PUNÇÃO DE VEIA AXILAR GUIADA POR ULTRASSONOGRAFIA VERSUS DISSECÇÃO DE VEIA CEFÁLICA PARA IMPLANTE DE ELETRODOS DE MARCAPASSO E CARDIODESFIBRILADOR: UM ENSAIO CLÍNICO RANDOMIZADO

Tese

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Punção de Veia Axilar Guiada por Ultrassonografia versus Dissecção de Veia Cefálica para Implante de Eletrodos de Marcapasso e Cardiodesfibrilador: um Ensaio Clínico Randomizado

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"Já é tempo de reconhecer o fato que ninguém pode se improvisar em cirurgião e que não é suficiente, para constituir um operador, estar apto a manipular, mais ou menos habilmente, algumas dúzias de pinças hemostáticas" (Thorek M. O cirurgião e sua arte. In: Thorek M. Técnica cirúrgica. Rio de Janeiro: Guanabara; 1941. p. 3-5).

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LISTA de ABREVIATURAS e SIGLAS

Dispositivos cardíacos eletrônicos implantáveis (DCEI)

European Heart Rhythm Association (EHRA)

Razão de dano ou hazard ratio (HR)

Intervalo de confiança (IC)

Razão de chances (RC)

Risco relativo (RR)

Ultrassonografia (US)

Versus (vs.)

Resumo

A punção venosa axilar guiada por ultrassonografia surgiu como uma alternativa válida para implante de eletrodos de marcapasso e cardiodesfibrilador. Objetivo: Comparar a punção axilar guiada por ultrassonografia com a dissecção de veia cefálica para implante de eletrodos de marcapasso e cardiodesfibrilador. Métodos: Ensaio clínico randomizado com arrolamento de 88 participantes adultos, na razão de 1:1. O desfecho primário foi a taxa de sucesso na obtenção do acesso venoso. Os desfechos secundários foram a necessidade de mudança do sítio de acesso venoso, o tempo para obtenção do acesso, o tempo total de procedimento e a taxa de complicação precoce. Os desfechos foram analisados por intenção de tratar. Os procedimentos foram realizados por operadores sem experiência prévia com o acesso axilar. Resultados: A taxa de sucesso (97,7% vs. 54,5%; p=0,001), a necessidade de mudança do sítio venoso (2,3% vs. 40,9%; p=0,001), o tempo para obtenção do acesso (5 vs. 15 minutos; p=0,001) e o tempo total de procedimento (40 vs. 51 minutos; p=0,010) foram significativamente melhores no grupo axilar, sem diferença significativa na taxa de complicação precoce (2,3% vs. 11,4%; p=0,20). Conclusão: Este é o primeiro estudo randomizado comparando a punção axilar guiada por ultrassonografia com a dissecção de veia cefálica no implante de eletrodos de marcapasso e cardiodesfibrilador. Os resultados demonstraram superioridade da estratégia de punção axilar guiada por ultrassonografia.

Palavras-chave:

Marcapasso; Cardiodesfibrilador implantável; Veia axilar; Veia cefálica; Punção venosa central guiada por ultrassonografia; Ensaio clínico randomizado.

Abstract

Axillary vein puncture guided by ultrasound has emerged as a valid alternative access route to pacemaker and defibrillator lead insertion. Objective: To evaluate whether axillary vein puncture guided by ultrasound compared to cephalic vein dissection improves success and early complications in pacemaker or defibrillator implant. Methods: Randomized clinical trial enrolling 88 adult patients, randomized 1:1 to axillary puncture guided by ultrasound (n=44) or cephalic vein dissection (n=44). The procedures were performed by operators with no previous experience in axillary approach. Primary endpoint was success rate. Secondary endpoints were venous access site change, time to obtain venous access, total procedural time, and early complication rate. Analyses were performed using the intention-to-treat principle. Results: Success rate (97.7% vs. 54.5%; p=0.001), venous access site change (2.3% vs. 40.9%; p=0.001), time to obtain venous access (5 vs. 15 minutes; p=0.001) and total procedural time (40 vs. 51 minutes; p=0.010) were improved in axillary group, with no difference in early complication rate (2.3% vs. 11.4%; p=0.20). Conclusion: This is the first randomized trial comparing self-learned ultrasound-guided axillar vein

puncture to cephalic vein dissection in cardiac lead implantation. The results indicate that the axillary approach was superior in terms of success rate, time to obtain venous access and procedural time, with similar complication rate.

Keywords

Pacemaker; Implantable cardioverter-defibrillator; Axillary vein; Cephalic vein; Ultrasound guided venous puncture; Randomized clinical trial.

1. Introdução

Dispositivos cardíacos eletrônicos implantáveis (DCEI), incluindo marcapassos e cardiodesfibriladores implantáveis, são ferramentas úteis para o tratamento de distúrbios do ritmo cardíaco, sejam eles bradiarritmias ou taquiarritmias, constituindo-se, por vezes, em uma terapia salvadora de vidas[1].

A punção da veia subclávia guiada por referências anatômicas, também conhecida como punção subclávia às cegas, e a dissecção da veia cefálica são as vias endovasculares preferenciais para a inserção de eletrodos de DCEI, apesar de estarem associadas a complicações intrínsecas ao método[2].

A dissecção da veia cefálica apresenta como principal vantagem a possibilidade de evitar uma punção venosa central e suas potenciais complicações. Este método é, porém, altamente dependente da anatomia venosa, do calibre do vaso e das habilidades cirúrgicas do operador[3]. Alta taxa de falha na inserção de eletrodos tem sido reportada com a técnica de dissecção da veia cefálica, tendo como principais razões a ausência de veia ou a presença de uma veia de extrema tortuosidade ou de calibre inadequado para acomodação de um ou múltiplos eletrodos. Além disso, quando o acesso através da veia cefálica requer ou utiliza fios guias e bainhas introdutoras, esta técnica exige o sacrifício da veia, resultando em procedimentos mais longos e com maior risco de sangramento[4].

A punção da veia subclávia guiada por referências anatômicas, por sua vez, apresenta alta taxa de sucesso e permite a inserção de múltiplos eletrodos. Entretanto, ainda que incomuns, complicações graves podem decorrer desta técnica, como pneumotórax, hemotórax, punção arterial inadvertida, lesão do plexo braquial e síndrome do *crush* subclávio com disfunção de eletrodos[5].

Com o objetivo de minimizar tais limitações, a punção da veia axilar surgiu como uma alternativa aos métodos convencionais previamente citados. Este acesso apresenta como principais vantagens sua localização extratorácica e calibre adequado para inserção de múltiplos eletrodos[6-8]. Em comparação com a veia subclávia, a veia axilar apresenta ainda o benefício de estar associada a menores taxas de síndrome do *crush* subclávio, uma vez que o eletrodo está menos propenso a ser aprisionado entre a clavícula e a primeira costela devido a um ângulo de entrada no sistema venoso menos agudo[6,9,10]. Apesar destes benefícios, a preferência pela veia axilar permanece incomum, principalmente devido à falta de treinamento adequado com esta técnica de punção e a escassez de evidências científicas que suportem seu uso rotineiro. Neste sentido, a punção da veia axilar guiada por ultrassonografia (US) poderia auxiliar a difundir o uso deste acesso venoso como rota de acesso para o implante de eletrodos de DCEI, além de possibilitar uma punção mais segura e eficaz, com uma curta curva de aprendizado[11,12].

2. Revisão da literatura

2.1 Implante de dispositivos cardíacos eletrônicos implantáveis

De acordo com a Diretriz Brasileira de dispositivos cardíacos eletrônicos implantáveis "as indicações consideradas clássicas para implante de marcapasso definitivo são as doenças do nó sinusal, o bloqueio átrio/intraventricular e a hipersensibilidade do seio carotídeo, sendo também consideradas as situações clínicas específicas como fibrilação atrial, cardiomiopatia hipertrófica obstrutiva e síncope neurocardiogênica. Quanto aos cardiodesfibriladores implantáveis, pode-se citar os casos de prevenção primária e secundária de morte súbita cardíaca" (Tabela 1)[1].

Já a Sociedade Europeia de Cardiologia cita que "embora ensaios clínicos randomizados formais de estimulação em bloqueios atrioventriculares não tenham sido realizados, é evidente, a partir de diversos estudos observacionais, que a estimulação cardíaca previne a recorrência de síncope e melhora a sobrevida em adultos e crianças"[13].

Segundo o Registro Brasileiro de Marcapasso, entre 1994 e 2013, 243.073 cirurgias de implante de DCEI foram registradas nacionalmente, sendo 173.621 implantes e 69.452 trocas de gerador[14]. Segundo dados do DATASUS, em 2019, foram realizados 22.527 implantes de DCEI (incluindo marcapassos definitivos, cardiodesfibrilador implantável e ressincronizador cardíaco) e 7.541 trocas de eletrodo, reposicionamento de eletrodo ou troca de gerador, totalizando 30.068 procedimentos (www2.datasus.gov.br).

Nos Estados Unidos, estima-se que 250.000 DCEI são implantados por ano[15] e que o número global de marcapassos implantados anualmente atingirá a marca de 1.43 milhões em 2023[16].

Tabela 1. Classificação e descrição dos dispositivos cardíacos eletrônicos implantáveis. Adaptada de Martinelli Filho e colaboradores, 2007[1].

Classificação dos DCEI	Capacidade principal	Função principal
Marcapasso	Estimulação/sensibilidade no átrio e/ou ventrículo	Terapêutica de bradiarritmias
Cardiodesfibrilador implantável	Cardioversão/desfibrilação por choque ou estimulação rápida	Terapêutica de taquicardia ventricular/ fibrilação ventricular
Ressincronizador cardíaco	Estimulação multi-sítio (biventricular)	Ressincronização ventricular (terapêutica da insuficiência cardíaca)
Cardiodesfibrilador implantável com ressincronizador cardíaco	Cardioversão/desfibrilação por choque ou estimulação rápida + estimulação multi-sítio (biventricular)	Terapêutica de taquicardia ventricular/ fibrilação ventricular e ressincronização ventricular

		(terapêutica da insuficiência cardíaca)

2.2 Vias de acesso para implante de dispositivos cardíacos eletrônicos implantáveis

Desde o primeiro implante bem-sucedido de um eletrodo temporário transvenoso de marcapasso via veia braquial por Furman e Schwedel em 1959[17], as técnicas para implante dos eletrodos de DCEI têm constantemente evoluído, assim como as indicações para o implante e, consequentemente, o número total de implantes realizados[2].

De acordo com a Diretriz Brasileira de dispositivos cardíacos eletrônicos implantáveis, "a escolha do acesso para implante de um DCEI deve considerar o local de implante do gerador e o tipo de abordagem venosa ou epicárdica para a introdução dos eletrodos. Deve-se levar em conta as características do paciente, tais como: utilização recente de marcapasso provisório, cateter de infusão venosa central, cirurgias prévias, infecções de pele e se o paciente é destro ou canhoto, dentre outros. A região da loja do gerador deve ser peitoral ou abdominal e o acesso venoso realizado, preferencialmente, por punção da veia subclávia ou dissecção da veia cefálica, utilizando-se como alternativas a via jugular, femoral ou axilar"[1].

Atualmente, as vias mais utilizadas para implante de eletrodos de DCEI são a endovenosa (eletrodos navegam através de um acesso venoso central até o endocárdio cardíaco onde são fixados) e a epicárdica (eletrodos são fixados diretamente na superfície epicárdica do coração). O acesso endocárdico é o acesso preferencial e o mais utilizado, uma vez que a via epicárdica requer a realização de uma pequena toracotomia e está associada a limiares de estimulação mais elevados e à falha de *sensing*[18-20].

A técnica de acesso venoso utilizando vasos centrais, geralmente veia subclávia, jugular interna ou femoral, firmou-se em 1953, quando Seldinger descreveu a técnica de cateterização venosa através de um fio guia metálico introduzido na veia subclávia por meio de uma punção venosa percutânea[21]. Com o advento de materiais mais flexíveis, adicionou-se à técnica de Seldinger o uso de um dilatador, inserido através do fio guia, a fim de facilitar o avanço do cateter.

Quanto às vias de acesso venoso central para implante de DCEI, múltiplas técnicas têm sido propostas. Durante o final dos anos 1960, a técnica de dissecção da veia cefálica tornou-se o procedimento padrão para inserção de eletrodos de marcapasso. Já no final dos anos 1970, a técnica de canulação percutânea da veia subclávia tornou-se altamente difundida para aferição de pressão venosa central, nutrição parenteral e introdução de eletrodos de marcapasso temporário[22]. Em 1979, o implante de eletrodos de marcapasso definitivo através de punção da veia subclávia foi introduzido por Littleford[23].

Mais recentemente, o uso de tecnologias de diagnóstico por imagem como fluoroscopia, venografia e ultrassonografia, ferramentas úteis, de aplicação prática, simples e reprodutível, vêm possibilitando o implante de eletrodos de DCEI de maneira mais segura e efetiva[24-30].

Apesar do desenvolvimento destas novas tecnologias, a dissecção da veia cefálica e a punção da veia subclávia guiada por referências anatômicas continuam sendo as rotas preferencialmente utilizadas para implante de DCEI. Em 2013, a Associação Europeia de Ritmo Cardíaco, a *European Heart Rhythm Association* (EHRA), pesquisou 62 centros quanto à técnica de acesso preferencial utilizada para implante de DCEI. Quando considerados todos os tipos de DCEI, incluindo dispositivos unicamerais, bicamerais e ressincronizadores, a veia cefálica foi a preferida em 60% dos centros pesquisados, seguida pela veia subclávia nos restantes 40%. Dos centros que preferiram a veia subclávia como primeira escolha, 48% reportaram usar a veia axilar e 52% o acesso subclávio intratorácico[2].

2.3 Implante de eletrodos de DCEI através de dissecção da veia cefálica

O acesso cefálico é realizado desde o final dos anos 1960[31,32], sendo considerado um acesso particularmente útil por eliminar o risco de pneumotórax. Entretanto, o calibre da veia é variável, podendo ser incompatível com a inserção de um ou múltiplos eletrodos. Além disso, a dissecção e o isolamento da veia cefálica consomem mais tempo, especialmente quando realizadas por operadores menos treinados, e o uso de introdutores, por vezes necessário para permitir a passagem dos eletrodos, resulta em sacrifício da veia e maior sangramento. Consequentemente, a taxa de sucesso com a dissecção da veia cefálica é altamente variável, situando-se entre 10% e 70%, de acordo com a literatura internacional[4,33-38]. Esta alta variação suporta o argumento de que o sucesso na técnica de dissecção cefálica é altamente operador-dependente[35].

Um estudo recentemente publicado avaliou a taxa de sucesso da utilização exclusiva da veia cefálica em 1091 pacientes submetidos a implante de ressincronizadores cardíacos ao longo de 8 anos. Neste estudo, a taxa de sucesso geral no implante cefálico foi de 73,4% e variou amplamente entre os operadores (12,5% – 88,3%). Os autores observaram que a proporção de implantes realizados exclusivamente por dissecção da veia cefálica foi maior entre operadores independentes (operadores com experiência prévia e aptos a realizar o procedimento sem orientação) do que entre aqueles operadores ainda em fase de treinamento (75,5% vs. 65,6%; p=0,003)[39].

2.4 Implante de eletrodos de DCEI através de punção da veia subclávia

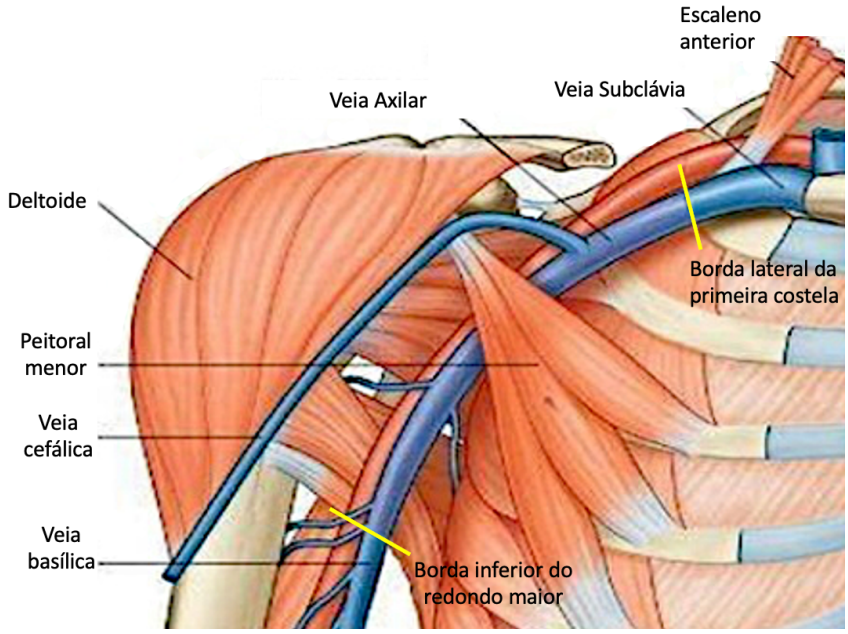
A técnica de punção da veia subclávia tornou-se uma das mais frequentemente utilizadas para implante de eletrodos de DCEI por ser de fácil aprendizado, rápida execução e associar-se a altas taxas de sucesso, variando de 94% a 96%[24,40-42]. Entretanto, esta técnica está associada a complicações imediatas potencialmente sérias como pneumotórax, hemopneumotórax, punção arterial inadvertida, injúria ao plexo braquial, bem como complicações a longo prazo como perda do isolamento do eletrodo e síndrome do *crush* subclávio, especialmente com eletrodos de cardiodesfibrilador implantável[8].

Em 2014, Kim e colaboradores publicaram análise retrospectiva de 655 pacientes (1161 eletrodos) submetidos a implante de eletrodos de marcapasso em um único centro, entre janeiro de 1992 e dezembro de 2005. Neste estudo, a punção subclávia foi comparada à técnica axilar (338 pacientes submetidos ao procedimento através de punção subclávia guiada por referências anatômicas e 317 através de punção axilar guiada por referências anatômicas ou venografia). Durante seguimento de 8 anos, complicações relacionadas aos eletrodos ocorreram com menor frequência no grupo axilar [17 eletrodos (3%); 13 fraturas de eletrodo, 4 defeitos de isolamento] que no grupo subclávio [31 eletrodos (6%); 26 fraturas de eletrodo, 5 defeitos de isolamento] (p=0,03). Em análise multivariada, acesso axilar foi o único preditor associado à redução de complicações tardias relacionadas ao eletrodo [razão de dano ou *hazard ratio* (HR)= 0,51; intervalo de confiança (IC) 95% 0,27 – 0,94; p=0,03][43].

2.5 Implante de eletrodos de DCEI através de veia axilar

Por definição anatômica, a veia axilar é a continuação da veia braquial, originando-se na margem inferior do músculo redondo maior e terminando na margem lateral da primeira costela, onde se torna a veia subclávia, sendo considerada, portanto, uma estrutura extratorácica e sendo nomeada, por vezes, como veia subclávia extratorácica (Figura 1).

Figura 1. Trajeto da veia axilar. Por definição a veia axilar origina-se na margem inferior do músculo redondo maior e torna-se veia subclávia ao cruzar a borda lateral da primeira costela.



A punção axilar guiada por fluoroscopia e pontos de referência anatômicos foi primeiramente sugerida como possível rota para implante de eletrodos de DCEI por Byrd em 1992[6]. Em 1993, este mesmo autor descreveu sua experiência inicial com a punção subclávia extratorácica como primeira escolha para inserção de eletrodos de marcapasso. Utilizando esta técnica, 208 (98%) de 213 eletrodos foram implantados com sucesso, levando o autor a declarar que, embora experiência adicional ainda fosse necessária, estes resultados iniciais eram encorajadores e suportavam o uso dessa técnica como padrão para inserção de eletrodos de marcapasso[7].

Desde então, a veia axilar tem se apresentado como uma excelente alternativa às técnicas convencionais. Sua localização extratorácica e distância da primeira costela explicam as menores taxas de pneumotórax, hemotórax, punção arterial inadvertida e síndrome do *crush* subclávio quando comparada à técnica de punção de veia subclávia intratorácica. Além disso, seu grande calibre permite a acomodação de múltiplos eletrodos[8]. Neste sentido, vários autores têm sugerido que o implante de eletrodos através da veia axilar evitaria o aprisionamento destes pelo músculo subclávio e pelo ligamento costoclavicular, o que tem sido implicado como causa de falha de eletrodos[6, 9,10].

Apesar desses benefícios, o implante de eletrodos via veia axilar permanece incomum na maioria dos centros, principalmente pela falta de treinamento na realização desta técnica. Objetivando-se desmistificar este conceito, Squara e colaboradores compararam a punção venosa axilar sem venografia, realizada por operadores treinados no implante de marcapasso, porém sem experiência prévia em punção axilar, com o implante padrão de dissecção da veia cefálica. Os autores demonstraram que a técnica axilar autoaprendida foi igualmente segura e efetiva, além de poder ser realizada em menor tempo cirúrgico. Destacaram ainda como principais vantagens do autoaprendizado da punção venosa axilar o fato desta ser uma alternativa útil para os casos em que a veia cefálica não pode ser encontrada ou é inadequada para uso (o que ocorreu em 24,3% dos pacientes neste estudo), evitando-se o acesso subclávio e o consequente risco de pneumotórax e complicações relacionadas ao eletrodo a longo prazo[37].

2.6 Utilização de ultrassonografia para guiar a punção venosa axilar

A utilização de ultrassonografia permite a visualização direta da veia axilar e das estruturas adjacentes, tornando a punção venosa mais segura e efetiva e reduzindo, assim, o tempo para o acesso venoso quando comparada a outros métodos de punção guiada, como a fluoroscopia e a venografia[44, 45]. Além disso, apresenta uma curva de autoaprendizagem relativamente curta[11, 12,40]. Quando comparada à venografia, a punção guiada por ultrassonografia apresenta a vantagem de evitar a necessidade de um acesso venoso ipsilateral e injeção de contraste, o que pode ser danoso em pacientes com insuficiência renal e poderia causar alergia induzida por contraste ou espasmo venoso induzido por contraste (descrito em até 8,1% dos pacientes)[46].

Desde 2001 a Agência para Pesquisa e Qualidade em Saúde nos Estados Unidos lista a inserção de cateteres venosos centrais guiados por ultrassonografia como uma das 11 práticas de segurança ao paciente[12]. No entanto, embora o uso de ultrassonografia para guiar punções venosas centrais seja fortemente recomendado para veia jugular interna[47-49], associando-se a menor incidência de complicações mecânicas imediatas e a aumento da taxa de sucesso da punção venosa[50], evidências para a cateterização da veia axilar guiada por ultrassonografia ainda são escassas.

A primeira descrição de uso de ultrassonografia para localizar a veia axilar foi realizada por Shregel em 1994[51], seguida do primeiro relato de utilização de ultrassonografia para guiar a canulação axilar em tempo real, inicialmente no eixo transversal por Nash em 1998[26] e, posteriormente, no eixo longitudinal por Sandhu em 2004[52]. Subsequentemente, vários relatos demonstraram redução no tempo para obtenção do acesso venoso, no número de tentativas de punção e na incidência de complicações relacionadas ao acesso quando este é realizado através de punção venosa axilar guiada por ultrassonografia[40,45, 53,54].

2.7 Comparação das técnicas de acesso venoso axilar, subclávio e cefálico para implante de DCEI

Ao analisar-se as taxas de sucesso do acesso venoso axilar guiado por ultrassonografia (80 – 99%)[26,40,45,53,54], percebe-se que estas assemelham-se aos valores previamente reportados para a punção axilar guiada por venografia (90 – 98%)[30,41,55,56] e para a punção subclávia convencional (94 – 96%)[24,40-42] e são comparáveis ou até mesmo superiores aos da punção axilar guiada por fluoroscopia (61 – 98%)[8,24,28,37,42,56] e aos dados mais recentes publicados referentes à dissecção da veia cefálica (64 – 87%)[4,37,41,45].

Em 2001, Calkins e colaboradores publicaram um ensaio clínico randomizado comparando a punção venosa subclávia extratorácica guiada por venografia com a dissecção da veia cefálica em 200 pacientes. Maior taxa de sucesso (99% vs. 64%; $p<0,001$) e menor tempo para obtenção do acesso venoso (10 ± 8 minutos vs. 25 ± 17 minutos; $p<0,01$) e tempo total de procedimento (86 ± 22 minutos vs. 98 ± 35 minutos; $p<0,01$), bem como menor perda sanguínea estimada (55 ± 13 ml vs. 115 ± 107 ml; $p<0,01$) foram observados no grupo subclávio extratorácico, embora sem diferença na taxa de complicações agudas (até 6 semanas do procedimento) (6% vs. 11%; $p=0,2$). Um caso de pneumotórax foi reportado em cada grupo. Em um seguimento médio de 540 ± 165 dias, nenhum caso de falha ou fratura de eletrodo foi registrado[4].

Em 2016, Liu e colaboradores compararam, através de ensaio clínico randomizado, o acesso venoso axilar guiado por fluoroscopia com o acesso subclávio convencional em 247 pacientes submetidos a implante de marcapassos ou cardiodesfibriladores implantáveis entre janeiro de 2013 e novembro de 2015. Todas as punções foram realizadas utilizando um kit de micro punção (agulha de 21-gauge, fio guia 0.018", introdutor 5F) e após 5 tentativas de punção falhas, injeção de contraste era recomendada. Os autores demonstraram uma taxa de sucesso geral de 95,7% para o acesso axilar vs. 96% para o acesso subclávio,

com uma taxa de sucesso na primeira tentativa de punção de 68,4% vs. 66,1% nos grupos axilar e subclávio, respectivamente. Tanto o tempo médio para punção venosa (45,9 ± 14,1 segundos no grupo axilar vs. 28,7 ± 13,9 segundos no grupo subclávio; p<0,001), quanto a taxa de complicações em seguimento médio de 24,1 ± 7,4 meses (1,6% no grupo axilar vs. 8,2% no grupo subclávio; p=0,016), diferiram significativamente entre os grupos, com 3 casos de pneumotórax e 2 casos de síndrome do *crush* subclávio no grupo subclávio. As duas complicações relatadas no grupo axilar foram um caso de descolamento de eletrodo e um caso de infecção de loja[42].

Ainda em 2016, Squara e colaboradores publicaram outro estudo randomizado comparando o acesso axilar autoaprendido sem venografia (guiado apenas por fluoroscopia) com a dissecção de veia cefálica em 74 participantes submetidos a implante de marcapasso (37 em cada grupo). Três operadores sem experiência prévia em punção venosa axilar, mas com vasta experiência prévia no implante de marcapasso, realizaram todos os procedimentos. A taxa de sucesso (81,1% no grupo axilar vs. 75,7% no grupo cefálica; p=0,57) foi semelhante nos dois grupos, assim como a taxa de complicações totais em 30 dias (13,5% no grupo axilar vs. 10,8% no grupo cefálica; p=0,71). O grupo axilar apresentou, contudo, menor tempo para obtenção do acesso venoso (da incisão até o posicionamento do fio guia ou dos eletrodos na veia cava superior) (5,7 minutos no grupo axilar vs. 12,2 minutos no grupo cefálica; p<0,001) e menor tempo total de procedimento (34,8 minutos no grupo axilar vs. 42,0 minutos no grupo cefálica; p=0,043). O tempo de exposição fluoroscópica [3,3 (2,5 – 4,1) minutos no grupo axilar vs. 3,4 (1,9 – 3,9) minutos no grupo cefálica; p=0,23] e a dose de radiação ($mGym^2$) [1463 (1122 – 1673,5) no grupo axilar vs. 1013 (732,1 – 1377,9) no grupo cefálica; p=0,12] foram semelhantes entre os grupos. Duas punções arteriais inadvertidas (5,4%) e dois episódios de distúrbio neurológico transitório no braço esquerdo, com recuperação completa e sem sequelas, foram registrados no grupo axilar. Nenhum caso de pneumotórax foi reportado. Este estudo demonstrou ainda que o grupo axilar não apresentou diferença na taxa de sucesso e no tempo para obtenção do acesso venoso de acordo com a experiência do operador. Durante os 5 primeiros procedimentos realizados por cada operador, apenas um hematoma de loja foi registrado como complicação no grupo axilar (p=0,86) e o tempo médio para obtenção do acesso venoso foi significativamente menor no grupo axilar [5,5 (3,9 – 9,1) minutos no grupo axilar vs. 12,2 (10,5 – 14,8) minutos no grupo cefálico; p<0,001][37].

Quanto ao acesso axilar guiado por ultrassonografia, Esmaiel e colaboradores também publicaram neste mesmo ano sua experiência retrospectiva com a punção venosa axilar guiada por ultrassonografia para implante de marcapasso em 403 pacientes. Neste estudo, os autores obtiveram uma taxa de sucesso de 99,2%, com uma média de 1,18 punções/paciente e um tempo médio para obtenção do acesso venoso (do momento em que o transdutor de ultrassonografia foi protegido até o posicionamento do fio guia na veia cava inferior) de 2,24 minutos. Todas as punções foram realizadas pelo mesmo operador e nenhuma complicação relacionada à punção foi reportada[57].

Em 2018, Liccardo e colaboradores compararam a punção venosa axilar guiada por ultrassonografia com a punção venosa subclávia para implante de eletrodos de marcapasso e cardiodesfibrilador implantável em 174 pacientes. Em um período pré-randomização, chamado de fase de autoaprendizado, 2 operadores realizaram 30 implantes de eletrodos em 23 pacientes cada e atingiram uma taxa de sucesso de 69%. Após este período de treinamento, a fase randomizada teve início e os pacientes foram arrolados na taxa de 2:1 (axilar:subclávia). Os operadores receberam um limite de tempo para completar a punção de 5 minutos no grupo axilar e 3 minutos no grupo subclávio. A taxa de sucesso do grupo axilar foi 91,4% (116 pacientes) vs. 94,8% (58 pacientes) no grupo subclávio. A causa mais frequente de falha foi tempo excedido (5,2% no grupo axilar e 1,7% no grupo subclávia). Falha na punção que não por motivo de tempo ocorreu em 4 pacientes no grupo axilar (3,4%) e 2 no grupo subclávia (3,4%). Em seguimento médio de 18 ± 6 meses, o número de complicações relacionadas ao eletrodo foi similar nos dois grupos (p=0,66). No grupo subclávia registraram-se, entretanto, dois casos de pneumotórax (3,4%) com necessidade de drenagem de tórax e consequente prolongamento da hospitalização em 2 a 4 dias. Nenhum caso de hemotórax, injúria de plexo braquial, trombose venosa ou deslocamento ou falha de eletrodo foi reportado. A punção venosa axilar foi considerada pelos autores como uma alternativa segura e efetiva ao tradicional método de punção venosa subclávia para implante de DCEI[40].

Em 2019, Jiménez-Díaz e colaboradores compararam o acesso venoso axilar guiado por fluoroscopia com a dissecção da veia cefálica. O estudo incluiu 240 pacientes randomizados para implante de eletrodos de DCEI realizado entre setembro de 2017 e outubro de 2018. Os implantes foram realizados por dois eletrofisiologistas experientes em ambos os métodos. A taxa de sucesso foi superior no grupo axilar (98,3% vs. 76,7%; p<0,001). No grupo axilar, para completar o acesso venoso, utilização de venografia foi necessária em 15 pacientes (12,5%). No grupo cefálico, o uso de uma guia hidrofílica foi necessário em 31 pacientes (25,8%). Tempo para obter o acesso venoso (6,8 ± 3,1 minutos vs. 13,1 ± 5,8 minutos; p<0,001) e tempo total de implante (42,3 ± 11,6 minutos vs. 50,5 ± 13,3 minutos; p<0,001) foram significativamente inferiores no grupo axilar. Não houve diferença na incidência de complicações totais (5% no grupo axilar vs. 9,1% no grupo cefálico; p=0,20). Taxa de sucesso, complicações e tempo para obtenção do acesso venoso foram semelhantes na análise inter-operadores. Em um seguimento médio de 12 ± 6 meses, ocorreram 1,25% infecções de loja e 2,5% tromboses venosas, sem diferença entre os grupos. Nenhuma fratura de eletrodo foi registrada[58].

Por fim, em 2020, Shi e colaboradores reportaram os resultados de ensaio clínico randomizado comparando a punção venosa axilar às cegas com a punção subclávia em 532 pacientes submetidos a implante de marcapasso ou cardiodesfibrilador implantável (272 via veia axilar e 266 via veia subclávia) entre janeiro de 2012 e junho de 2014. Similar taxa de sucesso (98,6% no grupo axilar vs. 98,4% no grupo subclávia; p=0,752) e complicações (14% no grupo axilar vs. 15% no grupo subclávia; p=0,725) foram

observadas. Não houve diferença no tempo para inserção dos eletrodos (2,30 ± 1,93 minutos no grupo axilar vs. 2,08 ± 1,11 minutos no grupo subclávio; p=0,109) ou no tempo de exposição à radiação (51,3 ± 10,4 segundos no grupo axilar vs. 54,6 ± 11,7 segundos no grupo subclávio; p=0,327). Seis pacientes desenvolveram síndrome do *crush* subclávio e 5 pneumotóraces foram reportados no grupo subclávio, enquanto nenhum caso de pneumotórax ou síndrome do *crush* subclávio foi observado no grupo axilar[59].

A segurança do acesso axilar guiado por ultrassonografia para implante de eletrodos de DCEI foi também avaliada em pacientes em uso de terapia antitrombótica ou anticoagulante em um estudo prospectivo. Duzentos pacientes (360 eletrodos) tiveram o procedimento realizado utilizando esta técnica, sendo que a maioria estava recebendo terapia antitrombótica ou anticoagulante (antagonista da vitamina K: 29%; anticoagulantes orais não dependentes de vitamina K: 23%; terapia antitrombótica dupla: 9%; terapia antitrombótica simples: 41%). Um único operador com experiência realizou todos os implantes. Sucesso foi observado em 91% dos casos, com tempo médio para inserção do fio guia de 4,7 ± 3,6 minutos. Nenhuma complicação foi observada durante seguimento médio de 45 ± 10 meses e o tempo para inserção do fio guia atingiu um platô após o caso de número 15[60].

Até a realização do presente estudo, um único estudo anterior havia relatado de maneira prospectiva, porém não randomizada, a comparação de punção venosa axilar guiada por ultrassonografia (realizada em 60 pacientes) com a dissecção da veia cefálica (realizada em 38 pacientes). Neste estudo, publicado por Jones e colaboradores em 2006, dois operadores experientes em implante de DCEI, porém sem experiência em punção venosa axilar guiada por ultrassonografia realizaram os implantes. Taxa de sucesso semelhante (88% no grupo axilar vs. 87% no grupo cefálico; p>0,05), embora com menor tempo para inserção do(s) eletrodo(s) (8 minutos vs. 12 minutos; p<0,05), foi reportada no grupo axilar. Os preditores independentes de tempo para obtenção do acesso venoso foram índice de massa corporal, operador que realizou o procedimento, estratégia inicial de punção e número de procedimentos realizados. As linhas de regressão para o tempo de inserção do eletrodo cruzaram-se após o caso de número 25 para o operador número 1, ponto de corte após o qual a utilização de ultrassonografia esteve associada a acesso mais rápido que a dissecção cefálica. Já para o operador número 2, a punção axilar guiada por ultrassonografia foi mais rápida que o acesso cefálico em todos os procedimentos realizados[45].

Por fim, a maior coorte de acesso axilar guiado por ultrassonografia foi publicada no último ano por Deluca e colaboradores. Neste estudo retrospectivo, a experiência de um único centro no implante de 987 eletrodos de DCEI (548 pacientes) utilizando a técnica de punção venosa axilar guiada por ultrassonografia ao longo de 5 anos (de janeiro de 2014 a dezembro de 2018) foi reportada. Uma taxa de sucesso geral de 99,8% (1 caso de falha), com taxa de sucesso na primeira tentativa de punção de 93,3% e tempo médio para obtenção do acesso (definido como tempo entre a punção cutânea e a aspiração de sangue) de 11 segundos (variando de 4 a 580 segundos) foi observada. O diâmetro médio da veia axilar foi de 8,4 mm no local de

punção (3 – 13,2 mm). As principais complicações observadas envolveram 3 casos de pneumotóraces (0,5%), 7 casos de punção arterial acidental (1,2%) e 12 casos de hematoma local (2,1%). Nenhum caso de síndrome do *crush* subclávio foi reportado e a incidência de infeção de loja/endocardite foi de 0,7%. Os autores destacaram que a maioria das complicações relacionadas à punção ocorreram na fase inicial, chamada de treinamento (de janeiro a setembro de 2014)[11].

2.8 Complicações relacionadas ao implante de DCEI

As complicações a curto prazo após inserção de eletrodos de DCEI, como pneumotórax, deslocamento de eletrodo, hematoma de loja e sangramento variam de 8% a 12%[61,62]. Estas complicações estão associadas a aumento de morbidade, custos e possível aumento de mortalidade[61].

Segundo o registro *DANISH* de marcapassos e cardiodesfibriladores, entre 5.918 pacientes consecutivos submetidos a implante de DCEI entre maio de 2010 e abril de 2011, um total de 562 pacientes (9,5%) apresentaram ao menos uma complicação. Reintervenções associadas ao eletrodo foram a complicação isolada mais comum (2,4%). Procedimentos de escalonamento de dispositivo ou revisão de eletrodos foram associados a taxas mais altas de complicações principalmente decorrentes de infecção ($p=0,001$) e revisão de loja devido a dor ($p<0,001$). A incidência geral de pneumotórax foi 1,6% e o risco aumentou com redução de índice de massa corporal (risco de 0,8% em pacientes com sobrepeso ou obesidade, 2,3% em pacientes de peso normal e 5,5% em pacientes com baixo peso). O risco de qualquer complicação foi maior em paciente do sexo feminino [risco relativo (RR)= 1,3, IC 95% 1,1 – 1,6], baixo peso (RR= 1,5, IC 95% 1,1 – 2,3), quando o implante foi realizado em um centro um volume anual de implantes <750 procedimentos (0 – 249 procedimentos: RR= 1,6, IC 95% 1,1 – 2,2; 250 – 499 procedimentos: RR= 2,0, IC 95% 1,6 – 2,7; 500 – 749 procedimentos: RR= 1,5, IC 95% 1,2 – 1,8), em caso de implante de cardiodesfibrilador implantável (RR= 2,0, IC 95% 1,4 – 2,7), cardiodesfibrilador ressincronizador (RR= 2,6, IC 95% 1,9 – 3,4) ou escalonamento ou revisão de eletrodo (RR= 1,3, IC 95% 1,0 – 1,7), se operador possuía volume anual <50 procedimentos (RR= 1,9, IC 95% 1,4 – 2,6) e se o procedimento foi realizado em caráter de emergência (RR= 1,5, IC 95% 1,0 – 2,3)[61]. Este estudo não reportou, contudo, a taxa de complicação de acordo com a via de acesso venoso utilizada.

Dados do *Truven Health Market Scan Research Databases*, o qual incluiu mais de 120 milhões de reclamações de pacientes reportadas nos Estados Unidos no período de abril de 2010 a março de 2014, indicou uma incidência de pneumotórax e hemotórax após implante de marcapasso de 2% e 1,4%, respectivamente[63]. Quanto à via de acesso venoso, a incidência de pneumotórax tem sido reportada variar de 1 a 3% para punção venosa subclávia às cegas, 0 a 1% para punção venosa axilar guiada por fluoroscopia[64], 0,5% para punção venosa axilar guiada por ultrassonografia[41].

Injúria nervosa associada à punção às cegas da veia subclávia para implante de eletrodos de marcapassos foi reportada em 0,6% dos casos[66,67], enquanto para a veia axilar, esta varia de 0% a 1,3%[37].

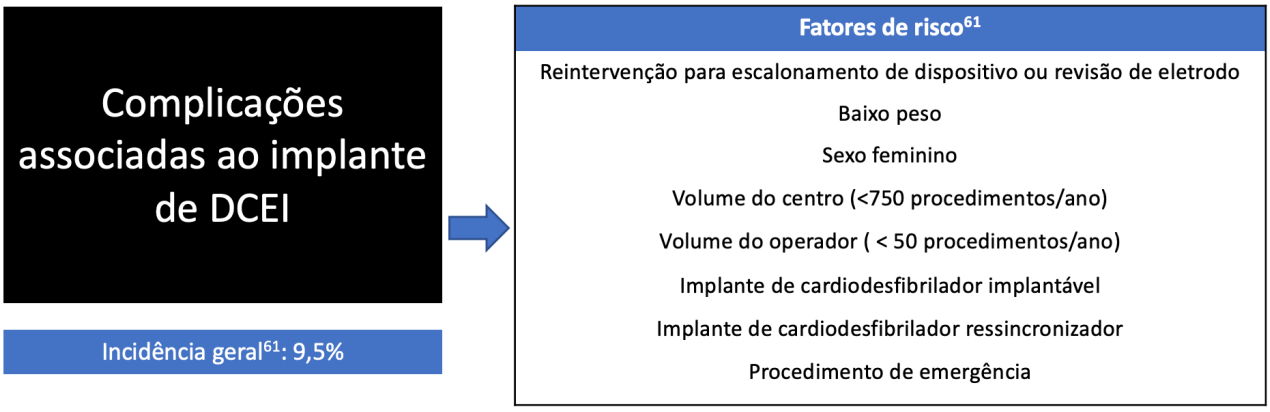
Taxas de infecção de DCEI variam largamente de acordo com a definição de infecção empregada, complexidade do dispositivo implantado e tempo de seguimento. Segundo dados da Sociedade Europeia de Cardiologia, taxa de infecção associada a DCEI varia de 0,61 – 1,3% e é considerada uma das complicações mais sérias do implante destes dispositivos, estando associada a significativa morbidade, mortalidade e aumento de custos do procedimento[68]. No registro *DANISH*, dentre os 46.299 pacientes submetidos a implante de marcapasso entre 1982 e 2007, a taxa de infeção dentro do primeiro ano após o implante foi de 4,82/1000 marcapassos-ano após o primeiro implante e 12,12/1000 marcapassos-ano após procedimentos de troca de dispositivo[69]. Greenspon e colaboradores reportaram que a incidência de infecção de DCEI nos Estados Unidos aumentou de 1,53% em 2004 para 2,41% em 2008[70]. No *U.S. National Cardiovascular Data Registry*, entre 2006 e 2009, a taxa de infecção global foi de 1,7%[71].

Na comparação entre as diferentes vias de acesso venoso para implante de DCEI, revisão sistemática e metanálise comparando o acesso cefálico com a punção venosa subclávia foi publicada em 2019. Neste estudo, um total de 20 estudos, englobando mais de 30.000 pacientes e mais de 50.000 eletrodos foram incluídos. A incidência de pneumotórax foi menor com a técnica cefálica [0,19% vs. 1,30%; razão de chances (RC)= 0,21, IC 95% 0,10 – 0,42; p<0,001]. Com relação à taxa de falha de eletrodos, o acesso cefálico foi associado com melhores desfechos [0,50% vs. 1,92%; RC= 0,25, IC 95% 0,13 – 0,51; p<0,001). Não houve diferença significativa em termos de sangramento (3,08% no grupo cefálica vs. 0,94% no grupo subclávia; p=0,50)[65]. Em 2020, outra revisão sistemática e metanálise comparou o acesso venoso axilar e subclávio com a dissecção da veia cefálica para implante de eletrodos de DCEI. Vinte e três estudos foram elegíveis, incluindo 35.722 participantes (18.009 no grupo subclávia, 409 no grupo axilar e 17.304 participantes no grupo cefálica). Quando comparado com o acesso cefálico, o acesso subclávio apresentou maiores taxas de pneumotórax [1,3% vs. 0,2%, RR= 4,88; IC 95% 2,95 – 8,06] e falha de dispositivo/eletrodo (2,3% vs. 1,1%; RR= 2,09; IC 95% 1,07 – 4,09), porém com maior taxa de sucesso (96,3% vs. 76.2%; RR= 1,24, IC 95% 1,0 – 1,53) e semelhante incidência de hematoma de loja/sangramento (1,9% vs. 5.8%; RR= 0,83, IC 95% 0,29 – 2,33) e infecção de dispositivo (0,8% vs. 0,9%; RR= 1,10, IC 95% 0,25 – 4,94). Já o acesso venoso axilar, comparado ao cefálico, apresentou maior taxa de sucesso (96,3% vs. 76,2%; RR= 1,25 IC 95% 1,18 – 1,32), com menor tempo total de procedimento (diferença média de -7,84 minutos, IC 95% -8,7 – -6,9). Não houve diferença no risco de pneumotórax (0% vs. 0,2%; RR= 0,20; IC 95% 0,01 – 4,12) ou falha de dispositivo/eletrodo (1,5% vs. 1,1%; RR= 0,78, IC 95% 0,26 – 2,37), hematoma de loja/sangramento (0,6% vs. 5.8%; RR= 0,33, IC 95% 0,05 – 2,06) e infecção do dispositivo (1,3% vs. 0,9%; RR= 0,96, IC 95% 0,14 – 6,44)[72]. A técnica de acesso axilar utilizada pelos estudos incluídos não foi especificada.

Comparando as três de vias de acesso venoso, axilar, subclávia ou cefálica, quanto a complicações tardias, Chan e colaboradores demonstraram que, em seguimento médio de 73,6 ± 33,1 meses, o único preditor independente de falha de eletrodo foi o uso de acesso venoso subclávio comparado ao acesso venoso axilar (HR= 0,261, IC 95% 0,071 – 0,954). Neste estudo, 409 pacientes submetidos a implante de eletrodos de marcapasso foram revisados (252 realizados via veia axilar, 217 via cefálica e 212 via veia subclávia). A incidência de falha de eletrodos foi de 1,2% no grupo axilar, 2,3% no cefálica e 5,6% no subclávia. Fratura do condutor radiograficamente visível foi observada em 5 eletrodos (25%), todos no grupo subclávia, fratura localizadas na junção costoclavicular em 4 eletrodos e localizada na loja em 1 eletrodo. A taxa de sucesso no grupo cefálica (78,2%) foi significativamente inferior ao acesso venoso axilar (97,6%) e ao subclávio (96,8%) (p<0,001). Venoespasmo foi observado em 6 casos de punção venosa axilar (2,4%) e 1 caso de pneumotórax foi registrado no grupo de acesso subclávio (0,5%)[41].

Um resumo das principais complicações citadas acima é apresentado na figura 2.

Figura 2. Complicações associadas ao implante de DCEI.



Comparação de acordo com via de acesso realizada[65,72,41]

Complicação	Cefálico	Subclávio	Axilar
Pneumotórax	0,2%	0,5% - 1,3%	0%
Falha de dispositivo/eletrodo	0,5% - 1,1%	1,92% - 2,3%	1,5%
Hematoma de loja/Sangramento	3,08% - 5,8%	0,94% - 1,9%	0,6%
Taxa de sucesso	76,2% - 78,2%	96,3% - 96,8%	96,3% - 97,6%
Infecção de dispositivo	0,9%	0,8%	1,3%
Falha de eletrodo a longo prazo	2,3% (78 ± 34 meses)	5,6% (77 ± 35 meses)	1,2% (66 ± 28 meses)

2.9 Descrição das duas técnicas de acesso venoso realizadas neste estudo

2.9.1 Etapas comuns aos dois procedimentos

Todos os procedimentos foram realizados sob anestesia local (lidocaína 1% e ropivacaína 7,5%, sem vasoconstritor) associada à sedação ou anestesia geral, a depender da indicação do anestesista assistente, e sob monitorização eletrocardiográfica, oximetria de pulso e pressão arterial.

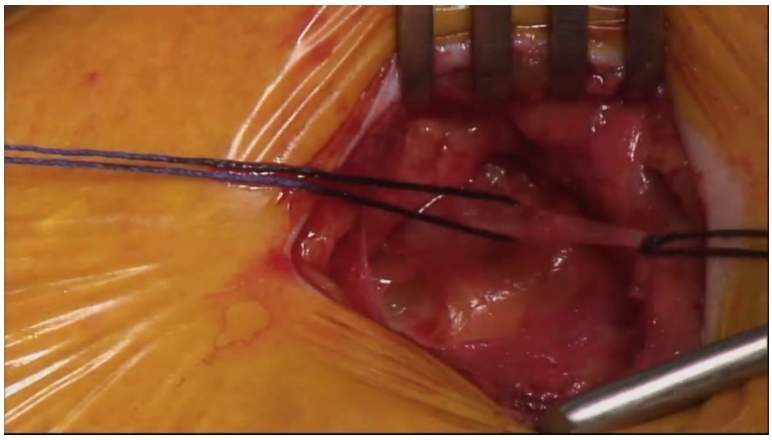
Os pacientes foram posicionados em posição prona e com braços estendidos ao longo do corpo. A degermação da pele foi realizada com clorexidine alcoólica, previamente à colocação de campos cirúrgicos estéreis. Antibioticoprofilaxia com cefazolina 2 gramas ou clindamicina 900 miligramas, em caso de alergia à penicilina, foi realizada antes da incisão da pele. Eletrodos de fixação ativa foram utilizados.

Raio-X de controle nas 24h subsequentes ao procedimento foi realizado em todos os pacientes para avaliar a posição final dos eletrodos e possíveis complicações.

2.9.2 Dissecção da veia Cefálica

Para a técnica de dissecção da veia cefálica, uma incisão paralela ao sulco deltopeitoral, cerca de 2-3 cm abaixo da clavícula, foi realizada utilizando lâmina de bisturi número 22. Seguiu-se a dissecação dos tecidos subcutâneos, identificação da fáscia e gordura sobrejacente à junção do músculo deltoide e do músculo peitoral maior para localização da veia cefálica e confecção da loja subcutânea ou submuscular. Uma exposição de cerca de 2 cm de veia cefálica ao longo de seu curso no sulco deltopeitoral utilizando-se dissecção romba e colocação de reparos proximal e distal com fio não absorvível (usualmente seda 2-0) foi então realizada (Figura 3). Uma pequena venotomia com lâmina de bisturi número 11 foi realizada a fim de proporcionar a colocação de uma pequena ferramenta para abertura da veia. Se a veia apresentasse calibre adequado, uma tentativa de inserção direta dos eletrodos era realizada. Caso contrário, a passagem de um fio guia em seu lúmen, com posterior introdução de um introdutor e dos eletrodos através deste era realizada. Caso não houvesse sucesso mesmo com a tentativa de passagem de um fio guia e introdutor, em decorrência de veia de pequeno calibre, obstruída com significativa tortuosidade, troca de sítio de acesso venoso era recomendada.

Figura 3. Dissecção e exposição da veia cefálica com reparos proximal e distal.



2.9.3 Punção da veia axilar guiada por ultrassonografia

Para realização da punção venosa axilar guiada por ultrassonografia, o transdutor do ultrassom foi posicionado ligeiramente medial e paralelo ao sulco deltopeitoral, visualizando-se a veia axilar em seu plano longitudinal. Seguiu-se a esta manobra uma rotação do transdutor no sentindo medial, deixando-o perpendicular a linha da clavícula até a visualização da veia e da artéria axilar em seu eixo curto (plano axial). A definição do melhor sítio e plano de punção (eixo curto ou longo) foi baseado na visualização destes dois eixos. A identificação da veia foi confirmada aplicando-se pequena pressão sobre a mesma e visualizando-se o seu colabamento, e através de análise do fluxo venoso pela onda de pulso do Doppler (Figura 4). A punção foi realizada utilizando-se a técnica de Seldinger modificada com agulha de 18-gauge conectada a uma seringa de aspiração. A agulha foi avançada mantendo-se sucção continua até obtenção de refluxo venoso (Figura 5). A seringa foi então desconectada e um fio guia de 0.035" foi introduzido até sua visualização fluoroscópica na veia cava inferior. Uma incisão oblíqua na pele, paralela ao sulco deltopeitoral, foi realizada para confecção da loja subcutânea ou submuscular. O fio guia foi então dissecado e trazido para dentro da incisão. No caso de necessidade de implante de dois eletrodos, dois fios guias eram introduzidos através do mesmo introdutor. O eletrodo era então introduzido através do introdutor, após retirada do fio guia e dilatador. Finalizada esta etapa, o procedimento transcorreu igualmente para os dois grupos com posicionamento dos eletrodos no endocárdio cardíaco e teste de parâmetros. Ao final do procedimento, o introdutor era removido e os eletrodos fixados com fio não absorvível de seda 2-0. O gerador era conectado aos eletrodos e inserido na loja previamente confeccionada. Fechamento da loja foi realizado com sutura interrompida e a aproximação do subcutâneo com sutura contínua de vicryl 2-0 e intradérmico contínuo com monocryl 3-0. O aparelho de ultrassom utilizado foi o Philips (Philips Healthcare, BG 5602 Eindhoven, The Netherlands) com transdutor vascular linear 7.5 MHz.

Figura 4. Mapeamento da artéria e veia axilar nos eixos curto e longo para identificação de sítio de punção.

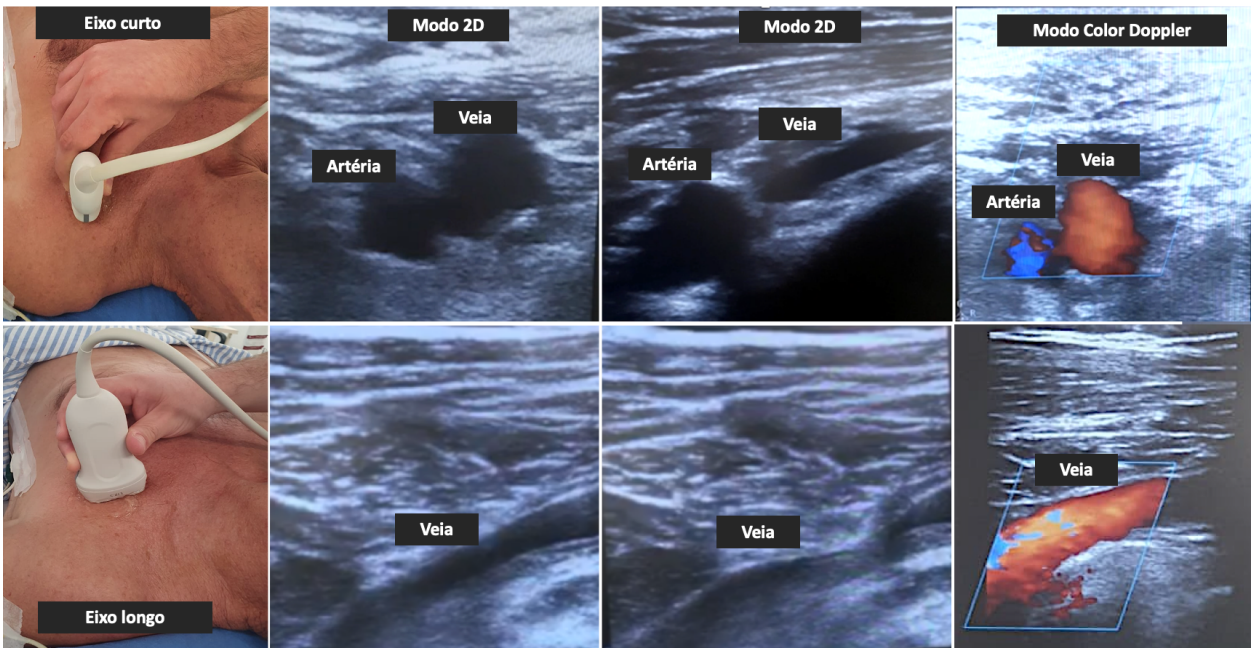
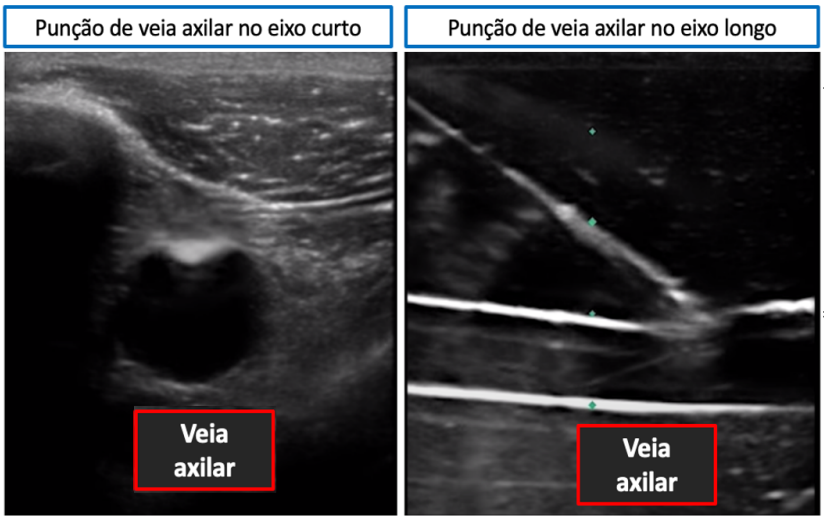


Figura 5. Exemplo de punção de veia axilar guiada por ultrassonografia nos eixos curto e longo.



3. Justificativa e Objetivos

3.1 Justificativa

Ainda que cada vez mais trabalhos venham indicando acessos alternativos e punções guiadas por ultrassonografia como opções seguras ao tradicional método de dissecção da veia cefálica, esta ainda é a via mais utilizada na maioria dos centros implantadores de DCEI.

Um ensaio clínico randomizado comparando a punção venosa axilar guiada por ultrassonografia com a punção subclávia guiada por referências anatômicas para implante de DCEI foi recentemente publicado

e demonstrou a segurança e eficácia do método axilar guiado por ultrassonografia quando comparado ao método tradicional subclávio[40]. Entretanto, nenhum estudo randomizado reportou a comparação da punção venosa axilar guiada por ultrassonografia com a dissecção da veia cefálica. Portanto, o presente estudo é o primeiro ensaio clínico randomizado, de que os autores tenham conhecimento, a avaliar a segurança e efetividade da punção venosa axilar guiada por ultrassonografia comparada à dissecção da veia cefálica para implante de eletrodos de marcapasso definitivo e cardiodesfibrilador implantável.

3.2 Objetivos

3.2.1 Objetivo Geral

Comparar a punção venosa axilar guiada por ultrassonografia com a dissecção da veia cefálica em termos de taxa de sucesso e complicações precoces durante o implante de eletrodos de DCEI em ensaio clínico randomizado realizado em dois hospitais universitários brasileiros.

3.2.2 Objetivos Específicos

Objetivo Primário

Comparar a taxa de sucesso das vias de acesso venoso axilar guiado por ultrassonografia e cefálico por dissecção durante o implante de eletrodos de DCEI. Taxa de sucesso na introdução do(s) eletrodo(s) endovenoso(s) foi adjudicada no período intra-operatório. Nos casos randomizados para acesso axilar, sucesso foi definido como o posicionamento do(s) eletrodo(s) em topografia de veia cava superior com, no máximo, três tentativas de punção venosa, com tempo total das três tentativas não devendo ultrapassar 15 minutos. Nos casos randomizados para acesso cefálico, o sucesso foi definido como posicionamento do(s) eletrodo(s) em topografia de veia cava superior em, no máximo, 15 minutos, independente da necessidade de uso de fio guia e/ou introdutor.

Objetivos secundários

Comparar as taxas de necessidade de mudança do sítio de acesso venoso para concluir a inserção do(s) eletrodo(s);

Comparar o tempo para a obtenção do acesso venoso utilizando a técnica de punção venosa axilar guiada por ultrassonografia com a técnica de dissecção da veia cefálica. Tempo para obtenção do acesso venoso foi definido como tempo do início do procedimento até o posicionamento do(s) eletrodo(s) em topografia de veia cava superior.

Comparar o tempo total de procedimento utilizando a técnica de punção venosa axilar guiada por ultrassonografia com a técnica de dissecção da veia cefálica.

Comparar as taxas de complicações precoces (durante o procedimento e em até 30 dias após o mesmo) utilizando a técnica de punção venosa axilar guiada por ultrassonografia com a técnica de dissecção da veia cefálica. Complicações precoces foram definidas como complicações imediatas ou em até 30 dias após procedimento, a saber: punção arterial inadvertida, pneumotórax, hemotórax, injúria nervosa, trombose venosa, hematoma de loja, infecção de loja, infecção de corrente sanguínea relacionada ao cateter, deslocamento de eletrodo e fratura do eletrodo.

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5. Artigos

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Article 1:

Axillary vein puncture guided by ultrasound vs cephalic vein dissection in pacemaker and defibrillator implant: A multicenter randomized clinical trial

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BACKGROUND Axillary vein puncture guided by ultrasound (USAx) has emerged as a valid alternative access route to pacemaker and defibrillator lead insertion. OBJECTIVE The purpose of this study was to evaluate whether USAx compared to cephalic vein dissection (CV) improves success and early complications in pacemaker or defibrillator implant. METHODS This prospective, multicenter clinical trial included 88 adult patients randomized 1:1 to US-Ax (n = 44) or CV (n = 44). All procedures were performed by operators with no previous experience in axillary approach. Primary endpoint was defined as success rate. Secondary endpoints were venous access site change, time to obtain venous access, total procedural time, and early complication rate. Analyses were performed using the intention-to-treat principle. RESULTS Median age was 70.5 years (58.2–79.7), and 60.2% were male. For the primary outcome, a higher success rate was observed in the axillary group (97.7% vs 54.5%; P <0.001), as well as a lower rate of venous access site change (2.3% vs 40.9%; P <0.001) and shorter time to obtain venous access (5 vs 15 minutes; P <0.001) and procedural time (40 vs 51 minutes; P =0.010), with no difference in complication rate (2.3% vs 11.4%; P 0.20). In multivariate analysis, US-Ax (P <0.001), single-chamber device (P =0.015), and body mass index (P =0.015) were independent predictors of overall success. CONCLUSION This is the first randomized trial comparing self-learned US-Ax to CV in cardiac lead implantation. Our results indicate that the axillary approach was superior in terms of success rate, time to obtain venous access and procedural time, with similar complication rate.

KEYWORDS Axillary vein; Cephalic vein; Implantable cardioverter defibrillator; Pacemaker; Randomized clinical trial; Ultrasound guided venous puncture

Introduction

Pacemakers and implantable cardioverter-defibrillators (ICDs) are useful tools for treating cardiac rhythm disturbances and providing lifesaving therapy.[1] Currently, subclavian vein puncture guided by anatomic landmarks and cephalic vein dissection are the preferred endovascular routes to lead insertion, despite some concerns intrinsic to these methods.[2] Cephalic vein dissection has the advantage of avoiding a central venous puncture and its complications, but it is highly dependent on venous anatomy, vessel caliber, and operator surgical skills.[3,4] Lead insertion failure rates vary from 10% to 70% due to vein absence or insufficient size to accommodate multiple leads. Furthermore, use of over-the-wire sheaths requires cephalic vein sacrifice, which can be time-consuming and cause excessive bleeding.[5–10] In contrast, subclavian venous puncture guided by anatomic landmarks has a high success rate, and it allows insertion of multiple leads. However, severe complications can occur, such as pneumothorax, hemothorax, arterial puncture, brachial plexus injury, and subclavian crush syndrome causing lead dysfunction.[11–16] Aiming to minimize the limitations of those 2 methods, axillary vein puncture has emerged as an alternative approach. Among its advantages are its extrathoracic location and large caliber.[11] Compared to the subclavian vein, the axillary vein has the advantage of avoiding subclavian crush syndrome because the lead used is not subject to entrapment between the clavicle and the first rib.[14,17,18] Despite these benefits, preference for the axillary vein remains uncommon, primarily due to the lack of proper training in puncture technique. Ultrasound (US)-guided puncture may overcome this issue, enabling a safe and effective puncture with a shorter learning curve.[10,19] However, substantial evidence supporting axillary vein puncture guided by US in pacemaker or ICD lead implantation is lacking. Therefore, the purpose of this prospective, randomized, multicenter study was to compare self-learned US-guided axillary vein puncture to cephalic vein dissection as an access route for cardiac lead implantation.

Methods

Between September 2018 and August 2019, 88 consecutive patients (age >18 years) referred for permanent pacemaker or ICD implant at 2 tertiary centers were randomized to US-guided axillary puncture (n = 44) or cephalic vein dissection (n = 44). The flow diagram is shown in Figure 1. Patients submitted to lead repositioning or device replacement or presented with upper limb venous thrombosis were excluded before randomization. Randomization was performed using a central computer system, and eligible patients were randomly assigned in a 1:1 ratio. The primary endpoint was defined as success rate, that is, all leads were inserted using the same randomized technique in no more than 15 minutes. The timer was controlled by an external observer and was stopped when all leads (1 in single chamber and 2 in dual-chamber devices) were fluoroscopically confirmed to be inside the superior vena cava. After 15

minutes, the attempt was recorded as a failure due to time criteria, but the operator was allowed to keep trying the same strategy or to change the venous approach based on personal preference. In the axillary puncture group, because the number of venipunctures is associated with mechanical complications, we decided to allow no more than 3 puncture attempts. One attempt was defined as needle passage through the skin and advancement until the end, without axis reorientation. Secondary endpoints were need for venous access site change; time to obtain venous access, defined as time from skin anesthesia to positioning of all leads inside the superior vena cava; total procedural time, defined as time from skin anesthesia to skin closure; and early complication rates. Early complications were defined as complications occurring within 30 days after the procedure, including inadvertent arterial puncture, hemothorax, pneumothorax, nerve injury, venous thrombosis, skin hematoma, lead displacement, and infection related to the lead or skin pocket. The study followed the Consolidated Standards of Reporting Trials (Consort) recommendations and was driven in accordance with the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). All eligible patients provided written informed consent before the procedure. The project was approved by the local research ethics committees and registered at ensaioclinicos.gov.br (RBR-6jp2qv).

Procedure

The procedures were performed by 2 operators: a cardiovascular surgeon and an electrophysiologist. Both professionals had no previous experience in US-guided axillary approach; however, they had expertise in pacemaker and ICD procedures (>300 cases per operator, mainly cephalic vein dissection). The operators also had previous experience in US guided jugular puncture (>50 venous punctures). In general, the surgeon performed the venous access and the electrophysiologist positioned the leads. The side of implant (left or right) was chosen based on personal operator and/or patient preference. Antibiotic prophylaxis was administered immediately before the procedure, according to hospital protocol. The axillary vein is the continuation of the brachial vein, originating at the lower margin of the teres major muscle and terminating at the lateral margin of the first rib. US characteristics that make the axillary vein easily distinguishable from the axillary artery are compressibility, lack of pulsation, and more medial and superficial position (Figure 2). To perform the axillary approach, patients were placed in the supine position with arms beside their bodies. The infraclavicular region was cleaned, and sterile surgical drapes were applied. A US machine (Philips Healthcare, Eindhoven, The Netherlands) in vascular mode with a high frequency linear transducer (7.5 MHz) was used. To maintain sterility, the US probe was covered in a dedicated sterile plastic cover, and sterile gel was applied directly on the skin. Local anesthesia was performed with lidocaine 1% in the incision line and puncture site. The extrathoracic portion of the vein was prescanned in long and short axes to determine the optimum

puncture site. Cannulation was attempted in-plane or out-of-plane, based on the best visualization plane. For the puncturing process, the first operator held the probe with the nondominant hand and performed the puncture with the dominant hand, using an 18-gauge needle. A single puncture technique, retaining the guidewire, was used for implant of 2 leads (Figure 3 and Supplemental Video 1). The skin was incised near the pectoral groove, and the device pocket was created. Surrounding tissues were dissected to allow guidewire identification, then the guidewire was pulled to the pocket region. A peel-away sheath was used to insert the lead. In case of failure, blind subclavian vein puncture or cephalic vein dissection was performed at the operator's discretion. In the cephalic vein approach, after vein surgical exposition, direct lead insertion through a small venotomy was attempted. In case of failure, a 0.035-inch guidewire was inserted, followed by an over-the-wire peel-away sheath. If this attempt failed, blind subclavian vein or US-guided axillary vein puncture was performed at the operator's discretion. Endocardial active fixation leads were used in all patients. Atrial leads targeted the right atrial appendage, and right ventricular leads were positioned in the interventricular septum or right ventricular apex. A control chest radiograph was obtained for all patients within the first 24 hours of the procedure and analyzed by a blinded radiologist to exclude complications. Each patient had a 30-day follow-up visit. Surgical wound and device parameters were evaluated by a blinded surgeon or electrophysiologist. Statistical analysis Given an expected success rate of 64% in the cephalic dissection group and 91% in the axillary group based on previous studies, a sample size of 88 patients was calculated to achieve a power of 80% and to detect a significant difference with 2- sided a <0.05.20,21 Quantitative data are expressed as mean 6 SD or median (Q1–Q3). Qualitative variables are expressed as frequency and percentage. Analyses were performed using the statistical package SPSS 19.0 (IBM Corp, Chicago, IL). Primary and secondary endpoints were analyzed following the intention-to-treat principle. Categorical variables were analyzed using the c2 test. Continuous variables were analyzed using the Student t test or Mann-Whitney U test, according to normality. Logistic regression was used to determine which factors contributed independently to the success rate. Two-sided $P<0.05$ was considered significant.

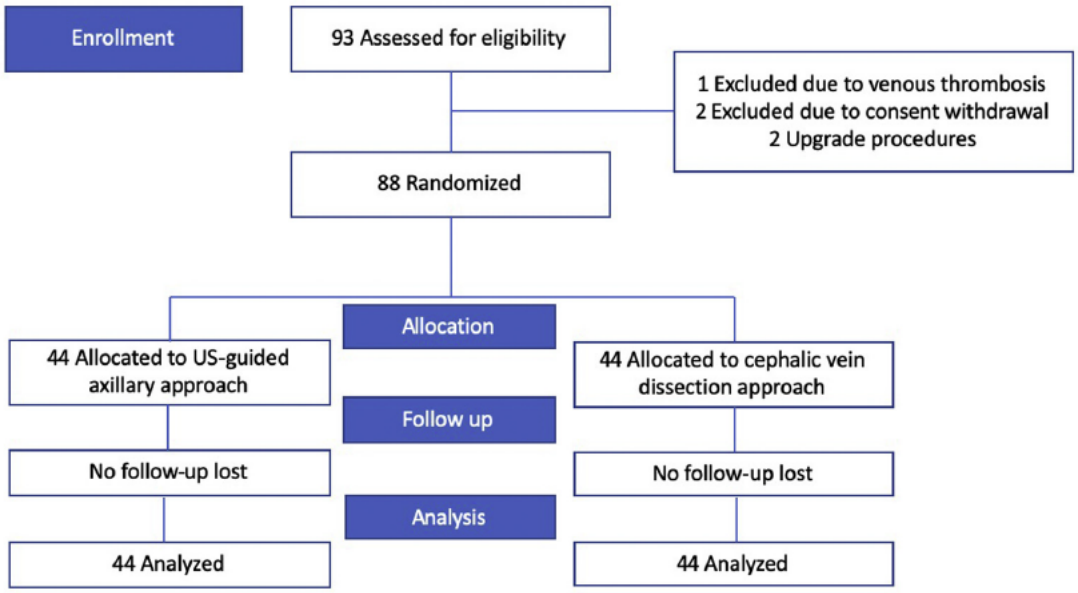

Figure 1 Study flowchart. US = ultrasound.

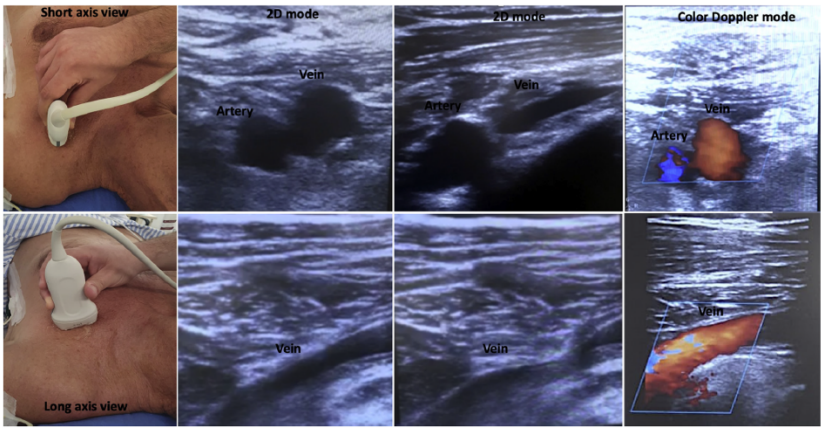

Figure 2 Ultrasound image of axillary vein and artery using 2-dimensional and color Doppler modes. Compressibility, lack of pulsation, and more medial and superficial position differentiate axillary artery and vein. To visualize the short axis, the ultrasound probe is held perpendicular to the vein, creating a circular image of the vessel. To visualize the long axis, the ultrasound probe is held parallel to the vein, creating a longitudinal image of the vessel.

Results

In total, 93 patients were considered for the study: 5 were excluded, and 88 were randomly allocated into one of the study groups (Figure 1). Median age was 70.5 years (58.2–79.7), and 53 participants (60.2%) were male. Baseline characteristics of the participants are detailed in Table 1. A total of 150 leads were implanted—118 for pacemakers and 32 for ICDs—equally distributed between groups (75 axillary vs 76 cephalic; P = 0.43). Procedural characteristics are given in Table 2. Primary and secondary outcomes are listed in Table 3. The success rate was significantly higher in the axillary group (97.7% vs 54.5%; P<0.001). Failures in the cephalic group were due to absence of vein or vein inadequate to accommodate at least 1 lead [10 (22%)]; inability to insert a second lead [7 (15.9%)]; guidewire non

progression [1 (2.3%)]; and time criteria [2 (4.5%)]. Among the 18 patients (40.9%) in whom the venous access site was changed, the new site was blind subclavian vein puncture in 15 and US-guided axillary puncture in 3. The only crossover from the axillary to the cephalic group (2.3%) was due to venous tortuosity, making guidewire progression impossible. The mean number of puncture attempts per patient in the axillary group was 1.66 ± 0.77, and the first puncture attempt was successful in 23 patients (52.3%). In a multivariate regression model, US-guided axillary puncture [odds ratio (OR) 53.33; 95% confidence interval (CI) 5.97–476.11; P<0.001)], single-chamber device (OR 8.71; 95% CI 1.51–50.05; P=0.015), and body mass index (BMI) (OR 1.23; 95% CI 1.04–1.45; P=0.015) were the only independent predictors of overall success rate. Total early complication rate was not statistically different between groups (2.3% axillary vs 11.4% cephalic; P=0.202) (Table 4). Major complications consisted of 2 pneumothoraxes, which were treated by Wayne (Cook Medical, Blooming, IN, USA) catheter insertion, one in each group. Minor complications comprised 3 lead displacements requiring repositioning and 1 pocket hematoma that did not require intervention, all in the cephalic group. The pneumothorax reported in the axillary group occurred during an extremely medial puncture. Because the patient was malnourished and the vein had a very small caliber, we attempted to access a larger vein portion by moving the probe as medial as possible; however, proper needle tip visualization was challenging due to the acoustic shadow of the clavicle. No inadvertent arterial puncture, hemothorax, nerve injury, venous thrombosis, or device-related infections were observed.

Table 1 Baseline characteristics

Characteristic	Total (N = 88)	Axillary (n = 44)	Cephalic (n = 44)	*P* value
Age (y)	70 (58.2–79.7)	67.5 (55–76)	74.5 (67–82)	.019
Male gender	53 (60.2)	26 (59.1)	27 (61.4)	1
Body mass index (kg/m^2)	28.2 (24.4–30.1)	27.1 (24.2–31)	25.9 (23.5–30.5)	.376
Hypertension	53 (60.2)	28 (63.3)	25 (56.8)	.663
Diabetes	28 (31.8)	18 (40.9)	10 (22.7)	.108
Active smoker	6 (6.8)	2 (4.5)	4 (9.1)	.676
Chronic obstructive pulmonary disease	5 (5.7)	2 (4.5)	3 (6.8)	1
Heart failure	26 (29.5)	13 (29.5)	13 (29.5)	1
Previous stroke	12 (13.6)	3 (6.8)	9 (20.4)	.118
Previous myocardial infarction	12 (13.6)	8 (18.2)	4 (9.1)	.352
Atrial fibrillation	20 (22.7)	8 (18.2)	12 (27.3)	.446
Chronic kidney disease	10 (11.3)	6 (13.6)	4 (9.1)	.739
Pacemaker indication	63 (71.6)	29 (65.9)	34 (77.2)	.199
Atrioventricular block	39 (44.3)	19 (43.2)	20 (45.5)	
Sinus node disease	17 (19.3)	9 (20.5)	8 (18.2)	
Other	7 (7.9)	1 (2.3)	6 (13.6)	
ICD indication	25 (28.4)	15 (34.1)	10 (22.7)	1
Primary prevention	17 (19.3)	10 (22.7)	7 (15.9)	
Secondary prevention	8 (9.1)	5 (11.3)	3 (6.8)	

Values are given as median (Q1–Q3) or n (%) unless otherwise indicated.
ICD = implantable cardioverter-defibrillator.

Table 2 Procedural characteristics

Characteristic	Total (N = 88)	Axillary (n = 44)	Cephalic (n = 44)	*P* value
Left-sided implant	56 (63.6)	30 (68.2)	26 (59.1)	.507
Type of device				.345
Pacemaker	63 (71.6)	29 (65.9)	34 (77.2)	
ICD	25 (28.4)	15 (34.1)	10 (22.7)	
No. of electrodes				1
Single-chamber	28 (31.8)	14 (31.8)	14 (31.8)	
Dual-chamber	60 (68.2)	30 (68.2)	30 (68.2)	
Pocket type				1
Subcutaneous	65 (73.9)	32 (72.7)	33 (75)	
Submuscular	23 (26.1)	12 (27.3)	11 (25)	

Values are given as n (%) unless otherwise indicated.
ICD = implantable cardioverter-defibrillator.

Table 3 Outcomes

Endpoint	Total (N = 88)	Axillary (n = 44)	Cephalic (n = 44)	*P* value
Primary outcome				
Success rate	67 (76.1)	43 (97.7)	24 (54.5)	<.001
Secondary outcomes				
Venous access site change	19 (21.6)	1 (2.3)	18 (40.9)	<.001
Time to obtain venous access (min)	8 (5–15)	5 (5–8)	15 (8.5–15)	<.001
Procedural time (min)	40 (35–60)	40 (35–47.2)	51 (35.5–68)	.010

Values are given as n (%) or median (Q1–Q3) unless otherwise indicated.

Table 4 Complication rates

Complication type	Total (N = 88)	Axillary (n = 44)	Cephalic (n = 44)
Total	6 (6.8)	1 (2.3)	5 (11.4)
Major	2 (2.3)	1 (2.3)	1 (2.3)
Minor	4 (4.5)	0	4 (6.8)
Pocket hematoma	1 (1.1)	0	1 (2.3)
Lead displacement	3 (3.4)	0	3 (6.8)

Values are given as n (%).

Discussion

The results of this randomized clinical trial demonstrate significant superiority of the US-guided axillary vein approach for cardiac lead implantation, even when performed by operators having no previous experience with the technique. The rationale for this study was based on previous literature data demonstrating high success rates of axillary vein puncture as the route for pacemaker and ICD lead insertion, mostly from case series and observational studies.[22–25] The high axillary success rate observed in our analysis (97.7%) was comparable to that of other US-guided reports (80%–99%)[22–25] as well as with other puncture methods such as venography (90%–99%)[4,20,26–28] and fluoroscopy guided puncture (61%–98%).[4,10,11,16,29,30] US-guided puncture has the advantage of obviating X-ray exposure and contrast use, avoiding the risk of renal failure, vein spasm, and anaphylaxis reaction, which are possible side effects of contrast use. Ultrasonographic vein imaging also allows the possibility of evaluating vein patency before pocket incision, which is especially useful in patients who previously had

undergone thoracic surgery or radiotherapy, or who had dialysis catheters in place.24 Our relatively lower success rate in the cephalic group (54.5%) compared to other trials (64%–75%)10,20 can be explained by our adoption of a rigid definition of success, considering success only if all leads were inserted inside the superior vena cava through the same site, within a time limit. However, even if those procedures that succeeded after the 15-minute time limit and those in which only 1 lead passed through the cephalic vein were not considered failures, the success rate still was significantly superior in the axillary group (97.7% vs 79%; P =0.003). Regarding our rate of absent or inadequate cephalic vein (22%), this definition comprises not only absence of vein but also cases of significant tortuosity or improper size to accommodate at least 1 lead, which was similar to that recently reported by Jiménez- Díaz et al.31 In that study, the authors reported the cephalic vein was absent in 11.9% of patients, tortuous in 7.5%, and dissected during manipulation precluding its use in 6.6%, for total failure of 26%.31 No difference in success rate was observed between hospitals where the procedures were performed (overall success rate 75.3% in hospital A vs 85.7% in hospital B; P = 1). With regard to complication rates, despite the study being unpowered to detect such differences, the self-learned axillary approach proved to be safe, even in the initial cases. The single complication occurred in an elderly, malnourished patient (case 25). The lower incidence of complications in the axillary group can be explained by its extrathoracic anatomic position, large caliber, and greater distance from the axillary artery.11 Compared to data previously reported in the literature, the incidence of axillary puncture complications in our study (2.3%) was similar to that previously reported by Liu et al,30 who demonstrated a complication rate of 1.6% (2/125; 1 lead dislodgment and 1 pocket infection) in the axillary group vs 8.2% in the subclavian group (P5 .016). However, our rate was much lower than that of Squara et al,10 who reported a 13.5% complication rate for self-learned fluoroscopy-guided axillary puncture compared to 10.8% for cephalic vein dissection (P=0.71). Our shorter time to obtain venous access in the axillary group reinforces the findings of Jones et al,23 who demonstrated in nonrandomized fashion a shorter time to position the leads in the superior vena cava using the US-guided axillary approach compared to cephalic dissection (8 vs 12 minutes; P <0.05). From a clinical point of view, longer procedure duration has been associated with increased infection risk,32 indicating that shorter duration interventions, in addition to enabling quicker operating room turnover and optimizing surgeons' time, may lead to better infective outcomes. When analyzing possible factors related to success, similar to the study by Jones et al,23 we found that US guided axillary puncture, single-chamber devices, and BMI were the only independent predictors of higher success rate in patients overall. According to Jones et al, BMI was a surrogate for easier venous access, possibly because malnourished patients often present less subcutaneous fat coverage, making cephalic vein dissection or axillary vein puncture more challenging. Kim et al33 reported that vein depth differs significantly according to BMI (P <0.001), with a trend toward larger vein caliber in patients with higher BMI values

(P =0.056). Similarly, Jeon et al34 evaluated predictors of internal jugular vein caliber measured by tomography and observed that higher BMI predicted larger vein caliber (OR 1.08; 95% CI 1.01–1.15; P =0.023). Although this finding was related to the internal jugular vein, they showed, in analogous fashion, that vein size can vary according to BMI, with higher BMI predicting greater success in obtaining central venous access. Considering the factor of age, although our baseline median age was different between groups, this variable was not associated with success rate in either our analysis or in previous studies.23,33

Study limitations

The short follow-up period of this study was not sufficient to allow evaluation of long-term lead-related complications. It was not possible to blind the physician to the type of technique, although statistical analyses and outcome assessment were blinded to the group assigned. Long-term follow-up is needed to confirm the hypothesis that axillary venous puncture is associated with reduced rates of subclavian crush syndrome and lead dysfunction. The sample size was calculated based on the primary endpoint. Analyses of secondary outcomes and factors associated with success, in the overall sample, had the main objective of raising questions and points to be discussed because the study was unpowered to draw conclusions about secondary endpoints.

Conclusion

To the best of our knowledge, this is the first randomized clinical trial to compare self-learned US-guided axillary vein puncture and cephalic vein dissection for permanent pacemaker and ICD lead insertion. We demonstrated that US guided axillary puncture is a useful first-line or alternative approach, especially in patients with a cephalic vein that is absent or unsuitable for insertion of multiple leads. Our outcomes indicate that the axillary approach was superior to cephalic vein dissection in terms of success rate, time to obtain venous access, and total procedural time, with similar complication rates.

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Ultrasound-guided Axillary Vein Puncture in Cardiac Lead Implantation: Time to Move to a New Standard Access?

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Abstract

Cardiac stimulation therapy has evolved significantly over the past 30 years. Currently, cardiac implantable electronic devices (CIED) are the mainstream therapy for many potentially lethal heart conditions, such as advanced atrioventricular block or sustained ventricular tachycardia or fibrillation. Despite sometimes being lifesaving, the implant is surgical and therefore carries all the inevitable intrinsic risks. In the process of technology evolution, one of the most important factors is to make it safer for the patient. In the context of CIED implants, complications include accidental puncture of intrathoracic structures. Alternative strategies to intrathoracic subclavian vein puncture include cephalic vein dissection or axillary vein puncture, which can be guided by fluoroscopy, venography or, more recently, ultrasound. In this article, the authors analyse the state of the art of ultrasound-guided axillary vein puncture using evidence from landmark studies in this field.

Keywords

Cardiac implantable electronic devices, permanent pacemaker implantation, ICD, ultrasound, axillary vein

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Cardiac implantable electronic devices (CIEDs), including permanent pacemakers (PPMs), ICD and CRT devices, are the mainstream therapy for many potentially lethal heart conditions, such as advanced atrioventricular block or sustained ventricular tachycardia or fibrillation. CIEDs can be implanted through endovascular or epicardial routes, with the former used the most because it is less invasive and provides better pacing thresholds.[1–3]

Since the first successful insertion of a temporary transvenous endocardial lead through the brachial vein by Furman and Schwedel in 1959,[4] many technical advancements have been described, culminating in the widespread use of the procedure.[5] It is projected that the global number of PPMs implanted annually will be 1.43 million by 2023.[6]

A European Heart Rhythm Association survey showed that cephalic vein dissection and blind subclavian vein puncture are the preferred techniques for the implantation of CIED leads in European centres.[5] However, these two techniques are associated with variable success and complications rates that can be reduced by using imaging guidance.

Cephalic access has been used as a route for endocardial lead implantation since 1960.[7,8] Despite its relative safety, by avoiding central venous puncture, the method is associated with high failure rates and longer procedure times.[9] Cardiac lead insertion is also highly dependent on venous anatomy, trajectory, calibre and operator skills,[10] which culminates in failure rates ranging from 10% to 70%.[11–15]

Conversely, subclavian vein puncture is a highly successful approach, but requires central venous puncture, the complications of which, although uncommon, can be potentially fatal.[16,17] In addition, leads implanted through subclavian puncture are more susceptible to long-term dysfunction secondary to subclavian crush syndrome.[18–22]

To address these problems, punctures guide d by fluoroscopy, venography and ultrasound (US) have emerged as feasible and reproducible alternatives to increase procedure success and safety.[7,23–28] Another relatively new method that has received increasing attention is axillary vein puncture, the first application of which in CIED implantation was described by Byrd in 1993.[29]

By anatomical definition, the axillary vein is a continuation of the brachial vein, originating at the lower margin of the teres major muscle and terminating at the lateral margin of the first rib. The extrathoracic location of the axillary vein and its distance from the first rib explain the lower rates of pneumothorax, haemothorax, inadvertent arterial puncture and subclavian crush syndrome following axillary vein puncture. In addition, the axillary vein has a large calibre, allowing multiple punctures or multiple lead insertions through the same puncture.[18]

Despite these benefits, lead insertion using the axillary vein remains uncommon in many centres, primarily due to the lack of proper training and concerns with a supposed long learning curve.

Ultrasound-guided Venous Puncture

US-guided puncture allows direct visualisation of the vessels and surrounding structures. Therefore, the puncture is safer and less time consuming.[30,31] Since 2001, US-guided central catheter placement has been recommended by the Agency for Healthcare Research and Quality as one of the 11 fundamental practices to improve procedural safety.[32] However, this recommendation applies mostly to the jugular vein, because there was not enough evidence supporting US-guided axillary vein puncture, especially during CIED implantation.[33–35]

The first description of US-guided axillary vein location was reported by Shregel et al. in 1994.[36] This was followed by the first real-time US-guided axillary vein puncture, initially using the short axis, by Nash et al. in 1998 and, posteriorly, using the long axis by Sandhu in 2004.[25,37] Subsequently, many reports have suggested that this method is associated with a short time to obtain central venous access, a reduced number of puncture attempts and low complication rates.[25,31,38–40]

Some ultrasound characteristics make the axillary vein easily distinguishable from the axillary artery and feasible for clinical use, such as the lack of pulsation, a more medial and superficial position and external pressure compressibility (*Figure 1*). Ultrasound scanning also allows evaluation of vein patency prior to pocket creation, which may be useful in patients with prior thoracic surgery, radiotherapy exposure or dialysis catheters.[39]

Another particularly relevant advantage of US is the detection of complications, such as pneumothorax, earlier than with radiological control. Whereas the presence of pleural sliding is the most important finding in a normal aerated lung ('seashore sign' using the M-mode), the lack of pleural sliding and the presence of parallel horizontal lines above and below the pleural line ('barcode' or 'stratosphere sign' using the M-mode) are indicative of pneumothorax.[41]

In terms of the US-guided axillary puncture, clear needle visualisation is a crucial step to enable proper puncture, avoiding damage to adjacent structures such as vessels, nerves and pleura. In cross-sectional images, the needle tip can be seen as a highly echogenic spot with surrounding artefacts caused by the scattering of the ultrasound beam, which is less easily visible within the heterogeneous appearance of body tissue. In the out-of-plane needle approach, the needle shaft is not visualised, and indirect evidence of vein compression may be seen (*Figure 2*).[42]

The probe most used to guide axillary vein puncture is the vascular high-frequency linear array probe (5–10 MHz), which provides a high-resolution image. If a more medial puncture is desired, a microconvex linear array probe with a smaller footprint may be an alternative to deal with the acoustic shadowing from the overlying clavicle.[43] A more medial puncture offers a less deep and steep puncture angle and reduces the risk of brachial plexus injury, the incidence of which in axillary puncture varies from 0% to 1.3%.[44] Symptoms related to brachial plexus injury can be attributed to direct trauma of the nerve by the needle due to repeated puncture attempts in a too lateral position or to brachial plexus block induced by lignocaine.[44]

Compared with fluoroscopy and venography, US-guided puncture has some advantages, such as a faster effective learning process and no requirement for extra X-ray exposure, additional peripheral access or contrast injection. These features may potentially avoid renal function impairment, allergic reactions and venous spasm related to the use of contrast.[45] Furthermore, the use of venography for axillary vein puncture is limited by the inability to estimate the depth of the puncture with this method.

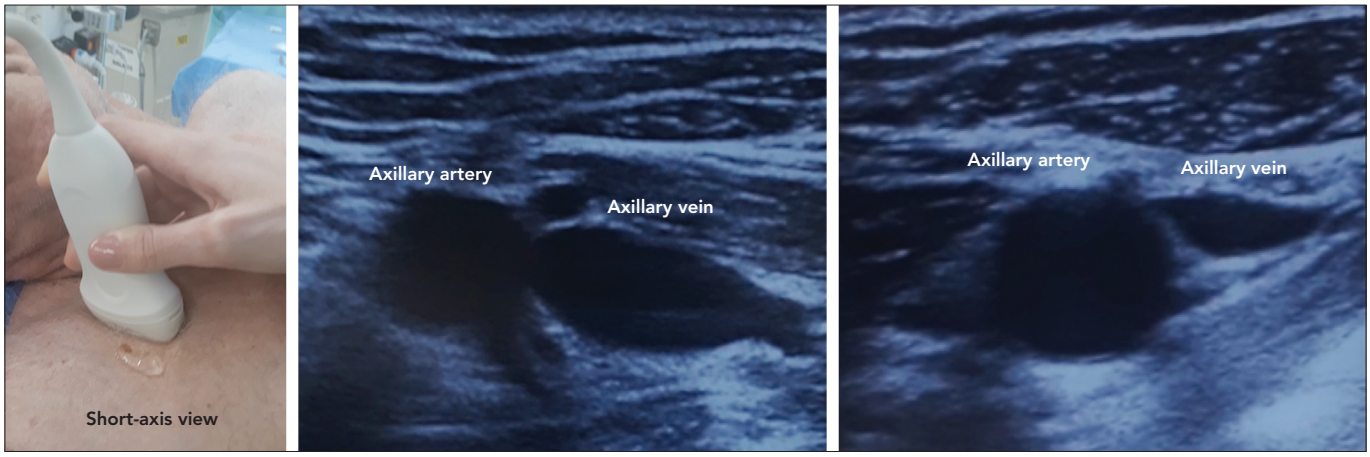
Scientific Evidence Comparing CIED Lead Insertion Through Axillary Vein Puncture With Other Techniques

Calkins et al. were one the first groups, in 2001, to undertake a randomised clinical trial evaluating venography-guided extrathoracic subclavian puncture versus cephalic vein dissection in 200 participants who had undergone PPM or ICD lead implantation.[46] The extrathoracic subclavian group had higher success (99% versus 64%; $p<0.001$), shorter time to obtain central venous access (mean ± SD: 10 ± 8 minutes versus 25 ± 17 minutes; $p<0.01$), shorter total procedural time (86 ± 22 minutes versus 98 ± 35 minutes; $p<0.01$) and lower blood loss (55 ± 13 ml versus 115 ± 107 ml; $p<0.01$), but there was no significant difference in early complication rates between the two groups (6% versus 11%; $p=0.2$).[46]

In 2016, Lui et al. published the results of another randomised control trial comparing fluoroscopy-guided axillary vein puncture to standard blind subclavian vein puncture in 247 CIEDs.[47] Comparisons of axillary and subclavian punctures revealed similar first-puncture attempt success (68.4% versus 66.1%, respectively; $p=0.597$) and overall success rate (95.7% versus 96%, respectively; $p=0.845$). Despite these similarities, the time to perform the puncture was shorter in the subclavian puncture group (46 ± 14 versus 28.7 ± 14 s; $p<0.001$), but, over a mean follow-up period of 24.1 ± 7.4 months, the complication rate was lower in the axillary puncture group (1.6% versus 8.2%; $p=0.016$). In terms of severe complications, three cases of pneumothorax and two of subclavian crush syndrome were reported with subclavian access.[47]

In 2018, Liccardo et al. compared PPM and ICD lead insertion through US-guided axillary vein puncture to anatomical landmark-guided subclavian puncture in 174 participants.[38] Before starting the comparative study, a training phase (60 axillary cases) was performed, during which an axillary success rate of 69% was achieved. During the randomised phase, no difference in success rate was reported (91.4% versus 94.8% in the axillary and subclavian groups, respectively). Over a mean follow-up period of 18 ± 6 months, lead complications were similar in both groups (2.6% versus 5.2%; $p=0.664$), with two cases of pneumothorax (3.4%) requiring thorax drainage and longer hospitalisation length of stay in the subclavian group. Axillary puncture was considered a safe and efficient alternative to the standard subclavian access for CIED implantation.[38]

Figure 1: 2D Ultrasound Image of the Right Axillary Vein and Artery in Short-Axis View



The probe marker is pointing cranially. Compressibility, lack of pulsation and a more medial and superficial position differentiate the axillary artery from the axillary vein.

In contrast to the finding of lower success in the initial training phase noted above, Squara et al. demonstrated excellent outcomes for a self-taught axillary technique from the first case.[44] That study was a prospective randomised trial comparing self-learned fluoroscopy-guided axillary vein puncture with cephalic vein dissection in 74 participants undergoing PPM implantation. Similar venous access success (81.1% versus 75.7% for axillary vein puncture and cephalic vein dissection, respectively; p=0.57) and 30-day complication rates (13.5% versus 10.8%; p=0.71) were obtained, with shorter venous access time (5.7 minutes versus 12.2 minutes; p<0.001), total procedural time (34.8 minutes versus 42 minutes; p=0.043) and X-ray exposure (1,463 versus 1,013 mGy·cm^2; p=0.12) in the axillary group.[44] These results were quite consistent throughout the study, independent of the number of cases performed by each operator. Based on these findings, the authors highlighted that one of the particular advantages of the axillary vein is its possible use as a bail-out alternative when the cephalic vein is absent or has an unsuitable calibre, avoiding intrathoracic puncture.[44]

Esmaiel et al. also reported their experience with US-guided axillary vein puncture in 403 consecutive patients who underwent a PPM implantation between 2012 and 2015.[48] In that study, a success rate of 99.2% was obtained, with a mean number of 1.18 venepuncture attempts per patient and a mean time of 2.24 minutes to obtain central venous access. No access-related complication was reported.[48] However, because that study was a retrospective, observational, single-centre and single-operator study, its external validity could be questionable.

An interesting point from the study by Esmaiel et al. is that the authors had described puncturing the vein from inside the pocket incision using a sterile covered probe.[48] According to Esmaiel et al., this puncture is performed 1–2 cm medial to the deltopectoral groove, therefore more medial and slightly cranial than the standard incision for a cephalic cutdown.[48] We prefer to puncture first and to create the pocket after because, with this technique:

- we can incise the skin in a medial position, far from the axillary region, in a location that we judge more comfortable to the patient;
- the puncture site does not get restricted to the incision area, which enables us to more easily change the position of vascular linear probe (e.g. from the short to long-axis or from lateral to medial), scanning the entire vein; and
- we avoid applying gel inside the pocket, even sterile gel, due to concern of infection.

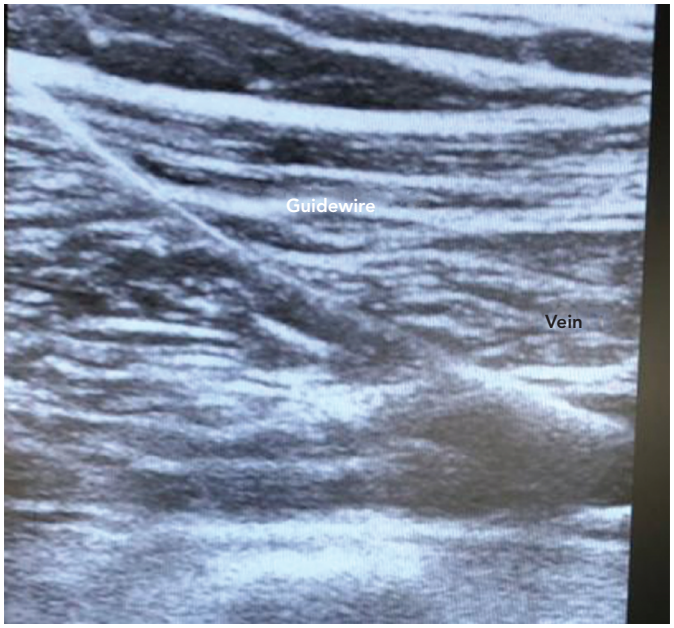
Despite these arguments, in obese patients puncturing from inside the pocket could be preferable because this technique facilitates vein visualisation by obviating imaging impairment due to the deep layer of subcutaneous fat.

In our practice, in chronological order, we first puncture the vein and insert the 0.035" guidewire. Second, we make the skin incision and build the pocket in a location that we judge more comfortable to the patient. Third, we dissect the tissues until we identify the 0.035" J-wire, which we then pull to the subcutaneous or submuscular space (i.e. subcutaneously in case of subcutaneous pocket and submuscularly in case of a submuscular pocket).

A 2006 prospective non-randomised study comparing PPM lead implantation by US-guided axillary puncture versus cephalic vein dissection evidenced similar success rates for the two approaches (88% versus 87%, respectively), with shorter lead placement time in the axillary group (8 minutes versus 12 minutes; p<0.05).[31] It was also reported that the operators achieved lead placement times with US-guided axillary puncture that were equivalent to those for cephalic dissection after 25 cases; however, once the US-guided technique was mastered, the operators had faster lead placement times with this method than with cephalic dissection. In this analysis, independent predictors of lead placement time were BMI, operator experience, initial strategy (ultrasound versus cephalic) and number of procedures.[31]

Regarding predictors of late lead complication, Chan et al. reported that, over a mean follow-up period of 73.6 ± 33.1 months, subclavian vein puncture instead of axillary vein puncture was the only independent predictor of pacemaker lead failure (HR 0.26; 95% CI [0.07–0.95]; p=0.042).[49] In this analysis, the success rate was significantly lower in the cephalic group (78.2%) than in the venography-guided axillary puncture or blind subclavian puncture groups (97.6% and 96.8%, respectively; p<0.001).[49] In addition, over a medium-term follow-up period (mean 45 ± 10 months), ElJamili et al. showed that, even in

Figure 2: Long-Axis Ultrasound-guided Axillary Vein Puncture



patients under oral anticoagulation or antithrombotic therapy, US-guided axillary puncture presented no postoperative complications and achieved a success rate of 95.78%, with the guidewire insertion time reaching a plateau after 15 patients.[50]

Considering all these studies, US-guided axillary vein puncture has a success rate ranging from 80% to 99%.[25,38–40] Compared with other available access routes, this rate appears better than that reported for cephalic vein dissection (64–87%)[31,44,46,49] and similar to that reported for venography-guided axillary puncture (90–98%),[10,28,49,51] fluoroscopy-guided axillary puncture (61–98%)[10,18,22,23,44,47] and even blind subclavian puncture (94–96%).[23,38,47,49]

Aiming to fill the evidence gap in the comparison between US-guided axillary puncture and cephalic vein dissection, as well as to provide a strong scientific basis for the use of US-guided axillary vein puncture as the standard technique for CIED implantation, Tagliari et al. recently published the results of the first randomised clinical trial comparing these two approaches during PPM and ICD lead implantation.[52] In that trial, the superiority of the US-guided axillary approach was demonstrated in terms of success rate (97.7% versus 54.5%; p<0.001), time to obtain central venous access (5 minutes versus 15 minutes; p<0.001) and total procedural time (40 minutes versus 51 minutes; p=0.010), with no increase in complication rate.[52]

Conclusion

CIEDs are a widely used, life-saving therapy for different heart rhythm conditions. Because of potential failures or complications of standard implant practices (i.e. cephalic dissection and subclavian vein puncture), alternative techniques have emerged. Among these, US-guided axillary puncture stands out because of its high success rate, associated with a low incidence of complications and short learning curve. In addition, this techniques aligns with the new trend to use US for safer vascular access in different contexts. The article by Tagliari et al. will hopefully contribute to shedding some light on this issue, and possibly to changing standard approaches.[52] ■

Clinical Perspective

- Despite not being the standard approach in many centres, axillary vein punctures guided by fluoroscopy, venography and ultrasound have emerged as feasible alternatives for the implantation of cardiac implantable electronic devices (CIEDs).
- Lead insertion through axillary vein puncture is associated with a short learning curve and procedural time.
- Ultrasound-guided axillary vein puncture has a high success rate with a low complication rate, which could make it the preferred approach for the implantation of CIEDs.

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Article

Insights from the axillary vein puncture guided by ultrasound versus cephalic vein dissection trial

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Abstract: Axillary vein puncture guided by ultrasound (US-Ax) versus cephalic vein dissection in pacemaker and defibrillator implant: a multicenter randomized clinical trial is a recently published study in which 88 patients were randomized in a 1:1 fashion to one of the two methods. Even being performed by operators with not previous ultrasound-guided axillary vein puncture experience, this group presented a higher success rate, lower procedural time and comparable complication incidence.

Lay abstract: Recently a study evaluating two different approaches to cardiac devices implant was published. In the study, 88 patients were assigned to one of two methods for this procedure. The operators had no previous experience in one of the methods, but it demonstrated a higher success rate, took less time and had the same number of complications as the method the doctors had experience in. This paper evaluated the study and discusses what changes might take place in clinics as a result of these findings.

Keywords: axillary vein • cephalic vein • implantable cardioverter defibrillator • pacemaker • randomized clinical trial • ultrasound-guided venous puncture

Introduction:

Bradyarrhythmias and tachyarrhythmias are part of a vast array of cardiovascular syndromes. They are associated with several cardiomyopathies and intrinsic rhythm disorders. Since they appear in different clinical contexts, they became part of the routine of every cardiologist, electrophysiologist and cardiac surgeon. For symptomatic bradyarrhythmias, as advanced atrioventricular block, symptomatic sinus-node disease and selected cases of cardioinhibitory vasovagal syncope, the treatment is permanent pacemaker implant [1]. Implantable cardioverter-defibrillator (ICD), in its turn, gained a widespread indication after aborted sudden cardiac death and as primary prevention in those with low-ejection fraction heart failure, and many other cardiopathies with high sudden cardiac death risk [2]. Historically the first route for lead implantation for most of operators was the subclavian vein due to its short path to the right ventricle and due to the already consolidated experience in performing the puncture guided by anatomical and fluoroscopical landmarks. However, the concern about the risks of puncturing an intrathoracic large vein, which is close to a large pulsating artery and pleura, led to the development and spreading of the cephalic vein cutdown technique. Despite its safer profile, the cephalic vein cutdown can be technically challenging and it is associated with a relatively long learning curve. Besides, it is more operator-dependent, which can be noted in its extreme heterogeneity of success rate (varying from 10 to 70%) [3,4]. Aiming to be a technique gathering the best of both worlds, the axillary vein puncture was brought to the clinical practice. In this context, fluoroscopy, venography or ultrasound can be used as guidance to reach the vein with the puncture needle. Notwithstanding these techniques have already been compared against each other in previous studies, most of them are nonrandomized and suffer from inherent bias. Tagliari et al. recently published a multicenter randomized clinical trial directly comparing ultrasound (US)-guided axillary vein puncture to cephalic vein cutdown as the approach of choice for pacemaker or implantable cardioverter defibrillator (ICD) implantation [5].

Study design & population

It was a 1:1 multicenter randomized clinical trial that enrolled 88 patients ≥18-year-old referred for pacemaker or ICD implantation. Were excluded those undergoing lead repositioning or device replacement, as well as those presenting upper limb venous thrombosis. Adjudicators were blinded. Patients were followed during the in-hospital period and after 30 days in a routine outpatient follow-up. The primary end point was defined as success rate, in other words, all leads insertion inside the superior vena cava (SVC) taking no more than 15 min. After this time limit, it was considered failure, but the operator was allowed to keep trying the same strategy or change based on personal preference. In the axillary puncture group, three puncture attempts were allowed (needle advancement forward until the end and back, without axis reorientation). After three attempts, it was registered as failure. Secondary end

points were: need for venous access site change; time to obtain venous access (from skin anesthesia to all leads inserted in superior vena cava); total procedural time; and early complication rate. Early complications were those occurring within 30-days after the procedure [5].

What was demonstrated by the study?

It demonstrated that the US-guided axillary vein puncture was associated with a higher success rate (97.7 vs 54.5%; $p < 0.001$) (Figure 1), a lower access site change (2.3 vs 40.9%; $p < 0.001$) (Figure 1), a shorter time to obtain venous access (5 vs 15 min; $p < 0.001$) and a shorter total procedural time (40 vs 51 min; $p = 0.010$). The complication rate was also numerically lower in the axillary group, but since just a few complications were observed, it did not reach statistical significance (2.3 vs 11.4%; $p = 0.202$) (Figure 1). The complications were one pneumothorax, three lead displacements, and one pocket hematoma, in the cephalic group; and one pneumothorax, in the axillary group. The only pneumothorax observed in the axillary group occurred in a malnourished patient with a small and barely US visible axillary vein, in the context of too medial puncture [5].

What explains the superiority of the axillary approach?

The higher success against cephalic cutdown can be explained by the fact that US-guided axillary puncture is a more pragmatic technique (Figures 2 & 3) (Supplementary Videos 1 & 2). Once the vein is visualized by the ultrasound, entering it with a needle is quite standard. For cases of difficult visualization, the technique should not be abandoned right away because, similarly to the jugular vein, maneuvers can be used to increase vein caliber like Valsalva, Trendelenburg and passive leg elevation [6]. Cephalic vein, on the other hand, has a smaller and more variable size and often cannot accommodate multiple leads. One may argue that the cephalic group had a very low success rate compared with previous studies and that the criteria for success may have handicapped this group. However, even after turning the criteria softer, by not considering failure those who succeeded after 15 min and considering success even those with a single lead inserted (in case of dual-chamber implants), the success rate remained significantly superior in the axillary group (97.7 vs 79%; $p = 0.003$).

I am a subclavian device implanter. Should I change my approach?

Subclavian puncture is a very well-established technique known to have a high success rate due to its large caliber and less variable anatomical position. However, compared with other techniques, it is also the one associated with a higher rate of complications, sometimes severe. A recent meta-analysis, comprising all device types, evaluated the subclavian vein puncture against cephalic vein cutdown. The incidence of pneumothorax was lower in cephalic approach (OR: 0.21; 95% CI: 0.10–0.42; $p < 0.001$),

and also the overall lead failure (OR: 0.25; 95% CI: 0.13–0.51; $p < 0.001$) [7]. So, even compared with the cephalic group, the subclavian approach has been shown to be inferior in terms of safety. In a contemporary nonrandomized study, comparing consecutive patients undergoing landmark fluoroscopic subclavian puncture (n = 46) to US-guided axillary puncture (n = 49), they found a reduction in fluoroscopy time and dose-area product to less than a third. This was achieved without increasing the procedural time and having the same success rate [8]. Thus, the US-guided axillary puncture, when compared with subclavian, offers a similar safety profile, it is more efficient, and reduces fluoroscopy. In our point of view, unless you are really an experienced subclavian vein operator with a proven low complication incidence, technique migration could be recommended.

I am a cephalic vein expert. Should I change my approach?

Cephalic vein, although safe, is associated with a significant failure rate, even in experienced hands. Besides, it requires surgical skills that take some time to be developed. A recent evidence comprising 660 patients submitted to ICD implant (75.4 axillary, 18 cephalic and 4.2% subclavian) showed that cephalic vein, mostly in multiple leads insertion, was associated with a higher rate of lead failure (11–19% in a mean of 667 ± 1 days follow-up), as defined by the Heart Rhythm Society consensus: patients with recurrent, nonphysiologically high-rate sensing; a change in pace/sense or high-voltage impedance (increase >100 or decrease >50%), or values outside of 200–1500 ohms, for pace/sense, or 20–200 ohms for high voltage and; a sudden or incremental increase in right-ventricular threshold, and/or decrease in sensing, without an alternate explanation. The authors hypothesize that it could be due to lead interaction with each other due to the constriction through all cephalic vein extension [9]. Due to the significant failure rate in the cephalic approach, it is essential for the implanter to master a bail-out technique. In this context, US-guided axillary vein puncture can be used as the second technique with a similar safety profile. Mastering US vein evaluation, besides guiding axillary puncture, can be used prior to the cephalic approach as a preprocedural success predictor. In a study by Staszewicz et al. the inability to visualize the cephalic vein in pre-operatively US examination predicted insertion failure of totally implantable venous access devices [10]. Also, Tagliari's study has demonstrated that the US axillary approach was associated with shorter procedural duration, translating into a higher surgical room turn-over. Besides, longer procedural duration has been shown as a risk factor for infection, so shorter procedures could potentially reduce the infection incidence [11].

I have never punctured the axillary vein under US guidance. Is it worth to learn the technique?

As mentioned above, axillary US-guided puncture is a simple method, almost analogous to US-guided jugular puncture. Tagliari AP et al. study found that there is no significant learning curve once a

short time to obtain central venous access and a high success are observed since the first cases (Figure 4) [5]. This finding is similar to the data from Squara et al. who evaluated fluoroscopy-guided axillary puncture. In this study, a success of 86.7% was observed from the beginning, with similar time to obtain venous access [12].

Conclusion

Cardiac implantable devices are implanted worldwide in very high volume. Thus, even little differences in efficacy and safety have an impact in absolute numbers. The mentioned randomized clinical trial has demonstrated superiority of the US-guided axillary puncture compared with cephalic cutoff, being associated with higher implant success, lower need for access site change, shorter time to obtain venous access and shorter total procedural time. There was no significant learning curve associate with the new method. Despite not powered to evaluate difference between complication rates; the incidences were low in both groups with no statistical difference.

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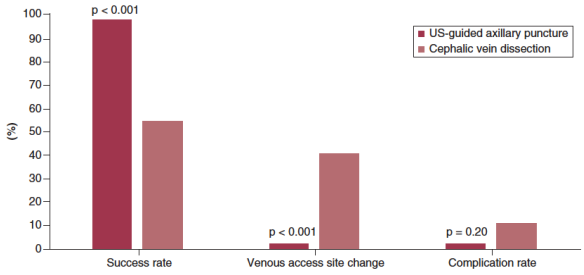

Figure 1. Success, venous access site change and complication rates compared between ultrasound-guided axillary vein puncture and cephalic vein dissection.
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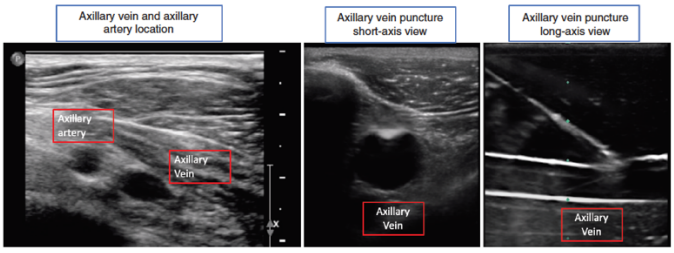

Figure 2. Ultrasound axillary vein localization and puncture in short and long-axis views.

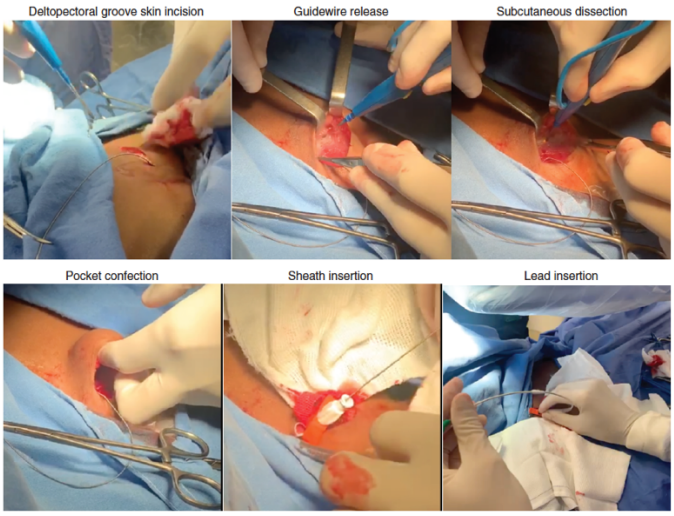

Figure 3. Surgical steps after venipuncture and guidewire insertion.

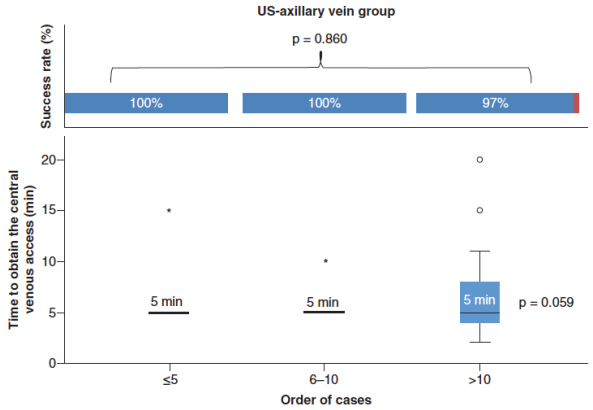

Figure 4. Procedural data and expertise in the axillary group.

6. Conclusão e considerações finais

Ainda que cada vez mais evidências demonstrem a superioridade dos acessos venosos centrais guiados por técnicas de imagem (venografia, fluoroscopia ou ultrassonografia), a utilização de técnicas alternativas ainda é incomum na maioria dos centros que implantam DCEI, bem como em nosso meio[2].

Neste estudo, objetivamos analisar as taxas de sucesso, bem como a factibilidade da utilização da técnica autoaprendida de punção venosa axilar guiada por ultrassonografia, em relação a técnica tradicionalmente utilizada de dissecção da veia cefálica.

O racional para tal escolha baseou-se em dados prévios de literatura que demonstraram altas taxas de sucesso com a utilização da veia axilar como via de acesso venoso para implante de eletrodos de DCEI (80 – 99%)[26,40,45,53,54], bem como expressivas taxas de falhas com o acesso cefálico (64 – 87%)[4,37,41,45] e a possibilidade de complicações tardias com o acesso subclávio[8].

As taxas de sucesso obtidas neste estudo foram semelhantes àquelas relatadas pela literatura corrente e indicaram superioridade do acesso venoso axilar quando comparado ao cefálico (97,7% para o grupo axilar vs. 54,5% para o grupo cefálica). Adicionalmente, observamos menor necessidade de troca de sítio de acesso venoso (2,3% vs. 40,9%), menor tempo para obtenção do acesso venoso (5 minutos vs. 15 minutos) e menor tempo total de procedimento (40 minutos vs. 51 minutos).

Menor taxa de complicação precoce, ainda que sem diferença estatisticamente significativa, também foi observada no grupo axilar (2,3% vs. 11,4%), reforçando a factibilidade do autoaprendizado da técnica de punção venosa axilar, semelhante ao previamente descrito por Squara e colaboradores[37], cujo estudo demonstrou que a técnica autoaprendida de punção axilar foi igualmente segura e efetiva quando comparada à dissecção da veia cefálica. Este dado, conjuntamente com a observação de uma curta curva de aprendizado, indica que mesmo operadores não experientes e não treinados em punção axilar guiada por ultrassonografia poderiam começar a utilizar este acesso como rota de escolha para implante de DCEI, sem aumento no risco do procedimento ou no tempo necessário para a realização do mesmo.

Acreditamos que este é um ponto importante a ser analisado uma vez que:

1. Maior taxa de sucesso, com menor necessidade de troca de sítio de acesso e menor tempo total de procedimento poderia resultar em maior rotatividade da sala cirúrgica, o que possibilitaria a realização de um maior número de procedimentos e atendimento de um maior número de pacientes que aguardam a realização do mesmo, sobretudo no Sistema Único de Saúde.
2. Ainda que não tenhamos tido poder e tempo de seguimento para analisar de maneira acurada a incidência de complicações relacionadas ao procedimento, sabe-se que a duração do procedimento está associada a maiores taxas de infecção de dispositivo[73]. Poderíamos hipotetizar, portanto, que menor tempo de procedimento e uma subsequente menor taxa de infecção, poderiam resultar em menor tempo de internação hospitalar, menor necessidade de

uso de antibioticoterapia e redução de custos, outra variável relevante, sobretudo no Sistema único de Saúde.

3. Curta curva de aprendizado facilitaria o treinamento de residentes ou mesmo de médicos assistentes já experientes na área, mas que ainda não utilizem o acesso venoso axilar como rota preferencial.

Quanto a factibilidade do método de punção venosa axilar guiada por ultrassonografia, ressaltamos que a única ferramenta adicional necessária para permitir a realização do mesmo é o aparelho de ultrassonografia, o qual já se encontra presente na maioria das salas de cirurgia cardiovascular ou de hemodinâmica, visto já ser rotina a realização de ecocardiografia transoperatória durante procedimentos cardiovasculares ou em cardiologia intervencionista. Ressaltamos, conduto, que embora tenhamos demonstrado uma curva de aprendizado muito reduzida para o método de punção axilar guiada por ultrassonografia para operadores sem experiência prévia com a punção venosa axilar, os operadores envolvidos neste estudo possuíam experiência prévia em punção venosa guiada por ultrassonografia (punção venosa femoral e punção de veia jugular interna). Assim, recomendamos que operadores sem nenhuma familiaridade prévia com o aparelho de ultrassonografia adquiram conhecimento do aparelho e suas funcionalidades antes de iniciar a técnica de punção axilar guiada por ultrassonografia.

O que diferencia este estudo dos descritos anteriormente é o fato de que este é o primeiro estudo, de que os autores tenham conhecimento, a comparar de maneira randomizada o acesso venoso axilar guiado por ultrassonografia com a dissecção da veia cefálica, uma vez que o único estudo prévio a comparar tais técnicas o fez de maneira não randomizada[45].

Os resultados finais deste estudo, demonstraram, portanto, que a punção venosa central da veia axilar guiada por ultrassonografia para implante de eletrodos de DCEI, em comparação à dissecção da veia cefálica, mostrou-se superior em termos de taxa de sucesso, necessidade de mudança de sítio de acesso venoso, tempo para obtenção do acesso venoso e tempo total de procedimento, sem associar-se a aumento na taxa de complicação precoce.

7. ANEXO 1

Artigos originais publicados durante o período de doutorado sanduíche no Hospital Universitário de Zurique/ Universidade de Zurique.

1. Tagliari AP, Ferrari E, Haager PK, Schmiady MO, Vicentini L, Gavazzoni M, Gennari M, Jörg L, Khattab AA, Blöchlinger S, Maisano F, Taramasso M. Feasibility and Safety of Cerebral Embolic Protection Device Insertion in Bovine Aortic Arch Anatomy. J Clin Med. 2020 Dec 20;9(12):4118. doi: 10.3390/jcm9124118. PMID: 33419286; PMCID: PMC7766100.
2. Tagliari AP, Miura M, Gavazzoni M, Haager PK, Russo G, Pozzoli A, Zuber M, Jörg L, Rickli H, Gennari M, Maisano F, Taramasso M. Bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction technique in transcatheter aortic valve-in-valve procedures: a single-center initial experience. J Cardiovasc Med (Hagerstown). 2021 Mar 1;22(3):212-221. doi: 10.2459/JCM.0000000000001104. PMID: 32890234.
3. Tagliari AP, Vicentini L, Zimmermann JM, Miura M, Ferrari E, Perez D, Haager PK, Jörg L, Maisano F, Taramasso M. Transcatheter Aortic Valve Neo-Commissure Alignment with the Portico System. EuroIntervention. 2020 Dec 22:EIJ-D-20-01095. doi: 10.4244/EIJ-D-20-01095. Epub ahead of print. PMID: 33342763.
4. Tagliari AP, Perez-Camargo D, Ferrari E, Haager PK, Jörg L, Gennari M, Chen M, Gavazzoni M, Khattab AA, Blöchlinger S, Maisano F, Taramasso M. Pre-Operative Continued Oral Anticoagulation Impact on Early Outcomes after Transcatheter Aortic Valve Implantation. Am J Cardiol. 2021 Mar 20:S0002-9149(21)00265-4. doi: 10.1016/j.amjcard.2021.03.022. Epub ahead of print. PMID: 33757781.

Article

Feasibility and Safety of Cerebral Embolic Protection Device Insertion in Bovine Aortic Arch Anatomy

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Abstract: Background: Cerebral embolic protection devices (CEPDs) have emerged as a mechanical barrier to prevent debris from reaching the cerebral vasculature, potentially reducing stroke incidence. Bovine aortic arch (BAA) is the most common arch variant and represents challenge anatomy for CEPD insertion during transcatheter aortic valve replacement (TAVR). Methods: Cohort study reporting the SentinelTM Cerebral Protection System insertion's feasibility and safety in 165 adult patients submitted to a transfemoral TAVR procedure from April 2019 to April 2020. Patients were divided into 2 groups: (1) BAA; (2) non-BAA. Results: Median age, EuroScore II, and STS score were 79 years (74–84), 2.9% (1.7–6.2), and 2.2% (1.6–3.2), respectively. BAA was present in 12% of cases. Successful two-filter insertion was 86.6% (89% non-BAA vs. 65% BAA; $p = 0.002$), and debris was captured in 95% (94% non-BAA vs. 95% BAA; $p = 0.594$). No procedural or vascular complications associated with Sentinel insertion and no intraprocedural strokes were reported. There were two postprocedural non-disabling strokes, both in non-BAA. Conclusion: This study demonstrated Sentinel insertion feasibility and safety in BAA. No procedural and access complications related to Sentinel deployment were reported. Being aware of the bovine arch prevalence and having the techniques to navigate through it allows operators to successfully use CEPDs in this anatomy.

Keywords: cerebral protection device; transcatheter aortic valve replacement; stroke; cerebrovascular events; bovine aortic arch

1. Introduction

Although newer-generation transcatheter heart valve devices and increased operator experience have reduced the incidence of cerebrovascular events during transcatheter aortic valve replacement (TAVR) [1,2], stroke remains one of the most feared procedural complications. This concern is especially relevant since TAVRis moving to low-risk and younger patients, a population in which a cerebrovascular event has even more impact on survival and quality of life [3–6]. Cerebral embolic protection devices (CEPDs) have been developed to work as a mechanical barrier to prevent embolic debris from reaching the cerebral vasculature, potentially reducing neurological events during TAVR procedures. The dual-filter-based SentinelTM Cerebral Protection System (Sentinel) (Boston Scientific, Marlborough, MA, USA) received CE Mark approval in 2013 and Food and Drug Administration (FDA) approval in 2017, and it is now the most widely used CEPD system [7,8]. Although no single study had demonstrated Sentinel benefits in terms of hard outcomes, two recently published propensity scoring match analyses have suggested that Sentinel use was associated with reduced post-procedural stroke and mortality rates. In the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) Registry, after propensity-weighted analysis, significant reduction in in-hospital stroke [relative risk (RR) 0.82; 95% confidence interval (CI) 0.69-0.97], in-hospital death or stroke (RR 0.84; 95% CI 0.73-0.98), 30-day stroke (RR 0.85; 95% CI 0.73-0.99), and 30-day mortality rate (RR 0.78; 95% CI 0.64-0.95) was observed in patients submitted to a protected TAVR [9]. Corroborating these findings, another propensity-weighted analysis from the National Inpatient Sample showed that Sentinel use was associated with lower risk of in-hospital ischemic stroke [odds ratio (OR) 0.24; 95% CI 0.09-0.62] and in-hospital death (0 vs. 1%; p = 0.036) [10]. Bovine aortic arch is the most common aortic arch variant and occurs when the brachiocephalic artery (or innominate artery) shares a common origin with the left common carotid artery. The bovine aortic arch prevalence is around 15% (range from 8% to 25%) [11], and its presence carries important implications for preprocedural planning and open or endovascular interventions involving the aortic arch. Indeed, the bovine arch has been associated with consistent geometric hostile features for endovascular procedures, namely angulation, tortuosity, and elongation

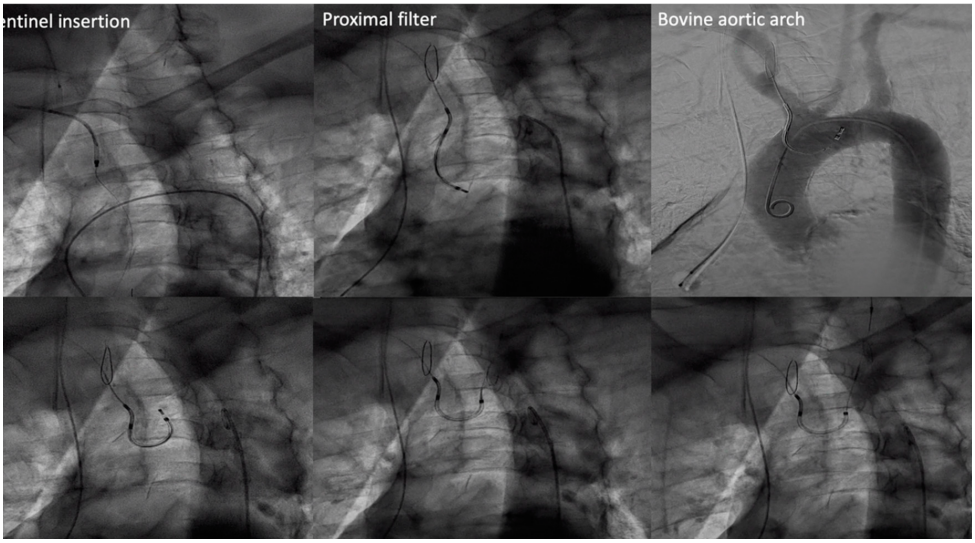
[12]. Bovine arch is also a recognized anatomic risk factor for carotid stenting, increasing the procedural difficulty level [13], and thoracic aortic disease development [14]. In this respect, in younger patients with this anatomical configuration, TAVR may represent a valid option considering that they could, in time, require an open aortic valve repair. Regarding CEPD insertion in bovine aortic arches, though there is no formal contraindication to apply the Sentinel system in this scenario, the angulation and tortuosity features related to this anatomical variant are frequent reasons to preclude Sentinel use in real-life procedures. Therefore, many patients who could benefit from cerebral protection are deprived of this strategy. Herein, we report the feasibility and safety of Sentinel insertion in bovine aortic arch anatomy and bovine arch prevalence in patients undergoing a TAVR procedure. This is the first study evaluating a cohort of patients with bovine aortic arch anatomy submitted to TAVR under cerebral protection.

2. Material and Methods

Single-center cohort study. Patients who underwent a transfemoral-protected TAVR from April 2019 to April 2020 were analyzed and divided into two groups according to the aortic arch anatomy: Group 1: Non-bovine aortic arch anatomy; Group 2: Bovine aortic arch anatomy. All procedures involving human participants followed the institutional research committee ethical standards in accordance with the 1964 Helsinki declaration and its later amendments. TAVR indication decisions were driven by the institutional heart team, and patients provided written informed consent before the procedure. Patients undergoing TAVR procedures in our institution are included in the nationwide Swiss TAVI Registry (NCT01368250; 2016-00587), a prospective multi-center and observational national registry collecting clinical characteristics of patients undergoing TAVR in Switzerland, which had been previously approved by local ethics committees [15,16]. Clinical, echocardiographic, and tomographic data were collected at baseline, discharge, and 30 days after the procedure. Clinical events were adjudicated according to the updated Valve Academic Research Consortium (VARC-2) criteria [17]. Combined procedures were defined as simultaneous elective interventions, such as coronary artery angiogram, percutaneous coronary artery intervention, left atrial appendage occlusion, intravascular

lithotripsy, bioprosthetic or native aortic scallop intentional laceration to prevent coronary artery obstruction (BASILICA), or pacemaker generator change. Significant tortuosity was defined, based on subjective operator judgment, as a brachiocephalic or left common carotid artery S- or C-shaped elongation or undulation, evaluated in the preoperative computed tomography (CT) scan. The cerebral embolic protection device used was the dual-filter-based Sentinel TM Cerebral Protection System (Sentinel) (Boston Scientific, Marlborough, MA, USA), which consists of a 6-Fr-compatible steerable catheter (100 cm long) carrying two cone-shaped, biocompatible polyurethane filters equipped with 140 μm pores to capture and retrieve debris during TAVR procedures. The sheath is inserted through the right radial artery, and the filters are targeted to the brachiocephalic artery (proximal target vessel) and the left common carotid artery (distal target vessel). Using an articulating sheath, the device's curve can be adjusted to accommodate anatomic variations of the aortic arch (Figure 1, Movie 1). In patients in whom the insertion of both filters was not possible, only the proximal filter was deployed. At the end of the procedure, both filters were checked for the presence of captured material. Successful Sentinel insertion was defined as a successful positioning and deployment of both filters in the correct anatomical position. Clinical, echocardiographic, and tomographic data were collected at baseline, discharge, and 30 days after the procedure.

Figure 1. Sentinel insertion in a bovine aortic arch anatomy.



3. Statistical analysis

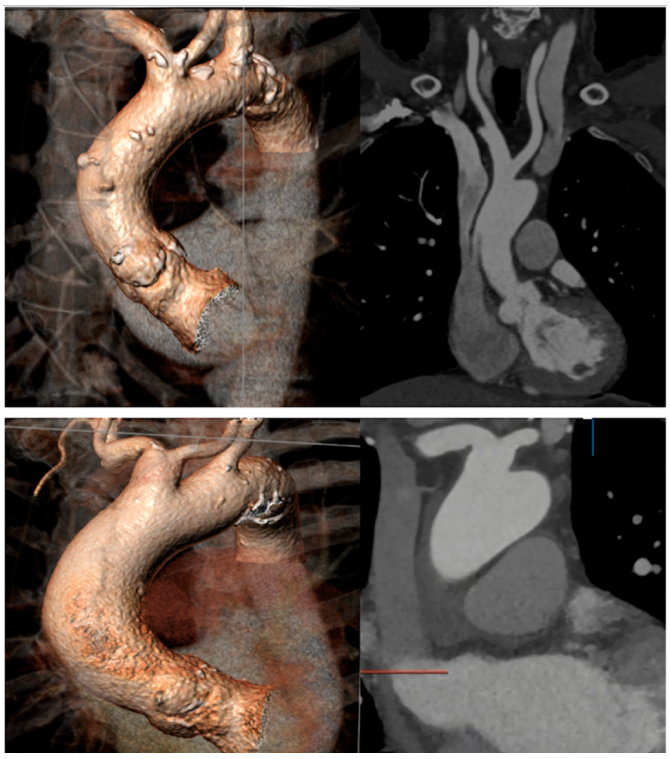
Quantitative data were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). Qualitative variables were expressed as frequency and percentage. Analyses were performed using the statistical package SPSS 19.0 software (Chicago, IL, USA). Categorical variables were analyzed using the chi-square test, continuous variables were analyzed using the Student's T test or the Mann–Whitney U test. A two-sided p-value lower than 0.05 was considered significant for all tests.

4. Results

From April 2019 to April 2020, 231 patients were submitted to a transfemoral TAVR procedure, 165 (71.5%) of them under cerebral embolic protection. The most common reasons to preclude Sentinel use were significant aortic arch branch tortuosity (22.3%, n = 15); emergency procedure or procedure performed under hemodynamic instability (10.4%, n = 7); no right radial artery suitable for Sentinel insertion (9%, n = 6) or no Sentinel progression (3%, n = 2); aberrant right subclavian artery (3%, n = 2); and previous left carotid endarterectomy (3%, n = 2). Overall, bovine aortic arch (Figure 2) was identified in 37 patients (16%, n = 37/231) and in 20 (12.12%; n = 20/165) of those submitted to a protected TAVR procedure. Type I (common origin of the brachiocephalic and left common carotid artery) bovine arch

anatomy was presented in 97.3% (n = 36) of the cases, and type II (left common carotid artery originating directly from the brachiocephalic artery, rather than as a common trunk) in 2.7% (n = 1). Comparison between patients who received a Sentinel device with those who did not are presented in the Supplementary Material (Table S1). There was no difference in procedural time (55 min (46–67) vs. 51.5 min (41.7–62.7); p = 0.492) or injected contrast volume (87 mL (69–133) vs. 102 (77–120); p = 0.071) between protected and unprotected TAVR.

Figure 2. Two examples of bovine aortic arch anatomy suitable for Sentinel insertion.



Among the 165 patients who underwent a transfemoral TAVR under cerebral protection, baseline clinical and aortic valve characteristics were similar between the bovine and non-bovine anatomy groups and are presented in Table 1. Significant aortic arch branch tortuosity was present in 27 patients (16.3%; 17.2% in non-bovine vs. 2% in bovine; p = 0.412). Successful insertion of two Sentinel filters was achieved in 143 (86.6%; 89.7% in non-bovine vs. 65% in bovine; p = 0.002). Debris was captured in the

filters of 158 patients (95.7%; 94.5% in non-bovine vs. 95% in bovine; p = 0.594). Procedure characteristics and outcomes are presented in Tables 2 and 3, respectively. There were no procedural or vascular complications associated with Sentinel insertion, nor intraprocedural strokes. Two non-disabling ischemic strokes (1.21%) were reported in the non-bovine group: the first case showed-up as aphasia on the first postoperative day, which completely regressed one day after; the second case presented hemiplegia on the third postoperative day, which also totally regressed at the hospital discharge. No new cerebrovascular events were reported between hospital discharge and 30-day outpatient evaluation. Total procedure time (55 min vs. 55 min; p = 0.654) and volume of contrast used (87mL vs. 89mL; p = 0.727) were similar in bovine and non-bovine aortic arches, respectively.

Table 1. Baseline clinical and aortic valve characteristics in patients undergoing transcatheter aortic valve replacement (TAVR) with concomitant cerebral protection.

Variable	Non-Bovine n = 145	Bovine n = 20	*p*-Value
Age, years median (IQR)	79 (74–83)	80 (77–84)	0.318
Male gender	86 (59.3)	14 (70)	0.359
EuroScore II, % median (IQR)	2.8 (1.6–6.2)	3.2 (2.2–6.3)	0.328
STS score, % median (IQR)	2.1 (1.6–3.2)	2.8 (1.6–3.7)	0.732
Weight, Kg mean ± SD	77.2 ± 14	75.9 ± 16	0.717
Height, cm mean ± SD	166.4 ± 8	170 ± 10	0.051
Severe aortic valve stenosis	142 (97.9)	20 (100)	0.516
Aortic valve regurgitation ≥ moderate	11 (6.6)	1 (5)	0.561
NYHA functional class III/IV	77 (53)	11 (55)	0.982
Arterial hypertension	103 (71)	13 (65)	0.580
Diabetes mellitus	41 (28.3)	2 (10)	0.081
Dyslipidemia	84 (57.9)	12 (60)	0.182
Coronary artery disease	64 (44.1)	12 (60)	0.191
Previous myocardial infarction	17 (12.4)	4 (20)	0.349
Previous stroke	11 (7.6)	3 (15)	0.265
Atrial fibrillation	50 (34.5)	11 (55)	0.075
Chronic obstructive pulmonary disease	17 (11.7)	3 (15)	0.674
Chronic kidney disease	44 (30.3)	6 (30)	0.975
Anemia	16 (11)	0	0.118
Peripheral artery disease	12 (8.3)	1 (5)	0.610
Active smoker	46 (31.7)	8 (40)	0.460
Previous PCI	37 (25.5)	9 (45)	0.069
Previous CABG	8 (5.5)	3 (15)	0.111
Previous aortic valve surgery	9 (6.2)	1 (5)	0.832
Previous permanent pacemaker	11 (7.6)	2 (10)	0.707
Bicuspid aortic valve	14 (9.7)	1 (5)	0.497
Aortic valve area, cm^2 median (IQR)	0.75 (0.6–0.9)	0.85 (0.7–0.97)	0.099
Aortic valve mean gradient, mmHg median (IQR)	42 (35–51)	45 (37–52)	0.703
LVEF, % median (IQR)	58 (45–65)	55 (47–60)	0.301

Values expressed as numbers (%) unless otherwise indicated. IQR = interquartile range; SD = standard deviation; CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = The Society of Thoracic Surgeons.

Table 2. Procedural characteristics.

Variable	Non-Bovine n = 145	Bovine n = 20	*p*-Value
Sedation	136 (94.4)	19 (95)	0.959
Combined procedure	9 (6.2)	0	0.252
Two Sentinel filters inserted	130 (89.7)	13 (65)	0.002
Type of bioprosthesis			0.908
Portico	49 (33.8)	9 (45)	
Edwards Sapien 3/Ultra	43 (29.6)	5 (25)	
Medtronic Evolut R/Pro	36 (24.8)	3 (15)	
Acurate Neo	12 (8.3)	2 (10)	
Allegra	3 (2.1)	1 (5)	
Lotus	2 (1.4)	0	
Procedure time, min median (IQR)	55 (45–67)	55 (48–61)	0.654
Contrast injection, mL median (IQR)	87 (68–130)	89 (72–145)	0.727

Values expressed as numbers (%) unless otherwise indicated. IQR = interquartile range.

Table 3. In-hospital outcomes.

Variable	Non-Bovine n = 145	Bovine n = 20	*p*-Value
All-cause mortality	1 (0.7)	0	0.710
Permanent pacemaker implantation	20 (13.8)	5 (25)	0.190
Non-disabling stroke	2 (1.3)	0	0.516
New onset of atrial fibrillation	6 (4.1)	0	0.354
Delirium	3 (2.1)	0	0.516
Aortic valve mean gradient, mmHg median (IQR)	8.8 (5–11)	7.7 (5–9)	0.309
Aortic valve regurgitation ≤ mild	135 (93.1)	18 (90)	0.909
LVEF, % median (IQR)	57 (49–63)	54 (49–57)	0.214
Hospital length of stay, days median (IQR)	5 (4–7)	6 (4–7)	0.554

Values expressed as numbers (%) unless otherwise indicated. IQR = interquartile range; LVEF = left ventricular ejection fraction.

5. Discussion

Cerebrovascular events are one of the most devastating TAVR complications, not only in terms of mortality but also regarding the potential sequelae and impaired quality of life [3–6]. Clinical strokes are related to an up-to-nine-fold increase in postprocedural mortality [4,18,19], non-return to working life in 50% of the cases [20,21], and an increase in index hospitalization cost of approximately 25,000 USD [22]. Almost 50% of all early post-TAVR strokes are directly procedure-related and occur within the first 24 h [3,19,23]. This post-TAVR stroke incidence peak is consistent with what has been observed in carotid stenting procedures, suggesting that stroke occurrence is related to hostile aortic arch and

anatomical features of supra-aortic vessels [24]. CEPDs were developed with the purpose of o_ering a safer procedure, mitigating cerebrovascular event risk, and improving TAVR-related outcomes [25–29]. Despite the worldwide spread of CEPD use, evidence about anatomical features associated with its unsuccessful implantation remains scarce [29]. As bovine aortic arch is the most common aortic arch branching variant in humans, the present study aimed to report the feasibility and safety of performing a Sentinel device insertion in this anatomy, as well as the prevalence of bovine aortic arch anatomy in patients who underwent a protected TAVR. Previous studies have indicated that bovine left common carotid artery configuration occurs in 8–25% of patients [11], a prevalence similar to that observed in our cohort (12%; n = 20/165). The presence of this type of anatomical configuration is associated with an increased endovascular device navigation complexity [30,31]. Comparing patients with or without aortic arch anomalies who underwent a carotid artery stent, Faggioli et al. observed that bovine arch was associated with increased neurologic events (20% vs. 5.3%; p = 0.039) and technical failure (89.6% vs. 76.4%; p = 0.1) due to the greater difficulty in navigating devices through tortuous vessels [30]. In addition, the presence of increased aortic arch angulation also reflects a hostile take-of angle of the supra-aortic branches [12]. In this scenario, Rozado et al. advocated that an extreme device tip flexure could help to advance a wire into the left carotid artery, allowing proper Sentinel advancement and positioning [32]. In our study, despite bovine aortic arch anatomy being associated with reduced two-filter insertion (89.7% vs. 65%; p = 0.002), this feature did not reflect an increase in procedural complication rate or postprocedural neurological events. Total procedure time (55 min vs. 55 min; p = 0.654) and volume of contrast used (87 mL vs. 89 mL; p = 0.727) were also similar in bovine and non-bovine aortic arches. Higher tortuosity degree and challenging device navigation were probably factors related to a lower rate of two-filter insertion in bovine group. However, since in bovine aortic arches, both common carotid arteries have the same origin and are in a close position, one filter properly positioned beyond their origins is probably enough to provide adequate cerebral protection. Furthermore, even if bi-carotid protection is not feasible, a single-filter insertion is possibly better than no cerebral protection at all. Indeed, further computational fluid dynamics studies may shed some light on stroke risk related to debris

distribution along the arch and supra-aortic branches according to the aortic arch anatomy. In our study, the Sentinel was not used in 28.5% (n = 66) of patients, a rate similar to that recently reported by Voss et al. (38.5%; n = 122). In this study, the authors reported that Sentinel ineligibility reasons, based on MSCT criteria, were as follows: inappropriate diameter within the target landing zone (n = 116); significant subclavian artery stenosis (n = 4) or an aberrant subclavian artery (n = 3); and clinical characteristics including hypersensitivity to nickel titanium (n = 1), radial artery occlusion (n = 1), or previous left common carotid artery interventions (n = 5) [33]. Another important anatomic consideration concerning Sentinel insertion eligibility is the presence of vascular tortuosity. Tortuosity hampers access to the filter-landing zone [34–36], increasing device manipulation, contrast use, vessel injury risk, and CEPD insertion failure [35]. Device instructions stipulate that Sentinel should be avoided in patients with "excessive" vessel tortuosity; however, there is no specific definition of what excessive tortuosity means. In our study, the overall prevalence of aortic arch branches tortuosity was 16.4% (n = 27/165), with no significant difference in tortuosity distribution between bovine and non-bovine Sentinel groups (17.2% in non-bovine vs. 2% in bovine; p = 0.412). Considering the benefits of cerebral protection during TAVR, even though no randomized trial had found significant stroke or mortality reduction, a propensity-matched cohort study by Seeger et al. identified lower mortality or all-stroke rate 7 days post TAVR when a CEPD was used (2.1% vs. 6.8%; p = 0.01). All-stroke rate was also inferior in protected TAVR (1.4% vs. 4.6%, p = 0.03; OR 0.29, 95% CI 0.10-0.93; NNT 31). In multivariable analysis, STS score (p = 0.02) and TAVR without cerebral protection device (p = 0.02) were independent predictors for the primary endpoint (mortality or stroke) [37]. Two years after this initial study, the same authors evaluated the incidence of procedural stroke within 72 h post-TAVR in a propensity-matched population comprising patients from the SENTINEL US IDE trial [24], the CLEAN-TAVI trial [34], and SENTINEL-Ulm registry (University Hospital of Ulm, Ulm, Germany) (n = 1306). The main result showed that the procedural all-stroke rate was significantly lower in the CEPD group compared to the unprotected group (1.88% vs. 5.44%; OR 0.35, 95% CI 0.17-0.72). In addition, the combined outcome of all-cause mortality and all stroke was significantly lower (2.06% vs. 6.00%; OR 0.34, 95% CI 0.17-0.68) in the protected

group [38]. These findings were supported by two recently released propensity scoring match analyses showing benefit in terms of stroke and mortality rate reduction when Sentinel was used [9,10]. Regarding Sentinel's cost-effectiveness, estimations show that the cost of preventing a single stroke or death is around 60,000 USD [39]. As the Sentinel device costs approximately 2800 USD, according to Giustino et al., a total amount of 61,600 USD should be spent to prevent one stroke or death. This value seems to be justifiable given the negative physical, emotional, and economic impact of stroke [40].

6. Limitations

The present analysis reflects a single-center, non-randomized, but prospectively acquired experience. Therefore, all the inherent limitations of such design need to be taken into account. In addition, our results are based on a single specific cerebral embolic protection device and cannot be generalized to other available devices. Despite our small sample size, this report represents the first cohort of patients with bovine aortic arch anatomy successfully treated with TAVR procedure under cerebral protection.

7. Conclusions

This study demonstrated Sentinel insertion feasibility and safety in bovine aortic arch anatomy. No procedural and access complications related to Sentinel deployment were reported. Being aware of the bovine arch prevalence and having the techniques to navigate through it allows operators to successfully use Sentinel in this anatomy.

Author Contributions:

Conceptualization, A.P.T., E.F., P.K.H., M.O.S., L.V., M.G. (Mara Gavazzoni), M.G. (Marco Gennari), L.J., A.A.K., S.B., F.M., and M.T.; Methodology, A.P.T., E.F., P.K.H., and M.T. Formal Analysis, A.P.T., E.F., P.K.H., and M.T. Investigation, A.P.T., E.F., P.K.H., M.O.S., L.V., M.G. (Mara Gavazzoni), M.G. (Marco Gennari), L.J., A.A.K., S.B., F.M., and M.T.; Data Curation, A.P.T.; Writing—Original

Draft Preparation, A.P.T., E.F.;Writing—Review & Editing, A.P.T., E.F., P.K.H., M.O.S., L.V., M.G. (Mara Gavazzoni), M.G. (Marco Gennari), L.J., A.A.K., S.B., F.M., and M.T.; Supervision, E.F., P.K.H., and M.T. All authors have read and agreed to the published version of the manuscript.

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Abbreviations

Bioprosthetic or native aortic scallop intentional laceration to prevent coronary artery obstruction (BASILICA); bovine aortic arch (BAA); cerebral embolic protection device (CEPD); confidence interval (CI); dual-filter-based SentinelTM Cerebral Protection System (Sentinel); Food and Drug Administration (FDA); interquartile range (IQR); multislice computed tomography (MSCT); odds ratio (OR); relative

risk (RR); standard deviation (SD); Society of Thoracic Surgeons/American College of Cardiology (STS/ACC); transcatheter aortic valve replacement (TAVR); The Society of Thoracic Surgeons (STS); Valve Academic Research Consortium (VARC-2).

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Article

Bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction technique in transcatheter aortic valve-in-valve procedures: a single center initial experience

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Abstract

Aim: To describe six cases using the bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction technique to prevent coronary artery obstruction during transcatheter aortic valve-in-valve procedures. Methods: All patients presented degeneration of a bovine pericardium bioprosthesis [four Trifecta (19, 21, 23, and 25 mm); two Mitroflow (25 and 27 mm)] resulting in severe aortic stenosis (n=5) or severe aortic regurgitation (n=1). Procedures were performed under fluoroscopic and echocardiography guidance, and the transfemoral access was used to deliver a self-expanding valve. Data are expressed as frequency or median (Q1–Q3). Results: Age, EuroScore II, and Society of Thoracic Surgeons score were 81 years (75–83.2), 2.9% (2.6–10.7), and 2.7% (2.3–3.2), respectively. Median left and right coronary heights were 9.1mm (6.2–10.3) and 12.4 mm (10–13.5), respectively, with a median virtual transcatheter heart valve-to-coronary distance of 2.9mm on the left and 4.6mm on the right side. Isolated left leaflet laceration was planned in four patients, and bileaflet in two. One unsuccessful right leaflet laceration was reported, corresponding to the first patient (success rate 87.5%). All other seven leaflets lacerations were successfully performed, with no intraprocedure complications. No coronary obstruction, in-hospital death, valve complication, cardiovascular event, or pacemaker implantation were reported. All patients are being followed in routine outpatient visits, and no adverse events were registered. Conclusion: The high procedural success and low complication rate reported in this initial experience, demonstrates that the bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction technique can be a viable solution to prevent coronary obstruction in selected patients undergoing valve-in-valve procedures. Operator experience, periprocedural imaging and teamwork are essential to enable an accurate and successful procedure.

Keywords: bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction technique, coronary artery obstruction, structural heart disease, transcatheter aortic valve implantation

Introduction

Coronary artery obstruction is a rare but threatful complication of transcatheter aortic valve implantation (TAVI) whose incidence varies from 0.4 to 0.5% in native TAVI to 2.5–3.5% in TAVI for degenerated surgical bioprosthetic aortic valves [valve-in-valve (ViV)].1 4 By definition, coronary artery obstruction occurs when the transcatheter heart valve (THV) displaces the underlying surgical or native aortic valve leaflets outward obstructing the coronary artery ostia, directly or by sequestering the sinus of Valsalva at the sinotubular junction (STJ).5 Low coronary ostia origin and narrow sinus of Valsalva are, therefore, the main risk factors associated with this condition. To reduce the risk of coronary occlusion in high-risk patients, some approaches have been proposed, such as coronary protection with a supportive coronary guidewire, undeployed balloon, chimney, or snorkel stents,6,7 and more recently, the bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction (BASILICA) technique.8 BASILICA is a novel transcatheter procedure, a member of the transcatheter electrosurgery family.8 It is derived from the LAMPOON mitral valve technique [intentional laceration of the anterior mitral leaflet to prevent left ventricular (LV) outflow obstruction]9 and it works by splitting the native or bioprosthetic leaflets to prevent critical coronary obstruction during TAVI.5 Based on the growing need to provide maximal safety in TAVI and to expand the ViV approach, the objective of this study is to describe six consecutive patients who underwent a ViV procedure with the BASILICA technique to prevent coronary artery obstruction at a single institution.

Methods

Six consecutive patients at high risk for coronary obstruction were submitted to the BASILICA technique during ViV procedures from November 2018 to March 2020. TAVI indication was driven by the institutional heart team and all patients provided written informed consent. Procedure planning Computed tomography (CT) is the gold standard to assess coronary obstruction risk, and was performed in all patients. Anatomical measurements included coronary artery height (distance from the virtual basal ring to the lower edge of the coronary artery orifices), sinus of Valsalva width and height, and STJ width.10,11 After that, a virtual THV was used to measure the virtual THV to coronary distance (VTC). CT evaluation followed the steps described below, adapted from Valvo et al.12: (1) Identification of the basal ring plane and the geometric center of the surgical heart valve. (2) Placement of a virtual cylinder representing the THV and its alignment in the middle of the basal ring. (3) Measurement of the horizontal distance between the ostia of the coronary arteries and the edge of this cylinder (VTC). (4) THV size decision based on annulus measurement and previously implanted bioprosthesis size. The valve-in-valve app was consulted for each case to ensure proper valve size selection (Bapat V, Valve in Valve Mitral app, http://www.ubqo.com/vivmitral). Regarding THV type selection for ViV procedures, it should be

individualized for each patient taking into account that retrieval after partial deployment or fully retrievable THV devices may be advantageous in patients at risk for coronary obstruction.12

Fluoroscopy projections

The BASILICA technique requires a precise laceration point location. The leaflet laceration has to start as close as possible to the nadir of the bioprosthetic leaflet, in its middle portion. To enable such precision, preprocedural CT planning is fundamental. For each leaflet laceration, two cardinal fluoroscopic projection angles were predetermined by CT analyses. To align the three commissures, each bioprosthetic valve commissure (right–left commissure, left-non commissure, and non-right commissure) was tagged. A side projection depicts the coronary artery tangential to its origin, while a frontal or en-face projection depicts the centerline of the leaflet. Therefore, the optimal left cusp side projection is the one showing right–left commissure and left-non commissure markers overlap, while the optimal left cusp frontal projection is obtained by centering the non-right commissure marker midway between the left-non commissure and the right–left commissure markers. In the same way, the optimal right cusp side projection corresponds to the one showing non-right commissure and right–left commissure markers overlap; and the optimal right cusp frontal, the one centering the left-non commissure midway between the right–left commissure and the non-right commissure markers (Fig. 2). An optimal right cusp side projection is usually not attainable, so a 'compromise' projection is obtained by moving the C-arm to a less acute angle.5 Illustrating these concepts, Fig. 3 shows the preprocedural planning.

Procedure description

All the procedures were performed under general anesthesia in a hybrid room, using a cerebral protection device. Percutaneous coronary intervention tools and extracorporeal circulatory support were readily available. Transoesophageal echocardiography (TEE) was used as complementary guidance to position the wires and catheters and to ensure proper leaflet laceration location. The first step consisted of positioning a 6 Fr sheath in the right radial artery to allow the Sentinel Cerebral Protection System (Claret Medical, Santa Rosa, California, USA) insertion, which was performed after full heparinization. Even though no randomized trial had found significant stroke or mortality reduction, the Sentinel device had a remarkable safety profile, effectively capturing circulating debris, and reducing new cerebral lesions in number and volume on Magnetic resonance imaging studies.13–16 In addition, a recent published propensity-matched analysis demonstrated a significant reduction in procedural stroke within 72 h when cerebral protection was used post TAVI (1.88% in the protected vs. 5.44% in the nonprotected TAVI group; odds ratio 0.35, 95% confidence interval 0.17–0.72, relative risk reduction 65%; P=0.0028).17 For these reasons, we have adopted cerebral protection routine employment, especially in patients with highly

calcified aorta or aortic valve leaflets, or when the procedure requires extensive manipulation, as in BASILICA cases. Ultrasound-guided arterial puncture was proceeded with in both right and left common femoral arteries. A 14/ 16 Fr DrySeal hemostatic sheath (Gore Medical, Flagstaff, Arizona, USA) was introduced through the TAVI access side (usually the right side) aiming to accommodate multiple catheters in parallel. BASILICA catheters for the first target leaflet were introduced through the DrySeal sheath and the snare through the contralateral side. The snare (Amplatz Goose Neck Snare - Medtronic, Minneapolis, Minnesota, USA) size was determined according to the LV outflow tract (LVOT) perimeter derived diameter, and it was positioned 5–10mm below the annulus plane using a 6 Fr multipurpose guiding catheter stabilized by a guidewire (V-18, Boston Scientific, Marlborough, Massachusetts, USA). The guidewire insertion also aimed to regain LV access in cases of inadvertent snare manipulation. For left cusp BASILICA, an 8 Fr Amplatz Left 3 catheter was used as traversal guide; while for the right cusp, multipurpose, or Judkins right catheters were utilized. After confirmation of proper snare and traversal guide position, an extra-long 5 Fr internal mammary diagnostic catheter and a 0.014 x 300 cm Astato XS 20 guidewire (Asahi Intecc USA, Inc., Tustin, California, USA), locked within a PiggyBack Wire Converter (Vascular Solutions, Minneapolis, Minnesota, USA), were advanced through the traversal guide. In a side projection, the traversal catheter contacted the leaflet base and pointed toward the LVOT, while the internal mammary catheter pointed downward, away from the coronary ostium toward the LVOT. Before the leaflet laceration, a pigtail catheter was inserted in the LV to allow rapid TAVI deployment, if necessary. The target cusp was then traversed using monopolar electrification, with no dextrose infusion. After electrosurgical radiofrequency energy application, the guidewire was snared in the LVOT and externalized to form a loop through the leaflet, between the two guiding catheters. The PiggyBack catheter was withdrawn to mark the point on the guidewire's midshaft, which was focally denuded (2–3mm) and kinked to create a lacerating surface (V shape). Following this step, the target leaflet was lacerated by pulling the electrified kink through the target leaflet (Fig. 4 and Movie 1–4). The presence of new aortic regurgitation confirmed a successful laceration (Movie 5). Finally, the ViV implant was performed as usual. During the electrification steps, the electrosurgical generator was set on 'pure cut' mode and the power was set according to the leaflet characteristic: 30W for porcine valve traversal, 50W for bovine or native valve, and 70W for severely calcified leaflets; 50W for porcine valve laceration, 70W for a bovine or native valve, and 100W for a severely calcified leaflet.18

Statistical analysis

Quantitative data were expressed as mean±SD or median and interquartile range (Q1–Q3). Qualitative variables were expressed as frequency and percentage. Analyses were performed using the statistical package SPSS 19.0 software (Chicago, Illinois, USA).

Results

From November 2018 to March 2020, out of 20 consecutive patients submitted to a ViV procedure, a high risk for coronary obstruction was identified in six (30%). Hence, a simultaneous BASILICA technique was indicated. Baseline clinical and bioprosthetic aortic valve characteristics are presented in Tables 1 and 2, respectively. Median age, EuroScore II, and STS scores were 81 years (Q1–Q3 75–83.2), 2.9% (Q1–Q3 2.6–10.7), and 2.7% (Q1–Q3 2.3–3.2), respectively. The mean time between the previous surgical aortic valve implantation and the current procedure was 87.3±13.4 months. The median left and right coronary heights were 9.1mm (Q1–Q3 6.2–10.3) and 12.4mm (Q1–Q3 10–13.5), respectively. The median VTC distance was 2.9mm (Q1–Q3 2.2–3.7) on the left side and 4.6mm (Q1–Q3 2.6–9.1) on the right side. Procedure characteristics and outcomes are presented in Tables 3 and 4, respectively. Isolated left leaflet laceration was planned in four patients and double leaflet laceration in two, totalizing eight leaflet laceration attempts. Only one unsuccessful right leaflet laceration happened (1/8, 12.5%), corresponding to the first patient. In this case, the right cusp BASILICA was not performed due to hemodynamic instability secondary to aortic regurgitation after the left cusp BASILICA. To protect the right coronary artery, a guidewire was positioned inside its ostia, and the TAVI was rapidly deployed, with prompt hemodynamic recovery. All the other seven leaflets were successfully lacerated, with no major complications. Median procedural and fluoroscopy times were 131 min (Q1–Q3 96–198) and 57 min (Q1–Q3 38–85), respectively. No coronary obstruction, in-hospital death, valve complication, cardiovascular events, or pacemaker implant were observed. Currently, all patients are being followed in routine outpatient visits, and no adverse events have been reported until now.

Discussion

Transcatheter aortic ViV implantation is a less invasive alternative to redoing surgery in patients with bioprosthetic aortic valve failure, especially in those inoperable or with high surgical risk.19–21 However, it carries a four to six-fold higher risk of coronary obstruction than TAVI in native valves, with a reported incidence of 2.5–3.5% and a related in-hospital mortality of approximately 50%.1–4 Aiming to reduce the risk of coronary artery obstruction during native and ViV TAVI, the BASILICA technique was developed, bringing the same concept of the previous LAMPOON technique, that is, to split the aortic leaflet using electrosurgical radiofrequency energy. Since its first application reported by Khan et al.,8 the method has become an excellent alternative to manage patients at high risk for coronary obstruction. Herein, we report our initial experience using the BASILICA technique during ViV. All patients were considered at high risk for coronary obstruction, and a doppio BASILICA was attempted in two of them. According to previous reports, low coronary ostia origin (coronary ostial height <10 mm), narrow sinus of Valsalva

(width <30 mm), and shorter VTC distance (<4mm) are the main risk factors associated with coronary artery obstruction. Other relevant factors are supra-annular bioprosthetic valve position; extended sealing cuff of high THV implantation; externally mounted leaflets ([Mitroflow aortic valve (Sorin Group USA Inc, Arvada, Colorado, USA); Trifecta aortic bioprosthesis (Abbott, St Paul, Minnesota, USA)]) or stentless bioprosthetic valves (homograft, stentless valve); bulky leaflets; and female sex.4,10,22,23 Considering these variables, as show in Table 2, all target leaflets had at least two of the three main CT risk factors for coronary obstruction: coronary height less than 10mm [left coronary height <10mm 5/6 (83%); right coronary height <10mm 1/6 (16%)]; sinus of Valsalva width <30mm [6/6 (100%)]; VTC less than 4mm [left VTC<4mm 5/6 (83%); right VTC<4mm 2/6 (30%)]. In addition to this, all bioprosthesis had externally mounted leaflets, representing an additional risk factor. We observed a high leaflet laceration success rate (7/8 leaflet, 87.5%), with the single failure occurring in the first patient, due to hemodynamic instability after the first leaflet laceration. This success rate is similar to that reported in the prospective multicenter safety and feasibility BASILICA trial. According to this study, success was obtained in 28 of 30 participants (93%) and in 35 of 37 leaflets laceration attempts (95%), with no coronary obstruction reported. The primary safety endpoint, defined as freedom from major adverse cardiovascular events, was reached in 21 patients (70%), driven by six (20%) major vascular complications related to TAVI, but not specifically related to the BASILICA technique, one death at 30 days, one (3%) disabling stroke and two (7%) nondisabling strokes. Transient hemodynamic compromise occurred in 7%, being promptly resolved with TAVI deployment.24 In this series, we have noticed a remarkable reduction in the contrast volume, total procedural time and fluoroscopy time following increased operator experience, reaching similar values to those previously reported in the BASILICA trial (total procedure time: 131 min in our study vs. 113 min in the BASILICA trial; fluoroscopy time: 57 vs. 75 min; contrast volume: 101 vs. 143 ml).24 Concerning the amount of contrast used, we have tried to reduce it by applying some complementary procedural steps, such as ultrasound-guided arterial punctures, instead of angiography-guided punctures; extensive preprocedural planning to define leaflet laceration and aortic implantation ideal projections; intraprocedural TEE guidance to help set the laceration point, to monitor eventual complications, and to evaluate the final result.24 It is also important to highlight that no coronary obstruction, vascular complication, bleeding, major stroke, or acute kidney injury type II or III according to the VARC- 2 criteria25 were observed. Despite these appealing initial results, it is fundamental to keep in mind that some anatomical characteristics, such as VTC $\approx$ 0mm and extremely calcified native or bioprosthetic valve leaflets can preclude a successful BASILICA. In addition, a combination of an extremely low coronary artery height with a narrow sinus can be a contraindication once the THV skirt itself could potentially occlude the newly formed ‘triangle of flow’.18 Furthermore, hemodynamic instability due to aortic regurgitation after laceration, thromboembolism related to cusps manipulation, injury to adjacent tissues, or arrhythmias during wire

electrification are possible challenges faced during the BASILICA execution.18 Given these particularities; BASILICA is recommended to be undertaken only after appropriate training. In cases of unfeasible BASILICA or at the operators' discretion, other techniques have been employed to mitigate coronary obstruction risk during high-risk TAVI procedures, such as upfront coronary artery protection by positioning a supportive coronary guidewire, an undeployed balloon or a stent prior to THV deployment.6,7 According to the recently published International Chimney Registry, acceptable medium-term (median 612 days) performance of the chimney stenting technique was demonstrated, with one case of possible late stent thrombosis and one stent failure (compression with restenosis) among the 60 performed cases. A noteworthy finding from this study was a lower event rate among those patients who received a prophylactic procedure compared with those who received it in the context of an established coronary occlusion.26 However, despite being an effective solution to address new coronary obstruction or to prophylactically protect those at impending coronary risk,27,28 chimney or snorkel stents are potentially prone to extrinsic compression, deformation, and thrombosis, which can lead to stent failure, late occlusion, and challenge future coronary reinterventions. 8 Compared with chimney or snorkel stents, the BASILICA technique presents some advantages, such as directly addressing the leading cause of coronary obstruction, the leaflets, and avoiding the implantation of prosthetic material, such as a coronary stent. Therefore, familiarity with both the BASILICA and chimney stenting techniques is advised for those performing TAVI in patients at risk for coronary occlusion.26

Conclusion

The high procedural success and the low rate of complications reported in this initial experience demonstrate that the BASILICA technique can be a viable solution to prevent coronary artery obstruction in selected patients undergoing TAVI for degenerated surgical bioprosthetic aortic valves. Operator experience, periprocedural imaging, and teamwork are essential to enable an accurate and successful procedure.

Limitations

The current article represents a single-center experience, limited by a small number of patients. Even though the operators had no previous experience with the BASILICA technique, they were experts in TAVI procedures, due to a high individual and institutional volume. Hence, the results demonstrated in this report may not be reproducible in less experienced centers. An extended followup is desired to evaluate long-term outcomes better.

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Conflicts of interest

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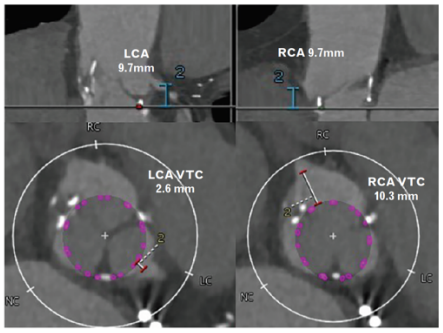
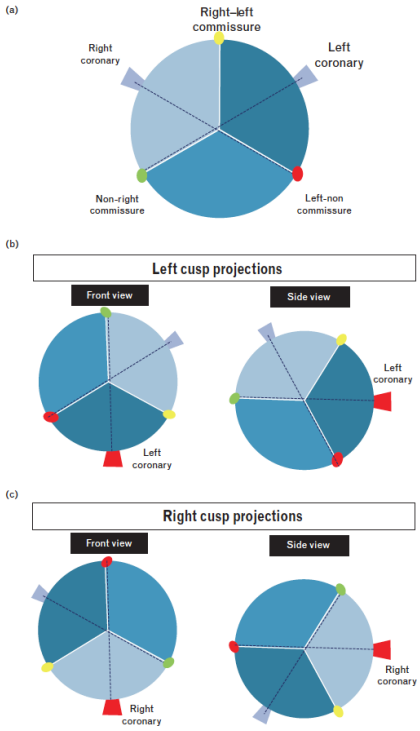
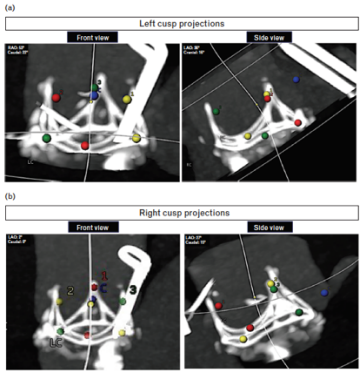


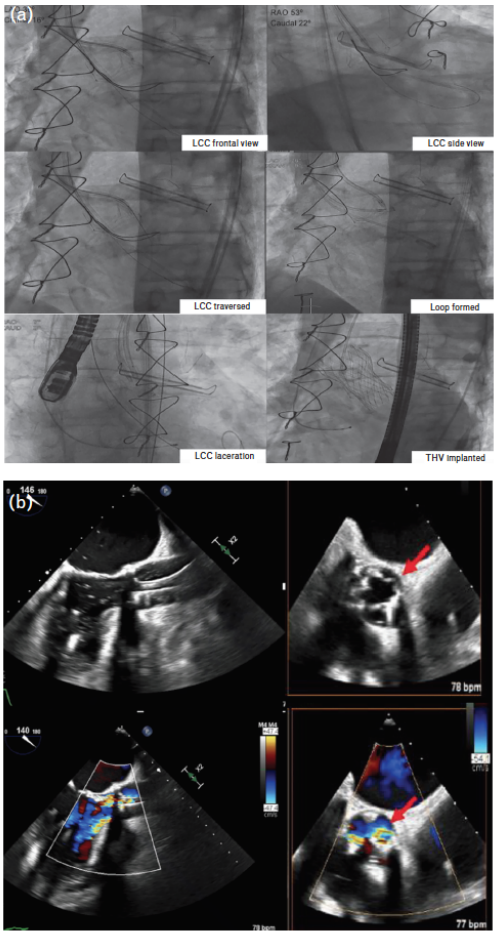
Coronary artery obstruction preoperative risk evaluation. LCA, left coronary artery; RCA, right coronary artery; VTC, virtual transcatheter heart valve-to-coronary distance.



(a) Illustration of aortic valve commissures. (b) Illustration of left cusp front and side view. (c) Illustration of right cusp front and side view.



(a) Fluoroscopy projections for left cusp bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction planning. Number 1 (yellow dot) = right–left commissure. Number 2 (red dot) = left-non commissure. Number 3 (green dot) = non-right commissure). Letter C (blue dot) = coronary artery ostium. (b) Fluoroscopy projections for right cusp bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction planning. Number 1 (red dot) = left-non commissure. Number 2 (yellow dot) = right–left commissure. Number 3 (green dot) = non-right commissure. Letter C (blue dot) = coronary artery ostium.



Bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction technique execution. (a) Fluoroscopic guidance imagens. (b) Intraprocedure transesophageal echocardiography showing leaflet laceration and aortic regurgitation (arrow). LCC, left coronary cusp; THV, transcatheter heart valve.

Table 1 Baseline characteristics

Patient number	All	1	2	3	4	5	6
Age (years)	81 (75–83.2)	84	83	81	81	74	76
EuroScore II (%)	2.9 (2.6–10.7)	12.08	3.08	2.75	10.3	2.83	2.38
STS score (%)	2.7 (2.3–3.2)	2.6	3.8	2.3	2.9	2.1	2.8
BMI (kg/m^2)	28.5 (25.5–36.6)	23	27.9	29.1	38.3	26.3	36.2
BSA (m^2)	1.9 (1.7–2.1)	1.80	1.75	1.76	2.15	2.14	2.14
Female sex	3 (50%)	No	Yes	Yes	Yes	No	No
Previous cardiac intervention	3 (50%)	No	No	PCI	CABG	Maze LAAO	No
Previous stroke	2 (33%)	Yes	No	No	No	No	Yes
Diabetes mellitus	2 (33%)	No	Yes	No	Yes	No	No
Hypertension	4 (66%)	Yes	No	Yes	Yes	No	Yes
Atrial fibrillation	3 (50%)	Yes	Yes	No	Yes	No	No
Peripheral artery disease	1 (16%)	Yes	No	No	No	No	No
Chronic kidney disease	4 (66%)	Yes	Yes	Yes	No	Yes	No
COPD	3 (50%)	No	No	No	Yes	Yes	Yes
NYHA class ≥III	3 (50%)	II	III	I	III	IV	I
LVEF (%)	68.5 (60–73)	72	67	76	60	60	70
SAVR year		2013	2011	2011	2013	2011	2013

Absolute number (%) or median (Q_1–Q_3). CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; LAAO, left atrial appendage occlusion; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement.

Table 2 Bioprosthetic aortic valve characteristics

Patient number	All	1	2	3	4	5	6
Externally mounted leaflets	6 (100%)	Trifecta	Trifecta	Trifecta	Mitroflow	Trifecta	Mitroflow
Bioprosthesis valve diameter (mm)	24 (20–25.5)	23	21	19	25	25	27
Bioprosthesis failure mechanism – AS	5 (83%)	Yes	Yes	Yes	Yes	No	Yes
AVA (cm^2)	0.7 (0.6–1.1)	0.8	0.6	1.4	0.7	2.3	0.6
AV peak gradient (mmHg)	69 (61.5–97.5)	119	59	69	64	–	76
AV mean gradient (mmHg)	45 (36.5–59.5)	71	37	36	45	–	48
Bioprosthesis failure mechanism – AR	1 (16%)	No	No	No	No	Yes	No
Aortic annulus area (mm^2)	329 (256–465)	330	267.5	223.5	583.1	328.3	426
Aortic annulus perimeter (mm)	64.7 (57–77)	64.7	58.4	53.3	86.2	64.8	74.1
STJ mean diameter (mm)	27 (25.7–28)	27.6	26.6	23.3	27.4	27	31
Sinus of Valsalva mean diameter (mm)	28.8 (25–29.4)	29.3	25.6	24.3	29.6	28.6	29
Ascending aorta diameter (mm)	34.5 (31–36.5)	38.6	35.8	31.4	30.6	35	34
Left coronary artery height (mm)	9.1 (6.2–10.3)	9.8	8.5	6.3	12.1	9.7	6.1
Right coronary artery height (mm)	12.4 (10–13.5)	10.4	13.4	12.2	14	9.2	12.7
Left coronary artery VTC (mm)	2.9 (2.2–3.7)	2.5	1.6	3.6	4.2	2.6	3.3
Right coronary artery VTC (mm)	4.6 (2.6–9.1)	4.8	4.4	3	1.7	10.3	8.8
VTSTJ (left side) (mm)	1 (0–1.7)	1	0	1.2	3.3	0	1
VTSTJ (right side) (mm)	3 (1.8–4)	3	2	1.3	4.2	3	4
TVH (mm)		Evolut Pro 23	Evolut R 23	Evolut R 23	Evolut R 26	Evolut R 26	Evolut R 29

Absolute number (%) or median (Q_1–Q_3). AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; STJ, sinotubular junction; THV, transcatheter valve heart; VTC, virtual valve-to-coronary distance; VTSTJ, virtual transcatheter heart valve to sinotubular junction distance. Trifecta aortic bioprosthesis (Abbott, St Paul, Minnesota, USA); Mitroflow aortic valve (Sorin Group USA Inc, Arvada, Colorado, USA).

Table 3 Procedure characteristics

Patient number	All	1	2	3	4	5	6
Procedure date		November 2018	July 2019	July 2019	November 2019	February 2020	March 2020
Doppio BASILICA	2 (33%)	Yes	No	No	Yes	No	No
Success leaflet laceration	7/8 (87.5%)	1/2	1/1	1/1	2/2	1/1	1/1
Procedure time (min)	131 (96–198)	312	133	129	160	80	102
Fluoroscopy time (min)	57 (38–85)	146	52	63	65	32	40
Contrast volume (ml)	101 (68–198)	360	145	112	62	70	90
Post dilatation	1 (16%)	No	No	No	No	Yes	No
Left traversal guide catheter		AL3	AL3	AL3	AL3	AL3	AL3
Right traversal guide catheter		MP	No	No	MP	No	No

Absolute number (%) or median (Q_1–Q_3). BASILICA, bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction; AL, Amplatz Left; MP, multipurpose catheter.

Table 4 Outcomes

Patient number	All	1	2	3	4	5	6
Intraprocedure outcomes							
Acute AR	1 (16%)	Yes	No	No	No	No	No
Coronary artery obstruction	No	No	No	No	No	No	No
Hospital length of stay after TAVI (days)	7 (4.5–12)	16	4	8	7	5	7
ICU length of stay (days)	1 (1–2.5)	2	1	3	1	1	1
Hospital discharge							
Survival	6 (100%)	Yes	Yes	Yes	Yes	Yes	Yes
AV mean gradient (mmHg)	8 (4.8–11.7)	14	8	5.4	11	3	8
AR grade		Mild	Mild	Trivial	Mild	Trivial	Trivial
LFEF (%)	68.5 (60–73)	67	68	61	40	56	53
Vascular complication	–	No	No	No	No	No	No
Bleeding complication (major or threatening)	–	No	No	No	No	No	No
Major stroke	–	No	No	No	No	No	No
Acute kidney injury (type II/III)	–	No	No	No	No	No	No
Permanente pacemaker	–	No	No	No	No	No	No
30 Days' follow-up							
Survival	6 (100%)	Yes	Yes	Yes	Yes	Yes	Yes
NYHA class		I	I	I	I	I	I
AV mean gradient (mmHg)	8 (4.7–9.5)	8	8	5	11	4	9
AR grade		Mild	Mild	Trivial	Mild	No	No
LFEF (%)	64 (54–72)	72	68	74	45	60	58

Absolute number (%) or median (Q_1–Q_3). Vascular complication, bleeding complication, major stroke and acute kidney injury were defined according to the VARC-2 criteria. AR, aortic regurgitation; AV, aortic valve; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TAVI, transcatheter aortic valve implantation.

Article

Pre-operative Continued Oral Anticoagulation impact on early outcomes after Transcatheter Aortic Valve Implantation

Running title**: Continued Oral Anticoagulation During TAVI**

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Abstract:

Considering that there is a lack of evidence and guideline-based recommendations on the best preoperative anticoagulation management (OAC) for transcatheter aortic valve implantation (TAVI), this cohort study aimed to evaluate bleeding, access site complications, and early safety in patients undergoing TAVI on continued OAC therapy vs. no-OAC therapy. Three-hundred forty-four patients submitted to a TAVI procedure (66.3% no-OAC vs. 33.7% OAC) were consecutively enrolled. Primary endpoint was defined as in-hospital VARC-2 life-threatening or disabling bleeding. Secondary endpoints were in-hospital VARC-2 major vascular complications, and VARC-2 early safety at 30 days. Propensity score matching analysis was performed to reduce potential distribution bias, resulting in 2 well-balanced groups (92 patients in each arm). In the overall cohort, mean age, median EuroScore II, and STS-score were 78.7±7.6, 2.9 (1.7-5.9), and 2.3 (1.6-3.6), respectively. Despite being older (78±8 vs. 80±6, p=0.004) and having higher STS score (2.1 vs. 2.6, p=0.001), patients on OAC had similar incidence of in-hospital VARC-2 life-threatening or disabling bleeding (1.3% vs. 0.9%, p=0.711), major vascular complications (4.8% vs. 5.2%, p=0.888), and VARC-2 early safety at 30 days (10.1% vs. 12.1%, p=0.575). No significant differences in the main outcomes were observed when propensity score matching was applied. In conclusion, the management of patients on OAC submitted to a TAVI procedure is challenging and requires balancing the risk of bleeding with the risk of thromboembolic events. The present study suggests that continued OAC was not associated with increased in-hospital VARC-2 life-threatening or disabling bleeding, major vascular complications, and VARC-2 early safety at 30 days.

Keywords: transcatheter aortic valve implantation; anticoagulation; bleeding; blood coagulation; aortic stenosis

Introduction:

Antithrombotic or anticoagulation therapy following transcatheter aortic valve implantation (TAVI) has been recently investigated in the POPular TAVI trial cohorts A and B, respectively (1,2). Results have suggested the superiority of single antiplatelet therapy (aspirin) in patients without indication for oral anticoagulation (OAC), and OAC alone in those with an OAC indication. These trials, however, focused on post-TAVI management and did not investigate the optimal pre-TAVI and perioperative regimen. Current European guidelines recommend vitamin K antagonists (VKA) discontinuation 5 days prior to elective cardiac surgery, aiming an INR (international normalized ratio) value <1.5 on the procedure day. Preoperative direct OAC (DOAC) discontinuation is recommended at least 48-96 hours before the procedure. However, no specific recommendation on how to manage these medications on the TAVI context has been provided (3). Trying to clarify this issue, a retrospective study showed that, in patients with atrial fibrillation submitted to transfemoral TAVI, the lowest rates of early safety (with lower values indicating superior safety) and 1-year mortality were observed in the continued DOAC group compared to continued or interrupted VKA. Continued VKA had similar incidence of bleeding and access site complication than interrupted VKA (4). These results are in line with the previous ones in which several DOAC regimens [dabigatran (5); edoxaban (6); apixaban (7); rivaroxaban (8)] were compared to warfarin in patients with atrial fibrillation. Considering the lack of evidence and guideline-based recommendations on the best pre-TAVI OAC management, this study aims to evaluate the impact of continued OAC. For that, we compared patients receiving continued OAC with those not receiving any OAC therapy in terms of bleeding, vascular complications, and early safety.

Methods:

From January 2019 to July 2020, 344 patients submitted to TAVI in a single center were consecutively enrolled. Patients were analyzed according to the perioperative OAC regimen. Group 1 (no-OAC): patients who were not on OAC at the time of the index procedure. Group 2 (OAC): patients who were on OAC (either VKA or DOAC) at the time of the index procedure. This comparison was possible since, as a local institutional routine, TAVI procedures are systematically performed without interruption of the ongoing antithrombotic or OAC regimen. Patients on VKA therapy were kept on VKA therapy during the whole periprocedural phase with an INR target range between 2.0 and 3.0, while patients on DOAC remained receiving the therapy during the whole procedural period, without skipping doses. TAVI indication was driven by the institutional heart team and patients provided written informed consent before the procedure. All patients undergoing TAVI in our institution are included in the nationwide Swiss TAVI Registry approved by local ethic committees (9,10).

During TAVI, intravenous heparin was administered, adjusted to baseline activated clotting time, aiming to reach an activated clotting time above 250 seconds in both groups. Decision about anesthetic approach and the access route were taken based on patient and devices characteristics, local expertise, and operator discretion. Cerebral embolic protection, using the Sentinel system (Boston Scientific, Marlborough, MA, USA), was routinely used. First choice access site was percutaneous transfemoral, performed through ultrasound-guided puncture. Second choice access was left subclavian artery and the third left carotid artery or transapical, performed by open surgical dissection. In the case of transfemoral route, closure devices, Perclose/ProGlide system (Abbott Vascular, CA, USA) or Manta (Essential Medical Inc, Exton, PA), were used. TAVIs were performed using CE-approved devices. Medtronic platform (Medtronic Inc., Minneapolis, MN, USA) has an integrated InLine Sheath (14F for the Evolut R 23, 26, 29mm, and 16F for Evolut Pro and Evolut R 34mm). Edwards Sapien Edwards Lifesciences, Irvine, CA, USA) was introduced through a 14-16F eSheath, which has a dynamic expansion mechanism (14F for 20, 23, 26mm, and 16F for 29mm). Portico (Abbott Vascular, Santa Clara, CCA, USA) previous generation was introduced sheathless, while the new FlexNav system has an integrated 14-15F sheath (14F for 23, 25mm, and 15F for 27, 29mm). Acurate-Neo (Boston Scientific Corporation, Natick, MA, USA) was introduced through a 14F iSLEEVE expandable introducer. Lotus Edge (Boston Scientific Corporation, Natick, MA, USA) and Allegra (New Valve Technology, Hechingen, Germany) platforms were used with an 18F sheath.

Baseline characteristics, procedural data, and outcomes were prospectively collected and adjudicated according to Valve Academic Research Consortium updated criteria (VARC-2) (11). Primary endpoint was defined as in-hospital VARC-2 life-threatening or disabling bleeding. Secondary endpoints were in-hospital VARC-2 major vascular complications, and VARC-2 early safety at 30 days (a composite of all-cause mortality, all-stroke, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure). Preoperative CHA_2DS_2-VASc and HAS-BLED scores were calculated as recommended by current guidelines (12). Sudden cardiac death (SCD) was defined as unexpected death from a presumptively cardiac cause that occurs in a short time period, generally within 1 hour of symptom onset or without prior symptoms (13).

Descriptive data were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). Statistical analyses were performed using the statistical package SPSS 25.0 software (IBM Corporation, Armonk, New York). Categorical variables were analyzed using Chi-square test, and continuous variables using Student's T-test or Mann-Whitney U test, according to the distribution pattern. A two-sided *p*-value lower than 0.05 was considered significant for all analyses. In order to reduce bias, a propensity score matching analysis was performed. Variables related to the primary endpoint or with an unequal distribution between

groups (p<0.2) were included in a 1:1 nearest neighbor model. The caliper width was equal to 0.15 of the standard deviation of the logit of the propensity score. The effectiveness of balancing was analyzed with propensity score histograms, estimating the reduction in the standardized percentage bias and performing Chi-square and T-tests between groups.

Results

Among the overall 344 evaluated patients, 116 (33.7%) underwent TAVI receiving continued OAC therapy, while 228 (66.3%) did not receive any OAC therapy. Applying propensity score matching, two well-balanced groups, with 92 patients in each one, were generated. Baseline characteristics and echocardiographic parameters for the overall cohort are presented in Table 1, and for the propensity score-matched cohort in Table 2. Before propensity score matching, patients in the OAC group were older, had higher EuroScore II and STS-score, and also higher previous permanent pacemaker prevalence, but lower previous acute myocardial infarction prevalence. As expected, patients on OAC had significantly higher CHA_2DS_2Vasc score (3.8±1.3 vs. 4.4±1.2, p<0.001) with similar HAS-BLED score (2.4±1 vs. 2.6±0.98, p=0.303).

Preoperative OAC or antithrombotic regimes are presented in supplementary Table 1. The main reasons for preoperative OAC indication were: atrial fibrillation (n=107/116, 92.2%), left ventricle thrombus (n=2/116, 1.7%), prior thromboembolism (n=5/116, 4.3%), mechanical mitral valve (n=1/116, 0.8%), and prior thrombus in the aortic valve (n=1/116, 0.8%). DOAC were taken by 87 patients (87/116, 75%) and warfarin by 29 patients (29/116, 25%).

Type of transcatheter heart valve used and other periprocedural features are presented in Table 3. Baseline and post-procedural laboratory values are displayed in supplementary Table 2. In patients on VKA, INR value was on target on the day before (2.3±0.5) and after the intervention (2.4±0.67).

In-hospital clinical and echocardiographic outcomes are summarized in Table 4. In the overall cohort, the primary outcome in-hospital VARC-2 life-threatening or disabling bleeding was not increased in the OAC group (1.3% no-OAC vs. 0.9% OAC, p=0.711) (Figure 1), as well as the secondary outcomes in-hospital VARC-2 major vascular complications (4.8% no-OAC vs. 5.2% OAC, p=0.888) and VARC-2 early safety at 30-days (10.1% no-OAC vs. 12.1% OAC, p=0.575). The overall rates of VARC-2 all-stroke (1.3% no-OAC vs. 2.5% OAC, p=0.398) and any red blood cell transfusion were also not statistically different between groups (1.8% no-OAC vs. 2.6% OAC, p=0.605). Similar results were observed in the propensity score-matched cohort, with a VARC-2 early safety at 30-days of 10.9% in the no-OAC and 14.1% in the OAC group (p=0.504) (Table 4). Since only 4 events were reported for the primary endpoint, a multivariate analysis could not be performed.

In the overall cohort, 30-day all-cause mortality was numerically higher in the OAC group (0.9% no-OAC vs. 4.3% OAC, *p*=0.033). However, when propensity score matching was applied, the difference in 30-day all-cause mortality lost statistical significance (1.1% no-OAC vs. 4.3% OAC, *p*=0.174). Death's specific reasons are presented in supplementary Table 3. On the last contact [median follow-up 80 days (36-262 days)], survival rate was similar between the groups [96.9% no-OAC vs. 94% OAC, *p*=0.188]. Kaplan Meier survival curves are presented in supplementary Figures 1 and 2.

Discussion:

In the last decade, TAVI has evolved from a procedure of exception, reserved for inoperable and high-risk patients, to a well-established intervention, even in low-risk populations. Herein, we reported early outcomes after TAVI according to the perioperative OAC regimen. The main differential of the present article lies in the discussion about perioperative TAVI OAC management, a controversial topic that lacks guideline-based recommendations. This issue is especially relevant once the 2 main trials recently published on TAVI antithrombotic or anticoagulant therapy focused only on post-procedural management (1,2). Furthermore, guidelines recommend preoperative VKA or DOAC interruption (3) and current TAVI trials have been, usually, performed adopting the interrupted OAC strategy (14).

One of the first evidences supporting the safety of continued OAC in patients with atrial fibrillation submitted to transfemoral TAVI was published in 2019 by Mangner et al. In this study, the lowest rates of VARC-2 early safety (13.2% DOAC vs. 19.7% continued VKA vs. 23.1% interrupted VKA, *p*=0.029) and 1-year all-cause mortality (8.8% DOAC vs. 13.7% continued VKA vs. 20.1% interrupted VKA, *p*=0.015) were observed in the continued DOAC group. Continued VKA regimen had similar outcomes compared to interrupted VKA in terms of all procedural bleeding (38.8% continued VKA vs. 34.8% interrupted VKA, *p*=0.097) and access site complications (40.5% continued VKA vs. 32.1% interrupted VKA, *p*=0.661) (4). Similarly to Mangner's study, our results supported the safety of the continued OAC strategy. Our VARC-2 early safety in patients receiving continued OAC (12.1%) was at least comparable to that presented by Mangner, whereas our in-hospital VARC-2 all-bleeding rate (16.3%) was even lower (27.5% in continued DOAC and 38.8% in continued VKA). On the other hand, while in the present study the majority of patients on continued OAC were receiving DOAC (75%), in Mangner's study the DOAC therapy had a lower prevalence (60%). Furthermore, we included also, even in a minority, non-transfemoral routes and patients receiving OAC due to reasons other than atrial fibrillation. Besides these points, the main difference between Mangner's and our study is that, while the former compared continued versus interrupted OAC strategies only in patients previously receiving OAC, we compared continued OAC in patients with indication and previously receiving OAC to those not previously receiving any OAC therapy. Thus, if the

continued OAC group had been associated with worse outcomes, our study would be more likely to detect a difference in bleeding rates since it compared ongoing OAC with a lower bleeding risk control group. Therefore, this study helps to answer the question: in a patient receiving continued OAC, should we expect worse outcomes after TAVI compared to those not receiving any OAC therapy?

In this same line, a letter from Brinker et al. reported that in patients on continued (186 patients) or interrupted (185 patients) OAC regimen submitted to transfemoral TAVI, the rates of periprocedural major or life-threatening bleeding (10.2% vs. 10.8%, p=0.85), major vascular complications (8.6% vs. 10.3, p=0.58), periprocedural stroke (0.6% vs. 3.2%, p=0.06), and 1-year mortality (9.38% vs. 9.83%, p=0.897) did not have statistical difference (15). These same authors recently published an update on the previous analysis with 584 patients receiving continued and 733 interrupted OAC. At 30 days, major or life-threatening bleedings (11.3% vs. 14.3%, p=0.39) and major vascular complications rates (11.0% vs. 12.3%, p=0.52) were similar, but packed red blood cell transfusion was less frequent in the continued group (13.7% vs. 17.7%, p=0.001) (16).

Two meta-analyses comparing continuous OAC versus heparin bridging in patients undergoing cardiac implantable electronic devices had suggested that OAC maintenance did not increase procedural adverse events. In the first, continued VKA was associated with significant lower postoperative bleeding risk [odds ratio (OR) 0.25, 95% Confidence Interval (CI) 0.17-0.36, p<0.001] and no difference in thromboembolic events (OR 1.86, 95% CI 0.29-12.17, p=0.57) (17). In the second, uninterrupted OAC was associated with significantly lower bleeding risk (OR 0.31, 95% CI 0.18-0.53, p<0.0001) and no difference in thromboembolic risk (OR 0.82, 95% CI 0.32-2.09, p=0.65) (18). Supplementary Table 4 presents TAVI outcomes observed in the present study in the context of current literature (1,2,4,14,19,20).

Although the present study had not observed differences in both, primary and secondary outcomes, patients on OAC presented a higher 30-day mortality rate (0.9% no-OAC vs. 4.3% OAC, p=0.033). Nonetheless, only 1 of the 5 deaths observed in the OAC group could be associated or worsened by anticoagulation (intraprocedural cardiac tamponade). It is relevant to highlight that when propensity score matching was performed, OAC was not associated with higher 30-day mortality rate (p=0.174).

Since DOAC has largely replaced VKA to prevent thrombotic events in atrial fibrillation, which is present in a significant number of patients undergoing TAVI (16-59%) (21), we performed also an analysis comparing DOAC to VKA. In this analysis, there's no significant difference in terms of main outcomes between the 2 regimens (supplementary Table 5).

We would like to highlight that, the present analysis reflects a single-center, non-randomized, but prospectively acquired experience. Hence, all the inherent limitations of such design need to be taken into account. Besides, this study focused on short-term results. Properly designed trials with long-term follow-up are required to confirm the best pre- and post-TAVI

anticoagulant management. The low number of observed events limits the statistical power of the logistic regression model. Therefore, even though continued OAC had not been associated with increased outcomes, it should be noted that we had a very low number of events, which may difficult a more generalized or definitive conclusion. Lastly, however DOAC comprised different active ingredients, with a predominance of rivaroxaban, clinical trials evaluating the safety and efficacy of DOACs have indicated a class rather than a specific drug effect.

In conclusion, the management of patients on OAC submitted to a TAVI procedure is challenging and requires balancing the risk of bleeding with the risk of thromboembolic events. The present study suggests that continued OAC was not associated with increased in-hospital VARC-2 life-threatening or disabling bleeding, major vascular complications, and VARC-2 early safety at 30 days.

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Table 1
Baseline characteristics and echocardiographic parameters before propensity score matching

Variable	All (n = 344)	OAC		p value
		No (n = 228)	Yes (n = 116)	
Age (years)	78.7 ± 7.6	78 ± 8.1	80.4 ± 6.1	0.004
Men	214 (62.2%)	149 (65.4%)	65 (56%)	0.092
Body mass index (Kg/m^2)	26.4 ± 4	26.4 ± 4.7	26.5 ± 4.7	0.921
EuroScore II (%)	2.9 (1.7-5.9)	2.7 (1.55-5)	3.4 (2.4-7.2)	0.001
STS-score (%)	2.3 (1.6-3.6)	2.1 (1.5-3.3)	2.6 (2.0-3.8)	0.001
CHA_2DS_2-Vasc score ≥3	311 (90.4%)	199 (87.3%)	112 (96.6%)	0.006
HAS-BLED score ≥3	157 (45.6%)	100 (43.9%)	57 (49.1%)	0.353
NYHA 3/4	185 (53.8%)	114 (50%)	71 (61.2%)	0.214
Coronary artery disease	170 (49.4%)	117 (51.3%)	53 (45.7%)	0.324
Previous myocardial infarction	51 (14.8%)	41 (18%)	10 (8.6%)	0.021
Previous coronary artery bypass grafting	35 (10.2%)	22 (9.6%)	13 (11.2%)	0.651
Previous percutaneous coronary intervention	103 (29.9%)	76 (33.3%)	27 (23.3%)	0.054
Previous pacemaker	30 (8.7%)	10 (4.4%)	20 (17.2%)	<0.001
Arterial hypertension	248 (72.1%)	164 (71.9%)	84 (72.4%)	0.925
Diabetes Mellitus	87 (25.3%)	57 (25%)	30 (25.9%)	0.827
Previous stroke	30 (8.7%)	18 (7.9%)	12 (10.3%)	0.446
Peripheral artery disease	40 (11.6%)	25 (11%)	15 (12.9%)	0.591
Chronic obstructive lung disease	47 (13.7%)	29 (12.7%)	18 (15.5%)	0.475
Active smoker	121 (35.2%)	89 (39%)	32 (27.6%)	0.036
Chronic kidney disease	125 (36.3%)	77 (33.8%)	48 (41.4%)	0.165
Indication				0.058
Native valve	330 (95.9%)	221 (96.9%)	109 (94%)	
Valve-in-valve	14 (4.1%)	7 (3.1%)	7 (6%)	
Echocardiographic variables				
Aortic valve main disease				0.107
Regurgitation	10 (2.9%)	9 (3.9%)	1 (0.9%)	
Stenosis	334 (97.1%)	219 (96%)	115 (99.1%)	
Bicuspid aortic valve	25 (7.3%)	19 (8.3%)	6 (5.2%)	0.286
Left ventricular ejection fraction (%)	54.4 ± 13	54.8 ± 12	53.5 ± 13	0.378
Mean aortic valve gradient (mm Hg)	44.5 ± 16	45 ± 15	44 ± 17	0.06
Peak aortic valve gradient (mm Hg)	69.9 ± 24	70 ± 23	69.7 ± 25	0.928

Variables are expressed as numbers (%), mean (±SD) or median (IQR). NYHA = new york heart association.

Table 2
Baseline characteristics and echocardiographic parameters after propensity score matching

Variable	OAC		p value
	No (n = 92)	Yes (n = 92)	
Age (years)	80.4 ± 7.5	80.6 ± 6.5	0.873
Men	58 (63.1%)	53 (57.6%)	0.451
Body mass index (Kg/m^2)	26.6 ± 4.7	27.3 ± 4.8	0.329
EuroScore II (%)	3.2 (2.2-5.7)	4.1 (2.4-7.4)	0.439
STS-score (%)	2.5 (1.8-3.7)	2.6 (1.9-3.6)	0.739
CHA_2DS_2-Vasc score ≥3	82 (89.1%)	88 (95.7%)	0.095
HAS-BLED score ≥3	44 (47.8%)	42 (45.7%)	0.768
NYHA 3/4	54 (58.7%)	54 (58.7%)	0.868
Coronary artery disease	44 (47.8%)	44 (47.8%)	1.0
Previous myocardial infarction	9 (9.8%)	8 (8.7%)	0.799
Previous coronary artery bypass grafting	10 (10.9%)	8 (8.7%)	0.620
Previous percutaneous coronary intervention	19 (20.7%)	23 (25%)	0.482
Previous pacemaker	7 (7.6%)	7 (7.6%)	1.0
Arterial hypertension	63 (68.5%)	66 (71.7%)	0.629
Diabetes Mellitus	14 (15.2%)	23 (25%)	0.090
Previous stroke	9 (9.8%)	8 (8.7%)	0.799
Peripheral artery disease	9 (9.8%)	11 (11.9%)	0.636
Chronic obstructive lung disease	16 (17.4%)	15 (16.3%)	0.844
Active smoker	30 (32.6%)	24 (26.1%)	0.331
Chronic kidney disease	35 (38%)	38 (41.3%)	0.651
Indication			0.515
Native valve	86 (93.5%)	88 (95.6%)	
Valve-in-valve	6 (6.5%)	4 (4.4%)	
Echocardiographic variables			
Aortic valve main disease			0.055
Regurgitation	6 (6.5%)	1 (1.1%)	
Stenosis	86 (93.5%)	91 (98.9%)	
Bicuspid aortic valve	7 (7.6%)	6 (6.5%)	0.774
Left ventricular ejection fraction (%)	54 ± 12	53 ± 12	0.444
Mean aortic valve gradient (mm Hg)	43 ± 13	44 ± 18	0.638
Peak aortic valve gradient (mm Hg)	65 ± 20	70 ± 27	0.174

Variables are expressed as numbers (%), mean (±SD) or median (IQR). NYHA = new york heart association.

Table 3
Procedural characteristics

Variable	Overall			p value	Propensity Score Matching		p value
		OAC			OAC		
	All (n = 344)	No (n = 228)	Yes (n = 116)		No (n = 92)	Yes (n = 92)	
Conscious sedation	318 (92.4%)	211 (92.5%)	107 (92.2%)	0.480	85 (92.4%)	86 (93.5%)	0.563
Vascular access				0.531			0.361
Right Transfemoral	283 (82.2%)	186 (81.5%)	97 (83.6%)		78 (84.8%)	81 (88.1%)	
Left Transfemoral	46 (13.3%)	33 (14.5%)	13 (11.2%)		12 (13.1%)	7 (7.6%)	
Left subclavian artery	12 (3.5%)	6 (2.6%)	6 (5.2%)		2 (2.2%)	4 (4.3%)	
Transapical	2 (0.5%)	2 (0.9%)	-		-	-	
Left carotid artery	1 (0.3%)	1 (0.4%)	-		-	-	
TAVI device				0.826			0.503
Portico	116 (33.7%)	79 (34.6%)	37 (31.9%)		30 (32.6%)	30 (32.6%)	
Sapien 3/Ultra	112 (32.5%)	75 (32.9%)	37 (31.9%)		23 (25%)	30 (32.6%)	
Evolut R/PRO	80 (23.2%)	51 (22.3%)	29 (25%)		30 (32.6%)	20 (21.7%)	
Acurate-neo	25 (7.3%)	16 (7%)	9 (7.8%)		5 (5.4%)	8 (8.7%)	
Other	11 (3.2%)	7 (3.1%)	4 (3.5%)		4 (4.3%)	4 (4.3%)	
Pre-dilatation	141 (40.9%)	96 (42.1%)	45 (38.8%)	0.509	36 (39.1%)	37 (40.2%)	0.880
Post-dilatation	45 (13%)	27 (11.8%)	18 (15.5%)	0.147	6 (6.5%)	14 (15.2%)	0.058
Procedure time (min)	54 (44-68)	53 (44-67)	55 (43-69)	0.974	52 (43-67)	53 (43-67)	0.713
Contrast dye (mL)	88 (70-122)	88 (73-120)	87 (67-125)	0.648	94 (71- 121)	86 (65- 124)	0.489

Variables are expressed as numbers (%), mean (± SD) or median (IQR).

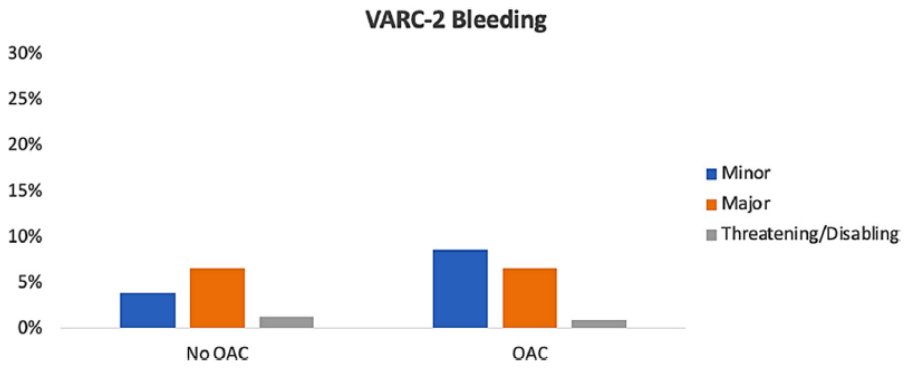
Table 4
In-hospital outcomes

Variable	Overall			p value	Propensity Score Matching		p value
		OAC			OAC		
	All (n = 344)	No (n = 228)	Yes (n = 116)		No (n = 92)	Yes (n = 92)	
VARC-2 all-bleeding	46 (13.3%)	27 (11.8%)	19 (16.3%)	0.338	13 (14.1%)	17 (18.5%)	0.425
Minor	19 (5.5%)	9 (3.9%)	10 (8.6%)	0.073	5 (5.4%)	8 (8.7%)	0.388
Major	23 (6.7%)	15 (6.6%)	8 (6.9%)	0.911	7 (7.6%)	8 (8.7%)	0.788
Life-threatening or disabling	4 (1.2%)	3 (1.3%)	1 (0.9%)	0.711	1 (1.1%)	1 (1.1%)	1.0
VARC-2 vascular complications	75 (21.8%)	48 (21%)	27 (23.2%)	0.892	17 (18.5%)	20 (21.7%)	0.581
Minor	58 (16.9%)	37 (16.2%)	21 (18.1%)	0.661	13 (14.1%)	15 (16.3%)	0.681
Major	17 (4.9%)	11 (4.8%)	6 (5.2%)	0.888	4 (4.4%)	5 (5.4%)	0.733
VARC-2 all-stroke	6 (1.7%)	3 (1.3%)	3 (2.5%)	0.398	3 (3.2%)	3 (3.2%)	0.549
Disabling	-	-	-		-	-	
Non-disabling stroke	5 (1.4%)	3 (1.3%)	2 (1.7%)		3 (3.2%)	2 (2.2%)	
TIA	1 (0.3%)	-	1 (0.9%)		-	1 (1.1%)	
VARC-2 myocardial infarction	2 (0.6%)	2 (0.9%)	-	0.312	2 (2.2%)	-	0.155
Second valve implant	5 (1.4%)	2 (0.9%)	3 (2.6%)	0.211	-	3 (3.2%)	0.081
Surgical conversion	1 (0.3%)	1 (0.4%)	-	0.475	1 (1.1%)	-	0.316
Any red packed blood cells	7 (2%)	4 (1.8%)	3 (2.6%)	0.605	2 (2.2%)	3 (3.2%)	0.650
New permanent pacemaker	51 (14.8%)	37 (16.2%)	14 (12.1%)	0.305	16 (17.4%)	11 (11.9%)	0.298
New atrial fibrillation	11 (3.2%)	10 (4.4%)	1 (0.9%)	0.079	1 (1.1%)	1 (1.1%)	1.0
Delirium	14 (4%)	11 (4.8%)	3 (2.6%)	0.321	6 (6.5%)	3 (3.2%)	0.305
All-cause mortality	6 (1.7%)	1 (0.4%)	5 (4.3%)	0.01	1 (1.1%)	4 (4.3%)	0.174
Hospital length of stay (days)	5 (4-7)	5 (4-7)	6 (4-7)	0.741	6 (4-8)	6 (4-7)	0.243
			Echocardiographic variables				
Left ventricular ejection fraction (%)	55.5 ± 11.5	55.3 ± 11	55.8 ± 11	0.683	55.1 ± 11.5	56.1 ± 10.9	0.565
Residual mean gradient (mmHg)	8 ± 3.9	8.2 ± 3.9	7.7 ± 3.8	0.330	7.9 ± 3.7	7.8 ± 3.9	0.905
Residual peak gradient (mmHg)	15 ± 6.9	15.9 ± 7	14.3 ± 6.5	0.076	15.5 ± 7.1	14.5 ± 6.7	0.407
Residual aortic regurgitation ≤Mild	320 (93%)	216 (94.7%)	105 (90.5%)	0.165	86 (93.4%)	83 (90.2%)	0.117

Variables are expressed as numbers (%), mean (SD) or median (IQR). TIA = transient ischemic attack.

Figure legend:

Figure 1. VARC-2 bleeding comparing no-OAC to OAC.



8. ANEXO 2

Referências dos demais artigos publicados durante o doutorado sanduíche no Hospital Universitário de Zurique/ Universidade de Zurique.

1. Tagliari AP, Taramasso M. Transcatheter tricuspid interventions: time to re-think guidelines? Aging (Albany NY). 2020 Jan 27;12(2):1037-1038. doi: 10.18632/aging.102805. Epub 2020 Jan 27. PMID: 31986123; PMCID: PMC7053612.
2. Tagliari AP, Santos DV, Saadi EK, Taramasso M, Mestres CA. Unsolved questions in prophylactic tricuspid valve repair and the possible role of transcatheter tricuspid intervention. Am J Cardiovasc Dis. 2020 Aug 15;10(3):142-149. PMID: 32923095; PMCID: PMC7486522.
3. Tagliari AP, Perez-Camargo D, Taramasso M. Tricuspid regurgitation: when is it time for surgery? Expert Rev Cardiovasc Ther. 2021 Jan;19(1):47-59. doi: 10.1080/14779072.2021.1854734. Epub 2021 Jan 20. PMID: 33244998.
4. Perez-Camargo D, Tagliari AP, Taramasso M. Is indexed right ventricular end-diastolic volume a new key for the tricuspid regurgitation puzzle? Rev Esp Cardiol (Engl Ed). 2021 Jan 13:S1885-5857(20)30526-0. English, Spanish. doi: 10.1016/j.rec.2020.12.002. Epub ahead of print. PMID: 33454244.
5. Lin SI, Miura M, Tagliari AP, Lee YH, Shirai S, Puri R, Maisano F, Taramasso M. Intraventricular Conduction Disturbances After Transcatheter Aortic Valve Implantation. Interv Cardiol. 2020 Jul 29;15:e11. doi: 10.15420/icr.2020.07. Erratum in: Interv Cardiol. 2020 Nov 24;15:e17. PMID: 32905123; PMCID: PMC7463330.
6. Tagliari AP, Saadi RP, Ferrari E, Taramasso M, Saadi EK. The Role of the Axillary Artery as a Second Access Choice in TAVI Procedures. Braz J Cardiovasc Surg. 2020 Dec 23. doi: 10.21470/1678-9741-2020-0343. Epub ahead of print. PMID: 33355810.
7. Tagliari AP, Gavazzoni M, Miura M, Taramasso M, Maisano M. SAM and Severe Mitral Regurgitation Post–Acute Type A Aortic Dissection Surgery Treated with MitraClip. J Am Coll Cardiol Case Rep. 2020 Aug, 2 (10) 1582–1586.
8. Tagliari AP, Taramasso M. Transcatheter aortic valve implantation combined with other heart interventions: current status and future perspectives. Vessel Plus 2020;4:16. http://dx.doi.org/10.20517/2574-1209.2020.05
9. Saadi EK, Saadi RP, Tagliari AP, Taramasso M. Routine use of cerebral protection devices during transcatheter aortic valve implantation: what does the evidence say?. Vessel Plus 2020;4:41. http://dx.doi.org/10.20517/2574-1209.2020.54