ainda mais relevantes para este ser o biomarcador de escolha[25]. Uma proporção substancial de infartos do miocárdio ocorre nos primeiros dois dias após a cirurgia,

quando os valores séricos de creatinoquinase (CK) são altos em consequência do trauma cirúrgico. O trauma cirúrgico pode resultar, ainda, na liberação de CK-MB do músculo esquelético, o que gera um valor falso-positivo para infarto do miocárdio. Além disso, o nível elevado de CK pode resultar em uma relação baixa e, portanto, falso-negativa entre CK-MB e CK total[26,27]. Desse modo, a elevação da troponina é mais sensível e específica que CK-MB para o diagnóstico de infarto do miocárdio em pacientes submetidos à cirurgia não-cardíaca[28].

Considerando esses pontos, a questão mais relevante é se a monitoração rotineira da troponina, após cirurgia não-cardíaca, pode auxiliar a detectar infartos do miocárdio silenciosos.

Além de ser um exame para auxílio diagnóstico, a troponina provou ser um fator prognóstico independente, estatisticamente significativo para eventos a médio e longo prazo - mortalidade e uma combinação de eventos vasculares maiores[29-34]. Esse achado persistiu mesmo nos estudos que excluíram pacientes que sofreram infarto do miocárdio perioperatório[30,31]. Assim como no contexto de síndrome coronariana aguda, parece haver uma relação dose-resposta: quanto maior o valor máximo da troponina, maior a mortalidade em um ano[29-32].

Esses resultados são promissores, todavia, pelas razões a seguir, não são definitivos. Os pacientes, na maioria dos estudos, restringiram-se aos submetidos à cirurgia vascular ou àqueles sabidamente coronariopatas ou de alto risco para doença arterial coronariana. Nenhum estudo teve poder estatístico suficiente devido ao pequeno tamanho da amostra para o número de variáveis avaliadas, nem incluiu, nas análises multivariadas, todos os fatores prognósticos para eventos vasculares maiores a médio e longo prazo. Os estudos usaram diferentes gerações de ensaios da troponina, com diferentes sensibilidades. De modo geral, os resultados demonstraram associações acentuadamente variadas com os resultados adversos, com amplos intervalos de confiança. Uma metanálise publicada, recentemente, demonstrou que o aumento dos níveis de troponina pós-operatório em pacientes submetidos a cirurgias vasculares é preditor independente de mortalidade total em 30 dias (*odds ratio* – OR 5,03; IC 95% 2,88 a 8,79). Os dados foram insuficientes para avaliação de desfechos a médio prazo[35]. Da mesma forma, Levy e

colaboradores realizaram uma metanálise incluindo 14 estudos com um total de 3318 pacientes e 459 óbitos. Foi demonstrado que um aumento de troponina pós-operatório em pacientes submetidos a cirurgias não-cardíacas é um fator independente para predição de mortalidade a longo prazo (OR 3,4; IC 95% 2,2 a 5,2), porém com uma heterogeneidade bastante expressiva (I^2 = 56%)[36].

A maior limitação dos ensaios padrões de troponina disponíveis, atualmente, é a sua baixa sensibilidade de detecção precoce do infarto do miocárdio. A demora na detecção dos níveis elevados de troponina na circulação sanguínea exige monitoração prolongada com séries de enzimas em seis e 12 horas, o que pode aumentar desconforto ao paciente, demora no diagnóstico de infarto e, consequentemente, no manejo de suas possíveis complicações.

Recentemente, a melhora na tecnologia dos ensaios de troponinas permitiu o desenvolvimento de exames com maior sensibilidade e maior precisão diagnóstica com ensaios ultrassensíveis com menores limites de detecção.

Reichlin e colaboradores avaliaram 718 pacientes consecutivos que apresentaram quadro clínico compatível com infarto agudo do miocárdio, visando a comparar o desempenho das troponinas ultrassensíveis com a troponina T padrão, no contexto de dor torácica, na emergência. Foi evidenciada uma área sobre a curva significativamente maior para os quatro ensaios sensíveis utilizados em comparação com o ensaio de troponina T padrão da Roche Diagnóstica. As áreas sobre a curva foram de 0,96 (IC 95% 0,94 a 0,98) para a Troponina I da Abbott-Architect; 0,96 (IC 95% 0,94 a 0,98) para a Troponina T de alta sensibilidade da Roche; 0,95 (IC 95% 0,92 a 0,97) para a Troponina I da Roche; e 0,96 (IC 95% 0,94 a 0,98) para a Troponina I ultrassensível da Siemens; em comparação com 0,90 (IC 95% 0,86 a 0,94) para a troponina padrão. Neste estudo, entre os pacientes que se apresentaram com três horas de evolução de dor torácica as áreas sobre a curva foram 0,93 (IC 95% 0,88 a 0,99); 0,92 (IC 95% 0,87 a 0,97); 0,92 (IC 95% 0,86 a 0,99); e 0,94 (IC 95% 0,90 a 0,98) para os ensaios de alta sensibilidade, respectivamente, e 0,76 (IC 95% 0,64 a 0,88) para o ensaio padrão. Esses dados demonstraram que os ensaios sensíveis de troponinas são superiores, podendo aumentar o diagnóstico precoce de infarto do miocárdio[37].

Da mesma forma, Keller e colaboradores avaliaram os níveis de troponina I mensurados por ensaios sensíveis, troponina T padrão e marcadores tradicionais de necrose miocárdica em uma coorte multicêntrica de 1818 pacientes com suspeita de infarto agudo do miocárdio na admissão, em três e seis horas após. A acurácia diagnóstica entre as amostras obtidas na admissão foi maior nos ensaios sensíveis de Troponina I com área sobre a curva de 0,96, comparado com 0,85 com os ensaios de Troponina T padrão. Utilizando um ponto de corte de 0,04 ng/ml na admissão, a sensibilidade para o diagnóstico foi de 90,7% e a especificidade de 90,2%. Esse efeito se manteve nas amostras seriadas, posteriormente, independente do tempo de dor torácica da apresentação. Em pacientes com apenas três horas de sintomas, uma única dosagem de Troponina I sensível apresentou um valor preditivo negativo de 84,1% e um valor preditivo positivo de 86,7%. Além disso, uma mensuração de Troponina I sensível, acima de 0,04 ng/ml, foi, independentemente, associada a risco de eventos adversos em 30 dias (*hazard ratio* - HR 1,96; IC 95% 1,27 a 3,05; p = 0,003)[38].

As troponinas sensíveis foram avaliadas, também, no contexto de doença arterial coronariana estável para estimação prognóstica. Omland e colaboradores avaliaram níveis séricos de troponina T, com ensaios de alta sensibilidade, em 3679 pacientes com doença arterial coronariana estável e função ventricular preservada para a avaliação de eventos cardiovasculares em cinco anos de seguimento. Após correção para fatores prognósticos independentes, níveis séricos elevados desse marcador associaram-se com aumento da incidência de mortalidade cardiovascular (HR ajustado 2,09; IC 95% 1,60 a 2,74; p< 0,001) e insuficiência cardíaca (HR ajustado 2,20; IC 95% 1,66 a 2,90; p< 0,001), porém não com infarto do miocárdio[39].

Kavsak e colaboradores avaliaram níveis pré e pós-operatórios de troponina T de alta sensibilidade em uma coorte de 325 pacientes submetidos à cirurgia não-cardíaca com o objetivo de determinar a proporção de pacientes com alteração desse marcador. Foi demonstrado que 21% dos pacientes apresentaram elevação de troponina T (≥14 ng/L) acima do percentil 99 no período pré-operatório e 45% no período pós-operatório. Comparativamente, apenas 9% dos pacientes apresentaram elevação de troponina pós-operatória, quando utilizados ensaios de quarta geração.

Os autores sugerem que mais estudos são necessários para a determinação do melhor ponto de corte para as troponinas de alta sensibilidade neste contexto[40].

Os ensaios de alta sensibilidade ainda não foram avaliados no contexto de detecção de infarto agudo do miocárdio perioperatório, assim como não se sabe qual o impacto prognóstico desses novos marcadores em pacientes de alto risco cardiovascular submetidos a cirurgias não-cardíacas.

2.2.2 Peptídeos natriuréticos

Dados da literatura sugerem que outros marcadores bioquímicos também podem auxiliar na predição de eventos perioperatórios. Os peptídeos natriuréticos, principalmente o peptídeo natriurético do tipo B (BNP) e seu produto de clivagem inativo do fragmento N terminal (NT-proBNP), quando mensurados no período perioperatório, podem identificar pacientes com alto risco de sofrer um evento vascular maior a curto, médio e longo prazos[41-43].

Entre todos os peptídeos natriuréticos, o BNP é o mais útil e mais estudado no diagnóstico e no manejo de quadros de descompensação cardíaca[44,45].

Além da produção cerebral, o BNP é um hormônio peptídeo produzido de maneira pulsátil no coração, principalmente pelos miócitos ventriculares, quando submetidos a alterações hemodinâmicas, como sobrecarga volumétrica, sobrecarga pressórica e aumento de estresse parietal[46] ou a alterações isquêmicas[47]. Nesse contexto, o aumento do BNP faz parte de uma resposta homeostática protetora, pois seus efeitos fisiológicos de diurese, natriurese e vasodilatação de musculatura lisa auxiliam a compensação da função miocárdica reduzida[44,45].

O NT-proBNP é um peptídeo sem atividade biológica que é liberado junto com o BNP durante o seu processo de secreção, após clivagem do pró-BNP[48].

De maneira semelhante ao BNP, o NT-proBNP vem sendo extensamente estudado como marcador bioquímico de função cardíaca nos contextos de cardiopatia isquêmica, disfunção ventricular e predição de eventos cardiovasculares[45]. As principais diferenças entre os dois marcadores estariam

relacionadas ao seu metabolismo. O NT-proBNP apresenta um tempo de meia-vida biológica mais prolongada, aproximadamente 120 minutos, comparado com uma meia-vida de 22 minutos do BNP. Essa diferença pode ser, em grande parte, responsável pelo fato de os níveis de NT-proBNP serem mais elevados do que os de BNP em uma mesma situação. Além disso, a excreção do NT-proBNP é renal, o que faz com que o declínio da função renal seja responsável pela elevação de seus níveis plasmáticos de uma maneira aparentemente mais significativa do que ocorre com o BNP[44]. À exceção de insuficiência renal, o NT-proBNP parece comportar-se de modo similar ao BNP em relação aos fatores que influenciam a sua interpretação[49].

Estudos demonstram concentração aumentada, tanto de BNP quanto de NT-proBNP, nos pacientes com disfunção ventricular, sendo identificados como marcadores de disfunção miocárdica (isquemia e estiramento) e amplamente investigados no contexto da insuficiência cardíaca congestiva (ICC), cardiopatia isquêmica (CI) e como preditores de eventos cardiovasculares na população geral[50-53].

Evidências da literatura apontam o BNP como um preditor poderoso de morte e eventos cardíacos maiores em pacientes com doença arterial coronariana estável[54], síndrome coronariana aguda[55] e insuficiência cardíaca[56].

Sem dúvida, o contexto mais estudado desse marcador é o de pacientes com insuficiência cardíaca sistólica ou diastólica estáveis ou instáveis. Diversos estudos vêm demonstrando que a utilização do BNP poderia ser eficaz e custo-efetiva em outras situações relacionadas à ICC, tais como guia para a otimização do tratamento farmacológico e como rastreamento de disfunção ventricular assintomática em populações de risco[57,58].

No contexto das síndromes coronarianas agudas (SCA), particularmente naquelas sem supradesnível do segmento ST, o BNP demonstrou-se capaz de predizer eventos adversos, como morte cardíaca, ICC, morte súbita e eventos coronarianos recorrentes, mesmo em pacientes que não apresentem disfunção ventricular sistólica ou sinais de ICC. Dessa forma, os níveis de BNP adicionam informação prognóstica que é complementar à da troponina[59].

Além do papel prognóstico em síndromes coronarianas agudas, a elevação do BNP reflete a presença e severidade de doença arterial coronariana em pacientes estáveis. A associação com eventos cardiovasculares adversos em populações de risco e em pacientes com angina estável ocorre mesmo após ajuste para fração de ejeção[59].

Cabe ressaltar que níveis elevados de BNP podem ser afetados por outras situações como idade avançada, sexo feminino, insuficiência renal, terapia de reposição hormonal, exercício físico extremo, fibrilação atrial e doenças pulmonares − tromboembolismo pulmonar, cor pulmonale. De outra forma, a obesidade é um fator que pode levar à redução dos níveis de BNP[44].

Entre as perspectivas de utilização do BNP que vêm sendo estudadas − insuficiência mitral crônica, diagnóstico diferencial entre pericardite constritiva e miocardiopatia restritiva, hipertensão pulmonar, sepse e estenose aórtica − a sua mensuração, no período perioperatório, apresenta resultados promissores.

Estudos recentes sugerem que a elevação pré-operatória de níveis séricos de BNP é preditora de eventos cardiovasculares perioperatórios em pacientes submetidos a cirurgias não-cardíacas[41-43].

A capacidade de os níveis de BNP predizerem eventos, nesse contexto, relaciona-se à sensibilidade da sua liberação em resposta a modificações na função ventricular, tanto sistólica quanto diastólica. Até mesmo mínimas modificações, na função ventricular induzida por isquemia transitória, produzem medidas de BNP mensuráveis no plasma[47,60]. Níveis, proporcionalmente, elevados são encontrados em pacientes com função ventricular esquerda comprometida[61].

Feringa e colaboradores sugerem que níveis séricos do BNP podem ser um teste prognóstico melhor que ecocardiografia de estresse com dobutamina para identificação de pacientes com alto risco cardiovascular no perioperatório[62-63].

Entretanto, até o momento, dispõe-se de poucos estudos, com medidas de associação amplamente variáveis, sendo que a maioria foi conduzida no contexto de cirurgias vasculares e cardíacas, analisando apenas o valor desses marcadores com uma dosagem isolada pré-operatória[42,62-66].

Estudos que avaliaram o valor prognóstico do BNP ou do NT-proBNP pré-operatórios em pacientes submetidos a diversos tipos de cirurgias, principalmente no contexto de cirurgias eletivas, demonstraram pontos de corte diversos para risco cardiovascular, variando de 40 a 189 pg/ml e 201 a 533 pg/ml, respectivamente. O grau de associação para eventos em 30 dias foi, da mesma forma, bastante diversificado com OR ajustado, variando de 5,34 a 104[62,67-74].

Dessa forma, não existe, até o momento, um valor definido para considerar um ponto de corte estabelecido que defina uma população de risco. Os estudos disponíveis utilizaram diferentes pontos de corte de BNP e NT-proBNP para representar um valor anormal. Acredita-se que não é um valor específico que define risco, e sim um aumento progressivo de risco, conforme os aumentos dos níveis séricos. Além disso, apesar de os graus de associação serem extremamente variados entre os estudos, todos são unânimes de que o risco existe e que é relevante.

Uma metanálise avaliou a utilidade do BNP e NT-proBNP pré-operatórios para predição de mortalidade e eventos adversos cardíacos maiores a curto (30 dias) e médio prazos (180 dias) em pacientes submetidos somente à cirurgia vascular. Sete estudos foram incluídos, abrangendo um total de 504 pacientes avaliados a curto prazo, e 623 pacientes a médio prazo. Limites elevados desses marcadores, acima do limite discriminatório se associaram com mortalidade cardíaca em 30 dias (OR 7,6; IC 95% 1,33 a 43,4; p = 0,02), IAM não-fatal (OR 6,24; IC 95% 1,82 a 21,4; p = 0,004) e eventos cardíacos maiores (OR 17,37; IC 95% 3,31 a 91,15; p = 0,0007). A médio prazo, houve associação com todas as causas de mortalidade (OR 3,1; IC 95% 1,85 a 5,2; p < 0,0001), IAM não-fatal (OR 2,95; IC 95% 1,17 a 7,46; p = 0,02) e eventos cardíacos maiores (OR 3,31; IC 95% 2,1 a 5,24; p < 0,0001)[42].

Os dados mais consistentes do impacto prognóstico perioperatório do BNP e do NT-proBNP em pacientes submetidos a cirurgias não-cardíacas estão documentados em duas metanálises que avaliaram se estes marcadores são preditores independentes de eventos cardiovasculares adversos.

Ryding e colaboradores demonstraram forte associação do valor prognóstico do BNP ou do NTproBNP pré-operatórios com eventos cardiovasculares maiores a curto (<42 dias) e longo prazo (>6 meses) em pacientes submetidos à cirurgia não-cardíaca. Esta metanálise incluiu dados de 15 publicações (4856 pacientes). A elevação desses marcadores foi associada com aumento de risco de eventos cardiovasculares maiores a curto prazo (OR 19,77; IC 95% 13,18 a 29,65; p<0,0001), mortalidade por todas as causas (OR 9,28; IC 95% 3,51 a 24,56; p < 0,0001), e mortalidade cardiovascular (OR 23,88; IC 95% 9,43 a 60,43; p < 0,0001). Foi evidenciado, da mesma forma, aumento de risco para eventos cardiovasculares a longo prazo (OR 17,70; IC 95% 3,11 a 100,80; p < 0,0001) e mortalidade por todas as causas (OR 4,77; IC 95% 2,99 a 7,46; p < 0,0001)[43].

Uma segunda metanálise, também publicada no ano de 2009, por Karthikeyan e colaboradores, avaliou nove estudos, incluindo um total de 3281 pacientes. Complicações cardiovasculares perioperatórias foram observadas em 314 pacientes. A proporção de pacientes com elevação de BNP foi 24,8% (IC 95% 20,1 a 30,4%). Todos os estudos mostraram associação estatisticamente significativa entre elevação de níveis pré-operatórios de BNP ou de NTproBNP com diversos desfechos cardiovasculares. Dados agrupados das sete coortes avaliadas demonstraram um OR de 19,3 (IC 95% 8,5 a 43,7). O BNP pré-operatório foi um preditor independente de eventos cardiovasculares entre os estudos que avaliaram apenas desfechos de morte, mortalidade cardiovascular ou infarto do miocárdio (OR 44,2; IC 95% 7,6 a 257,0), e aqueles que incluíram outros desfechos (OR 14,7; IC 95% 5,7 a 38,2). Esses resultados sugerem que tanto o BNP quanto o NTproBNP pré-operatórios avaliados de forma conjunta, neste estudo, são preditores robustos e independentes de eventos cardiovasculares nos primeiros 30 dias pós-operatórios[41].

As informações sobre a avaliação do valor prognóstico do NT-proBNP pós-operatório são limitadas. Mahla e colaboradores avaliaram se o valor do NT-proBNP pós-operatório adicionaria informação prognóstica à dosagem pré-operatória com relação a eventos vasculares intra e pós-hospitalares em 218 pacientes submetidos à cirurgia vascular. Após um seguimento de 826 dias, 20% dos pacientes sofreram um evento cadiovascular. Comparando o NT-proBNP pré e pós-operatório − medianas de 215 e 557 pg/ml, respectivamente −, verificou-se um aumento desse

marcador em torno de duas vezes. O ponto de corte mais acurado para a predição de eventos para as medidas pré e pós-operatórias foi de 280 pg/ml (IC 95% 123 a 400) e 860 pg/ml (IC 95% 556 a 1054), respectivamente. Após ajuste para múltiplos fatores, apenas o NT-proBNP pós-operatório permaneceu associado, significativamente, com eventos intra-hospitalares (HR ajustado 19,8; IC 95% 3,4 a 115) e desfechos cardíacos a longo prazo (HR ajustado 4,88; IC 95% 2,43 a 9,81), sugerindo que apenas uma dosagem de NT-proBNP pós-operatória determina importante informação prognóstica adicional aos níveis pré-operatórios e poderia influenciar decisões terapêuticas para a prevenção de dano estrutural miocárdico subsequente[68]. Da mesma forma, Rajagopalan e colaboradores acompanharam 136 pacientes por dois anos após serem submetidos à cirurgia vascular. Um ponto de corte de 625 pg/ml, definido para a dosagem de NT-proBNP, aferida no primeiro pós-operatório, foi um fator independentemente relacionado com mortalidade total (OR 3,9; IC 95% 1,5 a 10), porém não com eventos cardiovasculares maiores. Entretanto, em ambos estudos citados anteriormente, a análise multivariada não foi ajustada para os níveis pré-operatórios dos pacientes[75].

Ainda no contexto de pacientes submetidos à cirurgia vascular, Goei e colaboradores demonstraram, em uma coorte de 144 pacientes, que a diferença entre os níveis séricos de NT-proBNP pré e pós-operatórios foi o maior preditor independente de eventos cardiovasculares a longo prazo (OR ajustado 3,06; IC 95% 1,36 a 6,91)[76].

Outro estudo, publicado por Schutt e colaboradores, avaliou valores de NT-proBNP pré e pós-operatórios em 83 pacientes de alto risco cardiovascular submetidos à cirurgia não-cardíaca de risco intermediário a alto. A taxa de eventos foi de 33% em 30 dias de seguimento. Níveis de NT-proBNP pré-operatórios, acima de 457 pg/ml, foram associados, significativamente, com eventos pós-operatórios (OR 10,5; IC 95% 1,9 a 56,6; p=0,006). Após a cirurgia, 89% dos pacientes apresentaram aumento dos níveis em relação ao período pré-operatório. Níveis pós-operatórios, assim como a variação dos níveis pós-operatórios em relação ao pré-operatório (delta), não foram associados com eventos adversos cardiovasculares[77].

Em última análise, a dosagem desse marcador, no período perioperatório, se torna atrativa por ser um método rápido, acessível e de baixo custo capaz de auxiliar na predição de risco cardiovascular de pacientes submetidos a cirurgias não-cardíacas. Nesse contexto, recentemente, as novas diretrizes de avaliação perioperatória da Sociedade Brasileira de Cardiologia recomendam que a dosagem de BNP ou NT-proBNP, no pré-operatório, pode ser utilizada como um preditor de risco para eventos cardiovasculares e mortalidade perioperatória de cirurgias não-cardíacas[22]. Certamente, novos estudos são necessários para determinação do ponto de corte a ser utilizado, o momento ideal da dosagem desse marcador no período perioperatório, assim como sua indicação complementar às estratégias de estratificação já preconizadas.

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4 RACIONAL DO ESTUDO

Nas últimas décadas, houve avanços significativos na cirurgia não-cardíaca para o tratamento de doenças e para a melhoria da qualidade de vida dos pacientes.

Apesar de seus benefícios, a cirurgia não-cardíaca de grande porte está associada a eventos vasculares maiores no perioperatório − morte de causa vascular, infarto do miocárdio não-fatal, parada cardíaca não-fatal e acidente vascular cerebral não-fatal.

Estabelecer um método para facilitar uma avaliação do risco cardiovascular acurada pré-operatória de cada indivíduo é extremamente relevante, uma vez que permite guiar a equipe assistente para um manejo perioperatório adequado como técnica anestésica e ambiente de recuperação pós-operatória. Da mesma forma, permite aos médicos, aos pacientes e a seus familiares decidirem sobre a adequação do procedimento, considerando seus riscos e benefícios.

Como muitos pacientes são assintomáticos, do ponto de vista cardiovascular, muitas vezes, por patologias que conferem limitação para avaliação da sua capacidade funcional, os índices de risco cardiovascular apresentam um poder preditivo limitado nesse contexto. Com o intuito de aumentar essa predição de risco, técnicas não invasivas, como ecocardiografia de estresse com dobutamina e cintilografia miocárdica com dipiridamol, são, muitas vezes, utilizadas.

Apesar da limitação das informações, tais testes parecem acrescentar valor preditivo às variáveis clínicas em algumas situações, porém são de alto custo e de disponibilidade limitada.

Dessa forma, há uma busca contínua para a identificação de outros métodos mais rápidos, disponíveis e custo-efetivos com boa capacidade para predição de eventos cardiovasculares em pacientes submetidos a cirurgias não-cardíacas.

Nesse contexto, marcadores de lesão e de estresse miocárdico, como as troponinas e os peptídeos natriuréticos, vêm sendo estudados.

Os peptídeos natriuréticos (BNP e NT-proBNP) e as troponinas, quando mensurados no período perioperatório, podem identificar pacientes com alto risco de sofrer um evento vascular maior a curto e médio prazo. Porém, os dados na literatura sobre esses marcadores, nesse contexto clínico, são escassos, de forma que suas dosagens ainda não foram incorporadas na monitoração rotineira de pacientes de alto risco cardiovascular submetidos à cirurgia não-cardíaca.

Assim, o presente estudo se propõe a avaliar o valor prognóstico dos biomarcadores cardíacos no período perioperatório no contexto de pacientes de moderado a alto risco cardiovascular submetidos à cirurgia não-cardíaca.

5 OBJETIVOS

5.1 Objetivo geral

Avaliar o valor prognóstico dos biomarcadores cardíacos para predição de eventos vasculares maiores − morte de causa vascular, infarto do miocárdio não-fatal, parada cardíaca não-fatal −, no período perioperatório e 30 dias após a cirurgia, em pacientes de moderado a alto risco cardiovascular submetidos à cirurgia não-cardíaca.

5.2 Objetivos específicos

a) Avaliar a relação entre os níveis de NT-proBNP pré e pós-operatórios;

b) estabelecer o ponto de corte ideal do NT-proBNP pré e pós-operatórios como marcadores de risco vascular perioperatório;

c) avaliar a acurácia do NT-proBNP pré e pós-operatório para a predição de eventos em 30 dias;

d) avaliar a acurácia da troponina I ultrassensível para a predição de eventos em 30 dias;

e) estabelecer preditores de aumento de troponina I ultrassensível no pós-operatório.

6 ARTIGOS

6.1 Artigo I:

Additional value of postoperative NT-proBNP in intermediate and high risk patients submitted to noncardiac surgery

Short title: Perioperative NT-proBNP and cardiovascular prognosis

Word Count: Summary, 266; Total, 3597

Keywords: NT-proBNP, cardiovascular events, perioperative care

Summary

Introduction: Clinical assessment is not always sufficient to predict postoperative cardiac complications. Although preoperative N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been shown to predict adverse cardiac outcome, there is little consensus whether postoperative NT-proBNP determination could or not provide additional prognostic value in patients submitted to noncardiac surgery.

Methods: In this study, 145 patients aged ≥45 years, with at least one Revised Cardiac Risk Index risk factor and submitted to intermediate or high risk noncardiac surgery were prospectively enrolled. NT-proBNP levels were measured preoperatively and on postoperative day 2. Logistic regression models were performed to evaluate predictors of short-term cardiac outcome. The optimal discriminatory levels of preoperative and postoperative NT-proBNP were determined by receiver operating characteristic analysis.

Results: During a median follow-up of 29±9 days, 17 patients (11.7%) have experienced major cardiac events, including 14 nonfatal myocardial infarctions (9.7%), 2 nonfatal cardiac arrests (1.4%) and 3 cardiac deaths (2.1%). The optimum discriminatory threshold levels for preoperative and postoperative NT-proBNP were 917 and 2962 pg/ml, respectively. Pre- and postoperative NT-proBNP (OR 4.7; 95% CI 1.62–13.73; p=0.005 and OR 4.5; 95% CI 1.53-13.16; p=0.006; respectively) were significantly associated with adverse cardiac events in univariate analysis. After adjusting for several perioperative variables, preoperative NT-proBNP (adjusted OR 4.2; 95% CI 1.38-12.62; p=0.011) remained significantly and independently associated with adverse cardiac events.

Conclusion: This study confirms that NT-proBNP is a powerful marker of perioperative cardiovascular events in high risk patients. Although significantly related to worse outcomes, postoperative levels were less informative than preoperative levels. A single preoperative NT-proBNP determination should be considered in the current preoperative risk assessment.

Introduction

Current methods of risk stratification before surgery are mainly based on the identification of clinical risk factors for heart disease[1]. Clinical assessment is not always sufficient to predict postoperative cardiac complications. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a marker of myocardial dysfunction (ischemic and stretch), and a powerful predictor of death and major adverse cardiovascular events in patients with stable coronary artery disease[2], acute coronary syndromes[3] and congestive heart failure[4].

Preoperative NT-proBNP elevation is independently associated with adverse cardiac outcomes after major noncardiac surgeries[5-8], but it does not anticipate the dynamic consequences of anesthesia and surgery. It's unknown whether postoperative NT-proBNP levels indicate myocardial dysfunction and if it acts as a reliable indicator of cardiac stress and outcome. A single postoperative NT-proBNP level could provide additional prognostic information for major cardiac events[9]. NT-proBNP dosage has not yet been incorporated into the routine monitoring of intermediate and high risk cardiovascular patients undergoing noncardiac surgery[10], also, the value of postoperative NT-proBNP as a marker of in-hospital and short-term cardiac events is still unknown.

Thus, this study aims to evaluate the additional prognostic value of postoperative NT-proBNP in intermediate and high risk cardiovascular patients undergoing noncardiac surgery after adjusting for clinical factors and preoperative levels.

Methods

Patients Selection

After Institutional Ethics Review Board approval, all patients scheduled to undergo elective noncardiac surgery between June 2010 and February 2011 were screened for eligibility for this prospective observational study. Before participating, all patients provided written informed consent. Patients above 45 years of age, with one or more Revised Cardiac Risk Index risk factor (history of ischemic heart disease, history or presence of heart failure, history of stroke or transient ischemic

attack, history of insulin dependent diabetes mellitus, or renal insufficiency [serum creatinine level above 2 mg/dl, or those patients on renal replacement therapy]) and undergoing surgery defined as intermediate or high risk by the American College of Cardiology/American Heart Association[1] and who have been hospitalized at least one day before surgery were eligible for inclusion in the study.

The sample size estimated for the cohort study was based on an anticipated rate of combined major adverse vascular events (MACE − vascular death, nonfatal myocardial infarction, nonfatal cardiac arrest) of 6% based on previous studies[11,12]. It was expected that approximately 142 patients were to be included, assuming a hazard ratio of 4.0 for high BNP levels, with an 80% power and an alpha error of 5%[7].

Determination of Biochemical Markers

Blood samples were collected in serum and centrifuged within 10 minutes. After determination of troponin I, serum was frozen and stored in aliquots at -80℃. NT-proBNP was measured and analyzed after completion of the active inclusion period of the study.

Troponin I was determined on postoperative days 1 and 2 and whenever clinically indicated by signs and symptoms of myocardial ischemia or surgical complications. The Siemens troponin I Ultra assay was performed with the use of the ADVIA Centaur immunoassay system (Siemens), with a limit of detection of 0.006 μg per liter, a 99th percentile cutoff point of 0.04 μg per liter and a coefficient of variation below 10%, at a level of 0.03 μg per liter, as specified by the manufacturer.

NT-proBNP analyses were performed using the Roche Elecsys 2010 (Roche Diagnostics GmbH, Mannheim, Germany). Serum determinations (electrochemiluminescence sandwich immunoassay, Elecsys ProBNP; Roche Diagnostics) were performed the day before surgery and on postoperative day 2. The assay had an analytical sensitivity of 5 pg/ml, and intraassay and interassay coefficients of variance below 3%.

Perioperative Management

Serial 12-lead electrocardiogram recordings were performed postoperatively when troponin I values were greater than 0.04 µg/L or whenever clinically indicated. Standard two-dimensional, M-mode and Doppler echocardiography (Envisor C, iE33; Philips Medical Systems, Andover, EUA, Vivid 3 or Vivid 7; GE Healthcare, Milwaukee, EUA) was performed by a cardiologist postoperatively, in case troponin I values were greater than 0.04 µg/L and a nondiagnostic electrocardiogram, or whenever clinically indicated to diagnose heart failure and to guide therapeutic interventions.

The attending physicians were aware of perioperative echocardiographic data and troponin I levels of patients, but were unaware of the NT-proBNP levels. During hospitalization, a study protocol and the patients' records were used for data documentation and collection.

Follow-up

Patients were monitored on in-hospital and 30-day cardiac events. The primary outcome variable was a combined endpoint of vascular death, nonfatal myocardial infarction (MI) and nonfatal cardiac arrest after index surgery. Follow-up was performed in all patients 30 days after index surgery and included a telephone interview conducted by an investigator unaware of NT-proBNP levels. In case of hospital readmission or death since index surgery, hospital charts and death certificates were reviewed. In addition, time, number, and cause of noncardiac deaths were recorded. Vascular complications were documented by the study physicians and validated by two independent investigators. Both data collectors and outcome adjudicators were blinded to measured NT-proBNP levels.

Vascular death was defined as death due to myocardial infarction, stroke or vascular events of great vessels. Nonfatal cardiac arrest was defined as a cardiopulmonary event that led to initiation of a successful cardiopulmonary resuscitation. Nonfatal MI was diagnosed by a typical rise and fall of troponin I to greater than 0.04 µg/L, along with clinical signs or symptoms of ischemia or electrocardiographic findings (new Q waves or ST-T wave changes in at least two

adjacent leads, or new left bundle branch block) suggestive of acute myocardial ischemia.

Secondary outcome variable was a combined endpoint of death, nonfatal stroke, congestive heart failure, atrial fibrillation and acute coronary revascularization procedures. Stroke was defined as a new focal neurological deficit of vascular origin, with symptoms lasting for more than 24 hours. Diagnosis of congestive heart failure required one or more of the following conditions: development of symptoms or signs of pulmonary edema, evidence of left ventricular failure or some abnormal finding on chest radiography. Atrial fibrillation with haemodynamic compromise was considered significant. Acute coronary revascularization was defined as acute percutaneous transluminal coronary angioplasty/stenting or coronary artery bypass grafting related to persistent myocardial ischemia and hemodynamic compromise refractory to medical therapy.

Statistical Analysis

Results are presented as mean±SD, medians and interquartile range [25th-75th percentile], or absolute and relative frequencies as appropriate. Preoperative NT-proBNP values and their perioperative changes were compared using Mann-Whitney U test. In order to test the strength of the associations between NT-proBNP levels and other continuous variables, Spearman's rank correlation was used. To identify the best discriminatory level of NT-proBNP associated with the primary endpoint, receiver operating characteristic curves have been analyzed. To determine optimal values of specificity and sensitivity, the closest value to the best specificity and sensitivity point on the receiver operating characteristic curve has been identified. Sensitivity, specificity, and positive and negative predictive values were calculated. For the purpose of assessing event-free survival, a Kaplan-Meier analysis was performed. The event-time curve was separated into two curves, according to the discriminatory pre- and postoperative NT-proBNP, and these curves were compared by log-rank test. Univariate comparisons between patients with and without events were performed using the chi-square test, Fisher exact test, Mann-Whitney U test, or Student t test as appropriate. Multivariate analysis was performed to determine independent factors associated with cardiac complications. Only

clinically relevant variables with $p < 0.2$ on the univariate analysis were included in the multivariate model. The level of significance was set at a two-tailed p value below 0.05. Statistical analysis was performed using SPSS 18.0 for Windows.

Results

Between June 2010 and February 2011, all 155 consecutive patients scheduled to undergo intermediate or high risk noncardiac surgery that fulfilled inclusion criteria were enrolled. Before participating, all patients provided written informed consent. Ten patients (6.5%) had their surgeries canceled after enrollment. There was no statistically significant difference between the clinical characteristics of 10 patients who did not operate, in comparison with those 145 patients included in the study. Baseline characteristics of the 145 included patients are reported in Table 1. Perioperative patient characteristics stratified by the occurrence of cardiovascular events during follow-up are presented in Table 2.

Cardiac Events

During a median follow-up of 29 ±8.7 days, 17 patients (11.7%) have experienced major cardiac events, including 14 nonfatal myocardial infarctions (9.7%), 2 nonfatal cardiac arrests (1.4%) and 3 cardiac deaths (2.1%). Overall mortality (cardiac and noncardiac) was 6.9%, including 4 cases of sepsis, 3 cases of hemorrhagic shock and 3 cases of cardiovascular deaths.

Association of perioperative NT-proBNP and cardiovascular events

Median NT-proBNP has significantly increased from 332 to 1175 pg/ml (interquartile range, 115-1743 to 587-2987 pg/ml; $p<0.001$), before and after surgery, respectively. Overall, 109 patients (78%) had an increase in NT-proBNP after surgery. Preoperatively, median NT-proBNP levels were higher in patients who experienced postoperative cardiovascular events as compared with event-free patients (1730 vs. 288 pg/ml; $p=0.02$). In addition, the median postoperative NT-proBNP was greater in patients sustaining cardiovascular events when compared with the event-free patients (3699 vs. 1092 pg/ml; $p=0.01$; Figure 1). Pre- and postoperative NT-proBNP levels have correlated with each other ($r=0.74$; $p<0.001$)

and with postoperative troponin I levels (r=0.43; p<0.001, and r=0.40; p<0.001, respectively).

The association of perioperative NT-proBNP and cardiovascular events was assessed by means of a receiver operating characteristic curve (Figure 2). The area under the curve was 0.67 (95% CI 0.52-0.82) for preoperative NT-proBNP. The optimum discriminate threshold for preoperative NT-proBNP was 917 pg/ml, yielding a sensitivity of 65%, a specificity of 73%, a positive predictive value of 24% and a negative predictive value of 94%. For postoperative NT-proBNP, the area under the curve was 0.69 (95% CI 0.54-0.84). A discriminative threshold of 2962 pg/ml had the best combined sensitivity (56.3%) and specificity (78%) rates, a positive predictive value of 24.3% and a negative predictive value of 93.3%. Models including the Revised Cardiac Risk Index were characterized by a low discriminative power (c-index=0.61±0.08) in predicting major adverse cardiac events. The c-index has increased to 0.65±0.08 (p=0.39), 0.64±0.08 (p=0.31), and 0.65±0.08 (p=0.16) when preoperative, postoperative, and pre/postoperative NT-proBNP levels were included, respectively. The association of pre- and postoperative NT-proBNP and cardiovascular events are shown in Tables 3 and 4.

Figure 3 shows the Kaplan-Meier curve demonstrating event-free survival in patients with NT-proBNP levels less than and greater than the established threshold. When comparing by log-rank test, the combination of both pre- and postoperative NT-proBNP levels – under or above the optimum discriminate threshold – of patients with both negative results showed higher event-free survival rates than those with both positive results (p<0.001) during the 30-days postoperative follow-up period (Figure 3C).

Previous percutaneous coronary intervention, peripheral artery disease, Specific Activity Scale class, type of surgery (vascular vs. nonvascular), preoperative NT-proBNP, postoperative NT-proBNP, postoperative troponin and major transoperative bleeding were significantly associated with adverse cardiac events in univariate analysis (Tables 1 and 2). Adjusted for Revised Cardiac Risk Index, revascularization, preoperative use of beta-blockers, type of surgery (vascular vs. nonvascular) and preoperative NT-proBNP levels by logistic regression,

postoperative NT-proBNP levels were not significantly and independently associated with adverse cardiac events. In multivariate analysis, independent predictors of primary cardiac events were preoperative NT-proBNP level ≥917 pg/ml (OR 4.2; 95% CI 1.38-12.62; p=0.011) and vascular surgery (OR 3.2; 95% CI 1.06-9.53; p=0.04). Relative and absolute variations of NT-proBNP from preoperative to postoperative levels were not significantly associated with postoperative cardiac events in the study population.

When stratifying patients by Revised Cardiac Risk Index (RCRI) and the optimum discriminatory threshold levels for pre- and postoperative NT-proBNP, primary outcome was similar among patients in class II and III. Patients with the combination of both class IV and pre- or postoperative NT-proBNP below the optimum discriminatory threshold levels showed higher event-free survival rates than those with class IV and pre- or postoperative NT-proBNP above the optimum discriminatory threshold levels during the 30-days postoperative follow-up period (p=0.004 and p=0.002, respectively).

Discussion

This study demonstrates that postoperative NT-proBNP measurement provides valuable information for risk stratification of intermediate and high risk patients undergoing noncardiac surgery. Postoperative NT-proBNP levels greater than 2962 pg/ml conferred 4.5 times increased odds for major cardiovascular events in short-term follow-up period. Patients with both pre- and postoperative NT-proBNP levels under the optimum discriminatory threshold had higher event-free survival rates when compared with those with both positive results during the 30-days postoperative follow-up period. Yet, in multivariate analysis, most independent predictors of primary cardiac events were preoperative NT-proBNP levels.

This study confirms and extends previous findings on preoperative NT-proBNP as an independent factor associated with major cardiovascular events and can provide prognostic information to the current strategies used to estimate perioperative risks[9,13-18]. In contrast, it is still undefined whether the role of postoperative NT-proBNP determination in clinical decision making is a significant independent marker of major cardiovascular events.

As observed in this study and according to most studies, NT-proBNP levels vary substantially during the postoperative period[7,9,18-22]. Postoperative peptide levels may reflect the variable dynamic consequences of anesthesia exerted by intraoperative and postoperative catecholamine release and induced hypercoagulability, with the potential to precipitate prolonged postoperative ischemia, myocardial necrosis, and myocardial dysfunction after major surgeries.

However, few studies were designed to address diagnostic and prognostic values of postoperative NT-proBNP for adverse cardiac outcomes. Prior studies only evaluating vascular patients have found conflictive results[9,23,24]. Mahla et al. have examined 218 patients undergoing elective major vascular surgery and identified a greater rise in postoperative NT-proBNP in those patients who have sustained a cardiovascular events, in comparison with those who have not (609 vs. 183 pg/ml). It was concluded that a single postoperative NT-proBNP ≥860 pg/ml could provide better additional prognostic information than preoperative levels (in-hospital adjusted hazard ratio 19.8; 95% CI 3.4-115)[9]. In a cohort study involving 144 vascular patients, Goei et al. have demonstrated that the difference in NT-proBNP levels between pre- and postoperative measurements was the strongest independent predictor of long-term cardiac outcome (adjusted hazard ratio 3.06; 95% CI 1.36-6.91)[23]. Rajagopalan et al. have followed-up 136 vascular patients for 2 years, and defined a cut-off value of 625 pg/ml for NT-proBNP levels on postoperative day one. Postoperative NT-proBNP was an independent predictor of mortality but not of MACE[24].

Results of current investigations demonstrate that, although the substantial postoperative NT-proBNP elevation had a significant association with major cardiovascular events, only preoperative measurements remained statistically significant in multivariate analysis. Former studies have evaluated a population at higher risk and included older patients only submitted to vascular surgery. In Mahla's and Goei's cohorts, NT-proBNP was measured between postoperative days 3 and 5, and before discharge (mean length of hospital stay 6.8±3.1 days). Latter NT-proBNP dosage could eliminate possible confounders as patients were usually no longer receiving infusion therapies. Furthermore, in Mahla's and Rajagopalan's studies pre- and postoperative NT-proBNP levels were analyzed as exclusive predictors of long-

term outcomes. In addition, in multivariable regression analyses, no adjustments were performed for preoperative NT-proBNP level, which is the most evident confounder of increased postoperative NT-proBNP level. Another study, failed to demonstrate an association between postoperative levels of NT-proBNP and change in NT-proBNP with postoperative cardiac events, interestingly in a cohort of patients similar to the one followed in this study[7].

Efforts to identify patients at increased cardiac risk when undergoing noncardiac surgeries have led to the development of a variety of scoring systems[11,25,26]. The quoted utility of these indixes varies, depending on the system, the patient population studied and the identified end-points. In a multi-centre study comparing several of these risk stratification tools, the areas under the ROC curves ranged from 0.60 to 0.64[27]. Lee and colleagues quote an area under the ROC curve of 0.76 for the Revised Cardiac Risk Index's ability to identify patients who were likely to develop a postoperative cardiac events[11].

Data from this study have demonstrated that preoperative NT-proBNP measurements have a useful role, regardless of the risk index prediction in this setting. This finding suggests that high baseline NT-proBNP levels resulting from the activation of the cardiac neurohormonal system may be a unifying feature in patients at high risk for cardiovascular mortality or major adverse cardiac events. A postoperative level reflects the dynamic consequences of surgery and anesthesia and is related to major cardiovascular events, but the most important factor predicting postoperative cardiovascular outcomes is seemingly the baseline state of the patient.

In agreement with the results, evidence strongly suggests that there is an independent association between elevated preoperative NT-proBNP levels and increased risks of adverse perioperative cardiovascular outcomes[7,9,13-18,28-32], but risks widely vary among studies and there is uncertainty regarding the strength of the association. A recently published systematic review and meta-analysis intended to determine whether preoperative BNP or NT-proBNP were independent predictors of 30-day adverse cardiovascular outcomes after noncardiac surgery has included nine studies and a total of 3,281 patients. All studies included showed a statistically significant association between elevated preoperative BNP or NT-proBNP levels and

various cardiovascular outcomes. Data pooled from 7 studies have demonstrated an odds ratio of 19.3 (95% CI 8.5-43.7; I^2 = 58%)[6]. Yet, there has been a marked heterogeneity across study results.

This data concur and reinforce the association between elevated preoperative NT-proBNP levels and increased risks of short-term adverse cardiovascular outcomes after index surgery. However, the magnitude of this effect was not so striking as previously described. Different types of surgery (not only vascular surgery), a heterogeneous population of intermediate and high risk cardiovascular patients and a primary outcome restricted to consistent adverse cardiac events (vascular death, nonfatal myocardial infarction and nonfatal cardiac arrest) may explain such difference.

In addition, there is no established cut-off point for defining risks. Previous studies have used different thresholds, from 201 to 1619 pg/ml[9,15-18,21], for preoperative NT-proBNP assays, and from 625 to 860 pg/ml[9,24], for postoperative NT-proBNP assays to represent abnormal values. The cut-off point based on the closest value to the best specificity and sensitivity point on the receiver operating characteristic curve in relation to the primary outcome was 917 pg/ml for preoperative NT-proBNP, and 2962 pg/ml, for postoperative levels. Differently from Mahla's and Rajagopalan's cohorts, 25% of patients with renal failure were included in this study. This is one of the Revised Cardiac Risk Index's risk factor and it was aimed to evaluate whether NT-proBNP measurement had a useful role beyond of this risk index. NT-proBNP levels and its prognostic ability could be affected by renal failure[33], but it is important to remember that patients with progressive renal failure would have cardiovascular dysfunctions coupled to their degree of renal function, which in turn could result in higher NT-proBNP levels[34]. Moreover, the timing to measure pre- and postoperative NT-proBNP levels vary between studies. It is unlikely that there is a dichotomous threshold that defines a normal or abnormal NT-proBNP values. It's more presumable that perioperative cardiovascular risks increase as NT-proBNP concentrations increase. In order to establish whether there is a single threshold and which is the best time to measure this marker in the perioperative period, the evaluation of a large number of patients undergoing a broad range of surgical procedures is still needed.

In this study, a preoperative NT-proBNP <917 pg/ml had a negative predictive value of 94%. This finding is in agreement with previous studies involving patients undergoing nonvascular[31] and vascular surgeries[8,14], hence suggesting that patients with normal levels should directly proceed to surgery, with no additional preoperative cardiac testing. One may speculate that this approach is very likely to be cost-effective, but this hypothesis needs to be tested through a future prospective study.

This study has some limitations. The small number of some outcomes (vascular death, nonfatal cardiac arrest and coronary revascularization) has resulted in wide confidence intervals and may have resulted in unreliable associations. Nevertheless, a consistent outcome has been evaluated and the adjusted odds ratios were statistically significant. Multivariable models were not adjusted for functional class, given that it was not possible evaluate functional capacity of most patients limited by peripheral artery disease. In addition, the prognostic utility of NT-proBNP was tested in a heterogeneous cohort study of intermediate and high risk cardiovascular patients undergoing a variety of surgical procedures and those with renal failure have been studied.

The use of a biochemical tests for risk stratification has several advantages. It only requires a single and relatively inexpensive blood test; which is widely available on existing clinical biochemistry analysers and is routinely performed in many hospitals. In addition, a biochemical test avoids the difficulties inherent in applying complex scoring systems to individual patients and also provides an objective measure, without the risk of potential subjective interpretation of clinical parameters. A clearly defined ‘cut-off point’, such as the 917 pg/ml derived from the ROC curve analysis used in this study would be simple to use in a clinical setting. It is a seemingly fast and cost-effective method to enhance preoperative cardiovascular risk assessment and facilitate targeted interventions that may reduce morbidity and mortality.

Further work, however, is required to clarify the utility of postoperative NT-proBNP levels in addition to preoperative levels and in combination with the existing risk stratification tools. More importantly, studies designed to assess whether interventions that reduce preoperative NT-proBNP levels can prevent perioperative

complications are needed. While such data is not available, the precise role of NT-proBNP in this setting remains unclear.

Conclusions

Postoperative NT-proBNP determination has a significant association with perioperative major cardiovascular events, but its additional value to preoperative levels in risk stratification of patients undergoing noncardiac surgery remains uncertain. Preoperative NT-proBNP levels reflect underlying cardiovascular status, identifying patients with reduced cardiac reserves and greater risks of major perioperative cardiovascular events. A single preoperative measurement of NT-proBNP has an independent association with consistent cardiovascular events and could provide further prognostic information to the current strategies used to estimate perioperative risk predictions.

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Figures Legends

Figure 1. Box-and-whisker plots of preoperative (preOP) and postoperative (postOP) N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in the 17 patients with cardiac events after index surgery, in comparison with the 128 event-free patients.

Figure 2. Receiver operating characteristic curves for preoperative (A) and postoperative (B) N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels for the prediction of the combined endpoint of vascular death, nonfatal myocardial infarction or nonfatal cardiac arrest after index surgery. The dotted line presents the no-discrimination curve. AUC = area under the curve; CI = confidence interval.

Figure 3. Kaplan Meier event-free survival stratified by preoperative N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (A), postoperative NT-proBNP levels (B) and combination of both pre- and postoperative NT-proBNP levels (C), respectively, under (-) or above (+) the optimum discriminate threshold during the 30-days postoperative follow-up period.

Table 1 – Baseline characteristics for the entire cohort and for patients with and without 30-day cardiovascular events.

	All patients (n=145)	Cardiovascular events		p
		Yes (n=17)	No (n= 128)	
Men	70 (48.3)	8 (47)	62 (48.4)	1.00
Age, years	65.7±9.8	64.8±10.8	65.8±9.7	0.67
ASA scoring system				0.35
Class II	53 (36.6)	4 (23.5)	49 (38.2)	
Class III	86 (59.3)	13 (76.5)	73 (57)	
Class IV	6 (4.1)	0	6 (4.7)	
Specific Activity Scale*				0.01
Class I	49 (33.8)	4 (23.5)	45 (35.1)	
Class II	41 (28.3)	3 (17.6)	38 (29.7)	
Class III	33 (22.8)	2 (11.8)	31 (24.2)	
Class IV	13 (9)	6 (35.3)	7 (5.5)	
Revised Cardiac Risk Índex				0.19
Class II	13 (9)	1 (5.9)	12 (9.4)	
Class III	85 (58.6)	8 (47)	77 (60.1)	
Class IV	47 (32.4)	8 (47)	39 (30.5)	0.19
Current smokers	33 (22.8)	4 (23.5)	29 (22.6)	0.89
Diabetes mellitus	60 (41.4)	8 (47)	52 (40.6)	0.61
Atrial fibrillation	13 (9)	2 (11.7)	11 (8.6)	0.65
History of congestive heart failure	26 (17.9)	5 (29.4)	21 (16.4)	0.19
Left ventricular ejection fraction (%)**	61.5±10.1	57±12	62±9.5	0.06
Hypertension	125 (86.2)	15 (88.2)	110 (85.9)	1.00
History of myocardial infarction	49(33.8)	7 (41.2)	42 (32.8)	0.58
Previous percutaneous coronary intervention	24 (16.6)	6 (35.3)	18 (14.1)	0.04
Previous coronary artery bypass graft	17 (11.7)	4 (23.5)	13 (10.1)	0.11
History of cerebrovascular disease	47 (32.4)	6 (35.3)	41 (32.0)	0.78
Renal impairment ***	36 (24.8)	5 (29.4)	31 (24.2)	0.76
Peripheral artery disease	30 (20.7)	9 (52.9)	21 (16.4)	0.002
Preoperative laboratory tests				
Hemoglobin,mg/dl	11.8±2.3	11.5±2.6	11.8±2.2	0.53
Serum creatinine, mg/dl	1.11 [0.86-1.75]	1.34 [0.91 - 2.87]	1.09 [0.86 -1.72]	0.35
Creatinine clearence, ml/min	58.6±31.48	55.95±41.17	58.94±30.22	0.78
NT-proBNP, pg/ml****	331.6 [115-1743]	1730 [2234-9929]	288 [104 -1332]	0.02
Preoperative medication				
Aspirin	66 (45.5)	9 (52.9)	57 (44.5)	0.6
Clopidogrel	11 (7.6)	1 (5.9)	10 (7.8)	1.00
Insulin	33 (22.8)	7 (41.2)	26 (20.3)	0.07
Statins	76 (52.4)	9 (52.9)	67 (52.3)	1.00
β-Blockers	73(50.3)	12 (70.6)	61 (47.6)	0.12
ACE inhibitors	86 (59.3)	10 (58.8)	76 (59.4)	1.00

Data are expressed as number (percentage), mean ± SD, or median [interquartile range] as appropriate. p value indicates differences between patients with and without cardiovascular events. ASA= American Society of Anesthesiologists; NT-proBNP= N-terminal pro-B-type natriuretic peptide; ACE= angiotensin-converting enzyme. * n=136; **n=116; ***Serum creatinine ≥2.0 mg/dl or renal replacement therapy; **** n=142

Table 2 – Perioperative characteristics of all patients, stratified by the occurrence of 30-day cardiovascular events

	All patients (n=145)	Cardiovascular events		p
		Yes (n=17)	No (n=128)	
Postoperative laboratory tests				
NT-proBNP, pg/ml*	1175 [587-2987]	3699 [926 -12989]	1091.5 [558 -2759]	0.01
TnI postoperative day 1, µg/L**	0.018 [0.009-0.036]	0.049 [0.02 -0.425]	0.017 [0.008-0.032]	0.001
TnI postoperative day 2, µg/L***	0.019 [0.01-0.053]	0.192 [0.059-0.686]	0.018 [0.009-0.034]	<0.001
Transoperative events				
Hypotension (Systolic <100 mmHg)	93 (64.1)	10 (58.8)	83 (64.8)	0.6
Bradycardia (Heart rate <50 bpm)	33 (22.8)	4 (23.5)	29 (22.6)	1.00
Major bleeding****	19 (13.1)	6 (35.3)	13 (10.1)	0.01
Types of surgery				0.03
Abdominal	72 (49.7)	4 (23.5)	68 (53.1)	
Thoracic	10 (6.9)	0	10 (7.8)	
Vascular	46 (31.7)	10 (58.8)	36 (28.1)	
Prostate	4 (2.8)	0	4 (3.1)	
Hip	13 (9)	3 (17.6)	10 (7.8)	

Data are expressed as number (percentage), mean ± SD, or median [interquartile range] as appropriate. p value indicates differences between patients with and without cardiovascular events. NT-proBNP= N-terminal pro-B-type natriuretic peptide. TnI = Troponin I.
*n=142; **n=141 ; ***n=138 ****Major bleeding= bleeding requiring blood transfusion

Table 3 − Events during follow-up period, stratified by preoperative NT-proBNP

	All patients n=145 (%)	NT-proBNP <917 pg/ml n=96 (%)	NT-proBNP≥917 pg/ml n=46 (%)	OR (95% CI)	p
Primary outcome	17 (11.7)	6 (6.3)	11 (23.9)	4.71 (1.62 – 13.73)	0.005
Cardiac death	3 (2.1)	0	3 (6.5)	14.6 (0.7 – 275)**	0.03
Nonfatal cardiac arrest	2 (1.4)	0	2 (4.3)	10.84 (0.52 –226.29)**	0.10
Nonfatal MI	14 (9.7)	6 (6.3)	8 (17.4)	3.16 (1.03 – 9.72)	0.07
Secondary outcome	29 (20)	13 (13.5)	15 (32.6)	3.09 (1.32 – 7.23)	0.01
Death	10 (6.9)	2 (2.1)	7 (15.2)	8.43 (1.67 – 42.42)	0.005
Nonfatal stroke	5 (3.4)	3 (3.1)	2 (4.3)	1.41 (0.23 –8.74)	0.66
Congestive heart failure	12 (8.3)	8 (8.3)	4 (8.7)	1.05 (0.30 – 3.68)	1.00
Atrial fibrillation	7 (4.8)	1 (1.0)	6 (13)	14.25 (1.66 – 122.21)	0.005
Coronary revascularization	1 (0.7)	1 (1.0)	0	0.68 (0.03 – 16.62)**	1.00
Noncardiovascular outcome*	59 (40.7)	33 (34.4)	25 (54.3)	2.27 (1.11-4.65)	0.03
Noncardiac death	7 (4.8)	2 (2.1)	4 (8.7)	4.47 (0.79 – 25.4)	0.09
Infection	43 (29.7)	22 (23)	21 (45.7)	2.82(1.33 – 5.98)	0.01
Renal failure	7 (4.8)	2 (2.1)	4 (8.7)	4.47 (0.79 – 25.4)	0.09
Major bleeding	37 (25.5)	19 (19.8)	17 (37)	2.37 (1.09 – 5.19)	0.04

NT-proBNP= N-terminal pro-B-type natriuretic peptide; OR= odds ratio; CI= confidence interval; MI= myocardial infarction *Combined outcome of noncardiovascular events= noncardiac death, infection, acute renal insufficiency with necessity of renal replacement therapy or postoperative major bleeding (bleeding requiring blood transfusion). **Adjusted by adding 0.5 in each cell, if there is a zero frequency.

Table 4 – Events during follow-up period, stratified by postoperative NT-proBNP

	All patients n=145 (%)	**NT-proBNP < 2962 pg/ml n=105 (%)**	**NT-proBNP ≥ 2962 pg/ml n=37 (%)**	**OR (95% CI)**	**p**
Primary outcome	17 (11.7)	7 (6.7)	9 (24.3)	4.5 (1.53 – 13.16)	0.006
Cardiac death	3 (2.1)	0	2 (5.4)	14.86 (0.71 – 310.96)**	0.07
Nonfatal cardiac arrest	2 (1.4)	0	2 (5.4)	14.86 (0.71 – 310.96)**	0.07
Nonfatal MI	14 (9.7)	7 (6.7)	7 (18.9)	3.26 (1.06 – 10.05)	0.05
Secondary outcome	29 (20)	18 (17.1)	10 (27)	1.79 (0.73 – 4.33)	0.23
Death	10 (6.9)	4 (3.8)	5 (13.5)	3.94 (1 – 15.58)	0.05
Nonfatal stroke	5 (3.4)	5 (4.8)	0	0.24 (0.01 – 4.35)**	0.33
Congestive heart failure	12 (8.3)	9 (8.6)	3 (8.1)	0.94 (0.24 – 3.68)	1.00
Atrial fibrillation	7 (4.8)	3 (2.9)	4 (10.8)	4.12 (0.87- 19.37)	1.00
Coronary revascularization	1 (0.7)	1 (1.0)	0	0.93 (0.04 – 22.48)**	1.00
Noncardiovascular outcome*	59 (40.7)	37 (35.2)	21 (56.8)	2.41 (1.12 – 5.17)	0.03
Noncardiac death	7 (4.8)	4 (3.8)	3 (8.1)	2.23 (0.47 – 10.5)	0.38
Infection	43 (29.7)	25 (23.8)	17 (46)	2.72 (1.24 – 5.98)	0.02
Renal failure	7 (4.8)	3 (2,9)	4 (10.8)	4.12 (0.88 – 19.4)	0.08
Major bleeding	37 (25.5)	23 (22)	13 (35)	1.93 (0.85- 4.38)	0.13

NT-proBNP= N-terminal pro-B-type natriuretic peptide; OR= odds ratio; CI= confidence interval; MI= myocardial infarction *Combined outcome of noncardiovascular events= noncardiac death, infection, acute renal insufficiency with necessity of renal replacement therapy or postoperative major bleeding (bleeding requiring blood transfusion). **Adjusted by adding 0.5 in each cell, if there is a zero frequency.

Figure 1.

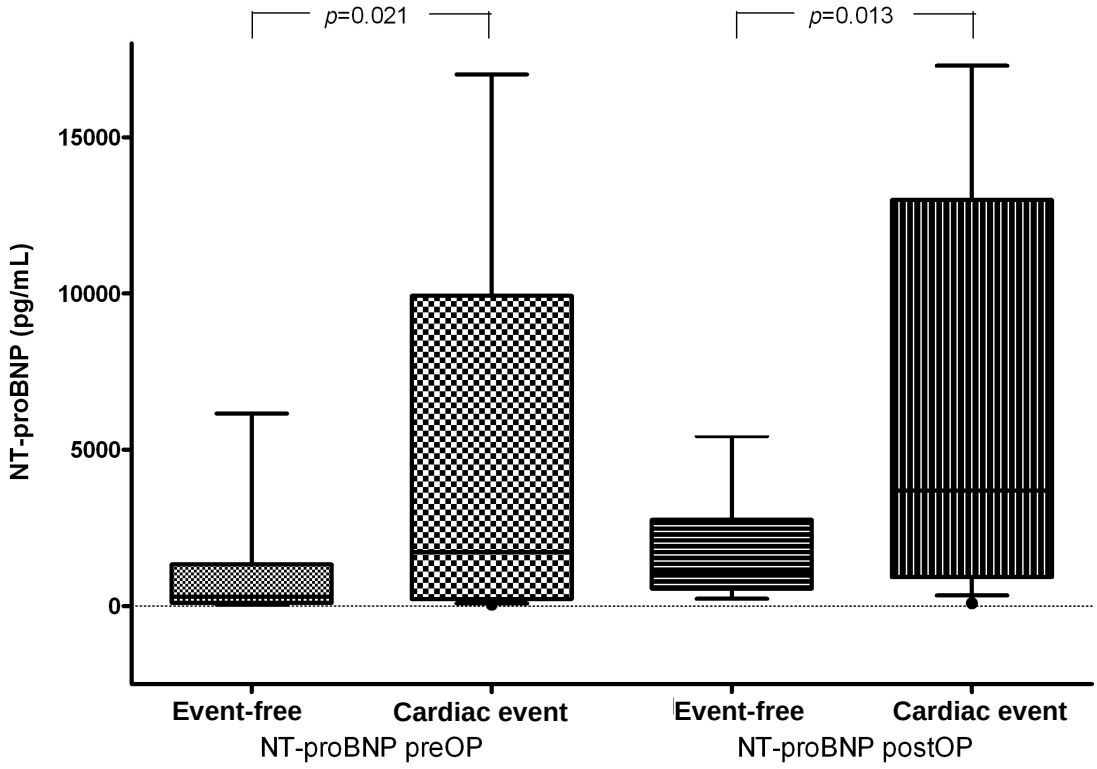

p=0.021
p=0.013
15000
10000
5000
0
NT-proBNP (pg/mL)
Event-free
Cardiac event
Event-free
Cardiac event
NT-proBNP preOP
NT-proBNP postOP

Figure 2.

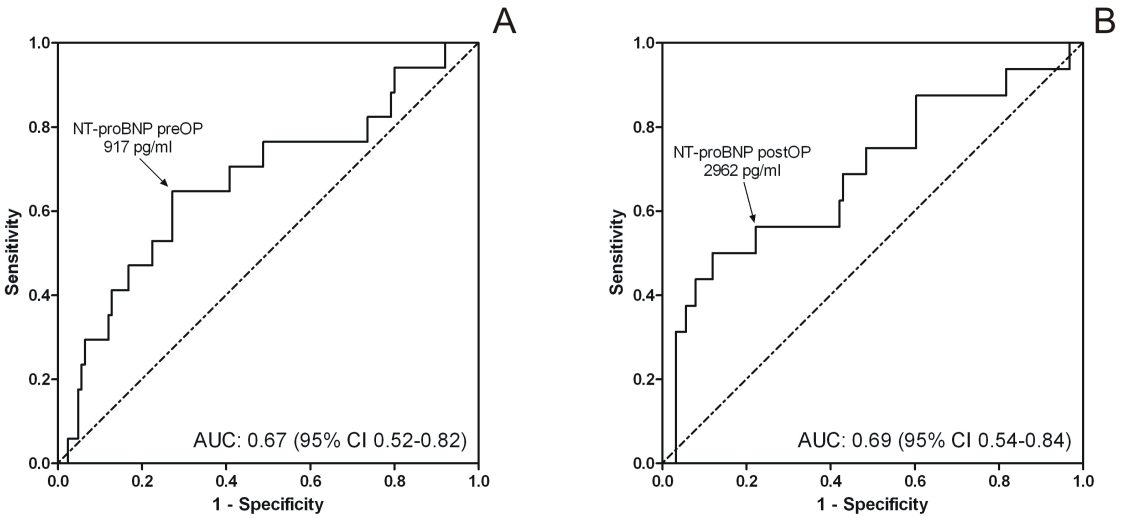
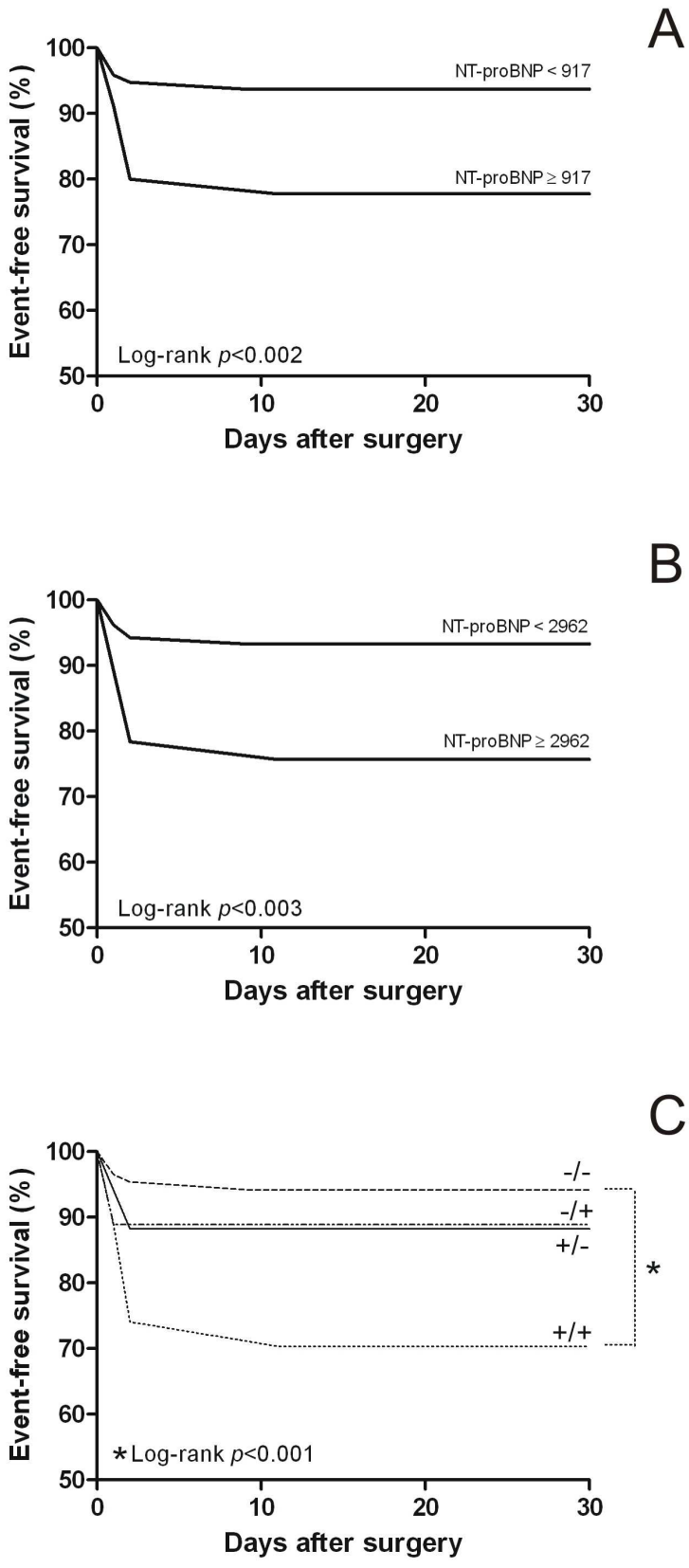

A
NT-proBNP preOP
917 pg/ml
AUC: 0.67 (95% CI 0.52-0.82)
Sensitivity
1 - Specificity
B
NT-proBNP postOP
2962 pg/ml
AUC: 0.69 (95% CI 0.54-0.84)
Sensitivity
1 - Specificity

Figure 3.


A
100
90
80
70
60
50
Event-free survival (%)
NT-proBNP < 917
NT-proBNP ≥ 917
Log-rank p<0.002
0
10
20
30
Days after surgery
B
100
90
80
70
60
50
Event-free survival (%)
NT-proBNP < 2962
NT-proBNP ≥ 2962
Log-rank p<0.003
0
10
20
30
Days after surgery
C
100
90
80
70
60
50
Event-free survival (%)
-/-
-/+
+/-
+/+
*
*Log-rank p<0.001
0
10
20
30
Days after surgery

6.2 Artigo II

CLINICAL USE OF TROPONIN I US IN INTERMEDIATE AND HIGH RISK NONCARDIAC SURGERY PATIENTS: PREDICTORS AND PROGNOSIS

Brief Title: Troponin I US in noncardiac surgery

Word count: Summary, 286; Total, 3393.

Key words: Troponin I US, cardiovascular events, perioperative

Summary

Introduction: Cardiac troponin elevation has shown to add value in detecting cardiovascular complications in patients submitted to noncardiac surgery. Although, in theory new generation ultrasensitive troponin I (TnI US) could add more accurate prognostic information, these assays were not yet tested in this setting.

Objectives: To evaluate the prognostic value of TnI US after noncardiac surgery in intermediate and high risk patients, and identify predictors of TnI elevation in this context.

Methods: 142 consecutive patients with Revised Cardiac Risk Index class ≥2, submitted to intermediate and high risk noncardiac surgery were included. TnI US was measured on postoperative day 1 and 2. Patients were followed-up during hospitalization and 30 days after index surgery for major adverse cardiovascular events (MACE) – vascular death, nonfatal myocardial infarction (MI) and nonfatal cardiac arrest – and overall mortality.

Results: TnI elevation (≥0.04 µg/L) occurred in 47 (33%) patients, and among these, 14 (30%) fullfield diagnosis of MI. After 29±9 days follow-up, 16 patients (11.3%) had MACE and 9 (6.3%) died. Excluding patients with final diagnosis of MI, the predictors of troponin elevation were dialysis, history of heart failure, transoperative major bleeding, pre- and postoperative NT-proBNP levels. Maximal TnI values had the best combined sensitivity (94%), specificity (75%), predictive values and overall accuracy (AUC 0.89; 95% CI 0.80-0.98; p<0.001) for MACE. After multivariate analysis, independent risk factors for MACE were postoperative TnI peak level (OR 9.4; 95% CI 2.3-39.2; p=0.002) and preoperative NT-proBNP level ≥917 pg/ml (OR 3.47; 95% CI 1.05-11.6; p=0.041).

Conclusion: TnI US was an independent prognostic factor for cardiac outcomes and should be considered as a component of perioperative risk assessment. Heart failure, renal insufficiency on dialysis, intraoperative major bleeding, pre- and postoperative NT-proBNP are related to troponin elevation.

Introduction

In the last years, many high risk patients are submitted to major noncardiac surgeries and suffer an adverse cardiac event. Perioperative myocardial ischemia occurs in up to 40% of patients at risk of coronary artery disease, but it is usually clinically silent, and, accordingly, difficult to detect[1-3]. More important, it is a major factor related to long-term adverse events, occurring in 5.6% of high risk coronary artery disease patients[4,5].

Several preoperative risk stratification scores have been developed and adjusted in recent years[4,6-8]. However, the prognostic accuracy of these scores is limited, once they considered patient's history and preoperative clinical status to predict short-term morbidity and mortality or to identify patients in need for more detailed cardiac testing. Patient's outcome does not depend only on preoperative findings and the surgery performed, but also on perioperative events.

Troponin elevation in the perioperative period has shown to add value in detecting cardiovascular complications[9-18]. Although many studies have demonstrated evidence that monitoring cardiac enzymes after surgery may help to identify a good proportion of silent perioperative myocardial infarction, they are limited once majority of patients were restricted to vascular surgery or had coronary artery disease. Also, studies used different troponin assays, with different accuracy and results showed a huge variability with conflictive adverse results and large confidence intervals.

New generation ultrasensitive (US) troponin assays are highly sensitive, more accurate to detect earlier minor myocardial ischemia and have prognostic impact in patients with acute coronary syndromes[19-21], with stable coronary artery disease[22] and with heart failure[23]. Until this moment, troponin US has not been tested in patients submitted to noncardiac surgery.

The present study aims to evaluate the prognostic value of cardiac troponin I ultrasensitive (cTnI US) assay in the perioperative period of noncardiac surgery in intermediate and high risk patients and to identify predictors of troponin elevation.

Methods

Patients selection

After institutional ethics review board approval, all patients scheduled to undergo elective noncardiac surgery were screened for eligibility for this prospective observational study. All patients gave written informed consent before participating. Patients ≥45 years of age, with hospitalization at least one day before surgery, with one or more Revised Cardiac Risk Index risk factor (history of ischemic heart disease, history or presence of heart failure, history of stroke or transient ischemic attack, history of insulin dependent diabetes mellitus, or renal insufficiency [serum creatinine level ≥ 2 mg/dl or patients on renal replacement therapy]) undergoing surgery defined as intermediate or high risk by the American College of Cardiology/American Heart Association[24] were eligible for inclusion in the study. Between June 2010 and February 2011, 155 consecutive patients were included in the study. Ten patients (6.5%) were excluded because they had canceled their surgeries after enrollment and 3 patients' postoperative blood samples were missed. There was no statistically significant difference between the clinical characteristics of 13 patients who did not operate in comparison with the 142 patients included in the study.

The calculated sample size of the cohort was based on an anticipated rate of combined major vascular events (vascular death, nonfatal myocardial infarction, nonfatal cardiac arrest) of 6 per cent based on previous studies[4,5]. We expected inclusion of approximately 142 patients assuming a hazard ratio of 4.0 for elevated postoperative troponin, with an 80% power and an alpha error of 5%[11].

Data collection

A standardized questionnaire was applied in all patients. Data about the demographic characteristics and detailed medical history were collected. All patients were classified according to Specific Activity Scale functional classification of Goldman et al for Cardiovascular Disease (SAS)[25], Revised Cardiac Risk Index

(RCRI)[4] and the American Society of Anesthesiologists class (ASA). This last one was obtained from the structured evaluation provided by the anesthesiologist in the medical record.

Determination of biochemical markers

Blood samples were collected in serum and centrifuged within 10 minutes. After determination of troponin I, serum was frozen and stored in aliquots at -80℃. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured and analyzed after completion of the active inclusion period of the study. Troponin I was determined on postoperative day 1, on postoperative day 2, and whenever clinically indicated by signs and symptoms of myocardial ischemia or surgical complications. The Siemens troponin I ultra assay was performed with the use of the ADVIA Centaur immunoassay system (Siemens), with a limit of detection of 0.006 µg per liter, a 99th percentile cutoff point of 0.04 µg per liter, and a coefficient of variation of less than 10% at 0.03 µg per liter, as specified by the manufacturer. NT-proBNP analyses were performed using the Roche Elecsys 2010 (Roche Diagnostics GmbH, Mannheim, Germany). Serum determinations (electrochemiluminescence sandwich immunoassay, Elecsys ProBNP; Roche Diagnostics; sensitivity: 5 pg/ml, intraassay and interassay coefficients of variance: <3%) were performed on the day before surgery and on postoperative day 2.

Perioperative management

Serial 12-lead electrocardiogram recordings were performed postoperatively in case of a troponin I US greater than 0.04 µg/L and whenever clinically indicated. Standard two-dimensional, M-mode and Doppler echocardiography (Envisor C, iE33; Philips Medical Systems, Andover, EUA, Vivid 3 or Vivid 7; GE Healthcare, Milwaukee, EUA) was performed by a cardiologist postoperatively in case of a troponin I greater than 0.04 µg /L and a nondiagnostic electrocardiogram, and whenever clinically indicated to diagnose heart failure and to guide therapeutic interventions. In two patients with early hospital discharge, echocardiography could not be performed.

Follow-up and outcomes

During hospitalization, a study protocol and the patients' records were used for data documentation and collection. Patients were monitored for in-hospital outcomes until discharge. An independent investigator, blinded to troponin results, monitored patients by a telephone call for the occurrence of cardiac events after 30 days of the index surgery. Events were validated by an independent senior investigator not involved in data collection.

The primary outcome was a combined endpoint of vascular death, nonfatal myocardial infarction (MI) and nonfatal cardiac arrest within 30 days postoperative. In case of hospital readmission or death since index surgery, hospital charts and death certificates were reviewed. In addition, information on noncardiac deaths was also recorded. Vascular complications were documented by the study physicians and validated by two independent investigators.

Vascular death was defined as death secondary to myocardial infarction, stroke or vascular event of great vessels. Nonfatal cardiac arrest was defined as a cardiopulmonary event that led to initiation of a successful cardiopulmonary resuscitation. Nonfatal MI was diagnosed by a typical rise and fall of troponin I greater than 0.04 µg/L, with clinical signs, symptoms, or electrocardiographic findings (new Q waves or ST-T wave changes in at least two adjacent leads) suggestive of acute myocardial ischemia.

Secondary outcome variable was a combined endpoint of death, nonfatal stroke, congestive heart failure, atrial fibrillation and acute coronary revascularization procedures. Stroke was defined as a new focal neurological deficit of vascular origin, with symptoms lasting for more than 24 hours. Diagnosis of congestive heart failure required one or more of the following: development of symptoms or signs of pulmonary edema, evidence of left ventricular failure or an abnormal finding on chest radiography. Atrial fibrillation with haemodynamic compromise was considered significant. Acute coronary revascularization was defined as acute percutaneous coronary intervention or coronary artery bypass grafting due to persistent myocardial

ischemia and hemodynamic compromise refractory to medical therapy. Major bleeding was defined as a bleeding requiring blood transfusion.

Statistical analysis

Results are presented as mean±SD, medians and interquartile range [25th–75th percentile], or absolute and relative frequencies as appropriate. Receiver operating characteristic (ROC) curves were constructed to assess the diagnostic accuracy for the primary outcome and overall mortality for cTnI-US. Optimal cutoff values of pre- and postoperative NT-proBNP were derived from ROC curves, and sensitivity, specificity, predictive values were calculated. To assess event-free survival, a Kaplan-Meier analysis was performed. The event-time curve was separated into two curves according to the 99^{th} percentile cutoff point of 0.04 µg per liter, as specified by the manufacturer, and these curves were compared by log-rank test. Univariable comparisons between patients with and without events were performed using the chi-square test, Fisher exact test, Mann-Whitney U test, or Student t test, as appropriate. Multivariable analysis by logistic regression was performed to determine independent factors associated with cardiac complications. Variables with p values < 0.20 in univariable analyses or with clinical relevance were included in the multivariable model. The level of significance was set at a two-tailed p value less than 0.05. Statistical analyses were performed with SPSS 18.0 for Windows (SPSS Inc., Chicago, IL).

Results

Baseline characteristics of all 142 patients are presented in Table 1 and perioperative variables in Table 2. During a median follow-up of 29±8.7 days, 16 patients (11.3%) experienced major cardiac events. Forty seven patients (33.1%) had troponin I US elevation (≥0.04 µg/L) at least in one of the postoperative samples collected. Among these, 14 patients fullfield diagnosis of acute myocardial infarction, 7 patients were completely asymptomatic. Median troponin levels were higher in patients who experienced postoperative cardiovascular primary events as compared with event-free patients: 0.049 vs. 0.017 µg/L for postoperative troponin day 1

(p=0.001), and 0.192 vs. 0.018 µg/L for postoperative troponin day 2 (p<0.001). Figure 1 shows the Kaplan-Meier curve demonstrating primary event-free survival and overall survival in patients with troponin peak levels less than and greater than 0.04 µg/L.

Association of perioperative troponin I US and primary cardiovascular events was assessed with a receiver operating characteristic curve. The area under the curve (AUC) for primary events was 0.75 (95% CI 0.64-0.87; p=0.001) for postoperative troponin day 1, yielding a sensitivity of 56.3%, a specificity of 80%, a positive predictive value of 26.5%, and a negative predictive value of 93.5%. For postoperative troponin day 2, the AUC was 0.87 (95% CI 0.76-0.98; p<0.001) yielding a sensitivity of 86.7%, a specificity of 78%, a positive predictive value of 32.5% and a negative predictive value of 98%. The combination of troponin peak values had the best combined sensitivity (94%), specificity (75%), positive predictive value (32%), and negative predictive value (99%) (AUC 0.89; 95% CI 0.80-0.98; p<0.001). The ROC-derived optimal cutoff values for pre- and postoperative NT-proBNP were 917 and 2962 pg/ml, respectively. Change in troponin levels between the first and the second measurement was related to adverse cardiac events (p=0.001). All patients with primary outcome had relative change in cTnI US levels over 30%.

Predictors of postoperative troponin elevation, excluding patients who had myocardial infarction, are presented in Table 3. Patients on dialysis (OR 3.38; 95% CI 1.01-10.5), with heart failure (OR 3.0; 95% CI 1.15-7.84), transoperative major bleeding (OR 3.38; 95% CI 1.01-10.5), preoperative NT-proBNP levels ≥917 pg/ml (OR 3.65; 95% CI 1.56-8.55), and postoperative NT-proBNP levels ≥2962 pg/ml (OR 3.63; 95% CI 1.51-8.72) were more likely to have cTnI elevated after surgery.

Twenty eight patients experienced secondary outcomes (19.7%). Data are detailed in Table 4. Previous coronary revascularization, peripheral artery disease, transoperative major bleeding, functional capacity, pre- and postoperative NT-proBNP, vascular surgery and postoperative cTnI levels were significantly associated with primary cardiac events in the univariable analysis (Table 1 and 2). In a model adjusting for RCRI, previous coronary revascularization, preoperative beta-blocker

use, vascular surgery, pre- and postoperative NT-proBNP, independent predictors of primary cardiac events were postoperative cTnI US peak level (OR 9.4; 95% CI 2.26-39.18; p=0.002) and preoperative NT-proBNP level ≥917 pg/ml (OR 3.47; 95% CI 1.05-11.55; p=0.041).

Patients with the combination of preoperative levels of NT-proBNP ≥917 pg/ml and postoperative troponin peak values ≥0.04 µg/L had 36% of primary cardiovascular outcomes comparing to none events in patients with both negative levels (p<0.001) (Figure 2).

Discussion

A perioperative increase in troponin I US was found to be highly predictive of short-term major cardiovascular events and added incremental prognostic information to established risk scores that only consider preoperative information. Besides this, postoperative cTnI US measure was a predictor of total mortality (OR 4.48; 95% CI 1.07-18.82).

Our results are in agreement with previous studies that evaluated conventional commercial assays of troponin T or troponin I and identified that these markers were independent prognostic factors to major cardiovascular outcomes[10-17]. This finding persisted even in studies that excluded patients with MI[11,12] and some of them showed a dose response relationship, ie., mortality increases as troponin levels increases[10,13]. Most former studies found a strong association between troponin elevation and cardiovascular outcomes in a selected population of patients restricted to vascular surgeries or high risk cardiovascular patients. We found a strong association in a population of intermediate and high risk patients.

Asymptomatic postoperative troponin elevation is a frequent event and a substantial proportion of our patients with diagnosis of MI (50%) presented silent ischemia detected only by active monitoring of cardiac markers. The postoperative management for cardiac ischemia may change these patients' prognosis. Accordingly, we can hypothesize that a substantial percentage of cardiac risk patients suffer during the perioperative period from the equivalent of an acute

coronary syndrome. This acute coronary syndrome often remains clinically undetected, but provokes myocardial cell damage with a rise in troponin levels. As in the nonsurgical patients, myocardial ischemia is associated with a worse prognosis. A strong association of perioperative ischemia and mortality is well-established[1,11,26]. A recent meta-analysis demonstrated that an isolated postoperative troponin leak (an elevation of troponin below the diagnostic threshold for a perioperative MI, without symptoms or ischaemic electrocardiography changes or echocardiography signs) was strongly predictive of all-cause mortality at 30 days after vascular surgery (OR 5.03; 95% CI 2.88-8.79)[27]. Levy et al also demonstrated in their meta-analyses that an increased troponin measurement after noncardiac surgery was an independent predictor of long-term mortality (OR 3.4; 95% CI 2.2-5.2), although there was a substantial heterogeneity[28].

Recently, improvements in the technology of cardiac troponin assays have allowed manufacturers to provide fully automated assays that meet the recommendations set out by the International Federation of Clinical Chemistry and Laboratory Medicine[29,30]: higher sensitivity than the previous assays and improved precision at the lower limit of detection. These assays have a lower limit of detection that is below the 99th percentile in a normal reference population. Reichlin et al. showed that, in patients within 3 hours of chest pain in emergency department, cTnI US had an AUC of 0.94 (95% CI 0.90-0.98) to detect myocardial infarction[20]. At the same time, Keller et al. found a better diagnostic accuracy with US assays comparing to traditional ones in patients with suspicion of MI. Also in patients with stable coronary artery disease, troponin levels appear to be independent predictors of cardiovascular mortality (adjusted HR 2.09; 95% CI 1.60-2.74; p<0.001)[22].

Until this moment, the prognostic value of cTnI US assays were not tested in noncardiac surgery to predict cardiovascular adverse outcomes. We demonstrated that the postoperative troponin peak values ≥0.04 µg/L on postoperative days 1 or 2 had the best combined sensitivity (94%) and specificity (75%), and a high negative predictive value of 99% to predict 30 days adverse cardiovascular outcomes (AUC 0.89; 95% CI 0.80-0.98; p<0.001). In the context of acute chest pain, cTnI US is an ideal marker with high sensitivity and high negative predictive value permitting discharge patients from the emergency department.

However, MI is difficult to define in perioperative setting, because patients often do not have the classical symptoms or electrocardiographic changes of myocardial infarction. So, there is a reasonable concern about false-positive results using ultrasensitive assays and possible unnecessary exams or treatment interventions. We demonstrated that, as in acute coronary syndrome[19], perioperative change in cTnI US levels >30% is an important finding to improve prognostic information. Our data reinforce the growing evidence based literature supporting the use of more analytically sensitive cTnI assays for improved accuracy for detecting patients at cardiac events risk and also provide preliminary information on the value of a rising pattern in serial cTnI US concentrations over time as an indicator of acute myocardial injury.

Excluding patients who had MI, heart failure, renal insufficiency on dialysis, intraoperative major bleeding, pre- and postoperative NT-proBNP were predictors of postoperative troponin elevation. It is known that clinical conditions other than ischemic heart disease, can result in increased troponin levels[31]. Microinjury to the myocardium is a frequently proposed mechanism for elevation of troponins in the absence of clinical, electrocardiographic or echocardiographic abnormalities and could explain elevation of this marker in patients with high risk features for minor myocardial cell injury as patients with previous renal and heart failure submitted to the stress of a major surgery. At the same time, major bleeding could explain myocardial ischemia and secondary troponin leak by a mechanism other than plaque rupture and acute coronary thrombosis. Probably, the administration of blood may conceal the importance of hypotension, tachycardia and severe anemia causing myocardial oxygen supply-demand imbalance. Given that cardiac troponins are markers of myocardial injury independent of its mechanism, serial determinations are especially important in these cases in order to diagnose or rule out myocardial infarction. Therefore, and especially at low cTnI US concentrations, the criterion of rise and fall of troponin concentration should be carefully followed before classifying a troponin elevation as a MI[32].

NT-proBNP is a breakdown product of BNP, a hormone secreted by cardiac myocytes, in response to myocardial stretch mediated by both pressure and volume, with hypoxia being more recently identified as a stimulus[33]. A recent meta-analysis

suggests that an increased BNP level can identify inducible myocardial ischemia as detected by standard noninvasive stress tests even in patients without ventricular disfunction[34]. Bolliger et al. demonstrated, in a study of 133 patients, a correlation between a rise in cardiac biomarkers and major cardiac events within one year after major vascular surgery. The prognostic value of preoperative BNP concentrations and postoperative troponin I measurements, when considered together as a single variable, had more than 20 times higher risk for a subsequent major adverse cardiac event, including mortality, compared with patients with a normal preoperative BNP value regardless of postoperative elevation in cTnI[35]. In our population, patients with high preoperative NT-proBNP levels had more chance to have postoperative troponin elevation and in multivariate analysis both were the most important predictors of primary outcome. This finding suggests that high baseline NT-proBNP levels due to activation of the cardiac neurohormonal system may be a predictor of postoperative myocardial ischemia detected by troponin measurement. At the same time, it could be speculated that a postoperative increase of both NT-proBNP and troponin reflect the physiologic consequences of anesthesia, fluid shifts, increased myocardial oxygen demand associated with surgery stress (pain and sympathetic stimulation) and intraoperative blood loss.

Our study has some methodological considerations. The number of patients studied was relatively small. Although we could identify clinical predictors of postoperative cTnI US elevation in patients without MI, our study is not powered enough to answer if in these patients elevation of troponin can be considered a false-positive result. A larger study is necessary to verify the high incidence of increased postoperative cTnI US found here and to define this question. Nevertheless, our sample size was large enough to address our main question, the correlation between cTnI US elevation and cardiac outcome. Data were collected in a single institution and we did not perform in-depth evaluation of our perioperative practice patterns to verify if care was adequate and if some factors, including transoperative medications and volume therapy could interfere in biomarkers measurement. However, the institution in which the study was performed is an academic hospital and physicians overall comply with recommended guidelines, suggesting that our results can be generalized. Furthermore, preoperative cTnI US was not measured in our population, and we cannot exclude that some patients, especially those with renal and heart

failure, did not present with preoperative abnormal cTnI levels. Nevertheless, our aim was not to address the question of when myocardial injury occurred, but to assess the incidence of myocardial injury and its association with short-term cardiovascular outcome. Our results cannot be applied to patients with a lower risk profile or to patients undergoing minor surgery, once we investigated selected patients at intermediate and high risk of coronary artery disease.

Conclusion

Ultrasensitive troponin I assay is highly sensitive and could detect postoperative minor myocardial ischemia. Postoperative TnI elevation identifies patients at high risk of cardiovascular events and predicts total mortality. Heart failure, renal insufficiency on dialysis, intraoperative major bleeding, pre- and postoperative NT-proBNP are related to troponin elevation. Troponin I US measurement should be considered as a component of perioperative risk assessment and this strategy could be evaluated in future studies.

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Figures Legends

Figure 1. Primary event-free survival (A) and overall survival (B) stratified by postoperative cardiac troponin I ultrasensitive (cTnI US) peak levels under (-) or above (+) 0.04 µg/L during the 30-days postoperative follow-up period.

Figure 2. Primary endpoint (%) according to combination of preoperative N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels under (-) or above (+) 917 pg/ml and postoperative cardiac troponin I (cTnI) ultrasensitive peak levels under (-) or above (+) 0.04 µg/L during the 30-days postoperative follow-up period.

Table 1 – Baseline characteristics of all patients stratified by the occurrence of 30-day cardiovascular events.

	All patients (142)	Cardiovascular events		p
		Yes (n=16)	No (n=126)	
Men	69 (48.6)	7 (43.8)	62 (49.2)	0.79
Age, years	65.5 ±9.6	65±1	65.6±9.7	0.80
ASA scoring system				0.47
Class II	52 (36.6)	4 (25)	48 (38.1)	
Class III	85 (59.9)	12 (75)	73 (57.9)	
Class IV	5 (3.5)	0	5 (4)	
Specific Activity Scale*				0.002
Class I	48 (33.8)	4 (25)	44 (34.9)	
Class II	40 (28.2)	2 (12.5)	38 (30.2)	
Class III	32 (22.5)	2 (12.5)	30 (23.8)	
Class IV	13 (9.2)	6 (37.5)	7 (5.5)	
Revised Cardiac Risk Index				0.29
Class II	13 (9.2)	1 (6.3)	12 (9.5)	
Class III	84 (59.2)	8 (50)	76 (60.3)	
Class IV	45 (31.7)	7 (43.8)	38 (30.2)	
Smoking	33 (23.2)	4 (25)	29 (23)	0.89
Hypertension	122 (85.9)	14 (87.5)	108 (85.7)	1.00
Diabetes mellitus	58 (40.8)	7 (43.8)	51 (40.5)	0.79
Atrial fibrillation	13 (9.2)	2 (12.5)	11 (8.7)	0.64
History of congestive heart failure	25 (17.6)	5 (31.3)	20 (15.9)	0.16
Left ventricular ejection fraction (%)**	61.3 ±10.1	56.19 ±12.3	62.17 ±9.5	0.20
History of myocardial infarction	48 (33.8)	6 (37.5)	42 (33.3)	0.78
Previous percutaneous coronary intervention	23 (16.2)	6 (37.5)	17 (13.5)	0.025
Previous coronary artery bypass graft	16 (11.3)	3 (18.8)	13 (10.3)	0.39
History of cerebrovascular disease	47 (33.1)	6 (37.5)	41 (32.5)	0.78
Renal impairment ***	35 (24.6)	5 (31.3)	30 (23.8)	0.54
Peripheral artery disease	30 (21.1)	9 (56.3)	21 (16.7)	0.001
Preoperative laboratory tests				
Hemoglobin, mg/dl	11.86±2.3	11.4±2.7	11.9 ±2.3	0.43
Serum creatinine, mg/dl	1.12 [0.87 -1.74]	1.48 [1.07-2.9]	1.09 [0.86-1.70]	0.23
Creatinine clearance, ml/min	58.40±31.21	59.02± 29.94	53.28±41.15	0.53
NT-proBNP, pg/ml	329.3 [117.4-1730]	1336 [181-10175]	288 [107-1303]	0.038
Preoperative medication				
Aspirin	65 (45.8)	8 (50)	57 (45.2)	0.79
Clopidogrel	11 (7.7)	1 (6.3)	10 (7.9)	0.39
Insulin	31 (21.8)	6 (37.5)	25 (19.8)	0.12
Statins	75 (52.8)	8 (50)	67 (53.2)	1.00
β-Blockers	72 (50.7)	11 (68.8)	61 (48.4)	0.18
ACE inhibitors	85 (59.9)	10 (62.5)	75 (59.5)	1.00

Data are expressed as number (percentage), mean ± SD, or median [interquartile range] as appropriate. p value indicates differences between patients with and without primary cardiovascular events. ASA= American Society of Anesthesiologists; NT-proBNP= N-terminal pro-B-type natriuretic peptide; ACE= angiotensin-converting enzyme.

*n= 133 ** n=114; *** Serum creatinine ≥2, mg/dl or renal replacement therapy

Table 2 − Perioperative characteristics of all patients stratified by the occurrence of 30-day cardiovascular events

	All patients (142)	Cardiovascular events		p
		Yes (n=16)	No (n=126)	
Postoperative laboratory tests				
NT-proBNP, pg/ml	1175 [586.97-2987]	3699 [926-12989]	1091 [588-2759]	0.013
Troponin I postoperative day 1, µg/L	0.018 [0.009 - 0.036]	0.049 [0.020 - 0.425]	0.017 [0.008 - 0.032]	0.001
Troponin I postoperative day 2, µg/L	0.019 [0.009 - 0.053]	0.192 [0.059 - 0.686]	0.018 [0.009 - 0.034]	<0.001
Delta cTnI >30%*	86 (60.5)	15 (93.7)	71 (56)	0.001
Intraoperative events				
Hypotension (Systolic <100 mmHg)	91 (64.1)	9 (56.3)	82 (65.1)	0.58
Bradycardia (Heart rate<50 bpm)	33 (23.2)	4 (25)	29 (23)	1.00
Blood transfusion	18 (12.7)	5 (31.3)	13 (10.3)	0.033
Types of surgery				0.046
Abdominal	71 (50)	4 (25)	67 (53.2)	
Thoracic	10 (7)	0	10 (7.9)	
Vascular	45 (31.7)	9 (56.3)	36 (28.6)	
Prostate	4 (2.8)	0	4 (3.2)	
Hip	12 (8.5)	3 (18.8)	9 (7.1)	

Data are expressed as number (percentage), mean ± SD, or median [interquartile range] as appropriate. p value indicates differences between patients with and without primary cardiovascular events. NT-proBNP= N-terminal pro-B-type natriuretic peptide. cTnI= cardiac troponin I.
*n=137

Table 3 – Predictors of postoperative troponin peak level in patients without myocardial infarction (n= 128).

	Troponin <0.04 (n= 95)	Troponin ≥0.04 (n=33)	p
Men	49 (51.6)	14 (42.4)	0.42
Age, years	65.5 ± 9.2	66.3 ±10.1	0.67
Revised Cardiac Risk Index			0.95
Class II	9 (9.5)	3 (9.1)	
Class III	57 (60)	19 (57.6)	
Class IV	29 (30.5)	11 (33.3)	
Specific Activity Scale*			0.86
Class I	32 (36)	12 (37.5)	
Class II	29 (32.6)	10 (31.3)	
Class III	23 (25.8)	7 (21.9)	
Class IV	5 (5.6)	3 (9.4)	
Vascular surgery	27 (28.4)	11 (33.3)	0.66
Smoking	22 (23.2)	7 (21.2)	0.38
Diabetes mellitus	38 (40)	14 (42.4)	0.84
Atrial Fibrillation	6 (6.3)	5 (15.2)	0.15
Heart failure	12 (12.6)	10 (30.3)	0.031
Hypertension	84 (88.4)	26 (78.8)	0.24
Coronary artery disease	49 (51.6)	17 (51.5)	1.00
Myocardial revascularization	21 (22.1)	8 (24.2)	0.81
Cerebrovascular disease	34 (35.8)	8 (24.2)	0.28
Renal impairment	20 (21.1)	12 (36.4)	0.10
Dialysis	7 (7.4)	7 (21.2)	0.047
Peripheral artery disease	14 (14.7)	8 (24.2)	0.28
Preoperative hemoglobin,mg/dl	12 ±2.2	11.2 ±2.1	0.08
Preoperative NT-proBNP ≥917 pg/ml	20 (21.5)	16 (50)	0.003
Postoperative NT-proBNP ≥ 2962 pg/ml	16 (16.8)	14 (42.4)	0.004
Preoperative medication			
Aspirin	46 (48.4)	12 (36.4)	0.31
ACE inhibitors	53 (55.8)	22 (66.7)	0.31
Beta-blocker	45 (47.4)	18 (54.5)	0.55
Statin	55 (57.9)	13 (39.4)	0.07
Transoperatory events			
Hypotention (Systolic<100 mmHg)	58 (61.1)	24 (72.7)	0.29
Bradycardia (Heart rate<50bpm)	23 (24.2)	7 (21.2)	0.81
Major bleeding	7 (7.4)	7 (21.2)	0.047

Data are expressed as number (percentage) or mean ± SD as appropriate. p value indicates differences between patients without and with troponin elevation. NT-proBNP= N-terminal pro-B-type natriuretic peptide.
*n=121

Table 4 − Events during follow-up stratified by postoperative troponin peak level

	All patients n=142 (%)	**Troponin ≥0.04 n=47 (%)**	**Troponin <0.04 n= 95 (%)**	**OR (95% CI)**	**p**
Primary outcome	16 (11.3)	15 (31.9)	1(1.1)	44.06 (5.60 – 346.9)	<0.001
Cardiac death	2 (1.4)	2 (4.3)	0	10.5 (0.5 – 218.97)*	0.19
Nonfatal cardiac arrest	2 (1.4)	1 (2.1)	1 (1.1)	2.04 (0.12 – 33.40)	1.00
Nonfatal MI	14 (9.9)	14 (29.8)	0	82.67 (4.87 – 1402.27)*	<0.001
Secondary outcome	28 (19.7)	17 (36.2)	11 (11.6)	4.32 (1.82 – 10.28)	0.001
Death	9 (6.3)	6 (12.8)	3 (3.2)	4.48 (1.07 – 18.82)	0.06
Nonfatal stroke	5 (3.5)	0	5 (5.3)	0.17 (0.01 – 3.11)*	0.17
Congestive heart failure	12 (8.5)	9 (19.1)	3 (3.2)	7.26 (1.86 – 28.30)	0.002
Atrial fibrillation	7 (4.9)	6 (12.8)	1 (1.1)	13.75 (1.60 – 117.92)	0.005
Coronary revascularization	1 (0.7)	1 (2.1)	0	6.16 (0.25 – 150.94)*	0.33

OR= odds ratio; CI= confidence interval; MI= myocardial infarction. p value indicates differences between patients with and without troponin elevation. *Adjusted by adding 0.5 in each cell if there is a zero frequency.

Figure 1.

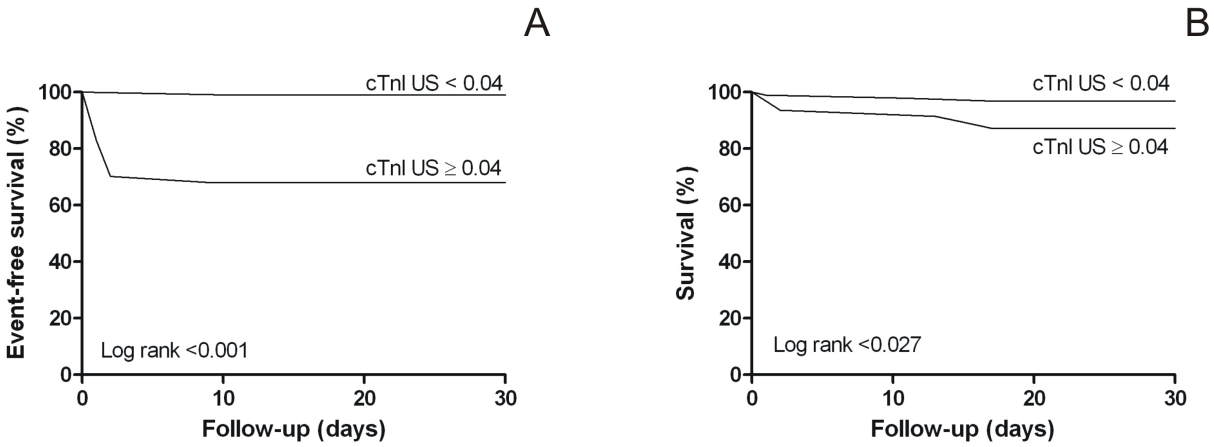
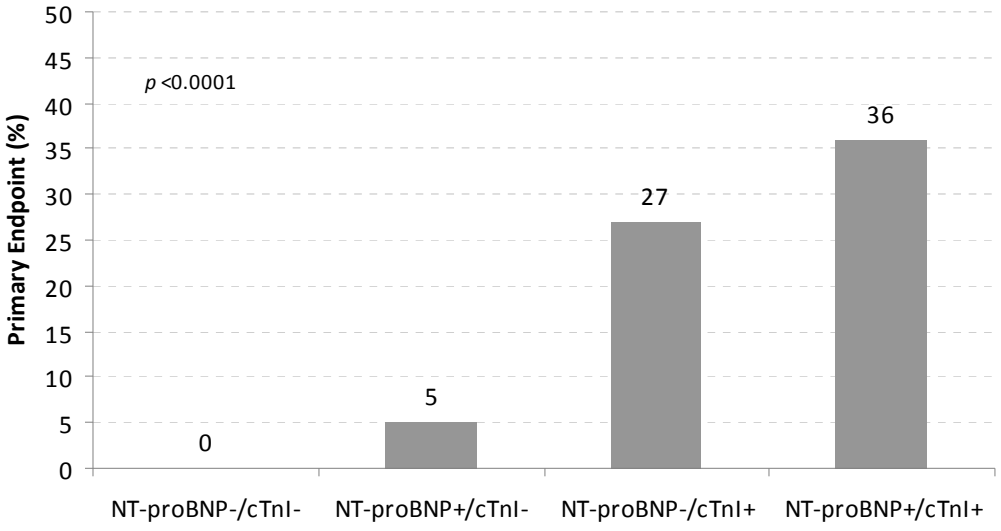

A
B
cTnI US < 0.04
cTnI US ≥ 0.04
Event-free survival (%)
Log rank <0.001
Follow-up (days)
cTnI US < 0.04
cTnI US ≥ 0.04
Survival (%)
Log rank <0.027
Follow-up (days)

Figure 2.


50
45
40
35
30
25
20
15
10
5
0
Primary Endpoint (%)
p <0.0001
0
5
27
36
NT-proBNP-/cTnI-
NT-proBNP+/cTnI-
NT-proBNP-/cTnI+
NT-proBNP+/cTnI+

7 CONCLUSÕES

I A mensuração do NT-proBNP, no período pré-operatório, tem associação independente com eventos cardiovasculares maiores em pacientes submetidos a cirurgias não-cardíacas e agrega valor prognóstico às estratégias utilizadas, atualmente, para estimar o risco cardiovascular perioperatório.

II A determinação do NT-proBNP pós-operatório apresenta associação significativa com eventos adversos cardiovasculares maiores no período perioperatório, porém seu valor prognóstico adicional aos níveis de NT-proBNP pré-operatórios permanece incerto.

III Os ensaios de troponina I ultrassensíveis são acurados para a detecção de isquemia miocárdica pós-operatória. A elevação desse marcardor identifica, de forma independente, pacientes com maior risco de sofrer um evento cardiovascular adverso a curto prazo.

IV Insuficiência cardíaca, insuficiência renal dialítica, sangramento maior intraoperatório e dosagens elevadas de NT-proBNP pré e pós-operatórias estão relacionados com elevação de troponina pós-operatória.

V A dosagem desses biomarcadores deve ser considerada como um dos componentes da estratificação de risco cardiovascular perioperatória de pacientes de moderado a alto risco submetidos à cirurgia não-cardíaca.

8 APÊNDICES

8.1 Apêndice I: Definições do estudo para cirurgias específicas e grupo de cirurgias comparáveis

1 Cirurgia vascular

1. Cirurgias vasculares para reconstrução da aorta torácica e amputação acima do joelho (reparo de aneurisma da aorta torácica, reparo de troncos supra-aórticos, não requerendo *bypass* cardiopulmonar total, reparo de aneurisma da aorta toracoabdominal com ou sem *bypass* átrio-femoral, amputação acima do joelho).
2. Cirurgia vascular de reconstrução aorto-ilíaca (reparo de aneurisma da aorta abdominal aberto, *bypass* aorto-femoral, *bypass* ilíaco-femoral, revascularização da artéria renal, revascularização da artéria celíaca, revascularização da artéria mesentérica superior).
3. Reconstrução vascular periférica sem pinçamento da aorta (*bypass* axilo-femoral, *bypass* femoro-femoral, *bypass* fêmoro-infragenicular, profundoplastia ou outros tipos de angioplastia das artérias infrainguinais).
4. Cirurgia cerebrovascular extracraniana (endarterectomia da carótida, *bypass* carotídeo-subclávia).
5. Reparo endovascular de aneurisma da aorta abdominal.

2. Cirurgia geral

1. Ressecção visceral complexa (cirurgia envolvendo o fígado, esôfago, pâncreas ou múltiplos órgãos).
2. Colectomia parcial ou total ou cirurgia do estômago.
3. Outra cirurgia intra-abdominal (vesícula biliar, apêndice, suprarrenais, baço, dissecção de linfonodos).

3 Cirurgia torácica

1. Pneumonectomia
2. Lobectomia
3. Outra cirurgia torácica (ressecção segmentar do pulmão, ressecção de tumor mediastinal, ressecção de grande porte da parede torácica).

4 Cirurgia ortopédica de grande porte

1. Cirurgia de grande porte do quadril ou da pelve (hemiartroplastia ou artroplastia total do quadril, fixação interna do quadril, artroplastia pélvica).
2. Fixação interna do fêmur.

5 Cirurgia urológica ou ginecológica de grande porte

1. Ressecção visceral (nefrectomia, ureterectomia, ressecção da bexiga, ressecção de tumor retroperitoneal, exenteração)
2. Cirurgia citorredutora
3. Histerectomia radical
4. Prostactectomia radical

6. Cirurgias de baixo risco

1. Cirurgias de baixo risco (paratireoide, tireoide, mama, hérnia, procedimento anorretal local, ooforectomia, salpingectomia, ablação do endométrio, cirurgia dos nervos periféricos, oftalmológica, ouvido/nariz/garganta, cirurgia do disco vertebral, fusão espinhal, cirurgia da mão, cirurgia estética, cirurgia de acesso arteriovenoso para diálise, outras cirurgias).

8.2 Apêndice II: Ficha de coleta de dados

Nº

Identificação

Nome:_____Prontuário: _____

Data de nascimento: __/___/___ Sexo: M ( ) F ( ) Peso:____kg Altura: ____

Etnia: Branco ( ) Negro ( ) Pardo ( ) Outro( ) _____

Endereço 1:

_____

Endereço 2:

_____

Telefone: 1-_____ 2-_____ 3-_____ 4- _____

Dados internação

Data da internação: ___/___/_____ Data da cirurgia: ____/____/_____Hora:____:_____

Cirurgia: _____

( ) Intra-abdominal ( ) Intratorácica ( ) Vascular ( ) Próstata ( ) Quadril

ASA: I ( ) II ( ) III ( ) IV ( ) Não avaliado ( )

( ) Anestesia: Peridural ( ) Raquidiana ( ) Geral ( )

SAS: I ( ) II ( ) III ( ) IV ( ) Não avaliado ( )

História de tabagismo ( ) Nunca fumou ( ) Tabagista ativo − últimas 8 semanas
( ) Ex-tabagista

Antecedentes médicos

- Fibrilação atrial
- ICC FE_____%
- Hipertensão
- **Angina** } Se ≤ 6 meses, data do evento mais recente __/___/_____
- **IAM** }
- Cateterismo Mês/ano: __/_____
- Cirurgia de RM Mês/ano: __/_____
- Angioplastia Mês/ano: __/_____
  - ATC balão
  - Stent
  - Stent farmacológico
- Parada cardíaca Mês/ano: __/_____
- TVP/TEP Mês/ano: __/_____
- Úlcera péptica nos últimos 6 meses (esofágica, gástrica ou duodenal)
- Neoplasia_____ ( ) ativa
- **AVC/AIT** Mês/ano
- **IRC** – creatinina____ - DCE_____
- Doença arterial periférica
- Doença pulmonar obstrutiva crônica
- Apneia obstrutiva do sono
- Estenose aórtica
- **Diabetes**
  Ano do diagnóstico
  Uso de insulina _____ sim ____ não

Nº

Exames pré-operatórios

Hemoglobina _____ g/dL __/__/____

NT-proBNP _____ __/__/____

Creatinina _____ mg/dL __/__/____

Glicemia _____ mg/dL __/__/____

Medicações pré-operatórias (utilizadas nos últimos 7 dias)

- AAS
- Insulina
- Hipoglicemiante oral
- Nitrato longa ação
- Anticoagulante oral
- IECA/ ARA II
- Betabloqueador
- Redutores de colesterol (não estatinas)
- Estatina
- Clopidogrel/ticlopidina
- AINE
- Alfa 2 agonista
- BCC controlador de FC
- BCC diidropiridínico
- Heparina profilática
- Anticoagulação (HNF, HBPM)

Medicações suspensas para cirurgia:

Nome	Último dia de uso
_____	___/___/_____
_____	___/___/_____
_____	___/___/_____
_____	___/___/_____

Medicações iniciadas para cirurgia:

Nome	Último dia de uso
_____	___/___/_____
_____	___/___/_____
_____	___/___/_____
_____	___/___/_____

Complicações intraoperatórias:

( ) Hipotensão (PAS <100 mmHg)
( ) Bradicardia (FC <55 bpm)
( ) Bradipneia (FR<10 mrpm)
( ) Hipoxemia (sat <90%)
( ) Sgto com necessidade de transfusão

Complicações pós-operatórias:

( ) Hipotensão (PAS <100 mmHg)
( ) Bradicardia (FC <55 bpm)
( ) Bradipneia (FR<10 mrpm)
( ) Hipoxemia (sat <90%)
( ) Sgto com necessidade de transfusão

Exames pós-operatórios:

NT-proBNP 48 horas _____ ___/___/_____ Hora:___:___

Troponina 24 horas _____ mg/dL ___/___/_____ Hora:___:___

Troponina 48 horas _____ mg/dL ___/___/_____ Hora:___:___

Nº

Complicações pós-operatórias:

- Óbito Data: ___/___/___ Motivo: CID_____
- SCA ( ) IAM com supra ( ) IAM sem supra (AI)
- Parada não fatal
- AVC/AIT
- TVP/TEP
- Sangramento
- IRA – com necessidade HD
- Infecções ( ) sepsia ( ) BCP
- ACFA clinicamente importante
- ICC FE_____%
- CAT
- Revascularização ( ) ACTP ( ) CRM
- Internação CTI: Sim ( ) nº dias _____
  Não ( )

Data da alta: ___/___/_____

Nº

Seguimento 30 dias

Data do seguimento de 30 dias: ____/____/_____

Seguimento completo? ( ) Sim ( ) Não Motivo: _____

Após a cirurgia, o paciente realizou exame de sangue? ( )Não ( )Sim Hb__ g/dL __/___/___

Cr ____ mg/dL __/___/____

Após a cirurgia, o paciente recebeu transfusão de sangue? ( ) Não ( ) Sim _____ unidades

Paciente foi reinternado após a alta? ( ) Não ( ) Sim Data: ___/____/___

Internação por motivo cardiovascular? ( ) Não ( ) Sim

Medicações após a alta

- AAS
- Insulina
- Hipoglicemiante oral
- Nitrato longa ação
- Anticoagulante oral
- IECA/ ARA II
- Betabloqueador
- Redutores de colesterol (não estatinas)
- Estatina
- Clopidogrel/ ticlopidina
- AINE
- Alfa 2 agonista
- BCC controlador de FC
- BCC diidropiridínico
- Anticoagulação (HNF, HBPM)

Medicações em uso no 30º dia pós-operatório

- As acima
- Drogas suspensas: _____
- Drogas iniciadas _____

Eventos clínicos (Não incluir os eventos que ocorreram enquanto o paciente estava internado)

1. Óbito ( ) Não ( ) Sim Data: ___/___/____ Motivo: CID_____
2. SCA ( ) IAM com supra ( ) IAM sem supra ( ) AI
3. Parada cardíaca não fatal ( ) Não ( ) Sim
4. AVC/AIT ( ) Não ( )Sim
5. TVP / TEP ( ) Não ( )Sim
6. Sangramento ( ) Não ( )Sim
7. Diálise ( ) Não ( )Sim
8. Sepse/infecção ( ) Não ( )Sim
9. Pneumonia ( ) Não ( )Sim
10. Nova fibrilação atrial ( ) Não ( )Sim
11. Insuficiência cardíaca ( ) Não ( )Sim
12. Cateterismo ( ) Não ( )Sim
13. Angioplastia ( ) Não ( )Sim
14. Cirurgia de RM ( ) Não ( )Sim
15. Amputação ( ) Não ( )Sim

Observações:

Ficha de Eventos

Nº

(Pacientes com TnI>0,04 ou com evento cardiovascular (SCA/ICC) pós-operatório)

Nome:_____ Prontuário: _____

Paciente apresentou sintomas anginosos ( )sim ( ) não ___/___/___ Hora:___:_____

Paciente apresentou dispnéia ( )sim ( ) não ___/___/_____ Hora:___:___

Paciente apresentou edema agudo de pulmão ( )sim ( ) não ___/___/___ Hora:___:_____

ECG 1: ___/___/_____ Hora:___:___

Tipo de alteração
( ) supra ST ( ) infraST ( ) inversão onda T ( ) alterações inespecíficas repolarização
( ) normal ( ) outro
_____

Local principal alteração
( ) anterior ( ) lateral ( ) inferior ( ) outro
_____
ECG 2: ___/___/_____ Hora:___:___

Tipo de alteração
( ) supra ST ( ) infraST ( ) inversão onda T ( ) alterações inespecíficas
( ) normal ( ) outro _____

Local principal alteração
( ) anterior ( ) lateral ( ) inferior ( ) outro _____
ECG 3: ___/___/_____ Hora:___:___

Tipo de alteração
( ) supra ST ( ) infraST ( ) inversão onda T ( ) alterações inespecíficas
( ) normal ( ) outro _____

Local principal alteração
( ) anterior ( ) lateral ( ) inferior ( ) outro _____

Marcadores
Troponina 1_____ mg/dL ___/___/_____ Hora:___:___
Troponina 2_____ mg/dL ___/___/_____ Hora:___:___
Troponina 3_____ mg/dL ___/___/_____ Hora:___:___
Troponina 4_____ mg/dL ___/___/_____ Hora:___:___

Ecocardiografia ___/___/_____ Hora:___:___
FE_____%

Déficit segmentar novo ( ) Sim ( ) Não

Local principal alteração
( ) anterior ( ) lateral ( ) inferior ( ) outro _____

Nº

Cintilografia miocárdica ___/___/_____ Hora:___:___

FE_____% repouso FE_____% esforço

Déficit segmentar novo ( ) Sim_____% ( ) Não ( ) reversível ( ) irreversível

Local principal alteração
( ) anterior ( ) lateral ( ) inferior ( ) outro _____

CAT ___/___/_____ Hora:___:___

FE_____%

Estenose >50% ( ) sim ( ) não

Vasos acometidos ( ) DA ( ) CX ( ) CD ( ) MG ( ) DP ( ) TCE ( ) Outro_____

Resultado:_____
_____
_____

Revascularização ( ) sim ( ) não ___/___/_____ Hora:___:___
( )ACTP balão ( ) ACTP *stent* ( ) ACTP *stent* farmacológico

Vasos revascularizados ( ) DA ( ) CX ( ) CD ( ) MG ( ) DP ( ) Outro_____

( ) CRM

Vasos revascularizados ( ) DA ( ) CX ( ) CD ( ) MG ( ) DP ( ) Outro_____

Ficha de ecocardiograma

Nº

Nome:_____ Prontuário: _____

Data Ecocardio: ___/___/___ Hora: ___:___

FE: _____ %

AE: _____

VED: _____

VES: _____

Septo: _____

Parede posterior: _____

Padrão diastólico:

( ) Normal
( ) Déficit
( ) Pseudonormal
( ) Restritivo

8.3 Apêndice III: TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Você está sendo convidado a participar de um estudo. O objetivo desse estudo é determinar o número de complicações vasculares que ocorrem durante a cirurgia em pacientes que realizam cirurgia não-cardíaca e determinar qual o melhor meio de medir o risco de sofrer essas complicações. Sabendo quantas complicações ocorrem e qual o risco de sofrer essas complicações, os médicos vão poder dizer qual é o risco de cada paciente sofrer uma complicação vascular e poderão ajudar os pacientes e seus familiares a decidirem se a cirurgia é adequada.

Esse estudo também irá determinar a utilidade de dois simples exames de sangue: se um deles pode ajudar os médicos detectarem infarto do coração que não seriam percebidos durante e após a cirurgia, e se o outro exame pode prever complicações vasculares como infarto do coração, parada cardíaca, derrame e mesmo morte por essas complicações durante 30 dias após a cirurgia.

A sua participação é voluntária. Se você aceitar participar desse estudo, serão coletadas informações pessoais, contato (telefone, endereço) e antecedentes (por exemplo: se você já teve infarto do coração). Será colhida uma amostra de sangue para realizar um exame chamado troponina, nas primeiras 24 horas e entre 24 e 48 horas após a cirurgia. Também será colhida, uma amostra de sangue para realizar um exame chamado NT-proBNP antes da cirurgia. Essas amostras de sangue seriam colhidas, durante a internação, mesmo se você não estivesse participando do estudo, pois elas servem para realização de outros exames de rotina após a cirurgia. Em alguns casos, será realizado um eletrocardiograma do coração que também é importante para o seu acompanhamento. É um exame rápido, confortável e não oferece risco algum, além de mostrar ao médico que estiver cuidando de você qual o ritmo de batimento do seu coração.

Após 30 dias, a equipe do estudo entrará em contato com você, por telefone, para saber como está sua saúde. Não há riscos e desconfortos adicionais se você aceitar participar desse estudo. Somente terá que fornecer informações aos investigadores e serão colhidas amostras de sangue.

Ao participar do estudo você estará contribuindo, para que muitos pacientes como você sejam beneficiados, pois saberão qual é, exatamente, o risco de sofrer uma complicação durante a cirurgia e poderão decidir se ela é apropriada.

Não existe custo algum para você ou sua família ou seu convênio de saúde. Você pode livremente escolher se quer ou não participar do estudo. Se não quiser, seu tratamento, nesta instituição, não mudará em nada e todos os cuidados, durante e após a cirurgia, serão oferecidos a você, da mesma maneira como se estivesse participando do estudo. Seus dados só serão usados para os propósitos do estudo. Os resultados do estudo serão divulgados, para fins acadêmicos e científicos, sem a identificação de nenhum paciente participante. Os resultados dos seus exames de sangue serão divulgados somente para você e seu médico assistente, para que ele possa realizar uma avaliação mais detalhada que possibilite a tomada de decisão mais adequada para o seu tratamento. Se decidir participar, voluntariamente, do estudo, você poderá retirar seu consentimento, em qualquer momento, sem que isso traga nenhum prejuízo para você. Seu tratamento, nessa instituição, continuará sendo exatamente o mesmo.

Este estudo foi aprovado pelo Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre. Os investigadores e a equipe de coordenação do estudo estão à disposição para prestar quaisquer esclarecimentos antes, durante e após o estudo nos seguintes telefones: Dra Flávia Kessler Borges − 33598152, celular 98472482 ou Dra Carisi Anne Polanczyk − 3359-8659.

Li e compreendi os objetivos do estudo, todos os procedimentos que serão realizados, estou ciente dos possíveis riscos e benefícios e, em caso de qualquer dúvida, poderei entrar em contato com a equipe do estudo.

_____
Nome do participante

_____
Nome do representante legal (se aplicável)

_____ ____/____/_____
Assinatura do participante ou representante legal Data

_____
Nome do Investigador / Coordenador do estudo

_____ ____/____/_____
Assinatura do investigador / Coordenador do estudo Data