心臓外科手術の術後合併症に関する外部専門家による評価結果について

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自治医科大学附属さいたま医療センター

本年２月に当センターにおける心臓手術の合併症について週刊誌等で報道され、患者の皆様へより一層安全・安心な医療を提供するため、本件に関するこれまでの当センターの分析と取組みについて、複数の外部専門家に評価いただくことといたしておりました。

この度、その検証評価結果がまとまりましたので、お知らせいたします。

当センターといたしましては、この度の検証評価結果を今後の医療安全対策の更なる推進のために活用してまいります。

自治医科大学附属さいたま医療センター

心臓血管外科周術期診療検証評価外部委員会

報告書

2019年5月20日

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1．はじめに

2018年5月から8月末にかけて自治医科大学附属さいたま医療センター（以下，当センター）において，心臓弁膜症手術の特異的な合併症とされる非閉塞性腸管虚血（NOMI）が疑われる事例が高い頻度で発生した。7月中旬には近接して2例のNOMIの発症を見たことから，心臓血管外科周術期死亡・合併症検討会（以下，M&Mカンファレンス）を7月30日に開催し，院内の医師および多職種の専門職が参加して要因を分析して改善策を実施していた。ところが，8月6日の手術後にNOMIが発生したため，センター長は8月8日から待機の心臓手術の中止を指示した。そして，8月10日には外部（関連ならびに非関連施設）の心臓血管外科医（以下，心臓外科医），麻酔科医，臨床工学技士（以下，体外循環技師）が参加して第2回M&Mカンファレンスを開催，7月と8月の3例を対象に詳細に要因を分析，対応策が検討された。その検討結果を元に，8月13日には心臓外科医および集中治療医が改善策を策定しセンター長に提出されたので，8月20日から心臓手術の再開を決定した。しかし，8月23日に行われた手術（手術再開後3例目）において，術中心筋梗塞から低心拍出量状態に陥り，それに起因すると考えられるNOMIが発生したため，センター長は再び手術中止を決定するに至った。8月31日には関連施設から7名の専門家（心臓血管外科および麻酔科）が参加した第3回M&Mカンファレンスを開催した。NOMIの発生要因は解明できなかったが，心臓血管外科スタッフ内のリスク共有やコミュニケーション，ガバナンスなどの問題点が指摘された。そこで，9月6日には当センターの医療安全管理室が主導する形で，心臓血管外科周術期診療改善検討委員会を設置し，9月末までに同検討委員会を3回開催，詳細な各種の改善策が立案された。さらに，10月には外部専門家2名による改善策の評価を受けて修正し，10月18日開催の第4回同検討委員会で最終案が承認されてセンター長に提出された。その改善策を実施し，進捗状況を確認した後に11月5日から心臓手術の再開を決定した。その後は，段階的に手術実施症例数を拡大することとしていた。

こうした中，2019年2月末に上記の一連の経過の極一端が週刊誌に掲載され，誌上で「手術および当センターの対応に問題があったのではないか」と指摘された。そこで，この記事に関連して3月1日には，これまでの当センターの取り組みと今後の方針についての説明文をホームページに公表した。なお，この説明の中には第三者による検証評価外部委員会を設置し，当センターの分析内容とその取り組みを検証することも表明していた。この心臓血管外科周術期診療検証評価外部委員会（以下，本委員会）の外部委

員の選任が３月下旬には整い，４月４日に第１回の本委員会開催となった。

本委員会の構成は別紙 (p.15) の通りである。

2.　心臓血管外科周術期診療検証評価外部委員会の役割

1)　本委員会の役割

上記のように心臓手術後に NOMI が疑われた症例について，当センター内における M&M カンファレンスおよび心臓血管外科周術期診療改善検討委員会の要因分析と講じられた改善策，さらに約半年間の当センターの組織対応・取り組みを本委員会は第三者として改めて検証・評価することにある。

2)　対象と方法

NOMI が疑われた６症例（NOMI と判定されたのは４例）が対象である。各症例の術後合併症が発生した際には，それぞれ迅速に症例検討会や M&M カンファレンスが開催されており，それらの記録と診療記録を照合した。さらに要因分析と対応策を検討し，改めて本委員会として精査すべきか，その要否も判断した。なお，体外循環（人工心肺）管理については，対象の診療記録や委員会記録以外の追加資料（手順書やマニュアル類）を検討した。

さらに，心臓血管外科周術期診療改善検討委員会が策定した改善策の内容についても，本委員会の評価の対象とした。すなわち，改善策の妥当性を検討し，また，当センターの組織としての対応についても検討した。

なお，本委員会の開催は３委員の日程調整が困難であったことから，各委員が専門領域の視点から検討した結果をメールで起案し，他の２名がそれに追記・修正案を記入することを繰り返して，３名の委員全員で合意決定した。

3.　心臓血管外科周術期診療の問題点と改善対応策の検証と評価

基本的には，当センターで行われた M&M カンファレンスおよび心臓血管外科周術期診療改善検討委員会が行った事例分析から，明らかになった各種のシステム要因とそれに基づく提言に問題はないと本委員会は判断した。また，本委員会が改めて各症例を精査すべき点はないことを確認した。そこで，外部委員の専門的立場から全例を包括的に評価した。

1)　麻酔科医の観点から

当センターの管理で注目された点は，手術・体外循環中，術後を通して輸液を可能な限り少なくする（ドライサイドとする）方針を徹底していたことである。すなわち，手術後にできるだけ過剰な水分バランスにならないようにとの輸液や輸血の方針である。これが術後の早い回復につながるとの考え方であった。この考えは間違いではないが，心臓外科手術においては必要十分な輸液を補う（ウエットサイドとする）管理を行ない，例えば，体外循環開始までに晶質液 1000ml，膠質液 500ml 程度を輸液するのが一般的である。標準的な体外循環回路のプライミングは，膠質液と晶質液にマニトールを混ぜた 1000ml 程度を充填していると思われる。高度の大動脈弁狭窄症などでは，循環血液量が少ない症例もあり，体外循環回路のプライミングには 5%アルブミン製剤 500ml が充填されることもよくある。なお，小切開手術（MICS）の症例では，右内頸静脈と大腿静脈２本脱血を要することから，1500ml 程度，脳分離循環を要する大動脈症例では 2000ml 程度で充填されることが多い。

当センターでは，体外循環による血液希釈を減じて輸血をできるだけ回避しようと，最低限のプライミング量（700ml）としていた。特に晶質液を排除して，ボルベン 440ml とマニトール 255ml，ヘパリン 5ml の組成で体外循環をプライミングしていたのは特異的と思われる。[下記の 2）でも詳述した]

輸血に関しては，体外循環技師，麻酔科医，心臓外科医で相談して要否を判断するのが一般的であるが，基本的に術後にヘモグロビン 8g/dL 以下になりそうな症例，また，重症心不全や高齢者では術中に 8g/dL を下回る時点で輸血する方針が取られることが多い。本委員会が対象とした高度大動脈弁狭窄症やリウマチ性弁疾患では，特に留意すべき点として，循環血液量が少ないことや心拍出量が低いことなどを考慮した輸血や輸液の管理方針が，チームで充分に認識されていなかったことがうかがわれる。特に体外循環技師への伝達が十分でなかった可能性があると思われる。

もう一点，体外循環の離脱時の問題が散見された。麻酔科医による経食道心エコー（TEE）による評価・診断は心拍再開直後より施行しているようである。弁置換では直後に，人工弁周囲逆流や縫合糸の絡み（jamming）による重度逆流などがないか迅速に診断して，体外循環離脱前に再修復の要否を判断することが必要である。特に新しい弁が導入された直後や新しい術者が施行した症例では詳細な観察が重要となる。

中枢温と末梢温の温度差は 1～2℃程度まで復温するウオームサイドでの管理が推奨されている。この復温中には，部分体外循環で自己心臓の拍動を保ち，十分に心機

脳を回復させることができる。また，心臓内に残存している空気を排除することは極めて重要で，この部分体外循環の間に残存空気がなくなったことをTEEで確認できる。さらに，十分に体温が暖まった状態で体外循環を離脱すれば，末梢血管は拡張して後負荷も軽減される。しかし，体外循環時間を短縮する意図が強いためか，部分体外循環が短い状態で離脱している症例が見受けられた。

麻酔科医はTEEで心機能を評価しており，体外循環離脱後の管理としては，ノルアドレナリンなどで末梢血管を締めることは容易ではあるが，収縮した末梢血管を拡張させることは困難なことが多い。

また，体外循環離脱後の体血圧が低めに管理されていた点が挙げられる。体外循環離脱後に大動脈に挿入した送血管を抜去する際には，収縮期血圧90mmHg前後に維持することは当然，必要であるが，もともと高血圧の症例ではその後は，ある程度の体血圧を維持しなければならない。こうした体外循環および離脱後の管理方針は，術前検討会でチームとして情報共有し管理する必要がある。

プロポフォールによる麻酔維持が末梢循環の血流を減少させている可能性が挙げられているが，プロポフォール5〜6mg/kg/hrで維持した場合にはNOMIの発症はほとんどなく，問題はないと考えられる。なお，レミフェンタニルを0.5〜0.6μg/kg/minの持続投与を併用すれば，末梢血管の拡張状態は維持できる。

集中治療の項目で後述するが，周術期管理については，肺高血圧や低心拍出量症例での肺動脈カテーテルを適応する基準を明確に決定されていなかったことも，不十分な指標での管理となった要因と言える。肺動脈カテーテルから得られる情報を元に，麻酔科医の観点からも術中に適切な膠質液の補充や輸血を行い，過剰な利尿剤投与は行わない管理が標準と考えられる。さらに，IABPやPCPS，Impellaなどの機械的補助循環についても，もう少し積極的に導入を検討することも勧めたい。

2)　心臓外科医の観点から

当センターの心臓血管外科では，年間1000例近い心臓血管外科手術を実施しており，長年の実績の蓄積から各種のマニュアルが策定されている。例えば，体外循環操作マニュアルについては20年にわたり継続的に改訂されており，その内容はホームページにも公表されている。ちなみに，2008年4月の第9版では，体外循環回路の充填（プライミング）はサリンヘス500ml，マニトール300ml，乳酸リンゲル液（晶質液）200mlの計1000mlで，晶質液も含まれていた。

(http://www.jichi.ac.jp/ocvs/me9.pdf)

2017年の第17版では，体外循環回路の充填は，サリンヘス440ml，マニトール260mlの700mlと減量され，晶質液は排除された。

(http://www.jichi.ac.jp/ocvs/wp/wp-content/themes/jichiidai/img/manual.pdf)

このように体外循環による水分負荷を避けることに集中したあまり，体外循環回路の充填には標準的に用いられる晶質液（乳酸リンゲル液など）は全く含まれず，充填液の電解質組成もかなり偏った内容となっていた。

ボルベンやマニトールは通常の医療では，点滴で1時間程度をかけて静脈内に注入するが，体外循環の送血ポンプでは1分足らずで700mlが大動脈から注入されることになる。循環する間に血液と混ざって薄まるとはいえ，何らかの問題は生じるであろう。それならば，体外循環の開始まで，あるいは体外循環中に回路に点滴する方が適切であり，体外循環開始時には，血漿に近い電解質組成や浸透圧の晶質液中心の充填が推奨される。ちなみに，本委員会のこの点に関連した検討と時を同じくして，2019年4月になって，体外循環回路の充填液の組成は，ビカーボン440ml（晶質液）とマニトール260mlの700mlに変更され，マニュアルは第19版になっていた。（現在のところ，非公開のようである）

また，回路や半閉鎖リザーバなどの導入により，総量700mlの充填で体外循環操作は可能であろうが，安全性の観点から回路なども見直して，1000ml程度にすることも検討の余地があろう。

ボルベンの充填によって膠質浸透圧を保ち，無輸血手術の達成を目指していたが，赤血球のヘモグロビンが少なければ酸素含有量が少ない状態である。つまり，酸素含有量の低い血液が，十分に循環しない状態となれば，組織への酸素供給が著しく不足し，NOMIの発生に関与した可能性が高い。3例は無輸血で手術を終了したが，1）で記載したように，症例に応じた適切な基準を設定し輸血を行う方針へ転換すべきであると考える。すなわち，血圧維持にカテコラミンを使用すれば，小動脈の収縮をきたし，血圧はあっても循環する血液量はむしろ減少する。さらに，頻脈になれば拡張期が短くなり，大動脈弁狭窄の左心室では拡張期の充満が悪く，拍出量は著しく減少する点にも留意しておかねばならない。体外循環中にマニトールで利尿を図っている状況では，循環血液量は少なくなり，心拍出量が低下した一因と思われる。

すなわち，体外循環からの離脱や周術期管理の指標が不足していたと言える。肺動脈カテーテルから得られる肺動脈楔入圧，心拍出量，混合静脈血酸素飽和度などの指

標のない状態で，これまで管理できたのは，長年の心臓外科医の経験の蓄積によるものであろう。しかし，心臓外科医の世代交代でその蓄積が十分に継承されなかったのかもしれない。当センターでは心機能に問題のない胸部大動脈手術，それも緊急が多いことから，弁膜症手術の心機能上の特徴的な問題点への対応が不十分となっていた可能性もあろう。

なお，本委員会の対象となったNOMIに関する治療戦略も，『NOMI管理バンドル』として，すでに2014年に策定しており，これも公表されていた。
(http://www.jseptic.com/journal/mm150608_03.pdf)

今回，2018年にNOMIが数例に発生したが，このNOMI管理バンドルが奏功したものと思われる。早期にNOMIの発症を疑い確定診断に向けて検査が実施され，治療も行われていた。腸管切除を要した症例もあるが，死亡例は1例であった。しかしながら，本委員会の対象となった6症例は全て心臓弁膜症に対する手術で，中でも4例は大動脈弁狭窄症であったが，NOMI管理バンドルに記載されていた予防策の持続的心拍出量モニター（CCO）付き肺動脈カテーテルは使用されず，確実に実行されていなかった事実も判明した。前述したように，NOMIは大動脈弁狭窄の手術後に発症しやすいと言われているが，大動脈弁狭窄では左心室肥大が高度で左心室容積は小さく，左心室の拡張機能にも問題があるため，前負荷を高く保って左心室に流入する血液量を維持しなければ，術後に心拍出量は不足するとされている。この前負荷の指標となるのは，左心房圧と左心室拡張終期圧であるが，周術期管理では肺動脈カテーテルを留置してあれば，肺動脈楔入圧あるいは肺動脈拡張期圧の測定で推定できる。特に，高度の大動脈弁狭窄に対する人工弁置換術後の管理では，これらの数値を15~18mmHgに維持することが推奨されている。さらに，持続的に心拍出量を測定できるので極めて有用であるのに，どのような経緯で肺動脈カテーテルを採用しないことになっていたのか，疑問が残る。

手術の質の指標として，手術時間や体外循環時間を短縮することを目指すのは，正しいことではあるが，体外循環離脱後の安定した心機能の維持には，部分体外循環（心停止した状態から心臓が拍動して機能回復に要する補助）の時間をある程度維持して，十分に復温してから離脱することが望ましい。一部の症例ではこの部分体外循環が不十分と思われた。すなわち，体外循環の離脱を判断する指標が不足しており，体外循環技師と心臓外科医，麻酔科医との情報共有が不十分であった可能性がある。手術記録や体外循環記録にある血圧と中心静脈圧（CVP），体温，体外循環中の静脈

血の酸素飽和度では不十分で，離脱後も肺動脈圧，肺動脈楔入圧，心拍出量，混合静脈血酸素飽和度などの指標が必要である。これは術後 1〜2 日の ICU における管理においても極めて有用な指標である。おそらく，肺動脈カテーテルの挿入に時間を要するため，手術時間の短縮のために省いたのかもしれないが，弁膜症に代表される心機能に問題がある手術には，上記の重要な情報を把握しておくべきであり，NOMI 管理バンドルに記載された適応基準を遵守して肺動脈カテーテルを留置すべきである。

3)　集中治療医の観点から

近年，術中水分管理の考え方が変化しており，主として腹部外科手術を対象に ERAS (Enhanced Recovery After Surgery)，また胸部心臓血管外科領域では Fast track ということで，輸液量を制限しつつ人工呼吸器からの離脱を速やかに行うという診療プロセスが台頭してきている。この場合，灌流圧の維持のために昇圧剤を使用する頻度が増加するという現実がある。ICU での昇圧剤，強心剤の使用について，当センターにおいて標準プロトコールがあるのかは不明であるが（恐らく血行動態に基づいて選択していると思われる），灌流圧の維持のための昇圧剤の使用と輸液量の制限はいずれも NOMI 発生要因でもあり，改善案に示された方針は妥当と考えられる。なお，NOMI については，J Cardiothorac Vasc Anesth 2019, 33:1290-97 の報告のように，集中治療医は臓器灌流不全，乳酸アシドーシス，腸管拡張の所見，腹痛や蠕動の低下等の所見がある場合には常に NOMI を念頭に置いて診断・治療を行う必要がある。すでに，NOMI 管理バンドルに示してあり，有益な情報と考えるが，この情報にタイムリーにアクセスできるように電子カルテ上の共通ホルダー等に保存しておき，医療スタッフにもアクセス方法を明示しておく必要がある。

ICU 専門医が従事しているので，以下のようなケアプロセスはないと思うが，renal dose と称するドパミンの不適切な使用もリスクになり得ることに留意しておかねばならない。バソプレシンについての記載があるが，通常の心臓手術後のケアではほとんど使用しないので，refractory septic shock（敗血症）に対して使用する等の但し書きが必要であろう。

術後患者の血行動態を良好に管理するためにターゲットとなる血行動態指標をどのように設定するかについて，これまでもいくつかのランダム化比較試験で検証が試みられてきたが，画一的な数値目標は存在せず，特に ICU に収容となるような重症患者ではその設定は困難であり，今後の重要な検討課題である。そのため各々の患者に対

して心臓外科医（主治医だけでなく），ICU 専門医等のチームで方針決定することを徹底する必要があると考える。（Curr Opin Crit Care 2018, 24:554–559）

上記の 2）に記載したように，NOMI のハイリスク患者と考えられた場合には，術中・術後を含め血行動態のモニタリング，ケアプラン策定のためには，肺動脈カテーテルの使用は必須であり，遵守すべきである。院内の報告書には今後の改善策として，ICU 入室後は血管内血液量（Intravascular volume）を維持するために，「術直後は補液を 200ml/hr 程度から開始する」としているが，術後管理は術中管理から連続して行われるため一概には言えないが，かなりの容量負荷（volume load）になると思われる。通常は，ICU 入室時はもう少し少量の設定を基準として開始し，ICU での肺動脈カテーテルの血行動態の指標，乳酸値，血液ガス所見，体温，末梢体温等を参考に調節するのが一般的と考えられる。改善策適用後の ICU 管理の実態がどのような状況であるかは不明であるが，短時間で輸液の投与速度を減少させているのかもしれない。繰り返しになるが，肺動脈カテーテルを留置して，術中から継続した管理指標を元に対応することが重要なのである。ただし，この循環血液量の管理指標の gold standard はないのが現状である。そこで，肺動脈カテーテルから得られる各種パラメータ以外に，心エコー検査の使用が近年盛んになっている。この心エコー検査の要否について改善策には記載がなく，不足している。もちろん，心臓エコー検査だけでは結論は出せないが，肺動脈カテーテルの心機能指標と合わせて，積極的な利用を推奨したい。

利尿剤の投与は，あくまでもその時点での循環血液量の状態，腎機能，心機能に基づいて考えるべきものであり，画一的な利尿剤の投与は控えるとされたのは，妥当な決定といえる。

なお，ICU 入室時および以後 2〜3 日毎に体重測定を行うとあるが，入室時は手術室からの搬送に伴い循環呼吸状態も不安定になるリスクがあり，必ずしも入室直後に体重測定を行う必要があるのかは疑問である。体重は水バランスの評価に有用なのは周知の事実であるものの，つり上げ式の体重計（確かに正確に測定できるが）で実施するのであれば，業務の簡素化のためにスケールを内蔵した ICU ベッドの導入が適切であろう。ただし，高額でもあり，導入する台数を検討する必要がある。

ICU での診療プロセスの改善策については，治療方針の決定は朝・夕の申し送りで多職種が参加して検討し，内容をチャートに To do list の形で記載して診療を行う

とされている。その内容（例えば，in/out バランスの目標，カテコラミンの使用方針，血行動態指標のターゲット等）については具体的に設定しておく必要があるが，改善案にはこうした記載もあるので，この点については評価できる。ただし，利尿剤の適応を認めた場合の対応として，このように細かくターゲットを設定して管理できるのかは疑問が残る。米国でも単なる to do list ではなく daily goal sheet という形で記載し，常に確認できる（いちいち電子カルテを開かなくとも良い）形式でフィードバックが行われるような診療業務の方が，安全と効率性の向上に有効であるとの報告がある。すなわち，回診や申し送りではこの To do list がどのように利用されているのかは，今後，検討されるべき課題と言える。また，このリストに NOMI に関するリスクを記載することも可能であるので，検討結果・方針について，効率的運用が可能となるように提言に盛り込まれるべきと考える。そして，治療方針の検討・決定に際しては，心臓外科医と ICU 医師，その他の医療スタッフとの間に権威勾配が存在するようなことはないか，気を配っておく必要がある。もしも，当センターでそうした傾向があれば，心臓外科医の意識改革，安全文化に対する教育等の取り組みが欠かせない。改善案の中には「コミュニケーションと人的配置」に記載があり，この通りに実現に向かえば問題はないと考えられるが，コミュニケーションの問題は常に重要な根幹をなすものであり，強調しすぎることはない。

2017 年，ICU 増床にともなうマンパワー不足が問題となり，各種の対策が講じられてきたが，長時間勤務では疲労による勤務効率の低下，エラーの増加が懸念されるため，今後も ICU の入室基準，管理業務の標準化等により，業務を整理・改善を図ることを継続していくべきである。また，麻酔科医の ICU 業務への関与，特に心臓血管外科手術については，術後管理を知らずして適切な麻酔管理を行うことは困難と考えられ，大学附属の当センターとしては，麻酔科医の ICU 業務への参画，麻酔管理から ICU 管理への緊密な連携が求められている。ちなみに，質管理では「後工程は前工程のお客様」といわれており，麻酔から ICU への連携もこのような組織文化となることが望ましい。

4)　心臓血管外科および当センターの組織体制

当センターの心臓血管外科では，上記のように各種のマニュアルを策定し継続的に改訂され，NOMI 管理バンドルも 2014 年に策定し公表されている。我が国において，NOMI に特化した検討を事前に行っている施設は殆どないと考えられるので，

NOMI管理バンドルにはNOMIのリスクファクターと考えられる項目が列挙されており，こうした取り組みは秀逸であり，当センターの医療の質管理の意識の高さを物語るものである。さらに，体外循環技師の技量も高く，研究，教育活動にも優れた実績を有する代表的施設であると言える。その一方で，40歳代以下の心臓外科医には体外循環の知識は不十分であり，特に管理や操作など技術的な点では，体外循環技師に一任してしまった状態にあると思われる。充填液の組成や容量，マニトールの混入量など，医師がどの程度まで理解できているのか，チームとして見直しが必要な状況にあると思われる。麻酔科医も同様で，経食道心エコーで心機能を判断していたとしても，体外循環の離脱に関しては体外循環技師の判断に頼りがちであったのではないかと思われる。すなわち，当センターでは，体外循環技師が最も豊富な知識と経験を有しており，心臓外科医や麻酔科医の方は，経験は元より，知識も不十分であったと思われる。従って，体外循環回路の充填液の組成が，どのような経緯で変更されてきたのか，その理由は何か，問題はどこにあるのか，医師がこれらを説明できるのか不明である。当センターでは，代表的なテキストとは異なる組成の充填液がこれまで長年使用されており，そのマニュアルは上記のようにホームページでも公開されている。従って，これを参考にして踏襲した施設も少なからずあるのではないだろうか。少なくとも体外循環マニュアルは，第10版からでも改訂しながら10年間継承してきているが，麻酔科医や心臓外科医も問題点をどの程度，認識していたのか疑問が残る。

当センターは自治医科大学の附属施設であり，心臓血管外科の診療科長は教授であり，数年前に交代があった。心臓血管外科周術期診療改善検討委員会の調査では，手術方針や手術チームの決定において，若干の変化があったことが判明している。心臓血管外科の伝統を継承するとはいえ，前任教授が定年退職後の新教授の着任であり，教授の世代が変わることになり，診療科内のいわゆるガバナンスに問題が生じた可能性はあったのではないかと思われる。

その一方で，当センター全体としては，心臓血管外科だけではなく，全診療科で合併症が発生した際のM&Mカンファレンスは適切に開催されており，いわゆる医療安全管理体制は確立されていたと言える。合併症に限らず，いわゆるインシデント報告件数は，当センターは間違いなく本邦のトップクラスであり，医療専門職の医療安全に対する意識の高さ，ならびにセンター全体の医療安全管理体制が充実していることは確認できた。

さて，我が国の工業生産の工程では，異常を発見した際はすぐに生産ライン止めて，不良品がどの工程で出たかを明確にする品質管理が実施されている。こうした本邦の品質管理は，世界的に高い評価を受けている一方で，医療施設では何らかの問題が起きた時には，組織としてどのように対処し，責任を果たすのかが優先されることが多い。すなわち，まずは発生した原因や要因を突き止めなくてはならないのに，多くの医療機関ではそのシステム分析ができない，あるいは管理規程はあっても機能しない状況にあると思われる。その点では，当センターはこうしたインシデント報告システムが整っており，迅速にM&Mカンファレンスを開催して対応されたことは高く評価するものである。おそらく多くの施設では， NOMIがこうした程度で発生しても，他の診療科には気づかれずに問題とされなかった可能性もあったと思われる。それは，心臓血管外科が施設内の唯一の専門家集団であり，それ以外の診療科や医療専門職には不明なことが多く，他の診療科に対する意見が出ないからである。こうした中，当センターでは「原因が解明できるまでは予定手術を中止する」との判断を院長が迅速に下すことができたのは，施設のガバナンスが効いていた証左であるといえる。もちろん，次第に頻度が高くなってきたことに端を発してはいるが，その中で原因究明については，前述したように，外部（非関連も含め）から専門家の参加を求めて検討していたことも適切な対応であったいえる。院内で検討した結果，保健所にも予定心臓手術の停止（緊急手術の受け入れは継続する）を届け出ており，公表せずに隠しておくとの判断があったのではない。また，いわゆる重大な過誤による事例ではなく，稀な術後合併症の発生であり，術後死亡は1例（それも他の要因による）のみであったことから，こうした場合にどの様に公表するかは，国立大学病院等の医療事故の公表基準においても定まっておらず，いまだに議論のあるところである。

なお，手術待機患者には，当センターが予定手術を一旦中止する状況を個別に説明されており，手術可能な施設を紹介して対応していた。そのため，本来は不要な当センターへの受診となったため，交通費を支給していたが，その理由が不十分な理解のままに2月に週刊誌に記載されて，問題視されたものと考えられる。

前述したように，工業界で用いられてきた品質の管理のシステム分析と改善への取り組みが，当センターでは心臓血管外科周術期診療改善検討委員会の活動によって，見事に短期間で実践されたことを本委員会は高く評価するものである。心臓手術の再開に向けての工程表も明確であり，改善策も極めて妥当で達成可能な内容であった。

5　おわりに

当センターでは，NOMIの発生に対して迅速に対応しており，全ての検討会や委員会の記録が確実に保管されていた。さらに，医療体制を含めたシステム分析が行われており，改善策を実現するためのプロセスまで明確に策定されていた。したがって，本委員会は，特異な経緯で設置された検証評価委員会であると認識している。すなわち，個別の事例の要因分析は的確に実施されており，本委員会はそれら分析結果と改善策を第三者評価の形で検討したものである。3名の外部評価委員会という構成から限界はあったものの，各委員が専門医として第三者の立場から改めて検証すると新たな問題点も見つかった。また，その内容は当センター内で分析されたものと同様でも，より現実的な改善策（明確な指標の設定など）を提案できたと考えている。

本委員会は，当センターでの医療の質改善への取り組みが一層高まることを祈念している。

心臓血管外科周術期診療検証評価外部委員会

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Cardiac Surgery in the Adult　5th Edition, 2017

P.311　priming

Traditional adult ECP circuit require 1.5 to 2.0 L of balanced electrolyte solution such as lactated Ringer's solution, Normosol-A, or Plasama-Lyte.

In the average-sized adult, the priming volume represents approximately 30 to 35% of the patient's blood volume and reduce the hematocrit to about two-thirds of preoperative value.

Sometimes 12.5g to 50g of mannitol is added to stimulate diuresis and passively minimize postoperative renal dysfunction.

12.5g to 50g of mannitol : 62.5ml ~ 250ml

Plasma-Lyte-A		Normosol-R
Sodium - 140 mEq Potassium - 5 mEq Magnesium - 3 mEq Chloride - 98 mEq Acetate - 27 mEq Gluconate - 23 mEq		Sodium - 140 mEq Potassium - 5 mEq Magnesium - 3 mEq Chloride - 98 mEq Acetate - 27 mEq Gluconate - 23 mEq
Osmolarity	294 mOsmol/L	294 - 295 mOsmol/L
pH	7.4 (Plasma-Lyte-A)	7.4 (Normosol-R pH 7.4)

D-マンニトール

通常 1 回体重 1kg 当り 1.0～3.0g（5～15mL)を点滴静注する。
なお、年齢、症状により適宜増減する。

投与速度は 100mL/3～10 分とする。

Kirklin/Barratt-Boyes：Cardiac Surgery 4th ed. 2012

Uniqueness of Cardiopulmonary Bypass

p.81 p.85

Perfusate

Diluent

The diluent (which is used to prime the pump-oxygenator system, wholly or in part, and for any erythrocyte-free additions during CPB) is a balanced electrolyte solution with a near-normal pH and an ion content resembling that of plasma.

Hemoglobin Concentration

At some institutions, in adult patients and even young patients, no effort is made to control hemoglobin concentration or hematocrit during CPB. Instead, the pump-oxygenator is routinely filled initially with a balanced salt solution.

p.86

Other colloidal solutions (dextran 40, dextran 70, hydroxyethyl starch) can also be added to the priming solution to attenuate loss of fluid from the intravascular space. However, none of them has been conclusively shown to have a beneficial effect.

Other Additives

Practices vary regarding addition of substances and drugs to the perfusate (by administering them into the priming volume of the pump-oxygenator or patient before CPB, or into the patient or pump-oxygenator during CPB), other than basic balanced salt solution and blood and its required additives.
Use of an *osmotic diuretic* may be advisable. Mannitol (≈0.5 g · kg^{-1}), a pure osmotic diuretic, can be included as part of the prime. Mannitol also has the advantage of being an effective agent against oxygen free radicals generated during CPB.

p.87

Changes during Cardiopulmonary Bypass

During CPB for cardiac surgery, blood loss in the operative field and gradual increase in interstitial fluid and urinary output combine to steadily deplete the patient-machine blood volume. Usual practice is for the perfusionist to add increments of a balanced electrolyte solution to maintain the volume at a safe level; in adults, up to 2000 mL may be added. Unless special precautions are taken, such as avoiding return of irrigating fluids to the pump-oxygenator by cardiotomy pump suckers and using ultrafiltration during the final stages of CPB, severe hemodilution results and persists into the postbypass period.

Special Features of Postoperative Care

Kirklin/Barratt-Boyes : Cardiac Surgery 4th ed. 2012

p.590

The thick-walled hypertrophied LV secondary to aortic valve disease requires a higher-than-usual filling pressure to distend it. Thus, a mean left atrial pressure of 8 to 10 mmHg, considered appropriate under many circumstances, may be inadequate to develop optimal LV preload early after operation in patients with important LV hypertrophy (see "Cardiac Output and Its Determinants" in Section I of Chapter 5). Reduction in myocardial compliance that occurs during cardiac surgery further increases the disparity between the usual mean left atrial pressure (LV filling pressure) and optimal preload.
For these reasons, unless cardiac performance is already optimal, left atrial pressure should be maintained at 15 to 18 mmHg by appropriate fluid infusion during the early hours after adult aortic valve surgery, particularly for severe aortic stenosis. This need is often less critical when operation has been done for aortic regurgitation, when the sudden reduction in LV stroke volume by eliminating the aortic regurgitant flow improves left compared with RV performance (see Chapter 5). Therefore, mean left atrial pressure may not be as elevated early postoperatively as when operation has been done for aortic stenosis.
Sinus tachycardia is frequently observed after operations on the aortic valve. When heart rate exceeds 100 beats · min^{-1} for several days and shows no signs of returning to normal, a β-blocker should be administered to reduce the rate. It may be necessary to continue this therapy for 2 to 3 months until heart rate control mechanisms are restored.

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Original Article

Establishment of Predictive Models for Nonocclusive Mesenteric Ischemia Comparing 8,296 Control with 452 Study Patients

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Objective: The aim of this study was to develop clinical preoperative, intraoperative, and postoperative scores for early identification of patients who are at risk of nonocclusive mesenteric ischemia (NOMI).

Design: A retrospective analysis.

Setting: Single center.

Participants: From January 2008 to December 2014, all patients from the Department of Thoracic and Cardiovascular Surgery were included on the basis of the hospital database.

Interventions: All mesenteric angiographically identified NOMI patients were compared with non-NOMI patients.

Measurements and Main Results: The study population of 8,748 patients was randomized into a cohort for developing the scores (non-NOMI 4,214 and NOMI 235) and a cohort for control (non-NOMI 4,082 and NOMI 217). Risk factors were identified using forward and backward Wald test and were included in the predictive scores for the occurrence of NOMI. C statistic showed that the scores had a high discrimination for the prediction of NOMI preoperatively (C statistic 0.79; $p < 0.001$), intraoperatively (C statistic 0.68; $p < 0.001$), and postoperatively (C statistic 0.85; $p < 0.001$). A combination of the preoperative, intraoperative, and postoperative risk scores demonstrated the highest discrimination (C statistic 0.87; $p < 0.001$). The combined score included the following risk factors: renal insufficiency (preoperative); use of cardiopulmonary bypass and intra-aortic balloon pump support (intraoperative); and reexploration for bleeding, renal replacement therapy, and packed red blood cells ≥ 4 units (postoperative). The results were similar in the control group.

Conclusions: These scores could be useful to identify patients at risk for NOMI and promote a rapid diagnosis and therapy.

Key Words: intestinal ischemia; cardiopulmonary bypass; systemic inflammatory response syndrome; sepsis; multiple organ failure; score

This study was registered at Clinicaltrials.gov (NCT 02901808) before data analysis.

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NONOCCLUSIVE MESENTERIC ISCHEMIA (NOMI) is the most dreaded gastrointestinal complication after cardiac surgery, with mortality rates of up to 90%.[1,2] It was first described by Ende in 1958[3] and commonly affects the ileum and distal jejunum.[1] NOMI is considered as an "intestinal gangrene in the presence of a patent arterial tree"[4] with extreme reduction or maldistribution of splanchnic blood flow.[5,6] NOMI leads to compromised mucosal integrity, bacterial translocation, bacteremia, and the development of multiple organ failure. The exact pathomechanism leading to NOMI currently is unknown.[5]

The clinical signs of NOMI, such as oliguria, increased serum lactate levels, decreased oxygenation, or hypotension, are unspecific. The same is true for abdominal pain that is suppressed by analgesics and sedatives.[7,8]

Mesenteric angiography is recommended for reliable diagnosis and classification of NOMI and specific treatment using application of vasodilators in the superior mesenteric artery.[9,10] A clinical method for early identification of patients at risk of developing NOMI could help to reduce morbidity and mortality resulting from NOMI.

A variety of risk factors has been proposed based on heterogenous patient cohorts. Among others, advanced age, renal failure, pulmonary hypertension, prolonged surgery time, different forms of shock, the use of an intra-aortic balloon pump, and need for blood transfusion have been found to be associated with NOMI.[1,5,11,12] The aim of this study was to develop a clinical preoperative, intraoperative, and postoperative model for the early identification of patients who are at risk of NOMI in a large cohort of 452 patients who were experiencing angiographically confirmed NOMI and to compare them with 8,296 control patients.

Material and Methods

The study was registered at Clinicaltrials.gov (NCT 02901808) before data analysis on September 15, 2016. Ethical approval for this study (Saarland Medical Chamber number 209/15) was provided by the Ethical Committee of the Saarland Medical Chamber on November 25, 2015. Written consent was waived because the data were collected retrospectively.

The inclusion criterion was postoperative stay in the Department of Thoracic and Cardiovascular Surgery at the Saarland University Medical Center, Homburg/Saar, between January 1, 2008, and December 31, 2014. Exclusion criteria were age <18 years and intraoperative death. According to the Ethical Committee, previously published data for 865 patients were excluded from the analysis (Fig 1).[12]

Radiographic Analysis

Angiography of the superior mesenteric artery was performed in patients with clinical changes suggestive of mesenteric ischemia, including new onset of oliguria (urine output < 0.5 mL/kg/h for at least 6 hours) or anuria, increased lactate levels >5.0 mmol/L or metabolic acidosis, base excess <−5 mmol/L, abdominal distention with decreased or absent bowel sounds, and increased need for norepinephrine support in the absence of hypovolemia and cardiogenic shock (cardiac index <1.8 L/min/m^2 measured using a pulmonary artery catheter).

In all cases, the common femoral artery was accessed and a 5 Fr sheath was inserted. The superior mesenteric artery was catheterized with a 4 Fr catheter (cobra tip configuration or sidewinder; Cordis, Bridgewater, NJ).

After mesenteric angiography, the sheath and the catheter in the superior mesenteric artery were left in place, fixed, and used for application of drugs in the intensive care unit. The sheath was used for continuous infusion of prostaglandin E1 (1.2 μg/h) into the femoral artery. The catheter in the superior mesenteric artery was used for continuous infusion of iloprost (4 ng/kg/min) as vasodilator therapy for the intestinal tract.

Angiograms were assessed and scored consecutively on a consensus basis by 2 experienced radiologists (10 and 7 years of experience) according to a previously published scoring system.[9] This score consists of the following 3 categories: vessel morphology, reflux of contrast medium into the aorta, and time to portal vein filling. According to the score, the severity of NOMI was classified as mild (1-3 points) or severe NOMI (4-7 points) (Supplement 1). A total score > 1 was classified as NOMI.

Parameters Studied

All analyzed data were collected from the hospital database. These included demographic and preoperative, intraoperative, and postoperative data (Tables 1 and 2).

Statistics

Continuous variables are expressed as means and standard deviations. Categorical variables are presented as absolute and relative frequencies. Dichotomous variables between patients with and without NOMI were compared using chi-square tests. Continuous variables were compared with the Mann-Whitney U test.

Risk factors finally were identified using multiple logistic regression and reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). At first, a potential confounder

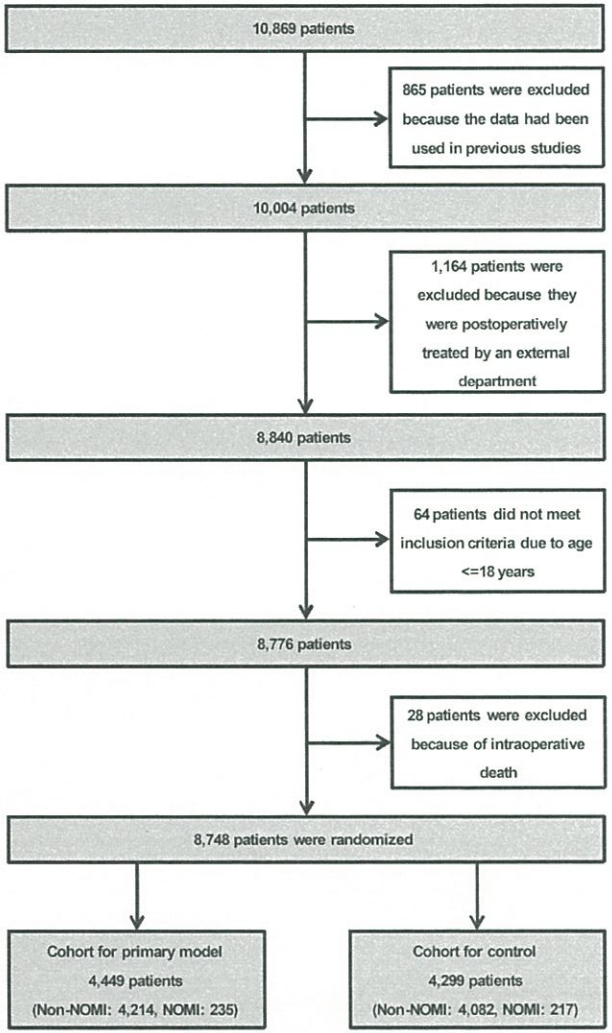

Fig. 1. Case selection. To create equality between the 2 groups, patients were assigned to either the "primary model" or "control" group based on the month they underwent surgery in an alternating manner. To avoid any bias associated with the month of surgery, a new group was started each year and alternation among months continued.

($p < 0.05$) from Table 1 was investigated in an univariate logistic regression model. Second, only significant risk factors of this model were used and included in a multiple logistic regression analysis using forward and backward Wald elimination with $p > 0.1$ for exclusion, resulting in the final risk factor models. In this way, preoperative, intraoperative, and postoperative risk factors were identified. Pairwise dependent variable constellations with Pearson or Spearman

Table 1
Population Characteristics

		Non-NOMI (n = 4,214)		NOMI (n = 235)		p Value
Preoperative						
	Male (%)	2,954	(70)	159	(68)	0.43
	Age ≥ 80 (y)	283	(67)	50	(21)	< 0.001
	Body mass index (kg/m^2)	26.4	(24.3-29.4)	27.6	(24.6-31.6)	< 0.001
	logEuroSCORE	4.5	(2.2-8.7)	11.5	(5.8-23.1)	< 0.001
	Missing values (%)	575	(14)	6	(3)	
	NYHA III/IV heart failure (%)	2,642	(83)	206	(92)	0.001
	Missing values (%)	1,026	(24)	10	(4)	
	eGFR < 60 mL/min (%)	971	(24)	139	(59)	< 0.001
	Missing values (%)	108	(3)	1	(0)	
	Pulmonary hypertension (%)	546	(13)	76	(32)	< 0.001
	Coronary artery bypass graft surgery (%)	1,342	(32)	128	(55)	< 0.001
	Valve surgery (%)	2,012	(48)	150	(64)	< 0.001
	Aortic aneurysm surgery (%)	664	(16)	28	(12)	0.14
	Carotid artery surgery (%)	38	(1)	4	(2)	0.22
	Lung surgery (%)	696	(17)	2	(1)	< 0.001
	Other surgery (%)	746	(18)	66	(28)	< 0.001
	Redo surgery (%)	872	(21)	66	(28)	0.007
	Emergency surgery (%)	372	(9)	40	(17)	< 0.001
Intraoperative						
	Surgery time ≥ 195 min (%)	1,016	(24)	116	(49)	< 0.001
	Cardiopulmonary bypass	3,139	(75)	216	(92)	< 0.001
	Cardiopulmonary bypass time (min)	75	(58-98)	93	(69-129)	< 0.001
	Aortic cross-clamp time (min)	50	(38-64)	58	(46-77)	< 0.001
	Hypothermic cardiac arrest (min)	13	(8-21)	9	(7-18)	0.06
	Intra-aortic balloon pump support (%)	46	(1)	21	(9)	< 0.001
Postoperative						
	Resuscitation (%)	49	(1)	27	(12)	< 0.001
	Reexploration for bleeding (%)	110	(3)	40	(17)	< 0.001
	New pacemaker (%)	29	(1)	15	(6)	< 0.001
	Renal replacement therapy (%)	59	(1)	80	(34)	< 0.001
	Packed red blood cells ≥ 4 (%)	218	(5)	88	(38)	< 0.001

NOTE. Continuous variables are expressed as median and interquartile range. Categorical variables are presented as numbers (percentages). Missing values are cases without documentation or implausible data.
Abbreviations: eGFR, estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation); NOMI, nonocclusive mesenteric ischemia; NYHA, New York Heart Association.

(quantitative *v* quantitative), Eta (quantitative *v* binary), or Cramer-V (binary *v* binary) correlation coefficients > +0.5 or < −0.5 were specified a priori as interaction terms in multivariate regression analyses to account for the issue of multicollinearity.

Considering the resulting covariate effects estimated from the data, a rule could be derived from the multiple logistic regression approach, predicting the probability of NOMI in each case using a score according to a so-called clinical science and symptom model.[13] A calculator for the scores that allows computation for combinations to be specified is provided as a supplement (Supplement 2). The calculator used the response function (ie, the inverse link function) of the following logistic regression model:

$$pr = \exp(\eta)/(1 + \exp[\eta]),$$

where η is the linear predictor of the multiple logistic regression and pr is the probability of NOMI. Receiver operating characteristic curves were constructed (C statistic) in the primary prediction model and control group to evaluate the prediction of the combination of preoperative, intraoperative, and postoperative risk factors in one model with respect to NOMI.

Data analysis was performed using SPSS Statistics 19 (IBM Corp, Armonk, NY). Two-sided p values < 0.05 were considered to be statistically significant.

Results

To create equality between the 2 groups, patients were assigned to either the "primary model" or "control" group based on the month they underwent surgery in an alternating manner. To avoid any bias associated with the month of surgery, a new group was started each year and alternation among months continued (see Fig 1).

In the primary model, patients who experienced NOMI generally were older and had a higher log EuroSCORE and poorer renal function. They also had more comorbidities, longer

Table 2
Outcome:

		Non-NOMI (n = 4,214)		NOMI (n = 235)		p Value
Postoperative						
	First mobilization (d)	1	(1-1)	1	(0-2)	0.002
	Missing values (%)	7	(2)	0	(0)	
	Mechanically ventilated (d)	0	(0-0)	4	(1-8)	< 0.001
	Missing values (%)	656	(16)	14	(6)	
	Renal replacement therapy (d)	3	(2-7)	5	(2-10)	< 0.001
	Length of stay (d)					
	In ICU	1	(1-1)	7	(4-13)	< 0.001
	Missing values (%)	656	(16)	14	(6)	
	In hospital	8	(6-11)	15	(8-25)	< 0.001
	Mortality (%)					
	In hospital	59	(1)	78	(31)	< 0.001
	Cardiovascular	35	(0.8)	29	(12)	< 0.001
	Noncardiovascular	21	(0.5)	48	(20)	< 0.001
	Unknown	3	(0.1)	1	(0.4)	0.08
	Discharged (%)					
	Walking	3,598	(85)	80	(34)	< 0.001
	Home	2,526	(60)	20	(9)	< 0.001
	Rehabilitation	231	(6)	20	(9)	0.05
	Hospital	1,398	(33)	117	(50)	< 0.001
	Discharged in-hospital mortality (%)	41	(1)	15	(6)	< 0.001

NOTE. Continuous variables are expressed as median and interquartile range. Categorical variables are presented as numbers (percentages). Missing values are cases without documentation or implausible data.
Abbreviations: ICU, intensive care unit; NOMI, nonocclusive mesenteric ischemia.

surgeries, and more postoperative complications and required more renal replacement therapy and packed red blood cells (see Table 1 and Supplement 3).

Patients who experienced NOMI compared with those without NOMI were ventilated mechanically longer and had prolonged length of stay in the hospital and increased hospital mortality (Table 2).

After the forward and backward Wald test was performed, risk factors having the highest predictive value for NOMI were identified (Table 3). The independent risk factors with the highest ORs were (preoperative) renal insufficiency (adjusted OR 3.4, 95% CI 2.5-4.5; $p < 0.001$); (intraoperative) intra-aortic balloon pump support (adjusted OR 5.8, 95% CI 3.4-10.1; $p < 0.001$); (postoperative) renal replacement

Table 3
Independent Risk Factors to Predict NOMI

(n = 4,449)		Adjusted OR (95% CI)	p Value
Preoperative			
	Age ≥ 80 (y)	2.1 (1.4-3.0)	< 0.001
	eGFR < 60 mL/min (%)	3.4 (2.5-4.5)	< 0.001
	Pulmonary hypertension (%)	2.3 (1.6-3.1)	< 0.001
	Coronary artery bypass graft surgery (%)	2.8 (2.1-3.7)	< 0.001
	Valve surgery (%)	2.0 (1.8-3.8)	< 0.001
Intraoperative			
	Surgical time ≥ 195 min (%)	2.4 (1.8-3.1)	< 0.001
	Cardiopulmonary bypass	2.9 (1.8-4.7)	< 0.001
	Intra-aortic balloon pump support (%)	5.8 (3.4-10.1)	< 0.001
Postoperative			
	Resuscitation (%)	4.5 (2.4-8.5)	< 0.001
	Reexploration for bleeding (%)	3.1 (1.9-5.0)	< 0.001
	New pacemaker (%)	4.3 (1..8-10.2)	0.001
	Renal replacement therapy (%)	19.8 (13.0-30.0)	< 0.001
	Packed red blood cells ≥ 4 (%)	5.1 (3.5-7.3)	< 0.001

NOTE. Data are expressed as adjusted odds ratio with 95% confidence interval.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation; OR, odds ratio.

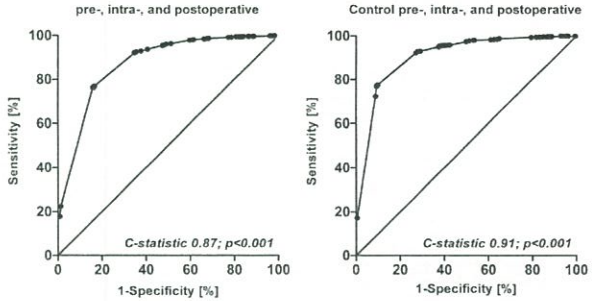

Fig. 2. Receiver operating characteristic curves were constructed (C statistic) in the primary prediction model and in the control group to evaluate the prediction of the combination of preoperative, intraoperative, and postoperative risk factors in one model with respect to nonocclusive mesenteric ischemia.. The model was identified using multiple logistic regression analysis using forward and backward Wald elimination.

therapy (adjusted OR 19.8, 95% CI 13.0-30.0; $p < 0.001$); and transfusion of packed red blood cells ≥ 4 (adjusted OR 5.1, 95% CI 3.5-7.3; $p < 0.001$; [see Table 3]). Goodness of fit for each adjusted model was assessed using Hosmer-Lemeshow tests and was not statistically significant.

C statistic showed that the preoperative risk factors for NOMI (see Table 3) had a high discrimination for the prediction of NOMI (C statistic 0.79; $p < 0.001$; Supplement 4). The discrimination for prediction of NOMI was lower with intraoperative risk factors (C statistic 0.68; $p < 0.001$; see Supplement 4) and higher with postoperative risk factors (C statistic 0.85; $p < 0.001$; see Supplement 4). The combination of preoperative, intraoperative, and postoperative risk factors for NOMI ([preoperative] renal insufficiency; [intraoperative] cardiopulmonary bypass and intra-aortic balloon pump support; [postoperative] reexploration for bleeding, renal replacement therapy, and packed red blood cells ≥ 4) had the highest discrimination for prediction of NOMI (C statistic 0.87, $p < 0.001$) (Fig 2). The results were similar in the control group.

Patients who experienced all preoperative risk factors had a 70% risk for developing NOMI (see Supplement 2). This was lower for intraoperative risk factors (38%) and higher for postoperative (99%) and the combination of preoperative, intraoperative, and postoperative risk factors (99%). Again, the results were comparable in the control cohort. Detailed information about the risk equation is reported in Supplement 2.

Discussion

Of the 8,748 patients treated in the Department of Thoracic and Cardiovascular Surgery at the authors' institution during the study period, 452 patients (5.2%) were identified as experiencing angiographically confirmed NOMI. All NOMI patients had clinical signs suggestive of mesenteric ischemia (eg, decreased urine output, absent bowel sounds, increased lactate, metabolic acidosis, and increased need for norepinephrine support). The authors developed the following 4 categories for the analysis: preoperative; intraoperative; postoperative; and a combination of preoperative, intraoperative, and postoperative. The final score included the combination of identified risk factors: renal insufficiency (preoperative), cardiopulmonary bypass and intra-aortic balloon pump support (intraoperative), and reexploration for bleeding, renal replacement therapy, and packed red blood cells ≥ 4 (postoperative). The scores had a high discrimination for prediction of NOMI (C statistic 0.87; $p < 0.001$). These findings confirmed the authors' previous observed risk factors for NOMI in 865 cardiac surgery patients.[12] However, the previously published study was limited by only a postoperative model. The present study included preoperative, intraoperative, and postoperative models and a combination of all models.

The incidence of NOMI in previous studies is reported at 1%, with mortality rates up to 90%.[1,5] This is in contrast to the authors' study population whereby the incidence was greater (5.2%) and the mortality rate was lower (31%). Differences are related to a more liberal use of mesenteric angiography in the present study, which showed more sensitive clinical changes suggestive of mesenteric ischemia. These clinical changes are unspecific and similar to clinical signs of systemic inflammatory response syndrome or septic shock. The data of the present and previous studies underline that patients with NOMI experience a worse outcome.[1,5,12] Therefore, the authors of the present study assumed that early identification of patients at risk for NOMI would allow for lowering the threshold for angiography as the essential diagnostic and therapeutic tool. For this reason, it is necessary to identify patients at risk for NOMI as early as possible.

The following preoperative known risk factors that also were found in the study's large population include advanced age, severe heart failure, and chronic renal failure.[11,14] Interestingly, chronic renal failure,[15,16] severe heart failure,[17,18] and pulmonary hypertension[19] are associated with increased endothelin-1 concentrations. Endothelin-1 is an independent preoperative risk factor for NOMI and is associated with mesenteric ischemia with and without cardiopulmonary bypass.[20-22] However, preoperative risk factors alone do not provide conclusive evidence but may be indicative for the susceptibility of patients to develop NOMI.

The pathomechanism of NOMI is not well-understood. It is unclear whether NOMI is simply the delayed result of microcirculatory alterations initiated during cardiopulmonary bypass or rather the manifestation of a separate disease. Several studies have documented alterations in intestinal microcirculation during cardiopulmonary bypass[20,23–25] and identified cardiopulmonary bypass as an independent risk factor for NOMI.[12] This is in line with the findings of the present study's authors. One reason for this could be the nonpulsatile flow, which is associated with expression of endothelin, leading to progressive vasoconstriction.[20] In line with this, the authors in their previous study identified elevated endothelin-1 concentration as an independent risk factor for NOMI.[21]

Impaired intestinal blood flow may result in destruction of the intestinal barrier, which contributes to further aggravation of the physiological alterations after cardiopulmonary bypass.[26] Alternatively, it may be assumed that the changes in the microcirculation are a consequence of the norepinephrine treatment that is necessary in many patients during and after surgeries involving cardiopulmonary bypass.[12,27,28] Although norepinephrine treatment is missing in the present analysis because it is not documented in the hospital database, the study's overall discrimination for prediction of NOMI is high (C statistic 0.87; $p < 0.001$).

Generally, NOMI is a well-known consequence of low cardiac output syndrome. Low cardiac output syndrome is a common complication in cardiac surgery patients, occurring in 3% to 14% of patients who undergo cardiac surgery with cardiopulmonary bypass.[29,30] In this context, intra-aortic balloon pump implantation often is used in addition to the usual inotropic support.[31] Despite possible beneficial effects, intra-aortic balloon pump use is known to be an independent risk factor for the development of mesenteric ischemia.[32]

In contrast to the authors' previous work whereby use of an intra-aortic balloon pump demonstrated a more than 150-fold odds increase for the development of NOMI in 865 patients, in the present study, a 6-fold odds increase was found in 8,748 patients,[12] which would appear more plausible (ie, if one risk factor [eg, intra-aortic balloon pump] is rare in the incidence and highly associated with NOMI in the analysis, the risk increases extremely). In the present study, the larger population balanced this effect. Nevertheless, intra-aortic balloon pump was the intraoperative risk factor with the highest odds for developing NOMI.

Low cardiac output also is known to occur during resuscitation; therefore, resuscitation also seems plausible as a risk factor. The same is true for the loss of sinus rhythm and the need for a new pacemaker after cardiac surgery.[12]

The authors previously found that intestinal ischemia alters the coagulation system with an increased risk for reexploration for bleeding and an increased need for packed red blood cells.[12] This also was examined in the present study's larger patient population.

NOMI may lead to a systemic inflammatory response syndrome and sepsis followed by multiple organ failure with the need for renal replacement therapy.[12,33,34] In line with this, renal replacement therapy after cardiothoracic surgery was identified as a risk factor for NOMI in the study's large population.

Taken together, most of the identified risk factors are directly related to disturbed conditions of circulation independent of the underlying pathophysiological cause. Disturbed cardiac perfusion leads to the need for intra-aortic balloon pump, acute kidney injury, and renal replacement therapy as a result of disturbed renal perfusion and NOMI as the result of altered intestinal perfusion. This hypothesis is supported by the highest OR found for NOMI for those 2 complications. Although the exact pathophysiological causes for NOMI are not understood, it is clear that preoperative risk factors represent arteriosclerosis, intraoperative risk factors have a negative effect on circulation, and postoperative factors are related to disturbed organ perfusion. NOMI or renal replacement therapy after cardiac surgery could be related to the same systemic pathophysiological pathway impairing circulation.

All postoperative predictors, however, have to be considered in the context of intraoperative changes in physiology and preoperative morbidity. Therefore, the authors calculated scores included independent risk factors for preoperative, intraoperative, or postoperative predictors and a final score as a combination of all identified risk factors for NOMI. The final score showed a possibility for NOMI of 99% in patients who experienced all 6 identified risk factors (renal insufficiency, cardiopulmonary bypass, intra-aortic balloon pump support, re-exploration for bleeding, renal replacement therapy, and packed red blood cells ≥ 4). Interestingly, the preoperative score also showed a possibility for NOMI of 70%.

In this study, NOMI was diagnosed and proven using angiography. However, angiography was not conducted in all patients but only in patients with clinical changes suggestive of mesenteric ischemia. Consequently, non-NOMI patients did not undergo angiography. This group included 9% emergency cases, 16% aortic surgery, and 21% surgical revisions. In non-NOMI patients, the hospital mortality was only 1% in contrast to 31% in NOMI patients. Therefore, the occurrence of NOMI in the non-NOMI group seems unlikely. Study results were confirmed in the control cohort of 4,082 non-NOMI and 217 NOMI patients. The control cohort was randomized before data analysis. Nevertheless, additional multicenter investigations are needed to prove the scores.

NOMI must be taken into consideration in patients after cardiac surgery who experience unclear symptoms of systemic inflammatory response syndrome and beginning symptoms of multiple organ dysfunction and have a predicted high score. The local and targeted therapeutic option is to improve intestinal blood flow by performing angiography and applying vasodilators selective in the superior mesenteric artery. The global therapeutic option is to improve low cardiac output (ie, avoid hypovolemia with vasopressor support) or therapy for any reason for the loss of systemic vascular resistance (eg, sepsis therapy). Moreover, the authors believe that preoperative screening to improve intestinal blood flow (ie, dilation or stenting of superior mesenteric artery stenosis) could be an option to improve postoperative outcome. The study's preoperative scores and the health history of the patients, in particular signs of chronic intestinal ischemia (abdominal pain, loss of appetite, costiveness, or diarrhea), needs attention in further diagnostic.

Conclusion

NOMI is an underrecognized disease. This study provides clinical preoperative, intraoperative and postoperative scores and the combination of all these scores to identify patients at risk for NOMI with a high predictive value.

Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1053/j.jvca.2018.08.194.

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Editorial

Predictive Modeling for Nonocclusive Mesenteric Ischemia

Predictive modeling is the process of using data to predict outcomes.[1] The application of predictive modeling that uses statistics to determine future performance based on current and historical data is termed *predictive analytics*.[2] Predictive analytics are used in various industries, such as insurance, marketing, stock trading, major league baseball, weather forecasting, and banking, among others.

The 2 most common techniques to analyze data in predictive modeling are linear and logistic regression analysis and neural networks. Certainly all physicians should be familiar with linear regression analysis in using medical data to try to predict statistically significant outcomes in medical research. Neural networks are used to analyze nonlinear data, which connect relationships and patterns between variables. The human brain is the most complicated form of neural network and is the basis for machine learning and artificial intelligence. Neural networks also are used in business to analyze patterns of product use by customers and by the government and crime investigators to detect patterns related to criminal activity.

In this issue of the *Journal of Cardiothoracic and Vascular Anesthesia*, Bomberg et al.[3] used predictive modeling to analyze data retrospectively in 8,748 patients to determine perioperative predictors in 452 patients developing nonocclusive mesenteric ischemia (NOMI) after cardiac surgery. They previously found in 865 patients in which 78 developed NOMI that the variables with the highest preoperative odds ratios to predict NOMI were renal insufficiency, diuretic therapy, and age >70; intraoperative predictors included pump time and ischemic time, and postoperative factors included intra-aortic balloon pump (IABP), lactate levels, metabolic acidosis, and the need for inotropic support.[4] In the present study, the clinical suspicion of NOMI was based on a variable pattern that included reduced urine output, increasing lactate levels or metabolic acidosis, abdominal distention or absent bowel signs, and increased need for norepinephrine support with a low cardiac index, and was confirmed by mesenteric angiography. The angiographic catheters were left in the superior mesenteric artery, and vasodilators were infused into the vessel to treat NOMI. A multiple logistic regression analysis was used for variables that then were scored and analyzed to predict preoperative, intraoperative, and postoperative associations with the diagnosis of NOMI. The authors found preoperative renal insufficiency, cardiopulmonary bypass (CPB) time, an IABP, postoperative re-exploration for bleeding, renal replacement therapy, and the administration of greater than 4 units of packed red blood cells had the highest predictive value for NOMI.

The pathophysiology of NOMI is not clear. Nonpulsatile flow of CPB is known to be more sensitive to maintain renal and mesenteric vascular flow, especially with prolonged pump times. In a review of almost 4,500 bypass cases with approximately half pulsatile CPB flow, almost 75% of abdominal complications came in the nonpulsatile group.[5] Endothelin is an inflammatory mediator that is released during CPB that can cause vasoconstriction of these vascular beds. Evidence of microcirculatory disruption created by nonpulsatile flow at the microvascular level can be seen via blood flow and tissue saturation.[6] Reduced perfusion with low cardiac output and perfusion pressure can result in vasoconstriction, which can reduce further the pulse pressure and could result in collapse of the microvasculature in the mesentery. In addition, vasoplegia and the requirement for vasoconstrictors such as norepinephrine and vasopressin likely play a role in intestinal ischemia.

However, the authors found the IABP to have to highest odds ratio as an independent risk factor. The IABP long has been known to be a risk factor for NOMI.[7] Maybe the blood flow characteristics are changed or plaque disruption could cause emboli to the mesenteric vessels with balloon inflation and deflation. A more obvious problem would be IABP malposition in the abdominal aorta with either the balloon or the balloon catheter causing malocclusion and affecting renal and mesenteric blood flow. One study looking at IABP positioning showed a 13-fold increased risk of major complications, including renal failure and mesenteric ischemia, compared to a properly positioned IABP.[8] Although not mentioned in their study, hopefully the authors corrected IABP malposition (or even removed it), which should be demonstrated on postoperative radiologic exams.

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Although rare, NOMI carries a significant associated mortality. If intestinal ischemia is suspected, NOMI must be differentiated from embolic, thrombotic, or even venous etiologies. Computed tomographic angiography (CTA) is often the initial imaging modality to help delineate the cause of ischemia, especially in patients too unstable to undergo angiography.[9] Because of the dynamic nature of NOMI and computed tomography scanning, vasospasm of distal branches may at times be difficult to appreciate on CTA; however, sensitivity of computed tomography in diagnosing the other possible causes improves accuracy of diagnosing NOMI via exclusion. Unfortunately, there was no mention of the use of CTA or the incidence of occlusive mesenteric ischemia by the authors in this study.

Once the diagnosis is made, the initial step is to eliminate or correct any contributing factors.[10,11] Angiography performed in a hypotensive or hypovolemic patient will demonstrate mesenteric constriction even when there is no intestinal ischemia. Vasoconstrictors should be discontinued, and if inotropes are required, the preferred agents are dobutamine, dopamine, or milrinone because they have less mesenteric constrictive effects. Hypovolemia should be corrected with appropriate fluid replacement. Other physiologic contributors that need to be addressed include heart failure and sepsis. After other physiologic parameters have been addressed, if there is no significant improvement in the patient's clinical status, angiography with administration of catheter-directed vasodilators (papaverine, prostaglandins, and nitroglycerin) in the superior mesenteric artery should be considered.[12]

The authors suggested the infused PGE1 through the femoral vein sheath and iloprost into the catheter in the superior mesenteric artery reduced their mortality to 31% compared to 90% in other studies. However, the incidence of NOMI in this study was 5.2% compared to 1% in other studies.[13] In their angiographic scoring system, a score of 1, which included any mesenteric vasoconstriction, was considered mild NOMI. However, it does not mean that there was ongoing intestinal ischemia even though there was mesenteric vasoconstriction. Thus, there was likely an overdiagnosis of NOMI in this study, plus the authors have great interest in this problem, which could have resulted in a selection bias. To confirm the diagnosis would require catheterization of mesenteric veins with documentation of mesenteric lactic acid production or possibly surgical exploration. To confirm the reduction in mortality, a randomized trial would be needed in patients with documented intestinal ischemia to prove ultimately the value of this selective vasodilator therapy in improving outcomes with NOMI, but this would be ethically difficult to perform in such a small group of patients with high mortality.

Prevention of NOMI may be more practical than catheter-based therapy. Should pulsatile flow on pump be used whenever a patient has known renal insufficiency or presents for surgery with low cardiac output and low urine output? The decision to use an IABP may be potentially modifiable. The development of small catheter-based rotary pumps such as the Impella device (Abiomed) may eliminate the occlusive problems related to an IABP owing to its location in the left ventricular outflow tract/ascending aorta when used as temporary support. Very little data are currently present regarding the risk of mesenteric ischemia from devices, such as the Impella, and are underpowered to draw conclusions.[14]

So what should be taken away from this study? The predictive modeling resulted in additional "unspecific" factors related to the diagnosis of NOMI. In theory, the best and most specific variable to indicate abdominal pathology in these patients might the abdominal exam. Most critical care providers often focus on hemodynamic data, echocardiograms, laboratory data, etc. and often overlook physical diagnosis. Unfortunately, most of the patients are (1) unable to contribute to the exam because of sedation or severity of illness, and (2) unlikely to reliably demonstrate abdominal symptomology, though lighter levels of sedation to diagnose abdominal pain have been suggested.[10] Proper positioning of the IABP should be documented. CTA should be performed to rule out obstructive pathology, and if negative, then mesenteric angiography considered. Critical care physicians managing these patients always should keep the diagnosis of NOMI as a possibility when the pattern of poor perfusion, lactic acidosis, evidence of bowel distension, abdominal pain, and gut immotility are present.

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REVIEW

Personalization of arterial pressure in the perioperative period

Thomas Godet[a], *Romain Grobost*[a], *and Emmanuel Futier*[a,b]

Purpose of review
This review aims to discuss recent findings on the relationship between intraoperative arterial hypotension and organ dysfunction in surgical patients and examines the available evidence for personalizing blood pressure (BP) management as a strategy to improve patient outcome.

Recent findings
Hypotension contributes to oxygen supply–demand mismatch and may cause an ischemia–reperfusion injury which may manifest as organ dysfunction. Evidence is accumulating suggesting that hypotension is associated with acute postoperative myocardial and kidney injury, and increased risk of mortality in surgical patients. In contrast to traditional BP management in which BP targets are empirically chosen, personalized BP management aims at individualizing BP targets according to individual patient physiology considering clinical conditions that may influence organ pressure-flow autoregulation. Recent randomized data provide clinically meaningful findings that a treatment strategy aims at targeting individualized BP values which may help improving outcome in surgical patients.

Summary
Hypotension is a common complication in surgical patients and is an important trigger of organ injury in surgical patients. Personalized BP management may contribute at reducing postoperative organ dysfunction in surgical patients.

Keywords
blood pressure, organ dysfunction, organ perfusion pressure, postoperative morbidity, surgical patient

INTRODUCTION

More than 300 million surgical procedures are undertaken annually worldwide, and the number of patients with comorbid conditions undergoing major surgical procedures is growing continuously with advancements in treating disease [1]. Many patients, however, still continue to experience severe perioperative complications with reported early postoperative mortality rates between 1 and 4% and morbidity rates of up to 10 times higher after major noncardiac surgery [2,3]. Findings from the recent observational International Surgical Outcomes Study, including data from 44 814 adult patients from 474 hospitals, suggested that one in six patients experienced a complication before hospital discharge and one in 35 patients subsequently died without leaving the hospital [4].

An important avoidable cause of organ dysfunction after surgery is arterial hypotension. Blood pressure (BP) management is receiving increased attention in recent years and there is accumulating evidence that hypotension is an important risk factor for myocardial injury, acute kidney injury (AKI) and increased mortality in surgical patients [5–9]. Arterial pressure is easily modifiable during the perioperative period using fluids and/or vasopressors. Surprisingly, hemodynamic management strategies in the past decade often used predefined population based on BP as therapeutic targets. However, a single BP therapeutic target does not necessary represent the optimal threshold value of an individual to maintain perfusion pressure, and BP targets tailored to individual patient physiology may be preferable in some patients. Understanding the importance of BP management to support perfusion of critical organs and determining optimal BP

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KEY POINTS

- Intraoperative hypotension is an important contributor to postoperative organ injury and mortality in surgical patients.
- Traditional BP management is often based on clinician knowledge and experience using empirically chosen targets.
- Personalized BP management aims at individualizing BP targets according to individual patient physiology and clinical context.
- The Intraoperative Norepinephrine to Control Arterial Pressure trial showed that individualizing BP target tailored to individual patient usual BP during the perioperative period can help to reduce postoperative organ dysfunction.
- Future clinical data are needed to more precisely determine whether personalized BP management strategies can be beneficial in patients requiring ICU admission.

treatment targets are thus particularly important in high-risk surgical patients.

The purpose of this review is to discuss the contribution of arterial hypotension to postoperative organ dysfunction, focusing on the promising findings of personalized BP treatment to improve outcome in surgical patients.

PROGNOSTIC IMPLICATIONS OF HYPOTENSION

Hemodynamic instability and various degrees of hypotension are common during surgery under general anesthesia, and arterial hypotension has long been regarded as a common side-effect of anesthetic drugs, with no harmful secondary effects. Importantly, there is no clear, unanimously accepted, definition of what constitutes a hypotension, with the most common definitions being a systolic BP lower than 80 mmHg, a mean arterial pressure (MAP) lower than 55–60 mmHg and a decrease in either systolic BP or MAP of 25% from baseline [10,11▪]. As a corollary, BP management decisions are often based on clinician knowledge, experience and beliefs. There is accumulating evidence, however, that even brief periods of intraoperative hypotension may be harmful, and that harms may start below a wide range of commonly encountered BP thresholds that are currently accepted as standard of care [12].

In the large multicenter randomized PeriOperative ISchemic Evaluation (POISE) study, a double-blinded trial of extended-release metoprolol and placebo in 8351 noncardiac surgery patients at risk of cardiac events following surgery, clinically significant intraoperative hypotension, defined as systolic BP below 90 mmHg requiring treatment, was found to have the largest population attributable risk for perioperative death and stroke [13]. Similarly, a large prospective multicenter cohort in 3387 noncardiac surgery patients with intermediate-to-high surgery-specific risk under general or regional anesthesia suggested that intraoperative hypotension, defined MAP lower than 20% from the patient's usual preoperative MAP value and requiring treatment, was independently associated with postoperative major adverse cardiac and cerebrovascular events [14]. Previous studies also identified a significant relationship between intraoperative hypotension and postoperative mortality among patients undergoing noncardiac surgery [9,15].

Significant associations were also identified between intraoperative hypotension and organ-specific injury. Of all organ function, renal function may be the most studied with regard to BP not only because kidneys are among the most sensitive organs to be affected by hypotension, but also because major surgery is the most common trigger for AKI after sepsis. Risk for AKI appears to start at MAP thresholds lower than 65 mmHg and to increase gradually with the severity of hypotensive exposure [5–7].

The risk of postoperative organ injury depends on the magnitude and the duration of the hypotension-induced injury. A recent systematic review summarizing available literature on the relation between intraoperative hypotension and outcomes suggested that organ injury might occur when MAP decreases below 80 mmHg for a duration exceeding 10 min [11▪]. Elevated risks are suggested for increased durations of MAP levels below 60–65 mmHg or for any exposure when MAP falls below 55 mmHg, without any obvious difference among organ systems.

RATIONALE FOR PERSONALIZING ARTERIAL PRESSURE TARGETS

Most anesthetic drugs affect cardiovascular function in a dose-dependent manner by reducing central sympathetic tone, attenuating baroreflex activity and inhibiting end-organ BP autoregulatory function [16]. Sympathetically mediated vasoconstriction plays an important role in the regulation of oxygen delivery between organ systems, allowing for the redistribution of blood flow and increasing the efficacy of oxygen extraction in conditions of reduced oxygen delivery [17,18]. Moreover, general anesthetics may act directly on vascular smooth

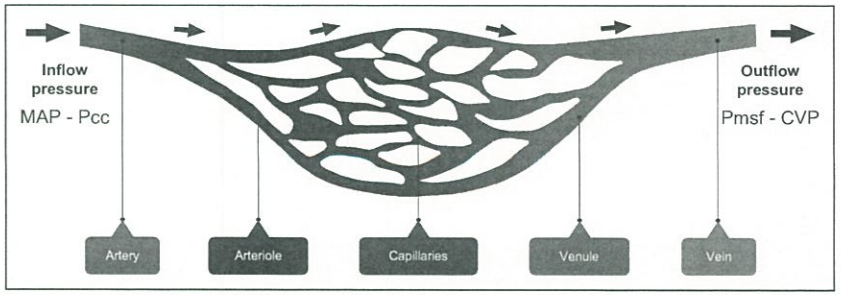

FIGURE 1. The organ perfusion pressure is the difference between the inflow pressure and the outflow pressure. The inflow pressure is the difference between the mean arterial pressure (MAP) and arterial critical closing pressure (Pcc), which is the BP value under which the flow between arterial and venous side of circulation is stopped despite the persistence of a pressure gradient. The outflow pressure is the difference between the mean systemic filling pressure (P_{msf}) and central venous pressure (CVP). Inflow and outflow pressures vary between organ systems.

muscle and/or endothelial cells, influencing therefore peripheral and/or regional vascular resistance, and hence blood flow [19].

Tissue hypoperfusion is an important trigger of organ injury and a critical issue in high-risk patients. Organ perfusion pressure is determined by the difference between the inflow pressure and the outflow pressure. A sufficient inflow pressure, which is the difference between MAP and arterial critical closing pressure, must be maintained to preserve organ perfusion [20] (Fig. 1). Inflow and outflow pressures differ between organ systems and, consequently, there is not a unique threshold value for MAP. Importantly, under normal conditions, organ blood flow is maintained stable within a wide range of MAP because of regional autoregulation resulting from changes in vasomotor tone. Vasodilatation is the main mechanism to increase organ blood flow. However, because the arterial critical closing pressure depends on the sympathetically mediated vasomotor tone, when vasodilation increases, the arterial critical closing pressure decreases toward outflow pressure [21]. Consequently, when perfusion pressure falls below the organ-specific autoregulation threshold level, organ blood flow decreases linearly with perfusion pressure and becomes dependent on BP, and thus MAP. In such circumstances, an increase in MAP may therefore become of particular significance to restore perfusion pressure. Importantly, in patients with chronic hypertension, the lower limit of organ-specific autoregulation threshold is shifted to the right and blood flow might become dependent on perfusion pressure for higher MAP values [22,23], thus suggesting targeting higher BP values in these patients. Moreover, targeting a single given BP therapeutic value may not necessary represent the optimal threshold value for an individual patient to maintain perfusion pressure.

Thus, personalized BP management, instead of targeting fixed BP threshold values, could be defined as a treatment strategy of targeting BP values tailored to each individual patient physiology, taking into consideration acute and chronic (comorbid conditions) pathophysiological cardiovascular alterations that may influence organ-specific blood flow autoregulation.

CLINICAL EVIDENCE FOR PERSONALIZING BLOOD PRESSURE MANAGEMENT IN SURGICAL PATIENTS

Although the relationship between hypotension and postoperative organ injury or death has been extensively suggested [5–8], the goals of intraoperative BP management are not well supported by a robust evidence base and there are few data to support any specific practice. For example, specifically regarding postoperative renal dysfunction, a common complication after major noncardiac surgery [24], current guidelines in the perioperative setting recommend maintaining MAP between 60 and 70 mmHg to prevent AKI, and to consider an MAP target higher than 70 mmHg in patients with chronic hypertension [25]. The recommendation was, however, based on limited evidence as most available data arise from observational studies or retrospective cohort analyses of data obtained from electronic medical records [5–7,26], in which the possibility of residual confounding factors is difficult to exclude. Another study, by analyzing a large database of 152 445 adult patients undergoing

noncardiac surgery, also suggested that targeting higher MAP values might be beneficial and that BP target values should be personalized according to whether or not patients suffer from chronic hypertension [12]. However, even though it may seem intuitive to adjust BP threshold targets to patient physiology, intervention trials are required to evaluate the causal relation between BP management and outcomes.

In this context, the Intraoperative Norepinephrine to Control Arterial Pressure (INPRESS) trial was developed to compare two intraoperative BP management strategies in high-risk noncardiac surgical patients [27▪▪]. In this multicenter randomized clinical trial, adult patients at increased risk of postoperative complications were randomly assigned to receive an individualized management strategy aimed at achieving and maintaining a systolic BP within 10% of the reference value using a continuous infusion of norepinephrine or a standard management strategy using intravenous boluses of ephedrine to treat any drop in systolic BP values below 80 mmHg or lower than 40% from the reference value during and for 4 h following surgery. A notable aspect of the trial is the use of a protocolized goal-directed fluid management therapy in the two groups, and the cumulative volume of fluids infused over the intervention period and the cardiac index values were not significantly different between study groups. The primary endpoint, a composite of systemic inflammatory response syndrome and dysfunction of at least one organ system by day 7 after surgery, occurred in 56 of 147 patients (38.1%) assigned to the individualized treatment strategy and 75 of 145 patients (51.7%) assigned to the standard treatment strategy [relative risk, 0.73; 95% confidence interval (CI), 0.56–0.94]. In addition, there was a significant reduction in renal dysfunction (adjusted relative risk, 0.70; 95% CI, 0.53–0.92) and a lower probability of postoperative organ dysfunction at 30 days (adjusted hazard ratio, 0.66; 95% CI, 0.52–0.84) in patients assigned to the individualized treatment strategy. Overall, the INPRESS trial suggested that a personalized BP management is an important consideration when defining an intraoperative BP target and that active management of BP may improve patient outcome.

In a second trial, 678 elderly patients with chronic hypertension who underwent major gastrointestinal surgery were randomly allocated to one of three target MAP groups (65–79 mmHg, 80–95 mmHg and 96–110 mmHg) [28]. A fluid management protocol aimed at maintaining stroke volume variation at 8–13% was used in each group and vasoactive agents (norepinephrine, phenylephrine, nitroglycerin and phentolamine) were introduced to adjust the MAP level. The primary outcome, the incidence of AKI after major abdominal surgery, was achieved in 6.3% of patients allocated to the 80–95 mmHg target group, as compared with 13.5 and 12.9% in patients allocated to the 65–79 mmHg and 96–110 mmHg groups, respectively.

An elegant prospective observational study of 410 patients during cardiac surgery with cardiopulmonary bypass suggested that individualizing MAP targets adjusted on individual patient's cerebral blood flow autoregulation using continuous monitoring of near-infrared spectroscopy signals might be useful to guide individual MAP targets to protect organ function [29]. The study showed that rather than absolute MAP values, BP excursion below the cerebral autoregulation threshold was associated with postoperative AKI.

Thus, taken together, these findings provide physiological rational emphasizing the importance of personalizing BP targets based on individual patient's characteristics and clinical conditions.

PRACTICAL APPROACH OF PERSONALIZED BLOOD PRESSURE MANAGEMENT IN SURGICAL PATIENTS

The available evidence suggests that targeting an MAP of 65–70 mmHg in a surgical patient who does not have preexisting risk factors is a reasonable approximation. In patients with comorbid conditions, personalized BP management should ideally set BP target considering the individual patient physiology (for instance in patients with chronic hypertension) and the clinical situation. There is, however, no simple way to determine the organ-specific autoregulation threshold level and different vascular beds have different autoregulation thresholds. A pragmatic approach during surgery is to set BP target based on the personal usual BP value of each individual patient and, where necessary, to promote continuous infusion rather than intermittent intravenous vasopressor adminsitration. On this respect, a particular feature of the INPRESS trial was the use of 10 μg/ml solution of norepinephrine administered using a dedicated peripheral intravenous line.

FUTURE DIRECTIONS FOR PERSONALIZED BLOOD PRESSURE MANAGEMENT IN HIGH-RISK PATIENTS

Personalized BP management requires access to individual patient BP value to be targeted. A notable aspect of the INPRESS trial was the use of the patient's resting BP as baseline reference value. Although it seems intuitive to target the patient's personal normal value, assessing individual BP values may obviously be challenging in patients requiring emergency surgery or in the ICU. Additional clinical data are needed to evaluate the conditions needed for the implementation and the effectiveness of personalized BP management in such situations.

Postoperative hypotension is common in patients undergoing major surgery. A recent substudy of the PeriOperative ISchemic Evaluation 2 (POISE-2) trial, a double-blinded factorial trial of aspirin and clonidine in noncardiac surgery patients, showed that hypotension during the first 4 postoperative days was strongly associated with a 30-day composite of myocardial infarction and death [30▪▪]. There are few data to support any specific BP target in surgical patients during the postoperative period. A retrospective observational study of consecutive adults admitted to ICU after cardiovascular surgery investigated the relationship between postoperative BP deficits and AKI progression (defined as an increase of at least one KDIGO stage from baseline premorbid creatinine level) in vasopressor-dependent patients [31]. Interestingly, although patients with AKI progression had equivalent MAP to those who did not [time-weighted average MAP of 73 mmHg (interquartile range 70–78) and 75 mmHg (interquartile range 72–79), respectively], the time-weighted difference between premorbid and achieved in-ICU deficits in diastolic arterial pressure (DAP), mean perfusion pressure (i.e. the difference between MAP and central venous pressure (CVP)) and diastolic perfusion pressure (i.e. the difference between DAP and CVP) was greater in patients with AKI progression. Although, more clinical data are needed to more precisely determine whether personalized BP management strategies may be beneficial in the acute postoperative period, this raises the possibility that adjusting BP values to preoperative (premorbid) levels may be important in high-risk surgical patients.

The issue of vasopressor choice needed to support a given MAP target needs to be further clarified. There are few data to support the superiority of one vasopressor over the others in this context. It may seem intuitive to prioritize sympathomimetic-based vasopressor agents acting predominantly on vascular smooth muscle α-1 receptor under hypotensive conditions. However, because of the ubiquitous distribution of adrenergic receptors, vasopressors carry a potential to induce adverse side-effects that can impair several organ functions, especially cardiac function. This is what makes BP manipulation particularly challenging, justifying therefore appropriate hemodynamic monitoring.

CONCLUSION

The available evidence suggests that hypotension is an important contributor to postoperative organ injury and mortality in surgical patients. BP management decisions are often based on clinician knowledge, experience and/or beliefs, using fixed population-based or empirically defined BP values as targets. However, the complexity of the mechanisms driving the regulation of organ perfusion pressure makes fairly unrealistic a 'one-size fits all' approach to BP, especially in high-risk patients or during major surgery with hemodynamic instability. Personalized BP management sets BP values tailored to individual patient physiology considering factors that may influence inflow and outflow pressures in determining organ perfusion pressure. Although there is little robust evidence base supporting a safety threshold for BP, targeting an MAP value of 65 mmHg during surgery may be considered a reasonable approach in patients under general anesthesia. However, because of the redistribution of blood flow and the pressure–flow relationship during hypotensive conditions, targeting higher MAP values might be more suitable in patients with advanced age and/or comorbid conditions such as chronic hypertension and atherosclerosis. Although this needs to be more extensively evaluated, personalized BP management may improve patient outcome after major surgery.

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Conflicts of interest

T.G. and R.G. have no conflicts of interests to declare.

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- ▪ of special interest
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JAMA Surgery | Special Communication

Guidelines for Perioperative Care in Cardiac Surgery
Enhanced Recovery After Surgery Society Recommendations

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Enhanced Recovery After Surgery (ERAS) evidence-based protocols for perioperative care can lead to improvements in clinical outcomes and cost savings. This article aims to present consensus recommendations for the optimal perioperative management of patients undergoing cardiac surgery. A review of meta-analyses, randomized clinical trials, large nonrandomized studies, and reviews was conducted for each protocol element. The quality of the evidence was graded and used to form consensus recommendations for each topic. Development of these recommendations was endorsed by the Enhanced Recovery After Surgery Society.

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Invited Commentary

Supplemental content

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Enhanced Recovery After Surgery (ERAS) is a multimodal, transdisciplinary care improvement initiative to promote recovery of patients undergoing surgery throughout their entire perioperative journey.[1] These programs aim to reduce complications and promote an earlier return to normal activities.[2,3] The ERAS protocols have been associated with a reduction in overall complications and length of stay of up to 50% compared with conventional perioperative patient management in populations having noncardiac surgery.[4-6] Evidence-based ERAS protocols have been published across multiple surgical specialties.[1] In early studies, the ERAS approach showed promise in cardiac surgery (CS); however, evidence-based protocols have yet to emerge.[7]

To address the need for evidence-based ERAS protocols, we formed a registered nonprofit organization (ERAS Cardiac Society) to use an evidence-driven process to develop recommendations for pathways to optimize patient care in CS contexts through collaborative discovery, analysis, expert consensus, and best practices. The ERAS Cardiac Society has a formal collaborative agreement with the ERAS Society. This article reports the first expert-consensus review of evidence-based CS ERAS practices.

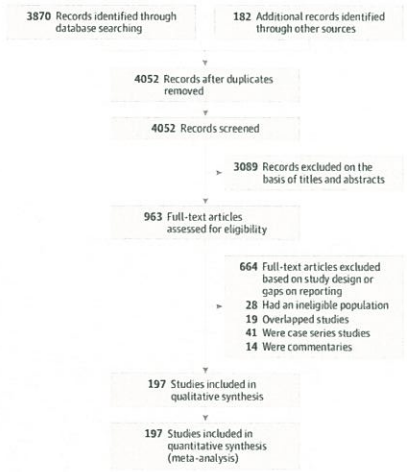
Methods

We followed the 2011 Institute of Medicine *Standards for Developing Trustworthy Clinical Practice Guidelines*, using a standardized algorithm that included experts, key questions, subject champions, systematic literature reviews, selection and appraisal of evidence quality, and development of clear consensus recommendations.[8] We minimized repetition of existing guidelines and consensus statements and focused on specific information in the framework of ERAS protocols.

As sanctioned by the ERAS Society, we began with a public organizational meeting in 2017 where broad topics of ERAS in CS were discussed, and we solicited public comment regarding appropriate approaches and protocols. A multidisciplinary group of 16 cardiac surgeons, anesthesiologists, and intensivists were identified who demonstrated expertise and experience with ERAS. The group agreed on 22 potential interventions, divided into preoperative, intraoperative, and postoperative phases of recovery.

After selecting topics and assigning group leaders, literature searches were conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure), and this included reviews, guideline documents, and studies that were conducted on humans since 2000, published in English, and retrievable from PubMed, Excerpta Medica (Embase), Cochrane, the Agency for Healthcare Research and Quality, and other selected databases relevant to this consensus.[9] Medical Subject Heading terms were used, as were accompanying entry terms for the patient group, interventions, and outcomes. Two independent reviewers (W.B.A. and 1 nonauthor) screened the abstracts considered for topics. Prospective randomized clinical trials, meta-analyses, and well-designed, nonrandomized studies were given preference. When multiple publications had sample overlap, the most recent report was selected. Controversies were discussed and resolved via in-person meetings, conference calls, and discussions. A minimum of 75% agreement on class and level was required for consensus.[10] Consistent with the Institute of Medicine guidelines, panel members with relevant conflicts of interest (COI) were identified and recused from voting on associated recommendations. The structure of the recommendations was modeled after prior published ERAS guidelines.[11] We used the Society of Thoracic Surgeons/American Association for Thoracic Surgery 2017 updated document "Classification of Recommendations and Level of Evidence," and American College of Cardiology/American Heart Association clinical practice guidelines to grade the consensus class (strength) of recommendation and level (quality) of evidence.[10,12] (Box; eAppendix in the Supplement).

Figure. PRISMA Flow Diagram



Box. Class of Recommendation and Levels of Evidence[a]

Class (Strength) of Recommendation

I (strong): benefit many times greater than risk

IIa (moderate): benefit much greater than risk

IIb (weak): benefit greater than risk

III: no benefit (moderate): benefit equal to risk

III: harm (strong): risk greater than benefit

Level (Quality) of Evidence

A
High-quality evidence from more than 1 randomized clinical trial
Meta-analysis of high-quality randomized clinical trials
One or more randomized clinical trials corroborated by registry studies

B-R
Moderate-quality evidence from 1 or more randomized clinical trial
Meta-analysis of moderate-quality randomized clinical trials

B-NR
Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies or observational studies

C-LD
Randomized or nonrandomized observational or registry studies with limitations of design or execution

C-EO
Consensus of expert opinion based on clinical experience

[a] Adapted from Jacobs AK, Anderson JL, Halperin JL. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force 1099 on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:1373-84.[13] (Reprinted with permission from Elsevier.)

Results

Resulting consensus statements are summarized in Table 1. They are organized into preoperative, intraoperative, and postoperative strategies.

Preoperative Strategies

Preoperative Measurement of Hemoglobin A_{1c} for Risk Stratification

Optimal preoperative glycemic control, defined by a hemoglobin A_{1c} level less than 6.5%, has been associated with significant decreases in deep sternal wound infection, ischemic events, and other complications.[13,14] Evidence-based guidelines based on poor-quality meta-analyses recommend screening all patients for diabetes preoperatively and intervening to improve glycemic control to achieve a hemoglobin A_{1c} level less than 7% in patients for whom this is relevant.[15] Despite this recommendation, approximately 25% of patients undergoing CS have hemoglobin A_{1c} levels greater than 7%, and 10% have undiagnosed diabetes, indicating a failure to apply current evidence-based recommendations for preoperative diabetes management.[16] A recent retrospective review demonstrated that preadmission glycemic control, as assessed by hemoglobin A_{1c}, is associated with decreased long-term survival.[17] It is unclear whether preoperative interventions in patients undergoing CS will result in improved outcomes. Based on this moderate-quality evidence, we recommend preoperative measurement of hemoglobin A_{1c} to assist with risk stratification (class IIa, level C-LD).

Preoperative Measurement of Albumin for Risk Stratification

Low preoperative serum albumin in patients undergoing CS is associated with an increased risk of morbidity and mortality postoperatively (independent of body mass index).[18] Hypoalbuminemia is a prognosticator of preoperative risk, correlating with increased length of time on a ventilator, acute kidney injury (AKI), infection, longer length of stay, and mortality.[19-21] Low-quality meta-analyses support measuring preoperative albumin to prognosticate postoperative CS complications.[21] Based on the moderate quality of evidence, it can be useful to assess preoperative albumin before CS to assist with risk stratification (class IIa, level C-LD).

Preoperative Correction of Nutritional Deficiency

For patients who are malnourished, oral nutritional supplementation has the greatest effect if started 7 to 10 days preoperatively and has been associated with a reduction in the prevalence of infectious complications in colorectal patients.[22] In patients undergoing CS who had a serum albumin level less than 3.0 g/dL (to convert to g/L, multiply by 10.0), supplementation with 7 to 10 days' worth of intensive nutrition therapy may improve outcomes.[23-26] Currently, however, no adequately powered trials of nutritional therapy initiated early in patients undergoing CS who are considered high risk are available.[27] In addition, this may not be feasible in urgent or emergency settings. Further studies are needed to determine when to delay surgery to correct nutritional deficits. Based on these data, we note that correction of nutritional deficiency is recommended when feasible (class IIa, level C-LD).

Table 1. Classification of Recommendation and Level of Evidence

LOE by COR	Recommendation
I	
A	Tranexamic acid or epsilon aminocaproic acid during on-pump cardiac surgical procedures
B-R	Perioperative glycemic control
B-R	A care bundle of evidence-based best practices to reduce surgical site infections
B-R	Goal-directed fluid therapy
B-NR	A perioperative, multimodal, opioid-sparing, pain management plan
B-NR	Avoidance of persistent hypothermia (<36.0°C) after cardiopulmonary bypass in the early postoperative period.
B-NR	Maintenance of chest tube patency to prevent retained blood
B-NR	Postoperative systematic delirium screening tool use at least once per nursing shift
C-LD	Stopping smoking and hazardous alcohol consumption 4 weeks before elective surgery
IIa	
B-R	Early detection of kidney stress and interventions to avoid acute kidney injury after surgery
B-R	Use of rigid sternal fixation to potentially improve or accelerate sternal healing and reduce mediastinal wound complications
B-NR	Prehabilitation for patients undergoing elective surgery with multiple comorbidities or significant deconditioning
B-NR	An insulin infusion to treat hyperglycemia in all patients postoperatively
B-NR	Strategies to ensure extubation within 6 h of surgery
C-LD	Patient engagement tools, including online/application-based systems to promote education, compliance, and patient-reported outcomes
C-LD	Chemical or mechanical thromboprophylaxis after surgery
C-LD	Preoperative measurement of hemoglobin A1c to assist with risk stratification
C-LD	Preoperative correction of nutritional deficiency when feasible
IIb	
C-LD	Continued consumption of clear liquids up until 2 to 4 h before general anesthesia
C-LD	Preoperative oral carbohydrate loading may be considered before surgery
III (No Benefit)	
A	Stripping or breaking the sterile field of chest tubes to remove clots.
III (Harm)	
B-R	Hyperthermia (>37.9°C) while rewarming on cardiopulmonary bypass.

Abbreviations: A, A-level evidence; B-R, B-level evidence, randomized studies; B-NR, B-level evidence, nonrandomized studies; C-LD, C-level evidence, limited data; COR, classification of recommendation; LOE, level of evidence.

Consumption of Clear Liquids Before General Anesthesia

Most CS programs mandate that a patient ingest nothing by mouth after midnight for surgery the following day, or at the very least, fast for 6 to 8 hours from the intake of a solid meal before elective cardiac surgery.[28] Several randomized clinical trials have demonstrated, however, that nonalcoholic clear fluids can be safely given up to 2 hours before the induction of anesthesia, and a light meal can be given up to 6 hours before elective procedures requiring general anesthesia.[28-30] Encouraging clear liquids until 2 to 4 hours preoperatively is an important component of all ERAS protocols outside of CS.[31] However, no large studies have been performed in populations undergoing CS. The supporting evidence is extrapolated from populations having noncardiac surgery. A small study in patients undergoing CS demonstrated that an oral carbohydrate drink consumed 2 hours preoperatively was safe, and no incidents of aspiration occurred.[32] Aspiration pneumonitis has not been reported, although this potential remains in patients undergoing CS who have delayed gastric emptying owing to diabetes mellitus, and transesophageal echocardiography may also increase aspiration risk. Based on the data available on CS, clear liquids may be continued up to 2 to 4 hours before general anesthesia (class IIb, level C-LD).

Preoperative Carbohydrate Loading

A carbohydrate drink (a 12-ounce clear beverage or a 24-g complex carbohydrate beverage) 2 hours preoperatively reduces insulin resistance and tissue glycosylation, improves postoperative glucose control, and enhances return of gut function.[31] In a 2003 Cochrane review[30] of patients undergoing CS, carbohydrate loading reduced postoperative insulin resistance and hospital length of stay. In a large randomized clinical trial[29,30] in patients undergoing CS, preoperative carbohydrate administration was found to be safe and improved cardiac function immediately after cardiopulmonary bypass. However, it did not affect postoperative insulin resistance.[33,34] Given the current minimal supportive data in patients undergoing CS, carbohydrate loading is given a weak recommendation at this time (class IIb, level C-LD).

Patient Engagement Tools

Patient education and counseling prior to surgery can be completed in person, through printed material, or through novel online or application-based approaches. These efforts include explanations of procedures and goals that may help reduce perioperative fear, fatigue, and discomfort and enhance recovery and early discharge. Data are emerging that software applications can engage patients, promote compliance, and capture patient-reported outcome measures.[35] They are designed to increase preventive care and encourage patients to perform physical exercise. These platforms have the potential to increase patient knowledge, decrease anxiety, improve health outcomes, and reduce variation in care.[36,37] Pilot studies in CS have demonstrated the effectiveness of e-health platforms without any evidence of harm. Thus, it is recommended that these efforts be undertaken[37] (class IIa, level C-LD).

Prehabilitation

Prehabilitation enables patients to withstand the stress of surgery by augmenting functional capacity.[38-40] Preoperative exercise decreases sympathetic overreactivity, improves insulin sensitivity, and increases the ratio of lean body mass to body fat.[41-43] It also improves physical and psychological readiness for surgery, reduces postoperative complications and the length of stay, and improves the transition from the hospital to the community.[38,39] A cardiac prehabilitation program should include education, nutritional optimization, exercise training, social support, and anxiety reduction, although current existing evidence is limited.[41-44] Three non-CS studies[45-47] have successfully demonstrated the benefits of 3 to 4 weeks of prehabilitation in the context of ERAS. Prehabilitation interventions prior to CS must be further examined to advance this area of research. The small number of studies and the diversity of validation tools used limits the strength of the recommendation. In

addition, this may not be feasible in urgent and emergency settings (class IIa, level B-NR).

Smoking and Hazardous Alcohol Consumption

Screening for hazardous alcohol use and cigarette smoking should be performed preoperatively.[48] Tobacco smoking and hazardous alcohol consumption are risk factors for postoperative complications and present another opportunity for preoperative interventions. They are associated with respiratory, wound, bleeding, metabolic, and infectious complications.[23,49-51] Smoking cessation and alcohol abstinence for 1 month are associated with improved postoperative outcomes after surgery.[51-53] Only a small number of studies are available, and further CS-specific studies are needed. However, given the low risk of this intervention, patients should be questioned regarding smoking and hazardous alcohol consumption using validated screening tools, and consumption should be stopped 4 weeks before elective surgery.[54] However, this may not be feasible in urgent or emergency settings (class I, level C-LD).

Intraoperative Strategies

Surgical Site Infection Reduction

To help reduce surgical site infections, CS programs should include a care bundle that includes topical intranasal therapies, depilation protocols, and appropriate timing and stewardship of perioperative prophylactic antibiotics, combined with smoking cessation, adequate glycemic control, and promotion of postoperative normothermia during recovery. Moderate-quality meta-analysis have concluded that care bundles of 3 to 5 evidence-based interventions can reduce surgical site infections.[55,56] This topic has been reviewed extensively with class of recommendation and level of evidence in an expert consensus review by Lazar et al.[57]

Evidence supports topical intranasal therapies to eradicate staphylococcal colonization in patients undergoing CS.[57,58] From 18% to 30% of all patients undergoing surgery are carriers of *Staphylococcus aureus*, and they have 3 times the risk of *S. aureus* surgical site infections and bacteremia.[59] It is recommended that topical therapy be applied universally.[60-62] Two studies validate the reduction of such infections in patients receiving mupirocin.[58,63] Level IA data exists suggesting that weight-based cephalosporins should be administered fewer than 60 minutes before the skin incision and continued for 48 hours after completion of CS. When the surgery is more than 4 hours, antibiotics require redosing.[64,65] Clarity on the preferability of continuous vs intermittent dosing of cefazolin requires further data.[66] A meta-analysis of skin preparation and depilation protocols indicates that clipping is preferred to shaving.[67] Clipping using electric clippers should occur close to the time of surgery.[68] A preoperative shower with chlorhexidine has only been demonstrated to reduce bacterial counts in the wound and is not associated with significant levels of efficacy.[57] Postoperative measures including sterile dressing removal within 48 hours and daily incision washing with chlorhexidine are potentially beneficial.[69,70]

In summary, we recommend the implementation of a care bundle to include topical intranasal therapies to eradicate staphylococcal colonization, weight-based cephalosporin infusion fewer than 60 minutes before skin incision, with redosing for cases longer than 4 hours, skin preparation, and depilation protocols with dressing changes every 48 hours to reduce surgical site infections (class I, level B-R). The bundle of recommendations to reduce surgical site infections is summarized in Table 2 with the classification of recommendations and level of evidence per Lazar et al.[57]

Table 2. Surgical Site Infection Bundle, Including Classification of Recommendation and Level of Evidence

LOE by COR	Recommendation
I	
A	Perform topical intranasal decolonization prior to surgery
A	Administer intravenous cephalosporin prophylactic antibiotic 30-60 min prior to surgery
C	Clipping (as opposed to shaving) immediately prior to surgery
IIb	
C	Use a chlorhexidine-alcohol-based solution for skin preparation before surgery
IIa	
C	Remove operative wound dressing after 48 h

Abbreviations: COR, classification of recommendation; LOE, level of evidence.

Hyperthermia

Moderate-quality prospective studies have demonstrated that when rewarming on cardiopulmonary bypass (CPB), hyperthermia (core temperature >37.9°C) is associated with cognitive deficits, infection, and renal dysfunction.[71-73] Any postoperative hyperthermia within 24 hours after coronary artery bypass grafting has been associated with cognitive dysfunction at 4 to 6 weeks.[71] Rewarming on CPB to normothermia should be combined with continuous surface warming.[74] Thus, we recommend avoiding hyperthermia while rewarming on cardiopulmonary bypass (class III, level B-R).

Rigid Sternal Fixation

Most cardiac surgeons use wire cerclage for sternotomy closure because of the perceived low rate of sternal wound complications and low cost of wires. Wire cerclage brings the cut edges of bone back together by wrapping a wire or band around or through the 2 portions of bone, then tightening the wire or band to pull the 2 parts together. This achieves approximation and compression but does not eliminate side-by-side movement, and thus rigid fixation is not achieved with wire cerclage.[75]

In 2 multicenter randomized clinical trials, sternotomy closure with rigid plate fixation resulted in significantly better sternal healing, fewer sternal complications, and no additional cost compared with wire cerclage at 6 months after surgery.[75,76] Patient-reported outcome measures demonstrated significantly less pain, better upper-extremity function, and improved quality-of-life scores, with no difference in total 90-day cost.[76] Limitations of these studies include a sample size designed to test the primary end point of improved sternal healing but not the secondary end points of pain and function; in addition, the studies were limited by unblinded radiologists. Additional research[77-79] demonstrated decreased mediastinitis, painful sternal nonunion relief after median sternotomy, and superior bony healing when compared with wire cerclage. Based on these studies, the consensus concluded that rigid sternal fixation has benefits in patients undergoing sternotomy and should be especially considered in individuals at high risk, such as those with a high body mass index, previous chest wall radiation, severe chronic obstructive pulmonary disorder, or steroid use. Rigid sternal fixation can be useful to improve or accelerate sternal healing and reduce mediastinal wound complications (class IIa, level B-R).

Tranexamic Acid or Epsilon Aminocaproic Acid

Bleeding is a common occurrence after CS and can adversely affect outcomes.[80,81] Publications on patient blood management are typically focused on reducing red blood cell transfusions through identification and treatment of preoperative anemia, delineation of safe transfusion thresholds, intraoperative blood scavenging, monitoring of the coagulation system, and data-driven algorithms for appropriate transfusion practices. This has been an area of focus in previously published, large, comprehensive, multidisciplinary, multisociety clinical practice guidelines.[82,83] The inclusion of all aspects of patient blood management are beyond the scope of these recommendations, although we encourage the incorporation of these existing guidelines within a local ERAS framework. This includes education, audit, and continuous practitioner feedback. Owing to the near-universal accessibility, low-risk profile, cost-effectiveness, and ease of implementation, we did evaluate antifibrinolytic use with tranexamic acid or epsilon aminocaproic acid. In a large randomized clinical trial of patients undergoing coronary revascularization, total blood products transfused, and major hemorrhage or tamponade requiring reoperation were reduced using tranexamic acid.[84] Higher dosages, however, appear to be associated with seizures.[85,86] A maximum total dose of 100 mg/kg is recommended.[87] Based on this evidence, tranexamic acid or epsilon aminocaproic acid is recommended during on-pump cardiac surgical procedures (class I, level A).

Postoperative Strategies

Perioperative Glycemic Control

Interventions to improve glycemic control are known to improve outcomes. Multiple randomized clinical trials[88-91] with diverse patient cohorts support intensive perioperative glucose control. Preoperative carbohydrate loading has resulted in reduced glucose levels after abdominal surgery and CS.[92,93] Epidural analgesia during CS has been shown to reduce hyperglycemia incidence.[94] After CS, hyperglycemia morbidity is multifactorial and attributed to glucose toxicity, increased oxidative stress, prothrombotic effects, and inflammation.[14,15,89,91,95] Perioperative glycemic control is recommended based on randomized data[96] not specific to populations undergoing CS and high-quality observational studies (class I, level B-R).

Insulin Infusion

Treatment of hyperglycemia (glucose >160-180 mg/dL [to convert to mmol/L, multiply by 0.0555]) with an insulin infusion for the patient undergoing CS may be associated with improved perioperative glycemic control. Postoperative hypoglycemia should be avoided, especially in patients with a tight blood glucose target range (ie, 80-110 mg/dL).[95,97,98] Randomized clinical trials support insulin infusion protocols to treat hyperglycemia perioperatively; however, more high-quality, CS-specific studies are needed (class IIa, level B-NR).

Pain Management

Until recently, parenteral opioids were the mainstay of postoperative pain management after CS. Opioids are associated with multiple adverse effects, including sedation, respiratory depression, nausea, vomiting, and ileus.[99] There is growing evidence that multimodal opioid-sparing approaches can adequately address pain through the additive or synergistic effects of different types of analgesics, permitting lower opioid doses in the population receiving CS.[100]

Nonsteroidal anti-inflammatory drugs are associated with renal dysfunction after CS.[101] Selective *COX-2* inhibition is associated with a significant risk of thromboembolic events after CS.[102] The safest nonopioid analgesic may be acetaminophen.[103] Intravenous acetaminophen may be better absorbed until gut function has recovered postoperatively.[104] Per a medium-quality meta-analysis, when added to opioids, acetaminophen produces superior analgesia, an opioid-sparing effect, and independent antiemetic actions.[105] Acetaminophen dosing is 1 g every 8 hours. Combination acetaminophen preparations with opioids should be discontinued.

Tramadol has dual opioid and nonopioid effects but with a high delirium risk.[106] Tramadol produces a 25% decrease in morphine consumption, decreased pain scores, and improved patient comfort postoperatively.[107] Pregabalin also decreases opioid consumption and is used in postoperative multimodal analgesia.[108] Pregabalin given 1 hour before surgery and for 2 postoperative days improves pain scores compared with placebo.[109] A 600-mg gabapentin dose, 2 hours before CS, lowers pain scores, opioid requirements, and postoperative nausea and vomiting.[110]

Dexmedetomidine, an intravenous α-2 agonist, reduces opioid requirements.[111] A medium-quality meta-analysis of dexmedetomidine infusion reduced all-cause mortality at 30 days with a lower incidence of postoperative delirium and shorter intubation times.[112,113] Dexmedetomidine may reduce AKI after CS.[114] Ketamine has potential uses in CS owing to its favorable hemodynamic profile, minimal respiratory depression, analgesic properties, and reduced delirium incidence; further studies are needed in the CS setting.[115]

Patients should receive preoperative counseling to establish appropriate expectations of perioperative analgesia targets. Pain assessments must be made in the intubated patient to ensure the lowest effective opioid dose. The Critical Care Pain Observation Tool, Behavioral Pain Scale, and Bispectral Index monitoring may have a role in this setting.[116-119] Although no single pathway exists for multimodal opioid-sparing pain management, there is sufficient evidence to recommend that CS programs use acetaminophen, Tramadol, dexmedetomidine, and pregabalin (or gabapentin) based on formulary availability (class I, level B-NR).

Postoperative Systematic Delirium Screening

Delirium is an acute confusional state characterized by fluctuating mental status, inattention, and either disorganized thinking or altered level of consciousness that occurs in approximately 50% of patients after CS.[120-125] Delirium is associated with reduced in-hospital and long-term survival, freedom from hospital readmission, and cognitive and functional recovery.[126] Early delirium detection is essential to determine the underlying cause (ie, pain, hypoxemia, low cardiac output, and sepsis) and initiate appropriate treatment.[127] A systematic delirium screening tool such as the Confusion Assessment Method for the Intensive Care Unit or the Intensive Care Unit Delirium Screening Checklist should be used.[128,129] The perioperative team should consider routine delirium monitoring at least once per nursing shift.[121]

Owing to the complexity of delirium pathogenesis, it is unlikely that a single intervention or pharmacologic agent will reduce

the incidence of delirium after CS.[127] Nonpharmacologic strategies are a first-line component of management.[130,131] There is no evidence that prophylactic antipsychotic use (eg, haloperidol) reduces delirium.[132,133] Based on moderate-quality, nonrandomized studies in patients receiving noncardiac surgery, delirium screening is recommended at least once per nursing shift to identify patients at risk and facilitate implementation of prevention and treatment protocols (class I, level B-NR).

Persistent Hypothermia

Postoperative hypothermia is the failure to return to or maintain normothermia (>36°C) 2 to 5 hours after an intensive care unit (ICU) admission associated with CS.[134] Hypothermia is associated with increased bleeding, infection, a prolonged hospital stay, and death. Large registry observational studies suggest if hypothermia is of short duration, outcomes can be improved.[135,136] Based on this evidence, we recommend prevention of hypothermia by using forced-air warming blankets, raising the ambient room temperature, and warming irrigation and intravenous fluids to avoid hypothermia in the early postoperative period[71,137-139] (class 1, level B-NR).

Chest Tube Patency

Immediately after CS, most patients have some degree of bleeding.[81] If left unevacuated, retained blood can cause tamponade or hemothorax. Thus, a pericardial drain is always necessary after CS to evacuate shed mediastinal blood.[80] Drains used to evacuate shed mediastinal blood are prone to clogging with clotted blood in up to 36% of patients.[140,141] When these tubes clog, shed mediastinal blood can pool around the heart or lungs, necessitating reinterventions for tamponade or hemothorax.[142-144] Retained shed mediastinal blood hemolyzes and promotes an oxidative inflammatory process that may further cause pleural and pericardial effusions and trigger postoperative atrial fibrillation.[143,145]

Chest tube manipulation strategies that are commonly used in an attempt to maintain tube patency after CS are of questionable efficacy and safety. One example is chest-tube stripping or milking, in which the practitioner strips the tubes toward the drainage canister to break up visible clots or create short periods of high negative pressure to remove clots. In meta-analyses of randomized clinical trials, chest-tube stripping has been shown to be ineffective and potentially harmful.[146,147] Another technique used to maintain patency is to break the sterile field to access the inside of chest tubes and use a smaller tube to suction the clot out. This technique may be dangerous, because it can increase infection risk and potentially damage internal structures.[148]

To address the unmet need to prevent chest-tube clogging, active chest-tube clearance methods can be used to prevent occlusion without breaking the sterile field. This has been demonstrated to reduce the subsequent need for interventions to treat retained blood compared with conventional chest tube drainage in 5 nonrandomized clinical trials of CS.[149-153] Active chest-tube clearance has also been shown to reduce postoperative atrial fibrillation, suggesting that retained blood may be a trigger for this common problem.[145]

While there are no standard criteria for the timing of mediastinal drain removal, evidence suggests that they can be safely removed as soon as the drainage becomes macroscopically serous.[154] Based on these clinical trials, maintenance of chest tube patency without breaking the sterile field is recommended to prevent retained blood complications (class I, level B-NR). Stripping or breaking the sterile field of chest tubes to remove clot is not recommended (class IIIA, level B-R).

Chemical Thromboprophylaxis

Vascular thrombotic events include both deep venous thrombosis and pulmonary embolism and represent potentially preventable complications after CS. Patients remain hypercoagulable after CS, increasing vascular thrombotic event risk.[155,156] All patients benefit from mechanical thromboprophylaxis achieved with compression stockings and/or intermittent pneumatic compression during hospitalization or until they are adequately mobile to reduce the incidence of deep-vein thrombosis after surgery even in the absence of pharmacological treatment.[157-159] Prophylactic anticoagulation for vascular thrombotic events should be considered on the first postoperative day and daily thereafter.[160] A recent medium-quality meta-analysis suggested that chemical prophylaxis could reduce vascular thrombotic event risk without increasing bleeding or cardiac tamponade.[161] Based on this evidence, pharmacological prophylaxis should be used as soon as satisfactory hemostasis has been achieved (most commonly on postoperative day 1 through discharge)[160-162] (class IIa, level C-LD).

Extubation Strategies

Prolonged mechanical ventilation after CS is associated with longer hospitalization, higher morbidity, mortality, and increased costs.[163] Prolonged intubation is associated with both ventilator-associated pneumonia and significant dysphagia.[164] Early extubation, within 6 hours of ICU arrival, can be achieved with time-directed extubation protocols and low-dose opioid anesthesia. This is safe (even in patients at high risk) and associated with decreased ICU time, length of stay, and costs.[165-172] A meta-analysis demonstrated that ICU times and length of stay were reduced; however, no difference in morbidity and mortality occurred, likely because of disparate study design and statistical underpowering.[173] Thus, studies have shown early extubation to be safe, but efficacy in reducing complications has not been conclusively demonstrated. Based on this evidence, we recommend strategies to ensure extubation within 6 hours of surgery (class IIa, level B-NR).

Kidney Stress and Acute Kidney Injury

Acute kidney injury (AKI) complicates 22% to 36% of cardiac surgical procedures, doubling total hospital costs.[174-176] Strategies to reduce AKI involve assessing which patients are at risk and then implementing therapies to reduce the incidence. Urinary biomarkers (such as tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7) can identify patients as early as 1 hour after CPB who are at increased risk of developing AKI.[177,178]

In a randomized clinical trial after CS, patients with positive urinary biomarkers who were assigned to an intervention algorithm had reductions in subsequent AKI.[179,180] The algorithm included avoiding nephrotoxic agents, discontinuing angiotensin-converting enzyme inhibitors and angiotensin II antagonists for 48 hours, close monitoring of creatinine and urine output, avoiding hyperglycemia and radiocontrast agents, and close monitoring to optimize volume status and hemodynamic parameters. Similar results have been reported in a randomized clinical trial after surgery in a population who received noncardiac surgery.[181]

Although many risk scores for AKI after CS have been published, these scoring systems have good discrimination in assessing low-risk groups but relatively poor discrimination in patients at moderate to high risk.[182] This would suggest that all patients undergoing CS may benefit from detection of modifiable early kidney stress to prevent AKI. Based on these studies, biomarkers are recommended for early identification of patients at risk and to guide an intervention strategy to reduce AKI (class IIa, level B-R).

Goal-Directed Fluid Therapy

Goal-directed fluid therapy uses monitoring techniques to guide clinicians with administering fluids, vasopressors, and inotropes to avoid hypotension and low cardiac output.[183] While many clinicians do this informally, goal-directed fluid therapy uses a standardized algorithm for all patients to improve outcomes. Quantified goals include blood pressure, cardiac index, systemic venous oxygen saturation, and urine output. Additionally, oxygen consumption, oxygen debt, and lactate levels may augment therapeutic tactics. Goal-directed fluid therapy trials consistently demonstrate reduced complication rates and length of stay in surgery overall and specifically in CS.[184-188] Based on this, we recommend goal-directed fluid therapy to reduce postoperative complications (class I, level B-R).

Other Important, Ungraded ERAS Elements

Preoperative anemia is common and associated with poor outcomes in patients undergoing noncardiac surgery.[189] Patients scheduled for CS may have multifactorial causative mechanisms for anemia, including acute or chronic blood loss, vitamin B12, or folate deficiency, and anemia of chronic disease.[190] If time permits, all causes of anemia should be investigated, but data supporting improved outcomes in the literature on CS is weak. Intraoperative anesthetic and perfusion considerations are also important ERAS elements. Impaired renal oxygenation has been demonstrated during CPB and is ameliorated by an increase in CPB flow.[191] This may contribute to postoperative renal dysfunction and suggests that goal-directed perfusion strategies need to be considered. Other anesthetic considerations may include a comprehensive protective lung ventilation strategy. Multiple studies have established that clinicians should use a low tidal volume strategy for mechanical ventilation in CS.[192] Early postoperative enteral feeding and mobilization after surgery are other essential components of ERAS surgical protocols.[1] We recommend that programs tailor these recommendations to achieve these goals working with staff with expertise in nutrition, early cardiac rehabilitation, and physical therapy.

Conclusions

In CS, a fast-track project to improve outcomes was first initiated by bundling perioperative treatments.[193] The ERAS pathway was initiated in the 1990s by a group of academic surgeons to improve perioperative care for patients receiving colorectal care, but it is now practiced in most fields of surgery.[1,194] Although ERAS is relatively new to CS, we anticipate that programs can benefit from these recommendations as they develop protocols to decrease unnecessary variation and improve quality, safety, and value for their patients. Cardiac surgery involves a large clinician group working in concert throughout all phases of care. Patient and caregiver education and systemwide engagement (facilitated by specialty champions and nurse coordinators) are necessary to implement best practices. A successful introduction of ERAS protocols is possible, but a broad-based, multidisciplinary approach is imperative for success.

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